Clinical Neurorespiratory Medicine

EDITED BY

Martin Groß, Eelco F.M. Wijdicks, Maxwell S. Damian and Oliver Summ



CAMBRIDGE Medicine

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Preface

Clinicians in many branches of medicine find that their work demands knowledge of respiratory physiology.
JF Nunn, Applied Respiratory Physiology, 1969

John Nunn's classic book, *Applied Respiratory Physiology* (now in its ninth edition and edited by Andrew Lumb and Caroline Thomas), promoted the integration of respiratory physiology with clinical teaching. He would be pleased to see his ideas cross-pollinated. This book is edited by neurologists from both sides of the Atlantic who are interested in how breathing is affected by the central and peripheral nervous system and who practise and conduct research. This book offers a clinical approach to the common problems of serious neurologic disease affecting respiration – acutely or chronically – encountered by clinicians caring for these patients.

Two key components of the respiratory system – respiratory regulation and the ventilatory pump – are perceived by many neurologists as outside their field of expertise and likewise their role in the treatment of respiratory impairment is often not established as a necessity. But neurologists are often judging neuromuscular respiratory failure and interpreting changing respiratory patterns with changing level of consciousness. Some run clinics in sleep disorders.

And this is not a new idea. Many neurologists in prior centuries were very much interested in respiration – Duchenne, Russell, Plum and Baker to name a few perceptive neurologists. The major poliomyelitis epidemics in the 1950s made us all aware of not only acute respiratory failure from neurologic disease but also the lack of resources. Respiratory impairment is often the first and most frequent life-threatening consequence of neurological diseases, and the number of neurological patients affected by respiratory impairment is growing. Neurological concepts for weaning patients from mechanical ventilation and for the long-term treatment of respiratory impairment are evolving, but on an international level, clinical knowledge, organizational structures and methods are far from being standardized.

Clinical Neurorespiratory Medicine is built around the concept of an emerging discipline comprising neuroanatomy and neurophysiology of breathing, coughing, and swallowing as well as diagnosis and treatment of respiratory changes in drive, rates, rhythm and strength from diseases of the brain, spinal cord, peripheral nervous system and muscles. The clinical application takes place in a variety of settings, for example, medical, surgical and neurosciences intensive care units, respiratory care, rehabilitation and long-term and palliative care. Not only neurologists but also other medical disciplines like pulmonologists, anaesthesiologists, intensivists and paediatricians are involved in diagnosis and treatment of neurological patients with respiratory impairment. The role of nursing staff, respiratory therapists, speech and language therapists and physiotherapists must not be understated and their contribution fits into the patients' care as a whole. This book is intended as a practical guide for all these specialties because it comprises the whole sequence of assessment, decision making, and treatment.

We open the book with the history of neurorespiratory medicine. Clinical observations of the neurology of breathing were not recognized concurrently with the early experimental studies on the regulation of breathing that emerged from the nineteenth-century physiological laboratories. We noted that clinical acumen came much later, and it led to a substantial change in outcome. We also decided to show emerging challenges upfront in another introductory chapter. The book then leads the reader through the physiological and pathophysiological fundamentals of lung, airways, respiratory regulation, ventilatory pump and sleep. After elucidating the highly relevant topic of dysphagia, the basics of

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neurorespiratory diagnostics, mechanical ventilation and management of tracheobronchial secretions are discussed. There are specific chapters on the clinical aspects of tracheostomy, continuous noninvasive ventilatory support, mechanical ventilation on the neurocritical care unit, and weaning and rehabilitation of the mechanically ventilated patient. We subsequently approached the topic of neurorespiratory aspects of different neurological conditions, comprising stroke, spinal cord injury, neuromuscular disease, sleep-disordered breathing and paediatric-specific problems. Reflections on the emerging role of respiratory therapy, the quality of life of the patients, the situation of the caregivers and palliative care follow. Finally, we summarized the organization of health care in different countries around the world and share our ideas on the future development of neurorespiratory medicine and how to make the treatment of these patients more rational. For some patients, their disease progression is destined to happen, for others it is not a work of fate and medical intervention matters. This remains a sensitive issue but we neither avoid the problems of ethics nor ignore the patient's autonomy.

We thank the experienced clinicians and authors comprising a large assemble of healthcare disciplines who helped us compile this book. Without our clinical teachers, we would never have acquired the expertise needed to edit this book. We are appreciative of the superb support from Cambridge University Press and unstinting help from Anna Withing and Camille Lee-Own. We would like to thank our spouses, partners, families, and friends who supported us during the time it took to complete the work that is in front of you. We hope we can contribute and improve the care of the patients described in this volume.

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About the Editors

Martin Groß, MD is a neurologist specialized in critical care, palliative care and sleep medicine. He is medical director of the Median Clinic Bad Tennstedt and President elect of the German Society for Out-of-Hospital Ventilation and Intensive Care (DIGAB). His main research topics are respiratory regulation and health services research.

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Chapter 1

A Historical Account of the Neurology of Breathing

Eelco F. M. Wijdicks

In times past, an inquisitive physician-scientist must have pondered these questions: How do we unknowingly breathe? What brain structures control our breathing? Why is breathing so perfectly rhythmic? Is there a lung–brain communication, and if so, how? But an even more fundamental question must have been: How much brain injury can one sustain before breathing stops? The scientist most deserving of recognition for this line of inquiry must be Julien (Jean César) Legallois. His discovery, detailed in *Expériences sur le Principe de la Vie*, was a result of vivisection experiments in the early 1880s, actually undertaken to discover the structures needed to sustain breathing and thus life[1]. It took two centuries (more or less) to answer the aforementioned questions and gradually add small pieces to a large (still incomplete) puzzle. We will notice that key pieces are still missing.

The respiratory center in the brainstem and its three classes of neural mechanisms—the central and peripheral chemosensitivity, central respiratory drive, and neuronal feedback from the muscles of respiration—were identified and characterized in the late 1800s and early 1900s. Similarly, the function of the respiratory muscles and its neural connection with cranial nerves (CN) became better known. For example, the muscles moving the alae nasi to decrease airway resistance (CN VII), the muscles opening the glottis (CN X), the major inspiration diaphragm muscle (cervical cord by the third to fifth cervical nerves merging into the phrenic nerve), and intercostal muscles from the dorsal spinal cord needed as backup during dyspnea were all identified.

At its most fundamental level, breathing acquires oxygen – our brains need it more than any other organ – and removes carbon dioxide. Many anatomists and physiologists worked on multiple aspects of the respiratory system, pulmonary function, and circulation under diverse circumstances.

This introductory chapter recounts the history of the neurology of breathing and, thus, the discovery of the respiratory center and the respiratory mechanics. Sections of the chapter review experimental and clinical discoveries of the central and the peripheral nervous system involved with breathing while acknowledging the interplay between the parts.

Understanding breathing requires knowledge of anatomy, physiology, and chemistry. Earlier experimenters needed sound knowledge of the work of others and expected to be checked by criticism of their results. Once these experiments were accepted, with results confirmed and known, investigators acquired increased understanding of how the nervous system controls our breathing and how disease can compromise, interrupt, and stop our breathing cycle. However, clinical observations of the neurology of breathing were not recognized concurrently with the early experimental studies on the course and regulation of breathing that emerged from nineteenth-century physiological laboratories. In fact, clinical acumen came much later, with the poliomyelitis epidemics and development of specialized ICUs to care for severe acute brain injury. Several perceptive neurologists and neurosurgeons deserve credit.

Central Segment of Breathing

The earliest experiments concentrated on the brain hemispheres and later more specifically on the anatomy of the brainstem after it was recognized as a major vital structure[2]. Parallel to finding the anatomic centers of breathing were advances in understanding the role of oxygen and carbon dioxide in the seventeenth and eighteenth centuries, and several physiologists (such as Lavoisier and Haldane) stand out because they directed attention to the central nervous system and away from the peripheral nervous system and in particular the vagus nerve[3].

Legallois designed crude experiments to determine the minimum requirements to maintain life in a diminishing dissected portion of a rabbit. He sliced the brain caudally to the spinal cord and found that respiration stopped when he reached the medulla oblongata at the

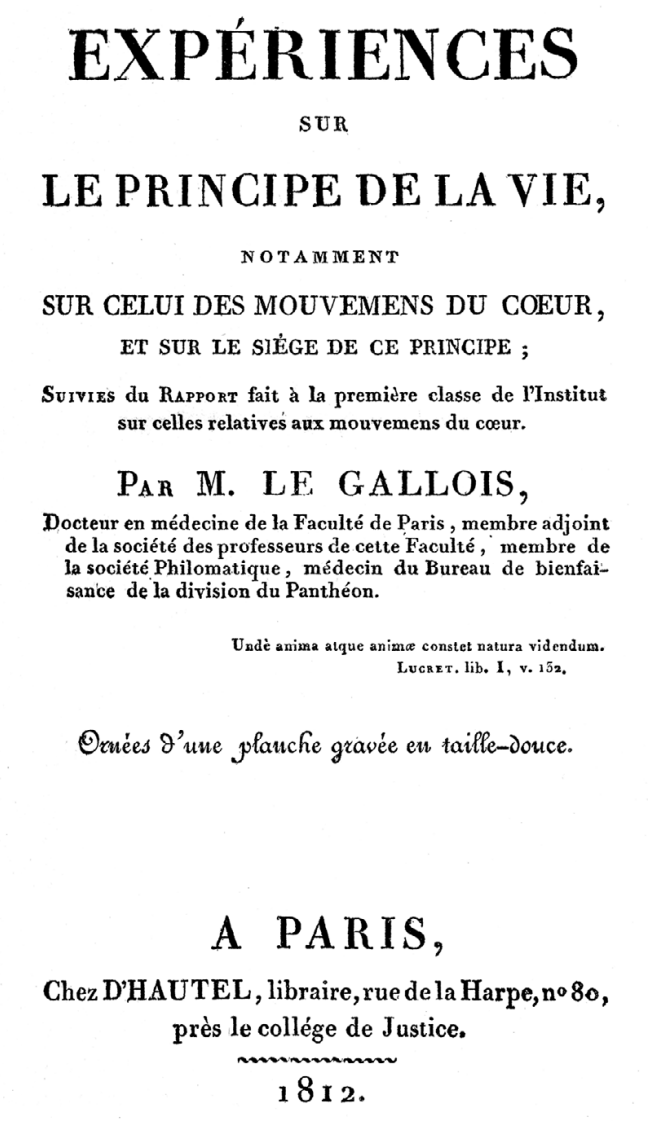
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level of the eighth CN nucleus. He did not specifically seek to illustrate how certain parts of the brain interact to maintain breathing (Figure 1.1).

Pierre Flourens further localized possible "centers" and also performed surgical ablation experiments[4–6]. These experiments involved severing the spinal cord at several levels. Dividing the cord at C7 did not interrupt the respiratory drive but only diaphragmatic contraction with no motion of the chest wall. Higher up at C3, the respiratory motions stopped, but there were ineffective rescue muscles such as the sternocleidomastoid and trapezius muscles. He discovered that the spinal centers of the respiratory nerves were subsidiary to some center at the lower end of the medulla oblongata because a higher cut (above the acoustic striae of the cochlear nucleus) did not affect respiration. Flourens identified a pinhead area, which he called vital knot or node (*noeud vital*), which was reed-like tissue measuring 2.5 mm in diameter in the medulla oblongata occupying a third of the floor of the fourth ventricle at the caudal end, continuous with the medulla oblongata (Figure 1.2). In the mid-nineteenth century, he arrived at this discovery by making high cervical transections in rabbits and discovering the existence of respiratory movements in the rabbit's muzzle without chest movements.

A number of physiologists, including Charles-Édouard Brown-Séquard, did not accept Flourens' conclusions[7]. Brown–Sequard claimed to have seen rhythmic respiratory movements in decapitated animals, postulating a respiratory center localized in the spinal cord, but other contemporary physiologists felt those movements were simply agonal and asphyxial. However, Brown-Séquard was supported by a number of other experimenters such as B. W. Richardson, who claimed to find a similar node in decapitated crocodiles, and most notably, by the experiments of Oskar Langendorff, who also strongly believed respiratory centers were present in the spinal cord[8,9]. The controversies on the role of the spine in regulating respiration and how it led to errors of interpretation in a number of experiments by many physiologists were summarized in detail by Porter[10].

Max Marckwald's work in *The Movements of Respiration* introduced new theories about the action of respiratory centers, the rhythm of respiration caused by the vagi, and the action of the glossopharyngeal nerves and others on the respiratory center[11]. Separation of the medullary center slowed respirations to two to four per minute, with inspiration much longer than expiration, and thus nothing else remained other than respiratory muscle



EXPÉRIENCES

SUR

LE PRINCIPE DE LA VIE,

NOTAMMENT

SUR CELUI DES MOUVEMENS DU CŒUR,

ET SUR LE SIÉGE DE CE PRINCIPE ;

SUIVIES du RAPPORT fait à la première classe de l'Institut sur celles relatives aux mouvemens du cœur.

PAR M. LE GALLOIS,

Docteur en médecine de la Faculté de Paris, membre adjoint de la société des professeurs de cette Faculté, membre de la société Philomatique, médecin du Bureau de bienfaisance de la division du Panthéon.

Undè anima atque animæ constet natura videndum.
LUCRET. lib. I, v. 152.

Ornées d'une planche gravée en taille-douce.

A PARIS,

Chez D'HAUTEL, libraire, rue de la Harpe, n° 80, près le collége de Justice.

1812.

Figure 1.1 Legallois experiments. Reproduced from[1], in public domain.

spasms. Mid-pontine decerebration resulted in slow – all or nothing – rhythm and was suppressed by cortical, upper-brainstem, or vagus input. Decerebration at the pontomedullary junction produced another rhythm with ataxic, irregular breathing in the animal medulla oblongata.

Much interest focused on how increased intracranial pressure-controlled ventilation (and, thus, patterns of breathing and gas exchange). As early as Cushing's experiments in 1902, both increased and decreased respiratory drive were noted with increased intracranial

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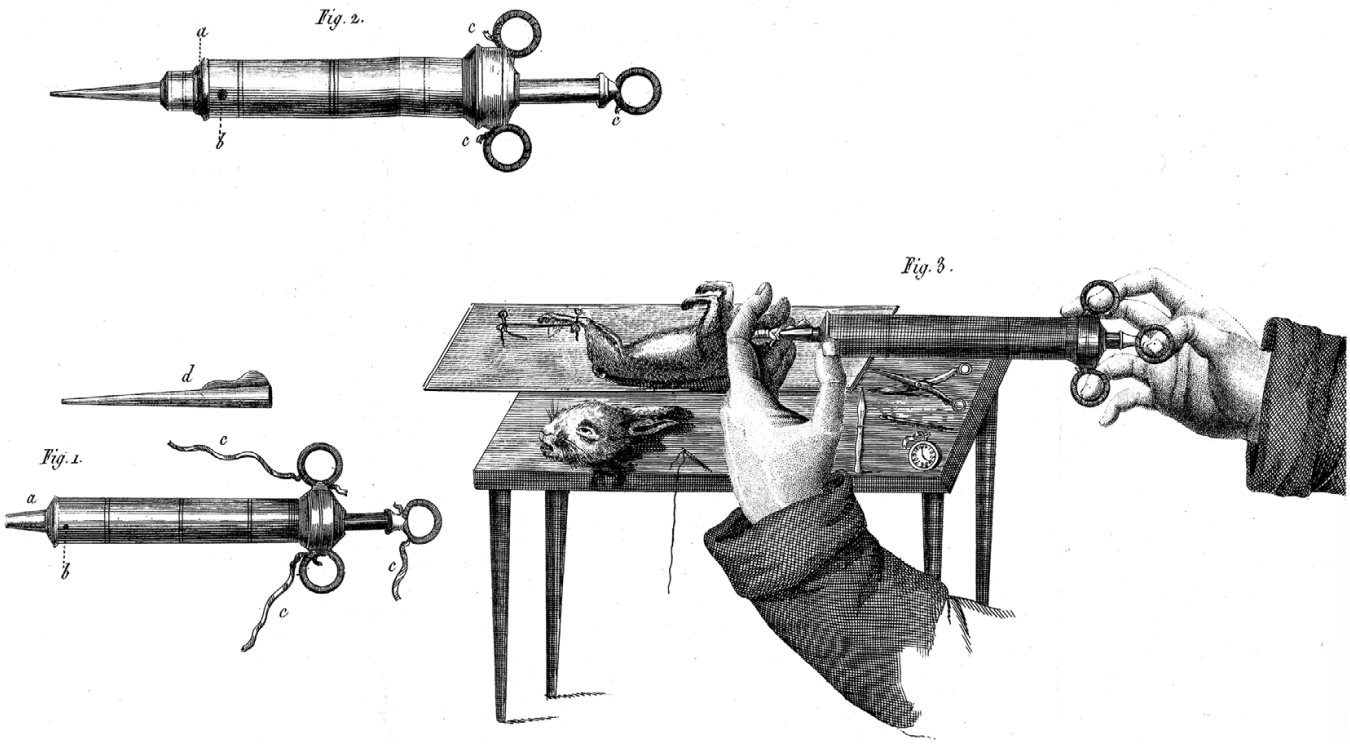


Figure 1.1 Legallois experiments in decapitated rabbits. Reproduced from[1], in public domain.

pressure (ICP). Persistent hyperventilation at high ICP was reported in some – but not all – animal experiments. Ventilation was often depressed with diminishing perfusion pressure, although this could have been a secondary effect of displacement, rather than ischemia, of the brainstem[12].

Further characterization of the respiratory centers had to wait until the 1920s, when Lumsden carried out transection experiments (Figure 1.3). Lumsden concluded there were pneumotaxic (ventral pons), apneustic (dorsal pons), and expiratory and gasping (medulla oblongata) areas. Lumsden's main technique was more selective damage to the brainstem, and he added a stimulant such as hypoxemia or hypercapnia. Eupneic breathing required intact pons and medulla oblongata. Transecting caudally to the rostral pons produced apnea with a sustained inspiratory hold (apneusis). Transection at the pontine medullary junction caused gasping rather than apnea. Transections to the obex stopped all chest and abdomen movements. Multiple transection and stimulation experiments located the rough outlines of a respiratory center underlying the caudal third of the fourth ventricle floor. Further morphologic experiments identified inspiratory and expiratory centers and later the pneumotaxic center. Lumsden's sectional experiments demonstrated a prolonged, inspiratory type of breathing produced by sectioning dorsal to the posterior quadrigeminal bodies. The "convulsive and incoordinate" apnea in the area he called "the apneustic center" was distinct from the so-called "gasping center" in the lower part of the spinal bulb. Lumsden observed that in asphyxia the nervous centers become afunctional caudally – first pneumotaxic center (apnea) followed by gasping as the last movement[13,14].

Once the brainstem was isolated, more animal experiments followed. The most celebrated of these were by Gesell[15,16] among others, who were able to make microelectric recordings and found a large number of active neurons in the dorsal medulla but very few "respiratory cells" in the suprapontine structures. He was unable to separate inspiratory or expiratory centers. "In many experiments, we were unable to find any respiratory potentials whatever, even with the most searching efforts. Such scarcity of potentials seemed to indicate that relatively few cells are needed in the medulla to activate enough ventral horn cells to carry on eupneic breathing"[15].

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ENCEPHALES DE LAPINS. — NOEUD VITAL. (*Voyez la Planche.*)

Fig. **1.** — 1. V de substance grise, marque indicatrice sous laquelle se trouve le nœud vital.
Fig. **2.** — 2. Limite supérieure du nœud vital.
3. Lieu précis où doit être faite la section du nœud vital.
4. Limite inférieure du nœud vital.
Fig. **3.** — 3. Lieu précis du nœud vital, détruit par l'emporte-pièce.
Fig. **4.** — 3. Lieu précis du nœud vital, coupé au moyen d'un scalpel à double tranchant.
Fig. **5.** — Emporte-pièce (3 millimètres).
Fig. **6.** — Scalpel à double tranchant (5 millimètres).

Comptes rendus des Séances de l'Académie des Sciences, Tome XLVII, Page 806.

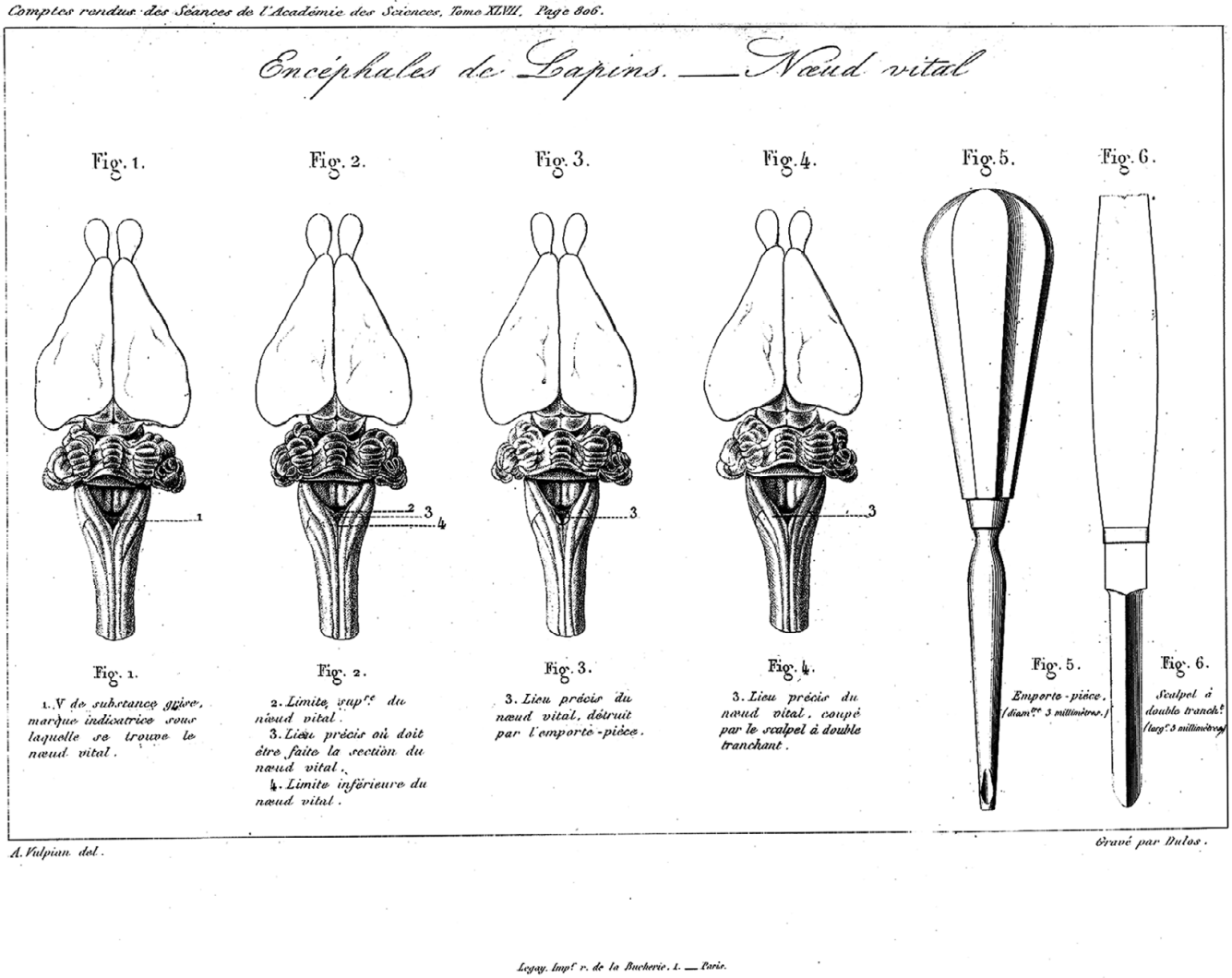


Figure 1.2 Flourens experiments "finding" the *noeud vital* using scalpel and pastry cutter. Reproduced from [6], in public domain.

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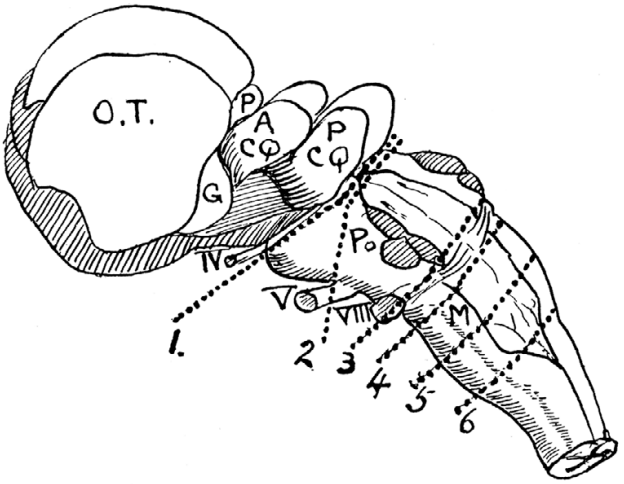


Figure 1.3 Brainstem centers. Reproduced from Lumsden[13], in public domain.

Later studies further differentiated the neuronal buildup of these centers – how individual cell groups could generate a "pacemaker" type action and how neurons could inhibit expiration and expiration. Moreover, Heymans found chemoreceptors in carotid and aortic bodies in 1927 and 1930 with afferent fibers in vagus and glossopharyngeal nerves followed by the identification of ventrolateral chemoreceptors of the medulla oblongata[17,18].

Most notable was the discovery that arterial PCO_2 could stimulate the carotid chemoreceptor through acidosis. However, a major advance came with Leusen's experiments[19,20]; he found that PCO_2 and pH of the cerebrospinal fluid (CS)F stimulate drive by denervating the peripheral chemoreceptors. While the pH of CSF does not exactly correspond with arterial pH as a result of the blood–brain barrier, increasing PCO_2 results in CO_2 diffusion, quickly altering CSF pH and making ventilatory drive responsive to ion change. A threshold for peripheral ventilatory effect of PCO_2 is between 30 and 40 mm Hg and linear in its effect. (The central ventilator effect for arterial PCO_2 was similar in range.) The retro trapezius nucleus consists of a cluster of chemoreceptor neurons that detect changes in CSF pH. These neurons adjust breathing rate, inspiratory and expiratory muscle activity, and resistance of the upper airway.

Research in the mid-twentieth century (and onwards to the next millennium) discovered a number of new respiratory neuronal groups in the pons and medulla oblongata that were characterized in the regulation of breathing. These included the Kölliker–Fuse nucleus, the parabrachial nuclei, the retrotrapezoid nucleus, the Bötzinger and pre-Bötzinger nuclei, the rostral and caudal ventral ventilatory group, and the nucleus ambiguus with the nucleus retroambiguus and nucleus tractus solitarius[21–23]. Neuroscientists actively continue trying to understand how these neuronal groups with their connections precisely interact., However, it remains unclear how further elucidation of their function could actually assist clinicians treating patient with acute brain injury.

This book has separate chapters on the pathophysiology and clinical management of primary breathing disorders in which the neural control of breathing is impaired including congenital central hypoventilation syndrome and central and obstructive sleep apnea. Neurologic disorders that commonly affect respiration include epilepsy, demyelinating disorders, stroke, and a number of well-defined neurodegenerative diseases, and readers will find comprehensive discussion on the mechanisms in each of these disorders and how to manage them clinically.

Peripheral Segment of Breathing

Traditionally, "peripheral" implies the trajectory of the phrenic nucleus to the muscle fibers of the diaphragm. The history of lung mechanics started before there was even a basic idea of central nervous system regulation. For example, Galen (Claudius Galenus AD 131–201) in *On the Natural Faculties*[24] was unclear and conflicted on the purpose of breathing (considered by some to cool inborn heat), but he identified the diaphragm as a major muscle not only separating the chest from the abdomen but also as a muscle of respiration. Since the early 1800s, biologists recognized that the cavity of the thorax enlarges in all directions during inspiration. The lungs expand to take up the created space. When the muscles relax, the gravitational force and elastic reaction of the thoracic wall and pulmonary tissue brings the thorax back to its original size. All mammals breathe with this mechanism; inspiration requires muscle contraction, and expiration is largely passive.

The great anatomist, physiologist, and illustrator Leonardo da Vinci was greatly interested in lung mechanics and lung inflation, and his drawings showed some preliminary concept of nervous control and the biomechanics of muscles[25]. These early observations were not followed by any new research for centuries. In the late 1800s, the physiologist Henry Newell Martin refocused on the muscles of respiration; he attempted to elucidate

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the additional role of the internal intercostal muscles and their function as accessories when the diaphragm fails and during extreme dyspnea. "The diaphragm, when the apnea passed off, made a few contractions without any activity of the intercostal muscle: but this latter soon began to contract in regular alternation with the diaphragm and before the occurrence of expiratory convulsions; in fact with the commencement of dyspnea"[26]. These muscles do have an inspiratory function but a secondary one, and over time, the same was found for the sternocleidomastoid muscles, which become active during labored breathing. Shafer's *Textbook of Physiology* in 1900 clearly identified them without specific attribution but also mentioned abdominal muscles for forced expiration. These basic biomechanics have remained the foundation of our understanding of respiratory mechanics (Figure 1.4). Later developments included the identification of the phrenic nerve motor neurons in the midcervical (C3–C5) spinal cord, "a straight, very discrete column of cells exactly paralleling the ventral longitudinal fissure"[27]. The phrenic nerve is a mixed sensory-motor nerve, and only recently, sensory-afferent neurons have been found to project to the cortex, explaining the perception of air hunger by patients[28]. However, the focus rapidly shifted back to characterization of the central respiratory drive, and interest in the workings of respiratory muscles waned. Further understanding of neuromuscular respiratory failure came with better understanding of the pathophysiology in acute neuromuscular disease, and clinicians led the way in explaining how diaphragm function and the upper airway could become affected. The rapid admission of a large number of dyspneic patients during the poliomyelitis epidemics put neuromuscular respiratory failure front and center.

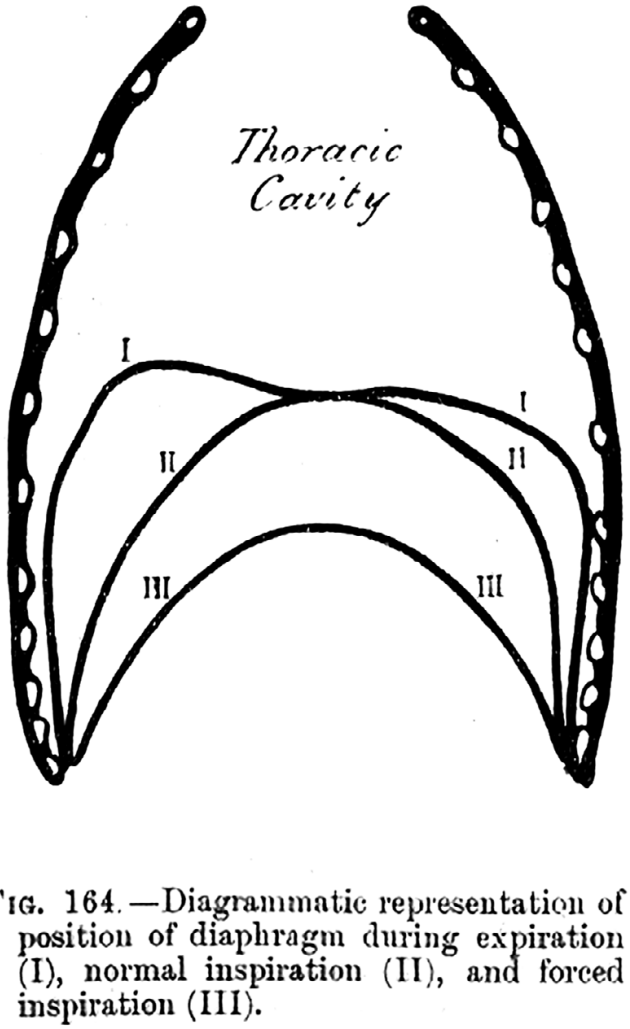


FIG. 164.—Diagrammatic representation of position of diaphragm during expiration (I), normal inspiration (II), and forced inspiration (III).

Figure 1.4 Diaphragm function as depicted in Shafer's textbook of physiology published in 1900. Reprinted with permission from Wijdicks EFM. Duchenne and paradoxical respiration. *Neurocrit Care.* 2024. https://doi.org/10.1007/s12028-023-01921-z.

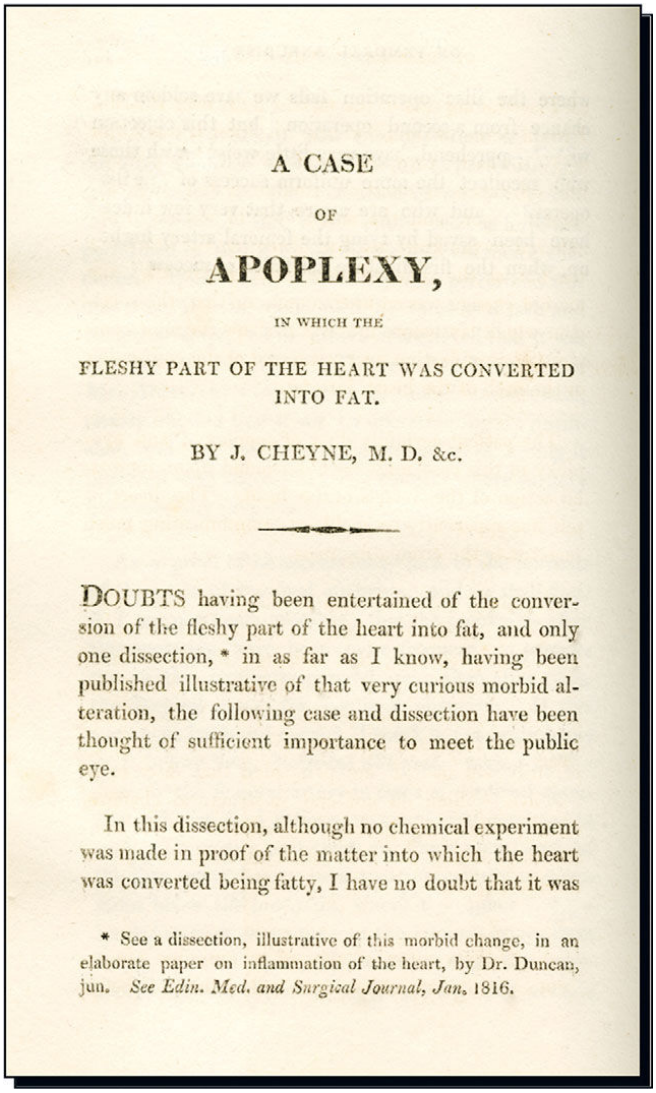
A History of Clinical Observations

Clinicians who took care of acute neurologic disease did observe a vast number of changes in respiration. Excluding yawning, hiccups, and respiratory tics such as puffing, hissing, and snorting, attention nearly always focused on change in respiratory rates and rhythms. Already in the 1800s, studies linked brain injury to periodic abnormalities of its rhythm. Cheyne and later Stokes described the ascending and descending waxing-and-waning pattern so well known to clinicians[29,30].

> The respiration is at first slow and heaving, then irregular and sometimes convulsive and lastly, interrupted. The patient from relaxation of the palate, snores loudly during inspiration, and sometimes during expiration the upper lip, from relaxation or palsy is loudly blown up from the teeth, as we often see it upon great exhaustion, as in the subsiding of an epileptic fit. Sometimes the breathing is soft. Immediately before death the respiration is irregular and is performed perhaps not more than three of four times in the minute. The irritability of the heart survives the respiration sting with my finger over the artery of a person who died of apoplexy. I distinctly felt the pulse beat after the last expiration. Interrupted respiration is justly considered as the most dangerous symptom. (Figure 1.5)

The neurologic diseases that could lead to Cheyne–Stokes pattern of breathing were meningitis, encephalitis,

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A CASE

OF

APOPLEXY,

IN WHICH THE

FLESHY PART OF THE HEART WAS CONVERTED INTO FAT.

BY J. CHEYNE, M. D. &c.

DOUBTS having been entertained of the conversion of the fleshy part of the heart into fat, and only one dissection, * in as far as I know, having been published illustrative of that very curious morbid alteration, the following case and dissection have been thought of sufficient importance to meet the public eye.

In this dissection, although no chemical experiment was made in proof of the matter into which the heart was converted being fatty, I have no doubt that it was

* See a dissection, illustrative of this morbid change, in an elaborate paper on inflammation of the heart, by Dr. Duncan, jun. *See Edin. Med. and Surgical Journal, Jan.* 1816.

Figure 1.5 Title page. Reproduced from Cheyne's paper.[30], in public domain.

cerebral hemorrhage, cerebral infarcts, cerebellar hemorrhage, and ruptured intracranial aneurysm but without emergence of a specific lesion, and it could be seen in both diffuse cortical and brainstem injury. Each of these disorders led to a markedly decreased level of consciousness, which led to Cheyne–Stokes. Many early clinicians interpreted this breathing abnormality as a signal of deterioration in clinical condition, an observation that is often still true to this day.

A related breathing abnormality was Biot's breathing. The breathing pattern Biot described is irregular and rapid, with 10- to 30-second rhythmical pauses but sometimes with alternating periods of apnea and tachypnea. This breathing pattern has none of the crescendo-decrescendo cycles of Cheyne–Stokes breathing and is completely irregular with varying periods of apnea. Therefore, it was sometimes called ataxic breathing (Figure 1.6)[31,32]. Biot connected this *rhythme meningitique* to tuberculosis but without claiming a possible connection with this (at that time) relatively common infection. In the German literature, the eponym appeared first in 1904 in Hofbauer's book *Semiologie und Differentialdiagnose der verschiedenen Arten von Kurzatmigkeit aufgrund der Atemkurve*[33]. In the English literature, it appeared in 1911 in the title of a review article by Connor who observed seven patients, six of whom had meningitis[34]. But perhaps the second most-known dysregulated respiratory rhythm identified as a neurogenic respiratory pattern was neurogenic hyperventilation. There was reluctance to attribute hyperventilation to a brain lesion rather than to a compensatory response in acute illness. Rapid hyperventilation was mostly seen as Kussmaul's breathing in patients with a diabetic coma. Alveolar hyperventilation was typically clinically seen as a response to hypoxia or metabolic acidosis or was associated with a specific pulmonary disorder. (Hyperventilation with respiratory alkalosis was also incidentally noted in hepatic encephalopathy and patients in the last stages of deep coma.) Hyperventilation associated with a brain lesion was first carefully described by Plum and Swanson. The study compared nine patients with acute lesions in the pons, mostly caused by acute embolus to the basilar artery, to patients with brain lesions elsewhere and who lacked hyperventilation (Figure 1.7)[35]. The authors hypothesized that structures in the medial pontine reticular formation were inhibitory to respiration, and thus, central neurogenic hyperventilation is the result of an uninhibited stimulation of the medullary respiratory centers by the lateral pontine reticular formation. We now know central neurogenic hyperventilation is indeed more common in pontine lesions (and not infrequently associated with primary brain tumor) but not exclusively so. It can be seen as part of sustained sympathetic hyperactivity in traumatic brain injury and in any severe global acute brain injury.

Finally, an extremely rare neurogenic breathing pattern was named after the original German fable "the curse of Ondine" by Giraudoux[36]. (The curse was a punishment for unfaithfulness when Ondine took away her husband's automatic functions. It included loss of all automatic functions – seeing, hearing, moving, and

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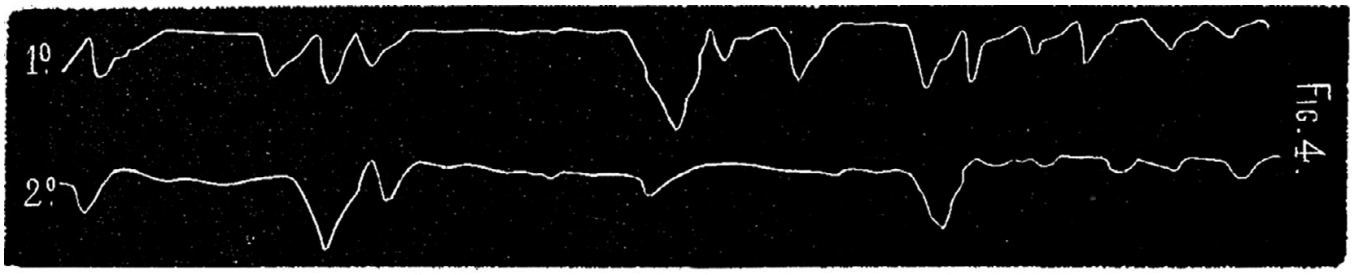


Planche IV. — Tracés pneumographiques dans la méningite tuberculeuse.

Figure 1.6 Biot's breathing. Reproduced from Biot MC. *Etude clinique et experimentale sur la respiration de Cheyne–Stokes*. Harper & Brothers, 1878.

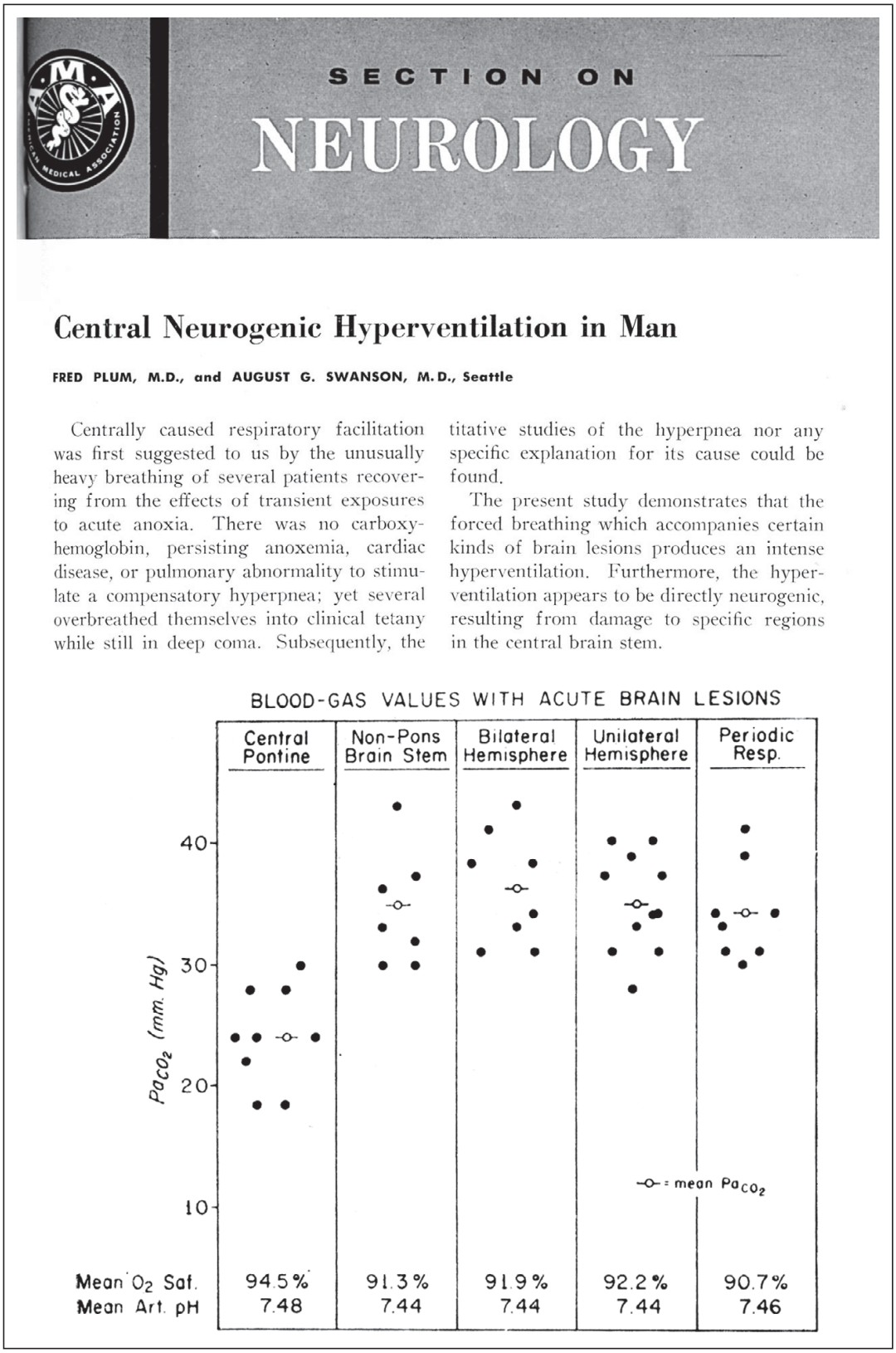
breathing.) The syndrome, described in 1962, belongs to the primary alveolar hypoventilation syndromes. Next to a genetic defect, acquired forms of Ondine's curse have always involved lesions in the respiratory centers of the medulla oblongata. Later, isolated cases of central hypoventilation were described with acute stroke, tumors, infections, and multiple sclerosis, but most authors struggled to link it with a specific condition[37].

When reading these original descriptions, there is no evading the point that circumstances have changed greatly. In our current world, clinicians in ICUs of major hospitals are less concerned with breathing patterns because patients are intubated, sedated, and mechanically ventilated, and each of these patterns may disappear once a patient is liberated from the ventilator. However, breathing patterns are important if only to show the presence of brain disease. If observed and particularly when sustained, MRI studies may be needed. Moreover, often these breathing abnormalities are seen in more or less stable patients, which allow detailed observations. In the more dramatic presentations, clinicians past and present recognize that respiratory difficulty in neurologic disease as an agonal phenomenon. In the past, of course, it was irreversible because artificial ventilation could not be provided. Some recognized (neurogenic) pulmonary edema when coma deepened, and the pupils became fixed. There was tachypnea with bloody sputum and tachycardia until death, which was explained by a major sympathetic storm causing massive vasodilation in the pulmonary vascular bed. Mouth-to-mouth resuscitation came into practice over the course of nineteenth-century resuscitation. Some might have suggested using bellows for ventilation, but this was potentially harmful because the pressure in the inflated lung could blow up the bronchiole and cause a fatal tension pneumothorax. In comatose patients with a major "apoplexy," breathing stopped and was considered part of the dying process – with no need or obligation to intervene.

In the premechanical ventilation era, it was far more difficult for clinicians to do anything other than to observe certain acute neuromuscular disorders that induced dying from cessation of respiration. Patients unable to move air in and out despite the will to do so were under a great amount of distress but could not be helped. One of the first observations came from the disorder now known as Guillain–Barré syndrome (GBS). In 1859, Landry reported a 43-year-old man with fatal progressive weakness starting in all four limbs and difficulty walking, followed by worsening weakness involving the diaphragm, facial, laryngeal, and jaw muscles[38]. Gradually, more severe cases of GBS were reported, but until the 1950s, these patients died from respiratory arrest. A case record from Massachusetts General Hospital in 1951 described a 13-year-old girl with GBS with "tired" breathing and "pharyngeal" mucus," requiring both suction and bronchoscopy and complicated by fatal aspiration pneumonia on the sixth hospital day. In this report, a "respirator" was used, most probably, a tank ventilator[39]. Bendz's important article on respiratory care in GBS begins with three patients placed in a cuirass who "died with gurgling mucus in the pharynx"[40]. A fourth case, that of a 28-year-old woman, rapidly progressing, again with a combination of dysphagia and respiratory distress leading to cyanosis and absent diaphragmatic breathing, was salvaged because a tracheostomy was performed promptly; the patient was connected to an Engström respirator and successfully weaned. This patient might have been one of the first published cases of successful respiratory care and positive-pressure mechanical ventilation in severe GBS (Figure 1.8).

Similarly, deaths were portended in myasthenia gravis with choking, fluid regurgitation through the nose,

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SECTION ON
NEUROLOGY

Central Neurogenic Hyperventilation in Man

FRED PLUM, M.D., and AUGUST G. SWANSON, M.D., Seattle

Centrally caused respiratory facilitation was first suggested to us by the unusually heavy breathing of several patients recovering from the effects of transient exposures to acute anoxia. There was no carboxyhemoglobin, persisting anoxemia, cardiac disease, or pulmonary abnormality to stimulate a compensatory hyperpnea; yet several overbreathed themselves into clinical tetany while still in deep coma. Subsequently, the titative studies of the hyperpnea nor any specific explanation for its cause could be found.

The present study demonstrates that the forced breathing which accompanies certain kinds of brain lesions produces an intense hyperventilation. Furthermore, the hyperventilation appears to be directly neurogenic, resulting from damage to specific regions in the central brain stem.

BLOOD-GAS VALUES WITH ACUTE BRAIN LESIONS

	Central Pontine	Non-Pons Brain Stem	Bilateral Hemisphere	Unilateral Hemisphere	Periodic Resp.
Mean O_2 Sat.	94.5%	91.3%	91.9%	92.2%	90.7%
Mean Art. pH	7.48	7.44	7.44	7.44	7.46

$Paco_2$ (mm. Hg) 40 30 20 10

○ = mean Pa_{CO_2}

Figure 1.7 Neurogenic hyperventilation. Reproduced from Plum and Swanson[35] with permission.

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RESPIRATORY PROBLEMS IN ACUTE GUILLAIN-BARRÉ SYNDROME

PER BENDZ, M.D., Stockholm

SINCE 1916, when Guillain, Barré, and Strohl [1] described two cases of radiculoneuritis with special findings in the cerebrospinal fluid (albuminocytologic dissociation), acute radiculitis has received attention throughout the world, innumerable cases having been described in the literature. Guillain's two cases were purely spinal with tetraplegia, and the prognosis quoad vitam did not come into question. But in acute polyradiculoneuritis nerves of vital importance may be attacked, i. e., the vagus, phrenic, and intercostal nerves. In such malignant cases the prognosis quoad vitam is serious, and in the literature the mortality rate varies between 15% and 75% in undifferentiated series.*

During the period from 1947 to March, 1953, the Stockholm Hospital for Infectious Diseases had a total of 15 cases of acute malignant Guillain-Barré syndrome attended by pharyngeal and respiratory paralysis, the patients comprising 11 adults and 4 children aged from 3 to 13 years. Seven (47%) of these patients required respirator treatment, nant cases is fairly consistent. The disease runs a relatively rapid course, usually about a week, and progresses toward a crisis, at which point it may be abruptly halted and then regress. The Landry type of paralysis is common. When the process commences to attack the pharyngeal and respiratory motor nerves, a life-endangering condition results. In pharyngeal paralysis quantities of mucus and saliva are formed which cannot be swallowed in the normal way but stagnate in the pharynx and run into the trachea and bronchi, with a major risk of obturation of the air passages. If the respiratory motor nerves commence to fail, there will be a threat of ventilatory insufficiency and respiratory standstill.

The condition in these malignant cases with pharyngeal and respiratory paralysis is similar to that in poliomyelitis, and the treatment, too, is largely the same. If patients with these malignant types of polyradiculitis are to survive the crisis, it is essential both to keep the air passages free by preventing aspiration of mucus and saliva and to give adequate artificial respiration, which implies sufficient oxygenation as well as elimination of carbon dioxide.

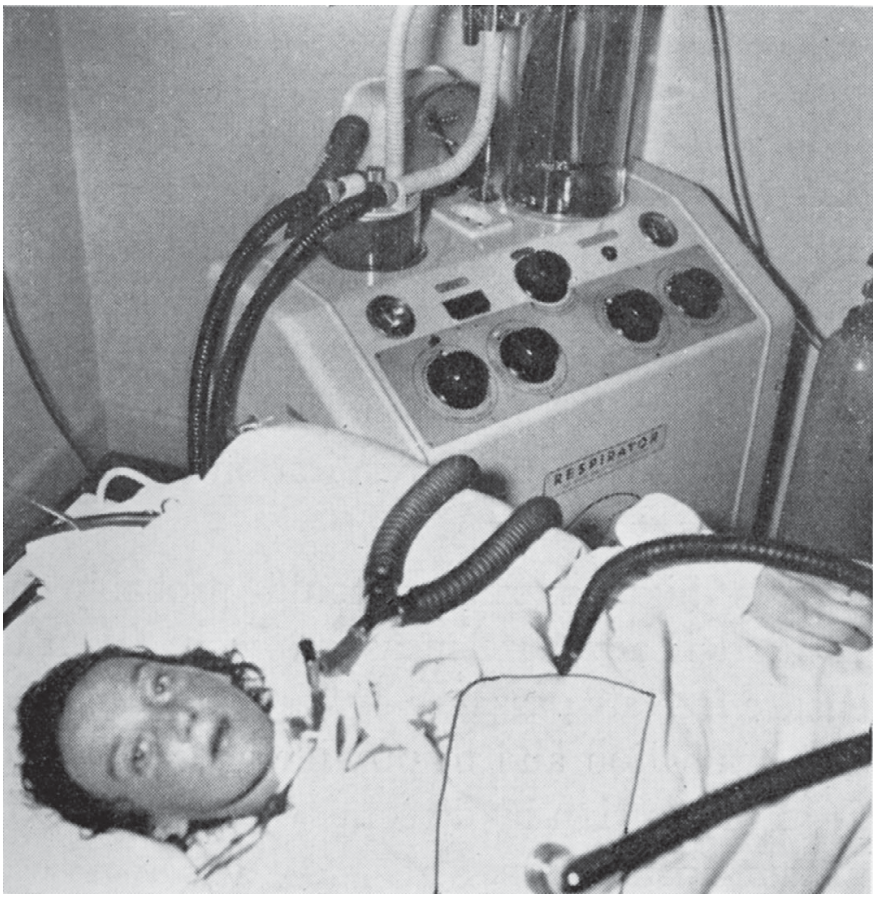


Figure 1.8 Mechanical ventilation with tracheostomy in Guillain–Barré syndrome. Reproduced from Bendz[40] with permission.

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diminished palatal reflex, and a lowered tone of voice suggesting weakness of the vocal cord adductors. Additionally, patients were unable to thrust out the cheek and avoid protrusion of the tongue. When chest movements were measured circumferentially, the difference between inspiration and expiration did not exceed a quarter of an inch. Dyspnea with exertion was common as well as "unaccountable attacks of breathlessness, during which the patient is in danger"[41]. Oral sputum accumulation accompanied these dyspneic attacks with patients unable to swallow or to spit it out. ("The tongue appears to sink back into the mouth.") Pulling back the tongue markedly improved the symptoms. The fatal cases were a result of choking, "dyspneic attacks," or "dyspneic attacks with pneumonia." It was concluded that "involvement of respiratory muscles with consequent attacks of dyspnea was a symptom of gravest significance," and the authors warned that death could occur during one of these attacks. Later, in a notable article, Rowland reported 39 fatal cases that he observed between 1930 and 1955. Presciently, he urged the physician to watch for premonitory attacks of respiratory distress, use sedatives cautiously, initiate early mechanical ventilation, and control for infection[41–44]

Engraved into our collective memory are the poliomyelitis epidemics that changed the healthcare landscape. The most severe summer outbreaks of poliomyelitis occurred in the United States and Europe in the 1950s. There were great challenges in managing large numbers of patients with poliomyelitis who presented in a brief time period and overwhelmed resources. Support of patients was initially rudimentary with little specific treatment. When the brainstem became involved, patients had difficulty clearing secretions from oropharyngeal weakness, and respiration became compromised. Many of these patients had back stiffness and severe pain from hypertonicity worsening respiratory excursions. These patients, in an early paralytic stage of anterior poliomyelitis, developed weakness of the respiratory muscle pump involving both intercostal and diaphragm muscles. In some, the neck muscles were able to create sufficient respiratory movements and compensate for diaphragm weakness. Critical shortages of ventilatory support in patients with the bulbar type of poliomyelitis resulted in serious accumulation of oropharyngeal secretions and diaphragmatic weakness and required both old (tracheostomy and negative-pressure ventilation) and new (positive pressure-ventilation) interventions. Specialized hospital units were necessary to provide this comprehensive care for these patients presenting with a new set of clinical problems. The worst cases needed prolonged placement in an "iron lung." Within the chamber – sealing the patient at the neck – a negative pressure caused the abdomen and thorax to expand with air flowing in. A cycle was produced by returning to atmospheric pressure. (Patients in the iron lung had their chest expanded every four seconds.) Many patients could be liberated from the device or transitioned to a cuirass ventilator, but some survivors remained permanently dependent (Figure 1.9)[45].

Neurologists have been struck by the fact that admission to intensive care is often a result of a neurologic disease, but the acute care of poliomyelitis was rarely the responsibility of neurologists, who delegated management to anesthesiologists and later to orthopedic surgeons, pediatricians, and physical therapists. There were, major exceptions[46]. Ritchie Russell at the University of Oxford became interested in respiratory insufficiency in poliomyelitis. He summarized his clinical work and innovations in poliomyelitis in an important, comprehensive, multifaceted book, which he wrote to address perceived gaps in knowledge because "it seems to be no one's task to study the disease as a whole"[47]. Ritchie Russell's articles were instrumental in identifying multiple types of poliomyelitis defined by their respiratory care exigencies. He divided cases into three categories: (1) patients with difficulty in swallowing but no respiratory weakness; (2) patients with weakness of respiratory muscles but no bulbar weakness; and (3) patients with paralysis of both respiratory muscles and oropharyngeal muscles. He included the need to examine the respiratory muscles and emphasized that the abdominal muscles played a key role in coughing up secretions. He mentioned inability to count beyond 10 in one breath as a sign of reduced vital capacity[46–48]. Care included postural drainage to avoid aspiration in patients without respiratory failure and the use of inverted V and tilted bed. Ritchie Russell discussed intermittent positive pressure ventilation, tracheostomy, bronchoscopy, and methods of chest physiotherapy[49]. He advised treatment that varied from continuing postural drainage to aspiration of secretions and tube feeding and use of tank respirators, later followed by the development of the Oxford respiratory pump for poliomyelitis. He pioneered, together with technicians and anesthesiologists, a positive-pressure respiration facility that was also later used for other conditions. He criticized Lassen's method of using medical students' bag ventilation and devised the Radcliffe respiration pump in 1953 with Edgar Schuster, which could more accurately

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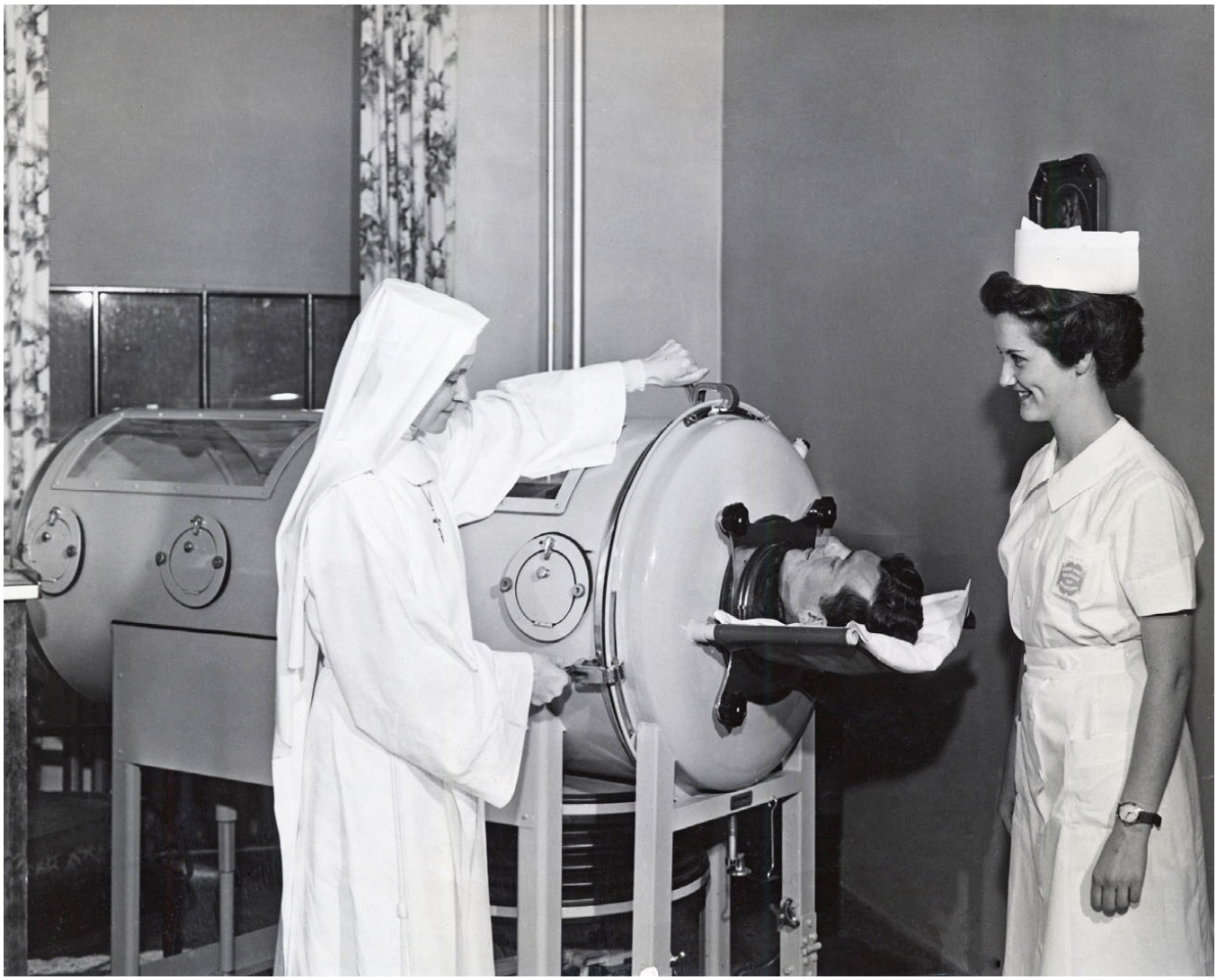


Figure 1.9 Iron lung. Courtesy of Mayo Clinic.

control amount of pressure, rate, and volume but also create a waveform with rapid flow rate and rise of pressure at inspiration to force air through the tracheostomy tube[50,51].

In the United States, A. B. Baker's contributions were also important in describing the essential involvement of the vagal nerve, which impaired swallowing and caused faulty innervation to the larynx leading to obstruction of the airway. He later noted that "we advocate a 'total push' form of physiologic support and understanding of respiratory failure in bulbar poliomyelitis and prevention of secondary systemic complications." Baker was instrumental in determining the essence of recognition of pooling of secretions and impaired speech, which indicated impending obstruction of the airway. Anxiety and restlessness associated with hypoxemia appeared to clear after adequate oxygenation. Baker's contribution was to emphasize that delay in performing a tracheostomy subjected the patient to severe hypoxemia and increased danger of pulmonary edema. Laryngeal stridor and dyspnea (despite adequate chest excursions), cyanosis, and encephalopathic symptoms were indicators of severe obstruction of the airway requiring emergency intubation or tracheostomy. Baker recognized that involvement of vital centers (without cranial nerve involvement) leads to irregular, shallow respiration in some patients and, in others, marked dysautonomic features (flushed skin, cherry red lips, tachycardia, and reduced pulse pressure with cold and clammy skin). He showed, in patients who

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came to autopsy, necrosis of areas below the floor of the fourth ventricle. A subgroup was found with both central respiratory centers and peripheral involvement requiring a respirator. To monitor for early anoxia, Baker used an oximeter or calorimeter attached to the earlobe (forerunner of the pulse oximeter[52–55].

Plum described the effects of cuirass-type ventilators, the effects of the rapid rocking bed on ventilation, carbon dioxide retention with normal oxygenation but a damaged controlling respiratory center from bulbar poliomyelitis and the presence of hypertensive urgencies in patients requiring ventilation in tank respirators. He clearly described carbon dioxide retention and its significance in determining adequate management. In patients with slowly progressive poliomyelitis, small degrees of failure of carbon dioxide elimination occurred in a considerable proportion of patients. He identified not only the effect of hypoxemia and hypercapnia but also observations on measurements of vital capacity. In addition, he emphasized that the respiratory center is depressed by high carbon dioxide tensions, and only the carotid bodies could provide chemical stimulation of respiration after the respiratory center is impaired and stimulated by hypoxemia. In 1952, he reported patterns of changes in pulmonary function in patients recovering from poliomyelitis[56–61].

Later, Plum studied patients with acute central respiratory failure in the wards of the King County Hospital, Seattle, Washington, and the Providence Hospital, Anchorage, Alaska. Patients with respiratory insufficiency convalescing from poliomyelitis were studied in the Northwest Respiratory and Rehabilitation Center. He developed a technique to minimize trauma while suctioning the patient after tracheostomy. Faulty suctioning could lead to severe mucous membrane damage and potentially asphyxiating tracheal bronchitis. Furthermore, in a clinical and pathologic study, Plum found that central respiratory failure in poliomyelitis was medullary in origin. He noted that permanent damage to chemoreceptive neurons in the respiratory center could explain low CO_2 responsiveness after poliomyelitis. Each recognized that airway obstruction and respiratory compromise in a neurologic disease shared some similarities with acute neuromuscular disease (myasthenia gravis and GBS), such as pooling secretions and predictive signs of early hypoxemia, but other observations, such as bulbar dysrhythmic respiratory failure, were new and original.

Another major development in understanding the neurology of breathing were the observations in neurosurgical trauma units. Neurosurgeons, ostensively more concerned with expanding contusions or cerebral edema, did not typically focus on abnormal rhythms of respiration, but the more astute ones would follow up after being alerted by neuroscience nursing staff that the breathing of the patient had changed.

Most known were periodic breathing surges during the rise and fall of ICP with irregular respiration and hyperventilation at the top of a plateau wave. Hoff and Breckenridge studied many clinical breathing patterns[62]. In a number of experiments, they found that an intrinsically slow rhythm of the brainstem, normally expressed in deep, "all-or-nothing," or gasping breathing, accounted for periodicity of breathing . In 1972, North and Jennett stated in the *Lancet*: "Abnormal breathing is often regarded as an incidental feature of brain damage, and little clinical attention is paid to it"[63].

Conventional wisdom prior to the 1970s held that respiratory patterns were of localizing value in neurological diagnosis and could identify specific lesions. Cheyne–Stokes breathing with localized deep hemispheric and basal ganglia lesions and central neurogenic hyperventilation with lesions of the upper brainstem but with lower lesions of the pontine tegmentum could lead to apneustic breathing, cluster breathing, and short-cycle Cheyne–Stokes respiration. Ataxic breathing was linked to lesions in either the medulla or lower portion of the pons. Others claimed that periodic breathing in humans was a result of supramedullary dysfunction[64].

However, a series of studies by Jennett and North carefully examined the respiratory responses in clinical cases of brain damage and demonstrated several variants for the first time. Most notably, they simplified (and denied) the claim that breathing patterns correlated with specific lesions in the brain and brainstem. They examined this localization paradigm in the neurosurgical ICU, hoping for clinical confirmation "if these associations could be applied not only to chronic neurological disorders but also to acute brain damage, then recognition of particular breathing patterns could be very useful." An early study in neurosurgical patients allowed recording of patterns and identified three main abnormalities A follow-up study in neurocritical care patients investigated 90 patients with traumatic brain injury and 43 patients with aneurysmal subarachnoid hemorrhage. The breathing pattern was recorded using an impedance pneumograph. Their definition of breathing patterns was as follows: *periodic breathing*, regularly recurring cycles of changing ventilation, the smallest tidal volume being

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not more than half that at the peak of the cycle; *tachypnea*, respiratory frequency over 25 breaths per minute; *irregular breathing*, an erratic variation in frequency and in tidal volumes, the smallest breaths being less than half the volume of the largest; and *sighing*, an occasional deep but prolonged breath, at least twice the usual tidal volume for the patient.

Jennett and North found no abnormal breathing patterns in a substantial minority (40%) of their patients. Periodic respiration was found in 41% of patients but with a preponderance of periods shorter than the typical one minute of Cheyne–Stokes respiration (Figure 1.10). Upper-airway obstruction caused the regularly recurring periods of apnea, and elevating the mandible restored a normal breathing pattern in some patients. Tachypnea was noted in over 25% of their patients, but many had normal $PaCO_2$ with abnormalities other than tachypnea. Tachypneic patients with hyperpnea showed a significant negative correlation between minute volume and $PaCO_2$, although the scatter was wide[65]. Irregular breathing was seen in a third of their patients, of whom only three showed irregularities of the degree and persistence to merit the term ataxic breathing. Thirty patients showed two different abnormal patterns during the recording, and two patients showed all three major abnormalities. Slow respiratory frequencies (7 to 10 breaths per minute) were recorded in 12 patients[66,67]. Sighing and gasping was seen in a few patients.

They concluded:

> The only breathing pattern that could be used reliably as a localizing sign in patients with acute brain damage was the gross and persistent irregularity associated with hypercapnia, which points to a lesion in the medulla. Otherwise, breathing abnormalities were common but diverse. Central neurogenic hyperventilation did not relate periodic breathing either to the site or the prognosis of acute brain damage. All patients with lesions in the medulla had abnormal patterns; medullary and pontine lesions were frequently associated with irregular breathing.

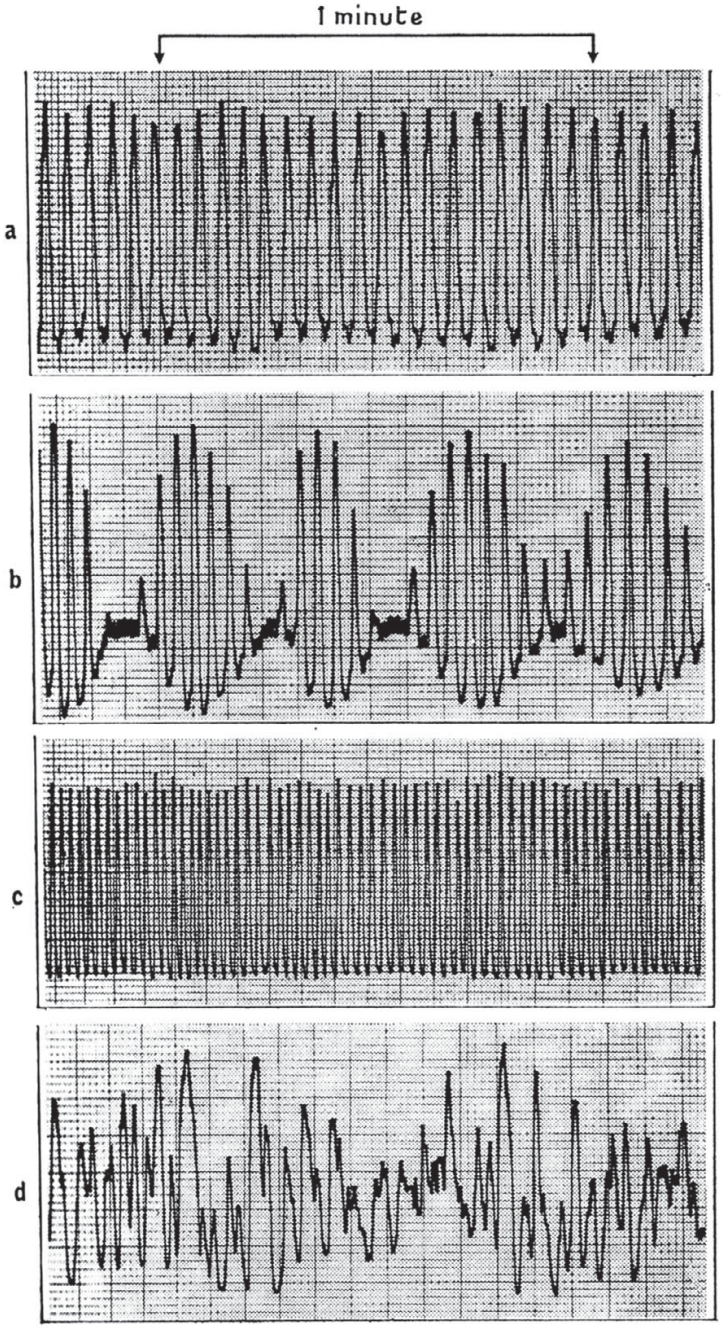
There were other observations by neurologists in the ICU. In 1962, Plum et al. studied the effect of brief hyperventilation (five deep breaths), which lowered the $PaCO_2$ by at least 6 mm Hg, in large groups of both normal subjects and patients with brain damage. They concluded that apnea greater than 12 seconds was sufficiently abnormal to be diagnostic of bilateral forebrain damage[64]. When apnea followed hyperventilation, its incidence and duration presumably correlated with the magnitude of the reduction in $PaCO_2$. Follow-up studies showed discrepancies in 100 abnormal patients from the neurosurgical wards of the Institute of Neurological Sciences. All had intracranial lesions but were sufficiently alert to cooperate in the test; most were suffering from traumatic brain injury, brain tumor, or recent subarachnoid hemorrhage. In one or more of the three tests, over half of them showed apnea more than five seconds longer than their greatest spontaneous interval. They found that the incidence of apnea correlated to drowsiness or disorientation. However, neither the value to which end tidal $PaCO_2$ was reduced nor the amount by which it was reduced bore any relation to the duration of apnea. This study confirmed that brief voluntary hyperventilation commonly causes apnea in patients with supramedullary lesions. Apnea was related to drowsiness rather than to the extent of the lesion; it was unrelated to the measured reduction in end-tidal carbon dioxide tension. There was no association between responsiveness to $PaCO_2$ and either bilateral forebrain damage or periodic breathing. (No mention was made of sympathetic storming, which is typically associated with paroxysms of tachypnea, sweating, and tachycardia.) Looking back, we can only conclude that the specific localizations attributed to certain breathing patterns were inconsistent or perhaps incorrect. We can additionally conclude that extrapolation of laboratory experiments to the bedside is again potentially problematic.

The Neurology of Apnea

Apnea is less common than hypoventilation and often short lived. When apnea is prolonged, it may be permanent. Historically, when did we discover that the respiratory drive can be permanently lost? For sure, any clinicians summoned to the bedside of a cyanotic patient, with or without a pulse, would not hesitate to resuscitate – just because these efforts can be successful. It is not exactly known how long we can "tolerate" apnea (within minutes followed by circulatory arrest), and thus, attempts continue with some patients breathing again. The apnea time intervals – from recovery to irretrievability – have been nothing but an educated guess, and the permanence of apnea has never been downright accepted despite expansive definitions.

The most apposite moment in the history of the neurology of breathing has been the discovery of permanent apnea in mechanically ventilated patients with acutely catastrophic brain and brainstem injury. This would occur only in brain death and only when

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Impedance pneumograms.

(a) Normal trace.
(b) Periodic breathing in a 16-year-old male with a third-ventricle tumour.
(c) Tachypnœa (f = 38 per minute) in a man of 36 with a head injury.
(d) Ataxic breathing in a woman of 21 with encephalitis.

Figure 1.10 Respiratory rhythms in acute brain injury.
Reproduced from Jennet and North [65] with permission.

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all brainstem reflexes became lost. In 1959, the neurosurgeons Pierre Wertheimer and Jacques Descotes with the neurologist Michel Jouvet were among the first to propose criteria for these new clinical states (*A propos du diagnostic de la mort système nerveux*). They not only observed apnea but stopped the ventilator to stimulate the respiratory centers with increasing respiratory acidosis, all to no avail[68]. The same condition was later called *coma dépassé* and said to be characterized by immobility of the eyes in a neutral position, mydriasis and absent light reflex, absent blinking with stimuli, absence of swallowing reflexes, drooping of the jaw, absence of motor responses to any stimuli, muscle hypotonia, tendon areflexia, equivocal plantar reflexes, absence of spontaneous respiration after discontinuation of ventilation, and also immediate cardiovascular collapse as soon as vasopressors were stopped. A disturbance of thermoregulation with core temperature depends on the environmental temperature[69]. Empirically, neurologists then found that respiratory drive stopped as one of the last acts of rostrocaudal damage to the brainstem commonly involving the bordering lower medulla oblongata pressure centers, which led to apnea and hypotension simultaneously. This presentation had the signature of a terminally dying person. It also became quickly understood that once apnea was found in a calamitous brain injury with no elicitable brainstem reflexes (not confounded by major toxin or other mimicker), breathing would never return. No medical or surgical intervention could reverse it. This comatose state therefore stood apart from other degrees of coma and was "beyond" (*dépassé*) what had been seen before, irrevocable and a neurologic definition of death. Finally, medicine found a solid criterion for apnea and added a key milestone.

Conclusions

This chapter has surveyed the experimental and clinical progress in understanding the neurology of breathing through the centuries but with a focus on the last century. Quickly recognized as vital for mammalian life, the regulation of breathing was beyond understanding for many investigators. The discovery of the respiratory centers in the lower brainstem opened a field of inquiry, and there is ongoing experimental research in defining its physiologic responses to changes.

The history of clinical observations was different and resulted from acute and astute observers but with fragmented attention. The localizing value of breathing patterns was limited, and more generally, neurogenic breathing patterns were exceedingly difficult to differentiate from lung injury or respiratory compensation of an acid-base disbalance. Any change in respiratory rhythm tells the clinician only that the patient is potentially deteriorating neurologically and that oxygenation may become marginal requiring endotracheal intubation and mechanical ventilation. The experimental localization paradigm could not always be confirmed in a clinical setting nor was there any indication that certain breathing patterns related to outcome. That is not to say that outcome was determinatively fatal once the respiratory mechanics failed in acute neuromuscular diseases. The development of the iron lung and other respirators[70,71] and, eventually, tracheostomy and positive pressure ventilation increased survival, a chance to heal, and even recover fully.

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Chapter 2

Neurorespiratory Medicine

Scope of the Problem

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For both developed and developing countries, the twenty-first century will be marked by great challenges for healthcare systems. Aging societies will face an increase in multimorbidity and chronic diseases, which again will include neurological diseases. Healthcare technology will improve life-supporting care and new pharmaceutic drugs will improve treatment of autoimmune and genetic neurological diseases. The probability of surviving acute illness and the possibility to prolong life in chronic-progressive disease will also improve. As a result the numbers of neurological patients with respiratory impairment caused by prolonged, chronic, or chronic-progressive life-threatening disease will increase. Minimizing dependency on life-supporting technologies and care, stabilizing vital functions, optimizing quality of life and participation, and alleviating suffering are paramount goals for these patients. The therapeutic approach therefore must integrate intensive care, neurorespiratory care, rehabilitation, and palliative care. Furthermore, patient-centered and family-oriented care, which covers the whole lifespan and bridges the gap between inpatient and outpatient care, is needed. Neurologists are expected to play a key role in coordinating care and organizing healthcare structures.

Chronic or Noncommunicable Diseases

The term "chronic disease," while widely used, is still lacking a uniform definition[1]. According to the World Health Organization (WHO) the terms "noncommunicable diseases" (NCDs) and "chronic diseases" are equivalent[2]. Increasing life expectancy is a key factor leading to this rise in NCDs[3]. NCDs cause 71% of all deaths worldwide[4]. The proportion of deaths from NCDs to all deaths will further rise until 2030, mainly due to improved treatment of infectious diseases. On a country level, an increase in income and urbanization as well as improved emergency medicine and long-term medical supply lead to a decrease of NCD mortality rates[5].

Multimorbidity

Multimorbidity is defined by the WHO as "co-existence of two or more chronic conditions in the same individual"[6]. The prevalence of multimorbidity increases with age and decreases with education. In countries with higher gross domestic product, the prevalence of multimorbidity is generally higher. However, its prevalence in low- to middle-income countries already approaches the prevalence in high-income countries[7,8]. Mortality from multimorbidity is higher in socioeconomically less developed areas[9]. Multimorbidity is expected to rise further and is acknowledged as one of the major challenges regarding the future of health care[10].

Neurological Diseases

Neurological diseases are the most frequent cause of disability worldwide[11]. The prevalence of dementia, stroke, and Parkinson's disease is driven by population aging. By 2050, the number of people with dementia will more than double worldwide as compared to 2019 to approximately 150 million cases[12]. In the European Union the number of stroke survivors will increase by 27% to about 12 million from 2017 to 2047[13]. From 2015 to 2040 the number of people living with Parkinson's disease will double worldwide to 12 million cases[11]. An epidemic that is much more difficult to grasp is the rise of critical illness polyneuropathy and myopathy (CIP/CIM). It affects 25%–45% of all critically ill patients leading to weakness of limbs and respiratory muscles, cough impairment and dysphagia[14,15]. A rise in intensive care capacities is bound to lead to an increase in the incidence of CIP/CIM, which thus will be one of the major future challenges for neurorespiratory medicine.

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Disability

"Persons with disabilities include those who have long-term physical, mental, intellectual, or sensory impairments which in interaction with various barriers may hinder their full and effective participation in society on an equal basis with others"[16]. The Global Burden of Disease Study showed a substantial increase of about 10% in years lived with disability between 1990 and 2013, with neurological disease being one major cause[17]. In a groundbreaking qualitative study in 1999, Albrecht and Devlieger found that more than half of persons with moderate to serious disabilities describe a good or even excellent quality of life, a fact also referred to as the "disability paradox"[18].

Intensive Care

The COVID-19-pandemic has triggered significant interest in understanding intensive care capacities on a global level. The lowest ratio of intensive care beds is found in low-income countries and the highest is found in high-income countries[19,20]. Nevertheless, there is no uniform definition of intensive care beds, and the number of intensive care beds per 100 000 population may differ dramatically between different high-income countries[21]. Until 2050 a certain decrease in hospital beds is expected, whereas the proportion of ICU beds among all hospital beds is expected to rise, as well as the number of ICU patients, the severity of illness, and the number of patients with sequelae of ICU treatment[22].

Rehabilitation

"Rehabilitation includes all measures aimed at reducing the impact of disabling and handicapping conditions and at enabling the disabled and handicapped to achieve social integration"[23]. Modern rehabilitation is an interdisciplinary, patient-centered, family-oriented, and – if necessary – lifelong approach. It offers a bundle of measures on an individual, community, and society level[23]. Rehabilitation is generally recognized as an essential part of health systems. Inpatient and outpatient care must be bridged and "specialized rehabilitation units for patients with complex needs" should be included in hospitals[24]. There is a global unmet need for rehabilitation, which will rise continuously[25]. The role of neurological disease in driving the need for rehabilitation is well established[26]. Specifically, there is an increasing need for institutions enabling the rehabilitation of neurologically severely impaired patients, including those requiring mechanical ventilation. From 2002 to 2014 the percentage of ventilated patients undergoing early neurological-neurosurgical rehabilitation rose from 15% to 25% in Germany, at the same time the average age of these patients increased from 61 to 68 years[27].

Long-Term Need for Life-Supporting Technologies

The number of patients with prolonged or persistent need for noninvasive ventilation, endotracheal suctioning via tracheal cannulas, or invasive ventilation has risen considerably during the twenty-first century, especially in high-income countries. In Germany, for example, the yearly number of patients, in whom home mechanical ventilation was initiated, doubled from 2008 to 2018[28], and approximately 23,000 patients receive out-of-hospital intensive care[29]. Patients with chronic dependency on life-supporting therapies have complex needs regarding medical treatment, nursing, vital parameter monitoring, rehabilitation, assistive technologies, and augmentative and alternative communication.

Conclusion

Care for severely affected patients of all medical disciplines will be one of the main challenges for medicine during the twenty-first century. Future demography and epidemiology as well as medical progress will present major challenges for neurologists. Severely affected neurological patients with acute, chronic, and chronic-progressive illness and patients with neurological sequelae of ICU treatment for primarily non-neurological conditions will need specific treatment concepts. There will be a growing need for comprehensive care concepts, combining intensive care, neurorespiratory care, rehabilitation, and palliative care. Intensive care and neurorespiratory care aim at optimizing medical treatment, rehabilitation aims at reducing dependency and disability and improving participation, and palliative care aims at relieving suffering. All these efforts must be focused on optimizing quality of life. One example for comprehensive medical concepts are the centers for weaning from mechanical ventilation in early neurological-neurosurgical rehabilitation recently introduced by the Germany Society for Neurorehabilitation, which provide a continuum of care from intensive care via weaning to early rehabilitation and integrate palliative care concepts[30]. When respiratory impairment persists, there is a

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long-term need for nursing, medical treatment, and a variety of other therapies like physiotherapy or speech-and-language therapy. A structured and pervious intersection between outpatient and inpatient care is fundamental to reduce loss of information and optimize the results of treatment during a possibly lifelong patient journey. If and how all this can be provided is country specific and depends on existing healthcare structures and economic aspects (see Chapter 25). Neurologists with expertise in neurorespiratory care will be at the forefront when it comes to future coordination of care and organization of healthcare structures.

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Chapter 3

Anatomy and Physiology of the Lower Airways and the Lung

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Comprehensive knowledge of the anatomy and physiology of the respiratory system is a requirement for clinical practice. A profound understanding of physiology allows the practitioner to deduce pathological processes and initiate therapeutic steps based on rational decisions. The choice of a suitable ventilation mode or setting typically stems from an understanding of the pathophysiological processes. This chapter facilitates an understanding of respiratory physiology. Understanding the respiratory chain at the cellular level, ventilation and perfusion, and the delicate interplay of macroscopic and microscopic mechanisms supports the development of precise and individualized ventilation strategies. Knowledge of mucociliary clearance and the various lung volumes is also crucial to ensure optimal management of tracheobronchial secretions, oxygen supply, and CO_2 elimination. For example, it is not uncommon that ventilatory therapy is initiated far too late due to a normal peripheral saturation. A comprehensive assessment of perfusion, ventilation, and hemoglobin concentration would have hastened the decision-making process. Usually, a male patient with a 97% oxygen saturation is considered noncritical. Considering a hemoglobin concentration of 11 mg/dl, it quickly becomes apparent that the concentration of dissolved oxygen is well below normal, indicating hypoxemia. This is a simple and well-known example, which demonstrates that profound physiological knowledge is necessary to unmask critical processes and to guide clinical decisions.

The Lung and Gas Exchange

The respiratory function is essential for the survival of the human organism. It guarantees the gas exchange between organism and environment. In this process, two interdependent systems operate: the respiratory and the cardiovascular system. A defect in one of these systems inevitably compromises the efficiency of the other. The lung, as an integral part of the respiratory system, serves as the site of gas diffusion. It not only serves gas exchange but also regulates the blood's pH value and eliminates pollutants[1,2].

In the alveolar structure of the lung, a gradient-dependent diffusion process occurs, wherein atmospheric oxygen (O_2) diffuses into the bloodstream, while carbon dioxide (CO_2), generated as a waste product of cellular metabolism, is transferred in the opposite direction. Once in the blood, O_2 binds to hemoglobin in the erythrocytes, ensuring its transport to the cellular structures of the tissues. Within cells, O_2 is utilized by the mitochondria in the respiratory chain to produce adenosine triphosphate (ATP), the central energy carrier of the cell. The resulting CO_2 from these processes is transported back to the lungs by dissolution in plasma and binding to hemoglobin, where it is exhaled and the blood is once again enriched with O_2[3,4].

External Breathing (Pulmonary Respiration)

The respiratory tract begins with the nose and mouth, both connected to the pharynx. From the pharynx, the airway leads into the larynx, which contains the vocal cords. Below is the trachea, which then divides into two main bronchi (right and left main bronchi) leading into the respective lung lobes. These main bronchi split into lobar bronchi and then into segmental bronchi. This branching continues into the conducting, terminal and respiratory bronchioles, followed by the alveolar ducts, finally ending in the alveoli[2,5,6].

The alveoli are microscopic air-filled sacs with a diameter of about 200–300 micrometers, grouped like grapes around the alveolar ducts. Approximately 1500–4000 alveoli in the supply area of a terminal bronchiole form the lung's smallest unit, the acinus. Around 12 acini constitute the basic units for a lung lobule measuring about 2×1 cm[5,7].

The total number of alveoli is estimated at 300–750 million with their total surface area ranging from

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80–200 m^2. Adjacent alveoli are separated by narrow septa, internally lined with a specialized cell type, pneumocytes or alveolar epithelial cells. They exist in two types. Type I cells are nondividing and have an extremely flat cell body, only about 0.2 µm thick. Although they make up only about 40% of the total pneumocytes, they cover 90%–95% of the alveolar surface. Type II covers only about 5% of the alveolar surface. Their primary function is surfactant production. They can also replace Type I pneumocytes. Beneath the alveolar epithelium, the septa contain subepithelial connective tissue referred to as the lung's interstitium. The interstitium is richly traversed by blood capillaries. Type I pneumocytes, along with capillary endothelium and a shared basal membrane, constitute the lung's blood–air barrier. On average, this barrier is 2.2 µm thick, but in especially thin places, it can be as little as 0.1–1.5 µm[2,5,7].

Internal Breathing (Cellular Respiration) and the Respiratory Chain

At the cellular level, the released oxygen is used in the mitochondria for the respiratory chain. This process comprises four main complexes and ATP synthase. Electrons are transferred through these complexes, starting with Complex I and ending with Complex IV, with oxygen serving as the final electron acceptor and combining with protons to form water. The energy released from the transfer of electrons is used to pump protons through the inner mitochondrial membrane into the intermembrane space, thereby creating a proton gradient. This gradient then drives ATP synthase, which links ADP and inorganic phosphate to produce ATP, the cell's main energy carrier[4,8].

Ventilation, Respiration, and Perfusion

Respiration encompasses both external and internal breathing and ventilation. It's a vital process that supplies cells with the oxygen needed for energy production and also helps rid the body of waste products[3,8].

Lung ventilation refers to the mechanical process of inspiration and expiration, allowing airflow into the alveoli and eliminating carbon dioxide from the body. This is made possible by the contraction and relaxation of the diaphragm and intercostal muscles. The diaphragm, the primary muscle of respiration, contracts during inspiration and enlarges the thoracic space thus creating a vacuum that draws air into the lungs. During stress or physical exercise, accessory respiratory muscles and expiratory muscles contribute to respiration[3,5].

There are remarkable inequalities in blood flow through various regions of the lung, which are mainly related to height above the heart. In an upright posture for instance this will result in a hydrostatic pressure difference of ca. 30 cmH_2O from the base of the lung to the apex. In the topmost zone 1 the pressure is just sufficient to perfuse the apices, in the middle zone 2 flow depends on the difference between arterial and alveolar pressures, while in the lowest Zone 3 flow is continuous because intravascular pressure always exceeds alveolar pressure. This gradient occurs in the vertical axis of the lung fields irrespective of body positions[5,9,10].

Additionally, hypoxia in an alveolus causes marked contraction of the smooth muscles present in the walls of nearby arterioles, markedly diminishing flow to the affected region, causing compensatory blood flow away from hypoxic lung regions to better oxygenated regions[3,5].

Pulmonary Surfactant System

The pulmonary surfactant system plays a vital role for the function and integrity of the human lung. Surfactant consists of a complex mixture of soap-like substances, mainly lipoproteins, which are primarily produced by Type II pneumocytes. The term "surfactant" is derived from "surface active agent," describing its primary function as a surface-active substance[11,12].

The primary function of surfactant is to reduce the surface tension at the alveolar air–liquid interface. Without surfactant, the alveoli would collapse, especially during expiration, due to the moisture film that constantly covers them. By lowering the surface tension, surfactant prevents this collapse in smaller alveoli; where the surface is less, the surfactant concentration is higher, thus reducing the surface tension more than in larger alveoli. This mechanism ensures even ventilation and expansion of the alveoli, which is essential for their stability[11,12].

Surfactant also plays a pivotal role in stabilizing the pulmonary fluid balance. By decreasing surface tension, surfactant reduces the suction pressure at the alveolar air–liquid interface to <2 mN/m. Disturbances in the surfactant system can increase this pressure to up to 25 mN/m, as evident in conditions such as acute respiratory distress syndrome[11,13].

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Surfactant facilitates the transport of mucus and inhaled particles. It acts as an antiadhesion factor by reducing adhesive forces both between mucus particles and between mucus and the bronchial wall[11,12].

A functioning surfactant system thus:

- Reduces surface tension, accounting for two thirds of the retraction forces in the lung
- Stabilizes alveoli and small airways, thereby enabling normal breathing with minimal effort
- Prevents pulmonary edema by reducing the pressure gradient directed into the alveoli thus stabilizing the fluid balance in the lungs
- Supports mucociliary clearance and contributes to lung cleanliness

Mucociliary Clearance

The term "mucociliary clearance" is derived from three fundamental components: "mucus" (Latin for slime); ciliated epithelial cells, which span from the upper respiratory tract to the terminal bronchioles; and clearance. This mechanism plays a pivotal role in maintaining the integrity and functionality of the pulmonary system[14].

Structure and Function

Epithelial cells are equipped with roughly 200 cilia per cell. These cilia oscillate continuously at a frequency of 15 to 25 beats per second. Their primary task is to move inhaled particles towards the pharynx, thereby effectively removing them from the respiratory tract. This mechanism serves as the primary cleaning process of the proximal bronchi and is complemented by reflexes such as coughing and sneezing[14].

The cilia are surrounded by a thin liquid sol phase, upon which a more viscous gel phase (mucus) rests. Foreign particles adhere to the mucus, while the sol phase acts as a lubricating layer for the movement of mucus by the cilia. About 10 ml of this mucus is produced daily, consisting of 97% water and 3% a combination of proteins, lipids, salts, and other solutes. Dysregulation of its composition, like reduced water content, can cause significant functional disturbances[14,15].

Factors Negatively Influencing Mucociliary Clearance

- *Inadequate respiratory gas conditioning*: Dry or insufficiently conditioned respiratory gas directly impacts the condition of the periciliary liquid film. Insufficient hydration can thicken the mucus, hampering its movement over the cilia. Moreover, dry conditions can damage the integrity of the respiratory epithelia, making them more susceptible to infections or injuries[15].
- *Hyperoxia*: Prolonged exposure to high oxygen concentrations can induce oxidative stress in the respiratory epithelia. The resultant oxidative damage negatively affects ciliary function and leads to inflammation and cytotoxic damage to the epithelium[16,17].
- *Exposure to toxic gases*: Toxic gases, such as tobacco smoke, induce oxidative stress and direct cytotoxic effects on the respiratory epithelia. These effects reduce ciliary beat frequency and may contribute to chronic respiratory diseases[14].
- *Medicinal influences*: Some drugs, like atropine, can decrease mucus production, leading to a deficiency in mucus necessary to trap particles and pathogens. On the other hand, β2-blockers can increase the tone of the bronchial muscles, reducing mucociliary transport efficiency, as increased tone can impede mucus flow[18].
- *Pathogens*: Many microorganisms, from bacteria to viruses, have developed mechanisms to bypass or disrupt mucociliary clearance. For instance, the SARS-CoV-2 virus destroys ciliated epithelial cells, severely impairing mucus and particle transport[19].

Factors Positively Influencing Mucociliary Clearance

- *Humidity*: A hydrated periciliary liquid film is crucial for efficient mucus movement. High ambient humidity helps to maintain this film in an optimal state and to optimize mucus viscosity and prepare it for transport by the cilia[20].
- *Medications*: Medications can influence mucociliary transport both directly and indirectly. β2-sympathomimetics like salbutamol not only widen the airway diameter, facilitating mucus flow, but can also enhance mucociliary clearance by directly stimulating ciliary activity[21,22]. There's also evidence suggesting β2-sympathomimetics can influence mucus secretion and modulate its viscosity, positively impacting mucociliary transport. Some studies suggest β2-sympathomimetics may also possess anti-

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inflammatory properties, indirectly aiding in preserving mucociliary function by safeguarding the respiratory epithelium's integrity. Glucocorticoids can suppress inflammatory processes that might otherwise hamper mucociliary transport[21]. Furthermore, acetylcysteine and ambroxol directly modify mucus to enhance its transport properties[21].

Inspiration and Expiration

Inspiration, commonly referred to as inhalation, is a pivotal process in ventilation. Inspiration is driven by the diaphragm and the inspiratory portion of the intercostal muscles. In typical, quiet breathing, the diaphragm acts as the dominant inspiratory muscle. Through its rhythmic contraction, the lung is expanded caudalward. Inspiration results in a decrease of intrathoracic pressure relative to the surrounding atmospheric pressure. The ensuing pressure gradient promotes the influx of air into the pulmonary alveoli[2,23]. Depending on the inspiratory volume, the intrapleural pressure decreases from −4 mmHg to a value of −12 mmHg. This pressure difference prompts the intrinsically elastic lung to follow the thoracic expansion, enlarging the lung volume and filling the alveoli with air[2,23,24].

Inspiration relies not only on contracting muscles but also on the pressure conditions within the airways and the lungs. At rest, the inspiratory airway pressure is determined by the pressure gradient between atmospheric pressure and intrapulmonary pressure. During regular, quiet breathing, the airway pressure is about +3 to −3 mmHg. This is sufficient to transport the volume of air necessary for O_2–CO_2 gas exchange processes into the alveoli[24].

Under physical strain or other conditions necessitating increased oxygen, breathing becomes deeper and more frequent. Here, the inspiratory airway pressure can drop to values of −74 mmHg, depending on the intensity of the exertion and individual physiological adaptation. These heightened negative pressures are required to draw a larger volume of air into the lungs to meet the body's increased O_2 demand[24].

These pressures can vary in clinical practice depending on factors such as age, gender, fitness level, and potential pulmonary diseases. Increased airway resistances, for instance due to obstructive lung diseases, also can elevate inspiratory airway pressures[3,24]. According to the Hagen–Poiseuille equation, the airway resistance is inversely proportional to the radius, to the power of four. Therefore, a small change in diameter has a huge effect, for example, halving the radius of an airway would cause a 16-fold increase in resistance[25].

In contrast to inspiration, expiration or exhalation is largely a passive process. When the diaphragm relaxes, the elastic components of the lung, including the elastic fibers and alveoli, allow the lung to return to its resting state. Due to elastic recoil, the intrapulmonary pressure rises above the atmospheric pressure, leading to the outflow of air from the lungs[23,24].

However, there are situations where expiration is actively assisted, such as during physical activity or forced exhalation. In these cases, the abdominal muscles contribute to accelerated expiration by contracting and pressing the abdominal organs against the diaphragm. For further details on respiratory mechanics and the respiratory muscle pump see Chapter 5.

Pressure in the Pleural Space and Transpulmonary Pressure

The lung is characterized by high elasticity, giving it a propensity to pull away from the chest wall. A minor breach in the thorax, allowing air to enter the pleural space, can cause the lung to collapse – a phenomenon known as a pneumothorax[26–28].

The lung is not rigidly attached to the chest wall. Between the lung, covered by the pleura, and the pleura-lined chest wall lies the pleural space. Negative pressure in the pleural space prevents the lung from collapsing. This pressure typically stands at about 4 mmHg below atmospheric pressure. With an atmospheric pressure of 760 mmHg, the pressure in the pleural space is thus 756 mmHg[26–28].

When the airways are open, the pressure in the alveoli equals the ambient pressure, in this example, 760 mmHg. However, the pressure in the pleural space is lower, at 756 mmHg. The difference between these two pressures, in this case, 4 mmHg, is referred to as the transpulmonary or transmural pressure. A positive transpulmonary pressure keeps the alveoli open. A negative value, on the other hand, can lead to the collapse of the alveoli, resulting in atelectasis – areas of the lung that are minimally or not at all filled with air[5,27,28]. The transpulmonary pressure is expressed by the following equation[5]:

$$Ptp = Paw - Ppl$$

(Ptp = transpulmonary pressure, Paw = alveolar pressure, Ppl = pleural pressure).

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Static Lung Volumes

Lung volumes refer to the various functional air quantities that occur in the lungs and airways during respiration. The values measured for an individual provide information about the function of their lungs. A distinction is made between static (time-independent) and dynamic (time-dependent) quantities. Static volumes always lie between two defined respiratory positions, such as the tidal volume achieved with one breath. Dynamic tidal volumes indicate the shift of static tidal volumes per time span. These values are measured using spirometry and whole-body plethysmography[2,24,28].

The following static lung volumes are distinguished, see Figure 3.1:

IRV: The inspiratory reserve volume describes the volume that can be additionally inhaled after a normal inspiration. Depending on the source, it is 1.9–2.5 L or 2.5–3 L.

TV: The tidal volume is the amount of air that is inhaled or exhaled during one respiratory cycle. According to most authors the normal adult value is 6–8 ml/kg normal body weight at rest and increases considerably with exercise[29].

ERV: The expiratory reserve volume is the volume that can be exhaled additionally after exhalation of a normal tidal volume, approximately 1–1.5 L.

RV: The residual volume describes the volume that remains in the lungs after maximum expiration and therefore cannot be exhaled or measured by spirometry. The measurement of RV is conducted using body plethysmography It is averaged at 1.2 L or 20-25 ml/kg.

FRC: The functional residual capacity is the amount of air remaining in the lungs at the end of a normal exhalation. It is calculated by adding together residual and expiratory reserve volumes (FRC = RV + ERV), approximately 1.8–3.0 L, equivalent to 25–40 ml/kg. Obstructive ventilation disorders lead to an increase in FRC. Restrictive ventilation disorders lead to a decrease in FRC.

VC: The vital capacity is the total amount of air exhaled after maximal inhalation. It varies according to age and

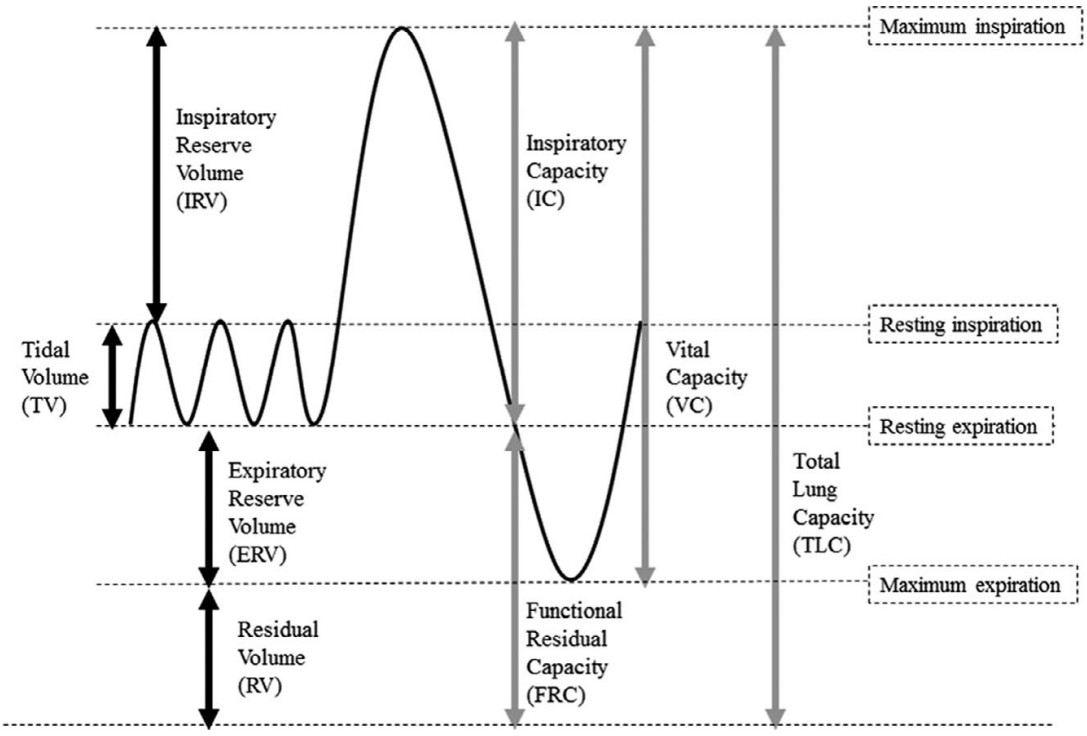


Figure 3.1 Lung volumes and capacities[30]. @ Lutfi, 2017, distributed under the terms of the Creative Commons Attribution License, Creative Commons disclaims all liability for damages resulting from their use to the fullest extent possible. URL: https://mrmjournal.biomedcentral.com/counter/pdf/10.1186/s40248-017-0084-5.pdf.

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body size. It is calculated by summing TV, IRV, and ERV. VC = TV+IRV+ERV, about 4.5–5 L or 65–75 ml/kg.

TLC: The total lung capacity is the maximum volume of air that the lungs can hold following a maximal inhalation. The TLC comprises the VC and the RV components (TLC = VC + RV). The measurement of TLC is conducted using body plethysmography, as the RV cannot be directly measured through simple spirometry.

Compliance of the Lung and Thorax

Compliance is defined as the volume increase of the lung per unit of pressure rise in the alveoli. Pressure units that can be used for description include *Pa* (Pascal), *mbar* (milliBar), cmH_2O (centimeters of water column), or *mmHg* (millimeters of mercury column)[1]. In a healthy adult, the typical compliance value at rest is about 1000 ml/kPa or 100 ml/mbar or 100 ml/cmH_2O or 133 ml/mmHg[2,3,27,28].

Decreased Compliance and Its Causes

Reduced compliance indicates increased stiffness of the lung and/or thorax. As a result, greater force is required to achieve a given volume change. Diseases that lead to decreased compliance include[27,28]:

- Pulmonary emphysema
- Pulmonary congestion/pulmonary edema
- Thoracic wall deformities

The higher the compliance, the lower the pressure must be required for mechanical ventilation, and the lower the compliance, the higher the pressure.

Airway Resistance

Airway resistance (R_{AW}) is defined as the pressure driving the air flow – which is the difference between atmospheric (P_{ATM}) and alveolar pressure (P_A) – divided by the flow velocity (υ):

$$R_{AW} = (P_{ATM} - P_A)/\upsilon$$

High compliance and low resistance minimize the required work of breathing[2,27,28]. Airway resistance is a critical parameter of lung function that primarily detects obstructions in the larger airways. Airway resistance is particularly significant during expiration, and it displays a circadian rhythm. In a healthy adult, the typical value ranges between 0.05 and 1.5 $cmH_2O/l/s$ or from 0.15 to 1.95 $cmH_2O/l/s$[28,31].

Increased Airway Resistance and Its Causes

The resistance in the airways, defined by the Hagen–Poiseuille equation, is inversely proportional to the fourth power of the bronchial radius. This implies that a halving of the bronchial radius increases the flow resistance 16-fold. Various conditions and diseases can lead to increased resistance, including asthma, chronic obstructive pulmonary disease, and pulmonary emphysema, which result in reduced diameter of the airways. Bronchial secretions, foreign bodies, and tumors also can lead to airway obstruction[2,28].

Work of Breathing and Ventilatory Failure

The area under dynamic pressure volume curve of the lungs is commonly used to estimate the work of breathing. The work of breathing comprises elastic work of breathing in inspiration and resistive work of breathing in inspiration and expiration. Elastic work of breathing is needed to overcome the elastic recoil of the chest wall and the lung, while resistive work of breathing is needed to overcome friction caused by moving air, organs and chest wall[28,32]. As inspiratory work of breathing exceeds expiratory work of breathing, surplus mechanical energy is converted to heat.

Reduced thoracopulmonary compliance – as is the case in restrictive lung diseases and thoracic restrictive disorders – and elevated airway resistance – as is the case in obstructive lung diseases – lead to an increase in work of breathing (see Figure 3.2). If there is a disproportion between the capacity of the ventilatory muscle pump (see Chapter 5) and the required work of breathing, ventilatory failure results. Accordingly, this may be caused by an elevated work of breathing. as is the case in restrictive thoracic disorders; by reduced capacity of the ventilatory muscle pump, as is the case in neuromuscular diseases or spinal cord lesions; or by a combination of both factors, as is the case in early onset neuromuscular diseases with consecutive kyphoscoliosis.

[1] Commonly used conversion factors are 100 Pa = 1 mbar = 1 $cmH_2O \approx 0.75$ mmHg.

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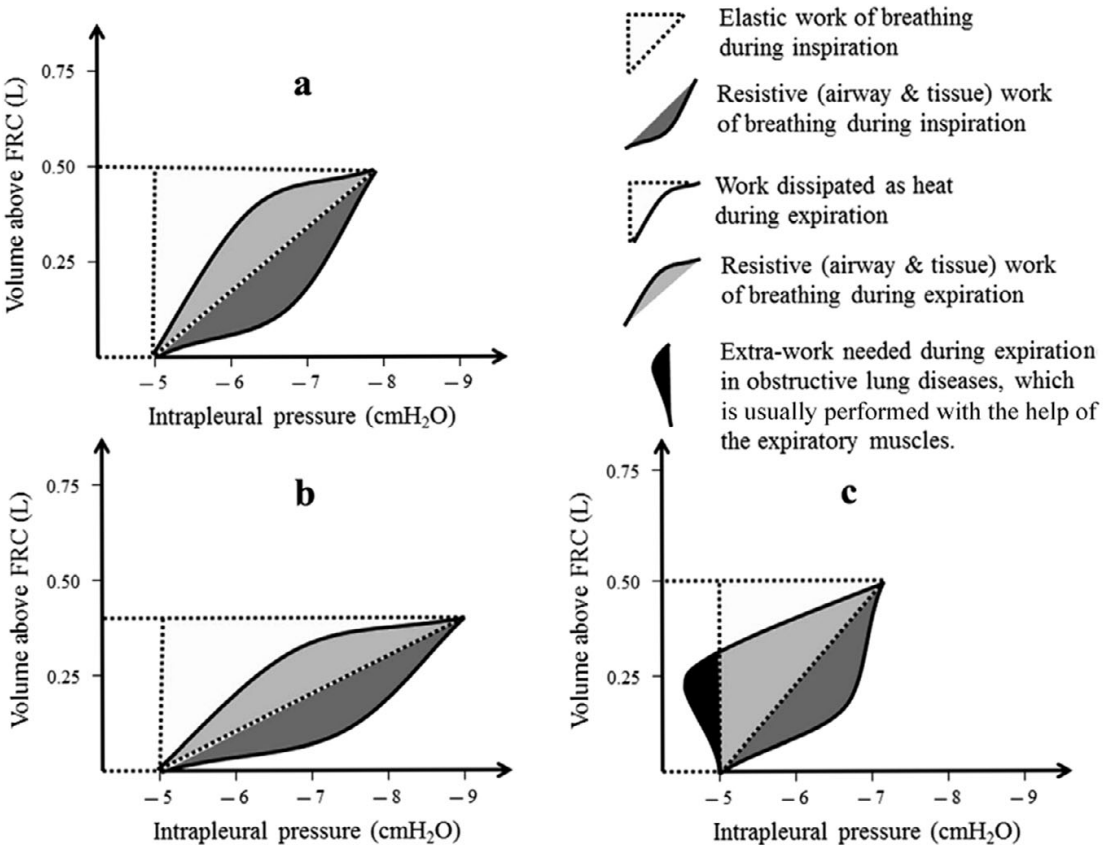


Figure 3.2 Work of breathing; (a) normal, (b) restrictive lung diseases, (c) obstructive lung diseases[30]. @ Lutfi, 2017, distributed under the terms of the Creative Commons Attribution License, Creative Commons disclaims all liability for damages resulting from their use to the fullest extent possible. URL: https://mrmjournal.biomedcentral.com/counter/pdf/10.1186/s40248-017-0084-5.pdf.

Dead Space

The anatomical dead space encompasses the region of the respiratory system, which is not actively involved in gas exchange. It includes the nasopharyngeal area, the trachea, the larynx, and the bronchi up to the terminal bronchioles. With each breath, approximately 30% of the inspired air remains in these areas, equivalent to about 150–200 ml or 1.5–2 ml per kg of body weight. An enlargement of the anatomical dead space can be induced by external breathing aids, such as snorkels or tubes[33–35]. The functional dead space comprises the anatomical dead space and those areas of the lung in which no efficient gas exchange takes place anymore, such as after a pulmonary embolism[33].The dead space ratio describes the relationship between the dead space volume and the total tidal volume. With typical breathing, this value is around 150 ml/450 ml, corresponding to a ratio of 0.3. This means that 70% of the tidal volume is effectively available for alveolar ventilation[33,36]. With rapid, shallow breathing or – in other words – with a low tidal volume combined with a high respiratory rate, there is a risk of reinspiring the already exhaled air that remains in the dead space and has an increased carbon dioxide content[33,36]. Under the conditions of mechanical ventilation, the alveolar dead space ventilation can increase to a value of up to 0.4. A dead space ratio >0.5 typically leads to CO_2 retention. A further increase in the ratio, especially values of around 0.7 to 0.8, makes spontaneous breathing virtually impossible as the CO_2 amount produced by the increased work of breathing exceeds the exhalation[33, 36,37].

Breathing Air

The inhaled air is a mixture of nitrogen, oxygen, carbon dioxide and other gases as well as water vapor. The individual gases in the air not only vary in concentration but also exert a specific pressure referred to as partial pressure or individual gas pressure. Adding up these

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partial pressures gives the total pressure of the air, typically 760 mmHg at sea level. This is the pressure of the surrounding atmosphere[38].

In a mixture of gases, different gases do not influence each other's partial pressure. The higher the concentration of a gas, the greater is its partial pressure. The concentration of a gas dissolved in the blood again depends not only on its partial pressure but also on the solubility coefficient of that particular gas. Some gases are highly soluble, while others have low solubility[38].

Water Vapor Pressure

All gases entering the lungs are humidified by the body. This water evaporates into the gas mixture and exerts a specific pressure, the vapor pressure. At 37°C, the vapor pressure is 47 mmHg; this must be taken into account in all calculations of alveolar air[38].

Composition of Breathing Air

At sea level, the inhaled room air initially has the composition shown in Table 3.1.

Room air is composed mainly of nitrogen and oxygen. Carbon dioxide is typically barely present, and the water vapor content is low. On its journey to the alveoli, however, this gas mixture becomes saturated with water vapor. Since the pressure of the gas mixture in the alveoli cannot exceed 760 mmHg, the gas mixture becomes diluted due to the added water vapor[38]. The composition of this humidified air changes as shown in Table 3.2.

Table 3.1 Composition of room air

Nitrogen	79%	pN_2	600 mmHg
Oxygen	20.9%	pO_2	159 mmHg
Other gases	0.1%		1 mmHg
Total	100%		760 mmHg

Mirabile VS, Shebl E, Sankari A, Burns B. Respiratory failure in adults. In: *StatPearls*. StatPearls Publishing; 2023. Accessed December 21, 2023. www.ncbi.nlm.nih.gov/books/NBK526127/.

Table 3.2 Composition of humidified air

Nitrogen	74%	pN_2	563 mmHg
Oxygen	19.7%	pO_2	149.3 mmHg
Water vapor	6.2%	pH_2O	47 mmHg
Total	100%		760 mmHg

Mirabile VS, Shebl E, Sankari A, Burns B. Respiratory failure in adults. In: *StatPearls*. StatPearls Publishing; 2023. Accessed December 21, 2023. www.ncbi.nlm.nih.gov/books/NBK526127/.

pO_2 and pCO_2 in the Alveoli

The O_2 concentration and the O_2 partial pressure in the alveoli depend on the uptake of oxygen into the blood and the ventilation of the alveoli with fresh air: The more oxygen diffuses into the blood, the lower the alveolar concentration and partial pressure become. On the other hand, the higher the minute ventilation volume, the higher the concentration and partial pressure of oxygen in the alveoli is. However, it should be noted that when breathing room air, the alveolar pO_2 can never exceed 149 mmHg, even with maximum ventilation[38].

Carbon dioxide from metabolism is continuously transported in the blood to the alveoli and from there exhaled through the process of ventilation. Alveolar CO_2 concentration and alveolar pCO_2 depend on the diffusion of carbon dioxide from the blood into the alveoli and the alveolar minute ventilation: The alveolar pCO_2 rises directly with increasing excretion from the blood. The alveolar pCO_2 is inversely proportional to the alveolar minute volume. Hence, the higher the minute ventilation volume, the lower the alveolar pCO_2 and vice versa[38].

Exhaled Air

Exhaled air is a mixture of dead space air and alveolar air. Its composition therefore depends on the composition of these two components (Table 3.3)[38].

It is clear that adequate lung ventilation and good perfusion are not enough to ensure that blood passing through the lung is well oxygenated and that CO_2 is removed. For this gas exchange to take place there must be a matching of ventilation and perfusion.

The inability to perform either or both of these tasks results in respiratory failure. *Type 1* respiratory failure occurs when the respiratory system cannot adequately provide O_2 to the body, leading to hypoxemia, and can be caused by alveolar hypoventilation, low atmospheric pressure/fraction of inspired O_2, diffusion defect, ventilation/perfusion mismatch, and right-to-left shunt. *Type 2* respiratory failure occurs when the respiratory system cannot adequately remove CO_2 from the body, leading to hypercapnia, and can be caused by respiratory pump

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Table 3.3 Composition of exhaled air

Nitrogen	74.5%	pN_2	566 mmHg
Oxygen	15.7%	pO_2	120 mmHg
Carbon dioxide	3.6%	pCO_2	27 mmHg
Water vapor	6.2%	pH_2O	47 mmHg
Total	100%		760 mmHg

Mirabile VS, Shebl E, Sankari A, Burns B. Respiratory failure in adults. In: *StatPearls*. StatPearls Publishing; 2023. Accessed December 21, 2023. www.ncbi.nlm.nih.gov/books/NBK526127/.

failure and increased CO_2 production[5,39]. These failures will have an effect on the composition of the exhaled air particularly pCO_2 and pO_2.

Peripheral Oxygen Content

The arterial oxygen partial pressure is a significant indicator for pathological conditions in the body. However, for a comprehensive assessment of oxygen supply, the oxygen content in the blood (CaO_2) and the peripheral oxygen delivery (DO_2) are crucial. DO_2 is the product of cardiac output and CaO_2. The DO_2 provides concise information about the distribution of oxygen to the organs via the peripheral capillaries. The body regulates this supply to match the current demand. Details about the calculation of CaO_2 and DO_2 and the oxygen demand of the peripheral organs are provided in Chapter 9.

Interestingly, a reduction in hemoglobin from 12 to 10 g/dl is often less noticed than a drop in oxygen saturation from 95% to 85%, which usually leads to immediate treatment. In anemia, that is, a deficiency of hemoglobin, cardiac output increases to meet the oxygen demand despite the reduced CaO_2, even if the oxygen partial pressure is normal. In patients with heart failure, this form of anemia is associated with a worse prognosis[40]. It is also observed that in heart failure, survival correlates with the treatment of anemia[41]. It has been noted that in patients with chronic hypercapnia during the weaning process, the correction of anemia can significantly reduce respiratory effort[29].

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Chapter 4

Respiratory Regulation

Martin Groß, Eelco F. M. Wijdicks and Nahid Hassanpour

Respiratory regulation comprises systems such as respiratory rhythmogenesis, formation of the respiratory motor pattern, control of blood oxygen and carbon dioxide, changes minute ventilation during physical activity, adaptation of respiration to the sleep–wake cycle, and coordination of breathing with swallowing, coughing, sneezing, choking, and voluntary activity such as speech or singing. Factors such as emotional state, core temperature and pain may change respiratory patterns. Evolutionary refinement led to these highly complex functional systems.

Animal models have been typically used to study respiration physiology, from crude to more specific. As mentioned in Chapter 1, Legallois with his infamous cutting experiments managed in 1812 to demonstrate in rabbits that the medulla oblongata is indispensable for respiration, while higher brain areas are not[1]. The presence of a respiratory rhythm generator in the brainstem is now known to be a common feature of all vertebrates[2].

In 1969 Fisher published his landmark article, "The Neurological Examination of the Comatose Patient," comprising an abundance of precise clinical observations on the respiratory rhythm[3]. While respiratory regulation in humans is subject to an increasing number of physiological, electrophysiological, neuroradiographic, histopathological, and genetic studies[4], Fisher´s observations have been indispensable to establish a conceptual framework for disorders of respiration in brain disease[5]. He pointed out that neurologists could learn from studying respiratory patterns at presentation and when patients worsened. "Innumerable respiratory patterns exist, each of which will probably prove to have its own significance, when better understood"[3]. Respiratory regulation is intricate and many of the details discussed in this chapter may not be immediately relevant to jobbing clinicians and even experts in clinical respiratory care. However, respiratory neurobiology changes in disease and therefore a brief review is warranted.

Neuroanatomical Structures of Respiratory Regulation

The network involved in respiratory regulation is highly complex and distributed throughout telencephalon, diencephalon, mesencephalon, pons, and medulla oblongata. Medullary and pontine regions are crucial for respiratory regulation. The key pontine region is the parabrachial complex–Kölliker–Fuse nucleus (PB-KF) region in the rostral dorsolateral pons[6]. In the medulla oblongata there are several regions important for respiratory regulation: The ventral respiratory group (VRG) is a column of neurons stretching nearly throughout the whole length of the medulla oblongata. The VRG can be divided beginning rostrally into the Bötzinger complex, the pre-Bötzinger complex, the rostral VRG, and the caudal VRG. In 2017 Anderson and Ramirez described a postinspiratory complex, located rostrally of the pre-Bötzinger-complex and dorsomedially of the nucleus ambiguus, but there is ongoing debate about its function[7,8]. The parafacial respiratory group (pFRG) is located ventrally and rostrally in the medulla oblongata, overlapping the retrotrapezoid nucleus (RTN) ventrally and medially, thus forming the pFRG/RTN complex. Other medullary structures involved in respiratory regulation are the nucleus tractus solitarius (NTS) and the nucleus retroambiguus (NRA). For an overview of the brainstem respiratory compartments in the rat, see Figure 4.1.

Numerous brain regions are involved in respiratory regulation, including the cortex, hippocampus, amygdala, hypothalamus, mesencephalic periaqueductal gray (PAG), fastigial nucleus, and the medullary raphe [9–15]. The areas involved in respiratory control are all interconnected, so it has been proposed that the respiratory control system is an integrated network rather than a hierarchical system[16]. Notably, not only respiratory neurons but also astrocytes contribute to respiratory regulation[17,18].

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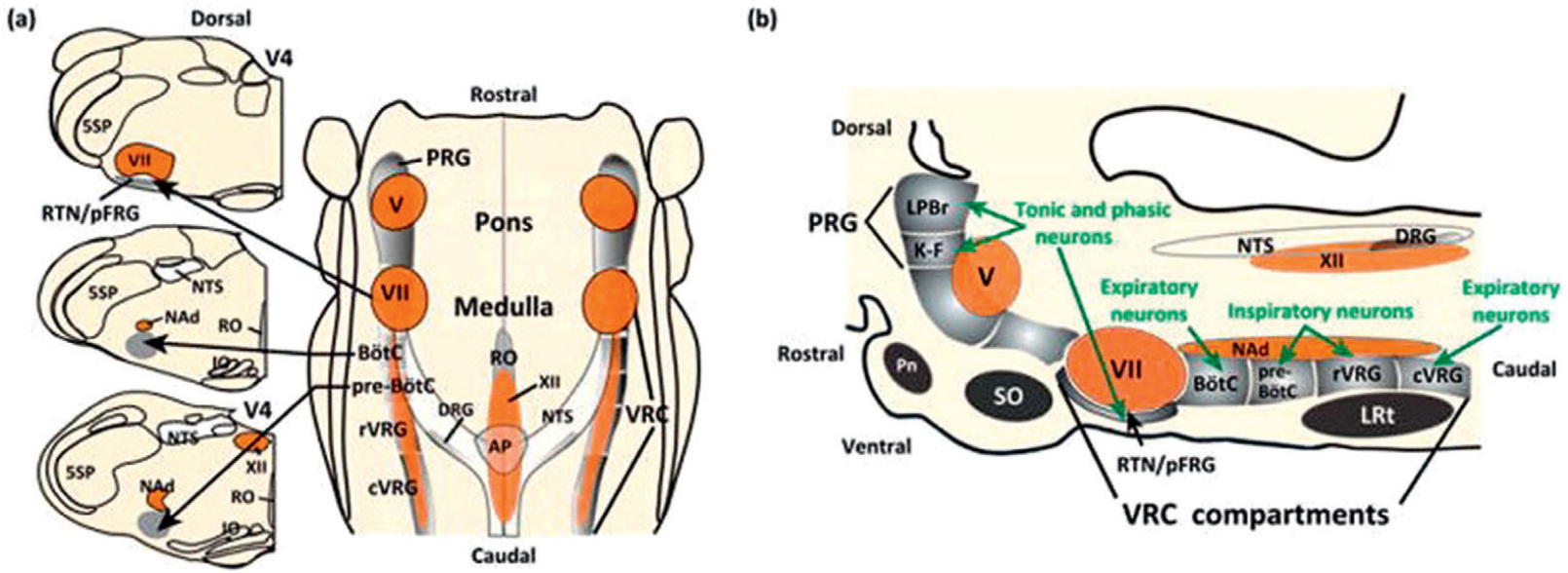


Figure 4.1 Respiratory areas in the brainstem of the rat. (a) horizontal (right) and coronal (left) sections and (b) unilateral parasagittal section. *Key regions of respiratory control:* cVRG: caudal ventral respiratory group; K-F, Kölliker–Fuse nucleus; LPBr, lateral parabrachial region; NTS, nucleus tractus solitarius; pFRG, parafacial respiratory group; PRG, pontine respiratory group; RTN, nucleus retrotrapezoideus; rVRG: rostral ventral respiratory group. *Other abbreviations:* AP, area postrema; BötC, Bötzinger complex; DRG, dorsal root ganglion; IO, SO; inferior and superior olivary complexes; LRt, lateral reticular nucleus; NAd, dorsal nucleus ambiguus; Pn, ventral pontine nucleus; RO, Raphé obscurus; V, motor nucleus of the trigeminal nerve; V4, fourth ventricle; VRC, ventral respiratory column; XII, hypoglossal motor nucleus; 5SP, spinal trigeminal nucleus. With permission from: Smith JC, Abdala AP, Borgmann A, et al. Brainstem respiratory networks: building blocks and microcircuits. *Trends Neurosci*. 2013;36(3):152–62.

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The Respiratory Cycle

The respiratory cycle comprises two to three phases. During the inspiratory phase inspiratory muscles contract and active inspiration takes place. Inspiratory muscles relax, and the individual passively expires due to elastic recoil, during the postinspiratory phase. The inspiratory phase and the postinspiratory phase form the respiratory cycle at rest. When the respiratory drive is elevated, for example, during exercise, there is an additional late-expiratory phase[19]. During the late-expiratory phase, expiratory muscles contract and active expiration takes place[20]. The neurons driving inspiration are located in the rostral VRG, and those driving expiration are located in the caudal VRG[21]. Respiratory phase transitions from inspiratory to postinspiratory and from postinspiratory to the late-expiratory phase are controlled by KF[22,23]. KF also regulates inspiratory airway patency[24].

The Respiratory Rhythm

The respiratory central pattern generator (rCPG) is the only CPG being active continuously[25]. Regarding its architecture, already in 1991 Smith et al. suggested pacemaker neurons located in the pre-Bötzinger complex (pre-BötC) generate the respiratory rhythm in mammals[26]. Pre-BötC sends wide excitatory and inhibitory projections to BötC, VRG, NTS, pFRG/RTN, PB-KF, PAG, and contralateral pre-BötC, all being involved in respiratory control[27]. The inter-pre-BötC tract synchronizes the pacemaker activity of left and right pre-BötC[28,29]. Pre-BötC and BötC form the core circuit of the rCPG but are embedded in a network of populations of respiratory neurons throughout the ventral and dorsal brainstem, the extent of which is not completely understood[25]. The neuronal network generating inspiratory behaviors might also be spatially dynamic. This again might contribute to the robustness and flexibility of breathing alike[30].

In humans, cerebral lesions can result in a variety of abnormalities of the respiratory rhythm, which may comprise central apnea and hypopnea, Cheyne–Stokes breathing, bradypnea, tachypnea, ataxic (or Biot's) breathing, and even two substantially different breathing rhythms suddenly switching from one to the other or existing at the same time[5]. The latter phenomenon had been described by Fisher in 1969, who named it "respiration alternans"[3]. The capacity of the rCPG to generate different breathing patterns at the same time strongly supports the network hypothesis summarized earlier in this paragraph. There is no conclusive research on life-threatening disorders of the respiratory rhythm, but those cases may be rare. Figure 4.2 shows polygraphic and MRI data of a patient with unilateral medullary stroke, who had been resuscitated for acute respiratory failure, probably resulting from a combination of severe hypopnea or apnea with acquired central hypoventilation syndrome.

Central Respiratory Chemoreceptors and Hypercapnic Respiratory Drive

Central respiratory chemoreceptors sense brain CO_2 by sensing changing H+-concentrations in the interstitial fluid and regulate breathing to keep arterial CO_2 stable[31–33]. Peripheral chemoreceptors do exist but contribute less to the hypercapnic ventilator drive[34]. A measure of the hypercapnic ventilatory drive is the increase in minute ventilation in response to a rising inhaled CO_2-fraction, which is called the hypercapnic ventilator response (HCVR, Figure 4.3). While different brain locations with CO_2/H+-sensitive neurons have been identified, the RTN has been best characterized[31–33] and was recently localized in humans[35]. RTN neurons regulate CO_2 by controlling breathing frequency in slow wave sleep and quiet wake, when the rCPG is autorhythmic[32]. Chemosensitivity in the RTN is modulated by serotonergic input from the medullary raphe, somatostatin signaling from CO_2/H+ sensitive parafacial neurons, and a variety of other neuromodulators[17,34,36,37].

This explains why unilateral lesions of the rostrolateral medulla can compromise the HCVR[38], and why medullary lesions have a potential to cause chronic hypercapnia, a condition called "acquired hypoventilation syndrome," sometimes referred to as "Ondine´s curse"[5]. From a genetic viewpoint, central respiratory chemoreception is closely linked to cells expressing PHOX2B, a transcription factor important for prenatal development[34,39]. Congenital hypoventilation syndrome, which leads to a reduced or absent hypercapnic ventilatory response especially in sleep, is caused by PHOX2B-mutations[40]. Furthermore, in sudden infant death syndrome developmental abnormalities of the RTN are observed more frequently than in controls[41]. Chronic hypercapnia, for example, due to chronic obstructive pulmonary disease

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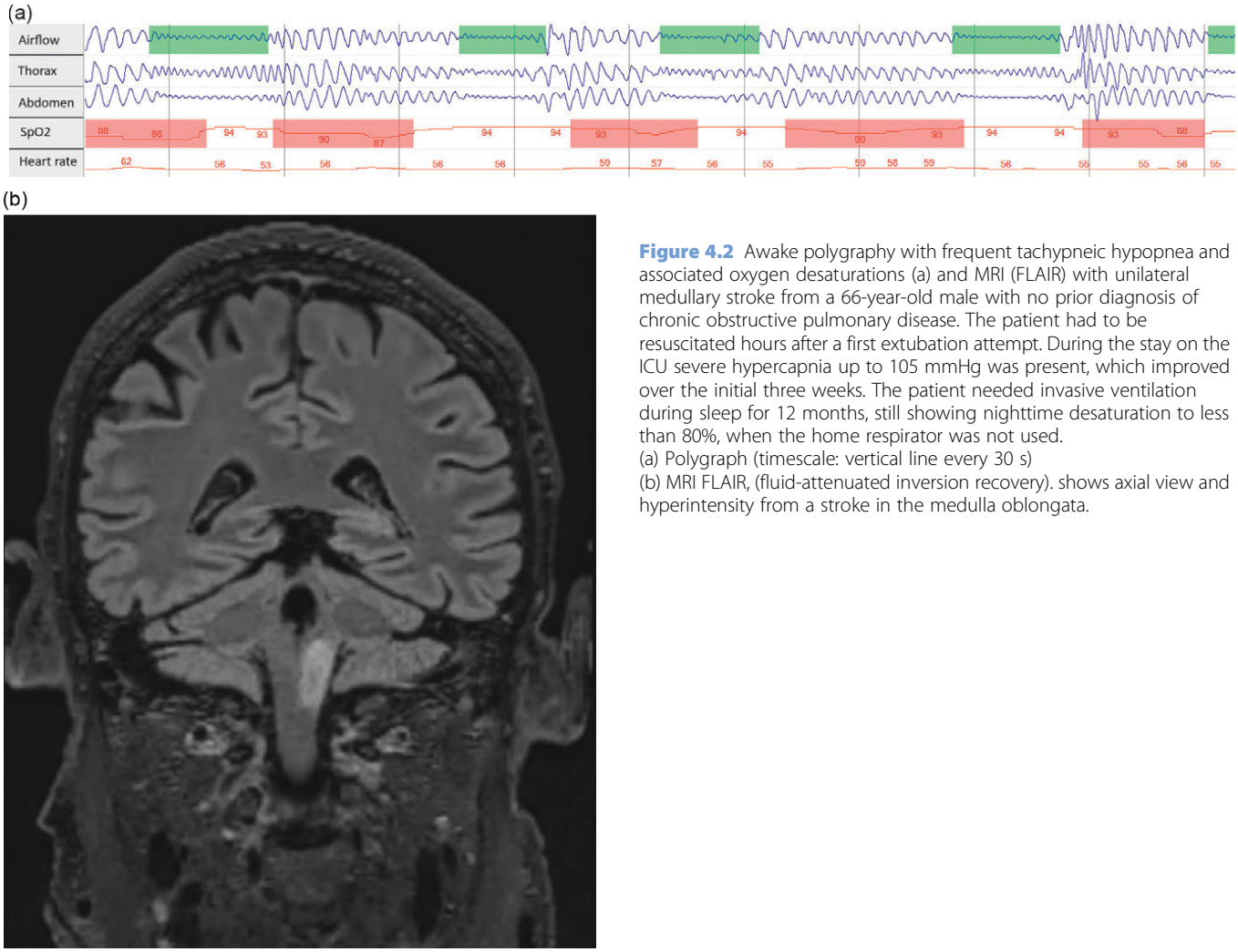


Figure 4.2 Awake polygraphy with frequent tachypneic hypopnea and associated oxygen desaturations (a) and MRI (FLAIR) with unilateral medullary stroke from a 66-year-old male with no prior diagnosis of chronic obstructive pulmonary disease. The patient had to be resuscitated hours after a first extubation attempt. During the stay on the ICU severe hypercapnia up to 105 mmHg was present, which improved over the initial three weeks. The patient needed invasive ventilation during sleep for 12 months, still showing nighttime desaturation to less than 80%, when the home respirator was not used.
(a) Polygraph (timescale: vertical line every 30 s)
(b) MRI FLAIR, (fluid-attenuated inversion recovery). shows axial view and hyperintensity from a stroke in the medulla oblongata.

or neuromuscular diseases with respiratory failure, also reduces the hypercapnic respiratory drive.

Arterial Chemoreceptors and Hypoxic Respiratory Drive

The carotid body, where oxygen is sensed by glomus cells, is the most important arterial chemoreceptor in humans. Adrenal medulla cells can respond to hypoxia, too, but this attribute becomes much less important in adult life.[42]. Afferents from the carotid body project to the NTS[43]. The hypoxic ventilatory drive is reflected by the hypoxic ventilatory response (HVR, Figure 4.3), which is the increase in minute ventilation in response to a falling inhaled O_2-fraction. Under isocapnic conditions only severe hypoxia <50–60 mmHg elevates the respiratory drive[44,45]. When hypercapnic patients receive O_2-insufflation, there is a significant risk of vital suppression of respiratory drive, hypercapnic coma, and consecutively death of the patient.

Sensory Pathways

Sensory information from the respiratory system is processed by the NTS. Information from arterial chemoreceptors is conveyed via the glossopharyngeal

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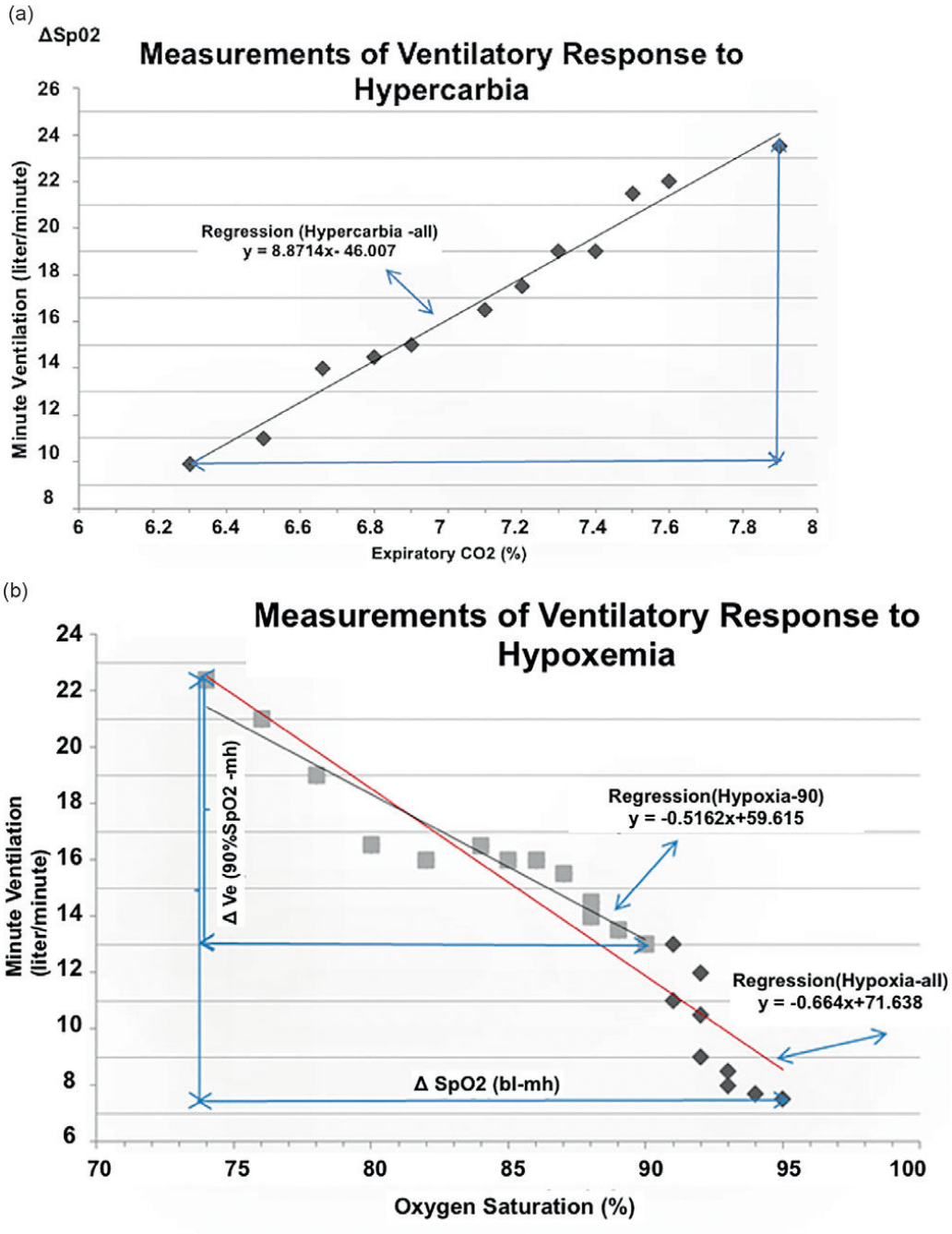


Figure 4.3 (a) Hypercapnic ventilatory response (HCVR = $\Delta Ve/\Delta CO_2$) and (b) hypoxic ventilatory response (HVR = $\Delta Ve/\Delta SpO_2$). © 2017 Goldberg et al., distributed under the terms of the Creative Commons Attribution License, Creative Common disclaims all liability for damages resulting from their use to the fullest extent possible. Goldberg S, Ollila HM, Lim L, et al. Analysis of hypoxic and hypercapnic ventilatory response in healthy volunteers. *PLoS ONE* 2017;12(1):e0168930.

nerve, and information from pulmonary stretch receptors and nociceptors is conveyed via the vagal nerve to the NTS[46,47]. Dense projections from the caudomedial NTS to RTN and rostral VRG were demonstrated in a rat model by Alheid et al. in 2011[48]. The NTS also coordinates respiratory and sympathetic responses to its respiratory and cardiovascular inputs[49].

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Coordination of Breathing with Protective Reflexes and Speech

Coordination of breathing with protective reflexes is vital to the integrity of any mammalian organism. Lack of coordination between breathing and swallowing leads to laryngeal penetration and aspiration, while lack of coordination between breathing, expiratory reflex, and coughing leads to insufficient airway clearance. The swallowing reflex dominates the respiratory rhythm and motor pattern under physiological conditions[50]. KF contributes more to the coordination of breathing and swallowing than PB[51]. Sequential pharyngeal swallowing, generated by the NTS, is coordinated by synaptic interaction with KF, which mediates a protective laryngeal adductor reflex[52].

PAG controls intrathoracic and intraabdominal pressure via NRA[53]. The NRA contains different groups of interneurons involved in the production of motor activities related to respiration, such as coughing, sneezing, vomiting, and vocalization[54,55]. To produce speech two motor systems must be activated: the prefrontal-PAG-NRA-motoneuronal pathway to generate vocalization and the corticobulbar pathway to modulate vocalization into speech[56].

Conclusions

The brainstem respiratory network is distinctly complex, multifunctional, and widely interconnected throughout the whole central nervous system[57]. It not only determines respiratory drive, respiratory rhythm, and respiratory motor pattern, but is also involved in the control of protective reflexes as coughing and swallowing and the generation of voluntary activities. In brainstem infarction these functions are prone to failure, possibly resulting in central hypoventilation syndrome, disorders of the respiratory rhythm or the respiratory motor pattern, cough insufficiency, aspiration, or retention of secretions in the upper and lower airways.

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Chapter 5

The Respiratory Muscle Pump and Respiratory Mechanics

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The respiratory muscle pump is the main the mechanism by which air is sucked into the lungs and exhaled after gas transfer in the pulmonary alveoli. A second function of the muscle pump is to clear airways by coughing. Speech and vocalization are further functions involving the respiratory muscles, together with oropharyngeal and laryngeal muscles, which are also needed to keep upper airways patent and protected from aspiration. This chapter focuses on the physiology of the muscles involved in respiration and the recognition of developing neuromuscular respiratory failure, its clinical evaluation and assessment, and basic principles of management.

Respiratory Mechanics

Respiratory mechanics and the function of the muscle pump are regulated by the neural mechanisms described in Chapter 4, within the constraints of chest wall flexibility and the ability to expand and contract chest volume. Therefore, scoliosis, chest wall deformity and conditions such as rigid spine syndrome, which is common in certain neuromuscular disorders such as spinal muscular atrophy, SEPN1 (Selenon) myopathy and Bethlem disease, limit the effectiveness of the muscle pump. The muscles of the pharynx and larynx, the diaphragm, the intercostal muscles and the muscles of abdominal wall, neck, shoulder girdle and possibly the spine all play a role in respiratory mechanics to a varying degree in inspiration or expiration. The pharyngeal and laryngeal muscles maintain the patency of the airway conduit, with a role for the vocal cords in providing airway closure by occlusion of the glottis when needed, for instance in coughing or to resist penetration of foreign bodies or saliva. Dysfunction of the upper airways can be acute, for instance with surgical trauma to the recurrent laryngeal nerves, or chronic, for instance with some genetic neuropathies[1] or anterior horn cell disorders.

The diaphragm is the main muscle of inspiration, but it is aided by the cranial-dorsal external and particularly the parasternal intercostal muscles[2]. The accessory muscles of inspiration (including sternoclei domastoids, scalenes[3], upper trapezoid[4], pectoralis major, serratus anterior[5], latissimus dorsi[6] and possibly paraspinal muscles[7]) are recruited in forceful breathing with physical exertion, when the diaphragm is weak (as in neuromuscular paralysis) or downward movement obstructed (as with severely increased abdominal pressure) or when diaphragmatic function is impaired in severe end stage chronic obstructive pulmonary diseasesevere end stage chronic obstructive pulmonary disease Figure 5.1). The activation pattern of the respiratory accessory muscles depends on gender and on the position of the body and arms[4,8,9] (Positioning the body and arms to facilitate the function of accessory respiratory muscles is used in respiratory physiotherapy[10].) The abdominal wall and the caudal-ventral external intercostal, the caudal-dorsal internal intercostal and transversus thoracis muscles are the muscles of expiration needed to produce an effective cough[11]. Notably, external and internal intercostal muscles may both have inspiratory or expiratory effect, depending on the distribution of activation. Probably due to their complex function they have a considerable representation in the primary motor cortex, which has recently been localized (Figure 5.2)[12].

Acute dysfunction with a neural trajectory from brainstem to muscle may change respiratory mechanics[13]. (Figure 5.3). Neuromuscular disease may affect multiple muscles involved in respiration at the same time, or involvement may be very selective, for instance with neuropathy affecting the phrenic nerves preferentially, or with genetic myopathies such as Pompe disease or HMERF (hereditary myopathy with early respiratory failure), where isolated diaphragmatic weakness can precede limb weakness[14,15] (Figure 5.4).

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Figure 5.1 Sternocleidomastoid and visible scalenes in an elderly patient with severe emphysema. With permission from: Thompson WT, Patterson JL, Shapiro W. Laboratory and clinical observations on the scalene "accessory" respiratory muscles. *Trans Am Clin Climatol Assoc.* 1964;75:78–91.

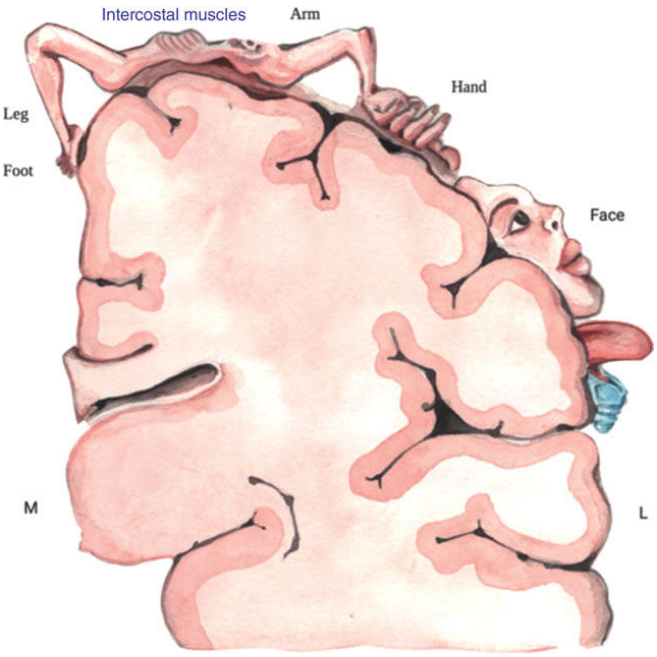


Figure 5.2 Cortical representation of the intercostal muscles, left part of the original figure. © 2021 Ghimire et al., distributed under the terms of the Creative Commons Attribution License, Creative Commons disclaims all liability for damages resulting from their use to the fullest extent possible. Ghimire P, Lavrador JP, Baig Mirza A, et al. Intraoperative mapping of pre-central motor cortex and subcortex: a proposal for supplemental cortical and novel subcortical maps to Penfield's motor homunculus. *Brain Struct Funct.* 2021;226(5):1601–11. doi: 10.1007/s00429-021-02274-z.

Mechanical Respiratory Failure

The diaphragm is the main muscle of inspiration. Contraction of the diaphragm causes it to flatten and expand lung volume. During contraction it exerts a so-called "insertional force," which acts on the lower margin of the rib cage in a cranial direction. Additionally, in the appositional zone, the intraabdominal pressure acts directly on the lower rib cage in a lateral direction, an effect called "appositional force." As a result of both forces, the lower ribs move in a cranial and lateral direction. Obstructive lung diseases with severe hyperinflation cause flattening of the diaphragm in expiration, resulting in a decrease in muscle length, thereby compromising inspiratory function of the diaphragm[11]. When it is paralyzed, the dome rises to an expiratory position and reduces lung volume, and inspiration depends on function of the accessory muscles of inspiration. The hallmark of developing diaphragmatic weakness is a difference between vital capacity upright and supine, because of increased pressure of the abdominal organs against the downward movement of a weak diaphragm when lying flat. One pointer towards developing diaphragmatic failure in clinical history is when patients with neuromuscular disease report needing an increasing number of pillows to sleep at night. In the case of severe diaphragmatic weakness, even the inspiratory effort of quiet breathing in an upright person requires visible recruitment of the accessory muscles of inspiration, as sternocleidomastoid and scalene muscles (innervated by cranial nerve XI and cervical-spine segments 1 and 2)[16–18].

Forceful inspiration achieves maximum expansion of the lungs by contraction of the diaphragm lengthening the chest cavity and moving the lower ribs in a cranial and lateral direction, and by contraction of the intercostal muscles moving the ribs in a ventral and cranial direction, thereby widening the chest[11]. Changes of lung parenchyma and chest configuration limit the degree this is possible. Quiet expiration is mainly passive due to recoil of the rib cage and the lung. The four layers of the abdominal wall muscles (rectus abdominis, transversus abdominis, internal oblique and external obliques) are innervated via the spinal segments Th6 to L1[19] and are needed to generate forceful expiration by pulling the ribs and sternum down and increasing intra-abdominal pressure. A strong cough requires coordination of the vocal cords, intrinsic laryngeal muscles, and the muscles of expiration, as an initial airway occlusion is required to create expiratory pressure. These muscles coordinate in the three phases of coughing (inspiratory, compressive and expiratory)[20] in a complex reflex arc to create intrathoracic pressures

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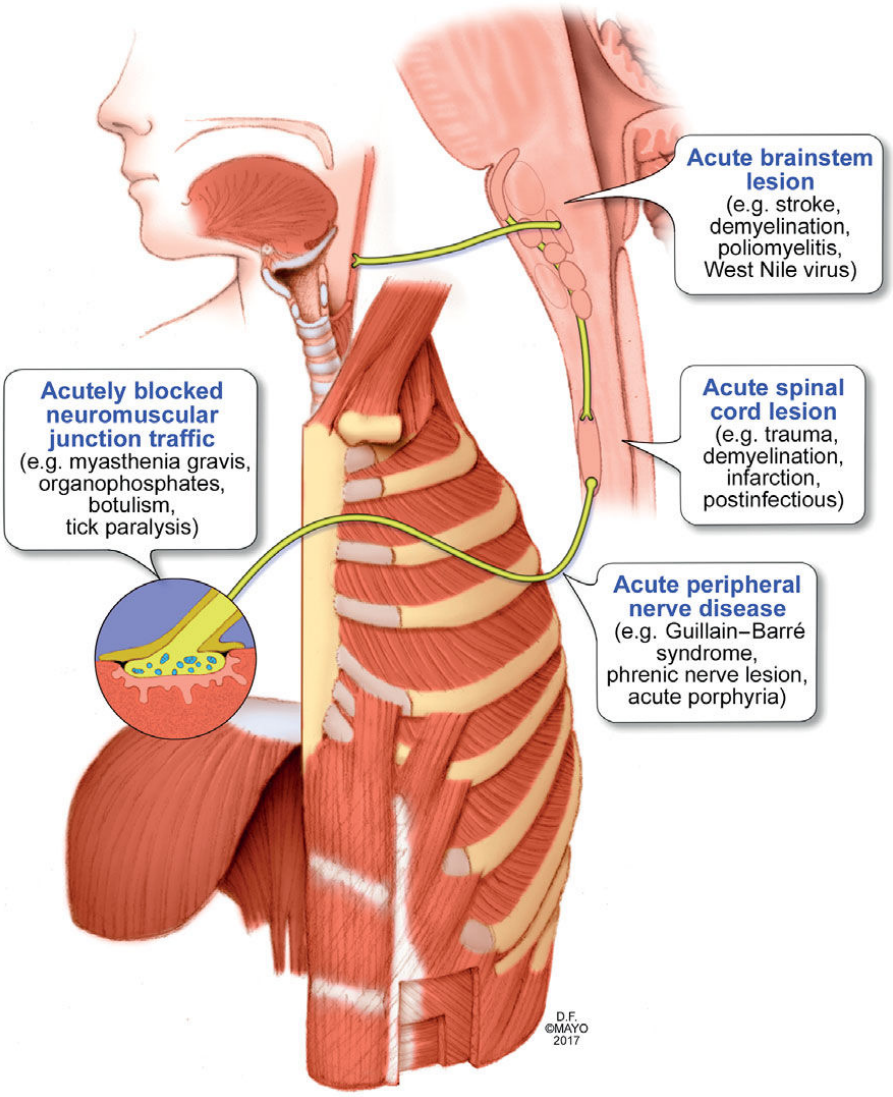


Figure 5.3 Schematic of the neural pathways involved in respiration; the main causes of acute mechanical respiratory failure are summarized. First published in: Wijdicks EFM. The neurology of acutely failing respiratory mechanics. *Ann Neurol*. 2017;81 (4):485–94. doi: 10.1002/ana.24908.

up to 300 mm Hg and expiratory peak flow of 400–700 L/min[21,22]. Muscle weakness will result in failure to clear secretions. Laryngospasm is the term for a spasm of the vocal folds that temporarily interrupts breathing, which can among other causes be observed in neurogenic conditions where vocal cord opening is impaired, such as amyotrophic lateral sclerosis or Kennedy's syndrome[23,24]. Hence, in practical terms, not only the vital capacity helps inform the likely success of weaning from the ventilator, but also the peak cough flow, by indicating whether there is a risk of failure to clear airways.

Pathophysiology in Mechanical Respiratory Failure

Reduced tidal volume shortens the inspiratory time of the respiratory cycle, leading to decreased respiratory compliance and poor alveoli deployment. Regional ventilation and perfusion mismatch in deflated alveoli lead to an early increase in alveolar-arterial oxygen gradient[25] with increased dead-space ventilation. Signals to the respiratory pattern generator from the abnormal, weak respiratory muscles as well as from chemoreceptors signaling hypoxemia cause rapid breathing as a compensatory

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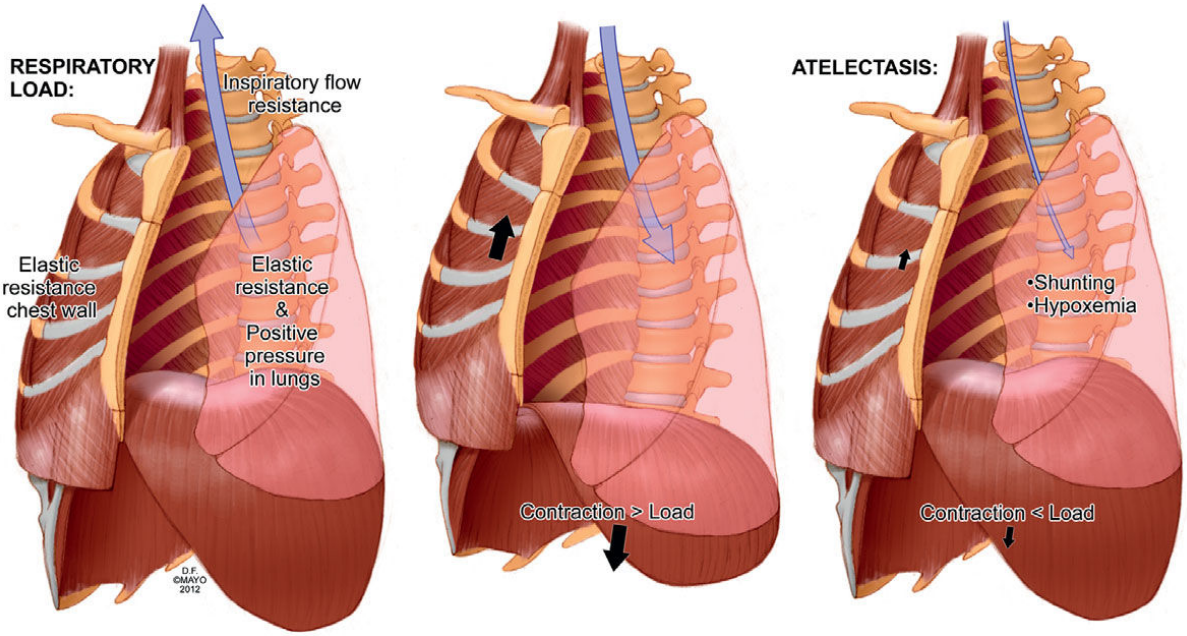


Figure 5.4 The effect of reduced diaphragmatic contraction on inspiratory volume and lung parenchyma, facilitating atelectasis and hypoxemia. © Mayo Clinic.

mechanism. Pulse oximeter measurement detects hypoxemia but does not identify when CO_2 retention develops. In a tachypneic patient, arterial pCO_2 is initially low, but normalizes and then rises above normal when the diaphragm becomes adynamic. Normal pCO_2 in a tachypneic patient may signal fatigue and impending failure of compensatory mechanisms because mechanical failure prevents the patient from reducing arterial PCO_2. Therefore, clinical expertise in recognizing the phases of respiratory failure and the risk of respiratory arrest is more important than consideration of blood gas values on their own.

Pulmonary function tests can inform on inspiratory muscle strength. Decreased vital capacity and mouth pressures are first of all a sign of diaphragmatic weakness. Normal baseline values for vital capacity are around 40–70 ml/kg/3–5 L, and a decrease by more than 50% is a significant abnormality. Slow vital capacity reflects the respiratory pump alone, and is therefore a better measure of respiratory mechanics, rather than forced vital capacity, which is more significantly affected by airway obstruction. Maximal inspiratory pressure is obtained by occluding the inspiratory valve at residual volume and ranges around −100 cmH_2O, measuring the force of diaphragm and accessory inspiratory muscles combined. Maximal expiratory pressure is measured at total lung volume by occluding the expiratory port (normal: 80 cmH_2O) and measures the combined force of muscles of expiration. Maximal expiratory pressure and peak cough flow (normal: >360 L/min) are important measures of the ability to cough effectively[26]. Bedside pressure tests can be easily obtained using handheld devices, but their correct application requires good instruction, patient cooperation and expertise from the operator. This complicates serial testing by different operators in evolving situations, for instance when monitoring evolving respiratory failure on the hospital ward. Correct mouth pressures also require an adequate mouth seal – difficult in patients with oropharyngeal weakness, facial diplegia or with a feeding tube in place. Sniff nasal inspiratory pressure is a way around this problem, available with the same handheld device using a nasal plug. Studies on nasal sniff pressure in Guillain–Barré syndrome (GBS) suggested better correlation with worsening weakness than traditional spirometry measures[27]. Nasal sniff pressures are more commonly used in chronic conditions where the mouth seal is impaired, such as amyotrophic lateral sclerosis with progressive bulbar palsy. Mask spirometry can also be used to avoid falsely abnormal values of pulmonary function tests due to poor closure[28]. Recognizing problems in performing the test and to suspect erroneously low values requires clinical

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expertise and appropriate evaluation of the clinical setting. The consequences to be taken from abnormal values (i.e. ICU admission or mechanical ventilatory support) need to be set in the clinical context, for instance, values that are highly threatening in a patient with acute disease might be unremarkable baseline performance in a patient with chronic neuromuscular disease. Finally, the nature of the condition causing respiratory weakness needs to be considered: A single test in a patient with severe fatiguing weakness, that is, myasthenia gravis or metabolic disorders including mitochondrial disease, may present reassuring test results at a single test, but the patient may unexpectedly decompensate. Serial studies may show a decline but often clinical judgment trumps any test. In others, borderline adequate respiratory mechanics may no longer suffice when chest infection develops, a problem seen in patients with stable neuromuscular respiratory weakness and COVID-19 pandemic.

In addition to the assessments detailed in Chapter 8, the neurophysiologic investigation of neuromuscular respiratory failure phrenic nerve stimulation may be useful to differentiate between a myopathy, myasthenic syndrome, or neuropathy. The phrenic nerve is located underneath the posterior border of the sternocleidomastoid muscle and can easily be stimulated once or repetitively. The diaphragmatic compound action potential is of low amplitude but affected by the respiratory cycle[29]. Needle electromyography (EMG) of the diaphragm can also be performed (needle entry at the sixth or seventh intercostal space), although it is not performed often, out of concerns of iatrogenic pneumothorax, even though that is infrequent[30]. Diaphragmatic EMG via an esophageal electrode can be used to assess respiratory drive and is a component of neurally adjusted ventilator-assisted ventilation[31,32], but its value in neuromuscular disease is unclear. Newer technology such as ultrasound imaging of the diaphragm provides dynamic information and can also improve the accuracy of testing for phrenic nerve conduction with a twitch seen on ultrasound after stimulation[33]. This may reduce false-positive results in nerve-conduction studies in patients without diaphragm dysfunction[33–35]. These three modes of testing combined have great potential in ICU settings. In acute neuromuscular diseases, however, comprehensive data are not available on whether phrenic-nerve and diaphragm EMG and ultrasound predict future intubation or a successful weaning trial. Dynamic MRI has been tested in chronic muscular disease[36,37], but the test is not yet validated for clinical practice in acute disease. Its short acquisition times (<30 minutes) may make it a potentially useful tool, particularly combined with imaging of chest wall muscles but limited availability, and problems around patients with impaired respiratory function tolerating the scan limit its current use[38,39]. Chest MRI may provide early information on diaphragmatic dysfunction in patients at risk, for instance with Pompe disease or with muscular dystrophies. Potentially, this may be evident even before function of the muscle pump is impaired in conventional pressure measurements[40].

Clinical Recognition of Acute Respiratory Failure

There is no substitute for clinical recognition of acute failure of respiratory mechanics. A number of clinical pointers are not reflected by test results alone, such as restlessness, tachycardia (>100 bpm), confusion or daytime sleepiness leading to CO_2 narcosis. Tachypnea (>20 per min), use of sternocleidomastoid or scalene muscles, failure to string more than a few words together in a sentence and asynchronous or paradoxical breathing are more obvious respiratory signs. Thoraco-abdominal dyssynchrony may be visible[16–18], in which instead of the abdomen and chest expanding and contracting in a synchronized fashion, there is a "rocking horse" effect (abdominal paradox, i.e. chest out, abdomen in). Subjective symptoms even in the presence of a normal arterial blood gas are a sensation of breathlessness and "air hunger" preceding obtundation when PaO_2 declines and $PaCO_2$ rises with overstimulated chemoreceptors. When the work of breathing relative to respiratory mechanical strength rises, patients may report a frightening feeling of not catching enough air and may report a struggle to breathe. These may be more obvious in acute disease, whereas clinical signs may be very subtle in chronic neuromuscular disorders. It is important to recognize these symptoms because it may imply the patient is in need of endotracheal intubation and respiratory support to avoid asphyxiation[41–43].

Causes of Acute Mechanical Respiratory Failure

Central causes of mechanical respiratory failure include stroke, acute demyelination, or infectious disorders causing lesions of the dorsolateral medulla oblongata. Poliomyelitis remains a healthcare problem in some parts

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of the world and may cause permanent respiratory failure[44]. West Nile virus infection may cause lesions of the brainstem or anterior horns of the spinal cord[45,46].

Acute traumatic spinal cord injury is the most common cause of acute spinal cord-associated respiratory failure. Other causes are upper cervical cord infarction and acute cervical myelitis associated with Neuromyelitis optica spectrum disorders[47,48].

Two disorders are the main nontraumatic causes of acute neuromuscular respiratory failure — myasthenia gravis and GBS[49]. The term myasthenic crisis is traditionally applied to myasthenia with respiratory failure requiring mechanical ventilation and purportedly occurs in 20% to 40% of admitted patients, not infrequently within the first 12 months of disease onset[50,51].

In GBS, facial and oropharyngeal muscles are affected in nearly 50% of cases. Respiratory failure occurs in about 20%–30% of patients and commonly within one week after the onset of paresthesia. The cause of GBS is a respiratory virus (most trivial influenza viruses) or enteric bacteria (*Campylobacter*). The Zika virus epidemic caused a spike in the prevalence of GBS[52], and a number of cases of GBS have been described in the recent COVID-19 pandemic caused by the SARS-CoV2 virus, but the true incidence is not yet clear and so far, it has not caused outbreaks of GBS[53].

Other acute disorders more rarely cause abnormal respiratory mechanics. Phrenic nerve injury and unilateral damage may cause marked breathlessness during any form of exercise and prevent the patient from lying flat. Unexplained cases of phrenic-nerve damage associated with shoulder pain may be due to brachial neuritis and are often associated with intense pain in shoulder muscles. Causes of phrenic nerve injury include compression of the brachial plexus due to tumors of the lung, aortic aneurysm, stretch injury in chest surgery, central venous cannulation, manipulation of the cervical spine, infection or autoimmune disease including immune checkpoint inhibitor treatment[54–57].

Myasthenia gravis can cause paralysis of the vocal cords, causing acute dyspnea[58,59], or the resulting increase of the work of breathing can cause secondary respiratory failure through fatiguing of the respiratory muscles. Likewise, barely compensated respiratory mechanics can decompensate if other circumstances change, such as increased work of breathing through exposure to altitude or, more commonly, lung infection and impaired alveolar gas exchange.

Intensive care unit acquired weakness or critical illness neuromyopathy causes weakness in patients undergoing treatment and mechanical ventilation in a critical care unit. The neurological condition worsens the marked decrease in respiratory muscle strength and diaphragmatic weakness that patients develop within weeks of mechanical ventilation[60]. Organophosphorus poisoning is common in accidental or suicidal self-administration and sometimes used in homicide or terrorist attacks; a combination of bronchoconstriction, hypersecretion and respiratory-muscle paralysis is typical[61]. Botulism and tetanus have become rare in countries with developed infrastructure and vaccination programs but are still common causes of respiratory failure and death in low-income societies[62–65].

Respiratory Mechanics in the ICU

Any indication of respiratory distress warrant admission to an ICU. Patients need to be positioned safely in an upright position, favorable for respiratory mechanics and safe in vomiting, which combined with a weak cough carries the risk of massive aspiration. Management of secretions requires frequent suctioning.

Oxygen administration should aim at oxygen saturation between 90% and 95%, but may cause CO_2 retention in patients with neuromuscular respiratory failure resulting in hypercapnic coma or respiratory arrest[66,67]. Mechanical ventilation is often preferable to supplemental oxygen in a patient with respiratory failure and oxygen desaturations. Noninvasive mask ventilation is an option, but endotracheal intubation is needed where there is rapid progression or risk of aspiration. Patients acutely in distress usually require immediate intubation. Other clear clinical signs are inability to cough up secretions, tachypnea, sweating, hemodynamic instability and abnormal arterial blood gas with hypoxemia or early hypercapnia. A patient with increased work to breathe or signs such as restlessness, sternocleidomastoid muscle contractions, nasal flaring (contraction of dilator muscle of external nares) and mouth opening should be preemptively intubated rather than guided by a pulmonary function test threshold.

To epitomize, the muscle pump is constituted by a complex interplay between muscles of respiration, lung parenchyma and the chest wall, regulated by a feedback mechanism under the control of the central nervous

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system. The respiratory mechanics shift in diaphragmatic weakness. The normal respiratory cycle of the chest and abdomen moving out with inspiration changes into assist by neck muscles and a paradox movement. where the abdomen draws in during inhalation and out on exhalation[68].

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Chapter 6

Sleep and Respiration

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Sleep is behaviorally defined as a reversible state of reduced motor activity and reaction to sensory stimuli. While sleep is essential for human survival, its function is still not completely understood. Sleep is associated with significant changes in respiratory drive, respiratory muscle tone, respiratory mechanics, and ventilation. Therefore, profound knowledge of the interactions between sleep and respiration is indispensable for clinicians and scientists in the field of neurorespiratory medicine. This chapter covers circadian rhythms, sleep, and arousal as well as interactions between sleep and respiration. Moreover, clinical implications are discussed.

Circadian and Ultradian Rhythms

Sleep regulation is deeply interwoven with the activity of the internal timekeeping system known as the circadian clock. Box 6.1 shows detailed information on the evolution of circadian clocks. The mammalian circadian clock drives daily rhythms in most physiological pathways and behavior, keeping them in synchrony with environmental light–dark cycles. In absence of external zeitgebers like light–dark cycles, the human circadian rhythm extends to 25 hours[1]. A wide variety of parameters such as body temperature, cortisol, and melatonin show circadian rhythmicity in humans.

Ultradian rhythms are defined as "short-term rhythms with a frequency of fewer than 24 h but commonly with periods in the range of 20 min to 6 h"[2]. Human sleep states follow an ultradian rhythm. Therefore, circadian as well as ultradian rhythms exist with respect to respiration in humans[3,4].

In mammals, the circadian system has a hierarchical architecture, with a master clock in the brain's suprachiasmatic nuclei (SCN) that receives photic inputs from the retina, leading to a synchronization with the environmental light–dark cycle. The SCN clock, in turn, entrains the self-sustained and cell-autonomous clocks that are found in most cells across tissues. These peripheral clocks are not light sensitive themselves, and multiple, partially redundant directly or indirectly SCN-controlled cues are involved in the entrainment, including hormonal signals (glucocorticoids, melatonin), fasting–feeding cycles, and body temperature rhythms. Molecularly, SCN and peripheral clocks all rely on negative feedback loops in transcription, driving a sizeable number of downstream target

Box 6.1 Evolution of circadian clocks

In evolution, the emergence of circadian clocks vastly predates that of sleep, as the first clocks evolved already an estimated one to three billion years ago in cyanobacteria[5]. Most eukaryotic organisms from fungi to plants and animals possess circadian clocks, yet it is interesting to note that from the diversity of molecular components and genes that make up the oscillators in distantly related organisms, it has been concluded that circadian clocks have likely been (re)invented several times over evolutionary history[6]. It has been proposed that the temporal organization of metabolic pathways constitutes the actual origin of circadian oscillations[7]. For example, as it would be impossible to accommodate certain anabolic and catabolic biochemical reactions simultaneously in the same cell, the solution of separating them in time (and gating them to the most appropriate time of day, e.g. to the light phase in photosynthetic organisms or to nutrient availability in others) may constitute the original rhythmic event from which a dedicated circadian clock mechanism that can measure near-24-hour rhythms (Latin: *circa diem*) even in the absence of the periodic environmental signals evolved. Thus, the rhythms in respiration at the cellular level (i.e. mitochondrial respiration) that are well described in organisms as simple as unicellular yeast, could represent the precursor of circadian clock regulation of respiration at the organismal level in humans. Indeed, sleep–wake cycles have been proposed to represent a means of metabolic compartmentalization as well[8].

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genes whose rhythmic expression is largely responsible for the various rhythmic physiological outputs across cell types and organs. At the organismal level, processes and parameters that are at least in part regulated by circadian rhythms include the endocrine system (e.g. secretion of cortisol, vasopressin, melatonin, and other hormones), most metabolic and digestive activities, blood pressure and heartbeat, body temperature, renal plasma flow, alertness, and, most evidently, sleep and wakefulness[9].

The partitioning of activity and inactivity to distinct phases of the day, which in most organisms is controlled by the circadian clock, can be considered the basis on which the daily cycles of sleep and wakefulness evolved. It is interesting to note that there are anecdotal cases of mammalian species whose behaviour is dominated by a noncircadian rhythm even when exposed to the daily 12 hour-light/12 hour-dark cycle. For example, the common vole (*Microtus arvalis*) follows an ultradian activity rhythm that is repeated three to four times a day, each cycle consisting of feeding, activity, and sleep[10,11]. From this and other observations, it can be inferred that the sleep–wake cycle appears to be more closely gated by activity/inactivity cycles, rather than the circadian cycle per se.

Sleep

Sleep is behaviorally defined as a reversible state of reduced motor activity and reaction to sensory stimuli[12]. It has been detected in all animals to some extent[13–15]. The function of sleep still remains unclear with hypotheses suggesting higher order cognitive or restorative functions[16]. Sleep deprivation has a detrimental effect on vascular health and neurocognitive functions in humans, but it is not yet clear if total sleep deprivation necessarily leads to death[17,18].

Terrestrial mammals and birds show two distinct EEG-defined sleep stages, slow wave sleep (SWS) and rapid eye movement (REM) sleep. Whales, again, present unilateral SWS, while REM is suppressed[19,20]. Aquatic animals face the necessity to keep up their body temperature, to screen the surface for predators, to breathe air at the surface and to avoid aspiration of water. These animals thus are the most prominent examples for the importance of the interaction between sleep and respiration. In humans four sleep states can be discriminated by polysomnographic criteria: REM and non-REM (NREM) sleep, the latter comprising sleep states N1, N2 and N3[21] (see Table 6.1, Figure 6.1).

A sleep profile or hypnogram shows the sleep states of an individual along the time axis (see Figure 6.2). In healthy persons a typical pattern can be observed with decreasing N3 periods and increasing REM periods during the sleep episode. Over the lifespan awakenings increase in frequency and duration and the proportion of REM decreases[22].

Regulation of Sleep

The two-process model of sleep regulation was introduced by Borbély in 1982[23]. "The model posits that a homeostatic process (Process S) interacts with a process controlled by the circadian pacemaker (Process C), with time-courses derived from physiological and behavioral variables"[24]. Sleep pressure is generated by both processes: Process S accumulates as long as a person stays awake and is reduced exponentially when a person falls asleep. Process C reflects fluctuations in sleep pressure dependent on the circadian rhythm (see Figure 6.3)[24]. In 2010, Saper et al. introduced a model of mutual inhibition between sleep- and wake-promoting neurons functioning as a flip/flop switch between sleep and wakefulness, thereby facilitating rapid awakening from sleep if necessary[25]. As this model could not explain the relatively slow onset of sleep, in 2018 Eban-Rothschild et al. proposed the

Table 6.1 Sleep states

State	EEG – rhythm	EEG – graphic elements	Typical motor activity
N1	Predominantly 4–7/s, lower amplitude	Vertex waves	Slow eye movements, amplitude of chin-EMG lower than awake
N2	Predominantly 4–7/s, lower amplitude	Sleep spindles, K-complexes	No slow eye movements, amplitude of chin-EMG lower than awake
N3	≥20% slow waves 0.5–2/s Amplitude >75 μV	Possibly sleep spindles and K-complexes	No slow eye movements, amplitude of chin-EMG lower than awake
REM	Predominantly 4–7/s, lower amplitude	Sawtooth waves	Rapid eye movements, chin-EMG lower than in other sleep states

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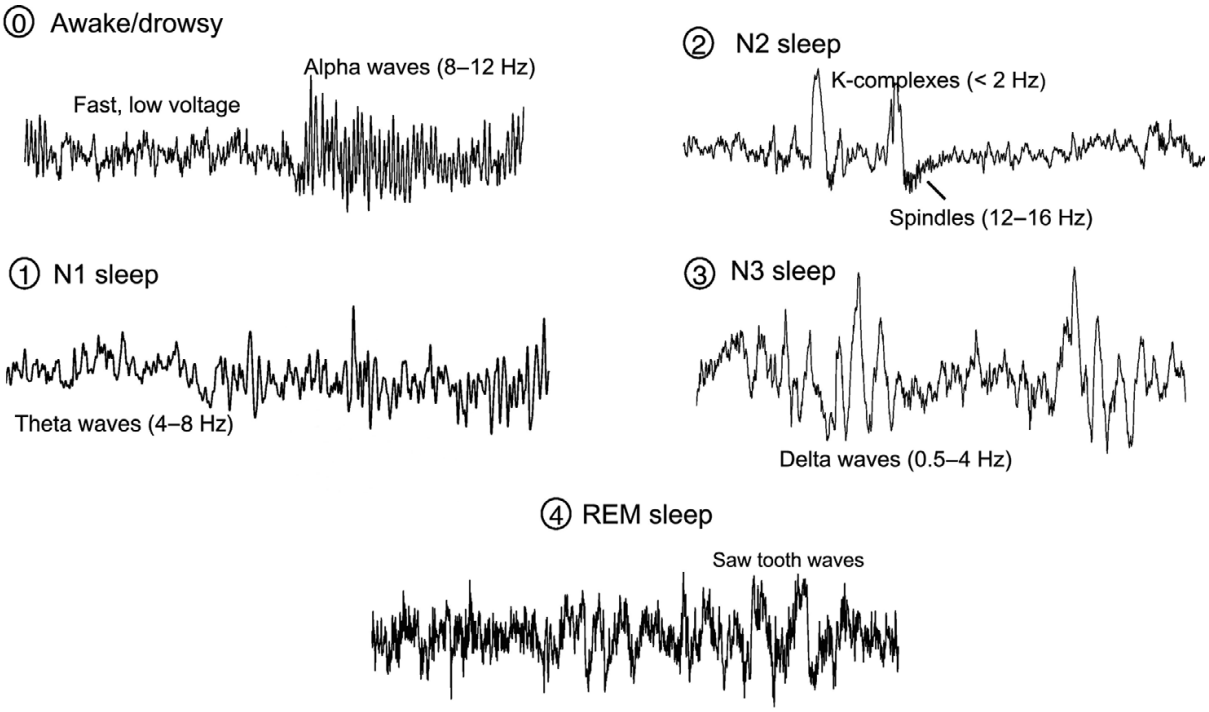


Figure 6.1 EEG characteristics of wakefulness and sleep states. Upper part of the original figure © 2021 Lechat et al., distributed under the terms of the Creative Commons Attribution License, Creative Commons disclaims all liability for damages resulting from their use to the fullest extent possible. Lechat B, Scott H, Naik G, et al. New and emerging approaches to better define sleep disruption and its consequences. *Front Neurosci*. 2021;15:751730. doi: 10.3389/fnins.2021.751730.

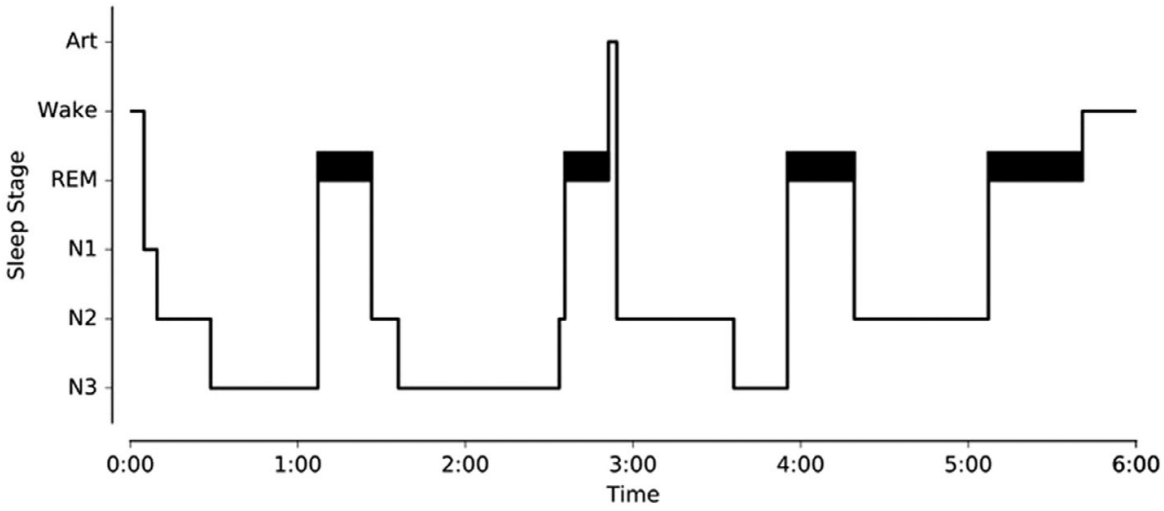


Figure 6.2 Normal hypnogram. REM, rapid eye movement, ART, artefact. Copyright © 2017 Combrisson et al., distributed under the terms of the Creative Commons Attribution License, Creative Commons disclaims all liability for damages resulting from their use to the fullest extent possible. Combrisson E, Vallat R, Eichenlaub JB, et al. Sleep: an open-source python software for visualization, analysis, and staging of sleep data. *Front Neuroinform*. 2017;11:60. doi: 10.3389/fninf.2017.00060.

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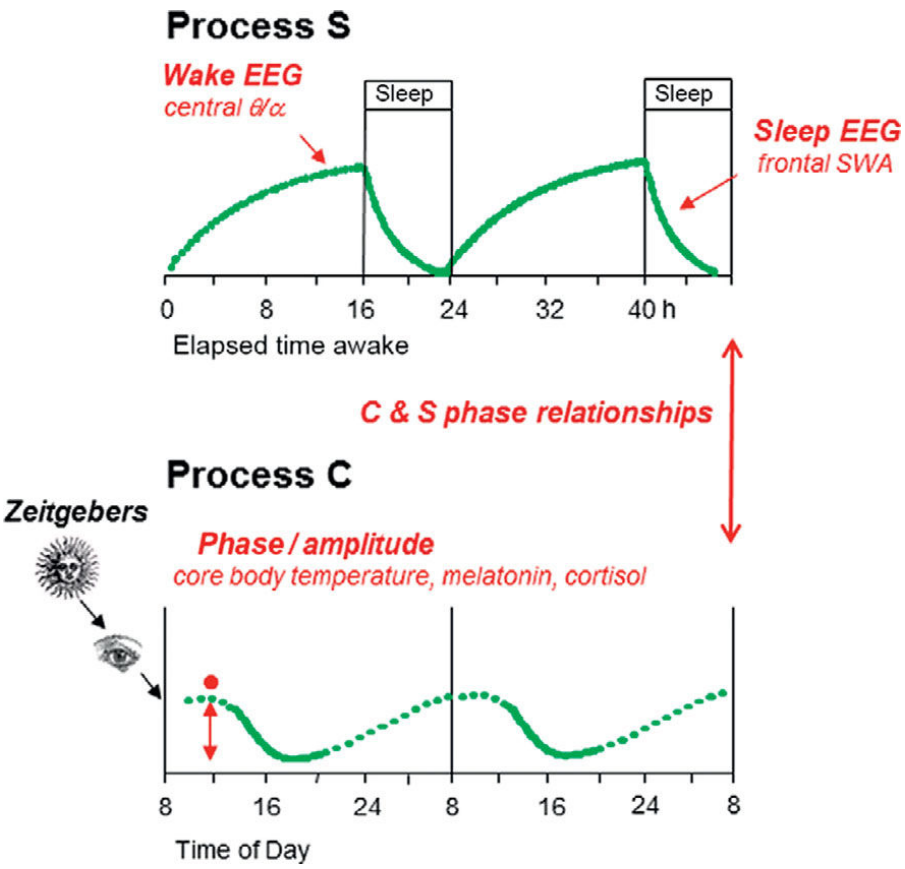


Figure 6.3 The two-process model of sleep. SWA, slow wave activity. With kind permission of John Wiley & Sons from: Borbély AA, Daan S, Wirz-Justice A, Deboer T. The two-process model of sleep regulation: a reappraisal. *J Sleep Res*. 2016;25(2):131–43. doi: 10.1111/jsr.12371.

existence of integrator neurons, which continuously integrate multiple inputs, classify states as sleep or wakefulness, and decide to stay inactive and promote sleep or to actively wake up an individual[26]. The mechanisms of ultradian control of the NREM–REM sleep cycle are not yet completely understood[27].

Arousal

A definition of generalized CNS arousal has been suggested based on increased responsiveness to sensual stimuli, motor activity and emotional reactions[28]. "Aroused state and sleep are two different sides of vigilance," and arousability might be an essential feature of sleep[29]. "Arousal from sleep" in humans has been defined by the American Academy of Sleep Medicine as a sudden change in EEG frequency lasting for at least 3 s and occurring after at least 10 s of stable sleep. In REM, an arousal necessarily leads to a rise in chin-EMG activity lasting at least 1 s[21]. If an individual stays awake after an arousal, the event is called "awakening from sleep". Hereinafter the term "arousal" is used in the sense of "arousal from sleep."

The combination of hypercapnia and hypoxemia triggers arousal more strongly than normoxic hypercapnia, and isocapnic hypoxia is the weakest of these three triggers. Hypercapnic arousal occurs when CO_2 rises 10–15 mmHg from baseline[30]. Whereas in healthy males the threshold for hypercapnic arousals is state dependent and higher in REM than in NREM, the threshold for healthy women is less state dependent and comparable to the threshold in males during NREM[31]. Interestingly, in a mouse model CO_2 proved to be capable of inducing arousals without stimulating breathing[32].

However, although hypoxemia and hypercapnia result in respiratory arousals, classic studies suggested that the final common pathway is increasing respiratory effort[33]: In a study published by Gleeson et al. in 1990, sleeping subjects with esophageal catheters had been

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stimulated by added inspiratory resistive load, hypoxemia, or hypercapnia in NREM, and the peak negative esophageal pressure for the last inspiration before arousal had been comparable in all conditions[33]. The respiratory arousal threshold is sleep-state dependent[34].

Sleep and Respiratory Mechanics

Pharyngeal cross-sectional areas are smaller in supine than in sitting position in healthy, awake humans[35]. Lung compliance was also found to be lower in horizontal than in sitting positions[36]. Supine position results in a higher respiratory variation of the volume of the abdomen and a lower variation of the volume of the rib cage when compared to sitting[37]. Furthermore, in more erect positions higher values for forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) are found. In spinal cord injury FEV1 and FVC are lower in sitting than in supine position[38].

Sleep and the Respiratory Muscle Pump

The genioglossal muscle, the palatal muscles, and the hyoid muscles are the most important dilatators of the upper airways, and they show increased activity during inspiration[39]. Upper airway collapsibility is lowest while awake, higher in SWS, still higher in N2 and highest in REM. Also, muscle tone of genioglossus and tensor palatini is lower in sleep than while awake[40]. Furthermore, airflow resistance is higher in sleep than wake state, with supralaryngeal structures primarily contributing to this increase in resistance[41].

Minute ventilation decreased in one study (n = 40) by 14% to 19% from wake state to sleep[42] and in another study (n = 25) by 11% from wake state to N2[43]. In a third study (n = 9) minute ventilation decreased by 8% from wake state to NREM and again increased by 4% from NREM to REM[44]. The decrease of minute ventilation from wake state to sleep has been attributed either to a reduction of tidal volume[42,43] or respiratory rate[44]. In NREM, the contribution of the ribcage to minute ventilation as well as the intercostal and diaphragmatic muscle activity increase when compared to wake state. This is probably due to a rise in work of breathing resulting from an elevated upper airway airflow resistance. Finally, in REM versus NREM there is a substantial increase in diaphragmatic muscle activity and abdominal contribution to minute ventilation and a decrease in intercostal muscle activity and rib cage contribution to minute ventilation[44]. Gothe et al. in 1981 demonstrated a higher contribution of the rib cage to tidal volume in N2 compared to wakefulness[43]. Table 6.2 compares key features of the respiratory muscle pump and respiratory regulation (see following paragraph) in wakefulness, NREM and REM.

Table 6.2 Respiratory muscle pump and respiratory regulation in wakefulness, NREM, and REM

	Awake	NREM	REM
Upper airway collapsibility	↔	↑	↑↑
Diaphragmatic muscle activity	↔	↑	↑↑
Minute ventilation	↔	↓↓	↓(↓)
Hypercapnic ventilatory response	↔	↓	↓↓
Hypoxic ventilatory response	↔	↓	↓↓

NREM, nonrapid eye movement; REM, rapid eye movement.

Respiratory Regulation during Sleep

During wakefulness, respiratory drive is mainly controlled by the cerebral cortex according to our willingness to breathe ("wakefulness drive") with lesser influence of the "chemical drive" (blood CO_2, O_2, and pH). During sleep, we lose our "wakefulness drive" and the "chemical drive" takes over the control of our respiration. When pCO_2 rises, or when pO_2 or pH decrease, respiratory drive increases and conversely decreases when pCO_2 drops and pH rises.

This subtle regulation of breathing during sleep is controlled by a feedback loop called "loop gain." Loop gain is the input–output function of the feedback loop controlling nocturnal ventilation: This loop gain determines the ventilatory response or increase in respiratory drive that follows a ventilation disturbance such as an apnea, It represents the sensitivity of the respiratory control of an individual: A person with high loop gain will be more likely to develop unstable breathing during sleep due to an excessive ventilatory response to mild breathing disturbances. This may generate a transient hyperventilation, which will in turn generate and excessive drop in pCO_2 level. If pCO_2 decreases below a certain level (apnea threshold) breathing may transiently stop until pCO_2 builds up to a level able to stimulate respiratory drive.

The contribution of hypoxia or hypercapnia to the respiratory drive can be measured via the ventilatory response, which is the increase of minute ventilation caused by hypercapnia or hypoxia (see Chapter 4). The

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hypercapnic ventilatory response and the hypoxic ventilatory response are reduced in NREM versus wake state and further reduced in REM[31,43,45,46]. In normal individuals arterial CO_2 increases 2–6 mmHg in sleep compared to wakefulness[47,48]. Additionally, sleep deprivation causes a reduction in hypercapnic ventilatory response and hypoxic ventilatory response while a subject is awake[49,50].

The retrotrapezoid nucleus (RTN) is the best characterized central chemoreceptor and controls the inspiratory amplitude during NREM and REM, while it controls the breathing frequency only in NREM. It thus regulates the respiratory rhythm in NREM probably via inputs to the pre-Bötzinger complex, but this regulation is overridden in NREM[51]. It is thus not surprising, that hypercapnia in congenital central hypoventilation syndrome, which is caused by mutations of the PHOX2B-gene, involved in the development of the RTN, is most severe during NREM[52].

Conclusions

Sleep-related breathing disorders are diagnosed by polysomnography or polygraphy. Alveolar hypoventilation and consecutive hypercapnia become evident in sleep rather than wake state in all clinical conditions. The extent of hypercapnia is stage dependent in many diseases: While phrenic dysfunction in neuromuscular disease results in hypercapnia especially in REM, congenital central hypoventilation results in hypercapnia especially in NREM[53]. When hypercapnia is suspected, transcutaneous capnometry and blood gas analysis are suitable diagnostic methods. As sleep deprivation reduces the central respiratory drive, weaning from the respirator always should first take place during the daytime. Additionally, any factor causing sleep deprivation should be avoided in patients with increased risk of ventilatory insufficiency and during weaning.

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Chapter 7

Neurogenic Dysphagia

Rainer Dziewas and Tobias Warnecke

Dysphagia is a frequent symptom, and when it leads to large volume aspiration, could impact outcome of the critically ill patient. Studies in unselected ICU patient populations showed that 50% to 70% manifested dysphagia[1–3]. Although dysphagia resolves in a number of patients until hospital discharge and during subsequent follow-up, Brodsky and coworkers found persisting dysphagia in 25% of acute respiratory distress syndrome survivors at six months. In a recent study in a neurological ICU there even was a dysphagia incidence of over 90%, and dysphagia persisted in half of the patients until the day of discharge[4]. Of relevance is the finding that dysphagia in intensive care patients is most severe and in 10%–20% of the patients accompanied by silent aspirations[5–7]. Regardless, dysphagia in critically ill patients is a significant predictor of complications, especially aspiration pneumonia and reintubation, and a key determinant of lengths of stay and patients' outcome[8–11].

In concordance with its clinical relevance, dysphagia has been identified as frequent problem in the ICU in two different surveys[12,13]. The MAD^{ICU}-Survey (**Ma**nagement of **D**ysphagia on the **I**ntensive **C**are **U**nit) explored differences in perception between neuro-ICU and ICU physicians. This survey showed that, due to its pronounced impact on the neurologically ill, the first group rated dysphagia as particularly important for patient care. In both surveys most participants correctly described and rated risk factors for the evolution of this syndrome and its complications. In addition, these two studies also showed that most participants had limited access to adequate diagnostic and therapeutic procedures.

Physiology of Swallowing

The act of swallowing transports saliva and food from the oral cavity into the stomach while simultaneously protecting the airway. Although swallowing can be initiated voluntarily, most swallows occur without conscious input. While awake, a healthy person swallows about once a minute between meals depending on saliva production, whereas during deep sleep, salivation and swallowing are completely suspended. Swallowing seems straightforward but it is not and requires a coordinated, bilateral activation and inhibition of more than 25 pairs of muscles in the oral cavity, pharynx, larynx and esophagus, which is executed by five cranial nerves as well as the ansa cervicalis (C1–C3)[14].

Swallowing can be divided into four phases: the oral preparatory phase, the oral phase, the pharyngeal phase, and the esophageal phase (Figure 7.1).

In the *oral preparatory phase*, food is chewed and mixed with saliva. The soft palate is lowered and together with the base of the tongue closes off the oral cavity, to avoid premature spillage of food into the oropharynx. The airway is open, and the pharynx and larynx are in their resting position. Towards the end of this stage the tongue keeps the food bolus in close contact with the palate.

In the *oral phase* the tongue elevates and rolls posteriorly in a peristaltic motion, making sequential contact with the hard and soft palate and thereby propelling the bolus into the oropharynx. The lips remain closed and the buccinator muscles remain contracted, thereby enabling slight negative pressure in the oral cavity to facilitate the bolus transport. The oral phase is executed voluntarily and ends with the elicitation of the swallowing reflex (Figure 7.1).

The *pharyngeal phase* is processed involuntarily. At the beginning of the reflexive movement pattern, the velum rises to close the nasopharynx and prevent nasal regurgitation of bolus material. The swallow is usually initiated during the expiratory phase of respiration. During the swallow, breathing is interrupted briefly. A rapid, piston-like backward movement of the tongue base presses the bolus into the hypopharynx. At the same time the hyoid and larynx rise anterior-superiorly, which enlarges the hypopharyngeal space, while the upper esophageal sphincter relaxes. Simultaneously the larynx is closed at the level of the arytenoids and the vocal folds;

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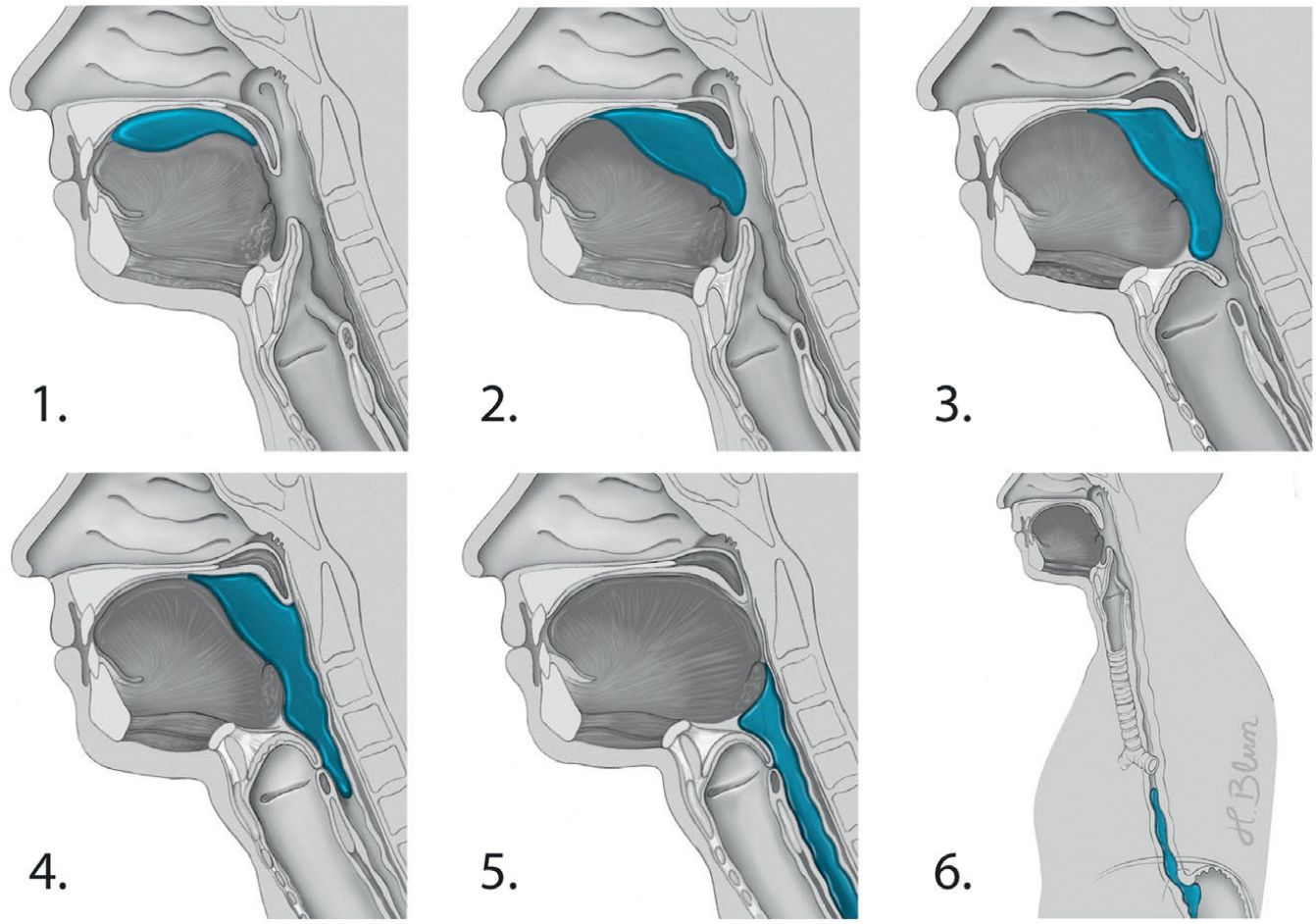


Figure 7.1 The act of swallowing; 1 = oral preparatory phase, 2 = oral phase, 3–5 = pharyngeal phase, 6 = esophageal phase) ©Heike Blum, Münster, reproduced with permission from [7].

in addition, the epiglottis being pushed backwards by the tongue retroflexes. The bolus slides over the inverted epiglottis and the pyriform sinus and is transported downstream by a sequential contraction of the pharyngeal constrictors into the esophagus.

The passage of the pharyngeal peristalsis through the upper esophageal sphincter terminates its relaxation and marks the transition to the *esophageal phase* of swallowing. Hyoid, larynx, and epiglottis return to their resting position. The velum relaxes, thereby reopening the nasopharynx and allowing breathing to continue. A primary peristaltic wave of the esophageal musculature propagates the bolus into the stomach. Secondary peristaltic cleaning waves are induced by local extensor stimuli.

The precise pattern of sequential stimulation and inhibition of the various muscles involved in swallowing is regulated by a swallowing center located in the brainstem. The center can be divided into three functional levels[15]. The input level is formed by peripheral afferents and efferent cortical signals. The neurons of the output level are connected to the motor cranial nerve nuclei. The organizational level consists of a group of interconnected interneurons that form the central pattern generator for swallowing. The central pattern generator is divided into a dorsal swallowing group, which lies in the solitary nucleus and the adjacent reticular formation, and a ventral swallowing group, which is placed above the nucleus ambiguus in the ventrolateral medulla oblongata. The reflexive pattern coordinated by the brainstem swallowing centers can be generated without supramedullary input. Under physiological conditions the network receives multiple signals from the supramedullary swallowing network, which thereby performs a coordinating function on the initiation and the execution of the

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swallow. Neuroanatomically, this network is extended across various brain regions and includes, among others the primary sensory and motor cortices, the supplementary motor area, the gyrus cinguli, the frontal operculum, the insula, secondary sensory areas, and the parietal association cortex[16].

Etiology and Pathophysiology of ICU-Related Dysphagia

The causes of dysphagia in the critically ill can be differentiated into three etiological categories[17]. Dysphagia

1. may be associated with the main diagnosis leading to ICU treatment
2. may be due to preexisting comorbidities
3. may be a consequence of the ICU treatment itself.

In most patients, however, more than one etiology will play a role, which is particularly true for the neurologically ill.

As shown in Figure 7.2, various neurological disorders, which typically require treatment in the ICU, impair the functionality of the swallowing network or the associated downstream nerves and muscles. Depending on the lesion location, stroke and inflammatory diseases of the CNS impair the supramedullary or medullary control of the swallowing. Guillain–Barré syndrome (GBS) and critical illness neuropathy or critical illness myopathy cause dysphagia due to an impairment of motor and sensory cranial nerve function. Disorders of swallowing muscles themselves, as they can be observed in inflammatory myositis, as well as disorders involving the neuromuscular junction, such as myasthenia gravis, finally lead to myogenic dysphagia.

Apart from the main diagnosis (e.g. acute stroke, GBS, brainstem encephalitis), comorbidities also play a key role in this context. A wide range of neurodegenerative (e.g. Parkinson's disease, Alzheimer's disease), neurovascular (stroke, subcortical arteriosclerosis encephalopathy), or neuromuscular disorders (polymyositis, amyotrophic lateral sclerosis) should be mentioned here. These disorders are either associated with preexisting dysphagia or increase the likelihood of a deterioration of swallowing function during ICU treatment. Although hospitalization

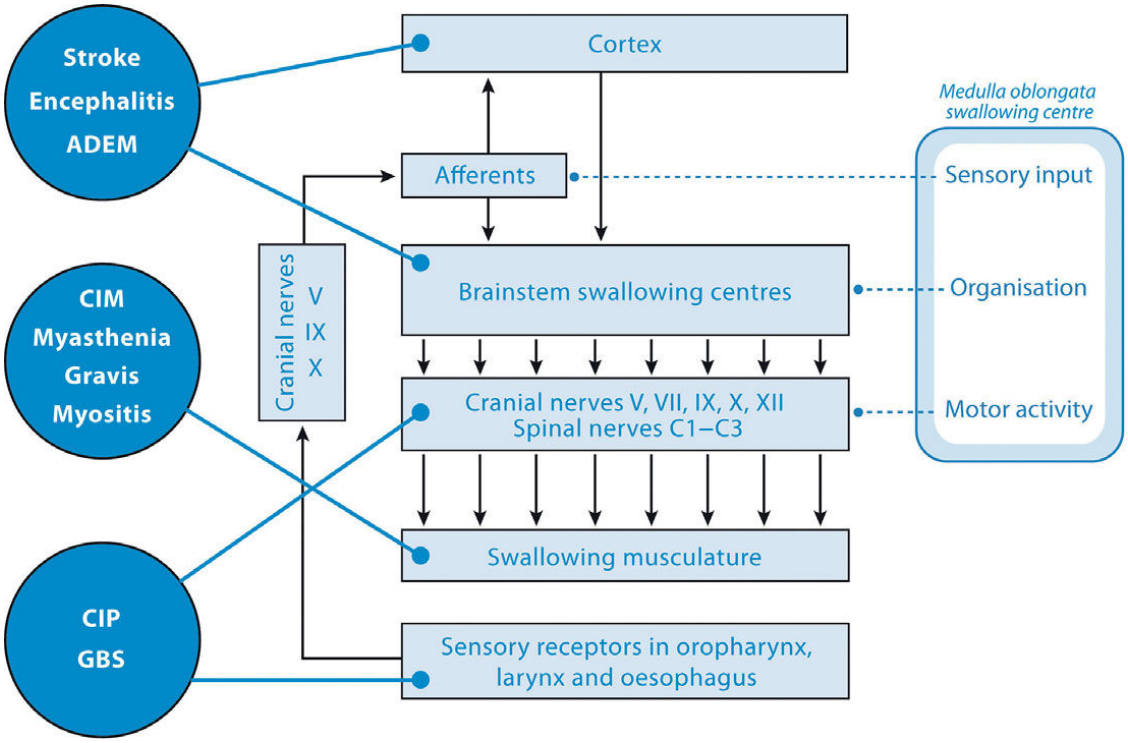


Figure 7.2 Neurological disorders that typically require treatment in the ICU and cause damage to different levels of the swallowing network. ADEM, acute disseminated encephalomyelitis; CIM, critical illness myopathy; CIP, critical illness neuropathy; GBS, Guillain–Barré syndrome. Reproduced and modified with permission from [71].

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in the ICU may be initiated because of urosepsis or myocardial infarction, for example, the further clinical course gets complicated because of decompensated dysphagia.

Dysphagia in the ICU may also be caused by the treatment itself and/or further environmental conditions. There are six pathomechanisms to differentiate as shown in Figure 7.3[4,18]. The endotracheal tube, the tracheal cannula, laryngeal masks, and nasogastric suction probes can lead to various injuries of the pharynx, larynx, or esophagus. Second, intensive care patients often develop a weakness of the swallowing muscles due to critical-illness neuropathy and myopathy. The third mechanism is the development of oropharyngeal and laryngeal sensory deficits. Among others this condition may be the result of sensory nerve damage due to critical illness neuropathy or because of local mucosal edema followed by a disruption of the sensory feedback. Fourth, qualitative and quantitative impairment of consciousness either as an effect of sedating medication or because of delirium are also involved in the development of dysphagia. Fifth, gastroesophageal reflux in critically ill patients causes insufficient supply of nutrients and is a main risk factor for aspiration. Finally, patients in the ICU often suffer from a dyssynchronization of breathing and swallowing. Both the duration of the swallowing apnea, as well as the coordination of the respiratory cycle and the moment of swallowing, may be impaired increasing the risk for aspiration.

Diagnostic Workup

Based on the result of swallowing assessment appropriate nutritional management and treatment strategies must be defined. This section describes a workflow applicable at the ICU.

Screening Tests for Aspiration

The aim of dysphagia screening in the ICU is to identify patients at risk of aspiration and, subsequently, to initiate preventive measures and to plan further diagnostic procedures. To this end, water swallowing tests are usually implemented. As a common feature of several different published protocols, the patient is asked to swallow a defined amount of water, while the investigator looks for clinical signs of aspiration (change in voice, cough, stridor)[19]. However, these tests usually do not have a sufficient sensitivity and/or specificity[20] to be propagated as a stand-alone solution. In addition, silent

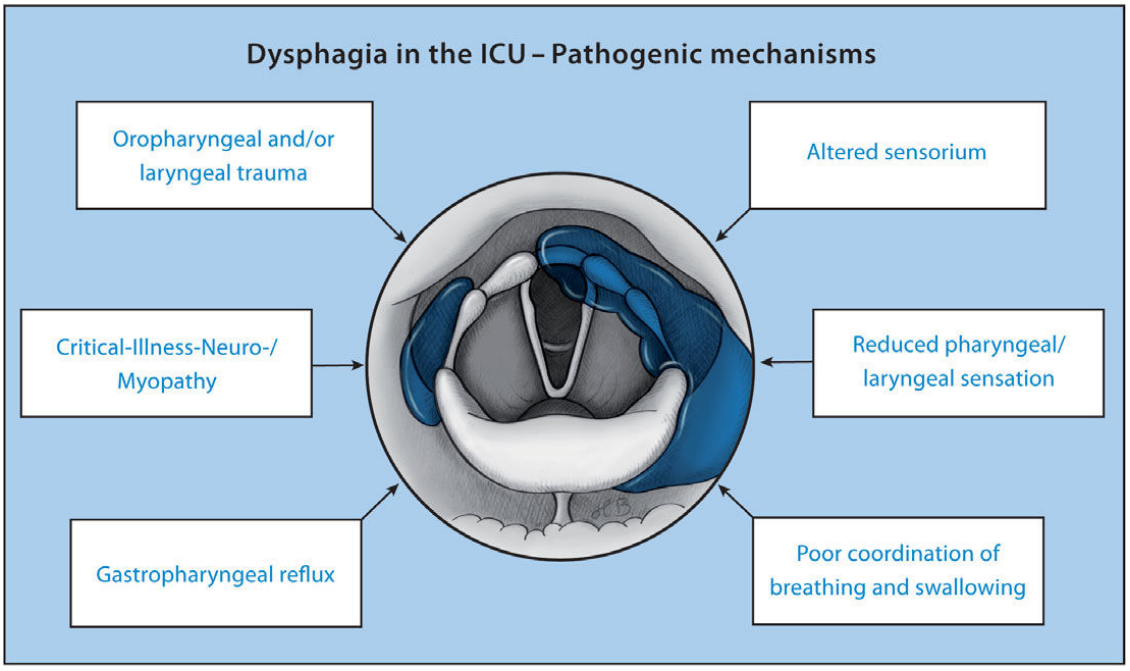


Figure 7.3 Potential pathogenic mechanisms for the development of dysphagia in the ICU. According to [72], reproduced and modified with permission from [71].

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aspiration, which is a key factor in the critically ill, cannot be detected by these tests[21].

Finally, it should be noted, that in many critically ill patients a water test is not feasible due to their clinical condition, so that in the end both the validity and the feasibility of these water tests in the ICU are significantly limited.

Clinical Swallowing Examination

The clinical swallowing examination (CSE) by an appropriately trained speech therapist is certainly the most frequently used diagnostic modality for the evaluation of dysphagia in the ICU. The CSE typically involves the examination of the oropharyngeal structures as well as swallowing tests with different consistencies[19]. Similar to the aspiration screening, the sensitivity, specificity, and reliability of the clinical swallowing examination are also questionable[22,23]. In the context of critical care, Hales et al. found in a prospective study of 25 tracheotomized ICU patients a sensitivity of only 66% for the detection of aspirations with a CSE[24]. In conclusion, the management of dysphagia in the ICU cannot be guided solely by clinical tools.

Flexible Endoscopic Evaluation of Swallowing

During the flexible endoscopic evaluation of swallowing (FEES), a flexible naso-pharyngo-laryngoscope is introduced transnasally into the pharynx for direct visualization of the swallowing act. FEES aims at (i) identifying pathological movement patterns, (ii) evaluating the effectiveness and safety of the swallow process, and (iii) recommending appropriate food consistencies as well as special diets or swallowing techniques on an individual basis. Available data indicate that FEES is a well-tolerated and safe examination. In 6000 investigations only 222 (3.7%) had to be stopped on the patient's request[25]. The most reported side effect was self-limited nosebleed being present in approximately 1% of cases. More serious events like vasovagal syncope and laryngospasms occurred in $\leq$0.05%[26–28].

Within the FEES-Registry-Study, which was performed in 23 sites in Germany and Switzerland and recruited 2401 patients, more than 50% of all FEES were done on an ICU or intermediate care unit. Mean examination time was around 10 minutes and side effects, which were all self-limited and mostly very mild, occurred in 2% of patients. In more than half of all cases, the feeding strategy needed to be adjusted after the FEES. Thus, more than 40% of patients could be given a more liberal diet, more than 15% could even be upgraded from artificial enteral nutrition to full oral intake. In more than 10% of patients FEES detected an underestimated swallowing problem resulting in a more restrictive feeding strategy. In addition, 25% of tracheotomized patients could be decannulated based on the results of FEES[29]. In a recent single-center study carried out at a neurological ICU, comparable results were reported[30]. In addition, Hafner and colleagues reported on their experience doing FEES in an ICU setting[31]. Altogether 913 FEES were performed in 553 patients over a period of 45 months at several intensive care units. Based on the result of FEES, 6.3% of the patients were tracheotomized to protect the airway, 49.7% received a feeding tube, and 13.2% a percutaneous endoscopic gastrostomy to ensure enteral feeding. In 30.7% of patients, oral diet was judged to be feasible.

Meanwhile, numerous studies have shown that FEES is equivalent to the historic gold standard, the videofluoroscopic swallow study in detecting the most important critical findings like aspiration and residues[32–35]. Apart from that FEES is also an extremely reliable method, which is underlined by an interrater consensus of over 90% in various studies[36,37]. In particular in the ICU, the essential practical advantages of FEES over a videofluoroscopic swallow study are that (i) the examination can be done at the bedside and also patients with highly restricted motor functions as well as bedridden or uncooperative patients can be examined, (ii) repeated follow-up examinations are safely possible without the issue of radiation exposure, and (iii) saliva management can be assessed directly[38,39].

The growing clinical impact of FEES is also evidenced by the fact that in different countries or scientific societies systematic educational curricula for this procedure have been issued[40–44]. While some of these are exclusively dedicated to specific professions[42–44], others are more comprehensive and multidisciplinary in nature[40,41].

Diagnostic Algorithms for the Management of Dysphagia in the ICU

In this section algorithms for the assessment of dysphagia both in nonintubated and in tracheotomized ICU patients are presented.

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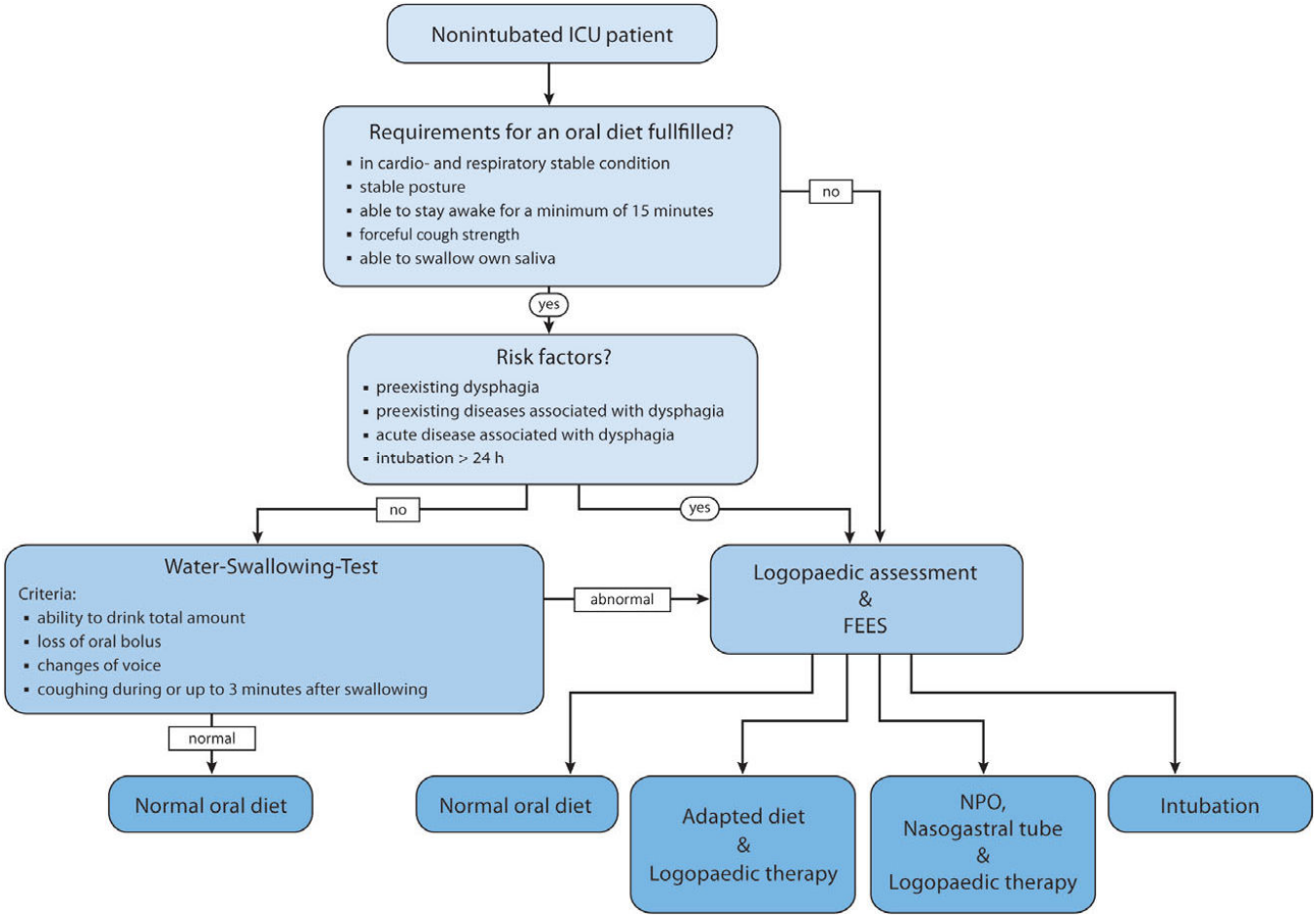


Figure 7.4 Diagnostic algorithm for the assessment of dysphagia in nonintubated ICU patients. FEES, flexible endoscopic evaluation of swallowing; NPO, nil per os. Reproduced and modified with permission from [71].

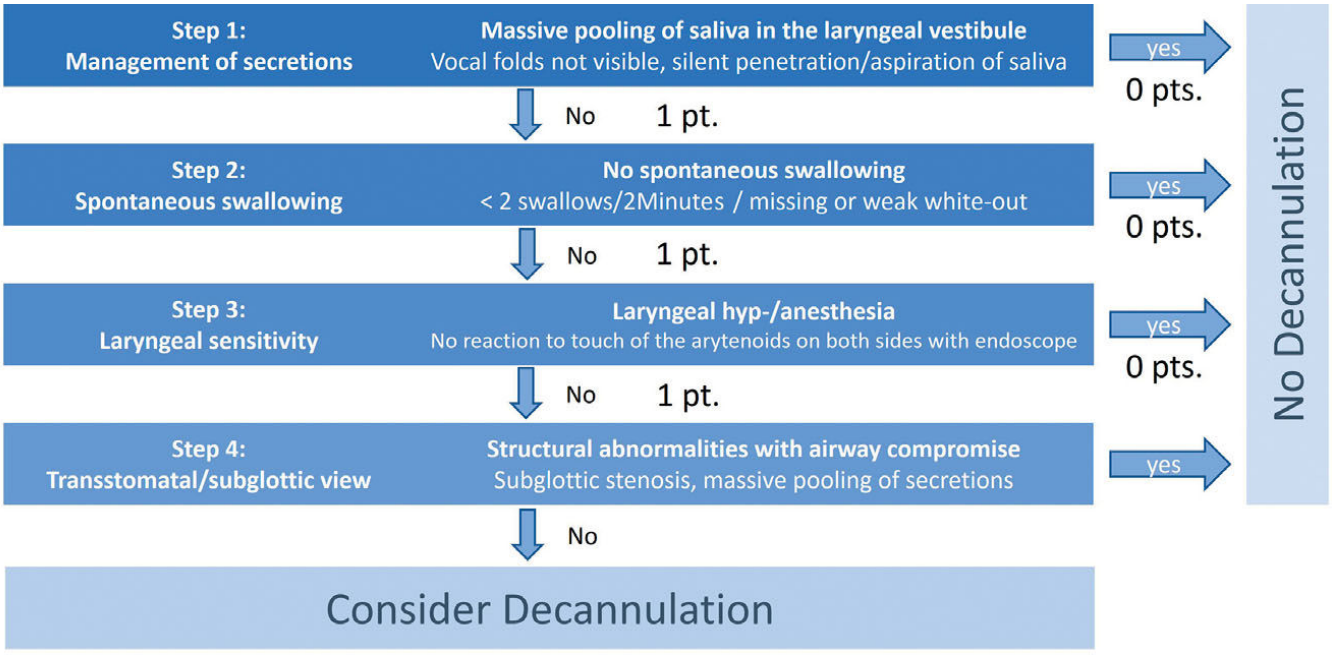
The Nonintubated Patient

In nonintubated ICU-patients dysphagia assessment provides valuable information for the selection of the appropriate diet and guides the initiation of further protective and rehabilitative measures. Although there is currently no standardized algorithm that was evaluated in prospective studies, the one proposed in Figure 7.4 considers the advantages and disadvantages of the various diagnostic modalities and implements existing knowledge to give pragmatic recommendations[17]. First, minimum basic requirements for an oral diet such as a sufficient state of vigilance and trunk stability are evaluated. Next, the risk factors for dysphagia are assessed. As mentioned in Section 7.2, apart from the patient's main diagnosis specific comorbidities need to be considered to this end. Since, as mentioned previously, dysphagia is at least in part a frequent side effect of the ICU treatment itself, the duration of intubation and artificial ventilation with a cutoff value of 24 hours is introduced as an additional criterion. In case none of these risk factors is present, for example, in a patient with an uncomplicated surgery followed by quick extubation, it is sufficient to carry out a simple aspiration screening. If this test is normal the patient may directly get an oral diet. If at any of the three steps just described indicators of dysphagia are present, a clinical swallowing examination by a speech therapist and, ideally, a FEES should be performed. With the help of these diagnostic procedures a decision whether the patient can receive a normal oral diet, requires a special consistency-adapted diet, needs tube feeding, or should be considered a candidate for intubation to secure the airway can be made.

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The Tracheotomized Patient

The tracheostomy, particularly the minimally invasive dilatational approach, is now a standard procedure in most ICUs. Therefore, in most long-term ventilated patients this airway access is used. After successful weaning from the respirator the question arises whether the removal of the tracheal cannula can be achieved. Due to the limitations of the clinical swallowing examination, assessment of the swallowing function in this context should include FEES[19]. To increase the reliability and reproducibility of the endoscopic examination, the Standardized Endoscopic Swallowing Evaluation for Tracheostomy Decannulation (SESETD) protocol has been developed and validated[45–47] (see Figure 7.5). According to this protocol, after suctioning pharyngeal and subglottic secretions and deflating the tracheal cuff, the extent and localization of salivary retentions are assessed and the spontaneous swallowing frequency is observed. To get a realistic impression of how and to what extent the patient manages the secretions, this part of the examination requires several minutes. In case there is massive pooling of saliva in the hypopharynx with concomitant penetration and aspiration, the tracheal cannula should not be removed. If there is no issue with pharyngeal secretions but the swallowing frequency is below one per minute or due to a missing whiteout a severe pharyngeal palsy is suspected, the tracheal cannula should also remain in place. However, now as well as after the subsequent steps, the cannula's cuff may be deflated intermittently to restore physiological airflow through the upper airway and thereby improve pharyngeal and laryngeal sensation[19]. The third step of the SESETD protocol consists in testing laryngeal sensibility by gently touching the aryepiglottic region with the tip of the endoscope. If there is no motor reaction to this procedure, a severe peripheral sensory disruption must be assumed and decannulation should be delayed. In case the patient coughs or swallows or shows any kind of reflexive movement, such as a laryngeal adductor reflex or pharyngeal wall contraction, the cannula may be removed for the protocol's last step, the transstomatal endoscopy. Here, the endoscope is briefly inserted through the stoma and flexed upward to visualize the subglottic structures and downward to inspect the lower trachea, in order to ensure that there are no structural abnormalities comprising the airway and precluding decannulation[48–51]. In patients also passing this step



Crit Care 2013; Warnecke et al., Neurol Res Pract 2020; Muhle et al., Neurol Res Pract 2021

Figure 7.5 Score (0–3) in Standardized Endoscopic Swallowing Evaluation for Tracheostomy Decannulation (SESETD) protocol. Modified with permission from [46,47].

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of the SESETD protocol, the tracheal cannula may be permanently removed, and the tracheostomy may be closed.

The application of this algorithm in 100 tracheotomized patients who were weaned from the ventilator on a neurological ICU allowed a safe decannulation in more than half of the patients[45]. In the further course of treatment, only one patient had to be recannulated. It was also noteworthy that the CSE, which took into account the parameters state of vigilance, cooperation skills, saliva swallowing, coughing, and amount of collected saliva from the tracheal cannula, would have allowed decannulation in only 27 patients, in two further patients the CSE underestimated dysphagia and related airway compromise and falsely suggested voted for decannulation. A second, larger prospective observational trial tested the validity of the SESETD in 377 patients[47]. Over the study period in 60% of patients the tracheal cannula was removed. Decannulation failure due to dysphagia-related complications was recorded in 3.5% of patients. In addition, the binary SESETD score was transformed into an ordinal sum score, ranging from 0 (= no item passed, most severe compromise of airway safety) to 3 (= all items passed, patient ready for decannulation). This sum score was closely related to the time and likelihood of later decannulation (Figure 7.6), which also matched the findings of an earlier study in a cohort of GBS patients[52]. Therefore, the SESETD score determined directly after successful conclusion of respiratory weaning may also be used as a predictor for the time course of dysphagia rehabilitation.

In an additional study the reliability of the SESETD was examined[46]. Experienced as well as less well-trained clinicians were able to reliably rate the single items, the resulting sum score, and the related binary decision, decannulation yes or no. With regard to the single items, the ratings of spontaneous swallowing frequency and management of secretion achieved the highest inter-rater reliability, while judging laryngeal sensibility showed the lowest levels of agreement both in the groups of experienced and inexperienced raters[46]. This study suggests that prior to introducing the SESETD in each environment, the involved clinicians should receive an appropriate training involving prototypical case presentations.

Dysphagia Therapy in the ICU

This section focuses on two options, which are particularly useful in the ICU.

The Ice-Chip Protocol

The ice-chip protocol has been proposed by Susan Langmore to assess and treat dysphagia in most severely impaired patients typically found in the ICU[53,54]. In these

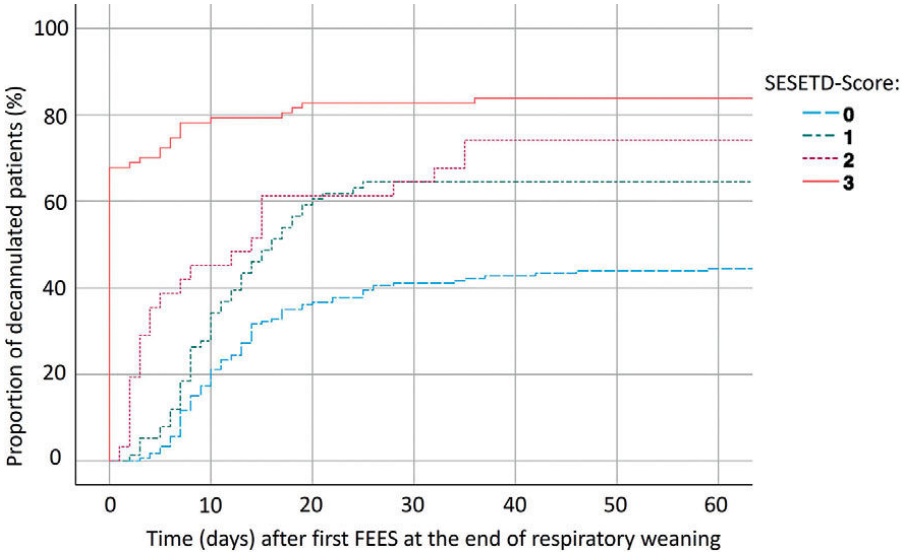


Figure 7.6 SESETD score determining decannulation during follow-up. FEES, flexible endoscopic evaluation of swallowing; SESETD, Standardized Endoscopic Swallowing Evaluation for Tracheostomy Decannulation. Modified with permission from [47].

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patients, ice chips are particularly useful because (i) the cold sensation represents a strong sensory stimulus increasing swallowing activity; (ii) due to their solid consistency ice-chips can be better controlled in the mouth than liquid boli, which more likely spill into the pharynx; (iii) they can be given in variable but defined amounts depending on the patient's swallowing abilities; and (iv) the patient is reasonably safe if aspiration occurs[55,56]. Ice chips should first be used within an FEES to assess the effect of this intervention on the swallowing frequency and pharyngeal secretions and to determine the most appropriate bolus size for the individual patient. Subsequently, ice chips can be implemented into the regular swallowing treatment. Often, ice chips are used to speed up the transition from nil-per-os to a modified oral diet[55].

Pharyngeal Electrical Stimulation

Pharyngeal electrical stimulation (PES) applies electrical stimulation to the pharyngeal mucosa via a specifically manufactured feeding tube that houses a pair of bipolar ring electrodes (Figure 7.7). One treatment cycle of PES consists of 10 minutes of stimulation given on three consecutive days. The stimulation intensity is individually adjusted for each treatment and is tailored to the patient's sensation and tolerance thresholds. Physiologically, PES has been shown to act on two levels. On the cortical level PES enhances reorganization of the swallow-related motor cortex and facilitates activation of corticobulbar pathways[57,58]. On the level of the peripheral nervous system, PES directly induces release of Substance P from the peripheral nerve endings, thereby strengthening afferent sensory input into the swallowing network[59–62].

In the clinical context, PES has been successfully adopted to treat dysphagia in tracheotomized patients. The PHAST-TRAC trial (PHAryngeal electrical Stimulation for early decannulation in TRACheotomised patients with neurogenic dysphagia after stroke) randomized stroke patients with a tracheal cannula and severe dysphagia precluding decannulation to one cycle of PES or sham stimulation[63]. While in the treatment group 50% of patients were ready for decannulation after the study intervention, spontaneous recovery of swallowing function allowing for a removal of the tracheal cannula

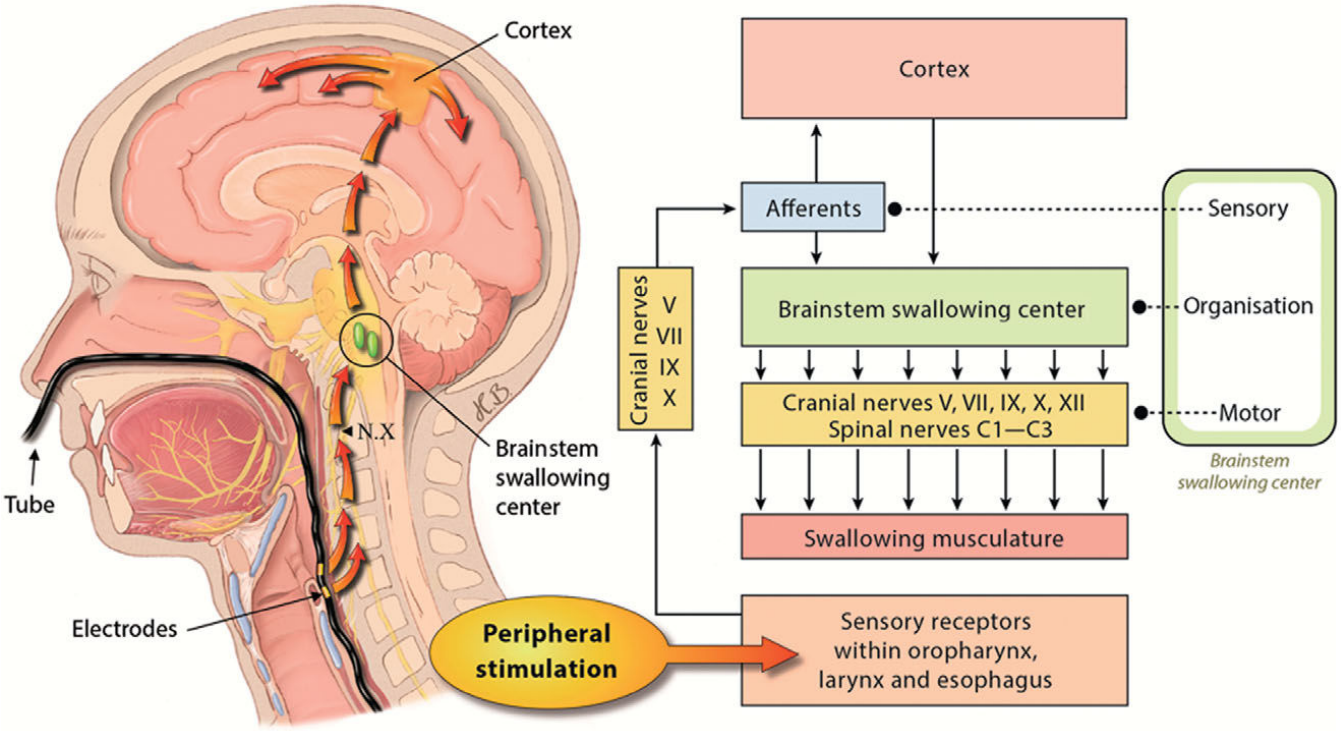


Figure 7.7 Pharyngeal electrical stimulation (PES). ©Heike Blum, Münster, reproduced with permission from [73].

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occurred only in 9% of patients. This treatment effect was in remarkable agreement with the finding of a previous single-center trial[64].

The subsequent PHADER registry (The PHAryngeal electrical stimulation for treatment of neurogenic Dysphagia European Registry), a prospective phase IV trial, documented PES treatment in 245 patients with different predefined main diagnoses[65]. Among others, stroke patients and nonneurological patients with a previous episode of mechanical ventilation were included. In all study groups dysphagia severity improved continuously across the observational period until day 92. Two thirds of the 99 tracheotomized patients included in PHADER were decannulated after treatment with PES, the majority within nine days after the first treatment had been applied. In addition to these larger trials PES has been used successfully in smaller observational trials and single cases in particular to address severe dysphagia in the ICU- or post-ICU context[66–69].

Based on these results PES is recommended in one national and one international guideline dedicated to the topic of dysphagia[19,70].

Conclusions

Failure to appreciate dysphagia is unfortunately common. Adequate diagnostic procedures should help to detect this disorder as precisely and timely as possible Different therapeutic methods are available for the treatment of dysphagia, including dietary, behavioral, pharmacological, and local interventional treatment options as well as neurostimulation procedures (for an overview see [19]).

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Chapter 8

Neurorespiratory Diagnostics

Stephan Wenninger

As has been stated before in prior chapters, The respiratory system is a complex anatomical system responsible for exchanging gases, primarily oxygen and carbon dioxide, between the body and the external environment. It consists of a number of key organs and structures that work together to facilitate breathing and to maintain the correct level of oxygen in the body.

Depending on the disease, respiratory dysfunction An important issue is how to use respiratory diagnostic tests in each of the pathologies. can occur at one or more of the following levels: central neurons including the upper motor neuron and specialized respiratory pacemaker neurons, lower motor neurons, peripheral motor nerves (phrenic nerves originating from cervical nerves C3–C5 and intercostal nerves, originating from thoracic nerves T1–T11), the neuromuscular junction, thoracic compliance including skeletal deformities, and the respiratory muscles themselves[1–3]. The diaphragm is the primary muscle of respiration, but weakness of the intercostal muscles can also contribute to a restrictive respiratory pattern.

Alteration of this finely tuned network typically causes hypercapnic and hypoxic respiratory failure with variability in degree, progression, and clinical symptoms (Figure 8.1). In contrast to lung diseases with altered perfusion and/or diffusion, it is crucial that most neurological conditions affecting ventilation are caused by an impaired breathing pattern and/or insufficient respiratory muscle pump function. This leads initially to acute, chronic, or acute-on-chronic hypercapnia and later to hypoxemia[4], which is why blood gas analysis with $PaCO_2$ measurement is so important (see Section 8.2). Thus, for an early and correct diagnosis and sufficient treatment, knowledge of the origin of hypoventilation is essential.

Any acute or chronic lesion or condition that affects the function or communication of specific central regions of respiratory control – that is, ischemic, traumatic, inflammatory, neoplastic, toxic, metabolic, endocrine, degenerative, etc. – can affect the respiratory system by altering breathing pattern and respiratory drive, leading to central breathing irregularities (see Chapters 4 and 16). Dysfunction of lower motor neurons, the peripheral motor nerves, the neuromuscular junction, and the muscle typically results in an impairment of the respiratory pump by the weakness of respiratory muscles which commonly leads to chronic hypercapnia, also called respiratory failure type 2. Moreover, weakness of bulbar muscles can cause an airway obstruction resulting in apneic periods with hypercapnia and hypoxemia. Of note, central and peripheral alterations simultaneously affect ventilation in some disorders, which highlights the need for a specific and sometimes individual diagnostic approach. Considering the impact of respiratory insufficiency on morbidity and mortality, the respiratory function must be assessed and monitored regularly (Figure 8.2)[2].

Spirometry

Spirometry is the most common, widely used, and most important pulmonary function test to detect respiratory impairment. Spirometry is a voluntary test that reflects the global respiratory system, including airway, inspiratory muscle strength, thoracic compliance, expiratory muscle strength, and the lung itself. With one assessment, several parameters are measured, most importantly the forced vital capacity (FVC), the forced expiratory volume within the first second (FEV1), and the peak expiratory flow, which is the maximum flow rate that can be achieved with forced expiration. Spirometry should be performed according to the European Respiratory Society/American Thoracic Society Statement recommendations[5] to ensure a high quality of measurement. These include at least three reproducible assessments graded "A" or "B," which requires a sufficient inhalation and a sufficient exhalation for at least six seconds. All measurements in spirometry should be documented as %predicted based on sex, age, and height. Therefore, to account for different populations, many equations have been published[6]. The lower limit of normal refers to the lower boundary of what is considered a normal value in a healthy person based on

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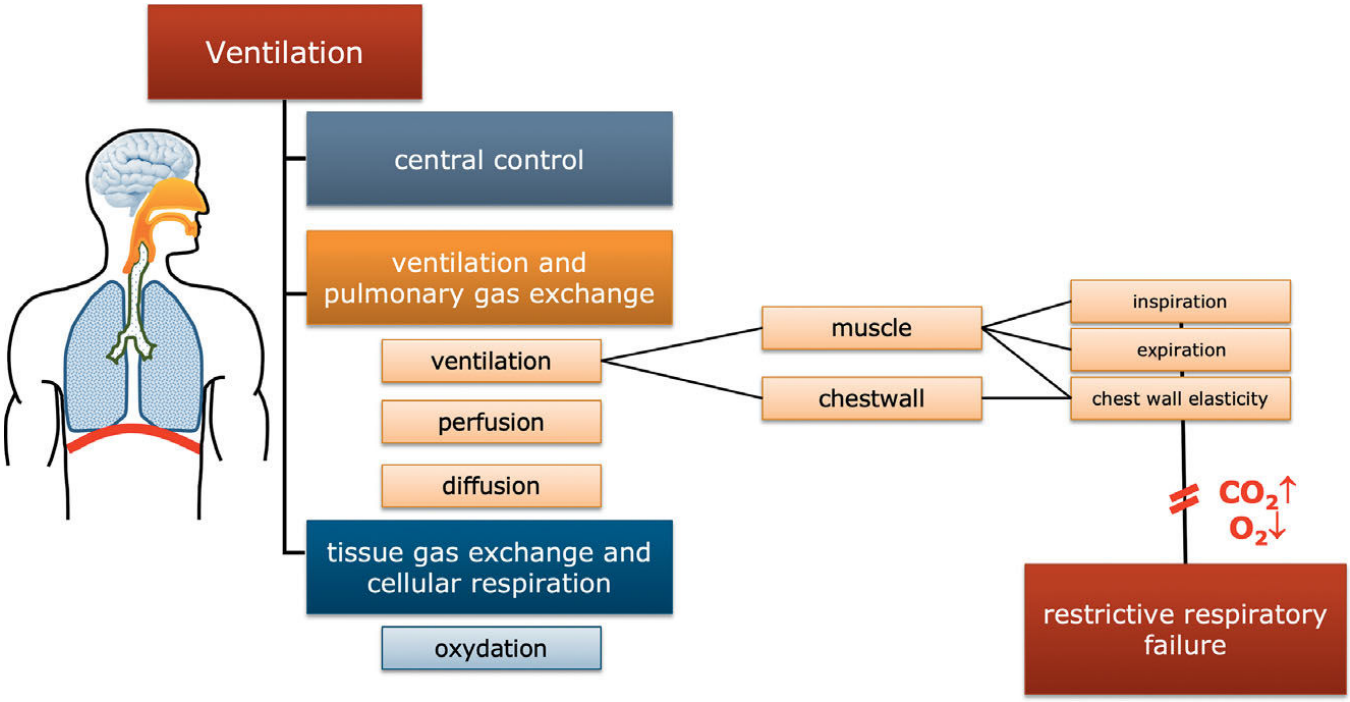


Figure 8.1 Simplified levels of respiration and sites of dysfunction.

their age, sex, and size. It is defined as the fifth percentile of a reference population.

FVC is the total amount of air exhaled during the FEV test and evaluates the capacity of the lungs regarding air volumes and respiratory flow rates. The maneuver starts with about three normal basal respiration cycles, is followed by a rapid and deep inhalation to total lung capacity, and then a maximum forced exhalation for several seconds all the way to residual volume. The volume and flow in the first second of exhalation are called FEV1 and the FEV1/FVC ratio is, according to the Tiffeneau–Pinelli index[7], useful for the diagnosis of a (possible additionally contributing) pulmonary obstruction. A restrictive condition can be suspected when FVC is reduced and FEV1/FVC is normal (>70%). There is no globally accepted cutoff for a "reduced FVC" but from a clinical point of view, values below 75% should be considered as abnormal and, consequently, regular follow-up-measurements for initiating treatment at the most ideal moment. The peak expiratory flow is measured at the beginning of expiration followed by mean expiratory flow at 75%, 50%, and 25% of the vital capacity (Figure 8.2). As spirometry can be exhausting, the slow vital capacity (SVC) can be assessed as a more comfortable measurement in patients with severe or rapid progression of respiratory failure. In healthy subjects, both FVC and SVC decline with age by an estimated −34 ml/year in men and −27.8 ml/year in women in longitudinal studies[8].

To detect weakness of inspiratory muscles by spirometry, it is recommended to accompany the routinely performed FVC in a sitting position by an FVC measurement in a supine position (FVC_{sup}). While a decline in FVC from sitting to supine position between −5% to −10% is normal, a positional drop of more than −10% indicates the first signs of muscle weakness of mainly the diaphragm but also – in a lesser degree – the external intercostals[9]. A drop of more than −20% is evident for a severe diaphragmatic weakness[9,10] (Figure 8.3b). The FVC drop is explained by the higher workload of the diaphragm when shifted cranially by the abdominal organs in supine position. This more detailed analysis of diaphragm strength is recommended for patients with neuromuscular disorders, as a decline in diaphragm strength is strongly associated with survival[11].

Expiration at rest is largely passive due to elastic recoil. For forced expiration during exercise or coughing, the sufficient contraction of mainly internal intercostal and abdominal muscles is necessary. In neuromuscular patients, measurement of the peak cough flow (PCF) is

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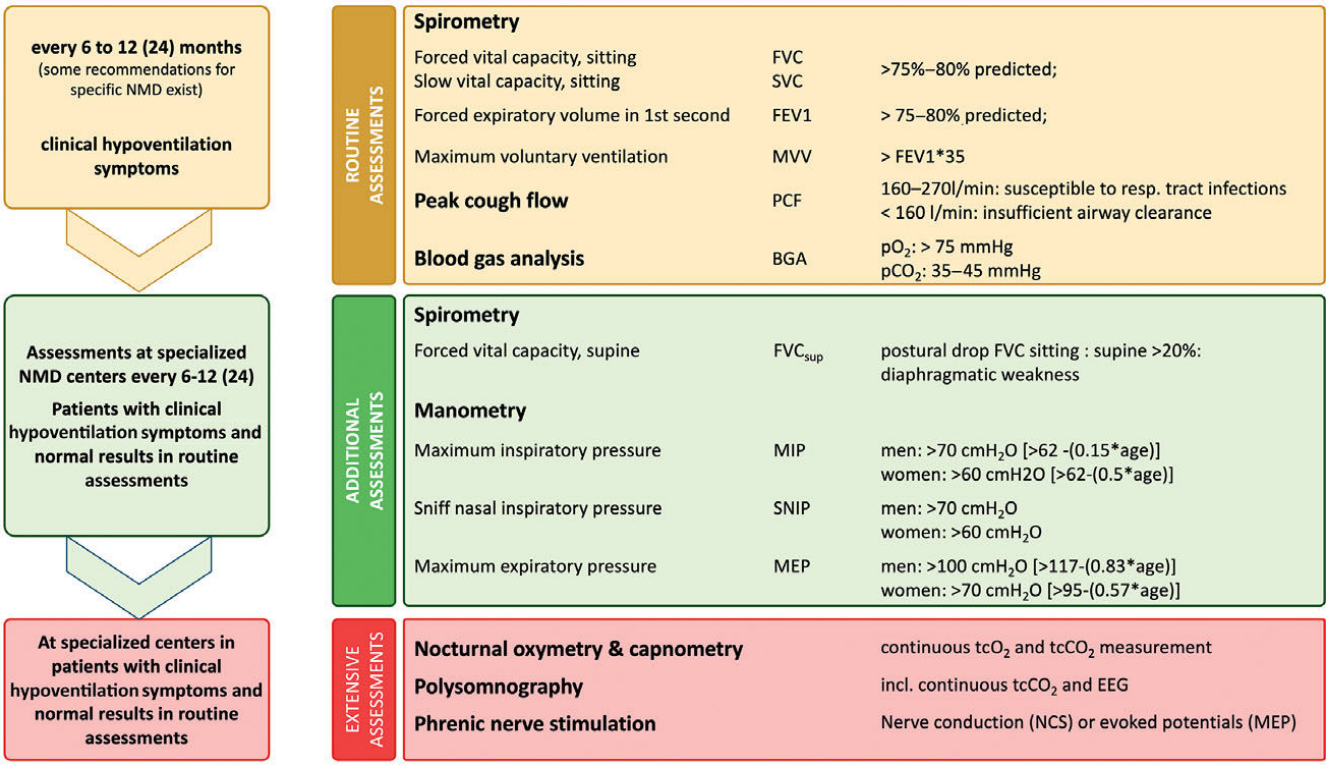


Figure 8.2 Flowchart for recommended regular respiratory assessments and normal values. MEP, maximum expiratory pressure; Reproduced from [2]. * denotes multiply cmH_2O, centimeters of water; EEG, electroencephalogram; l/min, liters per minute; mmHg, millimeters of mercury; NMD, neuromuscular disorders; PCO_2, partial pressure of carbon dioxide; pCO_2, partial pressure of oxygen; $tcCO_2$, transcutaneous carbon dioxide; tcO_2, transcutaneous oxygen.

recommended to assess expiratory muscle function and to estimate the probability of an increased risk of respiratory infections due to an insufficient airway clearance. Ability for deep inspiration of about 80% of FVC and a sufficient occlusion of the glottis are necessary for a sufficient cough. Thus, coughing ability reflects a global respiratory measurement and is reduced with poor deep inspiration, impaired forced expiration, or insufficient occlusion of the glottis. Susceptibility to respiratory tract infections is increased with a PCF of 160–270 L/min, and a PCF <160 L/min is associated with a highly increased risk of respiratory tract infections[12].

The maximal voluntary ventilation is an additional test that reflects the performance or endurance of the respiratory muscular function. It is measured by a 10-, 12-, or 15-second test of deep inspiration and expiration and is then extrapolated to one minute to determine the total respiratory volume per minute (L/min). However, for patients with limited respiratory muscular strength, this test can be strenuous and not well tolerated and may provide incorrect test results.

In summary, spirometry is a robust and widely used test that can be obtained easily in most patients, but some limitations must be considered for an accurate interpretation of the results. As spirometry is a global measurement, a decreased vital capacity is unspecific and may be caused by both inspiratory and expiratory muscle weakness, airway obstruction and restriction due to chest wall abnormalities or reduced thoracic compliance. Another limitation of spirometry is attributed to the fact that this assessment is voluntary and requires the motivation and understanding of the test procedure of the participant (e.g. Figure 8.3a). Especially in patients with respiratory muscle weakness, test results must be interpretated with care as measurements of FVC and maximal voluntary ventilation can be extremely exhausting and thus provides incorrect test results. Moreover, in patients with facial weakness, an inadequate labial seal may affect the validity of the test[13]. With conventional spirometry, neither gas exchange nor distribution of ventilation can be assessed, for example in patients with dystelectasis/atelectasis.

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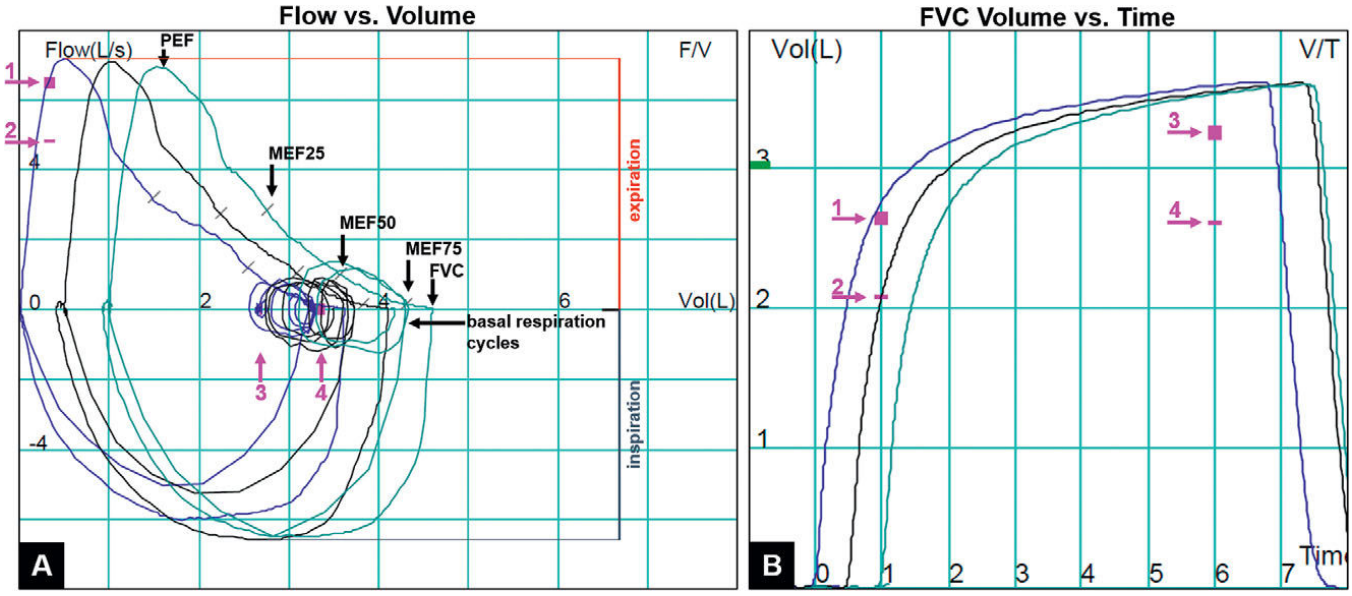


Figure 8.3 Spirometry diagram of a healthy subject. (a) flow-volume-diagram and (b) volume-time-diagram. Pink markers: 1 = FEV1 % predicted; 2 = FEV1 LLN; 3 = FVC % predicted; 4 = FVC LLN (see text for explanation). FVC, forced vital capacity; LLN, lower limit of normal; MEF25, mean expiratory flow at 25%; PEF, peak expiratory flow.

Blood Gas Analysis

In addition to spirometry and manometry, assessment of blood gas exchange is essential for monitoring and decision-making on therapy initiation in neurorespiratory diagnostics. Standard blood gas analysis reflects the function of the cardiovascular system, the relationship between cellular respiration, and the ability of the lungs and the respiratory muscle pump to supply O_2 and eliminate CO_2. In daily routine, blood draw from the arterialized earlobe (capillary blood gas analysis) is less invasive than arterial blood gas and provides same sufficient results. The most important values are PaO_2, $PaCO_2$, pH, hemoglobin, and base excess as well as routine electrolyte panel. Base excess comprises all bases with its greatest part serum bicarbonate and is an important indicator for differentiation between acute and chronic conditions. Hypercapnia is the hallmark of inadequate ventilation and reflects an insufficient respiratory muscle pump. In most neurological diseases with an impaired respiratory drive or restrictive ventilatory pattern with chronic progression, hypercapnia, and normal oxygen is a typical finding at early disease stages. This is due to the insufficient muscle pump leading to shallow breathing and inability to wash out CO_2 from venous blood, which results in the retention of carbon dioxide (hypercapnia). Physiologically, hemoglobin is responsible for the transport of oxygen from the lungs to the tissues and organs but also for the transport of carbon dioxide, produced by cells as a waste product, back to the lungs for exhalation. Hemoglobin has four binding sites of O_2 and CO_2. With increasing levels of CO_2, the binding sites are "blocked" and the ability to bind O_2 is impaired. This is explained by Dalton's Law of Partial Pressures as a fundamental principle in the field of gas physics and chemistry.

Another difficulty in properly interpreting possible respiratory weakness is that daytime $PaCO_2$ may still be normal while sleep-disordered breathing with hypercapnia is present, as hypercapnia can easily be compensated during routine daytime while sitting and standing and sleep-disordered breathing typically occurs during night time in supine position (see Section 8.2 and Figure 8.4b)[1,14–18]. At later disease stages, hypoxemia becomes apparent due to increasing shunt from rapid, shallow breathing. Associations between spirometry, manometry, and blood gases have mainly been investigated in chronic obstructive lung diseases but only rarely in neuromuscular patients. In one recent study, no association was found[19].

Manometry and Respiratory Muscle Function

Manometry of respiratory muscle strength is an important additional assessment for evaluation of pulmonary

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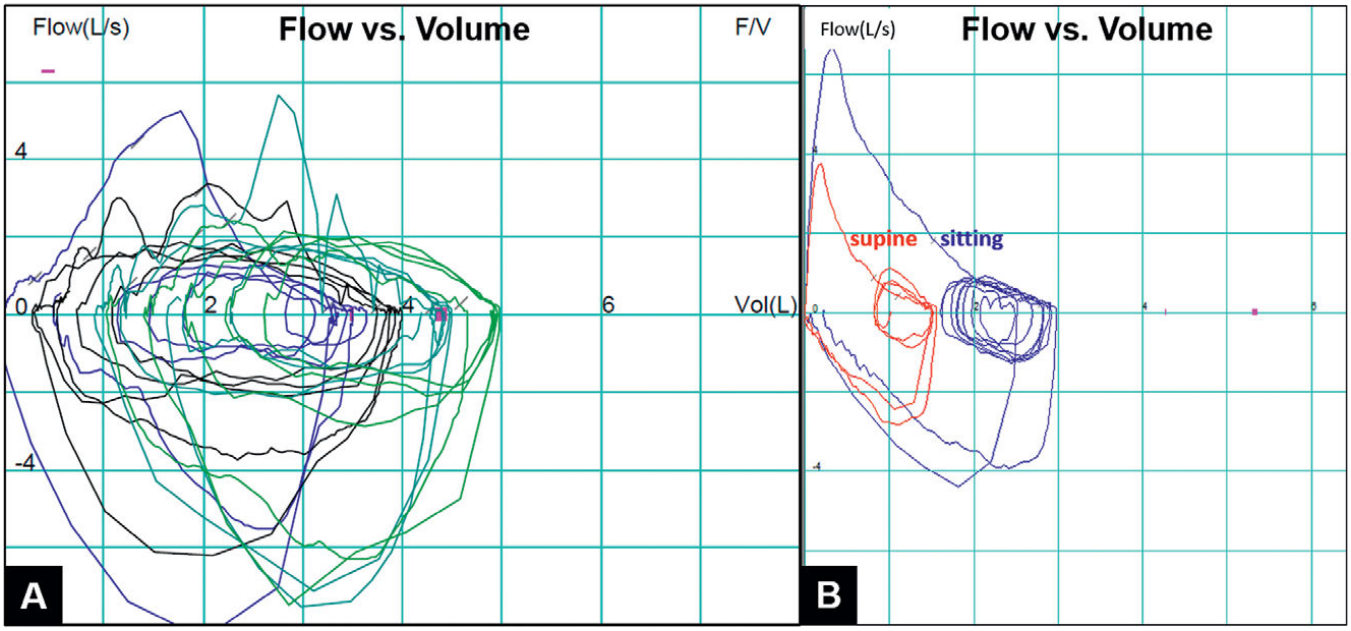


Figure 8.4 Conventional spirometry of (a) a patient with myotonic dystrophy type 1 with insufficient reproducible spirometry assessments. This patient was not able to perform reproducible inhalations and exhalations. Clinical aspects (motivation, understanding of the test procedure, and other contributing factors like coughing, anxiety, or panic during the maneuver should be documented. (b) A patient with Pompe disease with reduced FVC and a calculated significant FVC drop of −48%. FEV1/FVC ratio was normal, reflecting restrictive pattern due to a severe weakness of the diaphragm and no obstructive component. Even if the patient did not recognize clinical symptoms of hypoventilation, sleep-disordered breathing must be suspected in this patient and nocturnal oximetry and capnometry should be performed. FEV1, forced expiratory volume within the first second; FVC, forced vital capacity.

function. The combined maximum mouth closure pressure in inspiration (PI_{max}) and expiration (PE_{max}) provide robust values for the global respiratory muscle strength and are widely used because of their simplicity. They also provide an indirect measure for estimating central respiratory drive. While breathing at rest, a short sudden occlusion of the mouthpiece measures the negative pressure at 100 ms (P0.1), which reflects the respiratory effort and correlates with central respiratory drive[20–22]. P0.1 measurement can be considered as a nonvolitional test as it is typically not perceived by the patient and does not affect the respiratory cycle. Respiratory capacity is calculated independently of lung volume by $P0.1/PI_{max}$ ratio and provides an estimated value for the present workload of the respiratory muscles during inspiration[23]. If the critical limit of 20%–25% is permanently exceeded, respiratory failure due to muscle weakness is imminent. In healthy adults, normal values have been published of around 6–12 kPa. To assess disease progression, the proportion of maximal inspiratory effort required to maintain breathing at rest is measured. Normal values are <5%. Like FVC drop, the change from sitting to supine position causes an increase in the respiratory strain. A decreased PI_{max} is more specific for respiratory muscle weakness than a reduced FVC[24].

Maximum inspiratory and expiratory pressures (MIP and MEP) are easy to perform with simple handheld devices. They directly reflect respiratory muscle strength by separate measurements of inhaling or exhaling against an in-built resistance valve. Exhaling and inhaling should at least last 1.5 seconds to provide solid measurements. MIP reflects diaphragmatic strength with higher sensitivity and indicates respiratory insufficiency earlier than conventional FVC in spirometry[19,25–28]. Consequently, MIP and MEP are commonly used in clinical trials for treatment efficacy and became valid progression markers in routine diagnostics. MIP and MEP are commonly expressed as absolute values in cmH_2O or kPa, but the %predicted based on age and sex allow a more comprehensive evaluation[19,29–31]. Especially in patients with facial weakness and insufficient mouth seal, sniff nasal pressure (SNIP) is a useful method to assess inspiratory muscles strength. Using a nostril probe, the volunteer is asked to sniff or rapidly inhale for about 2 seconds. Results are comparable and correlate with MIP assessments, and moreover, SNIP may be easier and more

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intuitive to perform. A limitation refers on the measurement setting, as results highly depend on whether the contralateral nostril is open or closed during testing. SNIP with the contralateral nostril occluded results in higher values and correlates higher with MIP[13].

In conclusion, the predictive value of volitional measurements is essential for disease progression. In this context, FVC is characterized by a very good predictive power in amyotrophic lateral sclerosis regarding survival[32], whereas PCF, as well as MIP and MEP can reveal respiratory muscle weakness earlier and more sensitively than FVC[19,26]. Comparative studies between the different tests (mouth closure pressure, SNIP, MIP, FVC sitting and lying) show a very good correlation and an equivalent prognostic significance[33].

Sleep Diagnostics

In many neuromuscular disorders especially at early stages, weakness of respiratory muscles causes a slowly progressive hypercapnia at night. Clinical symptoms of nocturnal hypoventilation are unspecific and comprise morning headache, mental and physical fatigability, daytime sleepiness, concentration difficulties, depression, and more. For screening, nocturnal pulse oximetry (SpO_2) can provide important information of desaturation, but in patients with neurological diseases, nocturnal hypercapnia may evolve before hypoxemia occurs[17,18]. Of note, daytime measurement of CO_2 in blood gas analysis might be normal at early stages due to the ability of compensation during daily life activities. Therefore, polysomnography is recommended in patients with any clinical sign of hypoventilation. As a gold standard, polysomnography includes capnometry (e.g. $tcCO_2$ [continuous transcutaneous measurement of CO_2]) and an EEG to evaluate sleep stages (Chapters 6 and 19).

Imaging

Imaging in the context of respiratory diagnostics comprises chest radiography (CR), CT, MRI, and ultrasound of the diaphragm and intercostal muscles.

Conventional CR is often one of the first diagnostics in patients with respiratory symptoms and is sometimes followed by a CT scan. These imaging techniques can provide information about the shape, position, and motion of the diaphragm, the thoracic compliance in deep inspiration, skeletal deformities, obstructions of the airway, and certainly a possible contributing affection of the lung, such as inflammation or dys- and atelectasis. Movement of the diaphragm should be around 7–10 cm in healthy people, but insufficient motion of the diaphragm revealed by CR does not provide direct information on diaphragm function or predict FVC[34,35]. While unilateral diaphragm paralysis is commonly caused by traumatic lesions and sometimes by viral and rarely by bacterial infections (e.g. Lyme disease), bilateral paralysis is unspecific and is commonly caused by various antibody-mediated inflammatory neuropathies, upper or lower motor neuron lesions, neuromuscular junction diseases, or primary or secondary myopathies.

With dynamic MRI, diaphragm and intercostal muscle function and motion can be evaluated, but the prediction of respiratory impairment is still challenging. A moderate correlation between FVC and the motion of the diaphragm was found in patients with specific neuromuscular diseases[36]. Main limitations of this technique comprise costs, time, availability, and ability of the patients to remain in supine position, which is not well tolerated in patients with severe diaphragmatic weakness. Moreover, MRI examination of ventilated patients' needs to be well organized. To date, MRI remains an additional tool without the ability to replace conventional spirometry and has several limitations. Besides assessment of respiratory muscles, the amount of fatty replacement of thoracic, abdominal, and paraspinal muscles detected by muscle MRI may indicate respiratory involvement, as shown in a clinical study where fatty replacement correlated with low values of FVC % predicted in a study in patients with late-onset Pompe disease[37].

Ultrasound of the diaphragm is a fast, radiation-free, safe, and low-cost (screening) tool that can easily be performed in ambulatory patients as well as in mechanically ventilated patients. However, its usefulness depends on the specific clinical context and the goals of the evaluation. It is often used in conjunction with other diagnostic tools and clinical assessments to provide a comprehensive understanding of a patient's condition. Some experience of the examiner and efforts by the patients are usually necessary. Indications for routine assessment that is commonly combined with nerve conduction studies or electromyography comprise insufficient ventilation, paradoxical respiration, hypoventilation in supine position, and hypoventilation or dyspnea after trauma or surgical interventions. For patients with neuromuscular disorders who may develop respiratory failure and may need ventilation support, diaphragm ultrasound can help along with lung function assessments (FVC, SVC) and blood gas analysis to determine the optimal timing for initiating noninvasive

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ventilation or invasive mechanical ventilation (tracheostomy). Diaphragm weakness is reflected by abnormalities of muscle thickness, thickening while contraction, delayed orthograde excursion, and impaired motion as well as paradoxical motion[38], whereas diaphragmatic paralysis is indicated by absence of orthograde excursion on quiet and deep breathing[39]. A good correlation was found in the ratio of diaphragmatic thickness between inspiration and expiration and spiromanometry[38,40–42]. Limitations of this technique include the expertise of the assessor and the wide range of normal values. However, when performed by the same examiner, ultrasound is an easy and fast technique to determine disease progression in each patient individually. Besides diagnostics, diaphragm ultrasound can be used to monitor the function of the diaphragm in patients on mechanical ventilation, that is, in weaning patients. It can also help to assess the efficacy of ventilator settings on diaphragmatic function and guide adjustments to minimize ventilator-induced diaphragm dysfunction. Moreover, in neuromuscular patients who perform respiratory muscle training programs to improve respiratory function, diaphragm ultrasound can be used to monitor the effectiveness of such training programs[43].

Neurophysiology

Neurophysiology includes electrical or magnetic phrenic nerve stimulation as well as electromyography of the diaphragm or intercostals[44–47]. Nerve conduction studies (NCS) of the phrenic nerve and magnetic/motor evoked potentials of the diaphragm are mainly performed in specialized centers in patients with unclear respiratory impairment. The main goal is to differentiate between lesions of lower motor neurons, the phrenic nerve, the neuromuscular junction, or the muscle itself. NCS of the phrenic nerve allows differentiating between axonal and demyelinating affections and should always be performed bilaterally. As a limitation of electric stimulation of the phrenic nerve, co-stimulation of the brachial plexus results in artefacts of co-innervated muscles and lower accuracy of the diaphragmatic compound motor action potential (CMAP). The CMAP can be obtained by surface electrodes on the chest, but different protocols for the technique exist[48,49]. A reduced CMAP is suggestive of an axonal lesion of the phrenic nerve but can also evolve in advanced atrophy of the diaphragm, which can also be found in lower motor neuron diseases, prolonged mechanical ventilation, and some myopathies. Demyelinating lesions of the phrenic nerve result in a prolonged nerve conduction velocity or nerve conduction block, which results in a delayed or missing CMAP. As in axonal peripheral nerve lesions, abnormal results are not specific and can occur in acquired inflammatory and some hereditary neuropathies. An exceptionally good correlation was found between magnetic stimulation of the phrenic nerve and mouth closure pressure[50], and MIP and MEP were associated with diaphragm CMAP[38]. A decline of the CMAP was shown to predict functional decline in patients with amyotrophic lateral sclerosis[51]. Needle EMG of the intercostals and the diaphragm needs some expertise and is rather less frequently performed because of its perceived risk of causing a pneumothorax, but former studies consider this technique as safe[52]. Needle EMG is to be considered as a supplement to NCS and spiromanometry and helps to differentiate between acute and chronic myogenic and neurogenic diseases.

Conclusions

A variety of procedures is available to evaluate respiratory impairment, including imaging and electrodiagnostic assessments, but spirometry, manometry, and blood gas analysis remain the key tests.

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Chapter 9

Principles of Mechanical Ventilation and Respiratory Support

Dominic Dellweg and Robin Schlott

Let's get something straight. The most common question in neurorespiratory medicine is if the patient needs invasive or noninvasive respiratory support. To answer this question, it is necessary to recognize the pathophysiology of respiration and understand which physiological system has failed and needs to be supported. This requires a more detailed description of physiological and pathophysiological principles, the basics of which have already been outlined in Chapter 3.

Respiratory Insufficiency Type 1

The gas exchange between the alveolar gas and the blood depends on many factors[1] as illustrated in Figure 9.1.

Depending on the variables listed in Figure 9.1, CO_2 diffuses 23 times faster across the membrane than O_2[2]. For this reason, diseases affecting the alveolar-capillary unit always lead to isolated hypoxemia and not to hypercapnia (respiratory failure type 1/hypoxemic respiratory failure). The hallmarks of respiratory failure type 1 are a decrease in the partial pressures of oxygen and a decrease of the partial pressure of carbon dioxide, the latter caused by compensatory hyperventilation:

Respiratory failure type 1: $PaO_2 \Downarrow\Downarrow$ and $PaCO_2 \Downarrow$

Table 9.1 shows some examples of diseases leading to hypoxemia and their mechanisms at the level of the lung.

Respiratory Insufficiency Type 2

Whether a sufficient amount of gas per unit of time reaches the sections of the lungs involved in gas exchange is determined by minute ventilation minus dead space ventilation in the same unit of time. If alveolar ventilation falls below a critical value, CO_2 retention or type 2 respiratory failure/hypercapnic respiratory failure occurs. The hallmark of respiratory failure type 2 is an increase in the partial pressure of carbon dioxide and a decrease of the partial pressure of oxygen which is less pronounced:

Respiratory failure type 2: $PaCO_2 \Uparrow\Uparrow$ and $PaO_2 \Downarrow$

Respiratory failure type 2 is also referred to synonymously as respiratory pump failure. In essence, the respiratory muscles are overloaded due to a loss of respiratory muscular competence or an increase in the work of breathing (WOB) due to a pulmonary or extrapulmonary disease (Figure 9.2).

Table 9.2 shows some examples of diseases leading to hypercapnia and their mechanisms at the level of the lung:

It should be noted that certain diseases (e.g. chronic obstructive pulmonary disease [COPD], heart failure and pulmonary fibrosis) can cause both forms of respiratory failure, but by different mechanisms

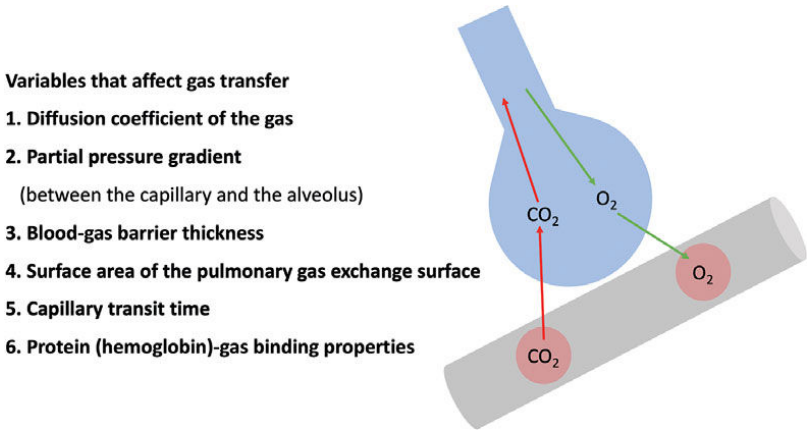


Figure 9.1 Variables that affect gas transfer over the alveolar-capillary membrane.

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Table 9.1 Mechanisms of respiratory failure type 1 in different diseases

Disease	Mechanism
Chronic obstructive pulmonary disease (emphysema, not obstruction)	Reduction of alveolar surface
Pulmonary embolism	Reduction of perfusion
Pneumonia	Perfusion/ventilation mismatch
Heart failure	Increased diffusion distance
Lung fibrosis	Reduction of alveolar surface and increased diffusion distance

Table 9.2 Disease mechanisms of respiratory failure type 2

Disease	Mechanism
Chronic obstructive pulmonary disease (obstruction, not emphysema)	Increase in airway resistance and hyperinflation
Neuromuscular diseases	Weakness of the respiratory muscles
Obesity	Extrapulmonary restriction and increased upper airway resistance
Scoliosis	Extrapulmonary restriction
Lung fibrosis	Decreased lung compliance
Heart failure	Increased airway resistance and decreased lung compliance

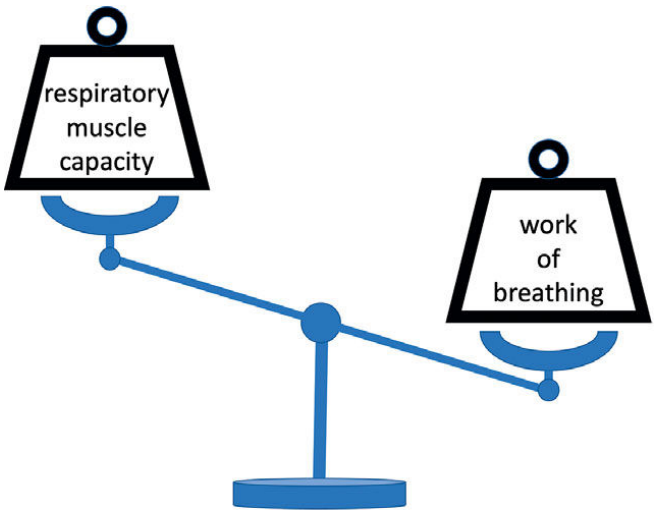


Figure 9.2 Pathophysiology of respiratory failure type 2.

respectively. Overloading of the respiratory muscles occurs when around 40% of the maximum strength of the muscles is exceeded long term. C. S. Roussos and P. T. Macklem were able to demonstrate this connection in an experiment on healthy volunteers[3] (see Figure 9.3).

This threshold value of 40% corresponds approximately to the proportion of fatigue-resistant type 1 muscle fibers in the respiratory muscles[4].

Treatment of Respiratory Failure Type 1

Critical Limits of Oxygenation

The limits of a critical oxygen supply are very heterogeneous. Cottrell and colleagues were able to show that the oxygen saturation in healthy flight attendants at cruising altitude (2430 m above sea level) was 88.6% on average[5]. In patients with chronic hypoxemia, even much lower values are tolerated through adaptation. In COPD patients, for example, a mean saturation nadir of 72.2% ± 9.1% was measured during a three-hour flight simulation in the negative pressure chamber without the occurrence of any critical incidents[6]. In the experiment, there was no correlation between the extent of hypoxemia and the subjectively perceived shortness of breath. Ultimately, oxygen saturation in the blood is only one aspect of oxygenation; the decisive factor is the oxygen supply to the end organ. The amount of oxygen present in the blood (oxygen content [CaO_2]) is calculated using the number determined by Gustav von Hüffner[7]:

$$\text{Oxygen content } (CaO_2) = \mathbf{\text{hemoglobin} \times \text{oxygen saturation} \times 1.34} + 0.003 \times PaO_2$$

The part of the equation shown in bold describes the amount of oxygen that is bound corpuscularly (to hemoglobin). This proportion makes up around 98% of the total amount, which shows that the freely dissolved part of the oxygen plays a negligible role. To calculate the amount of oxygen transported per unit of time and thus available to the organism (oxygen delivery = DO_2), the perfusion (Q), which is represented by the cardiac output (CO), must also be taken into account.

$$DO_2 = CO \times CaO_2$$

A DO_2 reduction can therefore be caused by poor blood oxygenation, anemia or a reduction in cardiac output. The critical limit of oxygen supply always seems to be the same, regardless of the cause[8]. In animal experiments, Cilley and colleagues determined the DO_2 by hypoxemia

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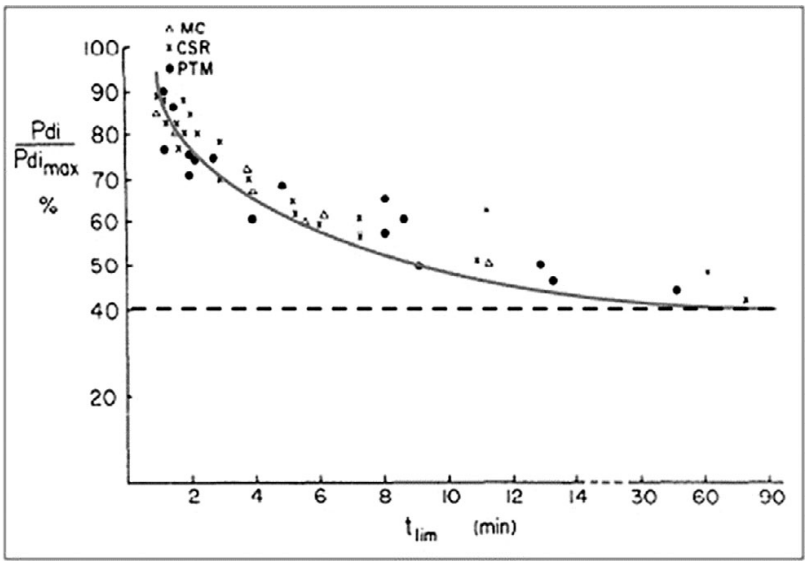


Figure 9.3 Up to 40% of the maximum inspiratory force can be managed permanently CSR, subject 1; MC, subject 3; Pdi, transdiaphragmatic pressure; Pdi_{max}, maximal transdiaphramatic pressure; PTM, subject 2. Modified reprint with permission from Roussos CS, Macklem PT. Diaphragmatic fatigue in man. *J Appl Physiol*. 1977;43:189–97.

(reduction of the amount of oxygen in the inhaled air), reduction of the cardiac output (induced by pericardial tamponade) or anemia (caused by hemodilution). The threshold at which oxygen uptake (VO_2) falls and lactate formation begins in the organism appears to be the same regardless of the cause (Figure 9.4).

From these data it can be deduced, that a halving of the cardiac output (CO) and a halving of the oxygen content (CaO_2) due to either anemia or hypoxemia is tolerated without harm by a healthy organism. While the current transfusion guidelines tolerate a reduction in hemoglobin levels of around 50%[10], there is a lack of studies that have investigated a corresponding reduction in oxygen saturation. Published studies on restrictive oxygen administration in hypoxemia are always in a range above 85% SaO_2[11,12]. The point at which intervention is required to improve tissue oxygenation depends primarily on whether comorbidities exist that additionally compromise organ-specific oxygenation, for example, coronary heart disease. In addition, the oxygen utilization of the body organs is different. Organs with high exhaustion (percentage consumption of arterial oxygen) have a lower reserve. Table 9.3 shows some guide values for the oxygen depletion of individual organs.

Noninvasive Therapies for the Treatment of Respiratory Failure Type 1

Isolated oxygen deficiency (respiratory insufficiency type 1) is rare in neuromuscular diseases and is always an expression of a complication such as secretion retention, atelectasis, pneumonia or pulmonary embolism. Treatment of the actual complication is always the main focus. However, it may be necessary to ensure the oxygen supply through adjunctive measures (oxygen administration, nasal high-flow therapy, continuous positive airway pressure [CPAP], noninvasive ventilation [NIV] or invasive ventilation). Table 9.4 shows the inspiratory oxygen fractions that can be achieved.

All these measures can improve oxygenation by increasing the inspiratory oxygen concentration (FiO_2). In addition, WOB and thus the oxygen consumption of the respiratory muscles (OCB) is reduced to varying degrees. OCB in relation to total oxygen consumption is 1%–3% in healthy people at rest[14], 10%–15% in trained athletes during exercise[15] and up to 25% in patients with pulmonary disease[16]. The actual OCB cannot be determined in everyday clinical practice, but the change in WOB due to the respective therapy is a good surrogate parameter.

In pure nasal oxygen therapy, the hypoxemic respiratory drive is removed. This results in a slight decrease in minute ventilation and WOB and a slight increase in CO_2[17]. Nasal high-flow therapy reduces the WOB significantly more, but leads to a reduction in PCO_2 due to the washout effect[17,18]. This CO_2 reduction is proportional to the set flow rate of the high-flow device[19]. NIV leads to an even greater reduction in the WOB[17]. The effect on the reduction of WOB and

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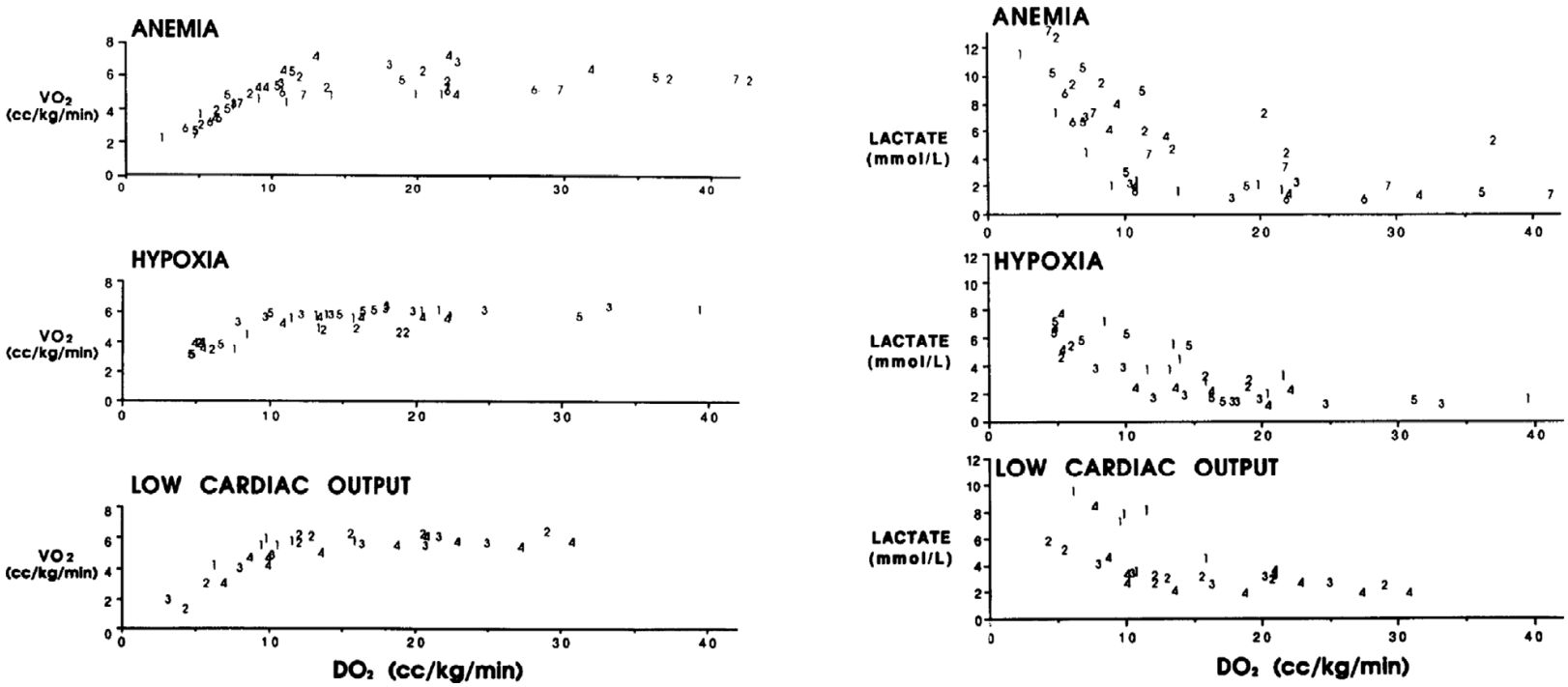


Figure 9.4 Impact of oxygen delivery (DO_2) reduction by different mechanisms on oxygen uptake (VO_2) and lactate production. Reproduced with permission from [9].

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PCO_2 depends on the level of inspiratory pressure applied[20,21]. The WOB required to trigger the ventilator in assisted mode is considerable and can be up to 43% of the total WOB depending on the setting and device[22]. This effect can be avoided by controlled NIV[23]. Asynchrony between the ventilator and the patient must be avoided at all costs, as this also increases the WOB. Table 9.5 provides a description of the common phenomena that must be avoided:

Table 9.3 Oxygen demand and utilization of different organs

	Oxygen demand (μM/min/g)	Oxygen utilization (%)
Heart	4.0	57
Kidneys	2.4	7
Liver	2.5	28
Brain	1.5	34
Skeletal muscle (at rest)	0.1	28
Skeletal muscle (at work)*	up to 8	90
Skin	0.04	4

* ensured by a corresponding increase in blood circulation.

Table 9.4 Flow rates and inspiratory oxygen fractions (FiO_2) of different oxygen supply systems[13]

Device	Oxygen flow rate (L/min)	FiO_2 (%)
Nasal cannula	1–6	24–44
Face mask	6–10	44–60
Nonrebreather face mask	15	65–90
Venturi mask	12–15	55–60
Nasal high-flow therapy	Up to 60	Up to 100

Invasive Ventilation for the Treatment of Respiratory Failure Type 1

In principle, invasive ventilation in isolated hypoxemia should be used very restrictively because, as described, there are noninvasive procedures with which high inspiratory oxygen concentrations can be achieved. In general, it should always be noted that high concentrations of oxygen are toxic to the lungs[25] and can also trigger acute respiratory distress syndrome (ARDS) in humans in the short term[26]. Strict intubation criteria are difficult to formulate and are therefore often formulated in generic terms (e.g. hypoxemia, impending respiratory failure, respiratory exhaustion). Even guidelines and reputable studies whose primary outcome is the intubation rate avoid a stringent specification and leave the decision to the clinical judgment of the treating physician[27,28]. As described previously, isolated hypoxemia can never be attributed to the underlying neuromuscular disease but has a different cause or is a consequence of the neuromuscular disease, for example, retention of secretions due to cough weakness and/or aspiration. Before intubation, the treatment options for the underlying disease or cause leading to hypoxemia must therefore always be considered. Intubation has considerable health risks, such as ventilator-induced pneumonia, which is reported to occur in up to 40% of all invasively ventilated patients[29], in industrialized countries, however, is more likely to be around 5% to 6%[30]. NIV, on the other hand, is also possible in cases of severe respiratory insufficiency with a low complication rate[31].

Intubation is usually accompanied by sedation of the patient, which may initially make the overall picture of the dyspneic patient more bearable for the care team and relatives. However, sedation often leads to a cascade of treatments and complications, such as systemic

Table 9.5 Common patient–ventilator asynchronies (adapted from [24])

Mechanism	Definition	Cause
Autotriggering	More than three rapidly delivered breaths by the ventilator above the set breathing rate	Fluttering rubber lip, water in the ventilation tube, inspiration trigger too sensitive
Double triggering	One breathing effort by the patient results in two pressure outputs on the device	Inspiration time too short, expiration trigger too sensitive
Ineffective triggering	Patient-initiated breath not responded by the device	Inspiratory trigger too insensitive
Prolonged insufflation	The pressure release on the device is too long and extends into the patient's expiratory phase	Inspiration time too long, expiration trigger too insensitive

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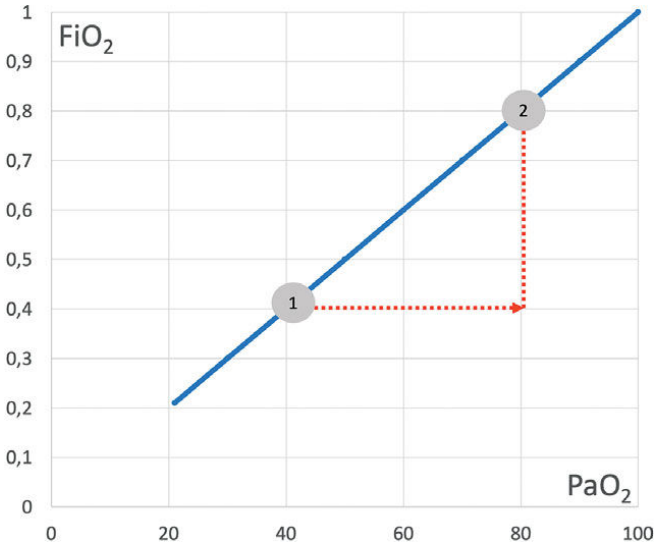


Figure 9.5 All datapoints along the blue line represent a Horowitz index of 1. The patient represented by the grey circle numbered 1 has a PaO_2 of 40 mmHg (representing hypoxemia) whereas the patient represented by the grey circle numbered 2 has a PaO_2 of 80 mmHg (no hypoxemia).

hypotension with the need to use vasopressors or the development of ICU delirium. Overall, the risk–benefit ratio must be discussed in detail with the patient or the authorized representative.

The authors of this chapter are critical of the use of the Horowitz index (PaO_2/FiO_2) as an intubation criterion, although this it is used in some guidelines[32]. The Horowitz Index is the ratio of oxygen supply (FiO_2) and the partial pressure (PaO_2, not the amount) of oxygen in the blood and only evaluates the ability to transfer oxygen. It is not a marker of oxygenation[33]. Figure 9.5 shows that the same Horowitz values can have completely different oxygen partial pressures in the blood.

Principles of Invasive and Noninvasive Mechanical Ventilation in Respiratory Failure Type 1

Expiratory Pressure

The expiratory pressure has several functions depending on the patient's underlying disease. In obstructive lung diseases, it prevents airway collapse during expiration. This reduces the intrinsic positive end-expiratory pressure (PEEP) and decreases the end-expiratory volume[34]. The intrinsic PEEP can be determined either by an occlusion maneuver in the expiratory phase or using an esophageal catheter. A correctly set PEEP increases the expiratory volume, reduces hyperinflation and successively lowers the CO_2 value.

During ventilation in ARDS, it is assumed that the cyclical closing and reopening of atelectatic lung areas and the stretching stress damages the alveolar space, the surrounding tissue and the vessels, thus exacerbating ARDS[35–37]. The decisive pathophysiological mechanism does not appear to be the absolute pressure, but rather the overstretching of the lungs[38]. According to data from the ARDS Network[39] a tidal volume of 4–8 ml/kg ideal body weight is therefore recommended. The recommended PEEP value depends on the required inspiratory fraction of oxygen and should be increased with increasing FiO_2 in accordance with the ARDS Network guidelines[39].

Some neuromuscular diseases may have cardiac involvement. In heart failure and cardiac pulmonary edema, an increase in intrathoracic pressure, whether due to inspiratory pressure or PEEP in the expiratory phase, has various mechanisms. Every intrathoracic pressure increase induced by ventilation reduces the venous return to the heart and thus reduces the preload on the right and left ventricle, but also the cardiac output[40].

Positive airway pressures assist in recruitment of alveolar units and counterbalances hydrostatic forces which otherwise could lead to pulmonary edema[41]. The afterload of the right and left ventricle is defined by the wall tension, which is calculated from the difference between the internal pressure and the ambient pressure of each system. An increase in the intrathoracic pressure due to ventilation therefore leads directly to a reduction in the afterload of both ventricles[40].

Inspiratory Pressure

Since CO_2 is not elevated in type 1 respiratory failure, inspiratory pressure is aimed solely at reducing increased WOB, dyspnea, and the oxygen cost of breathing. In animal experiments, pharmacologically induced hyperventilation can induce lung parenchymal damage[42]. In humans, this pathomechanism is referred to as patient self-inflicted lung injury (P-SILI). To avoid lung injury, excessive distension of the lung tissue should be avoided. It has already been pointed out earlier in the text that it is not the absolute pressure that is decisive for ventilation, but the resulting shear forces[38,43]. The applied driving pressure (delta inspiratory pressure minus PEEP) correlates well with the shear forces caused on the lung tissue[44]. Even during spontaneous breathing, hyperventilation and

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excessive negative pleural pressures can lead to an increase in shear forces. This phenomenon can also be observed with simultaneous ventilation. Increased spontaneous breathing under ventilation has been shown to worsen lung damage in animal experiments[45]. Similar observations had already been made during ventilation with the iron lung during the polio pandemic in the middle of the last century[46]. In general, a lack of diaphragmatic activity during ventilation quickly leads to ventilator-induced damage[47]. In situations where there is a conflict between diaphragm protection and lung protection, the latter must be periodized, as the potential lung damage is often irreversible[48].

The respiratory rate, the tidal volume, the absolute inspiratory respiratory muscle pressure (Pmus), the inspiratory occlusion pressure after 0.1 seconds (P01) and the pressure curve in the esophageal catheter serve as markers of an increased respiratory drive and thus an increase in the shear forces on the lung parenchyma[49]. It must be taken into account whether the resulting positive pressure (during ventilation) or negative pressure (during spontaneous breathing) can also exert shear forces on the lung tissue. Extrathoracic restriction prevents lung overstretching and thus protects against lung damage[38]. However, if the cause of the restriction is in the lung tissue, such as in pulmonary fibrosis, this does not appear to have a protective effect[50].

Critically, it should be noted that data on the P-SILI concept are derived mainly from animal studies and the concept has been questioned by a number of well-known authors[51]. Invasive mechanical ventilation to prevent P-SILI should therefore be performed in type 1 respiratory failure only if other therapies for critical hypoxemia are not sufficient or other measures to prevent critical hyperventilation are not effective.

Treatment of Respiratory Failure Type 2

Carbon dioxide is in equilibrium with bicarbonate and the pH:

$$\mathrm{pH} = 6.1 + \log_{10}\left(\frac{\left[\mathrm{HCO_3^-}\right]}{0.03 \times \mathrm{pCO_2}}\right)$$

Carbon dioxide fluctuations due to hyper- or hypoventilation can occur in seconds to minutes. Bicarbonate (HCO_3) regulation by the kidneys, on the other hand, is significantly slower and takes place over hours to days. If there is an increase in PCO_2 due to an overload of the respiratory muscles, this is automatically followed by an immediate drop in the pH. Carbon dioxide increases to over 260 mmHg[52] and pH drops down to 6.53[53] without lethal outcome have been described in the literature. In animal experiments, CO_2 values of up to 400 mmHg could even be generated without harming the animals[54].

Hypercapnic respiratory insufficiency (respiratory insufficiency type 2) is the principal problem in neuromuscular patients. It occurs when the underlying disease progresses or during an acute crisis. Such a crisis can occur, when acute illnesses compromise respiratory muscle competence or when the load on the respiratory system is increased by an acute illness. The capacity of the respiratory muscles can be acutely impaired, for example, by certain medications (e.g. benzodiazepines or opiates), trauma affecting the bony or muscular respiratory apparatus or acute diseases (e.g. myositis) in the context of infections or autoimmune diseases. Diseases of the lung parenchyma or the pleural cavity (e.g. pneumonia or pleural effusion), but also abdominal processes, which can increase the load on the diaphragm, lead to an acute increase in load. Obesity plays a special role here, as it tends to be chronic in nature but is potentially reversible.

It is therefore important to differentiate at the onset of hypercapnia whether it is a potentially reversible and therefore temporary situation or a chronic and therefore permanent situation. This information is essential to be able to discuss the choice of medical support, the prospects of success and the long-term prognosis with the patient. In case of progression of the underlying disease, the start of ventilation will be a lifelong therapy. If invasive ventilation is inevitable, the need for permanent tracheostomy should be discussed in detail with the patient in advance.

Noninvasive Therapies for Respiratory Failure Type 2

Nasal High-Flow

While there is very good evidence for the use of high-flow therapy in acute[55] and chronically adapted hypercapnia[56] in pulmonary diseases, there are few data available for its use in neuromuscular diseases. In a neuromuscular collective with chronic hypercapnia, nasal high-flow was clearly inferior to conventional NIV with regard to normalization of the transcutaneously measured CO_2 values and the respiratory disturbance index[57]. There are no data available on acute hypercapnia and current

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guidelines therefore do not make any positive recommendations in this regard[58].

CPAP

By definition, CPAP is not active ventilation. It shifts the WOB from the inspiratory to the expiratory muscles but does not produce a net reduction in the WOB. CPAP is helpful in certain forms of hypoxemia (see respiratory failure type 1). The only entity in which CPAP reduces WOB is upper airway obstruction in sleep apnea, obesity or neuromuscular disease with bulbar involvement.

Noninvasive Ventilation

The evidence base for the use of NIV in chronic hypercapnia in neuromuscular patients is broad. This applies both to slowly progressive[59,60] as well as for rapidly progressive neuromuscular diseases[61–63]. The same applies to acute respiratory failure type 2, where invasive ventilation can often be avoided by the use of NIV[64–66].

NIV aims to reduce the WOB and unloads the respiratory pump. Important principles on this issue have already been described for respiratory insufficiency type 1. Here, the driving pressure (inspiratory pressure minus expiratory pressure) determines the degree of support for the inspiratory muscles. The driving pressure correlates well with the reduction in WOB[20]. Due to the high compliance of the thorax and lungs neuromuscular patients without concomitant obesity or thoracic restriction can be managed with lower ventilation pressures than patients with obstructive airway diseases, who usually require high-intensity NIV[21].

The expiratory pressure can usually be kept low in the absence of additional obstructive airway disease unless there is additional obstructive sleep apnea. In this case, the expiratory pressure should be set at values keeping the upper airway is always unobstructed, so that the respirator can detect the patient's respiratory effort during assisted NIV. Nevertheless, in patients with severe bulbar dysfunction, the NIV failure rate is high.

Nocturnal hypoventilation varies with the stage of sleep and body position. To homogeneously normalize breathing during sleep, variable ventilation modes have therefore been developed that aim to keep minute ventilation constant while regulating the inspiratory pressure within a preselected range. Studies on these modes show inconsistent results. Three studies showed a reduction in the transcutaneously determined CO_2 values during the night when using such a mode compared to a conventionally adjusted NIV[67–69]. Crisafulli and colleagues, however, found only an improvement in sleep quality with unchanged CO_2 levels[70]. It must be mentioned as a limitation that none of the four studies mentioned was carried out on neuromuscular patients. Regarding synchrony between the patient and the respirator, the rules provided in Table 9.5 apply.

NIV can also be performed on awake patients in the form of a mouthpiece ventilation[71–73]. Patients with effective mouth closure can use mouthpiece ventilation at daytime without mouth seal. At nighttime, a mouth seal on the mouthpiece prevents a pressure drop in ventilatory circuit.

Invasive Ventilation for Respiratory Failure Type 2

Invasive mechanical ventilation is always indicated during cardiorespiratory arrest. Otherwise, invasive ventilation is indicated for respiratory failure type 2 only if NIV cannot be performed or fails. The aim of invasive ventilation is to normalize blood gases and reduce symptoms. The most frequent symptom here is dyspnea. The principles of ventilation settings do not differ significantly from NIV. A possible concomitant obstruction of the upper airway is effectively treated by the artificial airway (endotracheal tube or tracheal cannula). In the absence of additional lung or airway disease, the expiratory pressure (PEEP) can be set low. The respiratory rate and the inspiratory pressure, which determines the tidal volume depending on overall compliance, enable sufficient minute ventilation and should correspond to the patient's subjective needs. In the absence of an additional restrictive condition (obesity, thoracic restriction or restriction due to lung disease), overall compliance is usually high and does not require high inspiratory pressures. However, thoracic compliance may decrease with the duration of the disease[74], which requires an adjustment of the ventilator settings. Neuromuscular patients have a weakness of the respiratory muscles due to degeneration of the supplying motor neurons or involution of the muscle itself. The electrical activity of the respiratory muscle or the strength of the respiratory muscles can therefore not be taken as a surrogate parameter for the respiratory drive. The negative inspiratory pressure 100 milliseconds (P01) after the start of inspiration, which is generally used as a marker of relative performance and/or respiratory drive of the respiratory muscles[75] is no reliable marker in neuromuscular patients[76]. Imaging methods for assessing the

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respiratory drive at the cerebral level are currently being developed[77]. However, corresponding studies in humans, in particular in neuromuscular patients are not yet available. The patient's spontaneous breathing pattern can provide information about the strain on the respiratory muscles and the respiratory drive. Rapid and shallow breathing always occurs when respiratory muscle overload occurs[78] and is a strategy that reduces the WOB[79]. Neuromuscular patients who tend to have a high respiratory drive experience only a sufficient reduction in respiratory drive with mild hyperventilation. Respiratory alkalosis can generally be accepted, as there is no evidence of any harmful effects by hypocarbia. The lowest acceptable $PaCO_2$ is therefore the subject of debate.

Both NIV[80] and invasive ventilation[81] can be either volume- or pressure-controlled. With volume-controlled ventilation the upper bound pressure alarm and with pressure-controlled ventilation the lower bound volume alarm are of major importance, since barotrauma and hypoventilation are the most life-threatening complications. With regard to the ability to speak under invasive ventilation with a cuffless cannula, fenestrated cannula or unblocked cuff, pressure-controlled ventilation appears to have advantages over volume-controlled ventilation[81]. In the invasively ventilated patient, it may be necessary to use higher PEEP and preset inspiratory pressure (Pinsp) and to deactivate alarms to optimize the motivation and ability to speak and the possibility to be understood. In this situation the patient must continuously be under supervision by qualified personnel.

Weaning and Extubation in Neuromuscular Patients

Weaning is a complex process in which the aim is to improve the capacity of the respiratory muscles and reduce the respiratory muscle load until a load/capacity ratio is achieved that allows continuous spontaneous breathing (see Figure 9.3). In principle, discontinuous weaning is superior to continuous weaning and should also be preferred for neuromuscular patients[82], even if comparative studies in neuromuscular patients are lacking[83]. The peak cough flow is of crucial importance after extubation, as peak cough flow values below 160 L/min are associated with poorer outcome[84]. In general, NIV and mechanical cough support should be started immediately after extubation in high-risk patients[85].

Practical Aspects of Mechanical Ventilation

Masks for Noninvasive Ventilation

Physical Properties

Physically speaking, masks are comparable to a hovercraft that hovers over the facial skin of the patient. The mask is pulled toward the face by a strap system. The force of those straps must exceed the liftoff forces slightly so that the contact pressure on the skin exceeds the pressure within the mask corpus in order to achieve airtight sealing. The strap system generates a constant force, while the liftoff forces depend on the respiratory cycle. Lift forces decrease while the respirator applies the lower expiratory pressures, thus, skin contact pressure will be higher during expiration as shown by Figure 9.6[86].

The principles described here are important to prevent skin breakdown since the contact pressure in combination with shear forces are the major cause of skin injury (Figure 9.7). Contact pressure can be lowered by decreasing the delta pressure (inspiratory minus expiratory pressure) and by using masks with a larger contact surface or smaller mask corpus area[86].

Types of Masks

Different types of masks are available for noninvasive ventilation. Their specific advantages and disadvantages are as follows:

1. *Nasal mask*: This type of mask is comfortable for the patient and allows speaking during the treatment. Skin contact pressures are lower due to the lower mask corpus area. Nasal masks have the risk of mouth leakages especially with higher inspiratory pressures. However, significant proportion of patients will achieve sufficient mouth closure even when previously used to mouth breathing[87].
2. *Nasal prong masks*: These masks have plugs (prongs) that cover the nostrils. They have comparable characteristics to the classical nasal masks but have worse sealing properties and will not seal properly when higher pressures are being applied.

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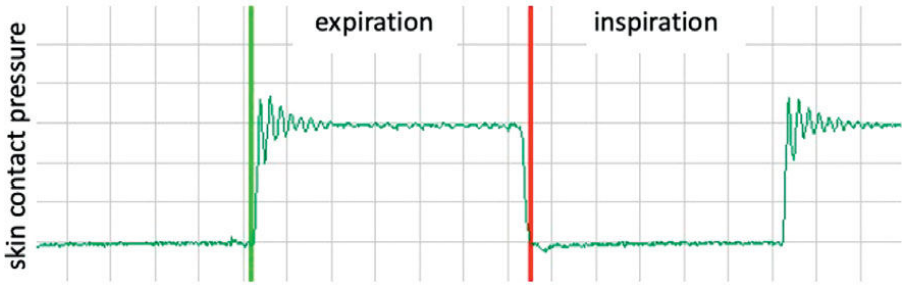


Figure 9.6 Skin contact pressure depending on respiratory cycle[86].



Figure 9.7 Skin lesion due to mask ventilation.

3. *Full face masks*: These are less comfortable for the patient and make communication more difficult but prevent mouth leakage. They usually have higher skin contact pressures with an increased risk for skin breakdown especially on the bridge of the nose, where shear forces are particularly high.
4. *Total face masks*: They lie on the outer edge of the face from the forehead down to the chin. The patient's eyes are within the mask corpus, which sometimes causes discomfort. This type of mask is usually used when skin breakdown has occurred during the use of nasal or full face masks or other forms of masks are not tolerated.

Vented versus Nonvented Masks

The CO_2 enriched exhaled air must leave the ventilator circuit in order to prevent CO_2 rebreathing. This can be accomplished either by using a nonvented mask with an expiration valve in the ventilator circuit close to the patient or by using a vented mask with an intentional leak. Vented masks require positive expiratory pressure to prevent CO_2 rebreathing into the ventilator hose while nonvented masks with a ventilator controlled expiratory valve allow for zero PEEP.

Inspired Oxygen Fraction (FiO_2) during Noninvasive Ventilation

ICU ventilators are in most cases driven by air and pure oxygen, both from the pressure connection from the ICU wall, and have a mixer (blender) enabling them to deliver pure oxygen (100%). When low pressure oxygen is supplemented into non-ICU (home) ventilators, the loss of oxygen depends on the type of mask in use (Figure 9.8). Nonvented masks have no loss of air during inspiration while vented masks will have a substantial loss (more than 50%) of pressurized air, which is proportional to the applied pressure and thus will be higher during the higher inspiratory pressures. Consequently, in case of hypoxemia, it might be useful to use a nonvented system to guarantee higher FiO_2 levels. Additionally, in non-ICU (home) ventilators the oxygen flow is constant, but minute ventilation may vary considerably. Therefore, the concentration of oxygen in the air inspired by the patient is lower in higher minute ventilation and higher in lower minute ventilation.

Complications of Noninvasive Ventilation

Barotrauma: Pressure related injury to the pleural surface (barotrauma) can cause the development of a

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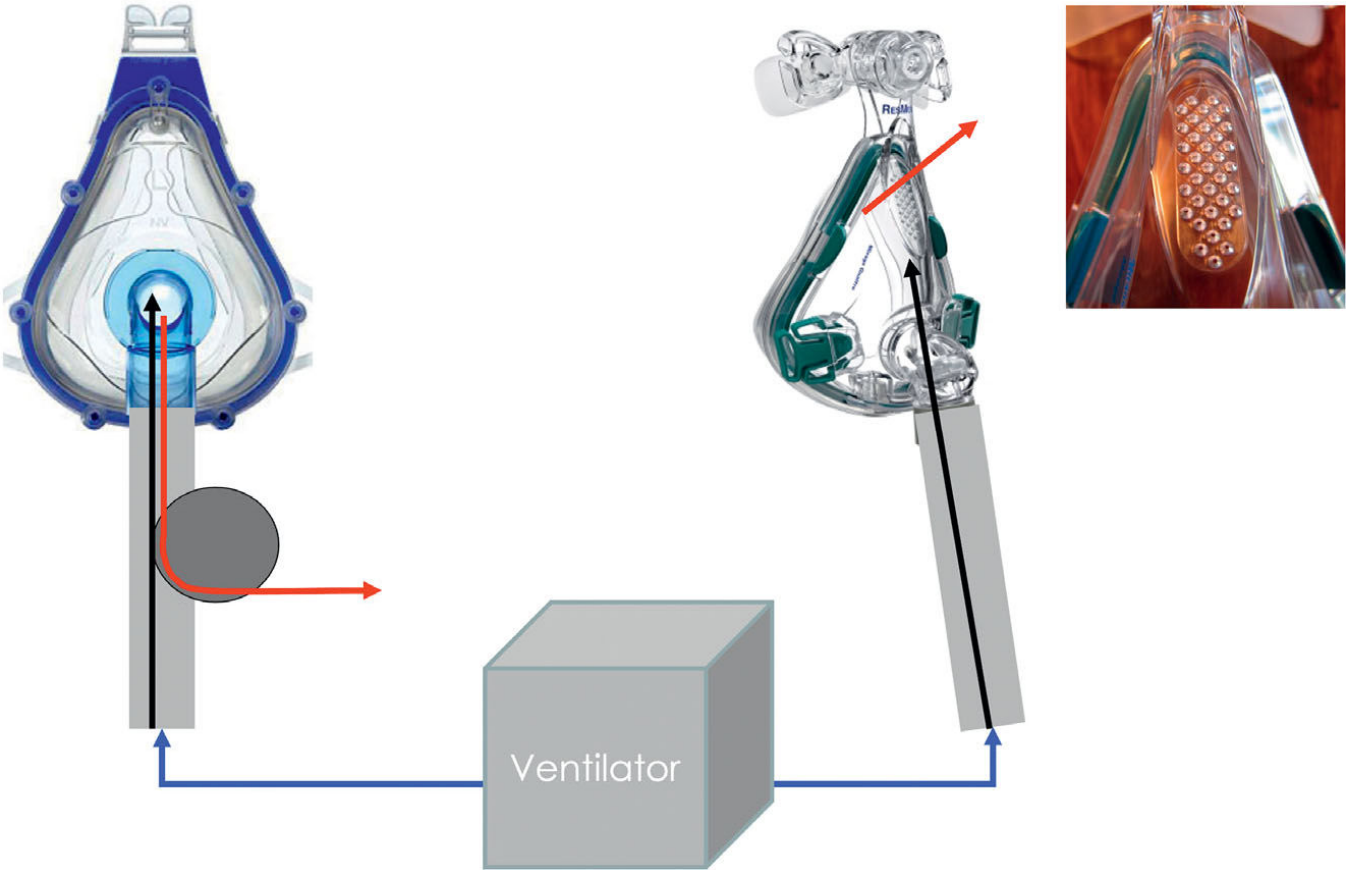


Figure 9.8 Nonvented (left) and vented mask (right) with their specific exhalation circuits.

pneumothorax[88]. This entity is rare, but the risk increases when the compliance of the respiratory system is compromised as in mucus plugging.

Aerophagia: The pressure delivered by the respirator is forwarded into the larynx where the entry of the trachea and the entry of the esophagus are in proximity. If the ventilator pressure exceeds the closing pressure of the upper esophagus sphincter, air will enter the gastrointestinal system. This problem is reported in up to 50% of patients[89]. This has several implications. It is uncomfortable for the patient who might recognize gastric or abdominal distension and the need to get rid of the air through the upper or lower gastrointestinal tract. Caution is warranted especially in patients with gastrointestinal disease to prevent ileus. Secondary gastric/abdominal distension will lower the compliance of the respiratory system, which compromises ventilation quality.

This complication can be prevented by using lower ventilator pressures. In severe cases where NIV is considered lifesaving, a nasogastric tube can be inserted to drain excessive air. In patients who have already a PEG tube, air can be drained through this device.

Skin breakdown: Pressure and shear forces can cause trauma to the underlying skin. This problem has already been discussed previously in the mask section.

Claustrophobia: Patients may perceive fear or panic when the nose and/or mouth are being covered with a mask and air/pressure is being delivered through the system. This might cause failure of a potentially lifesaving therapy. The incidence is reported as high as up to 20%[89]. To prevent claustrophobia, it is recommended to explain the goal of the therapy and to provide a precise visual description of what will happen during NIV initiation to the patient in advance. It might be helpful to place the mask on the uncovered forearm or palm of the patient while the ventilator is working to provide information about the skin contact and ventilator pressures. The continuous presence and support of the therapist, nurse or

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doctor at the start of therapy are essential to prevent failure. Anxiolytic medications (benzodiazepines) or opioids can be helpful in the treatment of anxiety and claustrophobia but might compromise the respiratory drive.

Aspiration pneumonia: The risk of aspiration of gastric content is increased while the mouth is covered with a mask and positive pressure is being delivered to the patient's larynx. The incidence is as high as 5% and increases with higher inspiratory pressures[89]. To minimize the risk of aspiration, the patient should be positioned in an upright position, meals should be given in small portions and ventilation should not be instituted directly thereafter.

Hypotension: As mentioned already in this chapter, ventilator pressures will increase intrathoracic pressures and might compromise venous return. This might result in a reduction of cardiac output and a drop in blood pressure. This might be aggravated by coexisting diseases such as cardiac arrythmias or coronary artery disease. Besides patient selection it is recommended to screen the hydration status and to apply infusions or reduce diuretics, if necessary.

Modes of Ventilation

In general, a distinction must be made between volume- or pressure-controlled and assisted versus controlled ventilation. The ventilator cycle can be separated into three phases from a technical point of view. During the initiation phase, inspiration is triggered by the patient according to a preselected trigger setting, or it is initiated by the ventilator according to a preselected respiratory rate. During the inspiratory phase a set pressure or volume is delivered to the patient and during the expiratory phase cycling off is initiated by the patient according to a preselected expiratory trigger or by the ventilator according to a preselected time (Figure 9.9).

Volume- versus Pressure Controlled Ventilation

Volume control means that a preselected volume is delivered during inspiration. The flow rate, which must be set, and the compliance of the patient's respiratory system determine how quickly this volume will be reached. Volume- and pressure-controlled ventilation are both feasible in neuromuscular patients[80]. However, patient comfort is higher and respiratory muscle unloading is more effective with pressure-set

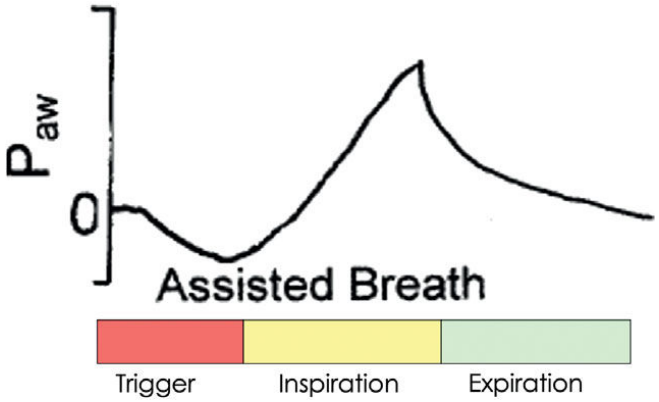


Figure 9.9 Phases of the respiratory cycle. The initiation phase is labeled as "trigger." Paw, airway pressure.

ventilation. With the volume preset high inspiratory pressures can be reached when respiratory compliance is low and with the pressure preset low volumes can be the consequence of low respiratory system compliance. This must be considered when setting the alarm limits.

Controlled versus Assisted Ventilation

Controlled ventilation means that the respirator controls the transitions of the respiratory cycles whereas assisted ventilation means that the patient is in control of the transitions. In general (and according to Figure 9.9) each respiratory cycle has two transitions, which are the initiation and termination of ventilator support, often termed as cycling on and cycling off. In controlled ventilation both transitions are controlled by the ventilator, and in assisted ventilation both transitions are controlled by the patient. Settings where only one transition is controlled by the ventilator are accordingly termed "assisted/controlled." Table 9.6 provides an overview of the most common ventilator modes for ICU ventilators and Table 9.7 accordingly for home care ventilators.

Quick Guide to the Initial Ventilator Setting

1. In awake and cooperative patients choose an assisted mode for reasons of patient comfort and therapy acceptance. However, be aware of the patient's ability to trigger the ventilator. This ability might be compromised in progressive neuromuscular disease, so that the selection of a controlled mode is required. In an assisted/controlled mode, the benefits of both assisted and controlled modes are present.

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Table 9.6 Common ventilator modes used in ICU ventilators

Assisted or controlled	Description	Label	Cycling on	Control/setup parameters	Cycling off	Special features
Controlled	Volume-controlled ventilation Volume-controlled continuous mandatory ventilation Intermittent positive pressure ventilation	VCV VC-CMV IPPV	Time cycled by preset of respiratory rate (RR)	Preset inspiratory flow determines the time needed to reach preset tidal volume	Time controlled, with reaching preset inspiratory time (Ti)	
Controlled	Pressure-controlled ventilation Pressure-controlled–continuous mandatory ventilation	PCV PC-CMV (BiPAP-CMV)	Time cycled by preset of RR	During inspiratory time a preset inspiratory pressure (Pinsp) is applied	Time controlled, with reaching preset Ti	
Controlled	Pressure-regulated volume-controlled ventilation	PRVC	Time cycled by preset of RR	The ventilator applies a constant inspiratory pressure that reaches the preselected tidal volume over the course of the inspiration phase. If resistance or compliance changes, the pressure is adjusted.	Time controlled, with reaching preset Ti	
Assisted/controlled	Assist-control ventilation Assist volume-controlled ventilation	A/C aVCV	Patient can trigger breaths if spontaneous RR is above preset RR; if RR drops below the preset rate, the ventilator operates time-cycled	The preset flow rate determines the speed at which the preset tidal volume will be reached.	Time controlled, with reaching preset Ti	
Assisted/controlled	Assist pressure-controlled ventilation	aPCV PC-AC	Patient can trigger breaths if spontaneous RR is above preset RR; if RR drops below the preset rate, the ventilator operates time-cycled	During Ti a Pinsp is delivered	Time controlled, with reaching preset Ti	
Assisted	Pressure-support ventilation; Synonym: assisted spontaneous breathing	PSV ASB	Every breath is triggered by the patient	During Ti a Pinsp is delivered	The expiratory trigger terminates the inspiration	
Assisted/controlled	Volume-controlled synchronized intermittent mandatory ventilation	VC-SIMV	Patient can trigger additional breaths between release of mandatory volume-controlled, time-cycled breaths	For mandatory breaths the preset flow determines the velocity by which the preset tidal volume is delivered. Triggered breaths will be supported by a preset pressure	Mandatory breaths are time-cycled, assisted breaths are cycled by expiratory trigger (flow-cycling)	
Assisted/controlled	Volume-controlled mandatory minute volume	VC-MMV	Patient triggers the ventilator and receives additional mandatory volume-controlled breaths when the preset minute ventilation is not achieved	The triggered breaths are supported by a preset pressure; if additional mandatory breaths are released the preset flow rate determines the velocity at which the preset tidal volume will be reached.	Mandatory breaths are time-cycled, triggered breath are cycled by expiratory trigger (flow-cycling)	If spontaneous breaths are sufficient to achieve preset minute ventilation (Vt × RR), no additional mandatory breaths will be delivered

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Table 9.6 (*cont.*)

Assisted or controlled	Description	Label	Cycling on	Control/setup parameters	Cycling off	Special features
Assisted/ controlled	Pressure-controlled synchronized intermittent mandatory ventilation	PC-SIMV	Patient can trigger additional breaths between the release of pressure-controlled, time-cycled breaths	For mandatory breaths a preset inspiratory pressure is applied during inspiratory time, triggered breaths are supported by a preset pressure.	Mandatory breaths are time-cycled, triggered breaths are cycled by expiratory trigger (flow-cycling)	
Assisted	Neurally adjusted ventilatory assist	NAVA	Trigger of inspiration by capturing the electrical signal of the diaphragm by the NAVA catheter	Delivered pressure support is proportional to the captured electrical signal of the diaphragm. Amplification ratio of signal must be selected	Expiratory trigger is set at 70% of peak Edi	
Assisted	Proportional assist ventilation Proportional pressure support	PAV PPS	Every breath is triggered by the patient	Measuring of the patient´s inspiratory effort by inspiratory flow, airway resistance and lung compliance. Application of inspiratory pressure support in proportion to the respiratory effort in which the gain factor can be manually adapted	Termination of inspiratory phase by expiratory trigger	
Assisted	Proportional assist ventilation with adjustable gain factors	PAV+	Every breath is triggered by the patient	Comparable to PAV, but with dynamic measurement of compliance and resistance	Termination of inspiratory phase by expiratory trigger	

BiPAP, bilevel positive airway pressure; Edi, electrical activity of the diaphragm.

Appropriate initial modes are S, S-T, pressure-support ventilation or assisted pressure-controlled ventilation.

2. Select an appropriate expiratory pressure. In the absence of obstructive airway and alveolar disease (e.g. lung edema) the expiratory pressure should be selected as low as possible (e.g. 5 cmH_2O or lower).
3. Too high pressure often leads to patient intolerance. Start with pressure controlled rather than with volume-controlled ventilation, because pressure-controlled ventilation allows titration of the initial pressure. Slowly titrate the pressure up until the desired CO_2 reduction is achieved or the patient does not tolerate a further pressure increase.
4. Set the inspiratory trigger as sensitive as possible. In case of autotriggering, decrease trigger sensitivity.
5. Set the expiratory trigger respectively the inspiratory time to match the neural inspiratory time of the patient. You might do so by placing your hand on the upper chest of the patient and comparing chest movements and the inspiratory cycle of the ventilator. If the patient already tries to exhale while the ventilator is still delivering the inspiratory pressure, increase the sensitivity of the expiratory trigger or decrease inspiratory time on the ventilator. If the

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Table 9.7 Common ventilator modes used in home care ventilators

Assisted or controlled	Description	Label	Cycling on	Control/setup parameters	Cycling off	Special features
Assisted	Spontaneous ventilation Pressure support ventilation	S-mode PSV	Every breath is triggered by the patient	During inspiratory time (Ti) a preset inspiratory pressure (Pinsp) is delivered	The expiratory trigger terminates the inspiration	
Assisted/ controlled	Assisted volume-controlled ventilation	aVCV	Every breath is triggered by the patient	The preset flow rate determines the speed at which the preset tidal volume will be reached.	Time controlled, with reaching preset Ti	
Assisted/ controlled	Spontaneous-timed ventilation	S-T	Patient can trigger breaths if spontaneous respiratory rate (RR) is above preset RR; if RR drops below the preset rate, the ventilator operates time-cycled	A preselected pressure is delivered between cycling on and off	The expiratory trigger terminates the spontaneous breath, for controlled breath (below preset RR) expiration starts when the preset inspiratory time (Ti) is achieved	
Assisted/ controlled	Assisted pressure-controlled ventilation	aPCV	Patient can trigger breaths if spontaneous RR is above preset RR; if RR drops below the preset rate, the ventilator operates time-cycled	A preselected pressure is delivered between cycling on and off	Time controlled, with reaching preset Ti	
Controlled	Timed ventilation	T	Time-cycled by preset of RR	A preselected pressure is delivered between cycling on and off	Time controlled, with reaching preset Ti	
Controlled	Volume-controlled ventilation	VCV	Time-cycled by preset of RR	Preset inspiratory flow determines the time needed to reach preset tidal volume	Time controlled, with reaching preset Ti	
Assisted/ controlled	Hybrid modes with assured minute ventilation	ST+V T+V AVAPS IVAPS		Inspiratory pressure varies within a preselected inspiratory pressure range in order to achieve a preselected minute ventilation		

AVAPS, average volume-assured pressure support; IVAPS, intelligent volume-assured pressure support; ST+V, spontaneous-timed mode with volume control; T+V, timed mode with volume control.

patient continues to show inspiratory effort when the ventilator has already cycled off, decrease the sensitivity of the expiratory trigger or increase inspiratory time on the ventilator.

6. Set the backup rate lower than the patient's spontaneous respiratory rate. It is therefore advisable to determine the respiratory rate before starting therapy. If the patient's respiratory rate decreases below backup frequency, controlled ventilation will be activated, which again increases respiratory muscle rest.
7. The rise time determines how fast the ventilator will build up the preselected inspiratory pressure. A low rise time (e.g. 100 milliseconds or less) is often perceived as uncomfortable unless the patient him/herself has a rapid inspiration as seen in obstructive airway disease (COPD) where patients try to minimize inspiratory time in favor of a longer expiration. A rise time of 200–300 milliseconds is a reasonable number for the initial ventilator setup in neuromuscular patients.

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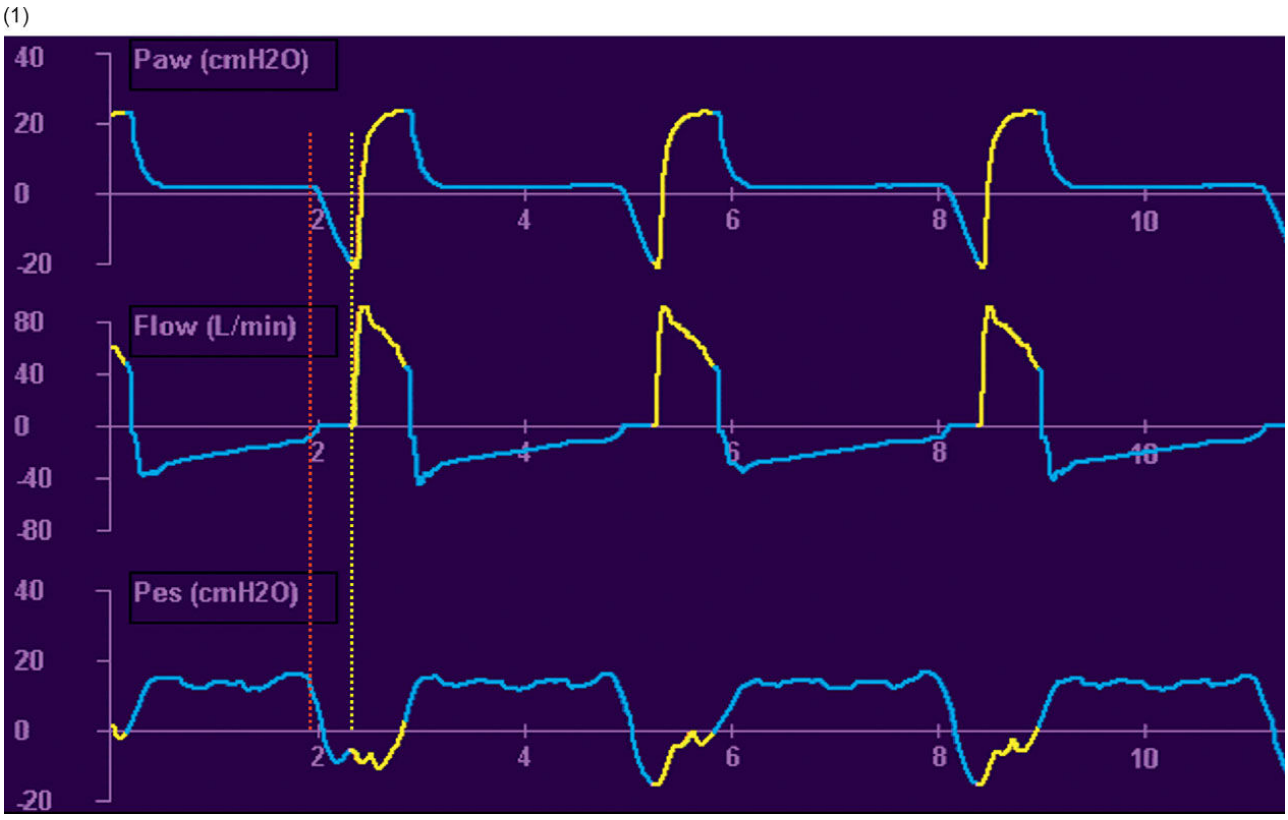


Figure 9.10 (a) shows a ventilator setting where the inspiratory trigger is set too insensitive. One can recognize a drop in the airway pressure curve (Paw) long before the ventilator detects the patient effort and cycles on. This problem can be solved by selecting a more sensitive inspiratory trigger. The results of this intervention can be seen in (b). (b) Airway pressure (Paw), ventilator flow (Flow) and esophageal pressure (Pes) are shown on the ventilator display. (1) The patient inspiratory effort starts at the dashed red line and can be recognized by the drop in Paw as well as the drop in esophageal pressure. There is a delay in ventilator response since cycling on occurs at the dashed yellow line. (2) With a more sensitive inspiratory trigger the patient effort as seen in the Paw curve of (a) is no longer detectable. Only the Pes curve detects the patient effort, which is markedly reduced when compared to (a).

8. Oxygen supply is needed only in hypoxia. Check oxygen saturation since increased minute ventilation during NIV support might lower oxygen requirements or make application of additional oxygen unnecessary.

Ventilator Graphics

Ventilator graphics are extremely helpful for the respiratory therapist, nurse or physician. They provide information on the quality of ventilation and on the patient–ventilator interaction. In ICU settings patient–ventilator asynchronies are frequently undetected with prior specific training and female gender being positive predictors of correct recognition[90]. Ventilator graphics are especially helpful to optimize cycling on and off criteria (see Figure 9.10a and 9.10b).

Ideally the inspiratory time of the ventilator (Ti) matches the neural inspiratory time of the patient. When Ti is selected too short or the expiratory trigger is set too sensitive, the ventilator will cycle off while the patient is still inhaling. This will generate air hunger on the patient's side, frequently leading to a rise in the patient's respiratory rate. In assisted modes there is also the risk for double-triggering as shown in Figure 9.11. Some ventilators can provide flow-volume curves similar to the curves used in lung function testing. These curves are especially helpful to detect problems during the expiratory phase.

In Figure 9.12a one can recognize a sudden drop in the expiratory flow, which represents airflow limitation (airway collapse) in obstructive airway disease. In Figure 9.12b this is counterbalanced by increasing the expiratory pressure (PEEP).

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(2)

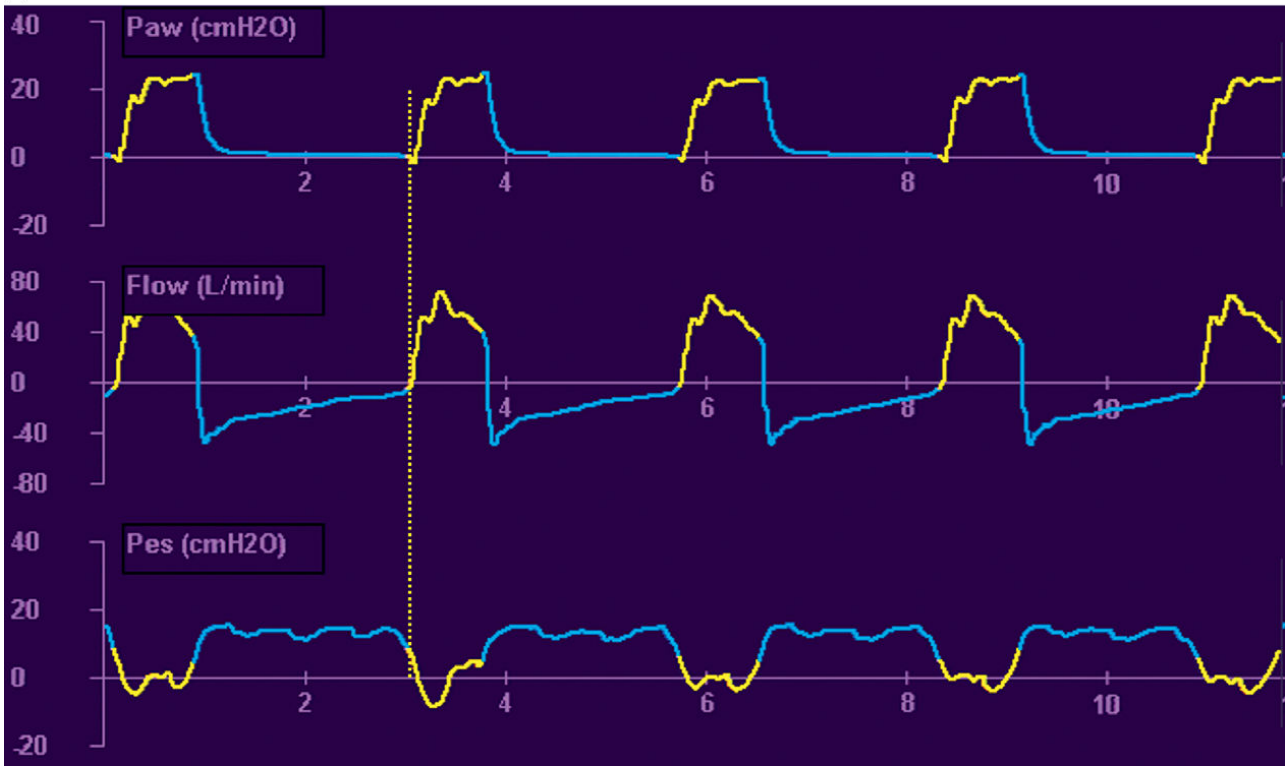


Figure 9.10 (*cont.*)

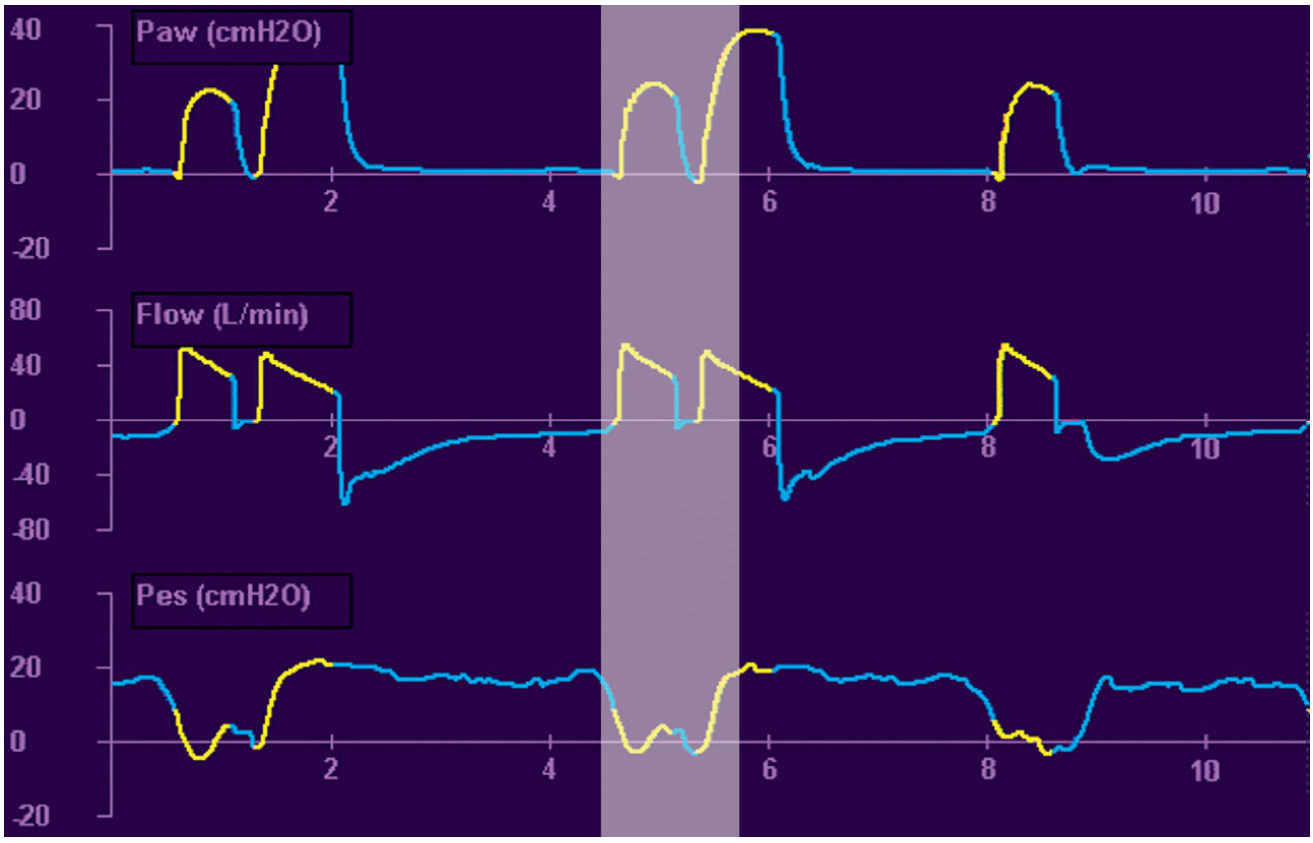


Figure 9.11 Airway pressure (Paw), ventilator flow (Flow) and esophageal pressure (Pes) are shown on the ventilator display. The Pes drop highlighted by the vertical bright bar represents the neural inspiratory time of the patient. The ventilator cycles off to early and a second ventilator cycle is being triggered within the same inspiratory time.

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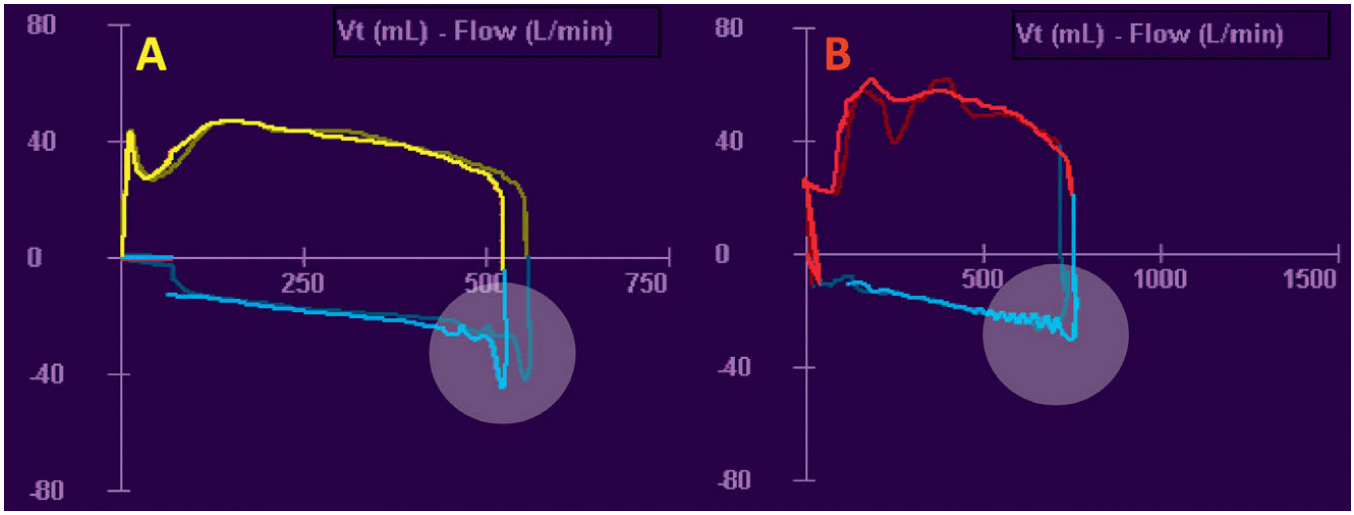


Figure 9.12 In (a) one can see a sudden drop in expiratory flow (highlighted circle) which is no longer present in (b) after the PEEP has been increased appropriately. PEEP, positive end-expiratory pressure.

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Chapter

10 Management of Secretions and Augmentation of Coughing in Diseases of the Nervous System and the Muscles

John R. Bach, David Troxell, Martin Groß and Jon Nilsestuen

Coughing, or comparable forceful expiratory airway reflexes, is probably present in all mammalian species[1]. Coughing is essential for survival as it clears secretions and foreign bodies from the central airways. The trachea divides into left and right main stem bronchi, which then divide about 26 more times[2]. From the first six divisions sputum and other debris must be expelled by coughing, manually assisted coughing, or mechanical insufflation-exsufflation (MIE). From the more peripheral divisions debris is cleared by the mucociliary elevator that moves debris towards the central airways by about 2.4 mm/min. Invasive mechanical ventilation, smoking, beta-adrenoreceptor antagonists, and glucocorticoids slow transport, which may increase risk of pneumonia[3,4].

Insufficient cough flows and aspiration of saliva are frequent problems in neurological illness and lead to tracheobronchial retention of secretions. Comorbidities like chronic obstructive pulmonary disease (COPD), certain medications, and iatrogenic failure to adequately humidify the lower airways can lead to hypersecretion, thick and tenacious secretions, and ciliary dysfunction, respectively. This can further aggravate any bronchopulmonary retention of secretions, finally leading to atelectasis, pneumonia, and respiratory failure as well as death.

Noninvasive ventilation support (NVS) is effective only if accompanied by adequate management of secretions. This chapter provides a comprehensive overview of the neuronal control, physiology, and pathophysiology of coughing, the pathophysiology of tracheobronchial retention of secretions, and effective techniques to reduce secretions and eliminate them from the airways. MIE as a particularly important method will be introduced on page 109 and discussed in depth on page 111ff.

Neuroanatomy of the Cough Reflex

The main body of knowledge about the neuroanatomy of the cough reflex is derived from animal models. Cough-related receptors are located in the extrapulmonary airways, comprising the larynx, trachea, carina, and main bronchi and to a lesser extent in other areas like the pleura and diaphragm[5]. The first sensory neurons of the cough reflex are located in the nodose and jugular vagal ganglia[6]. The vagal nerve sends afferent information to second-order neurons located in the nucleus tractus solitarii (NTS). These second-order neurons then project to the medullary ventral respiratory group and pontine nuclei involved in respiratory control. Both the caudal NTS and the caudal ventral respiratory group have been comprehensively described as key regions generating the motor pattern of the cough reflex[5]. Functional brain imaging in healthy humans demonstrates several cortical regions involved in the perception, facilitation, and suppression of coughing[7,8].

Physiological Coughing

An intact central reflex pathway as well as normal function of inspiratory and expiratory muscles and glottis are essential for an effective cough. The cough reflex is differentiated from the expiratory reflex, a forced expiratory effort without preceding inspiration or closure of the glottis[9]. The cough reflex is divided into three phases: The inspiratory phase comprises abduction of the vocal folds and a deep inspiration up to 90% of the total lung capacity. In the compressive phase the glottis is rapidly closed for about 0.2 seconds against a forced expiratory effort. In this phase the intrathoracic pressures are as high as 100–250 mm Hg and intraabdominal pressures reach >200 cmH_2O in males and >150 cmH_2O in females[10,11]. Finally, the glottis opens, and the expiratory effort is continued in the expulsive phase. In this phase, healthy individuals' cough peak flows (CPFs) are >360 L/min and average much higher[12].

While normal CPF for adults ranges from 400 to 1200 L/min, over 300 L/min are quite effective[13]. Bianchi

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et al. reported CPF standards for children 4 years and older. From age 4 to 18 for males the mean increase is 40 L/min/year with the mean at age 4 being 162 (range 130–230) L/min to age 14 with mean 728 (range 518–944) L/min. For females CPF increase by 24 L/min/year from a mean at age 4 of 147 (range 110–209) L/min to a mean at age 18 of 488 (range 399–639) L/min. Small children and the elderly have greater risks of pneumonia in part due to lower CPF[14].

Cough Pathophysiology in Spinal Cord Injury

In cervical and high thoracic spinal cord injury (SCI) there is paralysis of inspiratory and expiratory muscles compromising all three phases of the cough reflex. As a result, the effectiveness of coughing is severely impaired[15]. Weakness rather than spasticity of the respiratory muscle pump can compromise respiration and coughing in SCI[16] as well as in any patient with ventilatory pump failure (VPF) since both weak inspiratory and weak expiratory muscles decrease cough flows.

Cough Pathophysiology in Neuromuscular Disease

Inspiratory and expiratory muscles are also frequently paralyzed in neuromuscular diseases (NMDs) and cough flows are diminished. The pathophysiological pattern of respiratory mechanics can vary between various NMDs. In the long term, in progressive NMD there is a progressive decrease of compliance of lungs and thorax and decrease in vital capacity (VC). In amyotrophic lateral sclerosis (ALS), glottic dysfunction can severely impair the compressive phase of the cough reflex and diminishing airway patency for effective cough flows[17]. The fact that patients with ALS more often need tracheal tubes then patients with neuromuscular diseases like spinal muscular atrophy (SMA) may be explained by the fact that ALS is a multisystem degeneration affecting several cerebral structures[18]. Therefore, not only vocal cord palsy, but also pathological vocal cord adduction – either due to vocal cord spasticity, disinhibition of the laryngeal adductor reflex, or laryngospasm – can be found in ALS[19–22]. Pathological vocal cord adduction – and possibly upper airway dysfunction[23] – compromises upper airway patency and thereby reduces the flow that can be generated by MIE[19,21]. This again may result in a failure to clear tracheobronchial secretions, which makes tracheostomy inevitable in ALS. In SMA, a strictly lower motoneuron disease, with MIE flows of 50–70 L/min. in infants with SMA1, but 250–370 L/min. in 25- to 30-year-olds with SMA1 can be generated, whereas for ALS patients the MIE flows can start at 400 L/min. and then decrease to about 100 L/min, at which point a tracheal tube is needed[24].

Cough Pathophysiology in Cerebral Disease

Finally, cerebral disease may compromise the cough reflex on several levels. Cortical sensory, cognitive and motor processing, subcortical processing, and brainstem sensory processing in the NTS as well as the brainstem control of the cough motor pattern can be affected[25]. Accordingly, recent data from lesion mapping of stroke patients demonstrated that not only lesions of the brainstem but also of right hemispheric limbic structures and left hemispheric sensory regions lead to disturbances of the cough reflex[26].

Pathophysiology of Tracheobronchial Retention of Secretions

Many factors contribute to the tracheobronchial retention of secretions in neurological disorders. Aspiration, most prominently the aspiration of saliva, and ineffective cough flows are direct sequelae of neurological illness. The combination of aspiration and cough insufficiency occurs in cerebral disease, ALS, myopathies, critical illness polyneuropathy/myopathy, and SCI.[27–30]. Immobility further impairs secretion clearance[31]. When COPD, a frequent comorbidity is present, hypersecretion and ciliary dysfunction contribute to tracheobronchial retention of secretion[32]. Systemic anticholinergic medications and lack of humidification of the tracheobronchial mucosa lead to higher viscosity of secretions and reduce clearance. The retention of secretions causes pneumonia, atelectasis, and hypoxic respiratory failure and can be fatal.

In VPF, but not in cerebral illness, expiratory muscle weakness compromises thoraco-abdominal pressure generation and inspiratory weakness compromises deep inspiration. As a result, secretions can accumulate in peripheral airways, not so much because of excessive production, nor for their rheological characteristics as occurs in cystic fibrosis, but due to inability to cough them out. The peripheral airways' congestion can trigger

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a vicious cycle whereby respiratory muscle weakness, increased airway resistance, and decreased lung compliance progressively increase respiratory load and ventilatory demands.

A Diagnostic and Therapeutic Algorithm for Management of Secretions

Management of secretions in patients with VPF and cerebral illness can be addressed with the same diagnostic and therapeutic algorithm, which is visualized in Figure 10.1. Daily verticalization, postural drainage, and optimized conditioning of the airways are essential for all patients. Diagnostic measures with respect to coughing and swallowing lead to more specific therapies. Nevertheless, among the suggested measures targeting the various pathophysiological aspects of mucus retention the only one demonstrated to prevent pneumonias and need for hospitalizations for patients in acute on chronic ventilatory failure is MIE at the effective settings of 50 to 70 cmH_2O as used at in the 1950s but in few centers today[33]. With respect to cerebral illness, recently a case series was published, demonstrating potential of MIE to foster weaning from the ventilator[34]. Also recently, a study protocol of a randomized controlled trial on the effect of MIE on the duration of weaning of neurological patients has been published, and the results are expected to be published in 2025[35]. Diagnostic and therapeutic proceedings are detailed further in the following paragraphs.

Reduction of Saliva

Hypersalivation and aspiration of saliva can be reduced by systemic anticholinergic medication. Data from neuropediatric patients have shown that enteral administration of glycopyrrolate or transdermal application of scopolamine reduce salivation[36,37]. Parenteral administration of glycopyrrolate and enteral administration of amitriptyline are also used. Patients must be monitored closely for excessive thickening of secretions, tachycardia, and cognitive side effects, which may limit the usefulness of systemic anticholinergic agents.

Studies in children and adults with neurological disease have reported the efficacy of the ultrasound-guided injection of IncobotulinumtoxinA into the salivary glands. This can significantly reduce salivation for a reported four months. In adults, 30 units are injected into each parotic gland and 20 units into each submandibular gland[38,39]. Data from patients with ALS have also documented a reduction of salivation by radiation of the salivary glands[40].

Reduction of Aspiration

In the 1970s and 1980s the speech-language pathologists Dr George L. Larsen and Dr Jeri A. Logemann pioneered

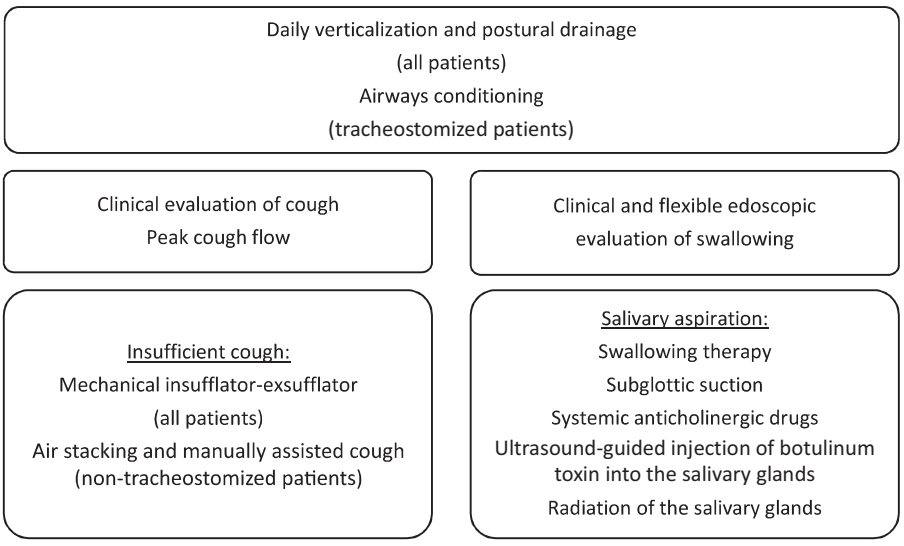


Figure 10.1 Bundle of diagnostic and therapeutic measures for management of secretions.

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diagnostic and therapeutic procedures and defined the role of the speech-language pathologist in the treatment of dysphagia[41–43]. Their techniques of swallowing therapy have been evaluated over the years[44]. Swallowing therapy by certified speech-language pathologists is now broadly established in centers treating neurological patients including stroke victims and ventilator users, and following decannulation[45,46]. Typical goals are optimizing the management of tracheostomy tubes, improving swallowing function, reducing the aspiration of saliva, reintroducing food, and reestablishing speech.

Subglottic suction is intended to remove aspirated saliva from the subglottic space. The use of tracheal tubes with subglottic suction can reduce the aspiration of saliva and thus pneumonia incidence during use of invasive mechanical ventilation[47]. Neurological patients, who aspirate saliva, might benefit most from subglottic suction. It is still unclear if continuous subglottic suction is superior to intermittent subglottic suction. In mechanically ventilated patients switching to cuffless tracheostomy tubes on pressure or volume preset ventilation and three to four times normal delivered volumes to blow secretions up and into the mouth for removal while providing full ventilatory support and permitting speech may be an alternative[48].

Facilitating Drainage and Expectoration

Regular body positioning and verticalization are essential for expectoration and drainage of secretions. Upright positioning can result in higher CPFs in most NMDs[49], but probably not in SCI since, in these patients and for spinal muscular atrophy, supine VC is usually greater than when sitting[15].

Viscosity of tracheobronchial secretions needs to be optimized, as secretions with too high or too low viscosity are difficult to eliminate from the airways. Also, secretions with too high viscosity can lead to mucus plugs in the airways and to obstruction of tracheal tubes. Secretions with high viscosity are the most prominent problem for tracheostomized patients, as their upper airways cannot warm up and moisturize inspired air. For tracheostomized patients frequent cleaning of tracheal tubes and optimal humidification are thus quintessential. The use of heat and moisture exchange (HME) filters, regular inhalation of sodium chloride solutions, and often heated humidification is required. Heated humidification systems are usually needed for tracheostomy mechanical ventilation users to achieve a higher absolute humidity than HMEs[50]. The concentration of sodium chloride to be inhaled ranges from 0.9% to 5.85%. Other secretolytic medications like acetylcysteine provide no additional benefit. There are several ways to nebulize medications: jet nebulizers, ultrasonic nebulizers, and mesh nebulizers as well as the application via inline spacers in combination with pressurized metered dose inhalers[51]. The choice of the inhalation system significantly determines the pulmonary deposition. The aerosol size must be approximately 0.5–5 μm to maximize the lung dose[52]. Notably, the deposition of inhaled aerosol particles is influenced by a variety of other factors, such as tidal volume and respiratory rate, the effect of which on pulmonary deposition again may vary depending on particle size[53]. The mesh nebulizer is more effective than the jet nebulizer regarding pulmonary deposition in noninvasive ventilation[54]. When using a high-flow nasal cannula, greater lung deposition correlates with lower flow rates. Comparing 10 L/min, 20 L/min, and 30 L/min, the highest pulmonary deposition can be achieved with 10 L/min[55]. While there is no consensus on the optimum position of aerosol devices in mechanical ventilation in combination with HMEs or heated humidification, a recent publication illustrates various possibilities from a practical viewpoint (see Figures 10.2 and 10.3)[56].

Conventional management of secretions may include medical interventions such as bronchodilators and mucolytics. A major concern regarding the use of bronchodilators and mucolytics for management of secretions in diseases of the nervous system with respiratory impairment is lack of evidence[57,58]. Anticholinergics can reduce mucus hypersecretion but may thicken the mucus, cause constipation, anxiety, and tachycardia; and sensitize the myocardium to sympathetic stimulation, which may be especially hazardous for patients with cardiomyopathies.

Finally, high-frequency chest wall oscillation, manual and mechanical chest percussion and direct oscillation of the air column are intended to reduce the viscosity of secretions. However, once the mucus arrives in the central airways it must still be expelled by flows generated by coughing or by MIE. Nevertheless, devices that oscillate, vibrate, or percuss the chest or the air column to treat lung and airways diseases are often routinely prescribed for patients with VPF without evidence of efficacy.

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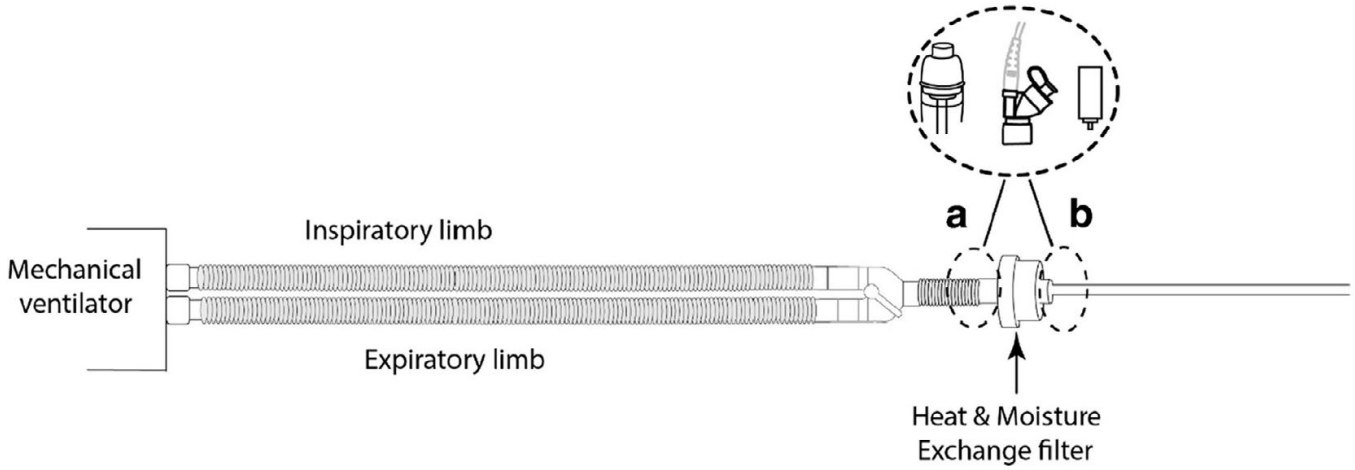


Figure 10.2 Locations where aerosol devices may be included in the passive, heat and moisture exchange (HME) mechanical ventilation setup. **(a)** Ventilator side of the HME. *Note*: This is suitable only when aerosol therapy is being administered in combination with a bypass HME or HME that allows aerosol to pass through the porous materials. **(b)** Patient side of the HME, between HME and patient interface, e.g. endotracheal tube (shown here), tracheostomy. Copyright © 2023 Fernández Fernández and MacLoughlin, distributed under the terms of the Creative Commons Attribution License, Creative Commons disclaims all liability for damages resulting from their use to the fullest extent possible. Fernández EF, MacLoughlin R. Aerosol therapy and humidification. In: Esquinas AM, ed. *Humidification in the intensive care unit*. Springer; 2023. https://doi.org/10.1007/978-3-031-23953-3_35.

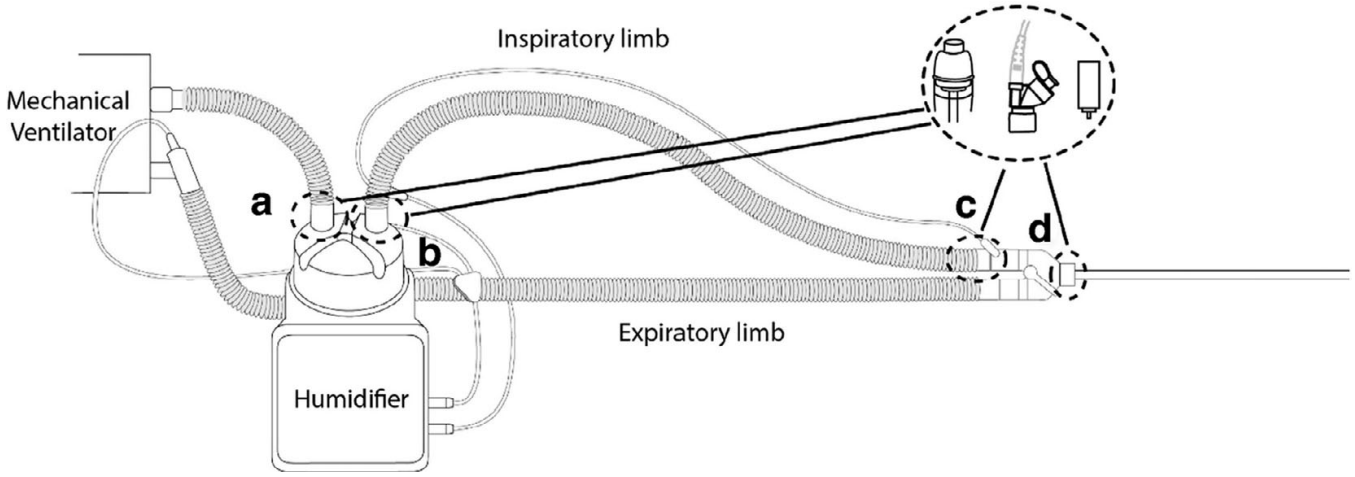


Figure 10.3 Locations where aerosol devices may be included in the active, heated humidified (HH) mechanical ventilation setup. **(a)** Ventilator or dry side of humidifier, **(b)** patient or wet side of humidifier, **(c)** inspiratory limb at the patient wye, and **(d)** between the patient wye and patient interface, e.g. endotracheal tube (shown here), tracheostomy. Copyright © 2023 Fernández Fernández and MacLoughlin, distributed under the terms of the Creative Commons Attribution License, Creative Commons disclaims all liability for damages resulting from their use to the fullest extent possible. Fernández EF, MacLoughlin R. Aerosol therapy and humidification. In: Esquinas AM, ed. *Humidification in the intensive care unit*. Springer; 2023. https://doi.org/10.1007/978–3-031–23953-3_35.

These include the Thairapy Percussion Vest™, Hayek Biphasic Ventilator™ for oscillation, the Forrest Bird Intrapulmonary Percussive Ventilator™, and other methods of chest physical therapy (PT), despite patients with VPF mostly having intact mucociliary elevators and requiring cough assistance instead. These PT modalities may only be helpful during respiratory tract infections. No one has shown that their use can re-normalize oxyhemoglobin saturation (O_2Sat) or improve prognosis for patients with VPF. Chest PT modalities are never substitutes for MIE for patients with VPF. Once third-party payers pay for these devices on a monthly basis, they can be reluctant to pay for the MIE that can be life saving.

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Mechanical Insufflation-Exsufflation

MIE refers to the passive inflation of the lungs to full chest expansion by way of positive insufflation pressure, followed by rapid deflation to full clinical chest wall retraction and lung emptying by way of negative exsufflation pressure. MIE is delivered invasively via endotracheal or tracheostomy tubes, or noninvasively via simple mouthpiece, nasal, or oronasal interfaces at positive and negative pressure ranges from 40 to 70 cmH_2O. The positive pressure fills the lungs with air (insufflation), and the abrupt switch to negative pressure generates an expiratory flow (exsufflation). Via airway tubes MIE cannot be blocked by glottis closure or other upper airway obstruction to flow, so the exsufflation flows (MIE-EF) are typically >180 L/min via 5–7 mm diameter tubes. For tracheostomized patients, MIE clears secretions from the left bronchial tree, which is usually not reached by conventional suctioning without the use of specifically directed catheters. It reduces the need for deep suctioning.

The Role of MIE in Cerebral Disease

Though distinct from a pathophysiological viewpoint, cerebral illness and VPF share key clinical features with aspiration of saliva, insufficient coughing and tracheobronchial retention of secretions often being present. In cerebral illness compared to VPF, salivary aspiration, disorders of consciousness and cognitive impairment are more often present, as are tracheal tubes. MIE is applicable to many patients with cerebral disease, especially if tracheal tubes are present, whereas manually assisted coughing, air stacking, or glossopharyngeal breathing are difficult or impossible to apply. Patients with cerebral diseases may be weaned from mechanical ventilation, but still require the long-term invasive or non-invasive use of MIE.

The Role of MIE in Ventilatory Pump Failure

With respect to VPF, countless publications state that when noninvasive ventilation (NIV) fails, the patients need to undergo tracheotomies[59] However, NIV has come to be synonymous with continuous positive airway pressure (PAP), which is useless for VPF, and bilevel PAP, used at less than NVS settings, that can optimally rest muscles and provide up to full ventilatory support when needed. NVS settings via an active circuit also permits the elimination of EPAP which is counterproductive and can be omitted when lung disease or tracheostomy tubes are absent (see Chapter 11). Neither NIV nor NVS should ever be used by people with VPF without introducing manually assisted coughing or MIE. These therapies are needed to avoid upper respiratory tract infections (URIs) from developing into pneumonias and respiratory failure, often long before NVS or continuous NVS (CNVS) is needed. Even when clinicians are familiar with MIE it is typically prescribed at two- to six-hour intervals like a regimen for chest PT, at inadequate pressures, at less than settings needed to achieve full lung expansion and retraction, and it is not generally being used via invasive airway tubes. Besides methods to increase cough flows being crucial for successful definitive noninvasive management of VPF, maintaining pulmonary compliance and predicted normal lung volumes is also important for the health of the lungs. This is accomplished by lung volume recruitment (LVR), both active and passive.

Air Stacking

Air stacking is active lung volume recruitment (see Chapter 11). A resuscitation bag or mechanical ventilator successively delivers air volumes to be stacked by being held by the patient's glottis. The patient closes the glottis after every delivered bolus of air. In this manner, deep lung volumes can be attained for coughing, maintaining lung compliance and volumes, and for better and longer speech. Active LVR can often increase lung volumes from slightly over tidal volumes to approach the predicted inspiratory capacity, in many cases to over 4 L. Whereas an average tidal volume may be 500 mL the average cough volume is 2.3 L[60], which is far greater than the VCs of many patients with VPF.

Patients with intact bulbar innervated muscles, such as patients with traumatic tetraplegia, can usually air stack to volumes of 3 L or more and, unless very scoliotic or obese, a properly delivered abdominal thrust can often result in assisted CPF of 300–450 L/min. These flows should be more than adequate to clear the airways and prevent URI pneumonias and respiratory failure. All cooperative patients with VPF can consistently avoid hospitalization by using an oximetry CNVS/MIE protocol to keep or quickly return O_2Sat to normal by using manually assisted coughing and MIE during intercurrent URIs except for some stridorous patients with upper

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MND and ineffective assisted cough flows or MIE exsufflation flows (MIE-EF).

When there is severe bulbar dysfunction with upper MND, inability to close the glottis, and upper airway collapse even at a minimal negative exsufflation pressures, passive LVR is performed by the delivery of maximal insufflation volumes by pressures of 60–70 cmH_2O. Secretions can then be huffed out to atmospheric pressure along with an abdominal thrust being applied. Upper airway collapse is mitigated by decreasing or eliminating the negative pressure that would have been delivered during an exsufflation phase of MIE. When the inspiratory pressure and time are properly titrated to get the individual into their inspiratory capacity range and when the patient is coached to provide a maximal effort huff cough – it can be possible to achieve clinically effective CPF rates without the use of negative pressure. As Andersen and colleagues have observed, it is important to analyze the MIE graphics for the LVR maneuver and the LVR + huff cough maneuver to ensure an appropriate laryngeal response pattern during insufflation[19]. If a strong, sustained reflex adduction response is identified, then adjustments to the flow setting, insufflation time, body position, and potential insufflation pressure are warranted. Thus, even with inability to close the glottis, huff cough flows from deep insufflation volumes assisted by abdominal thrusts applied can be effective to clear secretions.

For patients who can simply not close their glottis to air stack without necessarily having upper MND, the insufflation pressures of MIE alone can also be used to perform passive LVR to preserve thoracopulmonary compliance and perhaps slow the decline of VC, and abdominal thrusts can be applied after the deep insufflations to create effective "cough" flows. Insufflation at pressures of 50–70 cmH_2O multiple times three times daily is typically prescribed, 50–60 via the upper airway mouth or oronasal interfaces and 60–70 cmH_2O via airway tubes.

Manually Assisted Coughing

For patients with VCs <1500 mL, manually assisted coughing should begin with air stacking followed by an abdominal or thoracoabdominal thrust concomitant with glottis opening (Figure 10.4). CPFs of about 160 L/min are approximately the minimum needed to cough effectively. Risk of URI, pneumonia and respiratory failure increases as CPF decrease below 300 L/min (5 L/s)[33,61–63]. Sancho et al. suggested that at least 255 L/min is needed[63]. Manually assisted coughing should be taught when unassisted CPF are <300 L/min. Effective manually assisted CPFs are attained by patients with VCs <1500 mL by first air stacking before the abdominal thrust to generate the manually assisted cough. Since normal cough volumes are 2.3 L[50] the manually assisted CPF of patients with VCs much greater than 1500 mL are not very much increased by air stacking before the abdominal thrust. In the Sancho et al. study, manually assisted CPF were 255±100 L/min for patients whose unassisted cough flows were 150±120 L/min[63]. Patients unable to air stack due to inability to close the glottis can still have huff flows assisted by abdominal thrusts applied to deep breaths or insufflations as described previously. While abdominal thrusts are usually applied by a care provider, some patients position their arms in front of their abdomen while sitting and then push forward against their arms or a seat belt or actually drive their motorized wheelchairs into the edge of a table to create abdominal thrusts[13].

Patients with intact bulbar innervated muscles, such as most patients with SCI, can usually air stack to volumes of 3 L or more and, unless they are very scoliotic or obese, a properly delivered abdominal thrust can often result in assisted CPF of 300–450 L/min. These flows can be more than adequate to prevent URI pneumonias and respiratory failure. All cooperative patients with VPF can consistently avoid hospitalization by using an oximetry CNVS/MIE protocol to keep or quickly return O_2Sat to normal by using manually assisted coughing and MIE during intercurrent URIs except for some stridorous patients with upper MND with inadequate assisted cough flows.

Glossopharyngeal Breathing

Glossopharyngeal breathing (GPB; "frog breathing") can permit people dependent on CNVS, even with 0 mL of VC, to have ventilator-free breathing ability. It can also be used for unassisted air stacking to augment the inspiratory phase of coughing and CPF for patients with NMDs and SCI. With GPB the patient actively performs a maximum inspiration followed by repetitively pistoning boluses of air past the glottis and into the trachea to inflate the lungs. GPB, as well as air stacking to also increase lung volumes, increases the cough flows to enhance the expulsive phase for assisted coughs[64]. An abdominal binder has been reported to enhance expansion of the upper lobes during LVR, whether by GPB or otherwise air stacking, and to increase cough flows for patients with SCI[65].

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Figure 10.4 Manually assisted coughing. The resulting cough peak flow is measured with a hand-held peak flow meter.

History of Mechanical Insufflation-Exsufflation

MIE was first described in 1953 as a clinical support strategy to effect airway clearance and reduce the risk of pneumonia in iron-lung dependent post-polio patients in the United States[52]. The Cof-flator™, the original MIE device, was on the market only from 1953 to 1967; however, MIE has been used by many patients since then with many sharing the few Cof-flators™ available. MIE subsequently reappeared in clinical use in the United States with the launch of the In-Exsufflator™ in 1993 after Bach convinced Jack Emerson to remanufacture it in 1988.

The original Emerson CoughAssist™ used a two-stage centrifugal blower operated by a brushed alternating current motor. The current CoughAssist70-series and most modern MIE devices use a single stage blower operated by a brushless direct current motor. One newer MIE device (BiWaze®, ABM Respiratory Care, Eagan, MN, USA) by comparison, utilizes a dual blower system to create separate air inhale and exhale pathways. Modern MIE devices incorporate adjustable inhalation flows, insufflation and exsufflation pressures range from ambient to 70 cmH_2O and oxygen bleed-in compatibility. Unlike the Cof-flator™ and In-Exsufflator™ that were manual, currently available MIE devices are also used in automatic modes with advanced features such as triggering algorithms, oscillation features, the ability to deliver positive insufflation pressure only breaths. Some devices even have PAP during the pause phase, which is designed, though without justifying evidence, to mitigate derecruitment and micro-atelectasis.

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The original MIE device used in clinical practice was calibrated in mm Hg as compared to modern MIE devices, starting with the In-Exsufflator™ in 1993, which have insufflation and exsufflation pressures calibrated in cmH_2O. Early journal citations referring to the original OEM Cof-flator™ described the clinically effective pressure settings to be +40 to −40 mm Hg[66–70]. An accurate conversion of 40 mm Hg is 54.1 cmH_2O, thus, the common practice today of using ineffectively low pressures as compared to what had been described using the Cof-flator™.

Coughing and Mechanical Insufflation-Exsufflation

Like many physiologic functions, an effective cough is dependent upon the creation of pressure gradients – an important concept to understand when employing mechanical assistance to augment an impaired cough reflex or ineffective cough flows. An accurate understanding of the mechanism of operation of MIE is built upon the same foundation of pressure gradients required to achieve expiratory flow rates that are at or above the minimum threshold for effective airway clearance. A healthy cough reflex is composed of foreign matter causing airways irritation, followed by deep inspiration, which may approach inspiratory capacity. At the end of inspiration alveolar pressure is greater than atmospheric; however, the critical next phase of the cough further amplifies the pressure gradient. The compressive phase follows with closure of the glottis synchronized with chest wall and abdominal compression to greatly increase intrapleural pressure based on the inverse relationship between pressure and volume. The transient closure of the glottis during the compressive phase of the cough generates intrathoracic pressures that may reach as high as 300 mm Hg or 407 cmH_2O[71]. "The explosive phase" results when the glottis opens after the transient closure and results in the aforementioned CPFs over 300 L/min for adults.

Caution should be taken by clinicians to not oversimplify MIE comparing the therapy as being analogous to a vacuum device; that is the more negative pressure that is applied to the central airways and the longer the time the negative pressure is applied, the more effective airway clearance will ultimately be achieved. The mechanism of operation for MIE relies upon an interaction between positive insufflation pressure, insufflation time, pressure rise time (*referred to as a flow setting*), negative exsufflation pressure, and exsufflation time. Additional factors such as a functioning or dysfunctional larynx, MIE patient–device interaction (*active versus passive effort*), body position, device pressure performance, the application scenario (*noninvasive or invasive*), rheological factors of the sputum, and many other considerations also play an individual role as well as having a complex interaction on the impact and effectiveness of MIE for an individual subject.

Positive pressure serves to mechanically augment or assist the amount of operating lung volume achieved during the inspiration phase of the cough. Insufflation time controls the time that positive pressure is delivered; however, the actual amount of time spent at the set insufflation pressure is affected by both the pressure rise setting as well as the MIE interface seal. Both the insufflation time and rise time settings influence the amount of lung volume achieved during the initial phase of the mechanically assisted cough. Negative exsufflation pressures create a large gradient between intrathoracic and atmospheric pressure. Negative pressure may be combined with some level of glottic closure, with the patient attempting to synchronize their cough effort timed to the start of exsufflation, as well as with chest and abdominal compression depending on disease state progression or individual capabilities. Negative pressure should not simply be thought of as suction or a vacuum force that "pulls" secretions out of the central airways – rather this is a mechanical means to offset or replace the pressure differential that is created in healthy individuals during the compressive phase of a cough – namely the combination of chest and abdominal compression against the now closed glottic valve. Exsufflation time setting controls the length of time the upper and central airways are exposed to negative pressure. Given the potential for a large pressure gradient and high expiratory flow rates during the exsufflation phase it is feasible for the lung to quickly empty to or even past the individual's functional residual capacity and into the expiratory reserve volume. Lung emptying time underscores that the exsufflation time setting is far from arbitrary but plays an important role for optimal airway clearance[72–75].

Settings

The parameters that provide the maximal MIE-EF are almost always 50–60 cmH_2O via mouthpieces (see Figure 10.5) and oronasal interfaces, as they were in the 1950s and 1960s, except for patients with upper MNDs. The optimal settings are 60–70 cmH_2O via airway tubes. This is true even for small children. The insufflation and

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Figure 10.5 Dr Augusta Alba administering mechanical insufflation–exsufflation via a 22 mm mouthpiece to a post-polio patient who had 0 mL of VC for 49 years but used mouthpiece NVS for 24 hours per day without any respiratory complications. NVS, noninvasive ventilator support; VC, vital capacity.

exsufflation times are determined by measuring the time it takes at optimal pressures to reach complete expansion, then to fully retract the lungs and chest wall. Typically, insufflation times are about 2.5 seconds and exsufflation times about 1.5 seconds.

The MIE parameters need to be individually adapted to patients with upper MNDs because the typical optimal pressures via the upper airways of 50–60 cmH_2O may result in lower MIE-EF for these patients due to the spasticity and stridor often seen[64,76,77]. Bulbar ALS patients can also have inspiratory and expiratory laryngeal adductions that decrease MIE-EF so greater variability in timings and pressures are typically required to maximize MIE-EF[19]. When MIE-EF decreases to 100 L/min or less a tracheotomy almost certainly becomes necessary[19,76,77].

Complications of MIE

There are no reports on pneumothorax resulting from MIE in children or adults with cerebral illness[78]. Also, the use of MIE in critically ill patients using mechanical ventilation results in few complications[75]. Notably, two patients with GBS and severe cardiovascular autonomic dysfunction triggered by MIE have been reported in one publication[79]. Although clinical barotrauma is rare for patients with VPF, a few cases have been described when MIE is used in conjunction with ventilatory support. The insufflation pressures of MIE should only be those of the positive inspiratory pressures of the ventilator such as when MIE is needed for patients with chest tubes, bullous emphysema, and other conditions associated with severe lung fragility[80].

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Additional MIE Settings and Features

Most commercially available MIE devices have the following features and settings in common: the ability to set a positive inspiratory pressure, an inspiratory time setting, negative expiratory pressure, a corresponding expiratory time setting, as well as a pause time setting. MIE devices typically have a manual mode where inspiratory or insufflation time is manually controlled by the operator, as well as an automatic mode that uses the set insufflation and exsufflation times to deliver both the positive and negative pressures settings. The CoughTrak™ of the CoughAssist™ permits patient triggering, which may improve patient synchrony with MIE for infants and others unable to fully cooperate with it.

Modern MIE devices also have internal batteries and operate on external batteries as well. They have features that support autonomous use such as triggering features that automatically detect patient effort and initiate the insufflation phase and subsequently negate the need for a set pause time, pressure oscillations designed to enhance secretion mobilization and loosen mucus from the walls of the central airways, positive airway pressure during the pause time, and positive pressure-only breaths that can be incorporated into programmable MIE settings (see Figure 10.6).

The suggested oscillation specifications such as amplitude and frequency vary by manufacturer. Clinical evidence that the oscillation feature improves clinical outcomes when utilized during MIE therapy is lacking and may indicate a need for further algorithm work to improve the clinical impact of this feature.

Enhanced clinical monitoring features include the ability to incorporate oximetry, displayed and recorded MIE-EF, and device measured insufflation volume are present as well as pressure and flow waveform graphics on the T-70 CoughAssist™, (Philips, Pittsburgh, PA, USA) which is no longer manufactured. However, there are currently 2 MIE devices on the U.S. market and at least 10 others manufactured in at least 8 other countries at this time. These help to evaluate MIE effectiveness, patient compliance to MIE, guide in decisions regarding adjustment of the settings, and further assist in clinical management. The VOCSN and V+C ventilators (React Health, Bothell, WA, USA) with combined integrated cough assist technology (ICAT™), display live pressure and waveform graphics, which also may guide clinical management of MIE.

The role of MIE in Sustaining Life, in Extubation and in Decannulation

Since an effective cough is vital for survival but becomes inadequate in advanced VPF, MIE serves as a life-sustaining technology for patients using NVS. Therefore, randomized controlled trials on its use are unethical for people with VPF and difficult to design for any patient population[72,73]. MIE is needed to prevent URI pneumonias for anyone with VPF and cough flows <270 L/min as well as for patients for whom coughing is inhibited by pain. Such patients were among the first to have been described to effectively and painlessly clear their central airways since the 1950s[74]. MIE may be less effective but still helpful for people with upper MNDs (central nervous system lesions) as well as for extubating and decannulating

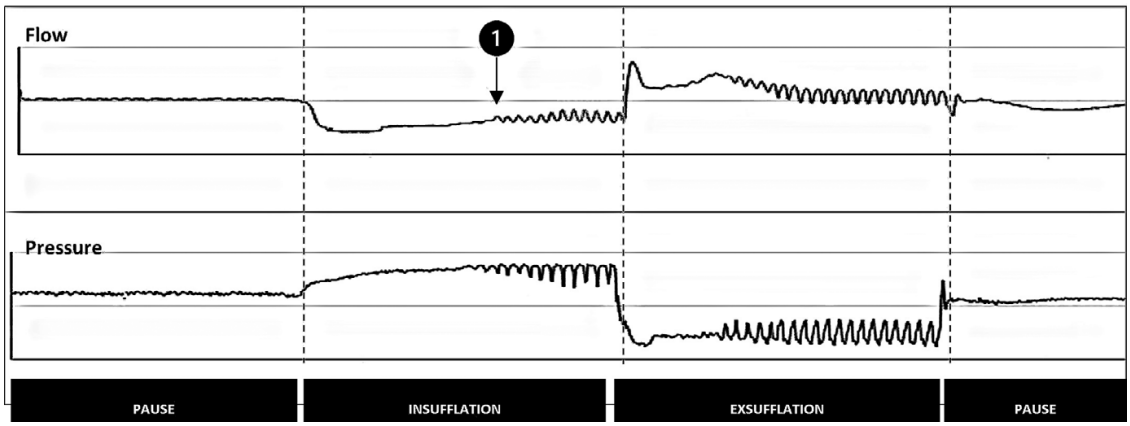


Figure 10.6 MIE device generated flow and pressure waveform graphic with the oscillation feature set to both the inhale and the exhale phase. In this graphic, the oscillation amplitude was 10 cmH_2O and the frequency was set to 12 Hz. Initiation of the oscillation feature is delayed, as seen in the pressure and flow waveforms **(**1**)** due to the blower's pressurization performance. MIE, mechanical insufflation–exsufflation.

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difficult-or impossible to-wean VPF patients. For the latter, MIE is absolutely crucial to prepare them for extubation by normalizing their O_2Sats in ambient air and for successfully extubating or decannulating difficult-or impossible to-wean VPF patients to CNVS by using it for every post-extubation/decannulation O_2Sat decrease <95%[81–83]. The use of MIE results in few adverse events, even in critically ill patients[75].

Issues Regarding MIE Implementation

While indications for prescribing MIE are CPF rates <270–300 lpm and difficulty clearing the airways, indications should not be restricted to any particular diagnoses. It has also been used effectively and been well tolerated by some debilitated patients with cystic fibrosis, bronchiectasis, COPD, and morbid obesity; however, currently MIE has not been widely adopted as the primary airway clearance therapy for these cohorts[81].

Inability to cough due to endotracheal tube placement, delivery of relatively dry gas during mechanical ventilation, ineffective CPF, and altered levels of consciousness as from sedation in the critical care setting increase risk of sputum retention and pneumonia and delay ventilator weaning and extubation. Invasive tracheal suctioning has been the primary intervention to mitigate retention of secretions, but it has been reported that the suction catheter can miss the left mainstem bronchus up to 92% of the time, resulting in the predominance of pneumonias occurring in the left lungs[84]. MIE has no preference for the right mainstem bronchus. Therefore it is virtually impossible to extubate ventilator unweanable patients with VPF to CNVS without it[82,83]. More studies are required to establish its use in successfully extubating other critical care populations[81]. While vital for central airway clearance, for MIE to become a standard of care as an adjunct to or replacement for invasive suctioning will require additional investigation and clinical substantiation.

Titration Methodologies and Clinical Consensus Recommendations

Volpe et al. found in a lung model, that a higher MIE pressure gradient, a higher ratio of peak expiratory to peak inspiratory flow, and a higher difference between peak expiratory and peak inspiratory flow correlate significantly with mucus displacement. Their findings support the use a high pressure gradient with a slow insufflation.[85].

A common recommendation for MIE implementation is the use of asymmetrical pressure settings, where exsufflation pressures are greater in magnitude than the corresponding insufflation pressure settings. The rationale for this oversimplified characterization of MIE mechanism of operation appears, in part, based on an infant lung model with tracheostomy bench study that determined that "higher insufflation and exsufflation pressures both increased *mean expiratory flow*, but greater exsufflation pressure had more substantial impact"[86]. This bench study is often cited when higher magnitude negative pressure settings compared to insufflation settings are recommended along with longer exsufflation to insufflation time settings[87,88].

For the MIE settings via invasive and noninvasive interfaces noted previously, it is only upper MND patients who appear to require individual calibration. For these patients, an O_2Sat baseline permanently <95%, in spite of optimal use of NVS and MIE, along with MIE-EF <150 L/min indicate the need for imminent tracheotomy for survival in ALS[82,83,89].

Box 10.1 summarizes the evidence for the use of MIE in the ICU.

Box 10.1 Emerging clinical evidence for the use of MIE in the ICU setting has indicated:

1. MIE is an effective technique for cough augmentation in ICU respiratory patients, either through an endotracheal tube or through a facial mask[69], or even a simple mouthpiece.
2. MIE can efficiently manage copious secretions and to help to avoid reintubation, as well as to improve NVS efficacy in patients who develop respiratory failure after extubation[69].
3. Use of MIE in critically ill patients is independently associated with a reduced incidence of hospital-acquired pneumonia[70].
4. MIE has been shown to decrease the rate of hospitalizations and the length of stay for patients with neuromuscular diseases[90–94].
5. Endotracheal suctioning is associated with more complications and can be less effective than MIE for clearing airways[95–97].

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Role of Flow and Pressure Graphics Analysis in MIE Management

Modern ICU ventilators are equipped with waveforms that provide critical information regarding the respiratory mechanics of the patient being ventilated. Clinicians rely on the waveforms to guide ventilator management and settings changes as well as to identify patient–ventilator asynchrony, measurements of lung compliance and airways resistance, and the presence of intrinsic positive end-expiratory pressure. Graphics analysis may also play a critical role in understanding an individual's response to MIE. Additionally flow and pressure waveforms have the potential to help guide airway and alveolar protective strategies when implementing and titrating MIE use. Unfortunately, the clinical community has yet to widely adopt the use of graphics to titrate settings and manage MIE. There is a need for manufacturers of MIE equipment to make flow and pressure waveforms available in both a real-time view as well as the ability to download and review data. Regardless of the usefulness of waveforms in guiding MIE, it is unlikely for waveforms to be adopted as a standard of care until clinicians have easy access to this critical tool across a wide range of MIE products.

This section is not an in-depth guide to MIE graphics analysis and interpretation. However, comprehensive explorations of MIE graphics analysis have been published elsewhere[98,99]. The focus of this section is to briefly introduce MIE pressure and flow waveforms followed by examples that underscore the clinical utility of graphics in the following key areas:

- The role of graphics in guiding MIE settings
- Evaluation of the dysfunctional larynx
- LVR and MIE salvage strategies

Introduction to MIE Graphics

MIE graphics have characteristics that are critical to understanding and interpreting the waveforms as demonstrated in Figure 10.7.

Role of Graphics in Guiding MIE Settings

Graphics analysis offers the opportunity for guiding MIE settings for the respiratory clinician. The following examples demonstrate just a few mechanisms by which analysis of the MIE graphics may reveal an indication of the need for MIE settings adjustment. Consider the MIE graphic examples presented in Figures 10.8–10.10.

Thus, analyzing the pressure and flow graphics can reveal to a clinician when the inhale time setting is set appropriately or when an adjustment is indicated. Fine-tuning the inhale time setting may ultimately lead to an improvement in patient comfort.

Another practical, yet important aspect of optimizing MIE is user technique. MIE devices currently do not have leak compensation algorithms. Interface seal, thus, directly impacts reaching the target insufflation and

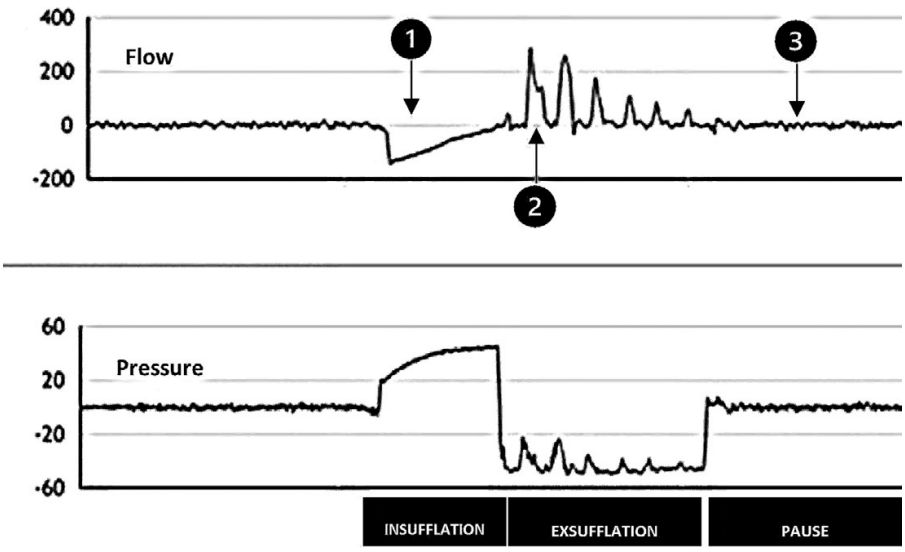


Figure 10.7 During the *Insufflation Phase* (1) flow coming from the MIE device creates a downward orientation with volume entering the patient dropping the flow pattern below the baseline zero-flow that exists during the pause following an MIE cycle. During the *Exsufflation Phase* (2) positive flow coming from the patient has a upward orientation rising above the baseline of zero flow, just as negative pressure has a downward orientation dropping below the baseline zero-pressure line. In this example, it should also be noted that six discernable cough efforts were made during the exsufflation phase with a decrease in peak cough flow with each subsequent cough effort. Finally, the *Pause Phase* (3) is associated with an absence of flow and a return to atmospheric pressure. MIE, mechanical insufflation–exsufflation.

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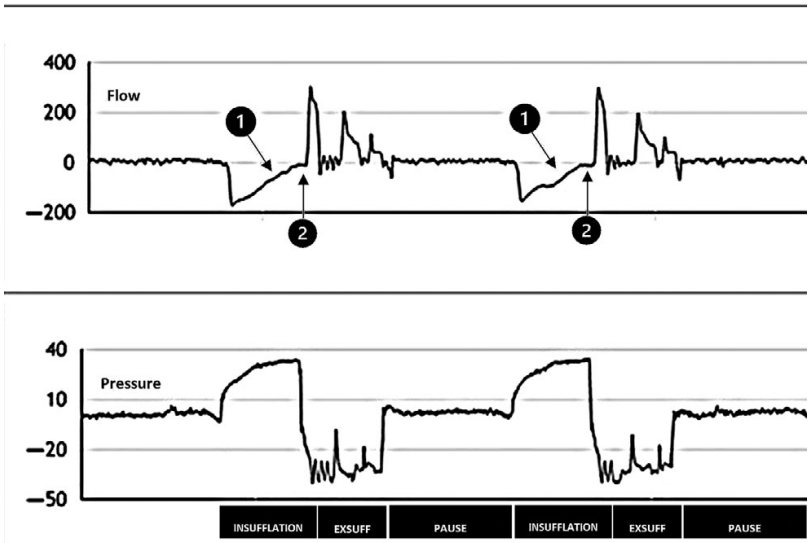


Figure 10.8 A good interface seal facilitates pressurization of the circuit, airways, and alveoli. As the pressure controller reaches the target insufflation setting, flow gradually decays (1) returning to baseline (2) at the end of the set insufflation time representing *an appropriately set insufflation time.*

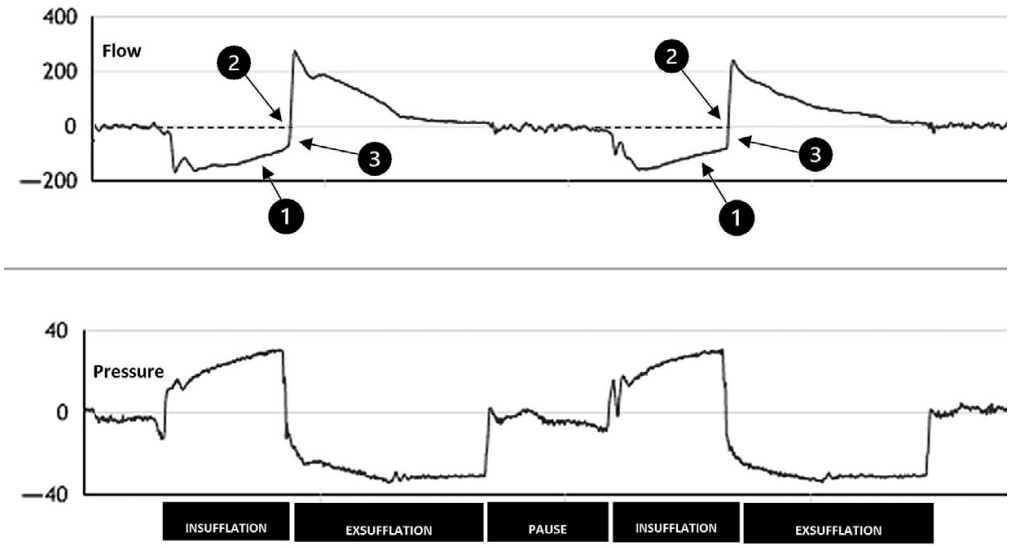


Figure 10.9 Flow is initially decaying returning toward baseline, indicating a good mask seal (1); however, the flow does not return to baseline by the end of the insufflation period (2) and creates a very distinct shoulder pattern (3) that is easily identified by a clinician. This indicates that insufflation time was *set too short.*

exsufflation pressures. Anecdotally, interface leak appears to be most problematic during the insufflation phase, whereas negative pressure during the exsufflation phase helps seal the interface to the face. Analysis of the graphics (Figure 10.11) can indicate whether leaking is a reoccurring issue for the user and the need for specific technique coaching by the clinician.

Patient–ventilator asynchrony is a well-known challenge when caring for patients being mechanically ventilated in the ICU setting[100]. Patient–ventilator asynchrony is defined as a mismatch between the time, flow, volume, or pressure demands of the patient's respiratory system and the ventilator that is supplying those demands during invasive mechanical ventilation. Asynchrony may also occur during MIE as demonstrated in Figure 10.12. Evaluation for the presence of asynchrony is an important aspect of managing MIE, though recognition of the occurrence of asynchrony during MIE may be difficult

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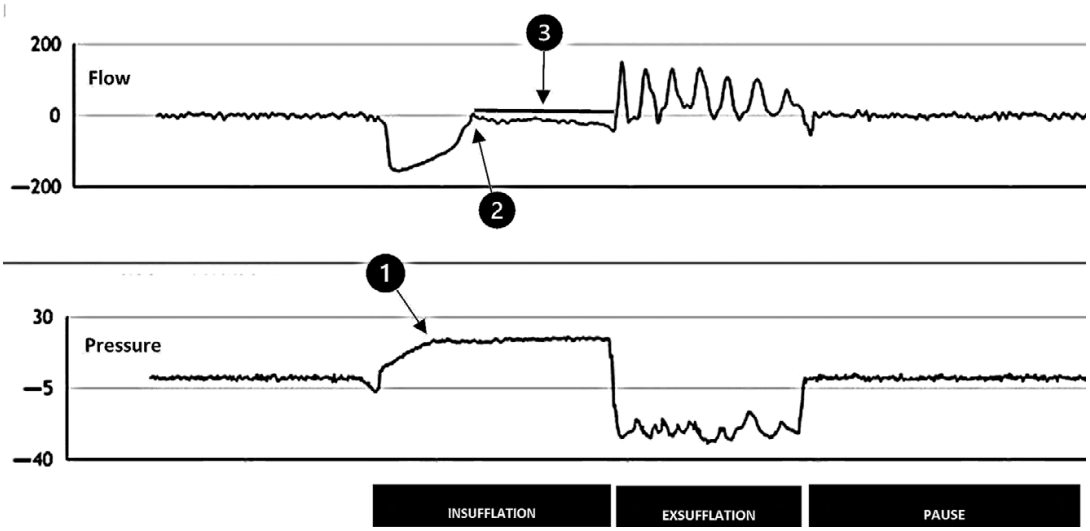


Figure 10.10 Illustrates an insufflation time that is *set too long,* an appropriate mask seal allows the device to reach the target pressure setting (1) and the flow decays reaching the zero-flow baseline prior to the end of the insufflation phase (2). The area of the flow curve highlighted by the bar (3) illustrates the unnecessary time spent in a zero-flow condition where the alveoli have already reached the target pressure setting, however, this delay in initiating exsufflation at deep lung volumes can be beneficial for passive lung volume recruitment (LVR) with the resulting inspiratory hold if tolerated by the patient. Passive LVR can be incorporated into an individual's treatment plan as an isolated maneuver after a series of mechanically assisted coughs or integrated into the mechanically assisted cough.

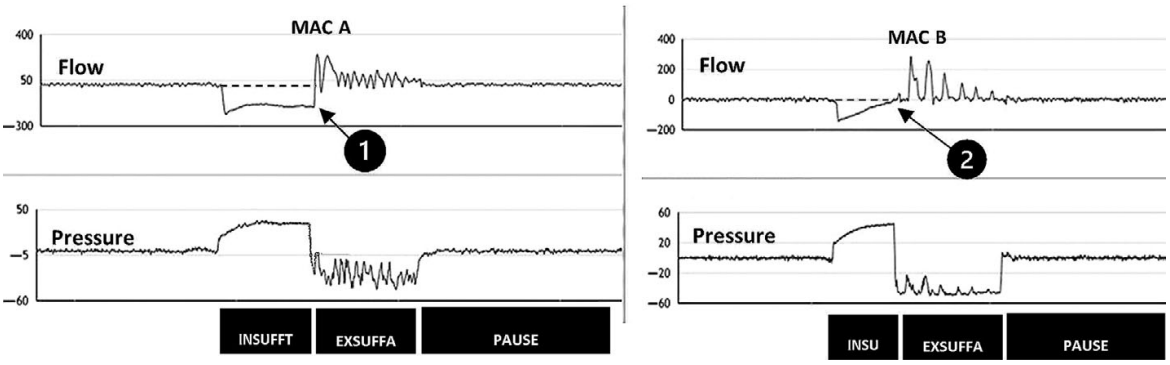


Figure 10.11 A side by side comparison of two mechanically assisted coughs (MACs) highlight the waveform characteristics when there is an interface leak as compared to a good seal. A poor interface seal and a large leak may negatively impact the controller's ability to reach the set insufflation pressure. MAC A reveals a large interface leak, which results in a failure of the flow to decay to the zero-flow baseline and creates an easily identifiable "shoulder" pattern as seen at (1). There is considerable noise in the exsufflation flow and pressure waveforms, whether the noise is created by mask vibrations due to the large leak, secretions in the upper airway, or vibration of the soft tissue in the posterior pharynx is unknown in this instance. MAC B by comparison reveals a good seal which enables the pressure controller to reach the set insufflation pressure and the flow to decay to a zero-flow baseline as seen in the graphic at (2).

with visual observation alone. Analysis of MIE graphics play an important role in confirming the presence of asynchrony and informing the clinician of the need to adjust the settings, such as use of a triggering algorithm, or the need to adjust the user technique during MIE to improve patient–device synchrony. Improved patient synchrony during MIE is likely to improve patient comfort and may have a beneficial impact on adherence and outcomes.

Evaluation of the Dysfunctional Larynx

One of the many use cases for the role graphics play in managing MIE is in the bulbar ALS patient population. Upper airway collapse is a known side effect in these patients[64,72,101,102]. Upper airway collapse though, is not the only laryngeal response pattern that occurs during MIE. Andersen and colleagues coined the term

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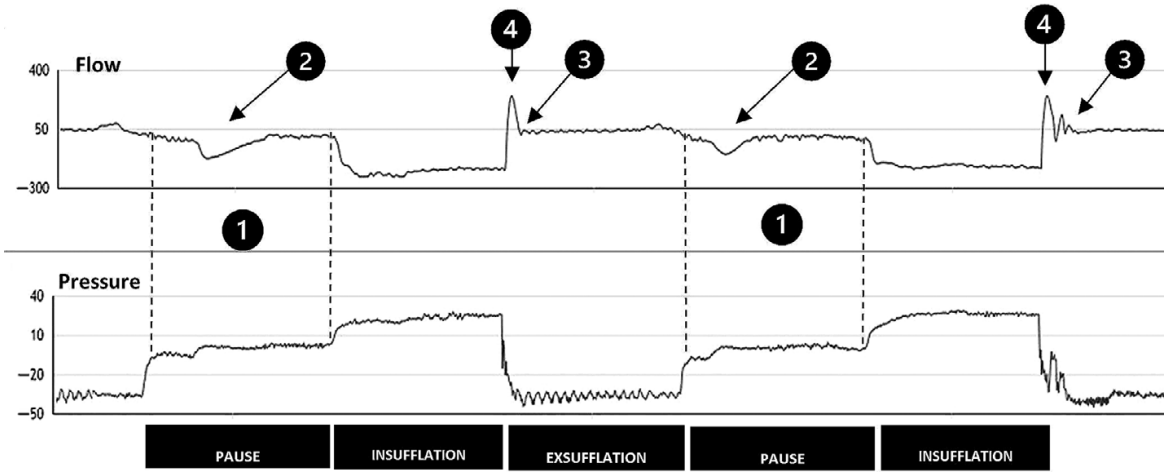


Figure 10.12 This graphic reveals the presence of patient–MIE device asynchrony. Here the clinician had opted to set a fixed 2-second pause time (1) instead of utilizing the automatic triggering algorithm feature available on the MIE platform. The patient attempts to breathe during the pause period (2) indicating that either the triggering algorithm should be initiated, or the pause time should be shortened. Another potential issue contributing to the presence of asynchrony is upper airway collapse (UAC) (3) occurring immediately after the gas decompression spike (GDS) **(**4**)** noted at the start of each exsufflation phase. MIE, mechanical insufflation–exsufflation.

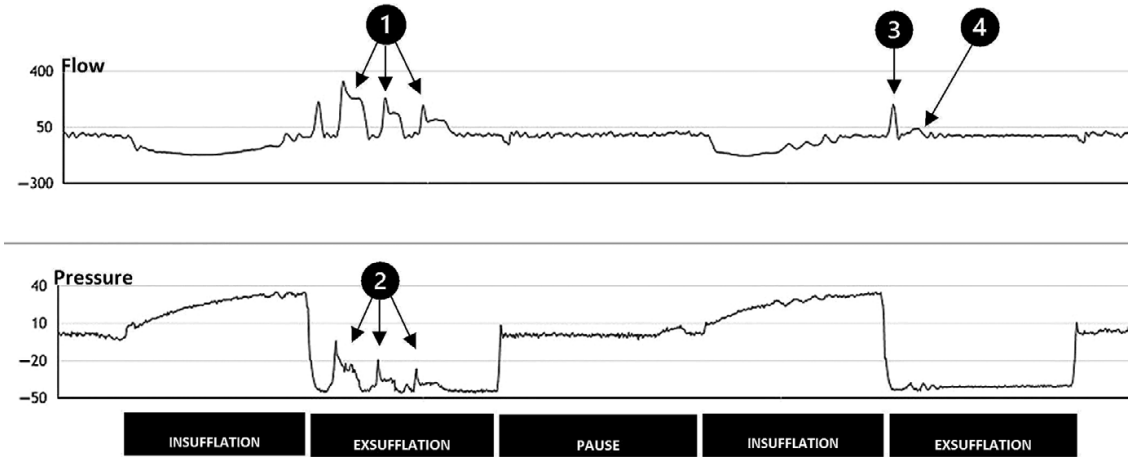


Figure 10.13 Upper airway patency is confirmed by the presence of three separate active cough efforts with glottic closure noted on the graphic to the left (1). Active cough efforts with glottis closure is confirmed by the presence of counterpressure spikes in the pressure waveform (2). By contrast, upper airway closure associated with no discernible expiratory flow following the gas decompression spike on the graphic to the right (3). The spike is flow generated by the depressurization of the 1.8 m tubing as opposed to flow coming from the airways. This gas decompression spike is the first noticeable expiratory flow pattern that is seen in both examples (4). It is incumbent upon the clinician to recognize the potential for upper airway collapse (UAC), to investigate the potential for the presence of UAC during MIE, especially in patients at greater risk, and ultimately to take the steps to minimize UAC when possible. MIE, mechanical insufflation–exsufflation.

"the dysfunctional larynx"[103]. Evaluation of the dysfunctional larynx includes reflex adduction during inspiration, as well as any degree of flow limitation during insufflation, and a range of degrees of flow limitation during exsufflation that include complete upper airway collapse. Laryngeal responses to insufflation pressure occur in the bulbar ALS cohort and are often revealed when evaluating MIE graphics as demonstrated by the graphic examples in Figures 10.13 and 10.14.

Ultimately, whether there is inspiratory laryngeal adduction or upper airway collapse and passive obstruction, the takeaway should be clear: Graphics can play a crucial role in determining laryngeal response patterns to MIE and should guide the clinician in determining appropriate

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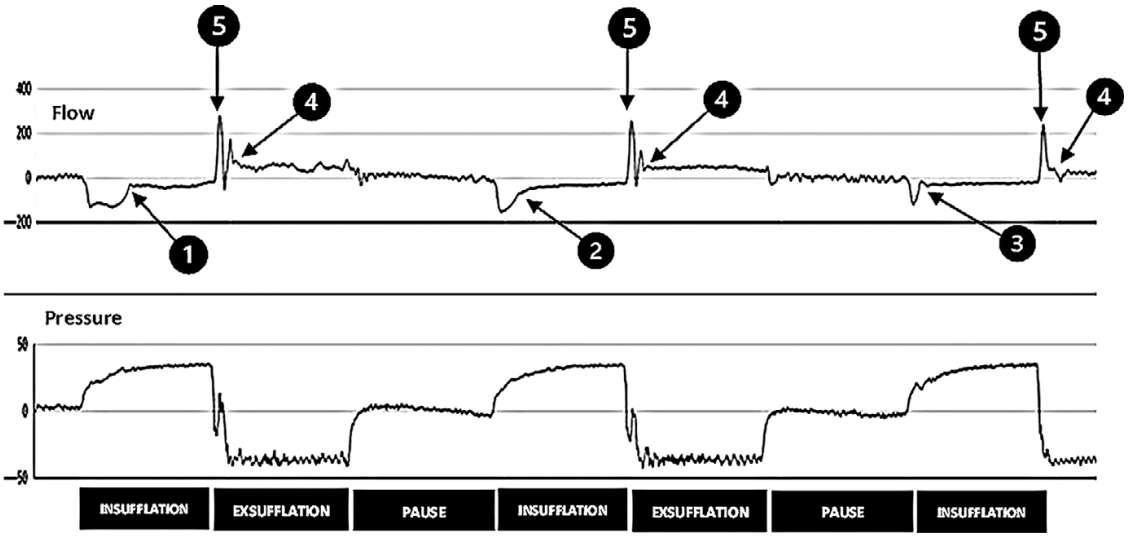


Figure 10.14 In this example, pressure and flow graphics from an ALS patient reveal progressive inspiratory flow limitation with each subsequent mechanically assisted cough (1–3). By the third cycle (3), negligible lung volume is achieved during insufflation and upper airway collapse during exsufflation is noted on all three cycles (4) following the GDS (5) indicating a need for both settings' adjustment and a change in technique. This patient would likely benefit from pausing in between each mechanically assisted cough to avoid progressive inspiratory airflow limitation. Additionally, the patient should practice a completely passive technique during the insufflation phase followed by an active huff during the exsufflation phase to improve MIE efficacy. ALS, amyotrophic lateral sclerosis; GDS, gas decompression spike; MIE, mechanical insufflation–exsufflation.

settings changes or even the need to deploy salvage MIE techniques. Additionally, since many clinicians use the MIE-EF as a principal indication for both need for tracheotomy as well as for safe decannulation, it is important to evaluate the presence of a gas decompression spike as the decompression spike may be greater than the actual flows via the subsequently patent airways. When possible, it is important that the gas decompression spike be minimized with synchronized patient effort at the start of the exsufflation phase by having the patient huff or cough upon onset of the exsufflation flow (MIE-EF) observed on the MIE user interface. Only by observations based upon graphic analysis can one be reasonably sure that the MIE-EF that we are seeing are not artifactual and that MIE-EF are being optimized to a clinically effective level to promote improved patient outcomes. Additional information on techniques to improve MIE efficiacy is available in[104].

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Chapter 11

Continuous Noninvasive Ventilatory Support and Mechanical Insufflation-Exsufflation for Long-Term Management, Extubation, and Decannulation of Patients with Ventilatory Pump Failure

John R. Bach, Kevin Huang and Yuka Ishikawa

This chapter concerns long-term management, including in patients transitioned from invasive mechanical ventilation to non-invasive technigues. No one needs a tracheostomy tube only for being too weak to breathe, that is, for people with ventilatory pump failure (VPF). Noninvasive ventilatory support (NVS) is safer, better tolerated, and better maintains quality of life than does ventilatory support via tracheostomy (TMV). At any age, people can become continuously dependent on (noninvasive) ventilatory support (CNVS) without ever going to a hospital or developing acute respiratory failure. People who depend on CNVS are more safely managed in their homes by trained care providers than in institutions or hospitals where supplemental oxygen therapy can result in acute respiratory failure.

Noninvasive Ventilation versus Noninvasive Ventilatory Support

While noninvasive ventilation (NIV) may be considered an all-inclusive term, it has generally become synonymous with continuous positive airway pressure (CPAP), and bilevel PAP delivered at settings sufficient to titrate away the central and obstructive apneas and hypopneas of sleep disordered breathing but not to provide full NVS or respiratory muscle rest for people with little to no vital capacity (VC) due to severe respiratory muscle weakness or paralysis. While sleep disordered breathing can cause symptoms that include fatigue, daytime drowsiness, and morning headaches, among many others[1], these symptoms are almost identical to those caused by chronic alveolar hypoventilation due to respiratory muscle dysfunction.

Routine polysomnography is programmed to interpret every apnea and hypopnea as being due to central or obstructive events but not to respiratory muscle weakness or dysfunction. While, with the relatively invasive placement of a lower esophageal pressure sensing electrode to sense diaphragm contraction, or the noninvasive monitoring of end-tidal or transcutaneous CO_2, the extent of symptomatic respiratory muscle weakness can be assessed, these have not routinely been done since 1965[2], because the great majority of patients have obstructive and central sleep apneas associated with old age and obesity. Respiratory muscle weakness that results in symptomatic hypercapnia indicates need for ventilatory assistance/support, that is, NVS settings, and not CPAP or low span bilevel PAP (NIV).

Settings for Noninvasive Ventilatory Support

While NIV can alleviate sleep disordered breathing and normalize the apnea-hypopnea index, with extreme obesity or respiratory muscle dysfunction the index can be normalized without normalizing $PaCO_2$ or relieving shortness of breath[3]. Assisting inspiratory muscles is a function of the volume or positive airway pressure applied during inspiration, minus any delivered expiratory positive airway pressure (EPAP) that prevents full expiration. People with extremely weak respiratory muscles who have little or no measurable VC require NVS, not NIV. This is air under a pressure of about 18–20 cmH_2O or about 600 ml of air delivered to the lungs from a volume or pressure set portable ventilator.

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The 18 cmH_2O can be considered "pressure support." This pressure can be delivered from a portable ventilator with or without continuous airflow that prevents full exhalation. The relatively high pressures permit better inspiratory muscle rest during sleep without causing excessive hyperventilation as can be seen from the many hundreds of patients whose lungs have been ventilated at these pressures since leaving iron lungs in 1954[4]. Many continue to do so today.

If bilevel settings are used and the EPAP is set to a 4 cmH_2O minimum, the inspiratory PAP needs to be about 22 cmH_2O for a pressure support of 22 minus 4 cmH_2O or at least 15–18 cmH_2O for NVS settings. Passive ventilator circuits and vented interfaces are used for NIV. However, besides being counterproductive, EPAP is potentially harmful. In a study using bilevel PAP for bulbar amyotrophic lateral sclerosis (ALS) patients, Crescimanno et al. reported that the 4 cmH_2O positive end-expiratory pressure (PEEP) increased sympathetic activation and arousals because of more leaks and increased low to high frequency heart rate variability with increased leaks[5]. In another study, PEEP also caused a reduction in non-rapid eye movement stage 2 sleep[6]. Autotriggering associated with the increased leaks due to EPAP and EPAP/PEEP offsetting the threshold load imposed by intrinsic PEEP was often followed by arousals and predominance of light non-rapid eye movement sleep while decreasing N3 sleep as well[7]. Nonrespiratory effects of EPAP include increasing or decreasing transvascular fluid flux that affects alveolar and extra-alveolar vessels, most often increasing lung water. Alveolar epithelial and pulmonary endothelial permeability, the bronchial circulation, cardiac function, regional distribution of systemic perfusion, central nervous system pressure and blood flow, and the kidneys are all affected by EPAP. EPAP induced mediastinal pressures occur nonuniformly and can be associated with left ventricular dysfunction. It also causes a vagally mediated reflex response to lung inflation that decreases heart rate, blood pressure, and stroke volume and it decreases left ventricular afterload. Reduced venous return affects cerebral venous pressures, renal blood flow, increases renal venous pressures, and decreases urine output and sodium excretion[8].

However, full NVS can also be delivered via portable ventilators without EPAP at a positive inspiratory pressure of 16–45 cmH_2O, that high for the morbidly obese[3], or assist/control volumes of 650–1500 ml via active circuits with nonvented interfaces. These settings, in open circuit systems of NVS, are needed to compensate for air leakage, to facilitate rapid return of any oxyhemoglobin desaturation (O_2 desat) to >94% when periods of air (insufflation) leakage causes transient desaturations, and they permit central respiratory drive located in the caudal pons to control the extent of alveolar ventilation. Rapid recoveries to normal NVS are suppressed by any supplemental oxygen administration or sedative medications, which should always be avoided for people using open circuit systems of ventilatory support since they can result in extreme hypercapnia[9].

Typically, NVS can be prescribed as a range of settings, volume preset 650–1500 ml, at physiologic back up rates of 10–12 per minute, via 15–22 mm mouthpieces and "straws" as well as via nonvented nasal or oronasal interfaces. With these ranges, therapists can work with users in their homes to determine their most comfortable settings and interfaces. Although most adolescent and adult patients initiate sleep NVS at settings of about 700 ml, almost all our patients eventually use settings of 1100–1300 ml. These allow for great tidal volume variability that helps preserve lung compliance and facilitate lung volume recruitment, cough flows, speech, and increased voice volume. Because upon routine annual evaluation these patients are never hypercapnic and rarely very hypocapnic, medullary and pontine areas of respiratory control are controlling how much air they take in from breath to breath (see Chapter 4). When these centers do not control alveolar ventilation, such as during closed circuit continuous tracheostomy mechanical ventilation (CTMV) when tidal volumes vary little and do not trigger bronchial dilatory reflexes, there is a tendency for dyspnea to result in settings to be adjusted for hyperventilation and hypocapnia. Efforts to reverse this, by increasing dead space breathing or decreasing ventilator settings lead to increasing dyspnea and are bound to fail, but with decannulation to NVS CO_2 levels tend to increase back to normal levels[10,11]. We reported that once daytime CO_2 levels are normalized by sleep NVS and patients continue to weaken to the point that daytime CO_2 levels begin to rise again, patients become symptomatic only when the hypoventilation that increases CO_2 results in O_2 desat <95%[12].

For people with excessive abdominal distension associated with volume preset ventilation, it is warranted to switch to pressure assist control ventilation at settings of 17–24 cmH_2O and rates of 10–12/min [4], but up to 55 cmH_2O may be required for the morbidly obese[3], or others with stiff lungs, to maintain normal lung ventilation and O_2 sat. Such high-pressure support cannot be delivered by most bilevel units but only by portable

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ventilators. While pressure preset ventilation better compensates for insufflation leakage, the gushing of air can also disrupt sleep and lend to ventilator autocycling. Also, it is not possible to "air stack" for active lung volume recruitment to facilitate lung volume recruitment, communication, and coughing when necessary.

Historical Perspective and Paradigm Paralysis

Physicians are taught that ventilatory support can be provided only via invasive airway tubes, that is, endotracheal and tracheostomy tubes. However, many hundreds of people, who have little or no respiratory muscle function, have now been using CNVS for over 65 years since permanently leaving iron lungs and other body ventilators for NVS in 1957. Still, extremely few physicians, essentially only those in BreatheNVS (www.breatheNVS.com) centers, use CNVS and extubate ventilator unweanable patients to it, instead of resorting to tracheostomy tubes[13–19]. The extent of rest, to normalize both sleep and daytime blood gases, is a dosage effect such that, if sleep NIV/NVS is discontinued, blood gases can deteriorate over a two-week period[14,16].

In the 1930s, 1940s, and early 1950s, NVS referred to the use of negative pressure body ventilators (Figure 11.1)[19]. Today, however, NVS refers to noninvasive positive pressure ventilatory support, at full

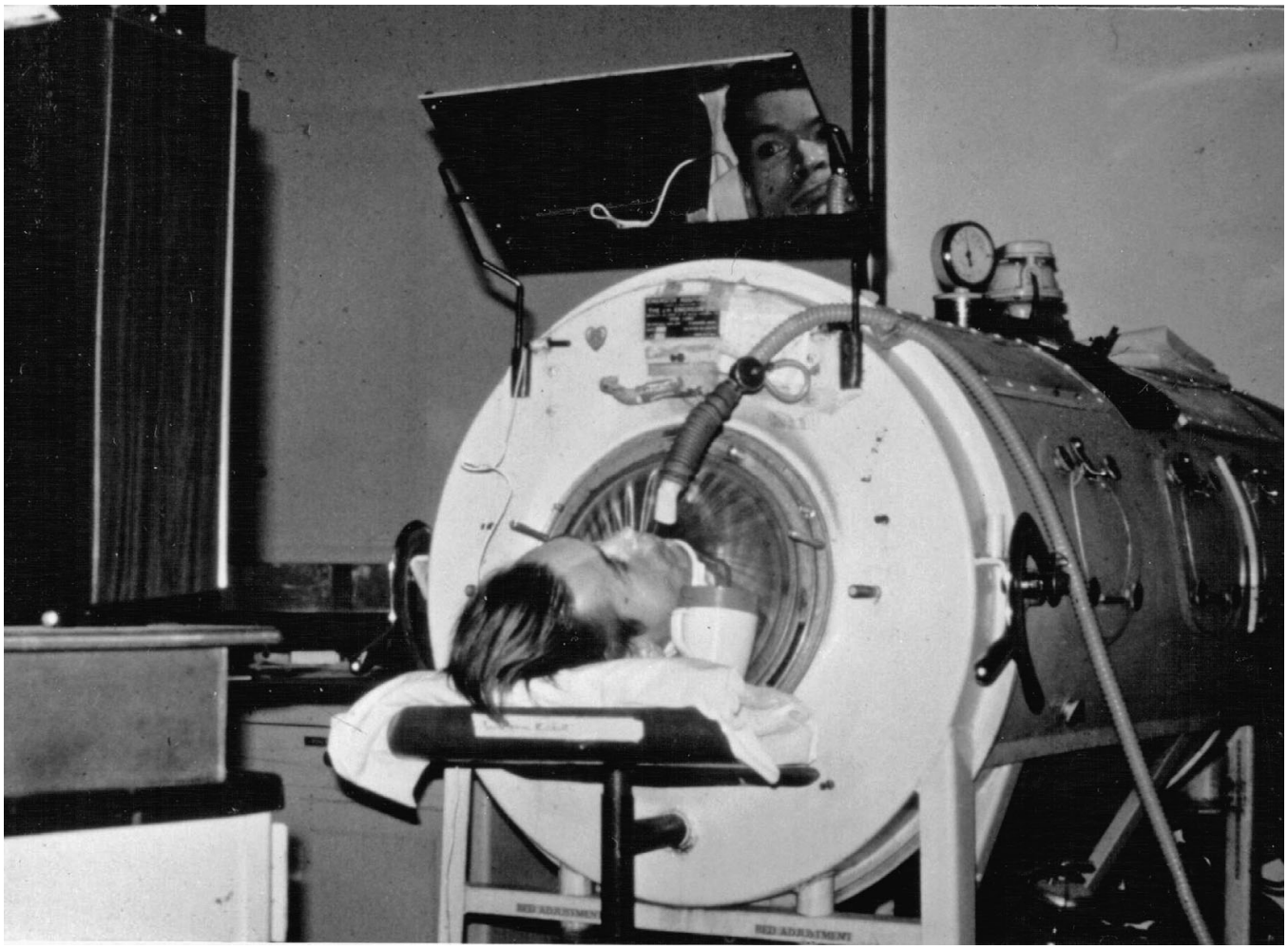


Figure 11.1 A 41-year-old with Duchenne muscular dystrophy who had a "chest cold". His lungs are being ventilated by using an iron lung and he is supplementing breaths from the lung by adding volumes of air from a portable ventilator delivered via a 15 mm angled mouthpiece. Although he had no measurable vital capacity and no autonomous ability to breathe, he was able to use mouthpiece CNVS for 18 years. CNVS, continuous noninvasive ventilatory support.

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Figure 11.2 A 40-year-old with Becker muscular dystrophy using a 15 mm angled mouthpiece for CNVS since avoiding intubation in 2015. CNVS, continuous noninvasive ventilatory support.

support settings, delivered via oral, nasal, or oronasal interfaces (Figures 11.2–11.4) directly to the airways. Jack Emerson's iron lungs had provided ventilatory support for many hundreds of post-polio survivors, people with spinal cord injuries (SCIs), muscular dystrophies, spinal muscular atrophies, and other neurological diseases[19]. Then, in 1952, with only one or two iron lungs to serve 400 respiratory poliomyelitis victims in Denmark, tracheostomy tubes were placed for ventilatory support (TMV)[20]. This invasive approach spread to the United States to get patients off body ventilators and into wheelchairs. However, in 1953 Dr John Affeldt of Rancho Los Amigos National Rehabilitation Center reported that, instead of TMV, patients had received full NVS via mouthpieces[21]. Since there were no portable ventilators, powerful blowers, like the Zephyr™, continuously delivered the air at pressures >50 cmH_2O so that the patient could take as much of it as desired during the day and as determined by their ventilatory drive during sleep. They had many O_2 desats due to air leaking but almost never lost the mouthpiece or they could have died since there were no alarms and most users had little to no upper limb function.

In 1957, Dr Augusta Alba switched 257 patients from body ventilators to mouthpiece CNVS delivered by a portable pressure cycling ventilator, the Thompson Bantam™, at Goldwater Memorial Hospital in New York City[22]. Some of these people are still alive and using mouthpiece CNVS for over 65 years with no respiratory complications or hospitalizations[4]. They receive NVS via various styles of mouthpieces during the day, and when it became available in 1964[4], they began to use the Bennett Lipseal™ for reliable sleep NVS (Figure 11.3).

In 1981 Drs Anne Delaubier and John Bach placed foley catheters into Bach's nose and nasal NVS was born. When used at NVS settings, nasal NVS was discovered to be able to provide full NVS without excessive air leakage out of the mouth. Dr Anne Delaubier described nasal NVS in her rehabilitation certification thesis in 1984[23]. In 1987 Bach used nasal CNVS for a woman with multiple sclerosis and 100 ml of vital capacity and, in doing so, avoided intubation[24]. Subsequently he used it for patients with 0 ml of vital capacity. Besides NVS via facial interfaces, the intermittent abdominal pressure ventilator is again available for daytime ventilatory support[25].

Indications for Tracheotomy

Clearly, because people with spinal muscular atrophy (SMA) type 1 can live over 25 years with 0 ml of VC using CNVS from as young as 4 months of age[26,27], because patients with Duchenne muscular dystrophy (DMD) can live into their 50s using CNVS over 25 years and without ever going to a hospital[3], and because post-polio survivors can depend on CNVS for over 65 years with no ventilator-free breathing ability (VFBA) or any respiratory complications[3], no extent of respiratory muscle weakness, in a cognitively functioning individual, including those with VCs down to 0 ml, indicates the need for a tracheostomy tube at any age[3]. However, only about 25% to 45% of ALS patients ever make it to CNVS dependence before requiring a tracheostomy[28]. Yet, their bulbar-innervated muscle function is no worse than that of SMA type 1 patients, infants and adults, who have absolutely no motor function at all other than eye movements. The obvious reason is that ALS is predominantly an upper motor neuron disorder while SMA is a lower

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Figure 11.3 A 40-year-old with Duchenne muscular dystrophy using mouthpiece/(Bennett)Lipseal™ for CNVS during sleep. CNVS, continuous noninvasive ventilatory support.

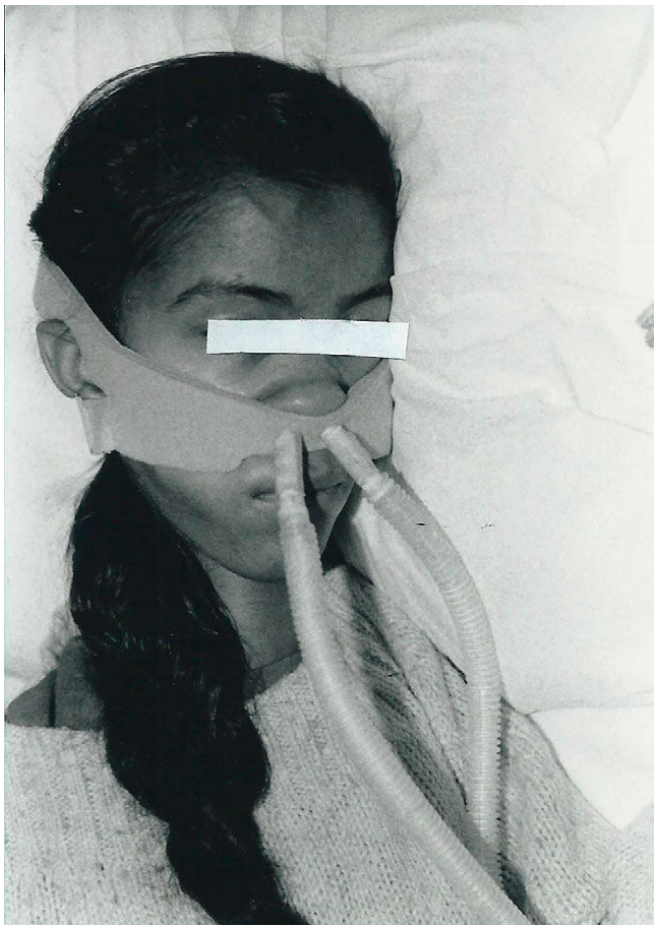


Figure 11.4 The first patient with a congenital myopathy and less than 200 ml of vital capacity using nasal CNVS before the advent of nasal interfaces in 1984. CNVS, continuous noninvasive ventilatory support.

motor neuron disorder. This can be further characterized by considering mechanical insufflation-exsufflation-expiratory flows (MIE-EF). While the MIE-EF remain constant or increase over the years for DMD and SCI patients, and increase markedly from the neonatal period to adulthood for SMA patients, they can decrease in upper motor neuron ALS patients[29]. When the MIE-EF decrease to approach 120 L/min or less, the upper airway is not sufficiently patent for MIE to expel airway secretions and maintain normal O_2 sat[29,30]. Patients become dyspneic and tracheotomy is needed for survival. This does not happen for any lower motor neuron or myopathic disease.

Outcomes of Tracheostomy Mechanical Ventilation

Today, it is recognized that ventilatory support via tracheostomy tubes (TMV) has poorer outcomes than CNVS for many diagnoses. Between 50% and 90% of the mortality of patients with muscular dystrophy, SCI, ALS, and certainly other diseases is due to the tube itself. For example, Carter et al. reported that 17 of 35 deaths of SCI CTMV users occurred in a mean 1.5 years post injury and were caused by the tracheostomy tubes[31]. At least 80% of the deaths of CTMV users with ALS (32 of 40) reportedly died from complications associated with the tracheostomy tube[32]. In another study 14 of 27 TMV users with neuromuscular disease died directly because of

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the tube and 24 of the 27 were probably due to the tube[22]. Indeed, while life expectancy for DMD has been reported in one center to be to 29 years of age with tracheostomy tubes, it approaches 40 years by using CNVS without them[33]. There are now over 1000 people with ventilatory pump failure using NVS around-the-clock, including via mouthpieces for daytime NVS[34].

Glossopharyngeal (Frog) Breathing

Ventilator unweanable post-polio survivors were described to have learned to ventilate their lungs by GPB or glossopharyngeal "frog breathing"[35]. Since 1924 both inspiratory and expiratory muscle function can be assisted or supported by GPB[36–40]. It can provide patients with no VC or VFBA with normal alveolar ventilation without using a ventilator, even for all day. A patient with 0 ml of VC using Lipseal™ NVS awoke frog breathing to discover that his ventilator had failed. Volumes much greater than the patient's VCs can be attained. GPB provides essentially perfect security in the event of sudden ventilator failure, day or night[37,38,41].

Some learn GPB on their own. Others are taught it via classical instructional videotapes available since 1954[41–43], training manuals[44], a video that breaks down every aspect of GPB[43], simple imitation of a clinician or a frog doing it, or by two recently described sucking and phonation training strategies that proved effective for five consecutive boys with DMD[45]. A nicely done new GPB video is now available from the BreatheNVS center in Ottawa: www.youtube.com/watch?v=9OswSaTG71I&feature=share&fbclid=IwAR0vbaXLsw7K7uTI9LfPUI3i23tIHW1rqff6X5ZMhA4eCX7xwMnm1v7EHUQ

GPB is performed by the tongue pistoning boluses of air past the glottis and into the lungs (Figure 11.5). The glottis closes to hold each bolus. One GPB breath typically consists of six to nine boluses of 40–200 mL each[46] (Figure 11.6). GPB efficiency is monitored spirometrically as the milliliters of air per bolus, GPB boluses per breath, and breaths per minute (Figure 11.6). The glossopharyngeal maximum single breath capacity (GPmaxSBC) is the greatest volume over the VC that the patient can attain by GPB. Seventy per cent of high-level SCI patients, post-polio survivors, and others with bulbar-innervated muscle function can master GPB[38–39]. One of our patients with no VFBA, who was a lawyer, used GPB rather than a ventilator for NVS to argue cases in court. Other patients have been described to spontaneously come out of anesthesia frog breathing and to come out of grand mal convulsions, surprisingly without being cyanotic, frog breathing without even realizing they were doing it. They subsequently consciously frog breathe[47].

GPB cannot be used by patients using TMV and is rarely effective for patients with tracheostomy tubes even when capped closed. Gulped air tends to leak around the outer walls of the tube and out the stoma as lung volumes and pressures increase during the GPB air stacking process. An exception to this, when there is a tight fit of the tube against the tracheal wall, was recently published by Bianchi et al. A tracheostomized six-year-old boy learned GPB after a cervical tumor resection and was able to use it for VFBA for up to 12 hours per day with the tube capped. By 22 years of age, while his VC was only 670 ml and he had no VFBA except by GPB, his GPmaxSBC was 3300 ml. However, at 2900 ml of lung inflation the GPB provided air began to leak around his tube and out of the ostomy. This did not prevent him from successfully using GPB rather than TMV

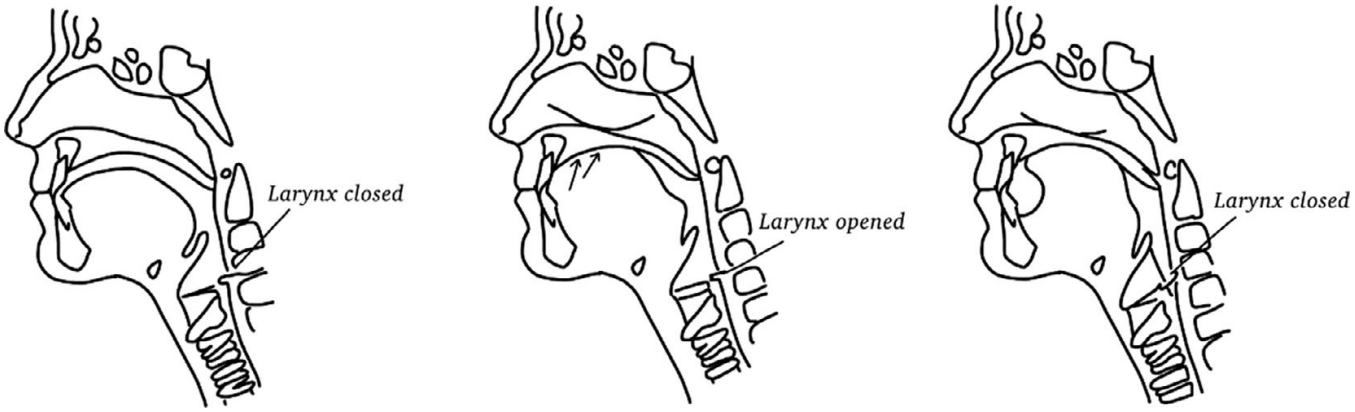


Figure 11.5 The pistoning action of the tongue propels boluses of air that are held by the glottis as it opens to receive the air and closes to retain it (with appreciation to Ms Leïla-Danaë Bach for the design).

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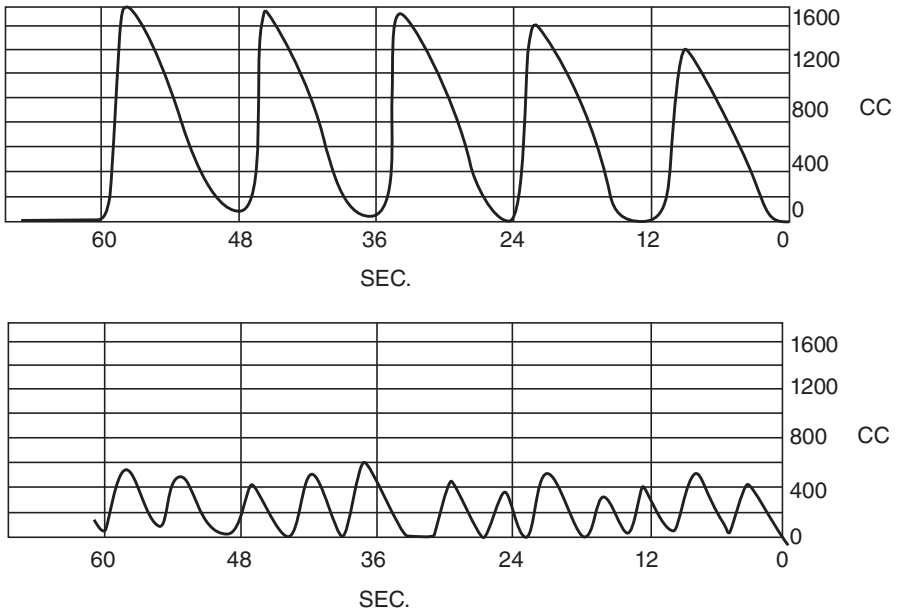


Figure 11.6 Top: Maximal GPB minute ventilation 8.39 L, GPB inspirations average 1.67 L, 20 gulps, 84 cc/gulp for each breath in a patient with a vital capacity of 0 cc. Bottom: Same patient regular GPB minute ventilation 4.76 L/min, 12.5 breaths, average 8 gulps per breath 47.5 cc/gulp performed over one minute. GPB, glossopharyngeal breathing.

throughout daytime hours[48]. Of course, he would have been better off had the trach tube simply been removed.

The safety and versatility afforded by GPB are key reasons to decannulate patients of their tracheostomy tubes in favor of NVS and MIE. GPB is the use of the tongue to project boluses of air past the glottis and into the lungs. With GPB rarely effective for TMV users, and CTMV users always afraid of sudden ventilator failure, accidental ventilator disconnections with low pressure alarms failing to sound because the tip of the dislodged tube rests against the ostomy dressing and skin have caused apnea and death in every hospital in which I have worked.

Besides permitting many patients with little or no VC to breathe up to all day and to air stack to high maximum insufflation capacity (MICs) without ventilator use or personal assistance, the GPmaxSBC can, at times, exceed volumes obtained by air stacking to the MIC receiving consecutively delivered volumes. Although severe bulbar-innervated muscle dysfunction hampers GPB, we have managed 13 DMD CNVS users with marked dysfunction who had no VFBA other than by GPB[41].

An Oxymetry Protocol to Identify the Indication for MIE in CNVS

NVS can be used long term, and for the extubation and decannulation of ventilator users, only if its use is complemented by the application of MIE (see Chapter 10). It must first be understood that normal oxyhemoglobin saturation (O_2 sat) of the blood is 95% or greater. When it is <95% with the person awake, and severe cardiovascular disease and artifact are ruled out, the following must be addressed: inadequate lung ventilation (hypoventilation) with elevated CO_2 levels, airway secretion congestion due to inadequate cough flows, and if the latter are not expeditiously expelled by MIE, lung disease with pneumonia, lung collapse, or gross atelectasis. Physicians typically administer O_2 for any respiratory symptoms but the O_2 not only does not correct what is causing the O_2 desat, it can greatly exacerbate the elevated CO_2 levels to cause CO_2 narcosis, coma, and respiratory arrest to necessitate intubation. Hypoventilation must be reversed by using NVS. Airway secretion congestion due to inadequate cough flows must be relieved by using MIE. Suctioning misses the left main stem bronchus, MIE doesn't. By normalizing lung ventilation and cough flows, blood O_2 sat levels typically return to normal and lung disease, typically pneumonia, is avoided perhaps 90% of the time[49].

Therefore, no one presenting to emergency services with respiratory symptoms should be administered O_2 if he or she is suspected of having respiratory muscle weakness and has no evidence of chronic lung disease that might be causing the O_2 desat and distress. NVS needs to

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be administered, not low pressure support bilevel PAP, if the CO_2 is elevated, and MIE administered if unassisted cough flows are measured by peak flow meter to be <300 L/min and the patient is clearly having difficulty expelling secretions. A 300 L/min threshold is used because in 2011 we demonstrated that none of over 100 patients with DMD with cough peak flows (CPFs) <300 L/min who had MIE to use during intercurrent respiratory tract infections developed pneumonias or were hospitalized over a 12-month period whereas one control patient with 305 L/min of CPF who was not equipped for MIE did develop pneumonia and require hospitalization during this time. Of course, by the time he developed pneumonia his CPFs were probably <300 L/min because of natural declines over the months and because unassisted CPFs are diminished during respiratory infections and illness in general. While the threshold figure is not important, what is important is that patients whose cough flows become ineffective to clear airway secretions during illnesses have rapid access to MIE at pressures of 50–60 cmH_2O pressure. Pressures of 60–70 cmH_2O need to be used via invasive airway tubes.

Emergency departments have transport ventilators, essentially portable ventilators, that can be used to deliver NVS or bilevel units can be used at NVS settings to normalize blood CO_2 and O_2 levels. If airway clearance is a problem and the emergency department does not have MIE devices, typically CoughAssists™ (Phillips-Respironics Inc., Murrysville, PA), then air stacking followed by abdominal thrusts for manually assist coughing can increase cough flows. While chest physical therapy, oscillation, vibration, and percussion are helpful to mobilize secretions from the small peripheral airways to get them to the larger central airways, these techniques are not substitutes for the effective cough flows (MIE-EF) needed to cough the secretions out to renormalize blood O_2 saturation levels and prevent pneumonia and need for intubation.

Lung Volume Recruitment

Daily routine passive lung volume recruitment via mouthpiece, or more often via nonvented oronasal interface, was first described when CNVS users, who did not frog breathe, turned up the pressures on their Bantam™ ventilators or MIE devices to get deep lung volumes to shout, cough, and mobilize lung tissues. In 1969 Alba described the maximum passive lung volume recruitment attained this way as the "artificial inspiratory capacity"[50], and we call it the "lung insufflation capacity"[51].

Active lung volume recruitment, or the air stacking of consecutively delivered volumes of air by having the glottis hold each volume until the maximum volume of air that can be held is attained, is called the "maximum insufflation capacity"[52]. It may have first been described in 1966 when Kirby, Barnerias, and Siebens reported that CPF could be doubled and readily exceed 360 L/min for many SCI patients by receiving, and holding with the glottis, a volume of air delivered at a pressure of 50 cmH_2O. Then the manually assisted CPF are achieved by an abdominal or thoracoabdominal thrust applied concomitantly with glottis opening[53]. They explained that an "average mean volume increased 1.85 L to 3.73 L (181%) and maximum flow increased 3.63 L/sec to 6.51 L/sec (194%)" for 12 patients. There have subsequently been many more publications documenting the efficacy of manually assisted coughing to greatly increase CPF. In 1998, we described the oximetry, CNVS, MIE protocol used for extubating six pediatric patients with no VFBA and used for avoiding intubation for four other pediatric patients, nine others with neuromuscular diseases, and one with high-level spinal cord injury. We also reported 12 such patients who became CNVS dependent without being hospitalized (Figure 11.7)[54]. The oximetry CNVS MIE protocol is essentially the use of oximetry as feedback to maintain normal O_2 sat by using CNVS and MIE. It is also instrumental in permitting the extubation and decannulation of ventilator unweanable patients to up to CNVS and MIE[55,56].

Extubation

Even when used optimally, manually assisted coughing, MIE, and up to CNVS can fail to prevent pneumonia and distress, and decreasing blood O_2 desat levels can result in intubation and invasive mechanical ventilation. However, pneumonia can resolve and O_2 sat return to normal by using MIE at 60–70 cmH_2O pressure via the tube[55,56]. People with ventilatory pump failure should not be extubated until the O_2 sat baseline has returned to normal in ambient air, the lungs are healthy, and the person is alert and ready to be extubated and placed on nasal NVS, that is, be able to breathe through the nose to trigger the air delivery from the ventilator[55,56]. Our center in New Jersey, and some other BreatheNVS centers, have a close to 100% success rate at extubating intubated, ventilator "unweanable" patients to nasal CNVS without resorting to tracheostomy tubes. Indeed, 83% of the initial 257 patients transferred to our centers intubated,

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Figure 11.7 A 51-year-old with Duchenne muscular dystrophy who has been CNVS dependent for 26 years without ever being hospitalized other than for a same day admission for placement of a gastrostomy tube under local anesthesia. CNVS, continuous noninvasive ventilatory support.

"unweanable" from ventilatory support, and having failed ventilator weaning parameters, spontaneous breathing trials, and/or extubation attempts in other intensive care units, arrived with ambient air O_2 sat baselines <95% when we turned off the supplemental O_2 they were invariably transferred to us receiving. Virtually all had their O_2 saturation baselines normalized, within one to three days, by our therapists using MIE at 60–70 cmH_2O pressures via the tubes every two hours. We then extubated them to nasal and mouthpiece CNVS.

The MIE was continued via oronasal interface, after extubation, administered by their families and care providers for O_2 saturation <95%. No patients are administered any supplemental O_2 in the 12 hours before or after extubation but virtually all maintain normal O_2 saturation by using NVS and MIE and they don't undergo tracheotomies. For more details see www.breatheNVS.com.

Decannulation

Any cognitively intact patient whose O_2 sat can be made to remain >94% in ambient air by using NVS and MIE, even if CTMV dependent with little or no VC, is a candidate for decannulation to CNVS and MIE. Decannulation of patients dependent on CTMV with <200 ml of VC was probably first done by Alba in 1969 and described in 1971[57]. In 1990 and 1991 Alba and I reported the decannulation of 50 patients with high-level SCIs to CNVS after satisfying criteria (Box 11.1), many of whom were dependent on CTMV

Box 11.1 Decannulation criteria for ventilatory pump failure

- Afebrile, medically stable
- Normal white blood cell count
- Fully alert, cooperative, and motivated
- O_2 discontinued, sedative medications minimized or discontinued
- No surgical procedures requiring general anesthesia planned
- Chest radiograph abnormalities cleared or clearing
- Carbon dioxide tension <40 mm Hg breathing autonomously or using ventilator at peak inspiratory pressures <35 cmH_2O with physiologic backup rate
- Oxyhemoglobin saturation baseline 95% or higher in ambient air
- Any oxyhemoglobin desaturations <95% reversed by mechanical nsufflation–exsufflation via invasive or noninvasive interfaces
- With tracheostomy tube cuff deflated, air leakage via upper airway sufficient for vocalization with increased settings to compensate for leak and continue ventilatory support
- Coughing, unassisted or assisted, or mechanical nsufflation–exsufflation expiratory flows >160 L/min

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Figure 11.8 Woman with no ventilator free breathing ability who was decannulated after five years of continuous tracheostomy mechanical ventilation and who mastered glossopharyngeal breathing for at least eight hours of autonomous ventilator-free breathing.

with no VFBA. All were decannulated to CNVS and MIE[37,38]. This included a woman who had been dependent on CTMV for up to five years, who had no VFBA, who had required continuous antibiotic therapy for several years due to chronic respiratory tract infections before decannulation, and who, after decannulation to CNVS, mastered glossopharyngeal breathing for up to eight hours of CvFBA (Figure 11.8). The steps for their decannulations are noted in Box 11.2.

Some decannulated patients with high-level SCIs have now been CNVS users for as long as 37 years. Most whose VCs eventually exceeded 250 ml weaned to part-time NVS following decannulation. They "weaned" themselves by taking fewer and fewer ventilator delivered volumes via angled mouthpieces (Figure 11.9). Alba included tracheostomy tube decannulation and transition to CNVS as fundamental to the rehabilitation of ventilator users with VPF[37,57].

Ironically, it is widely acknowledged that the most common cause of death in high-level SCI is from respiratory complications and that respiratory morbidity and mortality has not changed in 40 years. Despite this, not

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Box 11.2 Steps for decannulation

1. The patients are medically stabilized, CO_2 levels normalized by adjusting settings and at respiratory rates minimally exceeding physiologically set (12–14/min) ventilator rates.
2. Then supplemental O_2 is discontinued and MIE used aggressively via the tube to clear secretions, every two hours or so, and normalize and keep SpO_2 normal.
3. The cuffs are deflated for increasing periods, hourly, until continuous deflation is tolerated first during daytime hours then around the clock. Delivered insufflation volumes are increased to maintain the same inspiratory volumes and positive airway pressures as with the cuff inflated. When necessary, the patient's tracheostomy tube diameter is changed to permit sufficient leakage for speech while maintaining normal CO_2 levels. Tracheal integrity, tracheostomy tube width, cuff presence, and volitional glottis and vocal cord movements determine the volume of air entering the lungs and the volume "leaking" up through the vocal cords.
4. The insufflation leakage is used for crescendo/decrescendo inspiratory cycle speech. A low speech volume indicates either inadequate insufflation volumes, a tracheostomy tube too wide, or subglottic obstruction, usually by granulation tissue or edema. Optimal insufflation volumes for normal ventilation and effective speech are then obtained with cuff removal, by placing a tube of optimal diameter and clearing the airway. The expiratory valve can be capped to permit continuous speech without need for a Passy-Muir™ valve.
6. With CO_2 and bicarbonate levels normalized, a cuffless fenestrated tube or tracheostomy button is placed so that the airway is not obstructed for practicing NVS. Prolonged use of partial cuff deflation is discouraged because of the tendency of staff to gradually increase the amount of air in the cuff. The fenestration of the commercially available tubes may be malpositioned against the posterior tracheal wall where invagination of the tracheal mucosa into the fenestration can render it ineffective and cause bleeding and granulation. Proper positioning of the fenestration can be accomplished by ordering a custom-made fenestrated tube or changing to a smaller sized tube but we have never had to do this.
7. The patients are trained in mouthpiece and nasal NVS with the fenestrated tube capped or trach button in place. The patients learn to close off the nasopharynx with the soft palate to prevent nasal leakage and use the glottis to control lung ventilation and leakage for speech. Temporarily pinching the nostrils helps the patient understand why this is necessary. Patients need to resume reflex vocal cord abduction for breathing and effective NVS. Mouthpiece NVS normalizes speech rhythm, provides normal ventilation, and permits "air stacking" for volitional sighing, shouting, and assisted coughing.
8. After using up to continuous NVS as needed for a few days, the tube or button is permanently removed and the ostomy allowed to close. Once NVS is mastered, the patient can be decannulated to chest shell ventilator. This eliminates the need for a pressure ostomy dressing and facilitates rapid ostomy closure, or NVS. More experienced clinicians can decannulate directly to CNVS and MIE and place are pressure ostomy dressing using an occlusive dressing, cane tip, and Ace bandage (Figure 11.7).

a single SCI rehabilitation center in the United States has eliminated tracheostomy tubes for ventilator users[58], even though this is very feasible by using the guidelines in Table 11.1.

Conclusions

Acute and long-term ventilatory support for people with VPF can be provided via noninvasive interfaces, indefinitely, and has been now for some for over 65 years, and for some as young as four months of age for over 25 years. Noninvasive ventilation should be used at NVS

Table 11.1 Noninvasive ventilatory support alternatives for high-level spinal cord injury

Level of lesion	VC (mL)	Bulbar/ neck	Ventilation (day/ night)
Above C1	0	– / –	CTMV/CTMV
C1–C2	<200	+ / –	EPP/EPP, NVS
C3 or lower	>200	+ / +	NVS, IAPV/NVS

Bulbar/neck, function of bulbar innervated and neck rotation muscles; CTMV, continuous tracheostomy mechanical ventilation; EPP, electrophrenic/diaphragm pacing; IAPV, intermittent abdominal pressure ventilator; NVS, noninvasive ventilatory support; VC, vital capacity.

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Figure 11.9 A 72-year-old man with C3–4 motor complete spinal cord injury after fall from a tree, after 10 months of continuous tracheostomy ventilation, mastered mouthpiece NVS with his fenestrated tube capped all day. He also used nasal NVS for sleep. He was decannulated despite having a vital capacity of only 110 ml sitting, 190 ml supine, and no ventilator-free breathing ability. He used volume preset NVS 1400 ml, rate 12. Although people with over 250 ml of VC can wean by taking fewer and fewer mouthpiece ventilations, this patient's VC did not reach 250 ml. After decannulation he aspirated liquids and solids, and had a gastrostomy, but ate and used MIE to clear what he was aspirating with every three swallows. MIE, mechanical insufflation-exsufflation; NVS, noninvasive ventilatory support; VC, vital capacity.

settings only to optimally rest respiratory muscles. Bilevel PAP can be used at NVS settings but usually isn't. Clinicians fear NVS settings but barotrauma is extremely rare for VPF patients without primary lung disease. The EPAP of bilevel PAP is counterproductive and potentially harmful for people with VPF. Oxygen therapy is never a substitute for NVS and MIE to avoid intubation or permit successful extubation for patients with VPF. NIV and NVS should never be considered for people with VPF other than in conjunction with MIE for patients with peak cough flows <300 L/min. Intubated people with VPF do not need to pass ventilator weaning parameters or spontaneous breathing trials to be safely extubated to CNVS and MIE. Tracheostomy mechanical ventilation hinders and can entirely prevent ventilator weaning. CNVS-dependent children and adults can be discharged home safely once families are taught how to administer CNVS and MIE to keep oxyhemoglobin saturation ≥95%. www.breatheNVS.com centers have done this for more than 1000 CNVS-dependent individuals.

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Chapter 12

Tracheotomy and Tracheal Cannulas in Neurologic Disease

Janina Runkel and Teresa Grimm

Tracheotomy is inevitable in long-term critical illness. Similarly, tracheotomy is warranted in neurocritically ill patients with anticipated long recovery trajectories. Using tracheal cannulas for patients with neurogenic diseases is a common method to facilitate weaning from mechanical ventilation and/or reduce aspiration[1]. Tracheal cannulas can also be utilized outside the hospital for the long-term care of patients. This chapter presents in detail the different procedures of tracheotomy and complex care. Moreover, the complications that are associated with a tracheotomy are discussed. Different types of tracheal cannulas are introduced. This chapter also addresses home care with cannulas.

Definition of Tracheotomy

Tracheotomy[1] is a surgical method in which a tube is placed into the trachea to provide airflow[1]. In Anglo-American publications, there is no difference in meaning between "tracheotomy" and "tracheostomy"[2,3]. Both terms are therefore used in everyday language and the meanings overlap. However, following the Greek origin, "tracheotomy" refers to the creation of a tracheal incision, and "tracheostomy" to the creation of a permanent and epithelialized opening (Greek: *stoma* = "opening or mouth")[4, p. 413].

Indications for Tracheotomy

Mechanical ventilation is the main indication of tracheotomy in intensive care patients[5]. Patients are tracheotomized to alleviate the weaning process. In addition, severe swallowing disorders in neurological patients, for example after a stroke, require a tracheotomy to guarantee air circulation and prevent aspiration[6]. Aspiration, insufficient cough, or pulmonary comorbidities can result in tracheobronchial retention of secretions. If the endotracheal suctioning or invasive application of mechanical insufflation–exsufflation is needed to prevent or treat tracheobronchial retention of secretions, tracheotomy is indicated, too[7].

Procedures of Tracheotomy

The procedure of tracheotomy is usually performed with the patient's head retracted, as the altered position makes the trachea more accessible[8]. The three main tracheotomy techniques are open surgical tracheotomies, percutaneous dilatational tracheotomies, and coniotomies, which are conducted in emergencies[8]. In surgical tracheotomies, an incision of the trachea is made at the height of the isthmus thyroid gland[4]. The thyroid isthmus is retracted or transected for this purpose. In percutaneous dilatational tracheotomies, the trachea is punctured between the second and fourth tracheal braces[9]. The tissue is then dilated using the Seldinger technique[10] so that the tracheal cannula[2] can afterwards be inserted. The dilatation can be conducted by using various techniques such as using a hollow bougie[11] or conducting the translaryngeal tracheotomy[12], in which the bougie and the cannula are inserted through the mouth and the larynx. Surgical tracheotomies and percutaneous tracheotomies complement each other[9]. The decision for one of the two techniques depends on several factors such as the patient's health condition and prognosis. Poovathoor et al.[13] recommend the dilatational tracheotomy for patients in intensive care units (ICUs) because the severely affected patient does not need to be transferred into an operation room. Moreover, the dilatational tracheotomy offers advantages for patients with short ICU stays as it can be conducted quickly and there is no need for additional surgery after removing the cannula[9]. In contrast, patients who are expected to need a tracheal cannula for a longer period of time benefit

[1] This chapter focusses exclusively on tracheotomy and the handling of tracheal cannulas in adults.

[2] The terms "tracheal cannula" and "tracheotomy tube" have the same meaning and are therefore used interchangeably in this chapter.

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Table 12.1 Comparison of surgical tracheotomy versus percutaneous dilatational tracheotomy

Aspect	Comparison
Complications – primary outcomes	
Death related to the procedure	No significant difference between ST and PDT[14,15]
Intraoperative life-threatening events	No significant difference between ST and PDT [14,15]
Technical difficulties	Significantly more often in PDT[14]
Complications – secondary outcomes	
Major bleeding	No significant difference between ST and PDT[15]
Stoma infection	Significantly more often in ST[14,15]
Unfavorable scarring	Significantly more often in ST[15]
Tracheal cannula obstruction, accidental decannulation, difficult cannula change	No significant difference between ST and PDT[15]
Contraindications	Special anatomical characteristics coagulopathies, an obstructed respiratory tract, or already performed surgeries for PDT[14]
Time needed for the procedure	Shorter in PDT[16]
Cost	Lower in PDT[16]

PDT, percutaneous dilatational tracheotomy; ST, surgical tracheotomy.

from surgical tracheotomy because it can prevent accidental decannulation or mediastinal emphysemas[9] and makes the change of the tracheal cannula safer. Table 12.1 shows further comparisons between surgical and percutaneous dilatational tracheotomy.

In coniotomies, the cricothyroid ligament is separated to create the cannula access. This procedure is only conducted in life-threatening "cannot intubate, cannot ventilate"[17], p. 1 situations. The hollow between the ring cartilage and the shield cartilage is palpated for this purpose and an incision above the ligamentum conicum is made[18]. After the incision of the ligamentum, the gap between the thyroid and the cricoid is kept open, which can be achieved, for example, by using a cricoid hook[18]. This allows a tube to be inserted afterwards.

Timing and Outcomes

The most appropriate time for a tracheotomy depends on the cause of the disease, among other factors (see Cheung and Napolitano[19] for a review). Patients with little or no assisted breathing, head injury or stroke benefit from early tracheotomy[19]. Terragni et al.[20] included 600 patients with respiratory disturbances in a randomized controlled trial (RCT). One hundred forty-five patients received early tracheotomy and 210 patients received late tracheotomy. In the group with an early tracheotomy, 30 participants were diagnosed with ventilator-associated pneumonia. In the group with a late tracheotomy, 44 people were diagnosed with ventilator-associated pneumonia, which was a non-significant difference. The number of ventilator-free days and the number of ICU-free days were significantly greater in the group with the patients that received early tracheotomy than in the group that received late tracheotomy.

Young et al.[21] conducted an RCT with 909 mechanically ventilated patients in an ICU. The patients were assigned to one group with an early tracheotomy and to one group with a late tracheotomy. The group with the early tracheotomy received the tracheotomy within the first four days after admission and the other group with the late tracheotomy received the tracheal cannula on day 10 or later. The tracheotomies were dilatational or surgical. Thirty days after the study started, no significant difference in mortality was found in both groups. Moreover, there was no significant difference in the duration of the hospital stay and in the duration of mechanical ventilation between the two groups. Slightly fewer sedatives had to be administered in the early tracheotomy group than in the later tracheotomy group. In the group of late tracheotomies, 45 per cent of the participants received a tracheotomy. The other participants did not need a tracheotomy, for example, due to an improvement in their health condition. The authors concluded that early tracheotomy within the first four days after

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admission should be avoided as it did not reduce the mortality in their study.

Hosokawa et al.[22] conducted a systematic review and a meta-analysis in which they compared 12 RCTs with different times for tracheotomy. The aim was to analyze the implications of the timing of tracheotomy on health outcomes. For this purpose, they defined a tracheotomy within four days from the initiation of mechanical ventilation as very early, within the first 10 days as relatively early and after 10 days as late. They found out that early tracheotomy led to significantly more ventilator-free days, a shorter ICU stay, a shorter duration of sedation, and reduced mortality than late tracheotomy. However, adverse effects were not analyzed and the outcome measures of the included studies were heterogeneous.

Deng et al.[23] conducted a systematic review and a meta-analysis with 15 RCT studies including 3003 patients. They aimed to investigate if the time of tracheotomy has an impact on short-term mortality and ventilator-associated pneumonia in critically ill patients. Their analysis showed that the time of tracheotomy did not significantly influence the short-term mortality and the rate of ventilator-associated pneumonias. When the number of participants in pooled trials was $\geq$100, early tracheotomy led to a reduced risk of ventilator-associated pneumonia. Early tracheotomy was also associated with a shorter stay at the ICU and a shorter mechanical ventilation duration than late tracheotomy, which was shown in eight of the analyzed studies. However, the time of tracheotomy did not affect the duration of hospital stay and only three studies could be analyzed with regard to this aspect. The authors of this meta-analysis noted that the studies had different definitions of early and late tracheotomy: Early tracheotomy varied from one to eight days and late tracheotomy varied from six to 28 days. Therefore, the analyzed groups overlapped.

The findings of studies that deal with the impact of the timing of tracheotomy are heterogeneous. An early tracheotomy seems to lead to a shorter stay in the ICU and a reduced risk of ventilator-associated pneumonia. For other outcomes such as mortality, the results of the studies are either contradictory or the timing of the tracheotomy does not affect the outcome. As previously mentioned, the authors of the analyzed studies defined early and late tracheotomy differently[22,23]. Consequently, there is a need to define standardized time intervals for early and late tracheotomy. In addition, it is important to consider the aetiology in the decision for or against a tracheotomy at a particular time.

Complications

Depending on the time of the tracheotomy procedure and the time for how long the tracheal cannula is applied for a patient, there may occur complications[19]. Therefore, air embolism or loss of airway can occur during the tracheotomy. In addition, the operation could fail. Displacement of the tracheal cannula and pneumothorax are early complications. Haemorrhage is a complication which can occur at an immediate or early stage after tracheotomy and occasionally late after tracheotomy. Minor bleeding can be managed by covering the wound with gauze pads soaked with adrenaline or tranexamic acid[24]. If excessive oozing occurs, the vessel needs to be cauterized or a further operation is required[4,24]. Dysphagias and accidental decannulations can occur early or late after the tracheotomy. Granulations of tissue and pneumonias are common late complications. Children, overweight patients, or patients with burn injuries are at increased risk for complications[24].

Klemm and Nowak[25] conducted a systematic review and analyzed 109 publications with regard to tracheotomy-related deaths. The results showed that there was no significant difference in the number of deaths in surgical tracheotomies (0.62%) compared to percutaneous dilatational tracheotomies (0.67%). The reasons for the deaths were intraoperative and postoperative haemorrhages, pneumothoraces, intraoperative and postoperative losses of the airway, acute heart failure, and false passages. The authors suggest that there may also be a publication bias as not every tracheotomy-related death is reported. To reduce complications in a tracheotomy, Klemm and Nowak[25] propose to use a rigid tracheotomy endoscope while a tracheal cannula is being placed. They also conclude that it is safer to conduct a tracheotomy above the fourth tracheal ring so that the underlying vessels remain intact. Moreover, they emphasize that a tracheotomy should be conducted only by experienced physicians.

Types of Tracheal Cannulas

Tracheal cannulas have different shapes and sizes, and they are used for a variety of purposes. There are different types of tracheotomy tubes available and the patient should be given the most fitting tube[1]. Tracheal cannulas for adults consist of a curved tube of which one part is inside and one part outside of the tracheostoma[1]. Two-piece tracheal cannulas have an outer tube and an inner tube, which can be changed daily or more often as needed[4]. Inside the trachea, there is often a cuff around the cannula shaft

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Figure 12.1 Tracheal cannula made of silicone with a cuff. © ICUmedical.

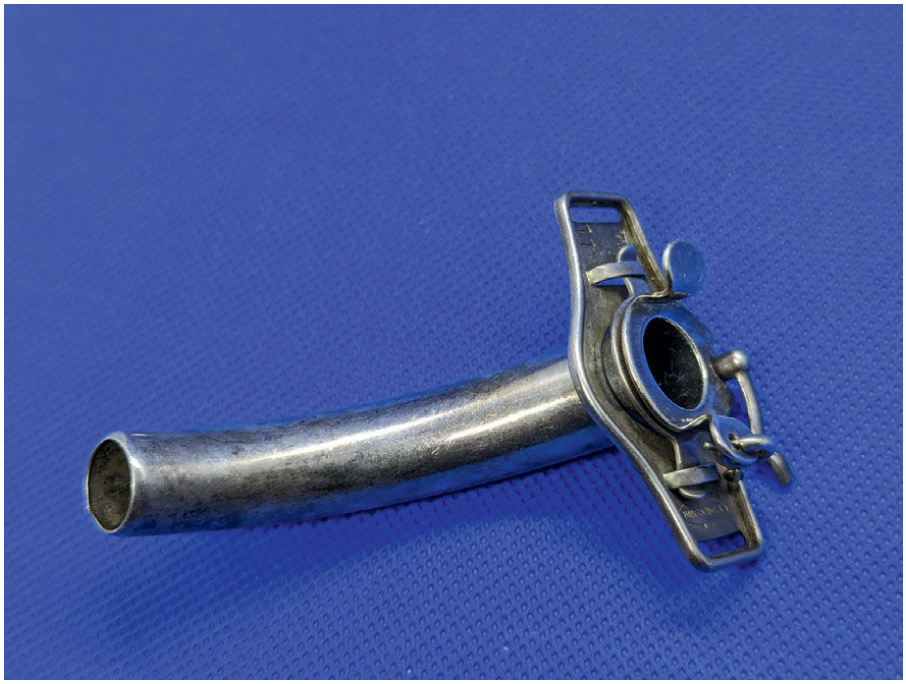


Figure 12.2 Metal cannula. © ICUmedical.

that can be inflated with air or water (see Figure 12.1). The cuff was designed to enable mechanical ventilation[26]. Even though the cuff is also intended to reduce aspiration, some saliva may flow past the cuff[1,27].

Tracheal cannulas can be made of plastic (polyvinyl chloride [PVC]), silicone or metal (see Figure 12.2)[4,26]. Metal or stainless-steel tracheotomy tubes are used for patients after laryngectomy. They are cuffless. Silicone

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Figure 12.3 Tracheal cannula with a port for subglottic suctioning. © ICUmedical.

tracheal cannulas are made for invasive ventilation. The silicone material makes it easier for clinicians to insert the tracheotomy tube into the patient's trachea. Tracheal cannulas made of PVC are used for assisting in breathing or administering oxygen therapy. They are used for invasive ventilation in patients with neurologic diseases or pulmonary disorders. PVC tracheal cannulas are less expensive compared to silicone cannulas but they have a higher risk of developing cracks or hurting the skin around the stoma, leading to granulation for example[5,28].

Some tracheotomy tubes have a port for subglottic suctioning to be able to remove saliva above the cuff (see Figure 12.3). A study[29] showed that suction-above-the-cuff tracheotomy tubes lead to a decrease in ventilator-associated pneumonia compared to tubes without the possibility of subglottic suctioning.

Outside the tracheostoma, there is a neck flange which is placed on the throat and a connector to which, for example, a ventilator tube can be fixed[1]. A heat and moisture exchanger (HME), the so-called artificial nose, can be attached to the end of the connector, too (see Figure 12.4). It has the function of preserving humidity and warmth inside the tracheobronchial system and preventing inhalation of particles in the air. An obturator facilitates the insertion of the tracheal cannula through the tracheostoma into the trachea. It is inserted into the tracheotomy tube to guide it during insertion and is removed after the tube has been placed.

A tracheal cannula has the effect of allowing exhaled air to pass out of the tracheostoma rather than through the vocal folds. This, however, prevents phonation. To enable patients to phonate and speak, speaking valves, closing caps, or speaking cannulas can be used. The speaking valve (see Figure 12.5) or the cap is placed on the connector. When the patient inhales through a speaking valve, air flows through the tracheal cannula into the lungs. During expiration, the valve closes and exhaled air flows through the vocal tract [30].

While capping the cannula, both inhaled and exhaled air flows through the larynx and not through the cannula. Capping the cannula can be dangerous for patients with neuromuscular disease or increased breathing effort, as capping the cannula – according to the Hagen–Poiseuille equation – elevates airway resistance by reducing the diameter of the airway and may result in respiratory failure. If the tracheal cannula is equipped with a cuff, it must be deflated while the speaking valve or cap is worn[31]. A speaking cannula is generally fenestrated. This facilitates exhalation through the vocal folds[32]. While speaking cannulas are fenestrated (see

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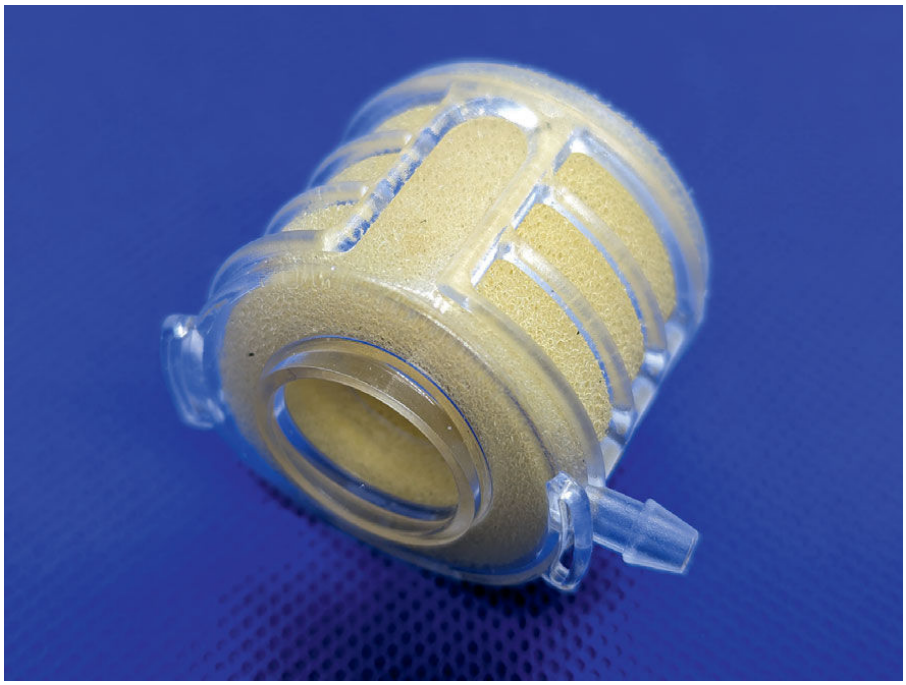


Figure 12.4 Heat and moisture exchanger (HME). © ICUmedical.



Figure 12.5 Speaking valve with an adapter for oxygen flow. © TRACOE medical GmbH.

Figure 12.6), any cannula can be used with a speaking valve as long as the cuff is deflated. To use a fenestrated cannula for phonation, its inner cannula must be fenestrated, too. A closed inner cannula generally should be used for ventilation (see Figure 12.7).

Considering all the different features, there are thus the following types of tracheal cannulas[28]:

- cuffed tube with a disposable inner cannula
- cuffed tube with a reusable inner cannula
- cuffed tube with suction aid, with an inner cannula or without an inner cannula
- cuffless tube with a disposable inner cannula
- cuffless tube with a reusable inner cannula

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Figure 12.6 Fenestrated speaking cannula. © TRACOE medical GmbH.

- fenestrated cuffed tube with a closed or fenestrated inner cannula
- fenestrated cuffed tube with a suction aid and an inner cannula that is closed or fenestrated
- fenestrated cuffless tube with or without an inner cannula
- metal tracheotomy tube
- metal fenestrated tracheotomy tube

Stoma Care

Stoma care is very important to keep the skin around the stoma clean, healthy, and without skin irritation. According to Wollina and Pabst[33], p. 223, the tracheotomy affects the skin around the stoma because of the following factors: "wet skin, salivary enzymes, [and] food stuff with mechanical or chemical irritation potential". Inflammation often affects the skin around the tracheostoma, too[34]. In stoma care, the area around the stoma is disinfected and treated with special creams for the affected skin[26]. The slot compress that is placed around the stoma should be replaced once per day or when it is wet.



Figure 12.7 Tracheal cannula with two closed inner cannulas, a cuff and a port for subglottic suctioning. © TRACOE medical GmbH.

Changing the Heat Moisture Exchanger and the Tracheal Cannula

The HME should be changed as the manufacturer suggests it or when it is contaminated, for example by secretions. If there is a hygiene department in the hospital, it may recommend changing the slot compress and the HME more often, for example every day.

Standards for cleaning and disinfection of the tracheal cannula vary depending on the tube material as well as whether the patient is at home or in a nursing home versus in a hospital with special hygiene guidelines. A routine for the changing process should be established in every hospital or at home or nursing homes for patients with tracheal cannulas. The cleaning and disinfection procedure of a tracheal cannula is described in every manufacturer's instruction, as well[26,34]. Additionally, the manufacturer's instruction informs about the frequency of changing the tracheal cannula. There is a difference between changing the inner cannula and the whole tracheal cannula. A changing interval of up to 28 days for the whole cannula is common if it has a cuff. Changing tracheotomy tubes with a cuff creates more stress for the patient and may be performed less frequently than changing cuffless tracheotomy tubes. Depending on hygiene standards and economic factors of the hospital, guidelines can be established on how often the tracheal cannula needs to be replaced. Cleaning the inner tracheotomy tube or the whole tube is also

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Figure 12.8 Cuff pressure gauge.
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possible and should be done as recommended by clinical staff such as nurses, physicians, speech and language therapists, or respiratory therapists. According to most instruction manuals, the inner tracheal cannula should be replaced or cleaned every day. For cleaning purposes, the inner cannula is taken out of the outer cannula, cleaned, and inserted again. Using tracheal cannulas with an inner cannula can be a solution to manage tenacious secretions, which tend to obstruct the tracheal cannula.

If not in an emergency situation, two people are needed for changing the tracheotomy tube: one person for preparation and taking out the old cannula (person A) and one person for inserting the new cannula into the patient's trachea via the stoma (person B). Person A provides the new tracheal cannula, the obturator, ties for the neck plate, water-soluble lubricating jelly, a cuff pressure gauge (see Figure 12.8), a syringe, and a slot compress. The patient is lying in bed during the whole procedure. If the patient shows reflux, the upper body is raised 30 degrees. The head should be flexed to the neck. After placing the patient, preoxygenation should be applied. Then, the suction unit should be prepared by switching it on and putting a suction catheter on the suction tube. If there is an inner cannula, person A uses the suction tube to suck the secretion from the inner cannula. The inner cannula is taken out and person A utilizes a new catheter for suctioning the tracheal cannula. During suctioning, person B takes the syringe to deflate the cuff from the cannula[5].

When the tracheal cannula is removed, the stoma could contract. After person A has disinfected the stoma, the new cannula should thus be placed rapidly[3]. Person B takes the used obturator out right after inserting the new tracheal cannula into the patient's trachea[5,34]. Then, the cuff should be inflated with a cuff pressure gauge. A new slot compress is placed and the neck plate is tied. Now, invasive ventilation can be started again or the HME can be applied.

Eating and Drinking with a Tracheal Cannula

There are various reasons that might impair a patient who wears a tracheal cannula: injured skin around the

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stoma[33], aspiration, or pneumonia[19]. Not only dysphagia but also the wrong tracheal cannula can lead to impaired secretion, for example, due to friction of the skin. However, a tracheotomy itself does not impair swallowing – the main reason is always dysphagia[35].

Eating and drinking with a tracheal cannula could thus be a step in a common dysphagia therapy in patients that are artificially fed, for example, via a feeding tube: Various consistencies of food and fluids are tested during speech and language therapy to see if they can be swallowed. Maybe a non-ventilated patient who is unable to eat solid food can drink fluids. Therefore, the tracheal cannula cuff is deflated and the patient is eating and drinking for therapeutic reasons or already for nutrition.

Patients with neurogenic dysphagia might need mechanical ventilation via a tracheal cannula with an inflated cuff[28]. For some ventilated patients, eating and drinking with an inflated cuff is possible and can enhance the quality of life. Also, in some ventilated patients, the cuff can be deflated over variable time spans, so the patient can speak, eat, and drink. Because of the ventilation, residual food which may be aspirated will be blown up to the upper airways, so that the patient has a chance to swallow the material[36]. Additionally, aspiration of saliva due to sialorrhoea can be treated with systemic anticholinergics or botulinum toxin which is injected into the salivary glands under sonographic control[37].

Speech and Language Therapy

Speech and language therapy for patients with tracheal cannulas comprises *dysphagia therapy* and *tracheal cannula management*. The goal of neurogenic dysphagia therapy is often decannulation[5] as well as eating and drinking without any limitations or help[34]. An efficient tracheotomy cannula management practice is to find the most suitable cannula type for the patient's needs and anatomy and to keep the process of decannulation short. This again must be coordinated with mechanical ventilation and weaning from mechanical ventilation, respectively.

Dysphagia therapy is based on the results of the dysphagia diagnostics with a flexible endoscopic evaluation of swallowing (FEES), which was established by Langmore and colleagues[38]. The assessment with a FEES is more reliable in detecting swallowing disorders than a clinical swallowing examination such as the Gugging Swallowing Screen[39,40]. A FEES is also conducted to decide whether a cannula can be removed or still must be applied. In dysphagia therapy, there are various options that can be used according to the patient's needs such as exercises for the musculature, manual or electrical stimulation, and medication[37,41,42].

Wearing a speaking valve or a cap and deflating the cuff is, in addition to an FEES, a way to detect neurogenic dysphagia as this is most similar to physiologic swallowing. Dysphagia therapy – further outlined in Chapter 7 – is thus best applied while the cuff is deflated and a speaking valve is used[5,37]. A speaking valve should not be used for more than 24 hours because of the dehydration of the tracheobronchial system. An inflated cuff actually prevents effective coughing and clearing of residual material from the upper airway and from the subglottic space above the cuff, which can enter deeper into the airways after deflation of the cuff [28]. Deflating of the cuff should thus always be conducted during tracheal suctioning to remove most of the secretions. Also, deflating the cuff helps to discover an impaired cough that occurs, for example, due to reduced laryngeal sensibility[28,37] (see Chapter 7).

Tracheal cannula management at the ICU or stroke unit consists of the following steps[5]. During the intervention, the patient is lying in a lateral position or sitting. First, there is a screening of the patient while the cuff is inflated to retrieve the following information: type of the tracheal cannula, the material of the cannula, size of the cannula, compliance of the patient, oxygen level, amount of additional oxygen via cannula or ventilation system, ventilator settings, and hours of ventilation versus spontaneous breathing. If there is no contraindication to deflate the cuff, it is deflated while the patient is being suctioned to estimate the severity of the dysphagia. If possible, a speaking valve is applied to allow speaking and foster swallowing. The patient is told to exhale through the mouth and nose to train physiological breathing and to restore sensation for saliva in the mouth and larynx. If the cannula has a small size, the patient gets more air while using a cap. Downsizing the tracheal cannula must be considered carefully because the thinner the cannula, the greater is its resistance to the airflow.

The Decannulation Process

Decannulation should take place as soon as possible in rehabilitating neurological patients[43,44]. When interdisciplinary early rehabilitation starts already at the ICU, the decannulation process is shorter than when rehabilitation starts later after the stay in the ICU[44].

The ability to wear a cap and to cough is, according to a review by Santus et al.[45], the most important factor for clinicians to presume an effective decannulation. If the patient remains stable for 24 to 48 hours with a deflated

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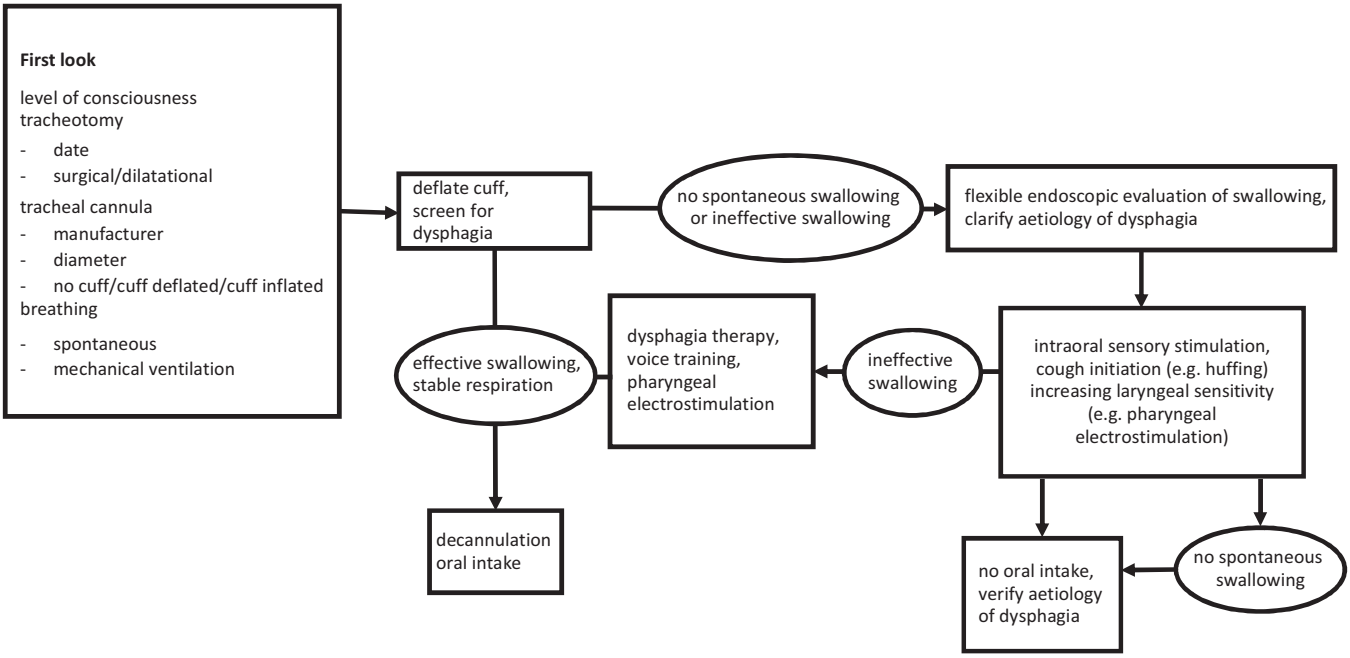


Figure 12.9 Outline of the management of dysphagia in tracheotomized patients.

cuff, the tracheal cannula can be taken out[46]. Detailed endoscopic assessments of the patient's airways (tracheoscopy) via the tracheal cannula, endoscopic inspection of the vocal folds from below and, as previously mentioned, FEES are further instruments to assess for safe decannulation. Dyeing saliva with blue food colouring to detect aspiration (blue dye test) is also helpful[47]. Other factors that can be taken into account are the level of consciousness and the ability to swallow and clear secretions completely[48]. Figure 12.9 gives an overview of the management of dysphagia in tracheotomized patients with the aim of decannulation.

Weaning from the ventilator and decannulation can occur simultaneously or one after the other, depending on the clinical situation of the patient. While weaning from the ventilator is trained by disconnecting the patient from the ventilator, weaning from the tracheal cannula is trained by deflating the cuff and applying a speaking valve. The time of disconnection or deflation is extended from day to day, if possible, following a structured protocol[44,49].

CONCLUSIONS

Placement of a tracheotomy is a relatively safe procedure. The most common reasons for long-term tracheotomy in neurological patients are mechanical ventilation and the need for endotracheal suctioning due to tracheobronchial secretions and insufficient cough[5,7]. However, a tracheotomy may cause complications and should be performed only by trained physicians[25].

The use of a tracheal cannula entails selecting the right cannula for the patient's needs and rehabilitation goals. Handling a tracheal cannula also consists of changing the cannula and cannula care. The aim of speech and language therapy along with dysphagia therapy is to enable the patient to participate in society. This includes the chance to talk, eat, and drink.

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Chapter 13

Critical Decisions in Ventilation with Acute Neurologic Injury

Eelco F. M. Wijdicks

Managing the mechanical ventilator in critical illness is far from formulaic. There is no hesitance to intubate when a patient is struggling to maintain a patent airway and further positioning or trumpet placement is not helping. Once the airway is secured, adjustments in ventilator settings and modes are continuously made, and there is a fair amount of trial and error. Weaning from the ventilator is not standardized (and probably never will be), and protocols (if there are any) are based on consultant preferences and and not always consensus. The injured vulnerable brain with a disrupted autoregulation may not tolerate changes in oxygenation or oxygen delivery, excessive amount of carbon dioxide or positive end-expiratory pressure which can increase intracranial pressure. But how tenuous is this clinical situation? The consensus statement of the European Society of Intensive Care Medicine on mechanical ventilation (MV) in acute brain injury has clearly shown that evidence for certain approaches to mitigate potential threats was either insufficient or lacking and that a substantial amount of research was needed to demonstrate the feasibility, safety, and efficacy of different management approaches in this category of patients[1, 2]. When it comes to recommendations, we are mostly left with generalities.

When airway management and invasive or noninvasive MV is needed in patients in the throes of an evolving neurologic critical illness, differences are immediately apparent. First, patients in the neurosciences ICU (neuroICU) are more likely to have normal (or nearly normal) baseline pulmonary function, unlike medical ICU patients with exacerbated obstructive respiratory disease or serious, newly acquired pulmonary parenchymal disease. Aspiration pneumonitis or pneumonia and pulmonary emboli from immobilization in a patient with prolonged unconsciousness are the most common disorders requiring MV. Neurogenic pulmonary edema is often paroxysmal and fleeting. Persistent pulmonary edema is more likely caused by cardiac dysfunction (i.e. stress cardiomyopathy) rather than a hypothalamus-based sympathetic overdrive. In patients who develop acute respiratory distress syndrome (ARDS), prone-position ventilation remains a serious concern when accompanied by increased intracranial pressure. Second, the mode of ventilation in acutely ill neurologic patients can vary, but the most used modes are pressure-support ventilation or settings that allow spontaneous breathing. Some patients may have a markedly increased respiratory drive soon after the ictus; this may require specific approaches to tone down the increased work of breathing with high tidal volumes, which could cause lung injury in the long run. Third, long-term ventilator dependency is also less common, except for patients with high cervical spinal cord transection or end-stage chronic neuromuscular disease – most acutely ill neurologic patients can be successfully liberated from the ventilator and often early in the clinical course. Fourth, patients with acute ischemic or hemorrhagic stroke who have been mechanically ventilated for a considerable amount of time are, by and large, severely compromised neurologically, and thus, high morbidity is expected. MV after acute stroke is a surrogate marker for severity of injury. Therefore, >75% of patients are transferred to a nursing home or long-term skilled nursing facility able to care for patients who have been tracheostomized with or without MV. A third of these patients may return home later but with major disabilities[3,4].

There are also similarities between the general medical and surgical critically ill patients and neurocritically ill patients. For example, treatment of neurogenic pulmonary edema is essentially similar to any treatment of ARDS. Moreover, general principles of lung protection during MV apply. Meticulous general critical care remains imperative. A prospective, single-center study of nearly 500 patients with acute brain injury (the majority of whom sustained a subarachnoid hemorrhage [SAH] or traumatic brain injury [TBI]) identified that lower tidal volumes and higher positive end-expiratory pressure (PEEP), along with probabilistic antibiotic therapy for hospital-acquired pneumonia and aggressive enteral nutrition achieving calorie goals early, resulted in decreased duration of MV and rate of complications[5].

In most patients with severe brain injury, MV starts with endotracheal intubation and ends with tracheostomy

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care and decannulation. This chapter complements Chapter 9, and herein, I review considerations in each intervention during the patient's clinical trajectory of ventilation in the neuroICU. Respiratory difficulties can result from central or peripheral nervous system disorders, and thus each section has recommendations for acute brain injury and acute neuromuscular injury. The reader will find that early intubation and MV are initiated because patients cannot protect their airways or have insufficient respiratory drive to maintain oxygenation and normocarbia. As anticipated, long-term MV identifies patients with major brain injury, which unavoidably and ultimately includes pulmonary complications. Personal, individualized recommendations are needed; the published literature is not only scarce but also derivative. It involves groups of patients rather than specific disorders and does not provide definitive conclusions on daily ICU practice. I will focus on differences in neurocritically ill patients drawn from clinical observations.

Decisions in Intubation

Acute Brain and Spine Injury

An abnormal respiratory conduit is more common in acute neurologic conditions involving the brain and brainstem because reduced wakefulness decreases the tone of several oropharyngeal muscles and changes the anatomic relationship. The tongue repositions to the back wall of the oropharynx, and further misalignment of the axis of the upper and lower airway occurs when the head is flexed. Such obstruction occurs rapidly but can be easily overcome with repositioning. Some basic maneuvers should be familiar to any physician and, in particular, neurologists, who are often called to the bedside for upper-airway obstruction. The airway can be reopened with the head tilt/chin lift. This maneuver tilts the patient's head backward to the "sniffing position," which improves the trachea and pharynx angulation, thus allowing for air transport. Next, the examiner uses the index and middle fingers to lift the mandible and bring the tongue forward. Another technique is the jaw thrust/head tilt. The examiner places three fingers under the patient's jaw and lifts the chin forward, leaving the index finger and thumb free to fit a mask snugly to the face and the other hand to operate a resuscitation bag, which can provide additional oxygen.

A more important question is whether endotracheal intubation should follow. There are conditions in which it is not necessary. Patients recovering from a generalized tonic-clonic seizure will often have transient audible respiratory sounds (stertor) and tachypnea, and side position with manual bagging is sufficient. An oropharyngeal airway placement may prevent further tongue biting. To place this oral airway device, open the mouth, and place a wooden tongue depressor at the base of the tongue. Apply downward pressure to displace the tongue from the posterior pharyngeal wall. Then place the oropharyngeal tube close to the posterior wall of the oropharynx and move it toward the tongue until the teeth are at the bite-block section. *Recurrent* seizures require additional lorazepam or IV anesthetics, and this changes the equation. These patients receive better protection with endotracheal intubation and mechanical ventilatory support. (Unfortunately, we more often see endotracheal intubation rather than cautious observation of patients who experience only a single seizure.) Another condition allowing postponement of endotracheal intubation is acute spinal cord injury with lesions below the level of C5, which spare the nerve connections to the diaphragm; however, impairment of the abdominal and intercostal muscles markedly reduces expiratory effort. Placing the patient in a supine position improves expiration by relieving pressure induced by abdominal contents in the chest; breathing becomes labored when the patient is placed upright in a chair. The call to postpone endotracheal intubation in acute neuromuscular disease hangs by a thin thread – often acceptable in myasthenia gravis and chronic exacerbations, but unacceptable in patients with rapidly progressive cervical myelopathies.

Elective endotracheal intubation must be performed in any patient with marginal oxygenation. Patients with mild tachycardia, evidence of hypoxemia on a pulse oximeter, evidence of increased effort to breathe with postural changes, or simple restlessness and shortness of breath must be intubated preemptively. Cervical spine injury should be anticipated in the appropriate circumstances. Studies of patients with TBI have reported coexistent spine injury in 8% to 15% of patients. Extension of the neck should be avoided, and during intubation, experienced personnel should immobilize the neck. When available, fiber-optic intubation may be helpful because it eliminates the need for traction of the neck. Videolaryngoscopy may provide a superior view to that obtained by direct laryngoscopy. Published literature suggests this benefit extends to both hyperangulated and Macintosh-style video laryngoscopes[6].

Intubation has evolved into a standardized approach known as rapid-sequence intubation, which entails the near-simultaneous administration of an induction agent and a paralytic agent. The induction agent rapidly causes

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unconsciousness, and most protocols use etomidate and rocuronium for this purpose. Life-threatening hyperkalemia after succinylcholine can be expected in chronically paralyzed patients but should be avoided altogether. Avoid or reduce the dose of propofol bolus and infusion, which may cause significant hypotension requiring vasopressors for one to two hours. Postintubation hypotension is troublesome in any patient with recent SAH or ischemic stroke and most certainly in patients with prior chronic kidney disease, which may result in acute tubular necrosis. Even brief hypotension during intubation remains a major concern in the neuroICU population. Relative hypotension may jeopardize patients with reduced (or marginally compensated) cerebral blood flow such as patients with severe intracranial stenosis from thrombus, atheromatous stenotic plaque, or cerebral vasospasm. Push-dose pressor sticks (100–200 mcg of IV phenylephrine) should be at the bedside; its strong (alpha) vasoconstrictor effect will immediately control hypotension. Interestingly, there is new compelling evidence that a single dose of 2 gram of ceftriaxone reduces later ventilator associated pneumonia[7]. This finding likely will change practices.

Acute Neuromuscular Injury

In acute neuromuscular respiratory disease and in the absence of airway obstruction and pooling of secretions, patients with neuromuscular failure may first benefit from a trial of bilevel positive airway pressure (BiPAP). It has been successful in patients with chronic neuromuscular disease and worsening respiratory mechanics[8–10]. Patients do not always tolerate BiPAP well and certainly when used for more than one day. Other patients may have copious secretions, and BiPAP impairs expectoration. In those patients, humidified high-flow nasal cannula (HFNC) oxygen therapy is a tried alternative (starting at 45 L/min and an FiO_2 of 0.25–0.30), reducing breathing effort through dead-space washout, reduced nasopharyngeal resistance, positive pharyngeal pressure, and alveolar recruitment. However, HFNC may not provide sufficient support to the diaphragm weak from neuromuscular disease and is inadvisable for patients with hypoxemia from shunting related to poor lung deployment with poor respiratory mechanics. It is best reserved for patients with hypoxemia from other causes.

Neuromuscular respiratory failure can be very subtle, but interrupted speech offers a clue; patients tend to speak with only a few syllables to each breath. In addition to increased respiratory rate and small tidal volumes, patients may have mild tachycardia and perspiration on the forehead. We have repeatedly seen patients with these clinical attributes progress in a matter of hours, and therefore, they are not safe outside a monitored area. Without exaggeration, we repeatedly see misjudgments. Rapid decline within the same day of admission, including "crash intubation" from sudden respiratory distress, may occur, surprising the uninitiated care provider. A pulmonary segmental collapse may also cause sudden worsening respiration early in the course (and, not infrequently, bronchoscopy after intubation detects a mucus plug). In our review of earlier cases on the ward, intubation between 6 p.m. and 8 a.m. was common, a strong indication that the early signs of acute neuromuscular failure went unrecognized during the day. The mechanism of these "after-hours" decompensation episodes may relate to nocturnal reduction of central respiratory drive or obstructive sleep apnea, along with poor pulmonary mechanics[11]. It is basic physiology: When acute neuromuscular weakness involves bulbar and respiratory muscles, a high risk of aspiration compromises any attempt at compensation of diaphragm weakness. Noninvasive ventilation can be tried in about 40% of MG patients in crisis. This intervention helps to avoid MV in a third of the patients and is associated with shorter duration of ventilation and ICU stay[12]. The myasthenia gravis variant muscle-specific kinase-positive disease presents with far more rapid progression than typical disease, and one major factor is the prominent bulbar symptoms. Decisions to proceed with aggressive (and by implication) permanent respiratory assistance in chronic forms of neuromuscular disease (i.e. progressive genetic myopathies and motor neuron disease) are discussed in detail in other chapters of the book.

Decisions in Mechanical Ventilation

Generally speaking, MV has evolved, and several modes are now proprietary[13–15]. Hamilton Medical has an adaptive-support ventilation (ASV) mode. It is a closed-loop ventilation, and the clinician sets the percentage of minute ventilation, PEEP, and FiO_2. The ventilator determines an optimal tidal volume and respiratory rate based on an internal algorithm. It ventilates the apneic patient in a control mode and changes to a spontaneous mode when patients are triggering breaths. (Other modes are proportional-assist ventilation on the Puritan Bennett ventilator or more sophisticated, neurally adjusted ventilator assist.)

Acute Brain Injury

In our neuroICU, ASV or continuous mandatory ventilation (CMV) is the preferred starting mode in patients with impaired consciousness from acute brain injury.

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CASE ILLUSTRATION

Comatose patient from severe aneurysmal subarachnoid hemorrhage (World Federation of Neurological Surgeons grade 5) from ruptured carotid artery aneurysm (Figure 13.1). MV was needed for neurogenic and cardiogenic pulmonary edema (echocardiography documented of Takotsubo cardiomyopathy with ejection fraction of <20%). Patient was ventilated on PCV with pressure support of 14, PEEP of 8, rate of 20 per minute and FiO_2 of 50%. Tidal volumes ranging between 280 and 320 and plateau pressures 22–24. Pulse oximetry remained in the mid-90s. MAPs were held between 65 and 75 mmHg requiring angiotensin II at 10 ng/kg/minute and norepinephrine at 0.06 mcg/kg/minute.

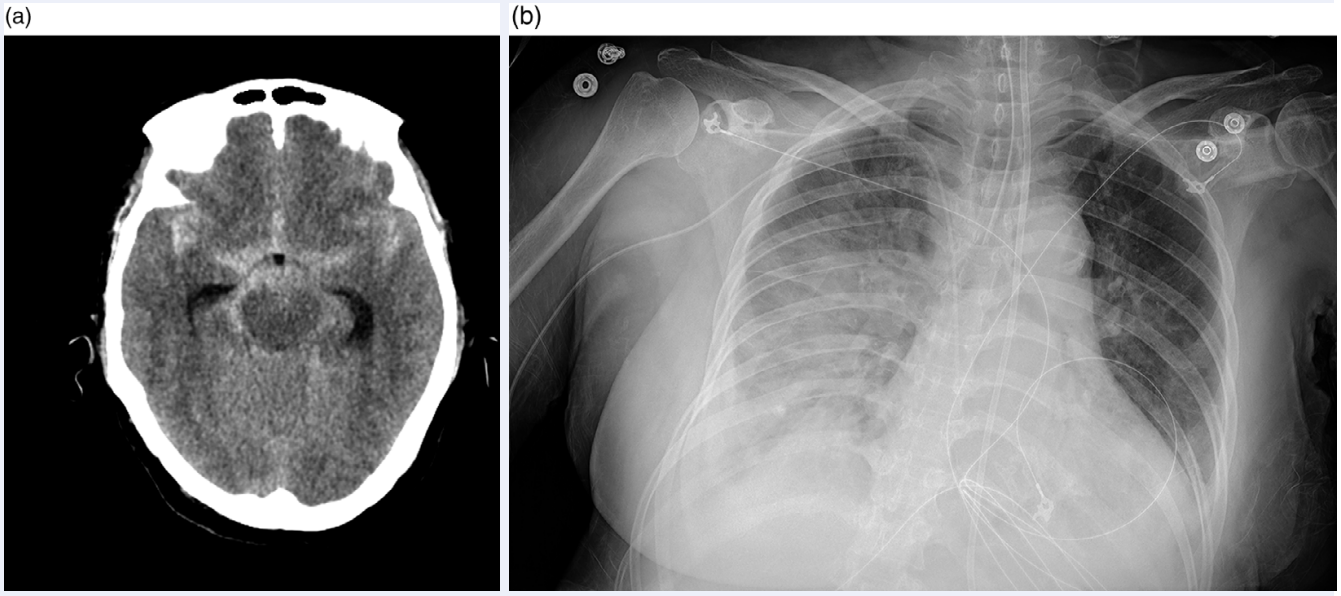


Figure 13.1 CT of the head (a) shows diffuse SAH and acute obstructive hydrocephalus. Chest X-ray (b) shows diffuse interstitial and alveolar airspace disease with peripheral septal lines evident and mild peripheral sparing of some of the airspace disease, altogether suggesting edema. Pulmonary function did not improve, and poor compliance required prolonged mechanical ventilation. SAH, subarachnoid hemorrhage.

ASV is a less frequent initial mode of ventilation in patients with less severe injuries but who have been intubated to avoid aspiration. An assisted breath occurs when the patient triggers the ventilator, and this breath is taken with the same settings as a machine-operated breath. This ventilatory mode often is poorly tolerated by awake patients who are acutely confused and may lead to patient–ventilator dyssynchrony that can be overcome only by additional sedation. The most common side effect of this mode of ventilation is respiratory alkalosis. This mode is also divided between assist-control-volume controlled (AC-VC) or assist-control-pressure controlled (AC-PC). VC ventilation mode is the most conventional mode. It follows a constant flow pattern to deliver a preset tidal volume in the preset inspiratory time, thus ensuring constant minute ventilation. However, this flow pattern generates high inspiratory pressure that can lead to lung injury from volume trauma. Pressure-controlled ventilation (PCV) mode is an alternative mode that delivers tidal volume at a preset pressure and inspiratory time. This mode decelerates flow. PC-CMV mode sets a target inspiratory pressure instead of volume limits. The flow-wave characteristics are different in volume control and pressure control.

CMV can be used in patients with no breathing drive. Some of these clinical situations result from a severed high cervical cord, treatment with generalized anesthesia drugs (ketamine, midazolam, and barbiturates) for status epilepticus, or when there is complete apnea such as in brain death. More often, it is used in mechanically ventilated combative patients treated with neuromuscular blockade, particularly in patients with multitrauma and significant respiratory distress. Its operating principle is a preset tidal volume with a fixed frequency with or without effort by the patient.

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Different modes of MV become operational when patients display so-called flash (neurogenic) pulmonary edema. When this occurs (on average, five to seven times a year in our neuroICU), there are difficult management issues. It is common in poor grade (comatose) patients after aneurysmal SAH. Not infrequently, the patient received cardiopulmonary resuscitation before reaching the hospital, and this presentation fits the pathophysiology of neurogenic pulmonary edema because pulseless electrical activity or ventricular fibrillation are also reflective of the sympathetic surge. Besides SAH, other conditions associated with neurogenic pulmonary edema include ganglionic hemorrhage, medulla oblongata hemorrhage, seizures and status epilepticus, TBI, and cerebellar hematoma. Neurogenic pulmonary edema is basically a form of ARDS[15–19]. In 2023 a new global definition of ARDS attempted to address practice changes that have occurred over the past decade. First, the increasing use of high-flow nasal oxygen (HFNO) delivery was acknowledged with the addition of a minimum HFNO flow rate of 30 L/min. Second, a move toward less invasive monitoring led to the addition of SpO_2:FiO_2 (SF ratio) with SpO_2 <97% as an alternative to identify and grade hypoxemia. As a result, either an arterial oxygen tension (PaO_2)/FiO_2 <300 or SpO_2/FiO_2 <315 (if SpO_2 <97%) identifies hypoxemia. Third, it added lung ultrasound as an acceptable imaging modality in lieu of chest radiography. The 2023 Global Definition of ARDS requires that all the following criteria are met to diagnose ARDS: (1) acute respiratory symptoms, defined as within seven days from a precipitating event or new or worsening symptoms during the previous week; (2) bilateral opacities consistent with pulmonary edema on chest radiography, CT scan, or lung ultrasound; and (3) respiratory failure not fully explained by cardiac failure or fluid overload, hydrostatic pulmonary edema as primary driver excluded by objective invasive (pulmonary artery catheter) or noninvasive (point of care ultrasound, echocardiography) evaluation, or by expert opinion[20].

In its full presentation, the clinical picture almost always appears soon after the initial brain injury. The clinical entity may be mistaken for other pulmonary conditions, such as massive aspiration pneumonia or pulmonary contusion. Recent observations in SAH and TBI raise provocative questions about the underlying mechanism and have challenged the classic explanation that pulmonary edema is of neurogenic origin[20]. Traditionally, neurogenic pulmonary edema was attributed to a massive sympathetic discharge, probably mediated by the anterior hypothalamus and triggered by an initial increase in intracranial pressure during the aneurysmal rupture. The increased sympathetic activity leads to generalized vasoconstriction, hypertension, and direct damage to endothelial cells, which may cause increased permeability (capillary leak) and subsequent airspace flooding. However, increasing evidence indicates a cardiogenic origin for pulmonary edema in SAH with structural damage to the myocardium amply documented. (See case illustration)

The clinical picture is unmistakably striking. Excessive sweating, hypertension, tachypnea, and production of frothy sputum are typical. The diagnosis of neurogenic pulmonary edema is supported by the combination of marked hypoxemic respiratory failure (hypoxemia, greatly increased A–a gradient). Chest radiography demonstrates diffuse pulmonary infiltrates and loss of airspace (see case illustration)

The cornerstone of ARDS management is lung-protective MV. This involves maintaining appropriate arterial oxygenation and protecting the injured lung from further injury by limiting alveolar overdistention, trauma from repetitive opening and closing of the alveoli, and the further release of inflammatory cytokines. The landmark ARDSNet trial, ARMA, randomized patients with ARDS to low tidal volume ventilation with an initial tidal volume of 6mL/kg ideal body weight and a plateau pressure of $\leq$30 cmH_2O or to conventional ventilation (at the time) of an initial tidal volume of 12mL/kg ideal body weight and plateau pressure $\leq$50 cmH_20. This strategy resulted in lower 28-day and hospital mortality[21]. But as tidal volume is reduced and plateau limited, the risk of alveolar hypoventilation increases. In severe cases with low lung compliance, hypercapnia and respiratory acidosis may need to be tolerated in order to maximize mean airway pressure and oxygenation. In the neurocritical population, permissive hypercapnia may be problematic because of increased cerebral blood volume through vasodilation. Lung-protective ventilation may also offer important benefits in patients with TBI. In a prospective observational study of 86 patients with severe brain injury, higher early tidal volume independently correlated with a 5.4-fold increase in odds of developing ARDS compared with lower tidal volume[22]. Moreover, conservative fluid management is beneficial. Lung function improved, and both ventilator-free days and ICU-free days increased without worsening nonpulmonary organ failure. However, its impact on the brain has never been investigated and may be harmful for similar reasons as with hypercapnia.

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Another major intervention is prone positioning, but the maneuver is immediately problematic in patients increased intracranial pressure (ICP), spinal instability, or unstable fractures. Generally, prone positioning (commonly for many hours daily) is a management strategy for mechanically ventilated patients with ARDS who are using low-tidal-volume MV and when the pressure:flow ratio is <150 mm Hg. Mechanical stress on the lung is reduced, and there is more uniform distribution in the prone position. Moreover, functional residual capacity is increased. Prone positioning can be sanctioned only if other measures to reduce ICP are taken, and ICP monitors would greatly assist in documenting efficacy of these measures. In any event, the clinical dilemma is increased ICP versus severe hypoxemia. Increased ICP and compartmental tissue shift might pose a greater danger than hypoxemia alone and should have preferential attention. In most severe refractory cases, extracorporeal membrane oxygenation (ECMO) has been advocated with variable success. ECMO can be life-saving therapy for severe ARDS patients who do not respond to conventional treatments. Once ARDS requires ECMO, we enter a likely outcome with associated high mortality rates, and we have no recorded successful experiences in our neurocritically ill patient population. Some suggestions are shown in Box 13.1.

Acute Neuromuscular Injury

MV in acute neuromuscular disease is not complicated, and sophisticated modes are rarely needed. Most patients are adequately managed with adaptive-support ventilation mode (ASV). Almost half the patients with MG crisis who require MV will require it for more than two weeks, and about 20% need some noninvasive assistance after discharge. Older age, late-onset MG, more severe disease at baseline, preexistent medical comorbidities, and the development of pneumonia are risk factors for prolonged MV. Some survivors of MG crisis require acute rehabilitation/weaning facilities, and eventually discharged home. This category of patients can expect a more complex and protracted clinical course, which includes the development of medical complications, longer hospital stays, and residual disability. These basic facts are important because pulmonary infections and sepsis are major problems, and we anticipate a large number of systemic complications as a result of ventilator dependency in our most severely affected patients with MG. Newer immunotherapies may improve outcomes in refractory MG crisis. In Guillain–Barré syndrome (GBS) MV also supports the lack of pulmonary mechanics. Once patients are on the mechanical ventilator, we can expect nearly absent vital capacity and pulmonary pressures for diaphragm standstill. As noted earlier, when MV is needed in progressive chronic neuromuscular disease, it often represents a fork in the road. Many patients decide against it knowing that their future will be ventilator dependency. (We have very occasionally seen patients who were only briefly intubated after an aspiration event that resolved.) Patients with a chronic neuromuscular disease who must make this decision in the ICU are in an invidious position and often would have benefited from prior discussions on their anticipated clinical trajectory which would allow a much better thought through decision.

Box 13.1 Essentials of lung protective strategies in the neuroICU

- PaO_2 should generally be maintained within 80–120 mm Hg
- Lung protective ventilation is targeting tidal volume of 4–6 mL/kg predicted body weight and to keep plateau pressure <30 cmH_2O
- Prone positioning may elevate baseline ICP, requiring clinicians to balance the benefits of improved oxygenation with the risk of adverse intracranial effects
- In patients with concomitant ICP elevation and ARDS, response to PEEP should be assessed by monitoring plateau pressure, ΔP, oxygenation, mean arterial pressure, and ICP.
- A disadvantage of pressure-related volume control is the potential for patient–ventilator dyssynchrony in patients with high respiratory drives. Increased work of breathing generates large tidal volumes at a given inspiratory pressure, results in less support from the ventilator and an increase in patient work of breathing.
- Less compliant, or "stiffer," lungs will require higher driving pressures to achieve the same tidal volume. Driving pressures strongly correlates with mortality in patients with ARDS, with values <15 cmH_2O thought to be protective.

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Decisions in Weaning and Discontinuation of Mechanical Ventilation

Acute Brain Injury

Even the most seasoned neurointensivist finds it difficult to judge accurately whether to extubate a patient with brain injury. The main question is how to develop neurologic criteria next to traditional pulmonary criteria. On the one hand, extubation failure, typically defined as the need for reintubation within one to two days after an extubation attempt, is not a failure of judgment nor does it result in change in outcome. Studies that try to link outcome to extubation failure must consider that in the neuroICU, extubation in the more severe cases of acute brain injury implies that reintubation will not be entertained. Conversely, delaying extubation may lead to greater rates of ventilator-associated pneumonia and longer intensive-care lengths of stay with higher costs. Patients being considered for extubation should demonstrate readiness to breathe unsupported by the ventilator (for example, through a spontaneous breathing trial.) Studies conducted specifically in patients with TBI have identified a Glasgow Coma Score (GCS) motor score $\leq$5, longer duration of MV, absence of coughing, and higher secretion burden as independent predictors of extubation failure[23–25]. A multicenter observational study designed to address the utility of specific prognostic factors for extubation success in patients with brain injury, including extubation-day GCS, was recently completed, with results expected soon. Extubation Strategies in Neuro-Intensive Care Unit Patients and Associations with Outcome (ENIO; NCT03400904) is an international, prospective observational study, in 73 ICUs in 18 countries from 2018 through 2020. Neurocritical care patients with a GCS $\leq$12 who received MV for $\geq$1 day were included. The primary endpoint was extubation failure by day 5. Among the 1193 patients who underwent an extubation attempt, one in five failed. Patients with extubation failure had longer MV duration, but the study did not identify specific neurologic criteria[26]. We believe extubation will fail in patients with major oropharyngeal weakness and poor cough. Others have found the strength of the cough is more predictive[27], but this is a very subjective assessment. Patients should be consistently alert, communicative, and ideally following commands. We do not extubate patients who undergo active measures to reduce intracranial pressure, or who have massive shift on CT scan. There should be no recorded episodes of apnea or low tidal volume breathing on spontaneous breathing trials.

Acute Neuromuscular Injury

In myasthenia gravis (MG) patients must be able to sustain a head lift for five seconds before being extubated. Extension of the head in MG is often much weaker than flexion, and this discrepancy may confuse general internists if a patient still is unable to wean. Failure to wean from the ventilator may have several causes. One particular clinical scenario that should be mentioned is MG crisis after thymectomy. Patients also may worsen dramatically because of lack of attention to their use of their home medication. The most significant complication is pneumothorax or hemothorax from transcervical thymectomy. With this operative approach, adherence of the thymus to the pleura and subsequent tearing after removal may cause right-sided pneumothorax. Immediate drainage is indicated.

In GBS patients at considerable risk of acute respiratory failure, early MV did not prevent the onset of ventilator-acquired pneumonia[28]. Tracheostomy is a common necessity in GBS, although some can be weaned within two weeks. There is no benefit of early versus late tracheostomy[29]. Weaning trials in GBS have not been compared, but one approach is to unload the ventilatory muscles with maximum pressure-support ventilation when vital capacity has reached 15 mL/kg and when the patient can deliver tidal volumes of 10–12 mL/kg. Pressure support is gradually reduced to 5 cmH_2O, a necessary value prerequisite for extubation. We showed that after one year, one in five patients had recovered at least one grade on the GBS disability scale, with nearly 10% of patients improving from a poor to a good outcome. Others found that patients with prolonged MV showed a slow recovery and regained the ability to walk unaided as late as the second and third year after onset of GBS[28,30]. Nevertheless, we can expect most patients to wean off the mechanical ventilator within three to six months. Ultrasound imaging of diaphragm function may help in monitoring improvements. Patients with acute axonal variants of GBS (often with an associated antecedent diarrhea from *Campylobacter jejuni*) may need prolonged (8–12 months) weaning effort. Ultimately, we guide our weaning attempt by pulmonary function tests. This does not require return to normal values, but weaning attempts can be started cautiously with VC >1 L and maximal pulmonary inspiratory and expiratory pressures in the 40s to 50s. (The expiratory pressures may have better predictive value for successful weaning because they reflect the strength

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Box 13.2 Don'ts in neurocritically ill patients

- Do not intubate every patient after a single seizure
- Do not intubate without adequate measures to avoid hypotension
- Do not administer succinylcholine in any neurological patient with paralysis
- Do not perform a tracheostomy in a patient with active treatment of increased intracranial pressure
- Do not admit patients with acute neuromuscular disease and oropharyngeal weakness to the ward.
- Do not use bilevel positive airway pressure in rapidly progressive Guillain–Barré syndrome
- Do not wean or extubate patients with myasthenia gravis without anticholinesterase inhibitors

of coughing using abdominal muscles.) Most patients will start with gradual 30 minutes to 1 hour of spontaneous breathing using a tracheostomy collar during the day and rest at night on a controlled mode of ventilation (i.e. pressure-controlled ventilation or ASV). Speaking valves are introduced once pressure support is at the minimal level.

Conclusions

There are a number of actions to avoid with respiratory care of acute neurologic conditions (Box 13.2). Care of neurocritically ill patients involves MV, which is most seen in the more severely affected patients. The full spectrum includes patients prematurely intubated (or to secure safe transport) and patients with severe pulmonary injury. The most common cause of acute hypoxemic respiratory failure in the neuroICU is ventilation–perfusion mismatch from atelectasis, aspiration, pulmonary edema, or pulmonary embolism. Thoracic injuries may be observed in some patients with TBI admitted to the neuroICU. Chest-wall injuries vary from a single rib fracture without significant impairment to major pulmonary contusions. Fracture of a first rib, however, is indicative of major trauma and may involve vascular structures. Most instances of chest trauma can be managed conservatively but emergency thoracotomy is indicated for cardiac tamponade, control of air embolization, and shock not responding to aggressive resuscitation. When pulmonary complications evolve into ARDS, the outcome dramatically changes, and mortality increases substantially. Most general ICUs see ARDS as a complication of sepsis, but in acute neurologic disorders, it is a serious, often fatal complication. It closely correlates with severe brain injury – worse brain damage results in worse systemic effects and from overdrive of the sympathetic nervous system, which is acute and cannot be mitigated.

Respiratory management can be very protracted in acute neuromuscular disorders, and it is not commonly appreciated that MV (despite immunomodulation) can last many months before restoration of respiratory mechanics.

Any subspecialty critical care group will have special considerations when it comes to MV. In the neurocritical care patient population, the brain causes systemic changes in organ function, which often includes the lung and heart. The immediate problem is that insufficient management of these systemic effects may affect the brain – a two-edged sword. It remains to be seen if prospective studies in these well-defined populations identify treatment strategies that can specifically guide clinicians.

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Chapter 14

Weaning from Mechanical Ventilation in Neurological Patients

Jens D. Rollnik

Long-term or prolonged mechanical ventilation is a challenge, in particular among neurological intensive care patients. While weaning from mechanical ventilation is widely regarded as a pneumological function[1], there are neurological weaning centers led by neurologists across Germany and Switzerland, specialized in early neurological-neurosurgical rehabilitation (ENNR) or paraplegiology. It must be taken into account when interpreting literature on ENNR that the same concept was named differently in the literature, for example neurological early rehabilitation or neurological-neurosurgical early rehabilitation. All of these terms describe the same concept, when it comes to publications from German-speaking countries: The basic idea of ENNR of critically ill neurological patients is to combine intensive care and rehabilitation interventions like physiotherapy or logopedics. Most studies on neurological intensive care patients cited in this chapter originate from ENNR centers because neurological patients frequently undergo prolonged mechanical ventilation and are referred to those centers for weaning in Germany.

Prolonged mechanical ventilation is defined as a period of two to three weeks; prolonged or difficult weaning refers to at least three failed spontaneous breathing trials (SBT) or mechanical ventilation of more than seven days after the first unsuccessful SBT[1].

Frequently, neurological intensive care patients have a high burden of morbidity[2], disorders of consciousness[3,4], poor functional status, and colonization with multidrug resistant (MDR) bacteria[5,6]. Frequently, they are subject to long-term mechanical ventilation and prolonged, difficult weaning[2,7–9].

This chapter focuses on clinical strategies and typical proceedings to wean critically ill neurological patients from the respirator.

Weaning Success in Neurological Intensive Care

A major goal in ENNR is to wean neurological intensive care patients from prolonged mechanical ventilation[10]. It is obvious that a recovery of spontaneous, nonassisted breathing function not only contributes to patients' independence and quality of life but also reduces complications and costs after discharge.

Pneumologists define weaning failure as (1) failed SBT, (2) reinsertion of endotracheal tube or tracheal cannula in connection with a restart of mechanical ventilation, or (3) death within 48 hours after extubation[11].

The rates of successful weaning from long-term mechanical ventilation among critically ill neurological patients average 76%[7–9,12,13] with a mean duration of weaning between 15 and 22 days[7,8]. The weaning rate of neurological is not worse than of nonneurological (e.g. pneumological) patients (50%–64%)[7].

Prediction of Weaning Success and Weaning Failure

Predictors of weaning success after acute respiratory failure are well known, such as respiratory frequency-to-tidal volume ratio (f/V_T), pulmonary gas exchange, maximum inspiratory pressure, vital capacity, mouth occlusion pressure, minute ventilation, and others[14]. f/V_T is measured during the first five minutes of SBT after discontinuation of mechanical ventilation, using a handheld spirometer connected to the endotracheal tube when the patient has established a regular respiratory pattern[14].

Weaning prediction for critically ill neurological patients on prolonged ventilation is more difficult: Due to central (in particular disorders of consciousness, aphasia, palsies, and neuropsychological problems) but also neuromuscular impairment like critical illness polyneuropathy/myopathy[15], their ability to cooperate and facilitate spontaneous breathing is limited[2–4], even in the absence of analgosedation. Nevertheless, it has been suggested that clinical factors, such as chronic pulmonary disease and the duration of inpatient stay prior to transfer to ENNR, might be more important predictors of weaning failure[16].

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In an observational, retrospective study from our center, it turned out that morbidity (number of co-diagnoses) and isolation due to colonization with MDR bacteria had an impact on the duration of the weaning process[17]. This finding could be reproduced in another study with 192 ENNR patients[18]. Morbidity indicators like colonization with MDR bacteria or need for renal dialysis were associated with weaning failure. It turned out that colonization with MDR, in particular gram-negative germs, was an independent predictor of weaning failure (MDR gram-negative germs: odds ratio = 3.19, confidence interval = 0.85–5.53)[18]. The more independent alert patients (in activities of daily living) were, the more likely they could be weaned from the respirator[18]. Weaning success did not differ between various neurological diagnoses (critical illness polyneuropathy, stroke, intracerebral/subarachnoid hemorrhage, hypoxic brain damage, and traumatic brain injury).

In summary, morbidity measures may influence the weaning process and prognosis among critically ill neurological patients.

Therapeutic Interventions in Mechanically Ventilated Neurological Patients

During weaning of critically ill neurological patients undergoing ENNR, a wide range of therapeutic interventions is offered, such as physiotherapy, ergotherapy (occupational therapy, basal stimulation), speech/swallowing therapy, psychological support[10], and (in particular during the weaning process) respiratory therapy (RT)[19,20]. RT has been established in North America for decades[20], whereas it is not very common in Europe. In Germany, RT is a special training program offered to intensive care nurses, physiotherapists, and logopedics. They are experienced in mechanical ventilation as well as pulmonary and physical rehabilitation facilitating the weaning process[19].

In the literature, it is a matter of discussion whether rehabilitation interventions such as physical therapy do have a beneficial impact on the weaning process on general ICUs[21–29]. There is limited scientific evidence that early physiotherapy might reduce length of stay on the ICU [22] and improve weaning success[26]; see Table 14.1.

With respect to ENNR, RT has shown to be beneficial[19]. While RT failed to prove a significant reduction of pneumonia incidence (approximately 20% during ENNR) in a matched-pair analysis (compared to a historic cohort without RT serving as control), morbidity among patients in the RT group was higher. This might indicate that RT at least prevented a higher pneumonia incidence among patients with higher disease burden. In addition, the study revealed that intensity of swallowing (dysphagia) therapy was efficient to reduce occurrence of pneumonia among neurological early rehabilitation patients[19]. This finding underlines the importance of swallowing/speech therapy as an essential component of therapeutic interventions during the weaning process of neurological patients.

A retrospective study enrolling 66 patients with severe acquired brain injury examined the effects of ENNR[30]. Patients in the ENNR group showed a shorter tracheostomy duration (61.0 versus 94.5 days, $p<0.05$), a higher probability of being weaned from the tracheal cannula and a shorter ICU stay (30.0 versus 52.0 days, $p<0.05$)[30].

But how much therapy is ideal? Patients undergoing ENNR in our center receive a mean of three hours of (rehabilitative) nursing and approximately two and a half hours of other therapeutic interventions per day[31] while the German Diagnosis-Related Group system demands an average of at least five hours of therapy per day (including rehabilitative nursing interventions) during ENNR[32].

As far as intensity of interventions is concerned, there is no linear dosage–response relationship. In a previous study, our group has published that there was no significant correlation between the amount of daily physio-, ergo-, or speech/swallowing therapy and ventilation hours during the weaning process[13]. There was, however, a trend that ventilation hours correlated negatively with daily cognitive therapy and total number of therapies per day. Cognitive therapy and a high volume of daily therapies demand patients' cooperation and interaction and it may be hypothesized that this ability had a positive influence on the weaning process. Further, it must be pointed out that only patients in stable cardiorespiratory condition are resilient enough to sustain a higher number of therapies. So, it is not surprising that there was a negative correlation between the daily amount of therapy and ventilation hours[13].

In a recent service review from the United Kingdom, increased physiotherapy capacity proved to reduce tracheostomy duration and hospital length of stay among patients with acquired brain injury[33]. With a 50% increase in staffing, physiotherapy rehabilitation sessions increased from two to four times weekly. A mean improvement was found for patient outcomes: time with tracheostomy in situ was reduced by 11 days and length of stay in hospital by 19 days[33]. In addition, functional

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Table 14.1 Therapeutic interventions during the weaning process

Study	No.	Patients	Intervention	Results
Nava, 1998[21]	80	Chronic obstructive pulmonary disease patients	Pulmonary rehabilitation (passive mobilization, early deambulation, respiratory and lower skeletal muscle training, if possible lower extremity training on a treadmill)	At discharge, exercise capacity (6-minute walking distance) and maximal inspiratory pressure (MIP) was better in the intervention group.
Morris et al., 2008[22]	330	Medical ICU patients on ventilation	Early physiotherapy, mobility protocol (<48 h)	Protocol patients were out of bed earlier (5 versus 11 days, $p<0.001$), had shorter length of stay on ICU (5.5 versus 6.9 days, $p<0.05$) and in hospital (11.2 versus 14.5 days, $p<0.01$).
Thomsen et al., 2008[23]	104	Respiratory failure patients requiring >4 days of mechanical ventilation	Early activity protocol on a weaning ward	After 2 days, the number of patients ambulating had increased threefold compared with pretransfer rates. Female gender, lower Acute Physiology and Chronic Health Evaluation II scores and absence of sedatives predicted an increased probability of ambulation.
Burtin et al., 2009[24]	90	Medical and surgical ICU patients	Respiratory physiotherapy and a daily standardized passive or active motion session and 20 min/day, using a bedside ergometer (intervention).	At hospital discharge, 6-min walking distance, isometric quadriceps force, and the subjective feeling of functional well-being were significantly higher in the intervention group ($p<0.05$).
Schweickert et al., 2009[25]	104	Sedated adults, on ventilation 24–72 h	Early exercise and mobilization (physical and occupational therapy) during periods of daily interruption of sedation	Patients in the intervention group had shorter duration of delirium (median 2.0 days, interquartile range 0.0–6.0 versus 4.0 days, 2.0–8.0; $p = 0.02$), and more ventilator-free days (23.5 days, 7.4–25.6 versus 21.1 days, 0.0–23.8; $p = 0.05$) during the 28-day follow-up period than did controls.
Yang et al., 2010[26]	126	Mechanical ventilation >14 days	Physical therapy (30 min/d)	Higher success rate of ventilator weaning in patients receiving physical therapy (58.2% versus 40.9%).
Pattanshetty & Gaude, 2011[27]	173	Intubated and ventilated medical and surgical patients in a tertiary care center	Multimodality chest physiotherapy (suctioning, vibrations, manual hyperinflation, positioning) twice daily till extubated	Intervention prevents ventilator-associated pneumonia and increases weaning rate (66.6% versus 27.9%).
Clini et al., 2011[28]	77	Tracheotomized patients of a regional weaning center (mean of 24 d on ventilation)	Daily comprehensive rehabilitation including peripheral muscle training	Mortality rate and weaning success might improve.
Cader et al., 2012[29]	28	Elderly intubated patients	Inspiratory muscle training (IMT) and physiotherapy.	IMT did not improve weaning success.

status at discharge also improved, with 33% of patients being able to mobilize with normal staffing levels and 77% with enhanced staffing levels[33].

Weaning Strategies among Neurological Patients on Prolonged Mechanical Ventilation

As a general rule, prolonged weaning of neurological patients from mechanical ventilation comprises a combination of synchronized intermittent mandatory ventilation and/or pressure support ventilation to give respiratory muscles time to recover and progressively extended spontaneous breathing intervals (SBI)[10]. Most neurological patients (up to 96%) undergoing prolonged weaning are supplied with a tracheal cannula with inflatable cuff to reduce the danger of aspiration and to facilitate spontaneous breathing[9]. During periods of recovery, the mechanical ventilation helps the patient not to overexert themselves. For recovery, combinations

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Table 14.2 Example of a standardized weaning protocol[16]

Step (day)	Spontaneous breathing intervals	Duration of spontaneous breathing intervals (total in min/day)
1	6 times 5 min	30
2	6 times 10 min	60
3	6 times 15 min	90
4	6 times 20 min	120
5	6 times 30 min	180
6	6 times 45 min	270
7	6 times 60 min	360
8	4 times 90 min	360
9	4 times 100 min	400
10	4 times 110 min	440
11	4 times 120 min	480
12	4 times 150 min	600
13	4 times 180 min	720
14	3 times 240 min	720
15	3 times 260 min	780
16	2 times 400 min	800
17	2 times 450 min	900
18	2 times 500 min	1000
19	2 times 600 min	1200
20	1 time 1200 min	1200
21	1 time 1320 min	1320
22	1 time 1440 min	1440

of assisted spontaneous breathing and controlled ventilation (assist-control ventilation and biphasic positive airway pressure [BiPAP]) can be used[34]. However, the question as to whether one ventilation mode is superior to another in weaning critically ill patients is a matter of opinion due to lack of scientific evidence[34].

It is most important to discuss and evaluate the weaning process by the experienced, multidisciplinary team which is the most decisive factor for a successful weaning.

German guidelines recommend the use of a standardized weaning protocol in ENNR[10]. Table 14.2 gives an example. The weaning protocol proposed by Oehmichen and colleagues consists of 22 standardized weaning steps, increasing the duration of SBI from one day to another, starting with six times 5 min/day until the patient is able to breathe independently throughout 24 hours (after three weeks)[16]. If the standardized protocol failed, an individual weaning approach was chosen. The weaning protocol was applied in 644 patients, most of them (98.6%) had a tracheotomy tube and morbidity was high (30.9% had a history of chronic pulmonary disease and 13.7% required dialysis). Weaning was successful in 77.3% (498 patients) of all cases with a mean duration of 22.0 ± 33.9 days[16]. Of those successfully weaned, a total of 85.9% were weaned according to the standard protocol. The duration of weaning was shorter (20.8 ± 35.6 versus 29.0 ± 19.9 days) for patients weaned following the protocol compared to those cases in which the protocol failed, mostly due to complications. Protocol failure used to be due to complications during the weaning process. In this study, chronic pulmonary disease and the inpatient length of stay prior to rehabilitation were predictors of weaning failure[16].

Another protocol suggested by Gross and coworkers allows quicker weaning steps (Table 14.3)[35]. During the night, patients get time to recover (using pressure support ventilation, e.g. bilevel PAP or BiPAP, assisting spontaneous breathing) while SBI in the daytime are gradually expanded. Bilevel PAP, like BiPAP, is a pressure-controlled ventilation mode which is time-triggered and time-cycled, allowing unrestricted, spontaneous breathing with or without pressure support.

It must be pointed out that noninvasive ventilation (NIV) is rarely used in the prolonged weaning of neurological patients because of dysphagia and the risk of aspiration pneumonia[10].

Another matter of discussion is whether the patient should be disconnected from the mechanical ventilator throughout the SBI (discontinuous weaning), with a heat and moisture exchanger placed on the tracheal cannula, or whether the patient should stay connected with the ventilator (continuous weaning) under continuous positive airway pressure. During continuous weaning, the respirator support is gradually reduced to train the respiratory muscles, while during discontinuous weaning, intervals of controlled or assisted ventilation alternate with spontaneous breathing. This second strategy is based on a successively increased frequency and duration of SBI following a step-by-step scheme, called "interval training for the breathing muscles"[36]. Results from a large study enrolling 546 non-neurologic patients (surgical and medical ICU) speak in favor of a discontinuous weaning strategy[37]. A once-daily trial of spontaneous breathing led to extubation about three times more quickly than intermittent mandatory ventilation and about twice as fast as pressure-support ventilation. Multiple daily trials of spontaneous breathing were equally successful[37]. There is only one neurological study on this

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Table 14.3 Weaning protocol for neurological patients with tracheal cannula suggested by Gross and coworkers[35]

Step (day)	Morning shift	Late shift	Night shift
1	1 × 30 min SBI	1 × 30 min SBI	PSV/bilevel
2	2 × 30 min SBI	2 × 30 min SBI	PSV/bilevel
3	60 min SBI	60 min SBI	PSV/bilevel
4	120 min SBI	120 min SBI	PSV/bilevel
5	180 min SBI	180 min SBI	PSV/bilevel
6	240 min SBI	240 min SBI	PSV/bilevel
7	300 min SBI	300 min SBI	PSV/bilevel
8	360 min SBI	360 min SBI	PSV/bilevel
9	420 min SBI	420 min SBI	PSV/bilevel
10	SB only	SB only	8 hours PSV/ bilevel
11	SB only	SB only	6 hours PSV/ bilevel
12	SB only	SB only	4 hours PSV/ bilevel
13	SB only	SB only	2 hours PSV/ bilevel
14	SB only	SB only	SB only

PSV, pressure support ventilation; SB, spontaneous breathing; SBI, spontaneous breathing interval.

topic[38]. In a prospective, randomized controlled study with 54 stroke patients adaptive support ventilation, a continuous weaning strategy, was compared with BiPAP in combination with spontaneous breathing trials. The median weaning duration was 10.7 days (± 7.0) in the discontinuous weaning and 8 days (± 4.5) in the continuous weaning group. The authors conclude that continuous weaning is more effective than discontinuous weaning in mechanically ventilated stroke patients[38].

To examine the efficacy of discontinuous weaning in neurological ICU patients, we carried out a – yet unpublished – study (matched-pair analysis) enrolling 20 patients (10 in the continuous versus 10 in the discontinuous weaning group). Patients were matched by age, gender, diagnosis, and morbidity. In prolonged weaning, we came to other conclusions than Teismann and coworkers[13]: Patients in the discontinuous weaning group were more frequently weaned than patients undergoing continuous weaning (90% versus 20%; $chi^2 = 9.899$; $p = 0.005$) and tended to have a shorter duration of mechanical ventilation.

To our knowledge, discontinuous weaning is the most common strategy among critically ill neurological patients although there is still a lack of scientific evidence.

Home Mechanical Ventilation

Data from our own weaning center suggest that <5% (4.6%) of the neurological patients must be discharged with home mechanical ventilation (HMV)[13]. This finding was reproduced by a recent German multicenter study (including 36 weaning units with a total of 496 beds)[12]. The authors found that out of 2516 weaning cases in 2019, 2097 (83.3%) could be successfully weaned from mechanical ventilation while only 120 (4.8%) had to be discharged on a home respirator[12].

Most nonweaned neurological patients still have a tracheotomy and are on (at least intermittent) mechanical ventilation at discharge. As mentioned, NIV is rarely applied, due to dysphagia and risk of regurgitation and aspiration. During outpatient care (at home or in nursing facilities), it is crucial that further weaning attempts are undertaken. Rate of successful weaning after discharge may be as high as 36% among neurological patients[39]. Thus, German guidelines recommend that outpatient facilities do cooperate with neurological weaning centers[10]. At discharge, a readmission should already be scheduled, for example after three months, to reconsider and evaluate patients' ability to be weaned from mechanical ventilation.

Data from literature suggest that patients on home care ventilation do experience a higher quality of life than in inpatient care. Some patients suffering from severe neurological diseases (e.g. muscle dystrophy, poliomyelitis, amyotrophic lateral sclerosis, spinal cord injuries) are even working part- or full-time despite mechanical ventilation[40]. However, return to work is a rare event among severely brain damaged nonweaned ENNR patients.

In a study from Poland, 29 neuromuscular patients (three fourths on invasive ventilation) were followed up during HMV[41]. Approximately 60% of the neurological patients described their quality of life as "moderate" or "good". The higher the stress levels of patients, the lower the quality of life in particular domains. The authors found that stress levels were significantly higher among neurological patients. It is obvious that patients undergoing HMV experience distress and anxiety, as they have a constant feeling of dependence. The authors concluded that improving the living conditions of HMV patients may help to improve their quality of life[41]. Psychological help (improving coping and stress prophylaxis) is strongly recommended, not only for patients but also caregiving relatives.

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Practical Recommendations and Case Report

When it comes to practical recommendations, evidence-based medicine gives little support on how to ventilate and wean neurological patients. A systematic review suggests that NIV should be the first option for ventilatory support for patients with a severe exacerbation of chronic obstructive pulmonary disease[42]. Neurological long-term ventilated patients frequently suffer from chronic obstructive pulmonary disease as a comorbid disease, but the use of NIV is limited due to aspiration risk[11]. In addition, lung protective ventilation with lower V_T and use of ventilator discontinuation protocols improve patient outcomes[42].

German guidelines on prolonged weaning of neurological patients give a few practical recommendations[10]:

1. Use a standardized protocol to monitor the process of prolonged weaning.
2. For spontaneous breathing trials, try to disconnect the patient from the ventilator.
3. Prolonged weaning is teamwork, including respiratory therapists.
4. Don't use NIV, in particular when patients suffer from dysphagia and are at risk of aspiration pneumonia.
5. Neurological patients are not only required to be weaned from mechanical ventilation, but also from tracheostomy. They do need swallowing therapy to improve dysphagia.
6. Consider psychological support for awake and cooperative patients during prolonged weaning.

To illustrate the challenges of prolonged weaning of neurological patients, allow me to discuss an 80-year-old female with Guillain–Barré syndrome (GBS) after COVID-19, initially admitted to a general hospital. She suffered from comorbidities like diabetes, arterial hypertension, and hypothyroidism. The patient presented with a progressive palsy of both legs, unable to walk, with a loss of sensation in feet and hands. Despite intravenous immunoglobulin therapy, the weakness extended to the upper extremities and breathing muscles. When respiratory distress occurred, the patient was supported with NIV but had to be ventilated invasively four days after admission. Weaning trials failed and a surgical tracheotomy and percutaneous endoscopic gastrostomy were applied after three weeks. Upon admission to ENNR, she had tetraplegia but was awake (no analgosedation) and able to communicate and fully cooperate. Even half a year after onset of GBS, nerve conduction studies revealed a severe demyelination and axonal damage (Figure 14.1a, b). At the

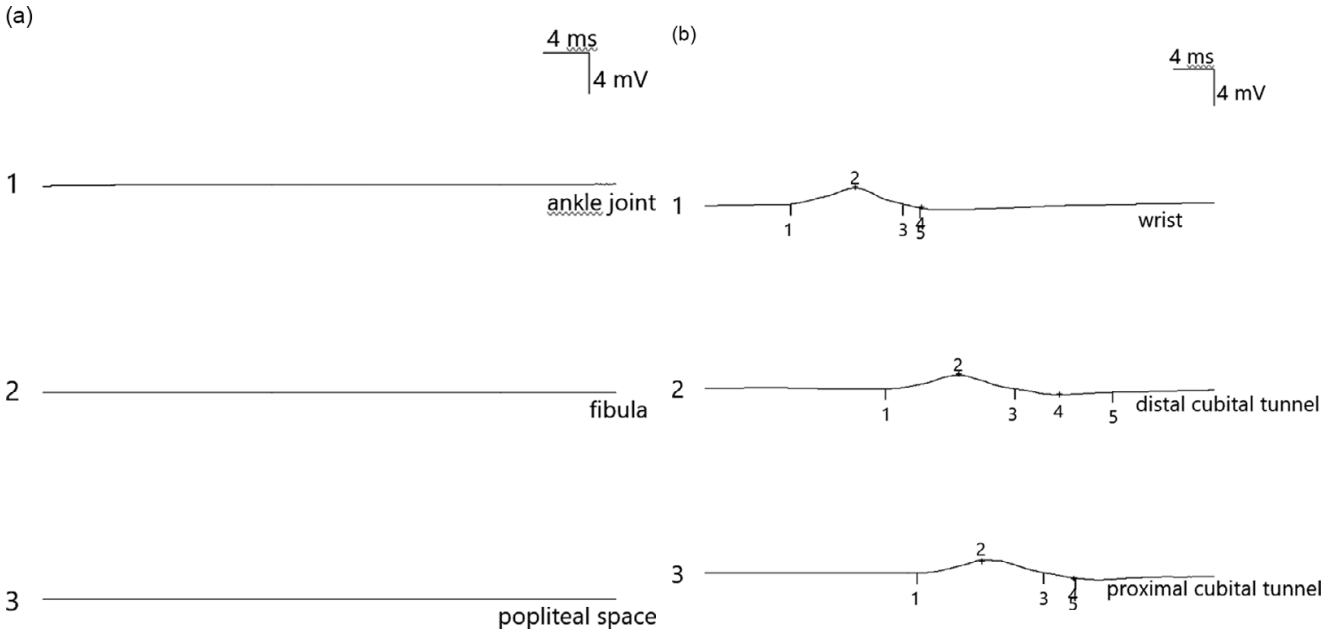


Figure 14.1 (a) Motor conduction studies of the left peroneal nerve, no compound muscle action potentials could be recorded, six months after GBS onset. No F-waves could be evoked. GBS, Guillain–Barré syndrome. (b) Motor conduction study of the right ulnar nerve: distal motor latency 8.4 ms, nerve conduction velocity 27 and 23 m/s. No F-waves could be evoked.

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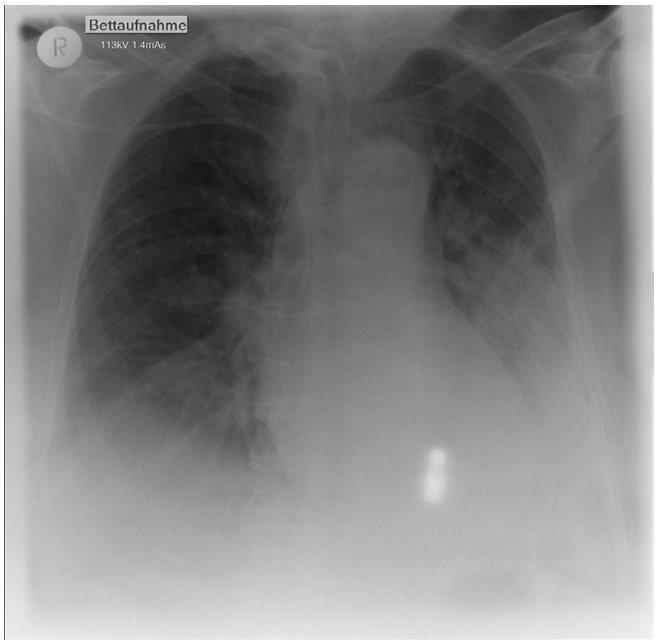


Figure 14.2 Chest X-ray upon admission to NER. It reveals a lung infiltrate on the left side and pleural effusion on both sides. NER, neurological early rehabilitation.

beginning of ENNR, the patient had almost no respiratory drive when she was set on continuous positive airway pressure/assisted spontaneous breathing and had to be on controlled ventilation (in BiPAP mode) around the clock. Respiratory therapists used a cough assist device to help clear secretions (phlegm) by providing pressure support to assist breathing. The cough assist was connected to the tracheal cannula. It took four weeks until she recovered from a ventilator-associated pneumonia (Figure 14.2) and was stable enough to perform the first SBT. Disconnected from the ventilator, the patient accomplished one hour of spontaneous breathing until she was exhausted. SBT were repeated almost daily, but the intervals could not be extended to more than 15–20 min once daily. Four weeks later, she accomplished one SBT of two to three hours per day, sometimes even with the tracheal cannula uncuffed. One week later, she underwent two SBTs of two to three hours daily and a tracheostomy cannula with fenestration could be inserted. This means that a cannula with a perforated area at their upper bending was used allowing phonation (because the air is lead through the opening into the larynx during exhaling). From that moment, weaning progressed rapidly, and SBT could be expanded to 5–12 hours twice daily over a period of three weeks. Weaning was concluded successfully after four months (total of 2.893 hours). Five weeks later, tracheal cannula could be removed completely.

CONCLUSIONS

Long- term (permanent) mechanical ventilation is uncommon and weaning from mechanical ventilation is an important goal for critically ill neurological patients. Neurological weaning centers are very successful in weaning (>90%) combining rehabilitation interventions and intensive care medicine. Among neurological patients on prolonged mechanical ventilation, discontinuous weaning strategies, gradually extending spontaneous breathing trials, have proven to be effective. After discharge, mechanically ventilated neurological patients should be reconsidered for weaning trials.

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Chapter 15

Rehabilitation of Mechanically Ventilated Neurological Patients

Marcus Pohl and Tobias Schmidt-Wilcke

Ventilation weaning of neurological patients in Germany takes place predominantly within the conceptual and structural framework of early neurological-neurosurgical rehabilitation (ENNR). Early rehabilitation measures should already be started in the primary care hospital. However, the resources of acute medical intensive care units are limited in this respect[1], so that neurological patients should be transferred as early as possible to specialised facilities or departments for (early) rehabilitation[2]. The ENNR acts at the interface between acute inpatient intensive care and further rehabilitation[3], and increasingly also at the interface with palliative care. The ENNR is designed for the treatment of patients with limited cooperation who are often still critically ill. Prolonged intensive care treatment with ventilation in general very often leads to neurological complications and comorbidities requiring treatment (critical illness neuropathy and myopathy, septic encephalopathy, hypoxic brain injury, protracted delirium)[2]. A significant number of patients are transferred from non-neurological/non-neurosurgical primary care to ENNR facilities. Especially in the field of early rehabilitation of ventilated patients, the function of the ENNR as an important component of the treatment chain for critically ill patients becomes clear for all intensive care units of maximum and priority care providers. Against this background, neurological early rehabilitation facilities with ventilation capacity must have a broad spectrum of medical disciplines (neurology/neurosurgery, internal medicine, anaesthesiology and intensive care medicine) and diagnostic possibilities (imaging, bronchoscopy, swallowing diagnostics, blood gas analyses, etc.) in order to do justice to their treatment mandate and their position in the care system[2].

Patients improve in neurological rehabilitation on the basis of functional recovery and by learning compensation options[3]. In the time window of the ENNR (weeks to a few months after the damage), the prognosis regarding possible future participation is formed. Almost 10% of patients die in the ENNR, two thirds of them after a change of therapy goal[4]. Therefore, medical, therapeutic and nursing competences are required that were previously unknown to rehabilitation.

The necessity of simultaneous intensive medical and early rehabilitation treatment of neurologically severely injured patients requires the special structures of a neurological early rehabilitation facility for their adequate care, which at the same time has expertise in ventilation and ventilation weaning.

Content-Related and Structural Requirements for Neurological Early Rehabilitation of Ventilated Patients

The content-related and structural specifications for ENNR are defined in the German Diagnosis-Related-Groups (DRG) system via a procedure definition that contains information on the content (therapeutic spectrum) as well as the duration of the therapies that must be fulfilled[2]. Patients who are ventilated generally fulfil the criteria for a ventilation DRG, which usually makes it unnecessary to bill the patient for the early rehabilitation procedure. Against the background that (intermittent) ventilation and ventilation weaning are understood as part of the ENNR in terms of content, it is nevertheless an important concern to provide this patient clientele with a correspondingly high amount of therapy (of 300 min/d), especially since the simultaneous rehabilitation of motor and cognitive deficits has a favourable effect on respiratory and, even more so, swallowing function. In addition, since January 2019, a procedure definition for ventilator weaning of a ventilated patient has been established. As the billing relevance between the institutions/parties (hospitals and health insurances) has not been clarified, we will not go into further detail on this procedure.

The Bundesarbeitsgemeinschaft für Rehabilitation (BAR) recommendations also provide detailed information on the treatment goals, services and tasks of early

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rehabilitation[5]. Treatment and rehabilitation goals are "improvement of the state of consciousness and establishment of the ability to communicate and cooperate, beginning mobilisation, reduction of the extent of damage to the CNS and PNS, avoidance of secondary complications, clarification of the rehabilitation potential [as well as] planning and initiation of further care"[5]. The curative measures begun in phase A should be continued and basic neurological diseases as well as accompanying diseases (comorbidities) should be treated[5]. The control of life-threatening complications and those that may occur during mobilisation must be guaranteed, as must continuous neuromonitoring[5]. The following rehabilitative tasks arise in BAR phase B: rehabilitative assessment, clarification of the rehabilitation potential, ensuring therapeutic-activating care, targeted functional treatment, prevention of secondary damage in the area of the locomotor organs (e.g. contractures or decubitus), "promotion of motor and sensory functions, . . . communication/interaction treatment and speech therapy, orofacial therapy (chewing, swallowing and eating training) and speech therapy, independence training (at basal level), counselling, instruction and support of relatives [and] clarification of the need for and initiation of further rehabilitation services (based on systematic observation of progress)"[5]. Information is also given on the density of therapy: "Intensive care/supervision including four to six hours of rehabilitation care (here as activating care) daily, . . . functional therapy in total several hours a day, often by several therapists at the same time"[5].

In addition to these structural requirements, the special features of ENNR are the definition of realistic participation goals, therapy planning and modification in a multi-professional team.

The German Society for Neurorehabilitation (DGNR) has produced an S2k guideline[2] which describes prolonged weaning in neurological-neurosurgical early rehabilitation in detail. In this guideline, the special features of ENNR in ventilated patients are highlighted and consensus recommendations are made, from which content-related and structural requirements for the ENNR of ventilated patients can also be derived. The most important recommendations of the guideline with regard to ENNR are as follows[2]. Ventilated patients with diseases of the central and/or peripheral nervous system and/or (neuro-)muscular diseases should be transferred as early as possible to a neurological-neurosurgical early rehabilitation facility with intensive care and weaning competence. This facility should have a multi-professional treatment team (activating therapeutic nurses, physicians, respiratory therapists, occupational therapists, speech therapists, music therapists, neuropsychologists and physiotherapists) with neurorehabilitative experience. Here, concepts for dysphagia and trach tube management as well as accompanying speech therapy in the weaning of ENNR patients should be implemented as standard and continuously evaluated. In addition, respiratory therapy can also be helpful in the ENNR during the weaning process. Furthermore, psychological support in the weaning process is indicated, especially in the case of anxiety disorders. Finally, palliative care for ventilated and nonventilated patients should be ensured in a neurological-neurosurgical early rehabilitation facility[2].

Treatment Concepts in Neurological Early Rehabilitation of Ventilated Patients

ENNR centres fulfill special tasks and requirements in the care of long-term ventilated patients. Some essential concepts are highlighted as follows[6]:

- Concepts for (renewed) intensive care treatment in case of complications (e.g. pneumonia with renewed ventilation requirement)
- Tracheal cannula management concepts
- Dysphagia management concepts
- Concepts for the treatment of patients with brain-organic psychosyndrome and specific neurocognitive dysfunctions
- Concepts for the rehabilitation of patients with paraplegic syndromes
- Concepts for the rehabilitation of patients with neuromuscular diseases (see Chapter 18)
- Concepts and therapy approaches to systematically increase independence in the activities of daily living and participation
- Concepts for the rehabilitation of patients with multi-resistant pathogens
- Concepts for the implementation of all common therapies of modern neurological (early) rehabilitation with transition management to further rehabilitation (phases C–D) and out-of-hospital care
- Concepts for the care of permanently ventilated patients with so-called "home ventilators" with transition management to out-of-hospital care
- Concepts for palliative care of patients (see Chapter 24)

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Tracheal Cannula Management

Almost all ventilated patients are invasively ventilated on admission to the neurological weaning centres[7]. In these patients, invasive ventilation is carried out almost without exception via a tracheostoma[2,4,7]. It follows that neurological weaning centres need a structured concept for dealing with and weaning from the tracheostomy cannula (TC)[2,7,8].

The contents of a structured tracheostomy management include[9]:

- Knowledge of the different tracheostomy appliance types
- Concepts for dealing with early and late complications in TC care
- Concepts for the use of endoscopic/imaging swallow examinations and examinations with blue swallow
- Concepts for the differentiated use of the various cannula types.
- Concepts for the use of speaking attachments and valves
- Concepts for the implementation and (work) organisation of TC changes
- Detailed knowledge of the impact of TC on swallowing in all occupational groups
- Dysphagia management with concepts for oralisation in blocked TC
- Oral care concepts
- Decannulation concepts

The detailed handling of the tracheostomy tube and the aforementioned concepts for tracheostomy tube management require very differentiated expertise and very good cooperation in the interdisciplinary team (nursing, respiratory therapists, speech and language therapists and physicians). In this context, reference should be made to further literature[1,9] and Chapter 12.

Dysphagia Management

A dysphagia requiring supervision is present in 87%–97% of patients admitted for weaning in the ENNR[4,10]. Dysphagia, in turn, has a significant impact on weaning from TC either after weaning from invasive ventilation or when switching from invasive to non-invasive ventilation. In the context of ENNR, the professional, multidisciplinary treatment of neurogenic dysphagia is part of the therapeutic setting.

In continuous weaning, in which the proportion of mechanical breathing is continuously reduced and the proportion of spontaneous breathing is increased accordingly, patients are not disconnected from the ventilator until weaning is completed, so that conventional tracheal cannula management (cuff down with speaking valve) is not possible in principle. However, when the patient is awake and various parameters and alarm settings are adjusted on the ventilator, it is possible to start practising swallowing functions by unblocking the cannula while the patient is ventilated and to improve tracheo-laryngo-pharyngeal sensitivity by physiological airflow control[11]. In assisted ventilation mode, for example, a Passy-Muir® speaking valve can be connected to the ventilation system[12]. The so-called above-cuff ventilation allows a (retrograde) air/oxygen supply via the side port of TCs with subglottic suctioning, which induces an expiratory air flow past the vocal folds with the resulting possibility for the patient to phonate (under continuous ventilation).

In discontinuous weaning with phases of spontaneous breathing without a ventilator, the patient can in principle be unblocked from the first spontaneous breath, depending on the current medical-respiratory situation.

Before oral feeding, the swallowing ability should be checked. This is also possible in ventilated patients and is absolutely necessary due to the high prevalence of dysphagia. According to the S1 guideline "Neurogenic Dysphagia" of the Deutsche Gesellschaft für Neurologie (DGN)[13] two diagnostic procedures are available for ventilated tracheotomised patients[14]:

1. The endoscopic transnasal examination (flexible endoscopic evaluation of swallowing) can also be performed bedside in patients with severe motor and cognitive impairment. The Penetration Aspiration Scale by Rosenbek and colleagues has been established for grading the severity of penetrations and aspirations[15].
2. To assess the risk of aspiration in tracheostomised patients, the modified Evans' blue dye test can be performed, in which saliva and food should be stained with blue food colouring and swallowed. This non-invasive procedure has high sensitivity and specificity. For this, the cuff should be unblocked and a speaking valve put on so that voice quality and effectiveness of the coughing blow can be assessed. However, since even a blocked cuff never seals 100%, aspiration of the dye is often visible even with a blocked cuff.

Diagnostic pathways together with therapy recommendations have recently been developed for this purpose[14,16].

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In general, oralisation with unblocked cuff with speaking valve attachment should be aimed for in the spontaneous breathing phases without ventilator or after successful weaning – on the one hand, because the subglottic pressure seems to be a key component of swallowing efficiency and patients often aspirate less after the attachment of a speaking valve, on the other hand, because aspirated food cannot be coughed up adequately with blocked TC, even if sensitivity is preserved[14]. However, a permanently blocked TC is in principle not an absolute contraindication to oral food intake[16]. If a patient cannot be disconnected or unblocked from the ventilator due to respiratory problems, but is awake, cognitively unimpaired and does not aspirate, he or she can be given oral food. A prerequisite for this, however, is an inconspicuous swallowing test, which should be carried out beforehand by means of a device (flexible endoscopic evaluation of swallowing) or Evans' blue dye test.

With regard to the therapy of swallowing disorders, see the S1 Guideline "Neurogenic Dysphagia" of the DGN[13], further literature[14] and Chapter 7.

Neurocognitive Dysfunction

In a multicentre study in 2014, 13% of patients admitted for weaning to the ENNR had a duty of supervision because of orientation disorder, 13% had a duty of supervision because of a behaviour disorder and 65% had a severe communication disorder[4].

Of the various forms of brain-organic psychosyndromes, (severe) vigilance disorders (up to coma) and delirious syndromes significantly complicate the weaning process. In addition, drive disorders, anxiety states, apraxia and depression are regularly found among ENNR clients. Overall, neurocognitive disorders are relatively common in this clientele and complicate compliance in the weaning process and reduce the rate of weaning[2].

Severe communication disorders, caused for example by aphasia and/or dysarthrophonia, are a particular problem. With regard to the diagnosis and therapy of neurogenic speech and language disorders, refer to the S1 guidelines "Rehabilitation of aphasic disorders after stroke"[17] and "Neurogenic speech and voice disorders" [18].

Another communicative obstacle in invasively ventilated patients is the blocked TC. In addition to written communication options (electronic aids, letter boards, etc.), assistive technology (a Passy-Muir® speaking valve) can be used to help the patient communicate with the tracheostomy tube[12,19]. Blom® tracheostomy tube, with a speaking valve integrated into the inner tube (no unblocking required), or above-cuff ventilation can be used to enable verbal communication under ventilation. Current data show good intelligibility of spontaneous speech under these devices[20,21].

In discontinuous weaning, a conventional speaking valve (cuff down with speaking valve) can be placed during the spontaneous breathing phases (depending on the severity of the dysphagia and the respiratory situation) or the cannula can be closed by finger occlusion during the expiratory phases[22]. These efforts to enable the ventilated patients to speak are particularly important in order to improve the patients' participation and ability to communicate, at least in phases, on the one hand, and to support the regression of delirious symptoms and cognitive disorders on the other.

Independence in the Activities of Daily Living

Neurologically ill patients who require prolonged ventilation are often significantly limited in their independence and require extensive assistance in performing the activities of daily living[23]. In the aforementioned multicentre study on the course of treatment in early rehabilitation/phase B rehabilitation, the mean Barthel index of patients admitted for weaning in 2014 was 3.3 ± 9.3 points (n = 150)[4]. This restriction in the patients' independence leads to a considerable need for care among the patients. Special care concepts are required here[3]. It is the core task of the ENNR to lead the ventilated patients to the best possible participation in the activities of daily living.

Accompanying Therapies

In principle, all therapeutic measures used in neurological rehabilitation are applied to ventilated patients in the ENNR[2,24]. This is particularly important because most patients have other, usually severe, neurological deficits in addition to respiratory insufficiency, which require rehabilitation. Although weaning from ventilation is a special challenge, it must be considered in an overall neurorehabilitative context. Prolonged intensive care leads to muscular deconditioning, which in turn has an adverse effect on ventilator weaning. Provided that patients are not put at cardiopulmonary risk, early mobilisation can potentially shorten the duration of weaning also in the context of ENNR[25]. Although studies show

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advantages, especially of early mobilisation and passive and active physiotherapy with regard to length of stay and weaning success, the studies did not involve long-term ventilated patient populations. In addition, the patients were generally not neurologically ill[2]. Despite a lack of evidence regarding an improvement in outcome, mobilisation is definitely recommended even for ventilated patients in the ENNR for various reasons (activation of the muscular and cardiovascular system, prophylaxis of orthostatic pneumonia, etc.)[2]. Early mobilisation to the edge of the bed, to a wheelchair and even to a standing position (as far as possible within the framework of the walk-in illnesses) are beneficial for ventilation weaning.

There is also little scientific evidence with regard to occupational therapy interventions[24]. However, there is a strong consensus that occupational therapy can improve outcomes (quality of life, participation, functional capacity), especially in combination with other therapies[2]. In the ENNR, the primary goal of occupational therapy is to support patients, taking into account individual contextual factors, in performing relevant activities of daily living and to enable the greatest possible ability to act, independence, quality of life and participation. The choice of therapeutic intervention is made together with the patient or the relatives (client-centredness), depending on the individual objective and focus of the therapy[26]. Different therapy methods and concepts are used for[2]:

- Training of activities of daily living (personal hygiene, dressing, eating and drinking etc.)
- (Sensori)motor training (arm motor skills, head and trunk control, standing up, standing, transfer, walking)
- Perception and sensitivity training (e.g. basal stimulation, Affolter, Perfetti)
- Cognitive training
- Counselling, adaptation and training regarding assistive devices
- Counselling to reduce barriers in the out-of-hospital environment
- Coping with the disease
- Counselling and education for relatives

When working with neurological-neurosurgical patients in the process of prolonged weaning, early occupational therapy in combination with other treatment procedures can help to preserve sensorimotor, perceptual and cognitive functions or restore damaged body functions (e.g. vigilance, muscular functions).

Psychological Interventions

In particular, patients without cognitive limitations (e.g. with critical illness polyneuropathy, high paraplegia, Guillain–Barré syndrome) also require psychological support during ventilation weaning. These patients are often of advanced age, difficult to wean from ventilation and have concomitant internal diseases (multimorbidity) that have a negative impact on their general condition. Ventilation prevents verbal communication, and in the case of high-grade paresis, written communication is often not possible either, as even touchpads can often not be operated. Emotional problems such as anxiety and depression are a frequent reaction to the environment of an intensive care unit, which is perceived as threatening, especially among this patient clientele. Mental illness significantly prolongs ventilator weaning and is even associated with a higher mortality rate[2].

Depression and adjustment disorders have an unfavourable influence on coping factors such as drive, hope, perseverance and self-efficacy beliefs in patients and thus impair their compliance. Psychotherapeutic techniques can significantly alleviate depression symptoms in addition to pharmacological treatment.

Patients with complications of ventilator weaning may develop an additional fear of spontaneous breathing. This anxiety disorder often occurs in connection with premorbidly impaired lung function or due to pre-existing panic disorders[27]. Here, psychological co-management should be used if there are repeated signs of anxiety during spontaneous breathing.

Measures such as cognitive behavioural therapy, client-centred interviewing, mindfulness exercises and stress management methods bring about improvements in mood and sense of control in patients with mental health problems. Patients additionally benefit from breath relaxation, biofeedback and autogenic training in this context.

Depending on the degree of neuropsychological impairment, the following neuropsychological interventions are used[2]:

- Bedside screening of mental performance
- External guidance
- Cognitive training, vision training
- Psychoeducation and counselling for relatives

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Multi- and Interdisciplinarity

ENNR is carried out within the framework of a multidisciplinary therapy approach. In addition to activating care, physiotherapy and occupational therapy, (neuro)psychological therapy, physical therapy and often also music therapy and, in the context of ventilation weaning, respiratory therapy are also applied. Weekly team meetings with logging of therapy progress and formulation of weekly therapy goals are an integral part of the ENNR. With ventilation weaning, a new therapy aspect is added for the patients concerned, which at the beginning of the clinical stay, in addition to intensive medical aspects, is decisive for the entire rehabilitation process. In this rehabilitation phase, respiratory therapists who, in addition to providing the actual therapy, are also allowed to make adjustments to the ventilator[28], play an essential role. The integration of this professional group into the rest of the team, with the formation of a common language and an understanding of respiratory-specific therapy goals (on the part of the other therapists) is essential for the overall interdisciplinary performance. In this context, physiotherapists, occupational therapists and music therapists, as well as speech therapists and nurses, must have a basic understanding of forms of ventilation, ventilation goals and the permissibility of their own forms of therapy under ventilation conditions. Thus, in principle, it is quite permissible (and desirable) for patients who are still ventilated (under ventilation) to be mobilised in standing and even gait. However, interdisciplinary, communicative and interactive fine-tuning is an important prerequisite for this.

Transfer of Ventilated Patients from ENNR to Out-of-Hospital Care

From the results of various studies, it can be deduced that with 5%–11%, only relatively few patients discharged from ENNR receive out-of-hospital mechanical ventilation[2]. After discharge, neurological patients with out-of-hospital ventilation need out-of-hospital intensive care, as do most tracheostomised neurological patients without mechanical ventilation. In out-of-hospital intensive care specialised nurses are continuously present. Out-of-hospital intensive care is delivered at home, in residential communities, in intensive care nursing homes, in long-term rehabilitation facilities (so-called "Phase-F facilities") and other suitable places. In addition to intensive care services, physiotherapy, speech therapy and occupational therapy are available to patients depending on regional availability; in Phase-F facilities these therapies are always available to the patients. All patients discharged from ENNR to an out-of-hospital intensive care setting due to persisting mechanical ventilation or tracheostomy should be linked to institutions specialising in ENNR. In particular, patients on out-of-hospital mechanical ventilation should also be linked to these institutions for regular checkups and to identify possibilities to optimise their quality of life and participation. In Germany, the patient journey has yet to be organised to meet those demands.

Conclusion

With the ENNR, a new sub-sector of acute inpatient care has emerged, which is necessary in the background of the DRG system, the optimisation of treatment chains and the successes of modern intensive care medicine, which are not always comprehensive in a timely manner[3]: Advancing treatment up to a possible prognosis in facilities that are suitable for managing complications and offering therapies individually tailored to the patient's pattern of disorders. Currently, the ENNR has about 5,000 treatment places in Germany[3]. According to the authors, ENNR is a sustainable component in the overall treatment concept of ventilated neurological patients in specialised departments or clinics. The ENNR as a whole, and the departments that offer additional ventilation weaning in particular, need the opportunity to continuously develop and to define structural, process and outcome criteria within the framework of professional quality management, the consideration of which leads to a continuous improvement in the clinical care of this very vulnerable patient clientele. With the certification of centres for ventilator weaning in the ENNR by the DGNR, a first important milestone has been reached[29].

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Chapter 16

Respiration in Brain Hemisphere and Brainstem Lesions

Mathieu van der Jagt, Leo Heunks and Martin Groß

Acute and chronic brain diseases can affect respiratory regulation. This chapter introduces a conceptual framework to classify disorders of respiratory regulation, and it explores the underlying pathophysiologies. By putting together pathophysiological and clinical information, this chapter should enable clinicians who encounter patients with brainstem and hemispheric lesions, which affect respiration, not only to better understand the presumed anatomical structures involved but also to manage these conditions.

Anatomical and Physiological Principles of Regulation of Breathing

The neuroanatomy of respiratory control in humans is incompletely understood and highly complex[1]. Furthermore, the localizing value of pathologic respiratory patterns might be limited[2]. However, some basic tenets of neuroanatomical physiology underlying human respiratory are important. While the components of the integrated neural network controlling respiration are discussed in detail in Chapter 4, they are succinctly summarized here to aid clinical interpretation of disorders of respiratory regulation.

First, there are three main cellular regions in the brainstem that regulate respiration: these are the ventral respiratory group (VRG), the parafacial respiratory group, and the nucleus retrotrapezoideus (RTN) in the ventral medulla oblongata; the nucleus tractus solitarius (NTS) in the dorsal medulla oblongata; and the mid-dorsal-pontine located pontine respiratory group (PRG)[3]. The NTS is involved in inspiratory regulation and accepts input from autonomous nerves associated with respiratory and cardiovascular reflexes as well as lung proprioceptive feedback through the vagal nerve due to volume changes of the lung[3,4]. The VRG consists of four parts, from rostral to caudal: the Bötzinger complex, the pre-Bötzinger complex, the rostral VRG, and the caudal VRG. The Bötzinger complex is involved in expiratory regulation, while the network of neurons of the pre-Bötzinger complex generates "rhythmic activity that is both essential and sufficient to drive inspiration"[5]. The rostral VRG – among a variety of inputs and outputs – delivers excitatory input to the phrenic motor nucleus in the mid-cervical spine[5–7] and to intercostal motoneurons[8], thus contributing to the inspiratory motor pattern[9]. The caudal neuronal network of the VRG again projects to motor neurons of upper airway, intercostal and abdominal muscles, contributing to the expiratory motor pattern and to the generation of the cough reflex[5,10,11]. In between NTS and VRG is the nucleus ambiguus that accommodates decreased upper airway resistance by means of the upper pharyngeal musculature. The PRG is involved in regulation of the inspiratory off-switch and the frequency of breathing. Of clinical importance (to understand the effects of high cervical spine injuries) is the notion that the upper odontoid (C2) notch is at the level of the ponto-medullary junction of the brainstem, which is similar to the cranio-cervical junction when taking the osseous landmarks as the reference.

Second, volitional respiratory control is an important part of respiration: it can override autonomous control and is principally absent during sleep, which is why central disorders of respiration tend to exacerbate during sleep[12]. This volitional part of respiration involves an extensive neuronal network comprising supplementary motor area, premotor cortex, motor cortex, and other regions of the cortex as well as the amygdala, globus pallidum, nucleus caudatus, different thalamic and hypothalamic regions, and the cerebellum[4,12–15]. The PRG is a relay station for signals from midbrain and cortical areas towards the VRG and vice versa and is as such involved in volitional respiration[16].

Respiratory Drive

Respiratory drive can be pragmatically defined as the neural output of the respiratory centers[17]. The respiratory drive is generated in specific areas in the brainstem (see Chapter 4).

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For inspiration, the pre-Bötzinger complex in the medulla oblongata plays a prominent role, generating the rhythm of inspiration. The intensity of the drive generated depends on positive and negative feedback from different pathways[18]. Three major pathways have been identified, including (a) chemoreception (central and peripheral receptors), (b) mechano- and irritant receptors in the lung and chest wall, and finally (c) cortical feedback.

Respiratory Rhythm

The respiratory rhythm is generated by the integrated respiratory network with brainstem regions at the core and comprises an inspiratory, a post-inspiratory and – for example in elevated respiratory drive – an expiratory phase (see Chapter 4), with different activation patterns of the respiratory muscle pump (see Chapter 5).

The normal spontaneous breathing in rest is traditionally said to be characterized by a tidal volume of ±7ml/kg normal body weight, but our extensive literature research back to Hutchinson´s groundbreaking publication on spirometry in 1846 did not clarify the deduction of this approximation[19–21]. Anyhow, it is well understood that gender, age, weight, and height are substantial determinants of tidal volume, and that there is a considerable inter- and intraindividual variability[22]. The normal respiratory rate is 12–19 breaths per minute and is lowest in individuals with normal versus low or high body mass index. Again, there is considerable inter- and intraindividual variability[23], the latter being reduced in sleep[24]. With increased ventilatory demands, first tidal volume will increase and if insufficient, respiratory rate will increase as well[25]. A prolonged expiration is seen in patients with obstructive lung diseases. In these patients, airway resistance is increased, and therefore more time is needed to empty the lung. Consecutively, expiratory flow has not reached zero, at the start of the next inspiration. A normal breathing pattern demonstrates occasional sighs, but more frequent sighs may be seen in hyperventilation syndrome.

Central and Peripheral Chemoreceptors

The RTN, located close to the facial nucleus, contains neurons, that are sensitive to H^+[26,27]. While the RTN is the most important candidate for the locus of central chemoreception, other brain regions are discussed as well [28]. Carbon dioxide (CO_2) can rapidly diffuse across the blood–brain barrier and change the pH of the cerebral spinal fluid. A small decrease in pH of the cerebral spinal fluid will have an immediate effect on respiratory drive. A change in $PaCO_2$ of ±5 mmHg can *double* minute ventilation in healthy subjects. On the other hand, when $PaCO_2$ decreases only a few mmHg below the set point, the respiratory drive will decrease and may even cause apnea, especially during sleep[29]. Although changes in arterial pH due to metabolic cause will also affect respiratory drive, this effect is much slower, as it takes several hours to change the electrolyte composition of the cerebrospinal fluid (CSF) due to slower transfer of ions other than H+ to cross the blood–brain barrier.

The most well-known peripheral chemoreceptors are in the glomus caroticum, located in the carotid bifurcation. The glomus caroticum contains cells sensitive to PaO_2, although the exact mechanisms of O_2 sensing remains to be established[30,31]. The output of the of these O_2 sensitive cell remains relatively stable over a wide range of PaO_2 values. Only when PaO_2 reaches values below 80 mmHg activity increases and rises steeply when PaO_2 reaches values below 60 mmHg. For additional information on hypercapnic and hypoxic respiratory drive see Chapter 4.

Mechanical Receptors

The chest wall, lungs, and respiratory muscles contain receptors or nerve fibers that provide sensory feedback to the central regions of respiratory control. Slowly adapting stretch receptors in the lung and muscle spindles provide information on the volume of lung and thorax. Receptors in the lung play a role in the well-known Hering–Breuer reflex, which terminates inspiration and facilitates expiration at high lung volume, but also are involved in generating sighs[32]. Irritant receptors in the lung epithelium are sensitive to inflammation and trigger increase in minute ventilation, even resulting in hyperventilation with infection, ischemia (pulmonary embolism), fibrosis, and other events that result in pulmonary inflammation.

Suprapontine Control of Respiration

It is well known that behavioral feedback, originating from the cerebral cortex affects respiratory drive. Emotional stress, for instance resulting from pain, agitation, dyspnea, or delirium, is quite common in ventilated ICU patients and affects respiratory drive probably through limbic structures[33–35]. Today, very few studies have specifically investigated the effect of cerebral cortex feedback on the respiratory drive in ICU patients. However, it has been proposed that hyperventilation associated with brain injury results from a reduction in

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descending cortical inhibitory feedback on the medullary respiratory regions[36]. Suprapontine sites in general are not crucial for control of resting respiration, but contribute more to the control of respiration in locomotion, defence reaction, hypoxia and hypercapnia[35].

To epitomize, the respiratory drive is generated by specific anatomical regions located in the pons and the medulla oblongata, but suprapontine regions also modulate respiration. Complex interactions exist between respiratory regions throughout the human brain that hamper the association of specific respiratory patterns to specific anatomical centers: abnormal respiratory patterns may coexist or dynamically change into one another within short periods of time[37].

Clinical Correlates and Consequences of Brainstem and Hemispheric Lesions Affecting Respiration

There are several reasons why clinical recognition of neurological disordered respiration in an acutely brain-injured patient is clinically relevant. Disordered breathing due to an acute brain disease could be life-threatening because its rhythm and depth do not provide sufficient oxygen and clear carbon monoxide. Characterization of respiratory abnormalities due to acute brain lesions may allow precise follow-up of the evolution of brain lesions, especially when the brainstem is involved. Indeed, the brainstem, and especially the lower parts involved in respiratory drive, contains brain nuclei that govern respiration which are localized in a small area within the brainstem. Therefore, small increments in the size of pathological lesions in this area may have serious consequences (e.g. bradypnea progressing towards apnea), whereas the reverse might also occur (e.g. multiple apneic spells improving to normal respiratory frequency, for example after evacuation of hematoma). Careful evaluation of respiratory disorders caused by acute brain lesions must help in advanced treatment planning, for instance such as tracheostomy in patients without much potential for rapid recovery.

Classification of Disorders of Respiratory Regulation in Brain Disease

While there is an abundance of descriptions of disorders of respiratory regulation in cerebral disease, a comprehensive classification of those is still in its infancy and there is considerable inconsistency of definitions throughout the existing literature[37,38]. We therefore suggest a classification that integrates pathophysiology, existing literature (mainly case reports and case series), and perspectives of sleep medicine, represented by the classification system of the American Academy of Sleep Medicine. Hereby we consider that it is required to record disorders of respiratory regulation, whenever possible, to achieve an accurate diagnosis. Polygraphy, polysomnography, transcutaneous and end-tidal capnometry, and blood gas analysis are the key diagnostic instruments for this goal. Starting point is a clear discrimination between respiratory rhythm and respiratory pattern. We suggest understanding in the context of classification *respiratory rhythm* as a term to describe all aspects of timing of respiration (e.g. respiratory rate, inspiration time, and expiration time) and *respiratory pattern* as a term to describe the combination of respiratory rhythm and effort respectively tidal volume, whatever is measured. Disorders of respiratory regulation generally do not affect the respiratory rhythm in an isolated fashion, but the respiratory pattern. We therefore propose a pragmatic classification into two main categories: respiratory pattern disorders and dyscapnic disorders. Important breathing abnormalities from both categories are shown in Figure 16.1.

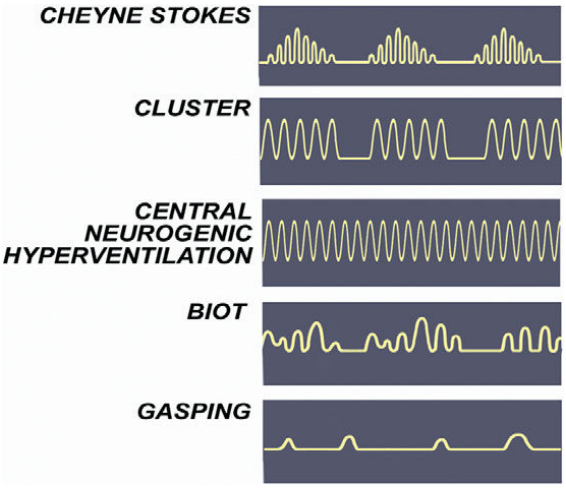


Figure 16.1 Important breathing abnormalities. Central neurogenic hyperventilation is accompanied by hypocapnia. From Wijdicks EFM. *The Practice of Emergency and Critical Care Neurology*. 3rd ed. Oxford University Press; 2024, used with permission.

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Respiratory Pattern Disorders

Bradypnea is a respiratory pattern characterized by low respiratory rate, for instance due to intoxication, drug overdose, or increased intracranial pressure. *Tachypnea* (high respiratory rate) may develop in patients with low respiratory compliance (pulmonary fibrosis, chest wall edema), but also in respiratory muscle weakness, hyperventilation syndrome and central neurogenic hyperventilation.

Apnea is an alarming feature of lower brainstem lesions, specifically affecting the dorsal pontomedullary junction and medulla oblongata. In this context we do not use the term apnea in the context of sleep medicine, defined by a reduction of airflow $\geq$90% for $\geq$10 seconds as proposed by the American Academy of Sleep Medicine, but we refer to an acute and life-threatening complete or nearly complete cessation of inspiration. In acute brain-injured patients who are comatose, apnea generally indicates either severe hemispheric brain injury with herniation and significant brainstem compression or posterior fossa space occupying lesions with posterior compression of the pons. This situation is often compatible with acute spontaneous intracranial hemorrhage in that region, but other rapidly progressive space occupying lesions can also cause this phenomenon. Another, less frequent, situation where a comatose state is combined with apnea is a sedated or brain-injured trauma patient with either a high cervical spine lesion affecting the phrenic nerve (C3–C5) with paralysis of the diaphragm or a very high cervical vertebral lesion above level C3, directly disrupting the ponto-medullary region[39]. Such injuries can be suspected especially in cases with odontoid fractures and atlanto-occipital displacement often accompanied by direct facial and jaw injuries and signs of severe injury to the neck[39]. In these patients, MRI can often characterize the involved areas of the ponto-medullary region. Of note, such local injury purely affecting respiratory drive that is not a direct consequence of herniation and global brainstem disruption due to mass effect or global ischemia (e.g. after cardiac arrest) may confound brain death diagnosis since the apnea might then be an isolated finding[40]. In such cases extra care should be taken to exclude the possibility of persisting consciousness. Furthermore, in awake patients with apnea the most probable cause is a progressive focal lesion in or above the medulla oblongata. Differential diagnosis includes malignancy, vascular malformation, demyelinating/inflammatory lesions, and other less frequent causes such as focal infection[41]. Finally, true apnea without another possible cause than devastating brain injury with involvement of the lower brainstem is obviously a key diagnostic feature of brain death diagnosis. Without it, brain death cannot be diagnosed in most countries, although excluding high cervical spine injury as a cause of apnea, as discussed, is addressed only in a minority of protocols worldwide[42].

Cheyne–Stokes breathing is characterized by periods of first increasing and then decreasing breathing amplitude (crescendo-decrescendo pattern), alternated by apnea or hypopnea[43,44]. The whole cycle including apnea or hypopnea lasts 40 seconds or longer – typically 45 to 90 seconds. This pattern is explained by a slow feedback loop (delay in detecting changes in arterial CO_2 by central respiratory centers). Cheyne–Stokes breathing pattern has been reported in patients with cardiac disease (low cardiac output) and diffuse brain damage. Cheyne–Stokes pattern has also been reported in the elderly during sleep, during sleep at high altitude and in newborn infants. Opioid-induced central sleep apnea may mimic Cheyne–Stokes breathing pattern[43], but is mostly characterized by bradypnea with hypoventilation. The breathing pattern is often ataxic in these cases. Cheyne–Stokes breathing may indicate a deteriorating patient but often it has little significance. According to Miller Fisher, "In the presence of Cheyne-Stokes respiration the patient's physician may with few exceptions retire for a night's sleep"[45].

Central periodic breathing (CPB) shows a crescendo-decrescendo breathing pattern, alternating with central apnea or hypopnea, and is caused by brain disease. It comprises Cheyne–Stokes respiration (CSR), in which the length of a cycle is 40 seconds or more, but also periodic breathing, in which the cycle lasts less than 40 seconds.

Biot or ataxic breathing pattern shows "irregular variability of breathing effort and timing". It is typically caused by medullary lesions[37]. Ataxic breathing in humans has rarely been reported; the recordings of one case are shown in Figure 16.2.

Cluster breathing is defined as "irregular cycles of deep breaths with variable periodicity", does not show a crescendo-decrescendo pattern, and might be a rare phenomenon[46] (see Figure 16.3). Cluster breathing has been described and recorded in a patient with bihemispheric infarction, in another patient with multiple infarctions of right basal ganglia, right frontoparietal cortical region, right occipital cortical and subcortical

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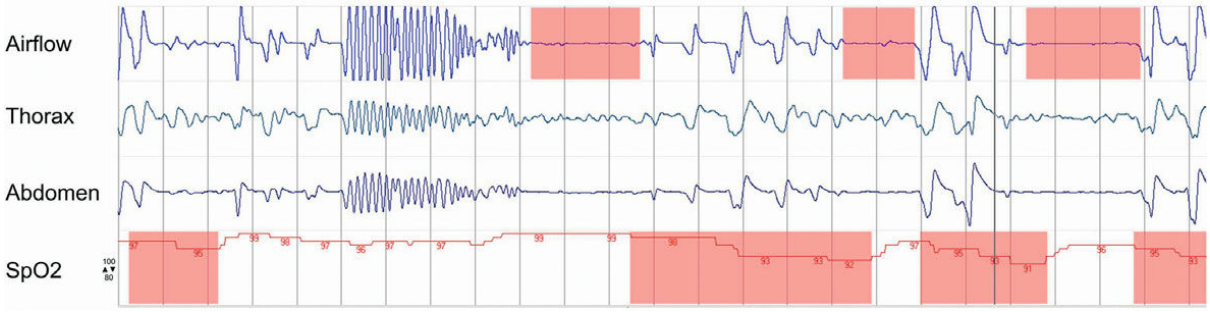


Figure 16.2 Ataxic breathing in a patient with left lateral medullary infarction vertical lines all 10 seconds.. The original figure showed six polygraphs, one of which is presented here. © 2022 Summ et al., distributed under the terms of the Creative Commons Attribution License, Creative Commons disclaims all liability for damages resulting from their use to the fullest extent possible. URL: www.sciencedirect.com/science/article/pii/S1569904822000283?via%3Dihub.

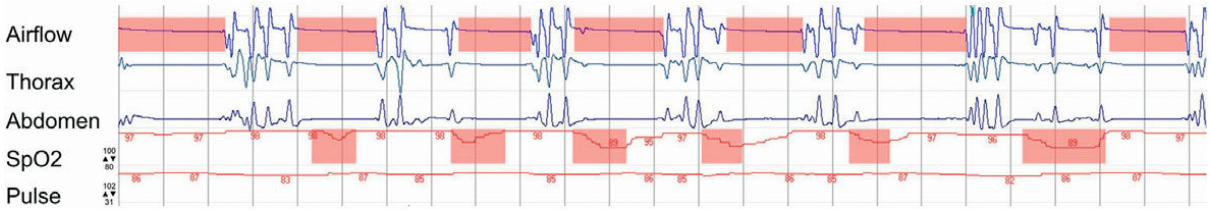


Figure 16.3 Cluster breathing in a patient with infarctions in right basal ganglia, right frontoparietal cortical region, right occipital cortical and subcortical region, and right cerebellum (territory of the posterior inferior cerebellar artery). Vertical lines all 10 seconds. The original figure showed six polygraphs, one of which is presented here. © 2022 Summ et al., distributed under the terms of the Creative Commons Attribution License, Creative Commons disclaims all liability for damages resulting from their use to the fullest extent possible. URL: www.sciencedirect.com/science/article/pii/S1569904822000283?via%3Dihub.

region, and right cerebellum and in a patient with anoxic encephalopathy. In both patients with infarctions the brainstem had been spared[37,47,48].

Apneustic breathing was defined by Plum and Posner in 1982 as a "respiratory pause at full inspiration"[49]. Expiration may be short and irregular. Apneustic breathing is rare but has been reported and occasionally recorded (see Figure 16.4) by different methods in a variety of conditions, often affecting the pons[50–53], with a first possible case dating back to 1929[54]. In a case series of twenty patients with classical locked-in syndrome (LIS), thirteen were diagnosed with apneustic breathing, and all of those had pontine lesions. The results of the latter study are difficult to interpret, as there was neither a definition of apneustic breathing presented nor recordings demonstrating the condition[55]. Considering findings in animal models, lesions affecting the pontine respiratory group, which is involved in phase transitions of the respiratory rhythm, may lead to apneustic breathing in humans[56].

Respiration alternans was first defined by Fisher in 1969 as consisting of "small breaths interposed between full breaths"[45]. To the best of our knowledge, the first ever published recordings of this phenomenon in humans were presented in a recent article by one of the authors of this chapter[37]. Figure 16.5 shows polygraphs from three patients, all of whom had brainstem infarctions. Two of the recorded respiratory patterns fit Fisher´s definition. Respiration alternans presented specifically as a combination of tachypneic CSR and bradypnea in both patients. The transition from one respiratory pattern to another may take place via respiration alternans or suddenly. These peculiar phenomena suggest the existence of a network of generators of the respiratory rhythm with the possibility of multiple generators functioning at the same time and producing different respiratory patterns in certain pathological conditions[37]. Therefore, we suggest broadening Fisher´s definition. *Respiration alternans* is the "occurrence of more than one respiratory pattern at the same time".

Prolonged expiratory apnea with cyanosis (PEAC) is also called "cyanotic expiratory apnea of central origin"[57,58], "centrally mediated expiratory apnea with cyanosis"[57] or briefly "prolonged expiratory apnea"[59]. This disorder was thoroughly recorded by Southall et al.

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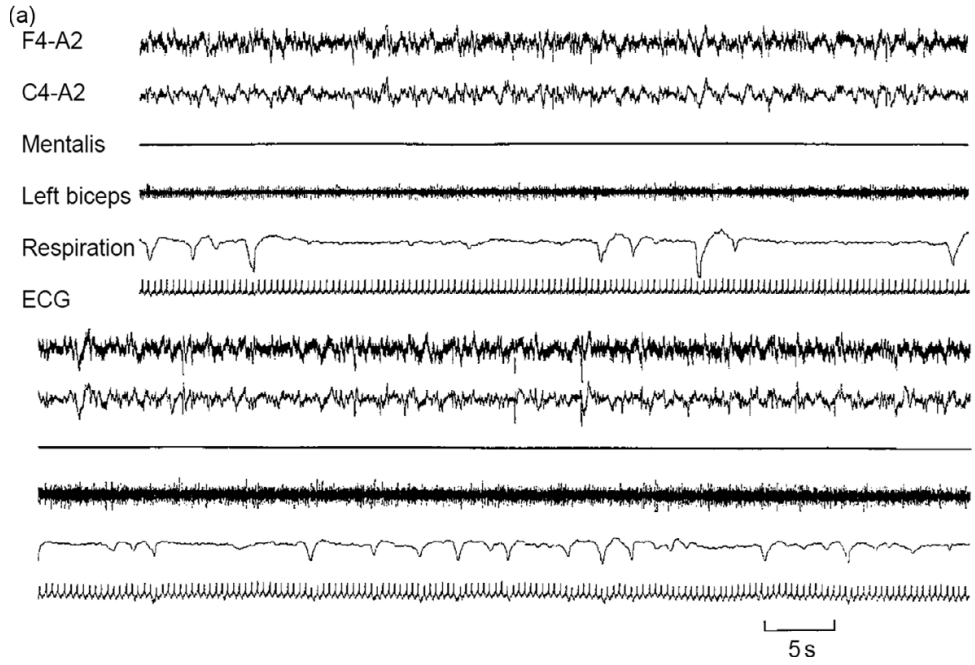


Figure 16.4 Apneustic breathing in a child with brainstem damage due to hypoxic-ischemic encephalopathy. Expiration occurs irregularly, followed by prolonged inspiration as long as 30 s. Paper speed 5 mm/s. (a). A sagittal section shows atrophy of whole brainstem and cerebellar vermis (b), With kind permission from: Saito Y, Hashimoto T, Iwata H, et al. Apneustic breathing in children with brainstem damage due to hypoxic–ischemic encephalopathy. *Developmental Medicine & Child Neurology*. 1999;41:560–7. https://doi.org/10.1111/j.1469-8749.1999.tb00656.x (figures 5d and 6).

in 1985 (see Figure 16.6) in 10 infants (see Figure 16.6). Four patients suffered from neurodevelopmental handicap and one patient having had viral meningoencephalitis. According to its pathophysiology, PEAC is defined as absence of inspiratory flow but "continued expiratory activity at low lung volume with partial or complete glottic closure", accompanied by cyanosis[59]. Already in 1978 Holinger et al. published that 14 out of their case series of 21 patients with Chiari II malformation, meningomyelocele, hydrocephalus and bilateral abductor vocal cord paralysis showed significant episodes of apnea with a duration of up to 60 seconds or longer, which were associated with cyanosis, and frequently would not be effectively treated by tracheostomy[60]. The occurrence of

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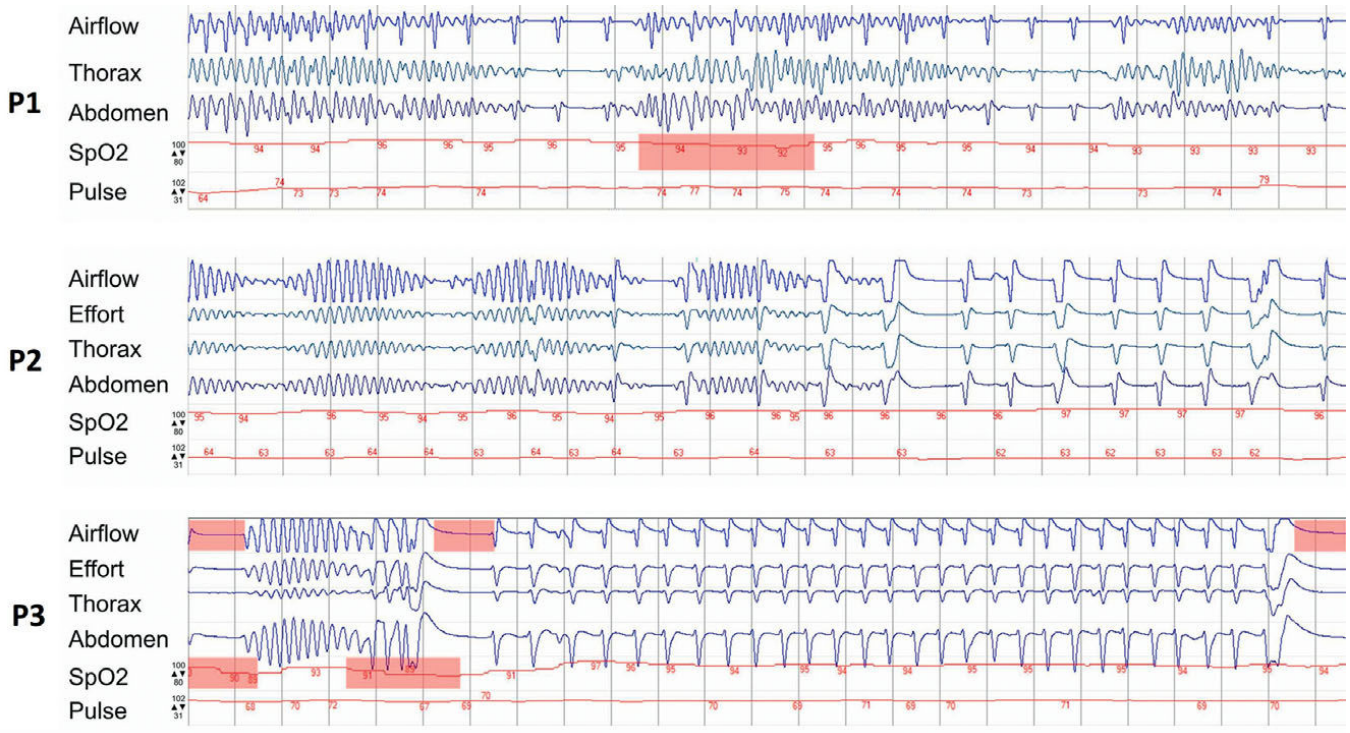


Figure 16.5 Polygraphs from patients with two different respiratory patterns. P1: Respiration alternans. P2: Respiration alternans and transition from tachypneic CSR to bradypnea. P3: Sudden switch from tachypneic CSR to bradypnea. Vertical lines all 10 seconds. The original figure showed six polygraphs, three of which are presented here. CSR, Cheyne–Stokes respiration. © 2022 Summ et al., distributed under the terms of the Creative Commons Attribution License, Creative Commons disclaims all liability for damages resulting from their use to the fullest extent possible. URL: www.sciencedirect.com/science/article/pii/S1569904822000283?via%3Dihub.

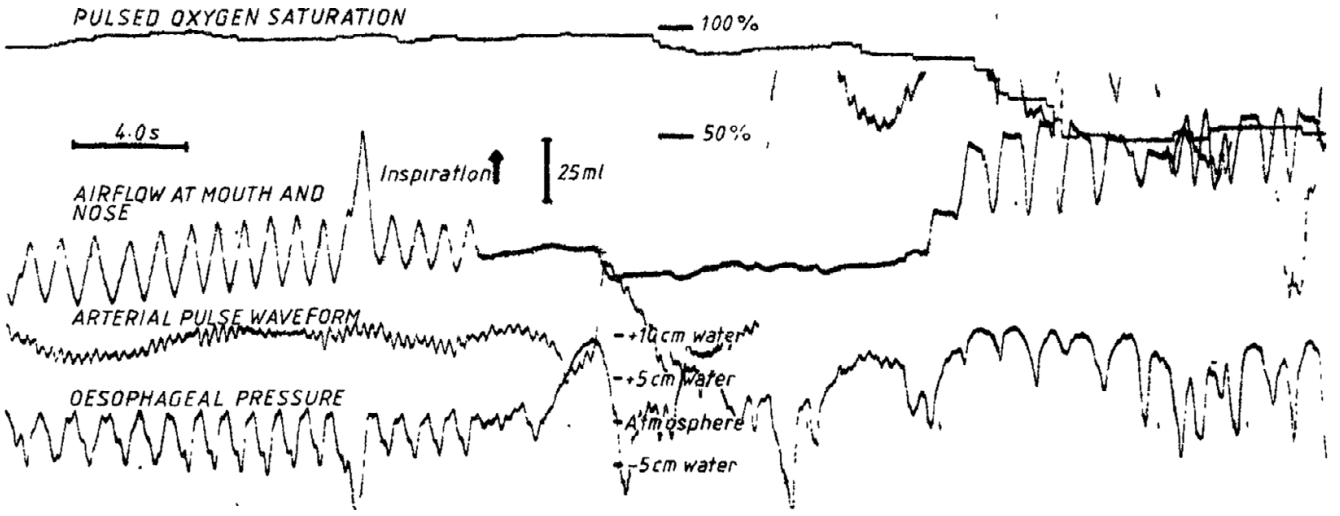


Figure 16.6 Recording from a child with diagnosis of chest infection at the age of two weeks and anemia at the age of four weeks. Symptoms began at the age of three weeks, and an identical twin died at the age of eight weeks. "Prolonged apnoea (absent inspiratory flow) begins at end-expiratory position and is associated with hypoxaemia. After 4 s, there is further expiratory flow associated with an increase in oesophageal balloon pressure. Negative excursions in balloon pressure are not associated with inflows of air until episode ends with an augmented inspiration". Caption and figure reprinted from: Southall DP, Talbert DG, Johnson P, et al. Prolonged expiratory apnoea: a disorder resulting in episodes of severe arterial hypoxaemia in infants and young children. *Lancet*. 1985;2(8455):571–7. doi: 10.1016/s0140-6736(85)90583-5 with permission from Elsevier.

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PEAC in patients with Chiari II malformation and meningomyelocele became known through a limited number of case series and case reports[57,58,61], and it has also been reported in a patient with meningomyelocele without Chiari II malformation[62]. In patients with Chiari II malformation and meningomyelocele, PEAC may be caused by brainstem compression, a disorganization of the brainstem respiratory network or brainstem epilepsy[63]. Patients showing PEAC are prone to sudden death[57,60]. Craniocervical decompression should performed in Chiari II malformation at the time of onset of PEAC, the use of tracheostomy and/or mechanical ventilation depends on the further clinical context, such as the presence of dysphagia or cough insufficiency[58].

Dyscapnic Disorders

Central hypoventilation syndrome (CHS) or "Ondine's curse" indicates lack of automated breathing upon relaxed wakefulness, drowsiness, or sleep (especially non-rapid eye movement sleep, see Chapter 6) thus when volitional breathing is reduced and "the brainstem respiratory pattern generator is in autorhythmic mode"[4,12,64]. Consequentially, patients with this syndrome lose the capacity to ventilate sufficiently when not awake. In its purest form patients require artificial ventilation or phrenic nerve pacing. CHS can be a congenital trait ('congenital central hypoventilation syndrome') or can be caused by a variety of neurological conditions ('Acquired central hypoventilation syndrome'). Acquired CHS may be a rare condition with predominantly case reports and case series to be found in literature. Its onset may occasionally be subacute, as was published for a patient after lateral medullary infarction[65]. For an overview over reported underlying conditions see Box 16.1. It must be noted that in the available body of literature, the definition of acquired central hypoventilation syndrome was not handled consistently and occasionally there were rivaling conditions reported that all might have been cause of acquired CHS.

A wide variety of causes of acquired CHS has been reported, many of them clearly documenting pathologies of the rostral medulla. Infarction of the ventro-lateral region of the rostral medulla oblongata is the best-established cause[66]. Accordingly, a landmark study documented a reduced hypercapnic ventilatory response (see Chapter 4) in six of nine patients with unifocal lesions of the rostrolateral medulla oblongata, while the hypercapnic ventilatory response was normal in all six patients with lesions in the medial medulla, cerebellum, or pons[92]. In humans, it has been suggested that the neurons of the RTN surround the nucleus of the facial nerve[93]. Animal studies have already identified the RTN

Box 16.1 Neurological conditions reported to cause acquired CHS

Lateral medullary infarction[65–73]
Anaplastic glioma of the brainstem, invading the fourth ventricle[68]
Low-grade pilocytic astrocytoma, compressing the pontomedullary junction and the upper medulla[74]
Recurrent acoustic neuroma at the cerebellopontine angle[75]
Bilateral schwannomas of the acoustic nerve at the cerebellopontine angle and scattered spinal neurofibromas[68]
Paraneoplastic brainstem encephalitis in small cell lung cancer, associated with ANNA-1 antibodies[76]
Paraneoplastic encephalomyelitis in different neoplasms and paraneoplastic brainstem encephalitis and paraneoplastic cerebellar degeneration in small cell lung cancer, all associated with HU-antibodies[77–79]
Encephalitis associated with teratoma and antibodies against EFA6A or anti-EFA6A–interacting proteins[80]
Western equine encephalitis[81]
Medullary lesions in an opportunistic infection by cytomegalovirus and varicella zoster virus in AIDS[82]
Listeria monocytogenes rhombencephalitis[83]
Pertussis encephalopathy[84]
Progressive supranuclear palsy[85]
Frontotemporal Dementia with Parkinsonism caused by *MAPT* variants[86]
Chiari I and 1.5 malformation[87,88]
Megadolichobasilar artery[89]
Brain herniation due to shunt malfunction[90]
Hypoxic encephalopathy[91]

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as the primary locus of central chemoreception, which provides CO_2-dependent regulation of "breathing frequency, inspiratory amplitude, and active expiration". PHOX2B mutations compromise RTN development and consecutively cause congenital central hypoventilation syndrome[26]. A neuropathological study revealed developmental abnormalities of the RTN in 12 of 22 patients with sudden infant death syndrome, but in none of the 11 infant controls[94]. In summary, it may be hypothesized that brainstem lesions affecting the anatomical regions mediating the central respiratory chemoflex cause an acquired central hypoventilation syndrome.

To diagnose acquired central hypoventilation syndrome, we suggest the following obligatory criteria:

1. Persistent or nighttime hypercapnia
2. Presence of a brain disorder, explaining hypercapnia.
3. No presence of other diseases, explaining hypercapnia, like obesity, chronic obstructive pulmonary disease, neuromuscular disease, or non-cerebral disease needing intensive care treatment

Acquired CHS must be considered when there is weaning failure[68] or persistent hypercapnia under mechanical ventilation in an assisted mode, a brainstem condition is present, and no alternative cause is present (see the case demonstrated in Figure 16.7). The treatment of the underlying disease is paramount[87]. If acquired CHS is clinically relevant, long-term mechanical ventilation in a controlled mode should be installed and regular clinical controls should be implemented to identify possible clinical improvement[81].

Central neurogenic hyperventilation (CNH) is defined as respiratory alkalosis combined with increased minute ventilation due to tachypnea or increased tidal volumes[95,96]. The underlying cause is a cerebral disease, and hyperventilation is not explained by any other mental (anxiety, delirium) or organic (e.g. pulmonary, cardiac, or metabolic) condition, or by pain. CNH may occur intermittently[97] or persistently. Typically, there is no hypoxemia in CNH. While CNH is attributed to brain disease, *Kussmaul breathing*, which is characterized by deep large tidal volume at constant respiratory rate (although the rate can be slow, normal, or fast), results from metabolic acidosis (e.g. diabetic ketoacidosis).

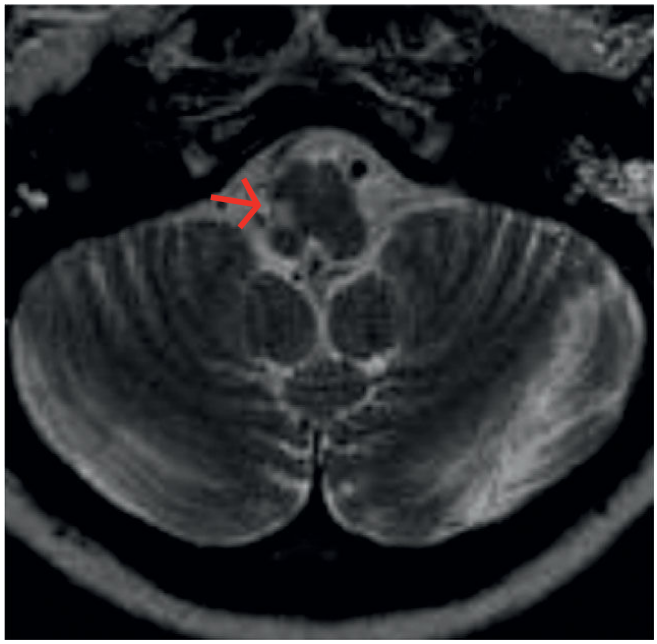
Only cases reports and case series can be found in literature, thus CNH is either a rare condition or underreported. CNH has been reported in females and males, in children[98,99] and adults and in patients with[95] and without[100] disorders of consciousness. The underlying condition is often a neoplastic CNS lesion, especially a primary CNS lymphoma or a glioma[100]. Nevertheless, cases with a variety of other causes have been published: pontine[95,101] and subcortical[102] infarcts, subarachnoid hemorrhage[103], periventricular leukomalacia[104], hypoxic encephalopathy[99], CLIPPERS[105], anti-NMDA-receptor encephalitis[97], multiple sclerosis[106], neuro-Behcet[107], a pontomedullary lesion in systemic histiocytosis[108], acute intermittent porphyria[109], and after third ventriculostomy[110]. Often the pons and/or the medulla oblongata are affected by the underlying lesions[111]. The breathing pattern was only occasionally recorded throughout the published articles and then appeared to be devoid of apnea or hypopnea[95,97]. In subarachnoid hemorrhage, brainstem infarctions, and cerebrovascular events in general, CNH has been associated with a poor prognosis[95,103,110,112]. In conscious patients with CNS neoplasm, treatment with opioids or sedatives can be effective[100], through their effect on neurons with μ-opioid receptors located in the parabrachial complex-Kölliker–Fuse nucleus region and – more importantly - the pre-Bötzinger complex[113].

Animal models showed that a stimulation of the medullary retrotrapezoid nucleus, being the key component for the CO_2-dependent respiratory drive, increases minute ventilation and breathing frequency, and that a stimulation of the pontine lateral parabrachial nucleus increases breathing frequency and tidal volume[114,115]. With respect to the role of catecholamines, animal models showed that adrenaline and noradrenaline increase minute ventilation[116], and that brainstem catecholaminergic neurons have an excitatory effect on respiration and central chemoreception, and thus amplify the CO_2-dependent respiratory drive[117]. Additionally, an experimental increase in intracranial pressure has been shown to increase minute ventilation through a rise in tidal volume and/or breathing frequency, giving way to respiratory depression at higher intracranial pressure (ICP) levels in cats[118].

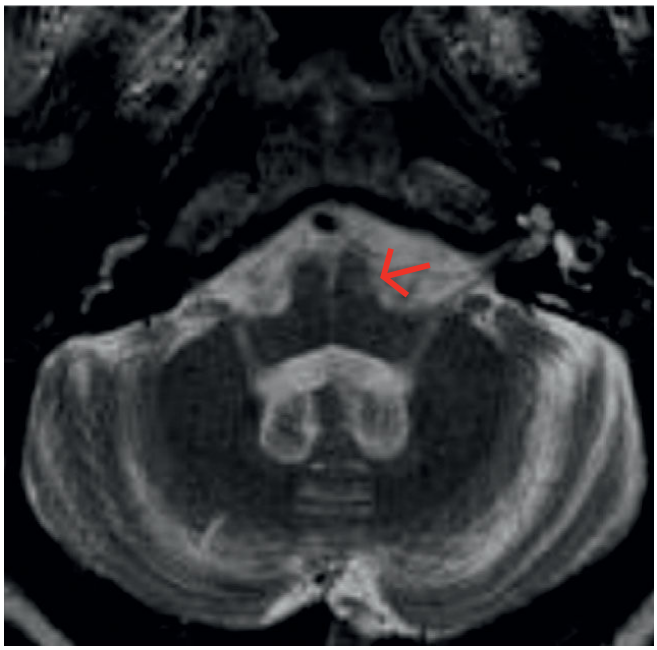
In conclusion, it may be hypothesized that the brainstem centers generating the respiratory rhythm might be intact in CNH, but subject to increased activation resulting from an increased CO_2-dependent ventilatory drive, and catecholamines might play a role in mediating this effect. In some patients, increased intracranial pressure may play a role in the pathophysiology of CNH, too. It remains yet to be clarified whether CNH is a uniform disorder or rather a repository for a subset of related disorders of respiratory regulation.

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(a)



(c)



(b)

26.09.2016 10:30	80	↑	mmHg
26.09.2016 08:28	109	↑	mmHg
26.09.2016 08:06	114	↑	mmHg
26.09.2016 07:47	94	↑	mmHg
26.09.2016 07:37	87	↑	mmHg
26.09.2016 07:33	82	↑	mmHg
26.09.2016 03:07	94	↑	mmHg
18.08.2016 09:59	54	↑	mmHg
17.08.2016 15:44	39		mmHg
12.08.2016 12:07	43		mmHg
11.08.2016 08:47	53	↑	mmHg
10.08.2016 09:38	43		mmHg
10.08.2016 05:12	42		mmHg
10.08.2016 01:57	41		mmHg

Figure 16.7 A 59-year-old female with antineutrophil cytoplasmic antibody-associated vasculitis, pulmonary involvement, and right lateral medullary infarction (a, T2-weighted MRI image, axial view) was successfully weaned from mechanical ventilation and transferred to a ward specialized in early neurological-neurosurgical rehabilitation. The still tracheostomized patient showed a sudden and marked increase in pCO_2 (b) and was retransferred to the neurological ICU. Hypercapnia could not be corrected by mechanical ventilation in an assisted mode (b). According to the cranial MRI a new tiny left lateral medullary lesion was suspected (c, T2-weighted MRI image, axial view). Mechanical ventilation in a controlled mode achieved normal pCO_2 levels, but in the further course of treatment any disconnection from mechanical ventilation led to rapid development of respiratory failure.

Clinical Aspects of Disorders of the Respiratory Regulation

Diagnostic and therapeutic approaches to disorders of the respiratory regulation are understudied. Frequently, central sleep apnea and obstructive sleep apnea (OSA) become apparent via short-lasting desaturations, registered by monitoring systems. In consequence, the nurse informs the doctor on duty, the doctor on duty informs the medical specialist, the case is discussed, and oxygen is applied. Notably, in tracheostomized, non-ventilated patients OSA can be excluded as a cause for desaturations, as the tracheostomy tube bypasses the upper airways. Table 16.1 provides suggestions for

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Table 16.1 Suggestions for diagnostic and therapeutic measures in disorders of respiratory regulation

Condition	Diagnostic measures	Therapeutic measures
Acute apnea	Immediate cerebral imaging	Intubation and mechanical ventilation
Cheyne–Stokes respiration	Echocardiography, cerebral MRI	Oxygen application Avoid mechanical ventilation in reduced left ventricular ejection fraction
Ataxic breathing, cluster breathing and apneustic breathing	Cerebral MRI with thin slices of the brainstem	Clinical decision on necessity and extent of controlled ventilation Avoid assisted ventilation
Acquired hypoventilation syndrome	Cerebral MRI with thin slices of the brainstem	Controlled ventilation, especially during sleep Avoid assisted ventilation Avoid oxygen insufflation in the absence of mechanic ventilation
Central neurogenic hyperventilation	Cerebral MRI with thin slices of the brainstem, in acute cases immediate cerebral imaging	Treatment of the underlying condition, opiates

diagnostic and therapeutic measures in disorders of respiratory regulation.

Respiratory Impairment in Movement Disorders

Respiratory impairment is found in primary and secondary movement disorders. Different aspects of respiratory impairment may add up (e.g. restrictive respiratory dysfunction and stridor both elevate the work of breathing) and additionally may be aggravated by presence of neurogenic dysphagia[119]. This section will focus on a couple of conditions that are more frequently met like Parkinson's disease and multisystem atrophy, yet respiratory impairment, especially sleep-disordered breathing, is encountered in a wide variety of neurodegenerative diseases with and without motor symptoms[120]. Among the secondary movement disorders spasticity is the most relevant when it comes to respiratory impairment.

Restrictive Respiratory Dysfunction

Elevated muscle tone elevates the work of breathing, which again may lead to restrictive ventilatory dysfunction and ultimately respiratory failure. Restrictive ventilatory dysfunction has therefore been described as an aspect of Parkinson's disease[119,121], multisystem atrophy[121], and tetanus[122] and it has been found in stroke survivors[123] and children[124] and adults[125] with cerebral palsy.

Sleep Apnea

It has been demonstrated that Parkinsonism and Parkinson plus syndromes are associated with OSA[126]. Additionally, patients with OSA have an increased risk to develop Parkinson's disease[127]. In multisystem atrophy, sleep-disordered breathing is common with a recent study reporting moderate to severe sleep-related breathing disorders, defined as an apnea-hypopnea index (AHI) of $\geq$15/h, in 62% of the patients with earlier studies reporting from 37.5 to 66.7%. Notably, in the latter study 18 of 21 patients had more hypopneas than all types of apneas – obstructive, mixed, or central – together[128]. Nevertheless, central apneas with a duration of up to 3 minutes had been documented in a series of four cases, in all of which autopsy revealed pontomedullary degeneration[129]. In another study, nontracheostomized patients with multisystem atrophy more often showed OSA syndrome and central sleep apnea syndrome, defined as an AHI of $\geq$5/h, compared with patients with other neurological diseases. All tracheostomized patients with multisystem atrophy had central sleep apnea, and in 71.4% it was severe, defined as an AHI $\geq$30/h[130]. Due to the potentially treatable nature of sleep-related breathing disorders, it may be concluded, that in primary movement disorders a sleep study should be performed, if the patient gets symptomatic, for instance with daytime sleepiness (see Chapter 19).

Acquired Central Hypoventilation Syndrome

Pathophysiologic, clinical, diagnostic, and therapeutic aspects of acquired hypoventilation syndrome have been discussed earlier in this chapter. Neurodegeneration in primary movement disorders may affect brainstem regions regulating the ventilatory response to CO_2. Hypoventilation may be observed only at night, or in

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more severe cases also at daytime. In a recent study 9 (27%) out of 34 patients with multisystem atrophy had sleep-related hypoventilation disorder, diagnosed by polysomnography and transcutaneous capnometry[128]. The occurrence of acquired central hypoventilation syndrome has been described in progressive supranuclear palsy[85] and familial Parkinsonism (Perry's syndrome)[131–133]. Therefore, polysomnographic studies in multisystem atrophy should be complemented by transcutaneous capnometry[134].

Stridor

Laryngeal dysfunction is a common feature of multisystem atrophy, affecting 93% of the patients (see Figure 16.8)[135]. Stridor frequently becomes life-threatening during the disease course and tracheostomy is required. Patients who have been tracheostomized live significantly longer than patients, in which stridor is treated with continuous positive airway pressure (CPAP) or is not treated at all[136].

Treatment

When treating respiratory impairment in movement disorders, treatment of the underlying disease is paramount. Nevertheless, respiratory impairment can require a variety of interventions such as CPAP, intubation and mechanical ventilation and tracheostomy, the latter intended for long-term management in multisystem atrophy. It has to be noted that antispastic agents like botulinum neurotoxin A[137] and dantrolene[138] can occasionally cause respiratory failure. While after treatment with onabotulinumtoxin A forced vital capacity decreases slightly, but significantly, this decrease was subclinical in a recent randomized controlled trial with 264 participants[139]. Therefore, stopping medications for spasticity is considered unlikely to result in clinically relevant improvement of respiration.

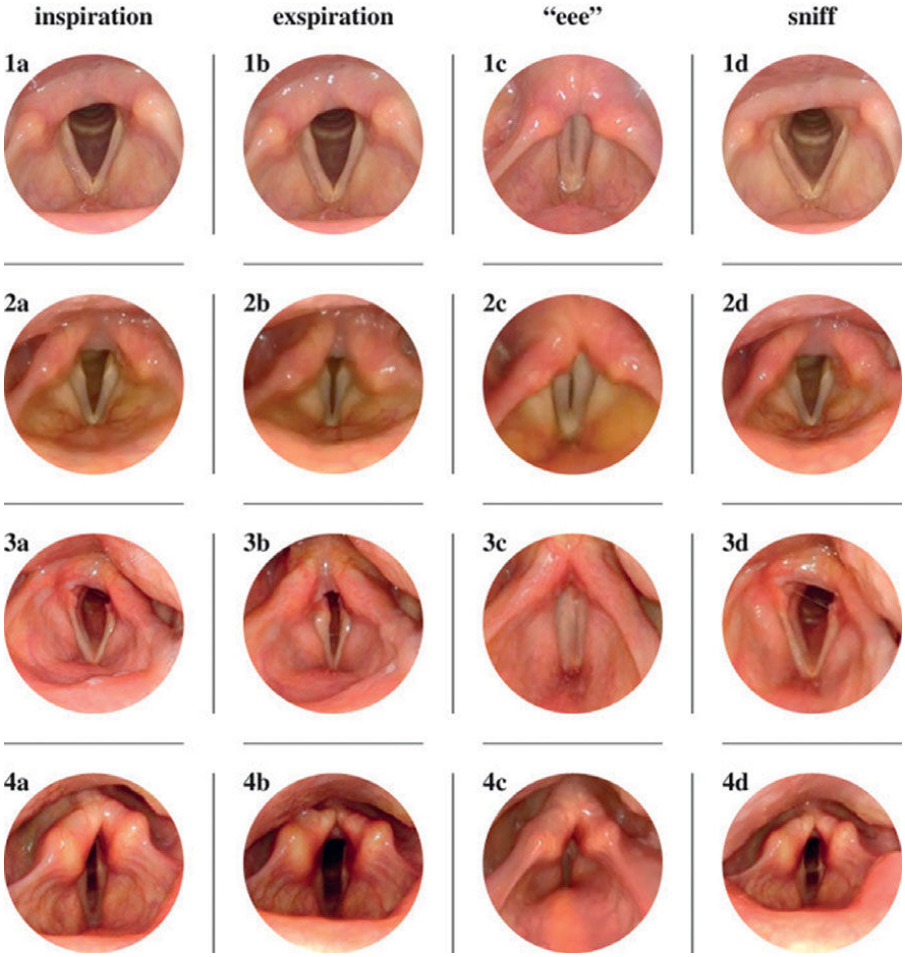


Figure 16.8 Vocal fold position during normal inspiration (a), normal expiration (b), phonation of "eee" (c), and sniffing (d) in a healthy subject (1) and patients with multiple system atrophy (MSA) (2,3,4). (1) Normal vocal fold motion with abduction during inspiration (a), slight adduction during expiration (b), near complete adduction during phonation (c), and near complete abduction during sniffing (d). (2) Example of vocal fold motion impairment (VFMI) in a patient with MSA with restricted vocal fold abduction during inspiration (a), pronounced vocal fold adduction during expiration (b), insufficient vocal fold adduction during phonation (c), and incomplete vocal fold abduction during sniffing (d). (3) Example of vocal fold fixation (VFF) in a patient with MSA with absent left vocal fold motion during inspiration (a), expiration (b), and sniffing (d) but normal vocal fold adduction during phonation (c). (4) Example of paradoxical vocal fold motion (PVFM) in a patient with MSA with paradoxical vocal fold adduction during inspiration (a), paradoxical vocal fold abduction during expiration (b), incomplete vocal fold adduction during phonation with consecutive activation of the false vocal folds (c), and paradoxical vocal fold adduction during sniffing (d). With kind permission from: Gandor F, Vogel A, Claus I, et al. Laryngeal movement disorders in multiple system atrophy: a diagnostic biomarker? *Mov Disord*. 2020;35(12):2174–83. doi: 10.1002/mds.28220.

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Dysregulated Breathing in Different Conditions

In general, disorders of respiration appear more prevalent in pathologies involving the brainstem and less common in single lesions involving the hemispheres, such as ischemic stroke[140].

Ischemic Stroke

Respiration may be disturbed in ischemic or other types of stroke due to disrupted central generation of respiratory pattern, disruption of descending pathways, or bulbar weakness causing loss of protective airway reflexes and secondary pulmonary complications[141].

Not only is obstructive sleep apnea an independent risk factor for ischemic stroke, but sleep apnea in general is also a sequel of ischemic stroke with more than half of the patients presenting with sleep apnea after an acute stroke and up to a third in the chronic phase[142]. Sleep apnea after an acute stroke is underdiagnosed, and there is uncertainty about the distribution of obstructive versus central sleep apnea. A recent review concluded that therapy of sleep apnea in during the acute phase of stroke is feasible and might favorably affect long-term outcomes, thereby suggesting a "multidisciplinary diagnostic, treatment, and follow-up strategy"[143].

CSR occurs frequently in patients with acute ischemic stroke. Clinical variables associated with this respiratory abnormality are large-artery atherosclerosis or cardioembolic stroke, bilateral hemispheric infarction and concurrent cardiac abnormalities (decreased left ventricular function and enlarged left atrium)[144]. Interestingly there was no difference in the proportion of supra- versus infratentorial strokes in patients with or without CSR in one study[144]. In the large-artery ischemic stroke group, stroke severity was also associated with CSR. However, CSR is rather unspecific, as illustrated by these diverse risk factors.

CPB in general is associated with worse outcome after ischemic stroke. A clear association of CPB with hemispheric stroke location is lacking[145].

Bilateral infarction of the medulla oblongata involving the pyramidal tract (i.e. the voluntary central motor neurons) interrupts volitional but not automatic breathing. Infarction of the medullary regions generating the hypercapnic respiratory drive, the respiratory rhythm, or the respiratory motor pattern can affect automatic breathing, sparing voluntary breathing while awake[3,146]. However, these functional patho-anatomical relations are not clear cut. Unilateral lesions might for instance lead to central sleep apnea, suggesting that there are functional cross-links between neuronal pathways. Also, central hypoventilation syndrome (or "acquired Ondine's curse") has been described as a rare consequence of unilateral medullary infarction as discussed previously[72].

In a case series of twenty patients with classical LIS, all had respiratory abnormalities, and thirteen were diagnosed with "apneustic breathing". There were neither a definition of apneustic breathing nor recordings demonstrating the condition published in this specific study though[55]. Another report shows a less uniform picture, for example, with apnea, Cheyne–Stokes, hyperpnea, or ataxic breathing, but also mention of normal breathing in spite of LIS[147]. It appears that in brainstem infarction, not accompanied by a classical LIS, respiratory abnormalities may be related more to size and bilaterality of lesions rather than the level of the lesion[148]. Apneustic and cluster breathing did not appear to be common in one study[148].

Spontaneous Intracranial Bleeding: Aneurysmal Subarachnoid Hemorrhage and Intracerebral Hemorrhage

Hypocapnia (spontaneous hyperventilation) on admission has been associated with adverse outcomes in intracranial hemorrhage[149], whereas incident hypocapnia during mechanical ventilation has been associated with adverse outcomes in aneurysmal SAH[150]. Causally, arterial cerebral vasoconstriction and decreased cerebral blood flow with ensuing hypoxia may play a role. The neuroanatomical substrate of hyperventilation in brain injury is not clear: the lateral parabrachial nucleus has been implicated as a focal site that upon stimulation may cause hyperventilation, but it is probable that multiple mechanisms are implicated, e.g. altered tissue- and possibly CSF pH[111]. The latter mechanism was recently supported in a series of aneurysmal SAH patients, in whom it was found that lactate production in CSF led to lower strong ion difference (acidifying CSF), which appeared to be compensated by lower CO_2 and compensatory alkalosis due to central hyperventilation[151]. In brainstem hemorrhage, respiratory disturbances varied according to clinical severity in one case series, with absence of clear respiratory abnormalities in those who recovered to independence, reflecting the low severity (and small size) of the hemorrhage, and the fact that it was most probably non-progressive during the clinical course[152].

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Traumatic Brain Injury

Similar to intracranial hemorrhage and subarachnoid hemorrhage (SAH) as described previously, spontaneous hyperventilation was associated with brain tissue hypoxia and worse outcome in TBI and other types of brain injuries, although cause and effect should be regarded as debatable, given the observational nature of the data[153,154]. In general, however, there is a dearth of studies on respiration in human TBI.

Seizures

Apart from the well-known phenomenon of hyperventilation after generalized tonic-clonic seizures, apnea is also well described as an immediate peri-ictal consequence of seizures and is linked to focal (temporally localized, including the amygdala) rather than generalized seizures[155,156]. It may even be the only phenomenon in a minority of focal seizures. Prolonged ictal apnea (>60 seconds) is dangerous due to the strong association with severe hypoxia[155]. As such unexplained central apnea should elicit consideration of temporal epilepsy and the risk of sudden unexpected death in epilepsy (SUDEP)[157]. Vice versa, focal epilepsies should urge clinicians to include respiratory monitoring when prolonged EEG monitoring is applied in such patients to detect apnea and patients at risk for SUDEP[158]. It has been demonstrated that a subset of patients with epilepsy has a clinically significant reduced hypercapnic ventilatory response, consecutively being prone to increased postictal CO_2, severe respiratory depression and SUDEP[159]. Serotonergic signaling has also been implicated in acute severe apnea that may result in SUDEP, and may represent a target to decrease risk of apnea in susceptible patients with epilepsy[160].

Cardiac Arrest

Agonal breathing is a key factor indicating cardiac arrest, before proceeding to apnea, which in turn is the trigger for bystander cardiac resuscitation (absent reaction to stimulus, indicating coma, and absence of spontaneous breathing). The apnea indicates insufficient perfusion of the respiratory centers in the brainstem, and although this mechanism is widely acknowledged and its consequence widely witnessed on a daily basis worldwide, it is conspicuous that there are very little reports on persistent central apnea or hypoventilation after cardiac arrest[91]. Apparently, the respiratory centers are resistant to hypoxia, in contrast to other parts of the brain especially rostrally of the pons.

Management Issues

As has been described in this chapter, at least three pathways provide feedback to the respiratory centers: chemoreception, irritant and mechanoreceptors, and cortical feedback. Modulating these pathways may be an effective approach to modulate respiratory drive[161]. Direct modulation of chemoreception, especially pH, using extracorporeal CO_2 removal is an effective way of controlling respiratory drive in patients on assisted mechanical ventilation[162]. However, given the invasiveness of this approach, and requirement for systemic anticoagulation, this technique is not feasible for the sole purpose of controlling respiratory drive. Other interventions may however be used to control respiratory drive in ventilated patients and are briefly summarized here.

Effect of Mechanical Ventilator Settings

The interaction between the brain and ventilator is complex, and both immediate and prolonged effects of mechanical ventilation on the brain have been reported. Experimental data suggest that mechanical ventilation may result in brain injury, so-called ventilator associated brain injury. For instance, experimental studies demonstrated increased hippocampal apoptosis and brain inflammation after 50 hours of lung-protective ventilation, as compared with unventilated controls[163]. Interestingly, ventilator-associated brain injury may be reduced by electrical stimulation of the diaphragm, possibly through phrenic nerve afferent signaling[164]. However, the prolonged effects of mechanical ventilation on the brain are beyond the scope of this chapter.

Mechanical ventilator settings may affect respiratory drive and effort. In patients on assisted ventilator mode, a reduction in inspiratory assist will often increase respiratory drive. Indeed, it has been demonstrated that in patients ventilated on a partially supported mode, decreasing inspiratory assist increases diaphragm electrical activity (estimate of respiratory drive) and transdiaphragmatic pressure[164,165]. Interestingly, the effect of inspiratory assist on respiratory drive in ventilated patients with brain injury has not been evaluated. However, it is the authors' clinical experience that in many patients with brain injury and high respiratory drive, increasing inspiratory assist has limited effect on respiratory drive. This could be related to reduced

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inhibitory feedback from the cortex to respiratory centers in the brainstem (see Section 16.1). However, this topic requires further evaluation.

Notably, positive end-expiratory pressure (PEEP) may affect respiratory drive as well. Morais demonstrated that in patients with acute respiratory distress syndrome on a partially supported mode, increasing PEEP reduced respiratory effort[166]. However, the underlying physiology of reduced respiratory effort due to increased PEEP appears complex. In some of these patients, increasing PEEP decreased respiratory drive (estimated by diaphragm EMG). Although the study did not specifically investigate how PEEP reduced respiratory drive, a possible explanation is that with increased PEEP, lung homogeneity improved, and such reduced feedback from pulmonary irritant receptors to the respiratory centers in the brainstem (see Section 16.1). Interestingly, in other patients, the reduced respiratory effort due to increased PEEP was accompanied by increased respiratory drive. Possibly, in these patients PEEP impaired diaphragm geometry, resulting in impaired diaphragm neuromuscular efficiency[167]. In conclusion, higher PEEP appears to reduce respiratory effort, but the underlying mechanisms depend on patient characteristics. Nevertheless, it seems reasonable to test the effect of higher PEEP on respiratory effort in brain injured patients, especially when the patient has spontaneous breathing effort and hyperventilates towards hypocapnia. However, the variable effects of PEEP on the injured brain should be carefully considered, although its application and especially effects on ICP may be less harmful than previously thought in the lower PEEP levels[168]. However, on an individual level PEEP may increase ICP when central venous pressure approaches ICP due to impeded venous return from the brain. Therefore it could be worthwhile to check and monitor both during increments of PEEP to ensure ICP stays acceptable[169].

A Role for Drugs?

Different types of sedatives are used in clinical practice, but the effect on respiratory drive varies among classes of sedatives, and the dose administered. Table 16.2 summarizes the effect of different sedatives on respiratory drive.

As previously stated, hyperventilation resulting in hypocarbia is associated with adverse outcomes in diverse types of acute brain injury. Therefore, avoiding hyperventilation is generally warranted, especially in brain-injured patients on controlled ventilation. However, the reverse also appears valid since early hypercapnia in brain injury is also associated with adverse outcome, but only when uncompensated (= accompanied by acidosis)[170]. Still, incident hyperventilation below a pCO_2 of 30 mmHg as applied in intracranial hypertension (variably so among European centers) was not associated with better (nor worse) clinical outcomes when comparing centers regarding their inclination for application of therapeutic hyperventilation in intracranial hypertension versus not having this general policy[171]. This observational study from one of the largest multicenter observational studies to date in TBI patients appears to support earlier consensus guidelines from 2020 on the use of temporary hyperventilation as a temporizing measure (but <1 hour) for impending herniation[172,173], given its known effect on ICP surges in clinical practice and the apparent lack of adverse outcome effect. However, only impending herniation is suitable for a hyperventilation trial and recent consensus guidelines do not recommend using it routinely in intracranial hypertension outside the setting of impending herniation[174]. Importantly, clinicians should appreciate the vulnerable balance between short-term hyperventilation and the real risk of aggravated cerebral hypoxia caused by hyperventilation when applied too long or too aggressively. Further, from a pathophysiological viewpoint it should be appreciated that next to vasoconstrictive effects of hyperventilation, it may result in hyperexcitability of neurons (resulting in increased demand for oxygen and glucose) and a leftward shift of the

Table 16.2 Effect of sedatives on respiratory drive

Class	Effect on respiratory effort	Effect on respiratory rate	Ventilatory response to $PaCO_2$ and PaO_2
Benzodiazepines	⇩	⇔ or ⇧ ⇩ at high dose	⇩
Propofol	⇩	⇔ or ⇧ ⇩ at high dose	⇩
Opioids	⇔ or ⇧	⇩	⇩
Alpha2-agonists (clonidine/dexmedetomidine)	⇔	⇔	⇔

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oxygen-hemoglobin dissociation curve due to alkalosis, further increasing the risk of imbalances between oxygen supply and demand[175]. Thus, when applied, some measure of adequacy of cerebral perfusion is advisable, such as brain oxygen partial pressure ($PBrO_2$), to ensure safe application.

How to Evaluate Apnea and Exclude Reversible Causes

Apnea testing is one of the most essential and definitive tests in the evaluation of patients for brain death (BD), given that it indicates total destruction of the brainstem from rostral to the most caudal parts and thereby total absence of brainstem function, a prerequisite for BD diagnosis. Methods for confirmation of apnea for BD diagnosis are well established and have been stable over time, although nuances have been proposed even very recently[176], and relate to addition of pH as criterion for ventilation triggering from the brain, baseline hypercarbia, preoxygenation with positive pressure support, and adapted thresholds for pO_2 and pCO_2 for patients on extracorporeal support[176]. Apnea typically lasts about 8–10 minutes, but much longer periods (up to 110 minutes) have been described in the setting of relative hypothermia around 36.0 °C[177]. In patients with acute respiratory distress syndrome, rendering apnea testing challenging because of risk of hypoxia, an adapted method for apnea testing has been described with a pretest recruitment maneuver and subsequent application of a CPAP valve set at 20 cmH_2O[178], even in settings of extracorporeal life support[179].

To determine the presence of true apnea, confounding factors should be vigorously excluded. Confounding factors that may result in apparent apnea, while in fact apnea is caused by another factor than total functional and structural disruption of the respiratory nuclei in the mid- and lower brainstem, are summarized and explained in Table 16.3. In exceptional cases, genuine apnea may even be reversible in patients with decompressive craniectomy, which has been described in single cases and has also been experienced by one of the authors of this chapter.

Table 16.3 Confounding factors for apnea

Confounder of apnea	Mechanism	Management options
Residual sedation (RS)	Impaired ventilator triggering due to sedative rather than respiratory center dysfunction only	Use antagonist. Monitor serum levels of sedative or opiate to exclude RS
High cervical spine injury	Fractures at the approximate level of odontoid (C2) and concomitant medullary injury may selectively result in apnea; such local injury in combination with reversible causes of coma and/or residual sedation may resemble BD	MRI to evaluate brainstem injury Ancillary testing
Isolated brainstem lesion or posterior circulation vascular lesion[180]	May yield false positive signs of brain death, e.g. apnea	In doubt perform ancillary tests MRI and/or CT angiography to determine focality of lesion
Rapidly progressive neuromuscular tetraplegia (e.g. Guillain-Barré syndrome), or selective diaphragmatic paralysis	Ventilator triggering not possible due to neuromuscular paralysis rather than brain injury	Clinical recognition/clinical course should generally provide clues
CO_2 removal by extracorporeal support life support	Ventilator triggering may be partly absent due to extracorporeal CO_2 removal	Use adapted thresholds for preoxygenation, pCO rise and adapted sweep gas flow[176]
Temporary/reversible apnea in patients after decompressive craniectomy[181]	Herniation, and subsequent reversal of (total) herniation resulting in temporary apnea, due to the decompressive craniectomy precluding "progressive" herniation	Take caution to diagnose brain death after apnea in such cases. May consider repeating test although official criteria supporting this practice have not yet been described
Auto triggering of artificial ventilator (or "ventilator self-cycling")[182]	Triggering of ventilator by cardiac oscillation due to trigger threshold of artificial ventilator set too sensitively, resembling true triggering (*NB other causes are possible, e.g. ventilator circuit leak, humidifier problems, other vibrations/movements*)	Decrease trigger sensitivity on ventilator/increase thresholds (*NB flow triggering is more sensitive to auto triggering than pressure triggering*)

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Chapter 17

Spinal Cord Lesions Affecting Respiration

Alexandru Budu, Sven Hirschfeld and Stasa Tumpa

The respiratory complex involves the spinal cord and is a highly differentiated conductive system. Respiration thus can be abnormal with acute spinal cord lesions and dependent on the level(s) involved. The pathophysiology is different than other lesions of the CNS and is discussed in this chapter. Care in the ICU is extraordinarily complex and often requires great skills and experience. Multiple teams are involved to guide the patient toward successful rehabilitation. This chapter goes beyond the crucial first phase in the ICU and includes long-term treatment of respiratory impairment and in particular how phrenic nerve stimulation can be utilised.

Definition and Epidemiology

Spinal cord injury (SCI) can be simply defined as damage to the neural elements of the spinal cord that can result as a consequence of trauma or increasingly due to chronic progressive disorders such as degenerative cervical myelopathy, inflammation, vessel pathologies or an underlying disease of the spinal cord, such as tumours. The high morbidity and often irreversibility associated with this condition make SCI a devastating condition not only to the patient but also to the family and society.

To put into perspective the significance of SCI, the following can be stated: The World Health Organisation estimates that every year, around the world, 250 000 to 500 000 people suffer an SCI. Following the Global Burden of Diseases, Injuries and Risk Factors Study (2016), the prevalence of SCI was estimated to reach 27.5 million with higher rates in high-income regions such as North America and Western Europe and high-income states in the Asia Pacific region. This geographical variation is attributed to survival bias, with higher rates of successful resuscitation in injury victims[1]. Given the reduced financial resources for neurotrauma research in developing countries, the frequency in these areas is estimated to be much higher than recorded taking into consideration the unknown number of SCI patients dying at the scene of an accident without ever being examined or treated in a hospital setting. This likely explains the high country-specific incidence of SCI in conflict-affected countries in the Middle East such as Syria, Yemen and Iraq.

Most of the traumatic SCIs (TSCIs) are caused in the setting of what can be considered preventable road traffic accidents and falls, thus making TSCI an increasingly recognised global health priority. There is a distinct bimodal distribution of age groups when it comes to the mechanism of injury. The first peak is observed in young adults and adolescents, who sustain most road traffic accident- and violent activity-related TSCIs. The second peak is observed in the ageing population (older than 65 years), who are more susceptible to fall-related TSCI[2]. It is worth adding that whilst public health measures for safer driving practices seem to have an impact on the rate of road accident rates, the average age of the injured remains preponderantly below the age of 30 in all countries studied, suggesting the need for better regulation for the young adult driver.

Lastly, beyond the significant physical and physiological toll exerted on the patient and relatives, an SCI generates an incalculable cost to the community and society as well as a significant lifetime healthcare cost. Due to the complete dependency on the healthcare system and family following an SCI event, it is estimated that the total cost of managing this condition can reach 3 million US dollars[1].

Anatomy and Pathophysiology

The traumatic insult to the spinal cord often results because of either blunt mechanical compression, such as a burst fracture; facet dislocations or flexion-distraction injuries, or a penetrating injury, such as a stab or gunshot wound. The forces transmitted to the spinal cord and nerve roots can result in sensory, motor or autonomic dysfunction. The sequence of events that ensue can be divided into primary and secondary phases (sometimes also referred as primary and secondary injury).

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The acute phase refers to the direct injury of the neural elements, such as the blunt injury and shearing or laceration of the spinal cord. The mechanisms of injury can be broadly divided into (a) impact with persistent compression, (b) impact alone with transient compression, (c) distraction and (d) laceration and or transection. By far the most common mechanism of injury is impact with persistent compression, typically from a burst fracture with fragments compressing on the cord (Figure 17.1). Another common mechanism of injury is by "fracture-dislocation" injuries, which result in impaction of the spinal cord and transient or persistent compression. Distraction represents the pulling apart of two elements, which stretches and tears tissue in the axial plane. It is rare for traumatic injuries to result in complete transection of the spinal cord. Transection injuries of the spinal cord are more commonly encountered in missile injury cases, and less frequently as a consequence of sharp bone fragment dislocation.

Regardless of the form of traumatic injury or non-traumatic event, the result is axonal injury, disruption of the blood vessels and cellular membranes in the spinal cord. This represents the contusion of the spinal cord.

The secondary phase results from the physiological response to the initial trauma. Inflammation, ischemia, free-radical formation, vascular dysfunction and neural apoptosis occur during this stage. This cascade of cellular mechanisms and effects leads to ongoing damage to the neural structures. The secondary phase temporal sequence of events can be further divided into immediate, acute, intermediate and chronic stages. The immediate stage is associated with the onset of the clinical "spine shock".

Within the next 2 to 48 hours, oedema, haemorrhage and a series of inflammatory events take onset. Axonal injury and cellular necrosis are further promoted by means of free-radical generation, ionic dysregulation, excitotoxicity (glutamate-mediated pathways), vascular disruption and immune-mediated neurotoxicity. Following this response, the next two weeks are marked

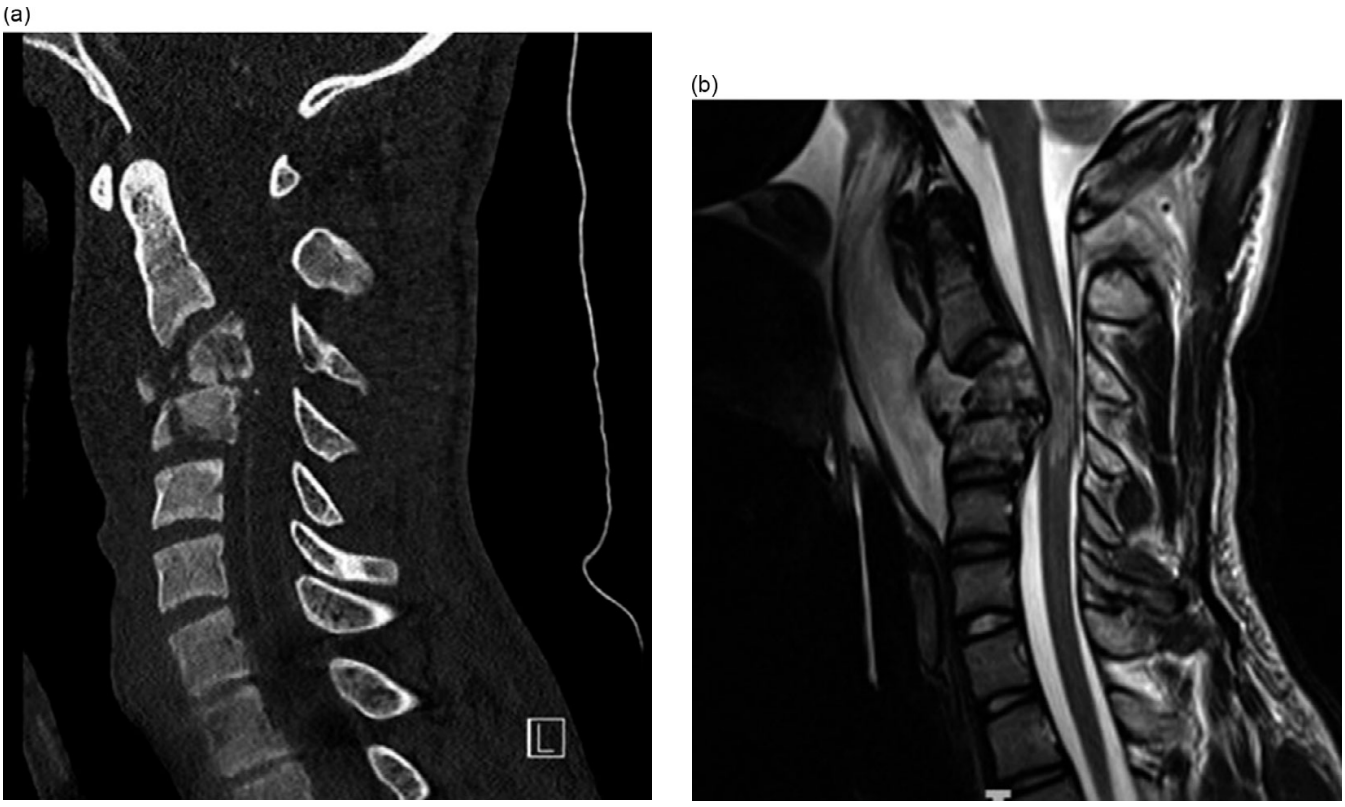


Figure 17.1 (a) C3 tear drop fracture with fragment retropulsion into the spinal canal, associated with bilateral C2 pars fracture (not displayed on the sagittal) and split of the C4 vertebra, (b) T2 weighted sequence revealing the contusion of the spinal cord as a consequence of the malalignment. A large pre-vertebral haematoma can be noted. (c) Post-operative CT scan following C3–4 corpectomy and expandable cage insertion.

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(c)



Figure 17.1 (*cont.*)

by a phagocytic response to the cellular debris caused. At the same time, peripheral intact astrocytes proliferate and attempt to re-establish ionic haemostasis and restrict immune cell inflow by restoring the blood–brain barrier that was damaged. The deleterious consequence is scar tissue formation which will act as both a physical and a chemical barrier preventing axonal regeneration (Figure 17.2). As the scar tissue progresses and maturates, syrinx formation and cystic cavitation ensue[3–5].

Classifying Spinal Cord Injuries

Generally, SCI can be classified as being either complete or incomplete. A complete injury is defined as a complete loss of motor and sensory function below the level of injury. Several classification systems have been described and utilised to help assess the severity and prognosis of SCI. The Fraenkel grading system was the first classification utilised, having been initially described in 1969. It introduced a five-grade system with a "Grade A" representing a complete SCI, "Grade B" as a complete motor loss with preserved sensory function and sacral sparing and grade E as free of neurological symptoms. The confusion and inconsistency in grading using this system are based on what one understands as a "Grade C and D", which represented incomplete motor loss with various degrees of power preservation, described as either "minimal power without practical use" (Grade C) or "useful power", able to ambulate with or without walking aids (Grade D).

The American Spinal Cord Injury Association (ASIA) scoring system is currently the most widely used and accepted clinical scoring system. The ASIA impairment score shares similarities with the Fraenkel grading by utilising five types; however, types C and D can be established based on how many of the key motor muscles retain antigravitation power (less than half of the key muscles for type C) (Figure 17.3).

Neural Circuitry Underlying Respiration

From the first breath to the last, breathing continues without interruptions and conscious efforts. Unless breathing becomes laboured such as when exercising or in disease states, it is an unconscious automatic and rhythmic act that is a result of the activity of neurons in medulla and pons. These neurons are embedded in a widespread cerebral respiratory network and direct the respiratory muscles to produce pressure gradients that move air in and out of the lungs and to regulate the upper airway muscle tone. Ventilation is thus realised through the musculoskeletal structures of the abdomen, thorax and pharynx. Differing from other organ systems, the respiratory system in the absence of pathology is deferential to voluntary control, though underlying involuntary regulation persists. This flexibility is ensured by sensors that are distributed throughout the body whose role is to send signals to the respiratory neural networks in the brainstem. For example, arterial chemoreceptors detect change in the blood oxygen level and mechanoreceptors monitor the expansion of the lung, the size of the airways and the force of the muscle contraction of the muscles involved in respiration.

Respiratory Mechanics in Spinal Cord Injury

The main muscle involved in breathing is the diaphragm; however, its role in breathing is assisted by a complex

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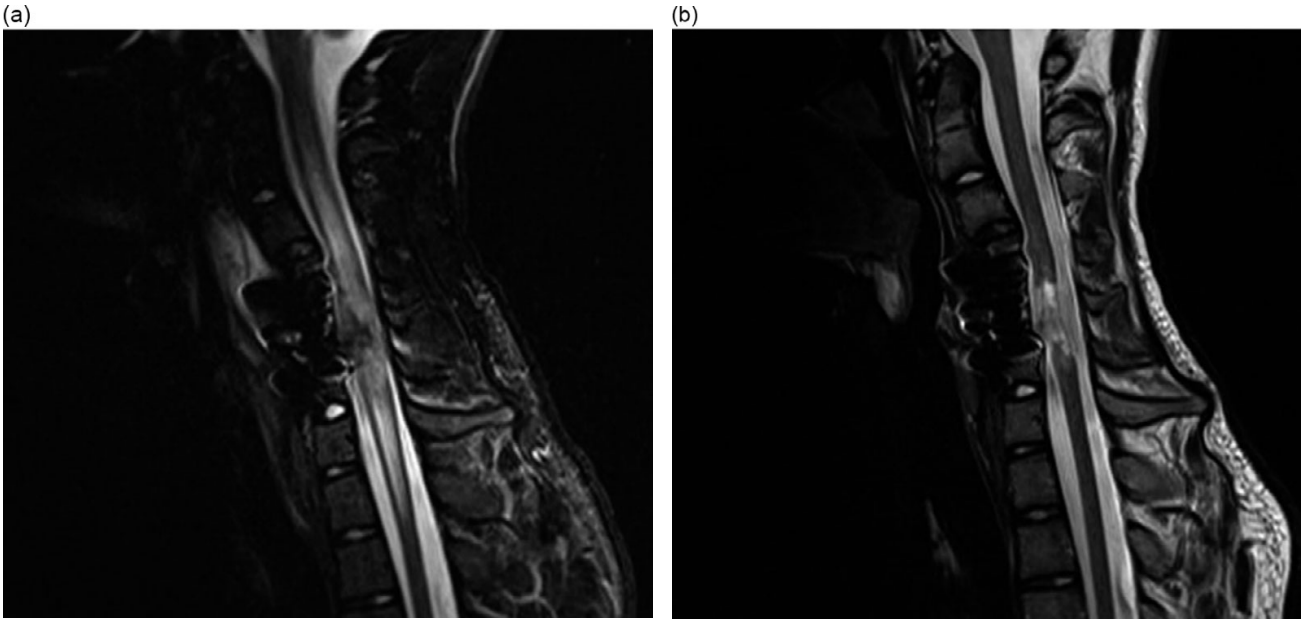


Figure 17.2 (a) T2 weighted MRI sagittal sequence of an early post-operative MRI scan in a patient with a complete spinal cord injury. An extensive diffuse intramedullary oedema can be noted, spanning from C2 all the way to T1. (b) One-year follow-up scan on the same patient revealing extensive scaring at the injury site.

group of other muscles. Amongst those are the intercostal muscles, abdominal muscles and the so-called accessory respiratory muscles such as sternocleidomastoids, scalenes, upper trapezoid, pectoralis major, serratus anterior, latissimus dorsi and possibly paraspinal muscles (see Chapter 5). Additionally, muscles in the laryngeal, oral and nasal pharynx play an important role in adjusting the resistance of movement of gases through the upper airways during inspiration and expiration. During inspiration the diaphragm flattens, extending the inferior dimension of the thoracic cavity, increasing the thoracic volume and therefore allowing air to move into the lungs. The parasternal intercostal are also activated, as they have the strongest inspiratory effect among the intercostals. During passive expiration the inspiratory muscles relax and consequently the volume of the thoracic cavity is reduced. To increase minute ventilation, inspiration is assisted by accessory respiratory muscles such as upper trapezoid, scalene, sternocleidomastoid, pectoralis major, serratus anterior, latissimus dorsi and perhaps paraspinals In active expiration the muscles of the abdominal wall increase the intra-abdominal pressure, pushing the diaphragm further upwards into the thoracic cavity, and the caudal-ventral external intercostal, the caudal-dorsal internal intercostal and transversus thoracis muscles are activated (see Chapter 5).

The neural circuitry responsible for the activation of the diaphragm has been well described in the literature and is mainly based on the research that was completed in rabbits, rats and cats[6]. This respiratory neural circuitry is composed of neurons located within the brainstem and spinal cord. Respiratory rhythm-generating neurons are located within the pre-Bötzinger complex which is found in the ventral lateral medulla. The respiratory rhythm-generating neurons are connected to propriobulbar neurons and to premotor neurons located in the ventral respiratory group (VRG, see Chapter 4). Mainly inspiratory bulbospinal neurons are found in the most rostral part of the VRG, whereas the caudal part of the VRG mainly contains expiratory bulbospinal neurons[7].

Axons from the VRG descend either unilaterally or bilaterally through the spinal cord in the lateral and ventral funiculi and enter the grey matter at the level of phrenic nucleus. There these neurons synapse directly onto phrenic motor neurons that extend rostrocaudally as an uninterrupted column of cells[8]. Segmental location of phrenic neurons in humans is C3–C5 and widely varies in different species[9].

In upper SCI the transmission of the respiratory signal from the brainstem to the phrenic motor neurons is often disrupted, resulting in paralysis of the

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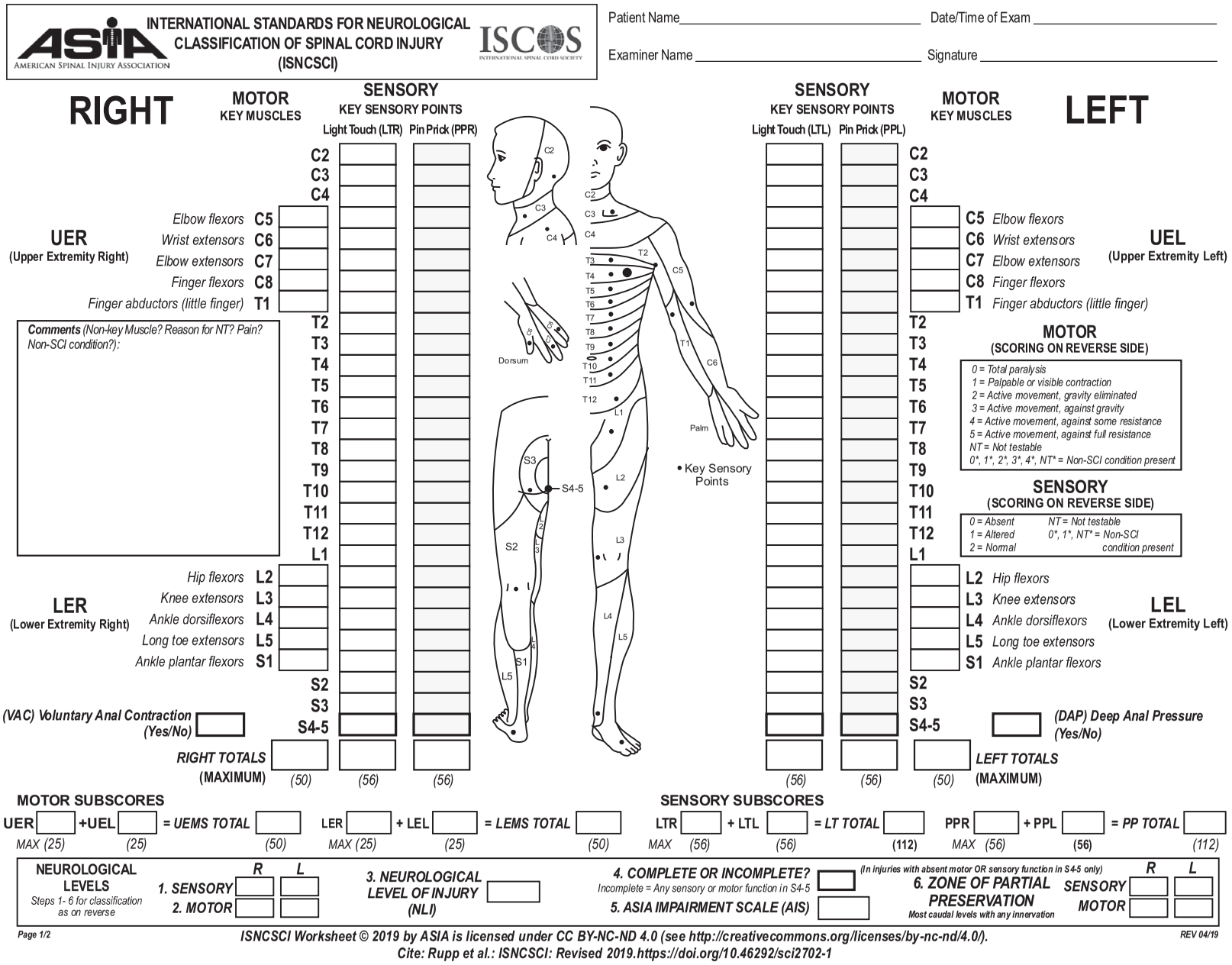


Figure 17.3 American Spinal Injury Association International Standards for Neurological Classification of Spinal Cord Injury, revised 2019; Richmond, VA.

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diaphragm. Since breathing is supported by many different muscles, any injury to the cervical region, even those below the phrenic motor nucleus, may affect breathing by affecting the neural transmission to the other mentioned respiratory muscles of the thoracic and abdominal musculature, leading to full or partial muscle paralysis.

The most commonly used model in studying basic science behind respiration after SCI is the hemisection model. Hemisection is a type of injury in which half of the spinal cord is transacted (either right or left side). A hemisection at the second cervical segment discontinues the descending respiratory projections to the phrenic nucleus ipsilateral to the hemisection, as a result paralyzing the ipsilateral hemidiaphragm. Because this type of injury produces a very precise lesion, it allows research into the respiratory muscle innervation and control, knowing which respiratory axons have been injured and which ones have been spared[10].

Research on anaesthetised rats has shown that following C2 hemisection injury, ipsilateral hemidiaphragm and intercostal muscles become paralyzed resulting in significant reduction in tidal volume, leading to the increase in respiratory rate to compensate for the reduction in volume[11–13]. These changes in breathing pattern are the result of vagal feedback, driven by the paralysis of the hemidiaphragm and intercostal muscles that result in changes in the lung and chest wall compliance. Studies have shown that in C2-hemisected rats, overall ventilation (breathing frequency $\times$ tidal volume) remains unchanged, despite the breathing pattern being significantly altered[14,15].

In real life, although hemisections do happen in humans, the more common type of the SCI is the contusion of the spinal cord. Therefore, more recently Baussart et al. have developed a C2 contusion injury model that shows very similar respiratory patterns to the C2 hemisection injury. The advantage of having this model is that it allows one to study activation and neuroplasticity of latent respiratory pathways and examine different strategies that are unique to the repair of the contused spinal cord[16].

The C2 contusion model has proved very helpful, as it enables researchers to apply different strategies, primarily regarding neuroprotection and repair of contused axons, but also regeneration and reconnection of destroyed descending fibres. All these strategies aim at reducing the effects of first and second phases of SCI, therefore increase axonal sparing and improve the overall breathing function in patients with SCIs[17].

An injury above the level of the phrenic motoneurons (C3–C5) will cause complete paralysis of the inhalation and exhalation muscles. The loss of diaphragmatic function makes patients with this injury ventilator dependent. A lesion within the territory of the phrenic nerve level, such as C4 or C5 level, will still cause impairment of the diaphragm; however, periods of unassisted ventilation are possible, likely due to the preservation of some of the motor neurons at the C3 level. Injuries below the phrenic neurons level, at the C6–C8 territory, allow for independent breathing in the long term. Due to the impaired function of the intercostal and abdominal muscles, a decrease in lung volumes and cough strength persists. Lesions at the lower cervical level allow for inspiration and coughing to be augmented by the accessory muscles, such as pectoralis major and minor. Finally, lesions at the level of the thoracic can be broadly divided into upper and lower thoracic segments, with the T5 as the border. This is due to the presence of abdominal muscle innervation from T6 to L1, while intercostal motor neurons are present at the T1–T11 level[18]. The higher thoracic segment injury will have some degree of intercostal activity; however, cough efficacy remains decreased due to expiratory (abdominal weakness). Respiratory function in a T12-level injury is comparable to that of a normal individual.

Management of Respiratory Function in Traumatic Spinal Cord Injury

Among the numerous challenges that individuals with SCIs face, respiratory distress stands out as a critical concern. As the spinal cord plays a pivotal role in regulating breathing, when injury occurs, it can lead to respiratory complications that demand immediate attention. Understanding the multifaceted nature of respiratory issues in the context of SCIs is essential for healthcare professionals, caregivers and patients alike, as it can pave the way for improved care and enhanced quality of life for those affected by these injuries.

Management of the respiratory function in the context of acute SCI starts from the early stages of the event by evaluating the current respiratory function and based on the level of injury, anticipating and preparing for the likely outcome of respiratory decline. A variable loss of lung volume and relative hypoxemia occurs in this early stage of the injury and thus a global hypoxemia is established with a negative feedback effect on the spinal cord and respiratory centres. As previously mentioned, 40% of

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the SCI occur at the cervical level, and thus respiratory decline is responsible for death in nearly 20% of the cases.

The most common respiratory dysfunctions in the acute SCI are:

Impaired inspiratory capacity

- Decreased respiratory muscle strength and fatigue
- Paradoxical chest wall movement causing an increase in effort of breathing
- Decreased inspiratory capacity
- Atelectasis
- Chest wall rigidity

Retained secretions and development of mucus plugs

- Increased secretion production
- Decreased cough effectiveness

Autonomic nervous system dysfunction

- Increased secretions
- Bronchospasm
- Pulmonary oedema

Management in Acute SCI and Chronic SCI with Pulmonary Complications

Intubation in the Context of SCI

Neurologic secondary injury as a consequence of intubation represents a genuine concern in the acute setting. The risk of this occurring remains unknown; however, it is believed to be in fact overestimated[19] reaching roughly 0.34% chance[20]. Rapid sequence induction and intubation using direct laryngoscopy with manual inline stabilisation still represent the gold standard in time-critical scenarios. Most of the movement produced during intubation takes place at the craniocervical junction with minimal displacement of the spine below and including C4[21]. If time and expertise is available, awake fibre optic intubation can be performed.

Several guidelines and protocols have been proposed to help guide the clinician regarding timing of intubation. As a general recommendation, all SCIs above C5 should be intubated as soon as possible. For general parameters for intubation see Box 17.1.

When in doubt, it is always safer to intubate early rather than wait for a situation that may lead to acute deterioration and need for emergency intubation. As mentioned earlier, due to general hypoxemia, spinal cord oedema, hypoperfusion and loss of respiratory musculature, vigilance in monitoring and anticipating respiratory failure is key.

Box 17.1 General parameters for intubation

- Obvious respiratory distress with tachypnoea
- Dyspnea
- Inability to hold breath for 12 seconds
- Have patient count as high as they can with one breath (<20 is concerning for respiratory compromise)
- Vital capacity <10ml/kg or decreasing vital capacity
- Appearance of "abdominal breathing"
- pCO_2 higher than 20 mmHg above baseline
- Patient complains of inability to "catch breath"

Extubation

When coughing is absent or weak and there is a tracheobronchial retention of secretions, the risk of extubation failure is high. Several factors should be assessed before considering extubation such as:

- No further surgery or invasive imaging required
- No significant hypoxia or reversible respiratory pathology
- Patient awake and able to co-operate with non-invasive ventilation (NIV)
- No contraindications for NIV
- Minimal tracheobronchial secretions
- Negative inspiratory pressure >20 cmH_2O
- Vital capacity >10 ml/kg
- Air leakage present after deflating the cuff, particularly after spinal stabilisation by anterior approach (cuff leak test)[22]

Failed extubation is associated with an increased risk of pneumonia, prolonged need for mechanical ventilation (MV) and thus prolonged length of stay in the ICU. These patients are also less likely to be successfully extubated again and will usually require a tracheostomy.

Tracheostomy

Tracheotomy is recommended for acute tetraplegia and for chronic SCI patients in case of pulmonary complications:

- In complete motor tetraplegia according to the American Spinal Injury Association Impairment Scale A and B[23]

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- In the presence of respiratory insufficiency
- In a vital capacity $\leq$500 ml
- In an Injury Severity Score >32

A recent metaanalysis indicated that early tracheotomy (defined differently among the analysed studies, but in any case <10 days after acute TSCI) reduces the total duration of mechanical ventilation, the length of stay in the ICU and the length of hospital stay[24].

The tracheotomy can be dilatational or surgical. There are different studies on the short- and long-term complications of dilatative and surgical tracheostomy[25–27]. With appropriate experience and depending on the expected duration of ventilation, both procedures can be used (see Chapter 12). The primary advantage of tracheotomy is the elimination of anaesthesia and thus the possibility to integrate the awake patient into the first phases of the interdisciplinary rehabilitation such as mobilisation in a wheelchair, speech training, oral feeding and weaning.

In rare cases, tetraplegics with a high level of paralysis can also be ventilated with NIV in the acute phase[28] or extubated early and then ventilated with NIV[29]. However, this approach should be reserved for experienced SCI centres.

In patients on permanent invasive ventilation, the tracheostomy should be stable to guarantee safe out-of-hospital intensive care[30].This is usually achieved with surgical tracheostomy, but in exceptional cases, a stable, non-epithelialized tracheostoma may be sufficient. Especially when changing the type or size of tube, and before decannulation, an endoscopic control is highly recommended[31].

Early Mobilisation

Additional risk factors in acute and long-term ventilation in people with ventilation are

- pneumonia[32]
- pressure ulcers[33]
- thromboembolism[34]

For this reason, early mobilisation of these patients with ventilation is recommended already on intensive care and intermediate care wards[33], taking into account the necessary equipment and staffing requirements.

Ventilator Weaning Strategies

For high-level injuries, the duration of mechanical ventilation may range from months to years and even ventilator dependency. MV settings in the initial stages will be heavily influenced by other factors such as the need for carbon dioxide control in traumatic brain injury or hypoxemia secondary to pulmonary contusion or infection and thus these particular settings and parameters will not be discussed in this chapter.

Box 17.2 Weaning criteria

- Lung disease is stable/resolving.
- Low FiO_2 (<0.5) and positive end-expiratory pressure (<5–8 cmH_2O) requirement
- Haemodynamic stability (little to no oppressors)
- Able to initiate spontaneous breaths (sufficient neuromuscular function)
- Vital capacity >0.8 L

Prolonged need for mechanical ventilation heavily affects life expectancy. Thus, early and daily consideration should be taken to assess if the patient is suitable for weaning (see Box 17.2).

Several studies have looked into specific weaning strategies for patients with SCI. Weaning in SCI patients is undoubtedly prolonged and should be performed discontinuously. Common suggestions include a twice daily trial, increased from day to day with two- to four-hour rest period between the trials and gradual increase of the session time frame. This should be approached as a diaphragm conditioning progress and thus fatiguing the muscle should be avoided[35]. Fenton et al. used a 20 mL/kg tidal volume compared to the standard 10 mL/kg tidal volume while attempting to wean patients off the ventilator over 14 days and found no difference in the days to wean or the number of pulmonary complications[36]. Zakrasek et al. used a combination of high-volume ventilation, positive pressure treatments, theophylline and mechanical insufflation–exsufflation to produce a weaning success rate of 83%[37]. At least 0.8 L of vital capacity is one important predictor for a successful weaning process in SCI patients[38].

A variety of measures can facilitate weaning the patient from the ventilator (see Box 17.3).

There is also evidence to suggest that building accessory muscle strength can lead to improved outcomes and weaning success. This has been reflected by a meta-analysis which confirmed that respiratory muscle training improves vital capacity, maximal inspiratory pressure and expiratory pressure in patients with cervical SCI[39].

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Box 17.3 Management to improve weaning success

- Optimize respiratory muscle power by assuring adequate nutrition, avoiding neuromuscular blocking drugs, encouraging spontaneous breathing and avoiding exhaustion
- Decrease respiratory work by sitting the patient up, decrease respiratory demand (treat pyrexia, agitation, correct metabolic acidosis), decrease resistance and increase compliance (treat lung disease, decrease abdominal distention)
- Optimise ventilatory drive by stopping sedation
- Increase oxygenation and carrying capacity by correcting anaemia and acid-base disturbance, sitting the patient up and avoiding atelectasis
- Address cardiac dysfunction if present
- Clear sputum through physiotherapy, suction, bronchoscopy, mucolytics

Inability to clear secretions significantly affects wean success and thus needs consideration in a holistic weaning protocol. Available techniques include manually assisted coughing, mechanical breath stacking, mechanical insufflation–exsufflation and glossopharyngeal breathing. The end effect is that of an increased peak cough flow when compared to unassisted cough. Additionally, the routine use of mechanical insufflation-exsufflation can lead to improved vital capacity in patients with SCI or neuromuscular disorders. Details on the mentioned techniques are provided in Chapter 10.

Studies comparing patients with a higher success chance of weaning noted that they had ability to shrug shoulders, higher vital capacity, higher forced vital capacity, higher maximal inspiratory pressures and lower level of spinal injury. In contrast, those more difficult to wean or unable to be weaned had a vital capacity <1500, body mass index >25 and chronic obstructive pulmonary disease.

Neurological Remission and Monitoring

In case of a neurological recovery process, patients should remain monitored non-invasively at least in an intermediate care unit (IMC) ward. Recommended are the following parameters:

- SaO_2
- pCO_2 (e.g. transcutaneous)
- Breathing frequency
- Heart frequency
- Blood pressure

After a stable period of three to five days monitoring, IMC treatment is no longer necessary.

Phase of Prolonged Specialised SCI-Treatment with Persistent Mechanical Ventilation

Chronic Ventilatory Pump Failure in SCI

As previously discussed, a cervical spinal cord injury above level C5 usually results in significant impairment of the respiratory function. Complete and also incomplete paralysis of the muscles needed for respiration, foremost the diaphragm, leads to a significant loss of vital capacity with the need of partial or constant mechanical ventilation[40]. The diagnosis and individualised therapy of respiratory dysfunction are complex and require lifelong and specialised treatment for inpatient and out-of-hospital treatment[41]. This not only relates to the setup of both non-invasive[28] and invasive ventilation, but also to weaning regimes and long-term ventilation including the implantation of an electrical diaphragm stimulator.

In general, the rule applies that the more cranial the level of lesion is located, the more the respiratory pump is affected. Several factors contribute to this including:

- The decreased strength of respiratory muscles[42],
- A reduced compliance of lungs and thoracic wall[43],
- A chronical central hypoventilation[44],
- Changes of the patency and reactivity of the airways[45] and
- Dyssynergies of muscles of thorax and abdomen[46].

Forms of Ventilation in Chronic SCI

Objective information about the pattern of use of artificial ventilation in the chronic stage after SCI is rare. The data from Germany presented in Table 17.1 may serve as a reference for the typical pattern of use in western industrial countries[47].

Invasive Mechanical Ventilation

In permanently ventilated patients normally pressure controlled modes are used (e.g. pressure-controlled ventilation), while volume-controlled modes are rarely applied (e.g. volume-controlled ventilation). The longer a patient breathes spontaneously, the more pressure-supported

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Table 17.1 Modes of ventilation in chronic SCI (N = 110)

Period of ventilation	Percentage (number of cases)
24 h-MV	45.5 % (n = 50)
24 h-PNS	20.9 % (n = 23)
MV/spontaneously	17.3 % (n = 19)
MV/PNS	10.9 % (n = 12)
PNS/ spontaneously	5.4 % (n = 6)

IV:NIV, invasive mechanical ventilation:non-invasive ventilation 93.7%; MV, mechanical ventilation; PNS, phrenic nerve stimulation.

modes are used (e.g. pressure support ventilation), especially during the daytime. The reason for this is the better ability to speak when using pressure-supported modes. Pressure-controlled modes are often applied during the night to reduce the breathing effort and to regenerate the ventilatory pump.

The following recommendations can be derived from the literature for invasive modes of ventilation and lung-healthy people with tetraplegia:

- Use pressure-controlled modes of ventilation with relatively high tidal volumes (starting at 8–10 ml/kg ideal body weight)
- Use of a safety/minimum volume under pressure-controlled ventilation, as spasm and lying spasm and positioning can immediately reduce tidal volume
- Due to vegetative dysregulation (temperature dysregulation, circulatory dysregulation etc.), it is often necessary to adjust parameters (e.g. inspiratory pressure or frequency) to the situation.
- Hypocapnia is tolerated if there is respiratory distress under normal conditions.
- To improve phonation and avoid tracheal injury, the tracheostomy tube of the patient should be unblocked during ventilation as long as possible/tolerated.

Non-invasive Ventilation

The main area of NIV application is the ventilatory support of SCI patients with signs of respiratory insufficiency during the night. NIV may be used as a long-term therapy to compensate alveolar hypoventilation, thereby also treating obstructive and central sleep apnoea[28,48]. NIV is contraindicated in persistent bowel mismanagement, poly(somno)graphic assessments, accompanied by transcutaneous capnometry are recommended to determine, if NIV is indicated, when one or more of the following conditions are present:

Table 17.2 Overview of long-term complications of non-ventilated and ventilated spinal cord injury patients

Type of complication	Percentage (number of cases) of non-ventilated patients (N = 994)	Percentage (number of cases) of ventilated patients (N = 110)
Urological complications	30.5% (n = 303)	23.6% (n = 26)
Decubitus ulcer	30.5% (n = 303)	12.7% (n = 14)
Pneumonia	8.5% (n = 84)	41.8% (n = 46)
Spasm	5.5% (n = 55)	10% (n = 11)
Fracture	2.7% (n = 27)	2.7% (n = 3)
Pain	11.0% (n = 109)	2.7% (n = 3)
Obstipation	8.3% (n = 83)	2.7% (n = 3)
Hypotonia	1.5% (n = 15)	2.7% (n = 3)
Others	1.5% (n = 15)	0.9% (n = 1)

- Arterial $PaCO_2$ >45 mmHg during the day
- Frequently decreased oxygen saturation at night
- Increased $PaCO_2$ or $tcCO_2$ at night >55 mmHg (1 out of 10 minutes), if measured at home
- Daytime sleepiness
- Lack of concentration during daytime

Mechanical ventilation requires an in-patient setting in a specialised centre, particularly in patients with more severe impairments of the respiratory function. During this inpatient stay individual and careful adaption of interfaces, respirators and ventilation modes should be accomplished. The patient must be observed closely, while using mask and ventilator. If finger- and/or hand functions are not sufficient and the patient is using a full face mask, any complication during ventilation (e.g. ventilator dysfunction, tube disconnection) could lead to a life-threatening situation, because the patient cannot remove the mask.

Long-Term Complications in Ventilated SCI Patients

A study published by one of the authors of this chapter included 1104 patients readmitted to hospital, who had been suffering from tetraplegia for a minimum of two years. Ventilated and non-ventilated patients with tetraplegia showed significant differences in the distribution of the causes of complications at the time of readmission to hospital (Table 17.2). Whereas pulmonary

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complications were most prevalent in ventilated patients, decubitus ulcers, obstipation and pain were the main reasons for rehospitalisation in the non-ventilated population[49].

The lower tidal volumes, the positive pressure ventilation and the persistence of the tracheostomy represent risk factors for pulmonary infections. Interestingly, in ventilated patients less severe decubitus ulcers occur. This may be a result of the 24 hours/day care at home. The professional caregivers not only take care for the proper ventilation, but also take measures for minimizing the risk of developing decubitus ulcers.

Mortality and Aging in Ventilated SCI Patients

The general mortality rate of ventilated patients with tetraplegia is high (30%) with an average survival time of 7.5 years after onset of SCI. Due to the demographic development this rate is likely to continue to increase within the next years. In approximately 75% of the cases ventilated patients die because of typical SCI complications such as pneumonia and ileus [49](Table 17.3).

It is remarkable, that ventilated compared to non-ventilated patients with tetraplegia have a significantly lower mortality rate during the primary rehabilitation stay (38% after the first year after SCI). This is explainable by the circumstance of permanent monitoring of the vital parameters on ICU or IMC. Within this setting any possible occurring complication can be detected and treated earlier.

This is different concerning the time after discharge. Here ventilated patients have a higher mortality rate within the first two years (62% in the first two years after discharge) compared to the non-ventilated population. But if ventilated patients survive the vulnerable first two years at home, their health status becomes more stable. This can be explained by the learning curve of the primary physician, nursing team and family members after discharge. Also mentionable is the low suicide rate (4%)[49,50].

Table 17.3 Causes of death of ventilated patients

Causes of death (inpatient phase)	50% pneumonia 20% ileus 5% thromboembolism 25% not SCI-related
Cause of death (after discharge)	50% pneumonia 10% decubitus ulcer 15% bowel/urological complications 2% suicide 23% not SCI-related

SCI, spinal cord injury.

Phrenic Nerve Stimulators

In case of spinal cord lesions above C3 resulting in permanent restrictions of the respiratory function, phrenic nerve stimulators (PNS) represent more than a therapeutic alternative to long-term invasive, artificial ventilation. The PNS was introduced in the mid-1960s for patients with severe respiratory insufficiency[51]. It has the advantage of the inhaled air being drawn into the lungs by the diaphragm under negative pressure, rather than being forced into the chest under positive pressure as in positive pressure ventilation. The first device with Conformité Européenne or Food and Drug Administration approval is the Atrostim Yukka® (Atrotech, Finland) and the second is the Avery System® (Avery Biomedical Devices Inc., USA).

In both systems, electrodes are surgically implanted for pressure ventilation. This is physiologically more accurate and comfortable for the patient. Currently there are two phrenic nerve stimulation systems commercially available on both phrenic nerves in the mediastinum at the third to fourth intercostal space. Electrode leads are intracorporeally attached to radio-frequency operated receivers. The receivers are supplied with energy and receive the stimulation command from an induction coil placed on the skin area over the implant. No transcutaneous cables are needed for these systems.

Contraindications for the implantation of a PNS system are severe cognitive restrictions, for example because of a head injury, a severe pre-existing condition of the heart and/or lung or an unfavourable prognosis in the case of terminally ill patients. Intact lower neurons of both phrenic nerves and an intact diaphragm muscle are general prerequisites for the use of an electrical stimulation system including PNS.

Possible complications during implantation, besides the general risks, are damages of the phrenic nerve (with consecutive dysfunctions) and persisting haemo- or pneumothorax.

Patients using a PNS are at much lower risk of upper airway infections including ventilator-associated pneumonia due to the reduction in suctioning, elimination of external humidifier and ventilator circuits and the

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Table 17.4 Causes of death of patients with PNS versus MV

Cause (after discharge)	PNS	MV
	30% pneumonia	70% pneumonia
	15% pressure sore	5% pressure sore
	17% bowel/ urological	13% bowel/ urological
	38% not SCI-related	8% not SCI-related
	0% suicide	4% suicide

MV, mechanical ventilation; PNS, phrenic nerve stimulation; SCI, spinal cord injury.

potential, also temporary (e.g. with stoma buttons) removal of the tracheostomy tube in appropriate patients[52–54]. Some studies showed significantly lower pulmonary complication rates and lower mortality rates. PNS provides some other benefits such as normal breathing and speech patterns, ease of eating and drinking and improved sense of smell, which result in an increased quality of life[52–54]. The external components of PNS systems are relatively small compared to the bulky tubing and batteries of mechanical ventilators and thereby they greatly improve the patient's mobility. The silent operation of a PNS enhances the patient's ability to participate in social and educational environments. Long-term observation studies showed that electrical motor thresholds do not change over time proving that the systems are suitable for chronic ventilation[55]. In contrast to external ventilators no consumables are needed resulting in an amortisation within a few years[54]. More than 70% of all patients use the PNS for 24 hours per day. However, PNS 24 hours per day is recommended only for adults. For children and adolescents, a maximum of 12 hours per day is recommended, because sufficient bony consolidation of the thorax must be ensured first.

Long-term studies regarding phrenic nerve stimulated patients show a significantly lower mortality due to the lower rate of pulmonary infections (see Section 17.8.5)[52,54]. The average survival time after SCI ranges from 7–8 years for mechanically ventilated patients to 8–10 years for PNS patients[52–54] (Table 17.4).

Diaphragm Pacemaker

In more recent times an alternative and more cost efficiently system for diaphragm pacing (DP) was introduced, the semi-invasive NeurX® (Synapse Biomedical, United States) system. In this system hook electrodes are laparoscopically inserted into the diaphragm muscle, and electrode cables are percutaneously connected to an external stimulator[56]. The system has the advantage that only a minimally invasive implantation procedure needs to be performed with lower general surgical risks and faster recreation. However, pneumothorax is one described complication during implantation. In chronic use careful care and inspection of the site, where the percutaneous leads pass the skin, needs to be regularly performed to avoid infections. Until now, sufficient data on associated infections are not available.

The contraindications of the DP system and the PNS are the same. At this point it needs to be explicitly mentioned that although the DP system uses intramuscular electrodes it is based on the stimulation of the phrenic nerves and its muscular endplates. Therefore, as in DP enough lower motor neurons of both phrenic nerves need to be intact for successful application. Permanent application over many years for 24 hours/ day in patients with high SCI are described[57]. Some patients with preserved sensory functions complain about pain under stimulation, which is most likely be caused by the relatively strong stimulation currents[58].

Regarding both systems late nerve complications are caused by infection, biofilm, scar formation, foreign body reaction, electrode misconfigurations and/or by an electrode dislocation. The unipolar and the four-pole PNS electrode do not encircle the nerve[55,59]. Late nerve problems are seen more often in the moving neck[59] than in the thorax and more often with nerve-encircling cuff type electrodes than with electrodes allowing the nerve to escape scar pressure[60]. The best place to implant is at the parietal pleura beside the upper mediastinum. MRI examinations could lead to nerve and/or muscle damage and therefore are contraindicated in both systems.

Quality of Life

A qualitative study from Canada that recruited 15 patients with chronic high cervical SCI, of whom only one third were breathing independently, revealed that all participants were glad to be alive and that a very high quality of life is possible, when there is support from society (see Figure 17.4). Patients need to refocus their values and to re-establish a view of themselves "as able and valuable following injury"[61]. They addressed "autonomy, meaningful use of time, and relationships" as central issues[61]. Self-efficacy has been shown to be negatively correlated

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Figure 17.4 Skiing with tetraplegia, tracheostomy and phrenic nerve stimulation.

with anxiety and depression in a general population of patients with SCI, accordingly[62]. Individualised assistive technologies are needed to guarantee equal participation in society and to foster independence and self-esteem[63]. Mobility, such as with individually adapted electric wheelchairs and wheelchair controls, and environmental control, such as to use mobile phones and computers, are central aspects for assistive technologies[64].

Studies linking quality of life with specific interventions in ventilated SCI patients are rarely found. One study associated higher quality of life scores in combination with suprapubic catheters, resulting from less urological morbidity in comparison with intermittent catheterization[65]. Furthermore patients prefer PNS, as they expect an improvement of their quality of life[47], arguments being that the PNS system is less externally apparent and there are fewer mobility restrictions when there is no ventilation hose present.

Mechanical Ventilation versus Diaphragm Pacing and Phrenic Nerve Stimulation

Modern electro-ventilation such as DP and PNS provide reliable full-time long-term artificial ventilation for some patients suffering central apnoea. With PNS, we found a tendency towards better survival compared to MV. The frequency of decubital ulcers and urological complications appear significantly more with MV than with PNS, proving enhanced mobility and facilitation of nursing with PNS. Patients prefer PNS and refuse randomisation, which may be taken as their opinion of the improved quality of life with PNS. The frequency of respiratory infections differed highly significantly in favour of PNS. Large savings are subsequently obvious.

The management of SCIs stands at the intersection of medical expertise, technological innovation and unwavering dedication to patient well-being. This multifaceted endeavour necessitates a holistic approach that extends beyond the immediate medical intervention to embrace the entire spectrum of rehabilitative care. Central to this approach is the collaborative effort of a multidisciplinary team comprising neurosurgeons, intensivists, physiotherapists, occupational therapists, psychologists and various specialists, synergizing their expertise to tailor treatment plans to individual needs. Rehabilitation emerges as a cornerstone in the continuum of care, fostering functional recovery, reintegration into daily life and the restoration of independence for those affected. Notably, the landscape of SCI management has been redefined by technological advancements, where innovations such as robotic exoskeletons, neural interfaces and assistive devices offer newfound hope by augmenting traditional rehabilitation efforts. Yet, amidst these strides, challenges persist, compelling the medical

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community to seek further breakthroughs. The journey ahead beckons with promise, as ongoing research endeavours delve into regenerative medicine, neuroprotection strategies and personalised therapies. Through this relentless pursuit, the horizon of possibilities broadens, nurturing a vision where spinal cord injury management transcends current limitations, offering not just treatment, but a pathway to renewed hope, autonomy and improved quality of life for those navigating the complex terrain of SCIs.

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Chapter 18

Neuromuscular Diseases

Stephan Wenninger, Susana Quijano Roy and Maxwell S. Damian

Respiratory involvement is common in many neuromuscular diseases (NMDs) but to a variable degree. In most NMDs, hypoventilation is due to insufficient respiratory muscle pump and results in reduced quality of life and increased morbidity and mortality. Moreover, upper airway muscles and brain can be involved resulting in obstructive sleep apnoea, central sleep apnoea, or even central hypoventilation syndrome. Especially in congenital neuromuscular diseases with early disease onset, skeletal deformities reduce thoracic compliance with resulting restrictive ventilatory pattern. In some NMDs, more than one system can be affected and thus an individual diagnostic and therapeutic approach is required. Table 18.1 highlights NMDs and their respiratory involvement.

Table 18.1 Common symptoms related to respiratory involvement in neuromuscular diseases*

Early-stage symptoms of inspiratory muscle weakness, usually unspecific	• Daytime sleepiness • Hypersomnia • Mental fatigue • Physical fatigue • Morning headache • Concentration difficulties • Impaired cognition • Impaired affect • Mood changes, mild to moderate depression • Reduced physical and psychological endurance • Uncomfortable feeling on immersion in water • Disrupted sleep
Later symptoms of inspiratory muscle weakness, usually more specific	Early-stage symptoms and • Exercise dyspnoea • Dyspnoea at rest • Speech dyspnoea • Orthopnoea • Dyspnoea on immersion in water • Recurrent respiratory tract infection
Severe symptoms of inspiratory muscle weakness	• Activation of accessory respiratory muscles • Paradoxical breathing
Symptoms of obstructive sleep apnoea, variable degrees	Early- and later-stage symptoms and • Snoring • Observed episodes of paused/stopped breathing during sleep • Abrupt awakenings accompanied by gasping or choking • Dry mouth or throat • Elevated blood pressure
Symptoms of respiratory muscle and glottic weakness, variable degrees	• Insufficient cough • Recurrent respiratory tract infections

*Some symptoms might not be recognized by the patient as associated with respiratory involvement, so examiner must ask about these symptoms regularly.

Muscles of Respiration and Coughing

Affected muscles of respiration and coughing vary among different NMDs and within the course of the disease. Depending on age and constitution, about two thirds of the main work of inhalation is performed by the diaphragm and the inspiratory portion of the intercostals (see Chapter 5). Accessory inspiratory muscles include the rectus abdominis, the scalene, sternocleidomastoidei, and trapezii muscles. Inspiration is always energy-dependent and about 2.5–3 joules/min are required to ensure sufficient inspiration at rest. A critical limit is reached at about 10–15 joules/min resulting in restrictive ventilatory failure if exceeded continuously[1–3].

Expiration at rest is largely passive due to elastic recoil. For forced expiration during exercise or coughing, sufficient contraction of rectus abdominis, external and internal obliques, transverse abdominis, and the expiratory portion of the intercostals is necessary. Insufficiency of expiratory muscles results in insufficient cough. Consecutively, insufficient airway clearance and airway tract infections may occur.

Airway muscles comprise the tongue, palate, pharyngeals, and laryngeals for a sufficient airway seal and efficient cough. Weakness of these muscles (often

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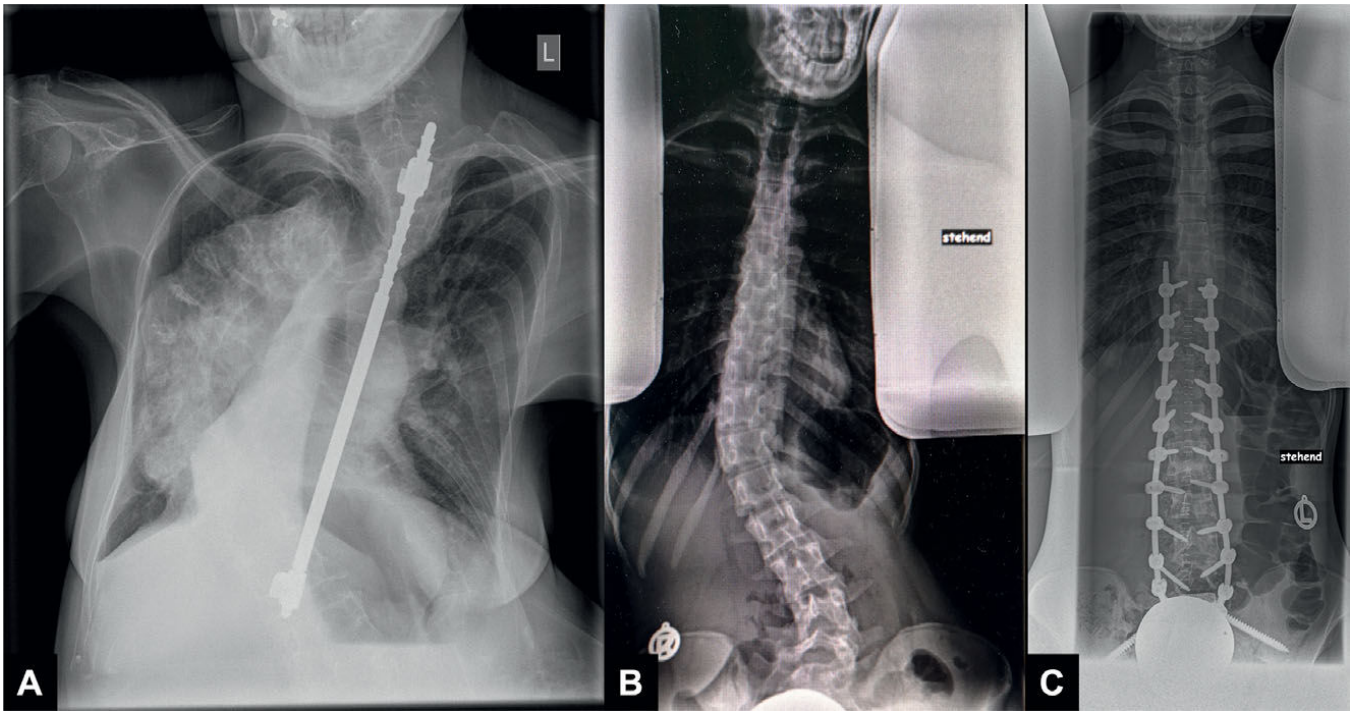


Figure 18.1 Severe thoracolumbar scoliosis and lordosis in two female patients (A) and (B, C) with congenital myopathy. Both patients underwent spinal surgery due to chronic musculoskeletal pain syndrome. Before and after surgery, no change in lung function was observed. Images provided by S. Wenninger, Friedrich-Baur-Institute, Munich, Germany.

summarized as "bulbar muscles") results in obstructive sleep apnoea, dysphagia, rhinophonia, dysarthria, cough insufficiency, and pulmonary infections due to aspiration or cough insufficiency (see Chapter 10).

Especially early-onset NMDs, such as spinal muscular atrophy type 1 and 2, congenital myopathies, and infant onset of metabolic myopathies, are associated with a marked weakness of the thoracic and paraspinal muscles. This leads to skeletal deformity of the thorax with a pronounced scoliosis and/or kyphosis in many cases (Figure 18.1) and typically the need for surgical intervention in childhood[4,5]. Particularly in structural myopathies (e.g. nemaline myopathy), a funnel chest with restriction in respiratory excursion may develop. Despite relatively sufficient respiratory muscles, skeletal/chest deformity causes severe restrictive ventilatory dysfunction. A markedly reduced forced vital capacity (FVC) of around 1.5–2 L (30%–50% of predicted) is a frequent finding in these patients. Clinically, most patients are asymptomatic at rest but exertional dyspnoea during physical activities and sleep-disordered breathing (SDB) emerges frequently. However, after surgical treatment of scoliosis/lordosis, improved vital capacity was found in only a proportion of patients in some publications. Data exist on various NMDs with negative outcomes after spinal surgery, most notably in spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD)[6–9].

Clinical Manifestations

Depending on the type of NMD, respiratory involvement can occur at any disease stage and in a variable severity and progression, but in most cases, respiratory involvement is slowly progressive. Therefore, regular assessments of clinical symptoms suggestive for hypoventilation and pulmonary functions tests are recommended (see Chapter 8). Of note, there is only a weak association between respiratory involvement and locomotor function, and some patients may present with respiratory impairment as their first clinical sign[10–12], so respiratory function can't be predicted by locomotor muscle weakness. In contrast to patients with lung diseases presenting with hypoxia, the hallmark for patients with NMDs is hypercapnia in a variable degree. But, as most patients with NMDs present with a progressive disease course, progressive respiratory muscle weakness

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can result in collapse or closure of small or larger lung compartments (dys- and atelectasis) and cause hypoxia due to impaired pulmonary gas exchange. In addition, continuously increasing blood levels of CO_2 result in decreasing ability for O_2 uptake, which is explained by Dalton's law regarding the relative partial pressure of gases in a shared volume[13].

SDB in NMD comprises obstructive and central sleep apnoea and respiratory muscle weakness leading to alveolar hypoventilation[14]. At early disease stages, hypoventilation first appears during sleep. Nocturnal hypoventilation causes unspecific symptoms such as morning headache, daytime sleepiness and hypersomnolence, mental and physical fatigue, concentration problems, and depression (Table 18.1)[15]. Because these symptoms are unspecific and commonly not attributed to respiratory involvement, there is some diagnostic delay in many patients. Therefore, frequent evaluation of clinical symptoms suggestive for hypoventilation is essential. Some clinical scores may help to identify those patients, for instance, Epworth sleepiness scale[16], but there is no generally applicable validated test or score that is sufficient for all different NMDs. As an example, the respiratory involvement checklist was established and validated for myotonic dystrophy type 1 (DM1)[17–20], but is less usable for patients with myotonic dystrophy type 2 (DM2)[21]. At early disease stages, routine spirometry is often normal. In patients with NMDs, FVC in the supine position should be added to routine assessments to evaluate diaphragmatic weakness, which is the main cause for SDB (Chapter 8)[22]. Patients with clinical hypoventilation symptoms and normal spirometry require blood gas analysis and sleep studies including transcutaneous capnometry to identify SDB (see Chapter 19).

Physiologically, oropharyngeal muscle activity decreases during sleep in healthy individuals, but in patients with NMDs, weakness of upper airway muscles contributes to upper airway obstruction, resulting in obstructive sleep apnoea (OSA). OSA may occur independently of central sleep apnoea or respiratory muscle weakness.

At later disease stages, patients present with dyspnoea while exertion or at rest and orthopnoea. In some patients, early signs of activation of accessory inspiratory muscles may become evident. At this point, FVC and maximum inspiratory and/or expiratory pressures (MIP/MEP) in manometry are usually decreased. With progression of respiratory muscle weakness, speech dyspnoea, tachypnoea, and shallow breathing with poor chest expansion emerges. Paradoxical breathing with the abdomen moving in during chest rise is also a frequent finding in patients with severe diaphragmatic weakness. In neuromuscular diseases, hypercapnic ventilatory failure is primarily driven by ventilatory pump failure, which may interact with reduced chest compliance, obstructive sleep apnoea, central sleep apnoea, impaired sleep, and reduced central respiratory drive (see Figure 18.2). In severe cases, the combination of upper airway obstruction and ventilatory pump failure may even lead to failure of non-invasive ventilation (see Figure 18.3). If cough impairment, aspiration, tracheobronchial retention of secretion or finally pneumonia further compromise the respiratory system, the patient is prone to acute respiratory failure.

Respiratory muscle involvement or glottic weakness reduce cough efficiency and compromise airway clearance. Especially when aspiration is also present, recurrent airway tract infections occur. For screening in daily routine, peak cough flow (PCF) measurement is recommended. Susceptibility to respiratory tract infections is increased with a PCF of 160–270 L/min, and a PCF $<$160 L/min is associated with a highly increased risk of respiratory tract infections[23].

For daily routine practice, evaluation of the progression of respiratory involvement is crucial. Most patients with hereditary NMDs present with slowly progressive respiratory involvement while many acquired NMDs rapidly progress and result in early respiratory failure. An acute-on-chronic respiratory failure in any NMD is not uncommon but should be avoided by regular assessments of lung function and early therapy.

Clinical Manifestations in Children

Respiratory difficulties observed clinically or described by the parents give important clues. Impairment of respiratory function may not be very evident in young children, who present with hypomotility, tachypnoea, walking or feeding refusal, weak cry or voice or staccato speech, discomfort breathing lying flat, or profuse sweating. If not treated, somnolence, loss of conscience or coma, and cardiorespiratory arrest may occur. In most cases, a chronic and progressive restrictive insufficiency develops over time and respiratory failure may be difficult to diagnose. Abnormalities will initially be detected only during sleep (hypercapnia, apnoea, or hypopneas) and will remain transitory, being compensated by an increased breathing rate (tachypnoea) or by frequent

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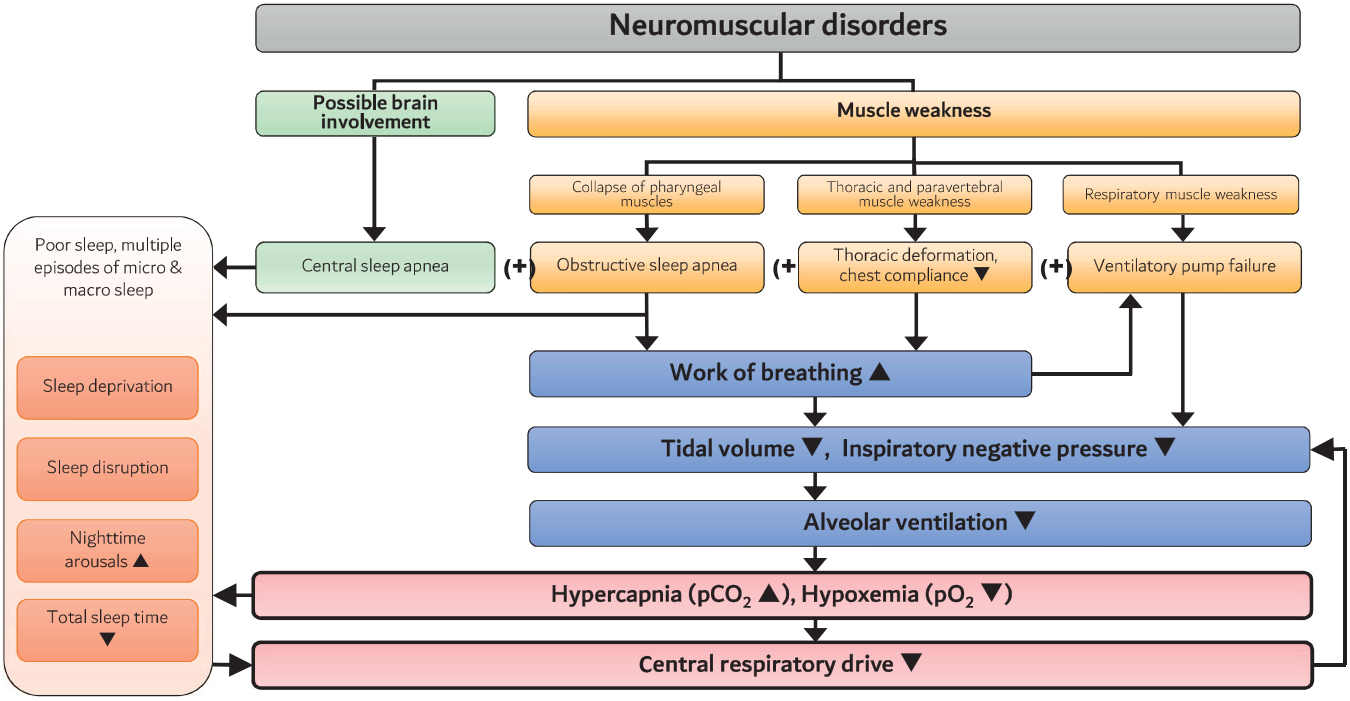


Figure 18.2 A model for chronic ventilatory failure in neuromuscular diseases. Image courtesy of Martin Groß, Stephan Wenninger.

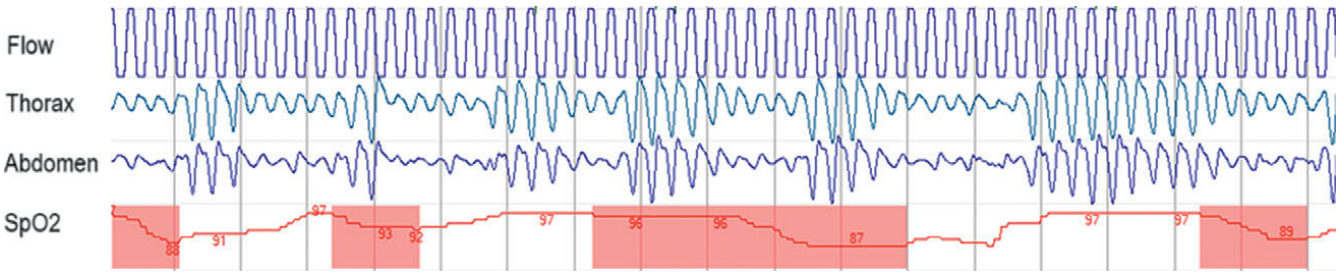


Figure 18.3 Polygraph of a young woman with congenital muscular dystrophy, continuous non-invasive ventilatory support (see Chapter 11) and excessive daytime sleepiness. Recurrent reductions in thoracic and abdominal respiratory movements, followed by oxygen desaturations (marked red) indicate obstructions of the upper airway. Vertical line every 10 seconds. Transcutaneous capnometry revealed a mean CO_2 of 69 mmHg. After tracheostomy, blood gas analysis was normalized, and daytime sleepiness was resolved. Image courtesy of Martin Groß.

night awakenings. Subtle signs and symptoms will be progressively identified also during the day (unexplained loss of weight, tiredness due to poor sleep, morning headaches, sleepiness, fatigue). It is in this period of "hidden" or minor symptoms when the risk of life-threatening complications is high because they may occur unexpectedly. Overexertion or inhibition of respiratory function (infections, fever, exercise, anaesthesia, sedation) may lead to acute respiratory failure or trigger a multisystemic failure (cor pulmonale) and end fatally.

Standards of Neurorespiratory Care in the Neuromuscular Clinic

There is no general recommendation on the frequency of visits at the neuromuscular centre or on the frequency of respiratory assessments as this depends on the clinical progression, contributing symptoms and their severity. However, based on experience, patients with neuromuscular diseases with respiratory involvement or when respiratory involvement is expected should be seen more

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Table 18.2 Recommended assessments in patients with NMD

Type of care and schedule	Suggested setting	Procedures
Standard care Regularly every 3 to 12 months, depending on disease course	Outpatient clinic or hospital ward	• Medical history about the disease course, e.g. progression of symptoms, respiratory tract infections, concurrent diseases • Clinical assessment of distribution of muscular weakness including bulbar muscles • Clinical assessment of unspecific symptoms suggestive for respiratory involvement • Dysphagia screening or flexible endoscopic evaluation of swallowing • Minimal standard respiratory assessments: (forced) vital capacity in sitting and supine position, peak cough flow, and capillary blood gas analysis. • In mechanically ventilated patients: blood gas analysis during ventilation (>1 hr) and analysis of ventilation data saved in the home respirator including ventilation hours, leakage, tidal volumes, apnoea-hypopnea index, and alarm history • Evaluation with respect to rehabilitative needs, assistive technologies, augmentative and alternative communication, and disease-specific medications • Coordination of physiotherapy, speech and language therapy, out-of-hospital care, rehabilitation, and palliative care
Specialized care As needed, depending on disease course every 6 to every 24 months	Centre for neuromuscular diseases	• Diagnosis of the NMD including genetic testing • Medical treatment of the NMD • Extensive respiratory assessment: Manometry of respiratory muscles (MIP, MEP, SNIP) • In unclear cases phrenic nerve stimulation (nerve conduction studies, motor evoked potentials), electromyography of respiratory muscles, ultrasound of respiratory muscles
Specialized care As needed, depending on disease course	Centre for neuromuscular diseases, pulmonological or sleep medicine department	• SpO_2, $tcCO_2$, and poly(somno)graphy and early morning blood gases in non-ventilated patients with hypoventilation symptoms and normal or unclear results in spirometry and/or manometry and in in mechanically ventilated patients with need for optimizing NIV, e.g. when airway obstructions under NIV are possible

MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure; NIV, non-invasive ventilation; SNIP, sniff nasal inspiratory pressure.

frequently. As an example, in motor neuron diseases, respiratory involvement can occur subacutely and progress rapidly in patients with amyotrophic lateral sclerosis (ALS), so they should be seen at least every three months. In contrast, respiratory involvement in patients with SMA 3 (newer clinical classification: "walkers") is rare, so clinical assessments every 12 months are sufficient for most patients. Table 18.2 provides recommendations for respiratory and holistic care in patients with NMD that must be adapted to regional healthcare structures. As there is a high burden in patients with neuromuscular diseases to attend regularly at clinical sites, some clinical studies evaluate the suitability of utilizing digital media, such as smartwatches with O_2 and heart rate measurement or smartphones with specific patient questionnaires.

Neuromuscular Diseases

Knowledge of the disease, the distribution of weakness ("neuromuscular phenotype") and the involvement of respiratory function is essential for an early and sufficient treatment. Diagnostic delay increases risk of a severely reduced quality of life, recurrent airway tract and pulmonary infections, and premature death. In children it may have an impact on growth. Despite slowly progressive respiratory muscle weakness (RMW) is common in most hereditary NMDs, time of onset and progression of the respiratory involvement is highly variable, therefore regular assessments are crucial. In contrast, acquired NMDs are often subject to a more acute or subacute respiratory involvement with higher probability of acute respiratory failure than inherited diseases. However, a

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Table 18.3 Clinical variants of motor neuron diseases and their estimated survival, based on different natural history studies

Initial symptom (onset)/clinical variant	Subtype frequency	Mean survival	10-year survival	References
Bulbar	10%–20%	2 years	3%	[86–88]
Spinal/hypoventilation	3%–5%	1.4 years	–	[86–88]
Progressive muscular atrophy	5%	2–5 years	10%	[86]
Flail arm	11%	4 years	17%	[87]
Flail leg	6%	5.8 years	64% 5-year survival	[87]
Primary lateral sclerosis	3%–5% of all MNDs	>20 years	95%	[86]
ALS-frontotemporal dementia	5%	2.4 years	8%	[78,89]
Classic ALS (first and second motor neuron)	60%–90%	2–4 years	10%	[86,88,90]

ALS, amyotrophic lateral sclerosis.

rapid deterioration of respiratory function may be seen in every patient with RMW due to respiratory tract infection associated with dysphagia and/or an inadequate cough. Although there is no general recommendation for routine assessments of respiratory function in NMDs, some recommendations for specific diseases exist, like Duchenne muscular dystrophy, DM1 and DM2, glycogen storage disease type 2 (GSD2, Pompe disease), and motor neuron disease like SMA and ALS[24–32]. Of note, recommendations might be slightly different between paediatric and adult care. Table 18.3 highlights the most common NMDs and their respiratory involvement. Some are additionally discussed in Section 18.14.

Muscular Dystrophies

DM1 and DM2 represent the most frequent dystrophic myopathies in adulthood[33]. Both feature autosomal-dominant inheritance and are classified as repeat expansion disorders. In DM1, expansion of CTG repeat length is roughly associated with onset of clinical symptoms as well as disease progression and severity, ranging from mild to severe phenotypes. The “adult-onset” or “classic” phenotype is associated with a CTG repeat size between 50 and <1,000, while childhood/juvenile phenotypes with early onset have CTG repeat expansions around 800. In addition, anticipation can cause more severe phenotypes in following generations primarily when maternally transmitted[34]. The phenotype in DM1 patients is characterized by a distinctive combination of muscular symptoms (facial weakness, ptosis, grip myotonia, and distal muscle weakness with muscular atrophy, respiratory muscle weakness) in combination with extra muscular symptoms like cognitive impairment, cataracts, and diabetes mellitus[35]. Congenital myotonic dystrophy is associated with very large CTG repeat expansions and represents the most severe phenotype. During pregnancy, fetuses with congenital myotonic dystrophy often present before birth as polyhydramnios and reduced fetal movement. Clinical characteristics after delivery include muscular hypotonia, generalized muscle weakness, hyporeflexia, bilateral talipes, contractures, arthrogryposis, facial dysmorphia (carp mouth, ptosis, long neck and face, temporal muscle atrophy), and a weak cry. Feeding tubes because of a weak sucking and ventilator support because of respiratory muscle weakness is present in about 50% of newborns and is the main cause of a high mortality rate of 30%–40%[36]. Surviving infants have delayed motor and cognitive milestones but might be able to walk independently. In contrast to DM1, there is no known association between the CTG repeat length and clinical symptoms in DM2, and there is no anticipation. Both myotonic dystrophies present in a high variability of clinical symptoms, and due to non-muscular involvement, both are considered as multisystemic diseases[37]. Early diagnosis of respiratory involvement is sometimes challenging in both DM, as non-muscular symptoms like daytime sleepiness, fatigue, and concentration difficulties are core clinical features of the multisystem involvement. In DM1, all levels of the respiratory system can be affected: central sleep apnoea and OSA at early disease stages as well as progressing bulbar dysfunction and respiratory muscle weakness are common findings[38]. Interestingly, expiratory muscles are affected earlier than inspiratory muscles causing insufficient cough and recurrent airway tract infections[21,39]. Typically, patients with DM1 develop OSA at early stages with necessity for continuous positive airway pressure (CPAP) ventilation,

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but with disease progression and contributing respiratory muscle weakness, CPAP is no longer sufficient and non-invasive ventilation (NIV) becomes necessary. In DM1, a reduced central respiratory drive may also be present. In this case, blood gas analysis shows considerable hypercapnia and hypoxemia, but dyspnoea is absent. This condition is most prominent during sleep, so the patient must be treated with NIV in a controlled ventilation mode, whenever he sleeps. Treatment with oxygen alone without mechanical ventilation further elevates CO_2 levels, and hypercapnic coma may result. In DM2, which is commonly considered as a less severe phenotype, central apnoea, SDB, and OSA occur less frequent compared to DM1. RMW is not a typical finding in DM2, but some cases are described.

DMD is an x-linked dystrophinopathy and the most common muscular dystrophy in children. Beginning with an early onset of skeletal muscle degeneration, continuous progression of the disease affects bulbar and respiratory system at around age of 10 years and mechanical ventilation at ages 15 to 20[40,41]. Annual decline of vital capacity is estimated around 8%[42]. RMW is rare in the milder Becker muscular dystrophy phenotype (BMD). However, OSA and inadequate cough may evolve. Due to cardiac involvement in both dystrophinopathies, pulmonary oedema and respiratory decompensation may occur.

Facio-scapulohumeral muscular dystrophy (FSHD) is inherited as autosomal dominant and the third most common form of hereditary myopathies. Disease severity and respiratory involvement are inversely associated with D4Z4 fragment length[43], but FSHD presents with a high variability on clinical onset and disease progression[44]. Due to pronounced weakness of facial and sometimes oropharyngeal muscles, OSA and SDB are found in a high proportion of patients[43,45–48]). Up to 38% of patients may develop hypoventilation at later stages due to involvement of inspiratory and expiratory muscles[43]. In patients with early onset disease, skeletal deformities might contribute to a thoracic restriction.

Congenital Muscular Dystrophies

Six major entities have been described in this group of muscular dystrophies with presentation at birth or in the first two years of age by hypotonia or motor delay. Muscular enzymes are increased in those with merosin deficiency *(LAMA2* gene) and *alpha-dystroglycanopathies* (more than 20 different genes described). Merosinopathies are very retractile myopathies which show no selective respiratory muscle involvement, but global progressive restrictive respiratory insufficiency due to spinal and thoracic stiffness (see Figure 18.4). Non-ambulant patients

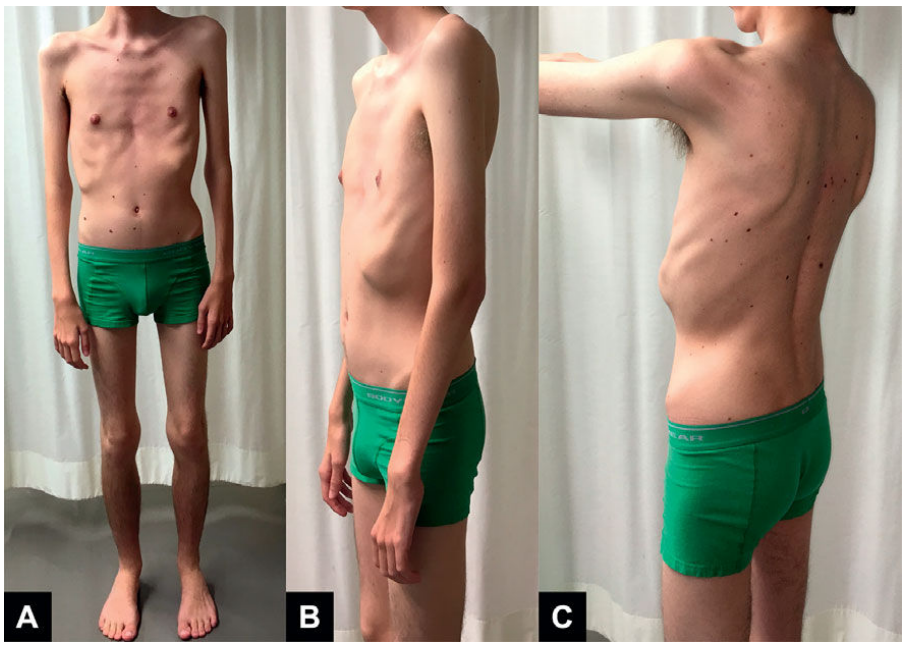


Figure 18.4 Male 22-year-old patient with congenital nemaline myopathy due to mutation in the *LMOD3* gene[50] with marked facial weakness, generalized muscular hypotrophy, and deep funnel chest with Harrison's groove. Respiratory function was normal. Images provided by S. Wenninger, Friedrich-Baur-Institute, Munich, Germany.

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require nocturnal ventilation from childhood. Ambulant patients usually do not show hypoventilation. Dystroglycanopathies show diaphragmatic selective failure and they are not initially retractile, but often associate cognitive involvement, which makes respiratory function assessment and management difficult. Certain forms associate brain malformations (Walker–Warburg syndrome, muscle-eye-brain disease, Fukuyama muscular dystrophy).

Concerning the forms with normal or subnormal creatine kinase levels, four entities are well described: Ullrich congenital muscular dystrophy (CMD) due to mutations in *COL6A1*, *COL6A2* or *COL6A3* genes is characterized by axial and proximal contractures and distal streaking hyperlaxity. The course is similar to merosinopathies, although this disease requires earlier respiratory support due to an early and selective involvement of the diaphragm which is associated with Ullrich CMD. This is also observed in the myopathy related with *SELENON* (previously known as *SEPN1*). Finally, the congenital laminopathies (*LMNA* gene) show loss of head support (dropped head syndrome) or absent motor acquisitions and patients become very stiff, retracted, and paralytic. Their survival is related to respiratory failure in the most severe and early cases, while those with longer survival show rhythm or heart muscle dysfunction.

All CMDs sooner or later develop spinal, thoracic, neck, and temporomandibular contractures, what makes it difficult to manage them on home ventilation. An abdominal belt may facilitate nocturnal ventilation if high pressures are required due to the progressively decreased compliance of the thoracic cage, by increasing the abdominal pressure and therefore reducing the air that derives from the respiratory to the digestive tube. Since proactive ventilation has shown to promote chest and lung growth in children in diseases associated with progressive stiffness of the thoracic cage, CMDs are particularly concerned. Early intervention may improve their respiratory and global prognosis[49].

More than 30 subtypes of limb-girdle muscular dystrophies (LGMD) have been described, most of them with autosomal recessive and some autosomal dominant inheritance. Clinical phenotype depends on the age of onset and severity of the disease, but a core feature is a predominant weakness of limb-girdle and axial muscles. According to a recent registry-based analysis on the incidence of respiratory involvement in a large cohort of LGMDs, hypoventilation due to respiratory muscle weakness is generally uncommon, but occurs frequently in some very rare LGMS subtypes like sarcoglycanopathies (LGMD R2–R6), calpainopathy (LGMDR1), and fukutinopathy (LGMD R9). However, as bulbar muscles may be affected, OSA may evolve at later stages in many LGMDs[51–53]. Table 18.4 highlights respiratory involvement in different LGMDs.

Metabolic Myopathies

Metabolic myopathies are a heterogeneous group of inherited muscle diseases with disrupted energy production in the muscle, resulting in muscle fatigability, impaired muscle endurance, muscular nociceptive pain, and muscular weakness. The most important ones are the glycogenoses, of which Pompe disease (GSD 2) and McArdle's disease (GSD 5) are the most common, the lipid storage myopathies with primary and secondary carnitine deficiency syndromes and defects of fatty acid oxidation, and the mitochondrial myopathies due to defects of the mitochondrial respiratory chain. Respiratory involvement is frequent in GSD 2 (Pompe disease) with autosomal recessive mutation in the *GAA* gene. Some mutations cause a complete lack of lysosomal enzyme activity of α-1,4-glucosidase (acid alpha-glucosidase, GAA) which leads to the severe infantile phenotype (infantile onset Pompe disease) with generalized muscular weakness ("floppy infant"), cardiomyopathy and respiratory involvement with early need for ventilation and premature death before adolescence. In adult Pompe patients (late-onset Pompe disease), residual activity of α-1,4-glucosidase is present, and the clinical picture comprises muscle weakness and reduced muscle endurance of axial and proximal muscles. About two thirds of patients with late-onset Pompe disease develop hypoventilation due to predominant diaphragmatic but also abdominal and oropharyngeal muscular weakness. An FVC drop of $>-20\%$ from the upright to the supine position is one of the hallmarks in diagnosing Pompe disease[54]. With some exceptions and early and severe respiratory muscle weakness, respiratory involvement is typically slowly progressive and starts with nocturnal hypoventilation[55]. Although enzyme replacement is available for these patients, numerous longitudinal studies showed a marked slowing of disease progression or even stabilization in the first three to five years of treatment but then continuous slow progression of the disease[56–65].

Mitochondrial Diseases

Dysfunction of the mitochondrial respiratory chain or metabolism causes mitochondrial myopathies with a wide range of clinical presentation[66]. Muscular

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Table 18.4 Characteristics of common neuromuscular diseases

NMD	Age of onset	Progression	Respiratory muscle weakness	Central respiratory involvement	Bulbar muscle involvement	Skeletal deformities	Probability of acute respiratory failure
Hereditary neuromuscular diseases – myogenic							
Becker's muscular dystrophy	Variable, adulthood	Slowly progressive	Variable, poor coughing in some patients	SDB	Rare, depends on severity of the disease	No	Rare
Congenital muscular dystrophies	Variable, some with early onset in infancy	Developmental disorder of musculoskeletal system, early respiratory involvement, slowly progressive	Common	Common	Dysphagia → aspiration	Yes, depending on severity of disease scoliosis and lordosis	High, acute-on-chronic
Congenital myopathies	Variable	Developmental disorder of musculoskeletal system; almost no or only very slow progression after childhood	Common, both inspiratory and expiratory muscles	SDB	Dysphagia → aspiration	Yes, scoliosis and lordosis, depends on severity of disease	Possible, acute-on-chronic
Duchenne's muscular dystrophy	Infants to teen boys	Chronic, acute-on-chronic	Common, inspiratory, and expiratory muscles	SDB	Yes, dysphagia → aspiration; Macroglossia → OSA	Depends on severity of the disease	High, acute-on-chronic
Facioscapulohumeral muscular dystrophy	Variable	Slowly progressive	Rare, only reported in severe disease	SDB rare	Rare	Rigid spine, bent spine, weakness of thoracic muscles and shoulder girdle	Rare
Limb-girdle muscular dystrophies (LGMD), >25 autosomal-dominant (D) and autosomal recessive subtypes (R), for more details see Table 18.5	Variable, late teenage to late adulthood	Slowly progressive	Variable, early and prominent in LGMD R9 (FKRP mutation), later in LGMD R3–6 (sarcoglycanopathies)	Variable, SDB, OSA, Cheyne–Stokes respiration	Variable	Variable, rigid spine, scoliosis	Variable
McArdle disease; glycogenosis type V	Variable	Relatively stable	Rare	No	No	No	Resp. failure with acidosis
Mitochondrial myopathies	Variable	Slowly progressive	Sometimes, both inspiratory and expiratory muscles	Sometimes, SDB, CSA	Sometimes	Sometimes	TK2 myopathy (frequent in early progressive infantile form and at late stages of juvenile or adult form)

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Table 18.4 (*cont.*)

NMD	Age of onset	Progression	Respiratory muscle weakness	Central respiratory involvement	Bulbar muscle involvement	Skeletal deformities	Probability of acute respiratory failure
Myotonic dystrophy type 1 (DM1)	Adolescence (if not congenital)	Slowly progressive	Common, inspiratory, and expiratory muscles early and predominantly expiratory muscles	Common: SDB	Common, weakness and myotonia of laryngeal/ pharyngeal muscles → Dysphagia OSA	Rare	Possible, acute-on-chronic
Myotonic dystrophy type 2 (DM2)	Adulthood	Slowly progressive	Yes, less frequent than DM1	Common: SDB	Myotonia of laryngeal/ pharyngeal muscles → dysarthria, dysphagia OSA	No	Rare
Non-dystrophic myotonias	Teenage to adulthood	Relatively stable	Predominantly myotonia of thoracic muscles, may be followed by transient respiratory muscle weakness	No	Myotonia of pharyngeal muscles → dysphagia	No	Rare, depends on severity of dysphagia
Oculo-pharyngeal muscular dystrophy	Adulthood	Slowly progressive	Not common	SDB	Dysphagia → aspiration	No	Possible, depends on severity of dysphagia
Pompe disease, classic infantile onset; glycogenosis type 2	<6 months	Fast, high mortality in infants	Common, both inspiratory and expiratory muscles, early ventilation in infants	Not known	Common, dysphagia, aspiration, tracheostomy in all cases	Yes, depending on severity of disease scoliosis and lordosis	High, acute-on-chronic
Pompe disease, late-onset (adult onset); glycogenosis type 2	Variable	Slowly progressive	~two thirds of patients at later disease stages	SDB	Rare	Scoliosis	Possible, depends on disease onset and severity
Hereditary neuromuscular diseases – neurogenic							
Amyotrophic lateral sclerosis, familiar	Variable, early to late adulthood, some with early onset (teenage)	Slowly progressive	Variable both inspiratory and expiratory	Depends on respiratory muscle weakness, SDB	Common	No	Depends on respiratory muscle weakness and bulbar involvement
Charcot Marie Tooth disease	Variable	Very slow progressive	Rare, depends on phrenic nerve dysfunction	Rare	Rare	Rare	Rare
Spinal muscular atrophy type 1	Infancy	Developmental disorder of musculoskeletal system; slowly progressive	Yes, more expiratory muscles than inspiratory muscles → cough assistance	Rare	Common, dysphagia, aspiration, tracheostomy depending on disease severity	Yes, depends on severity of disease scoliosis and lordosis	High, acute-on-chronic

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Spinal muscular atrophy type 2	Childhood, young adulthood	Variable, possible developmental disorder of musculoskeletal system; slowly progressive	Yes, more expiratory muscles than inspiratory muscles → cough assistance	Rare	Common, dysphagia, aspiration, nocturnal non-invasive ventilation and in severe cases tracheostomy	Depends on severity of disease; scoliosis and lordosis	Possible, acute-on-chronic, depends on severity of dysphagia and lung involvement
Spinal muscular atrophy type 3	Late childhood, young adulthood	Slowly progressive	Occurs after loss of ambulation or as a result of scoliosis	Rare	Rare	Depends on severity of disease scoliosis and lordosis	Rare
Spinobulbar muscular atrophy	Adulthood	Slowly progressive	Rare	No	Common → dysphagia	No	Possible, depends on severity of dysphagia
Hereditary spastic paraplegia	Adulthood	Slowly progressive	No	No	No	No	
Hereditary neuromuscular diseases – neuromuscular junction							
Congenital myasthenic syndrome	Variable, early childhood to adulthood	Variable, possible developmental disorder of musculoskeletal system; relatively stable in chronic phase, but myasthenic crisis may occur	Common	No	Dysphagia	Common	Acute-on-chronic, depends on severity of respiratory muscle involvement and dysphagia
Acquired neuromuscular diseases (neurogenic, myogenic, neuromuscular transmission)							
Amyotrophic lateral sclerosis, sporadic	Variable, 25–80 years	Variable progression, depends on clinical variant (see Table 18.3)	Yes, inspiratory, and expiratory muscles	Uncommon	Common, depending on disease course	No	High, acute-on-chronic
Antisynthetase syndrome, immune-necrotizing myopathy	Adulthood	Slowly progressive, depends on treatment	Common	No	Common, dysphagia	No	Possible, acute-on-chronic, depends on severity of dysphagia and lung involvement (interstitial lung disease)
Dermatomyositis	Adulthood	Slowly progressive	Rare	No	Common, dysphagia	No	Possible, depends on severity of dysphagia
Endocrine myopathies	Adulthood	Slowly progressive, depends on treatment	Uncommon	No	Uncommon	No	Uncommon
Guillain–Barré syndrome (GBS, AIDP)	Variable	Acute and subacute	Variable, both inspiratory and expiratory muscles	Rarely, SDB, depending on disease course	Yes, depending on disease course, transient tracheostomy possible	No	High, acute, and subacute

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Table 18.4 (*cont.*)

NMD	Age of onset	Progression	Respiratory muscle weakness	Central respiratory involvement	Bulbar muscle involvement	Skeletal deformities	Probability of acute respiratory failure
Inclusion body myositis, sporadic	Adulthood >50 years	Slowly progressive	No	No	Dysphagia, OSA	No	Rare, depends on severity of dysphagia
Lambert–Eaton myasthenic syndrome	Adulthood	Slowly progressive, depends on treatment	Uncommon, but myasthenic crisis may occur with respiratory muscle weakness	No	Uncommon, but myasthenic crisis may occur with dysphagia	No	Uncommon, but myasthenic crisis may occur
Myasthenia gravis	Variable	Acute and subacute	In myasthenic crisis, both inspiratory and expiratory muscles	Not common	Yes, depending on disease presentation dysphagia, aspiration	No	High, acute, and subacute
Post-polio syndrome	Variable, >15 years after acute poliomyelitis	Almost no progression in chronic phase after acute infection, might slowly progress due to aging	Rare; depends on respiratory Involvement in acute disease	Rare	Yes, but depends on muscular involvement in acute disease		Rare; depends on respiratory Involvement in acute disease
Toxic myopathies, e.g. statin-induced myopathy	Adulthood	Slowly progressive, depends on treatment	Uncommon	No	Uncommon	No	Uncommon

AIDP, acute inflammatory demyelinating polyradiculoneuropathy; CSA, central sleep apnoea; OSA, obstructive sleep apnoea; SDB, sleep-disordered breathing.

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Table 18.5 Limb-girdle muscular dystrophies and possible respiratory involvement

Respiratory involvement	LGMD subtype
Frequent and early stages	LGMD2C-F (R3-R6) SGCA-SGCD
	LGMD2I (R9) FKRP
May occur at later stages	LGMD1F (D2) TNP03
	LGMD1G (D3) HNRNPDL
	LGMD1I /2A (D4/R1) CAPN
	LGMD2G (R7) TCAP
	LGMD2J (R10) TTN
	LGMD2K, M, N, O, P (R11, R13, R14, R15, R16) dystroglycan
	LGMD2Q (R17) PLEC
	LGMD2S (R18) TRAPPC11
Rarely and uncommon	LGMD2B (R2) DYSF
	LGMD1D (D1) DNAJB6
	LGMD2L (R12) ANO5
	LGMD2T (R19) GMPPB
	LGMD2U (R20) ISPD

Note: new nomenclature for LGMDs was published in 2017 and some former LGMDs (e.g. LGMD1A (MYOT), LGMD1B (LMNA), or LGMD2V (GAA)) are no longer classified as typical LGMD[115].

symptoms comprise fatigability, exercise intolerance, and weakness of facial, oropharyngeal, axial, and limb muscles. Weakness of the diaphragm is rare but described. Obstructive sleep apnoea is frequent in patients with oropharyngeal muscle involvement[67,68]. Mitochondrial diseases taken together are not rare and affect about 1 in 5,000 adults and children[69]. The clinical diagnosis of a mitochondrial disease is challenging, owing to the diverse genetic background, and the fact that presenting symptoms can be vague (fatigue or abdominal discomfort), or may be common in the general population, such as migraine or diabetes. The range of phenotypes associated with mitochondrial disease is continuously expanding, but several syndromes have been well defined. Syndromes seen in adults include MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes) due to 3243A>G mtDNA point mutations and POLG mutations, MERRF (myoclonic epilepsy with ragged red fibres) due to A8344G mutations of mtDNA, Kearns–Sayre Syndrome due to large-scale mtDNA deletions, and MNGIE (mitochondrial neuro-gastro-intestinal encephalopathy) with TYMP mutations. Other clinical syndromes, such as Pearson Syndrome, Leigh Syndrome, Benign reversible myopathy, and Alpers–Huttenlocher Syndrome are seen in children mainly. Lactic acidaemia is common, but not always present. In the neuromuscular field, mitochondrial myopathies such as TK2 deficiency have a progressive course and may lead to life-threatening respiratory failure and death, due to diaphragmatic failure.

Motor Neuron Diseases

Diseases of the motor neuron comprise inherited SMA with affected lower motor neuron, sporadic and inherited (familial) amyotrophic lateral sclerosis (sALS, fALS) with affected upper and lower motor neuron, and acquired poliomyelitis with post-polio syndrome with affected lower motor neuron.

Respiratory involvement usually occurs in SMA type 1, less frequently in type 2 and rarely in type 3[30,39,70]. Due to prominent weakness of expiratory and intercostal muscles and relatively spared diaphragm, patients develop a bell-shaped chest with sternal depression[71]. Respiratory involvement is typically due to a combination of an impaired chest wall and lung development, scoliosis, and respiratory muscle weakness.

ALS is a progressive neurodegenerative disorder caused by degeneration of the upper and lower motor neurons. It is the most common motor neuron disease in adults, with a prevalence approximately 4–10/100,000 and incidence up to 3 per 100,000 persons per year, more often in males and people over 45 years of age[72,73]. About 10% of ALS cases are inherited, most of them caused by autosomal dominant gene mutations and of those, most common monogenic causes are mutations in the C9orf72 gene (up to 50%), followed by the *SOD1* gene (20%) and less often *FUS* and *TARDP* gene mutations[74]. ALS produces primarily motor symptoms but is a multisystem degeneration. Therefore, frontotemporal dementia frequently occurs, and there may be vegetative or sensory symptoms as well[75]. In both fALS and sALS, a variable but progressive weakness of skeletal muscles, including the diaphragm, intercostal, bulbar, and accessory respiratory muscles, develops[76]. In about 3% of patients, respiratory muscle weakness is the first clinical sign, and in most patients, respiratory involvement is present about 12 months after diagnosis. Death occurs

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within five years in the majority of patients, mainly due to respiratory and bulbar dysfunction[77]. Progression and survival depend on the clinical variant (subtype) with mainly respiratory and bulbar involvement (Table 18.3). Overall, older age, bulbar onset, widespread disease at presentation, and pronounced weight loss all predict shorter survival, likewise the presence of a C9orf72 mutation and the presence of frontotemporal dysfunction or frank frontotemporal dementia[78,79]. Survival after diagnosis varies and mainly depends on respiratory and bulbar muscles (aspiration). Upright vital capacity has been shown to be a significant predictor of survival, and a vital capacity $<50\%$ indicates shorter life span[80,81]. Riluzole, the only drug that is approved by both the European Medicines Agency and the Food and Drug Administration, prolongs the time to death or survival by three months according to clinical trial data[57,82]. Data from population studies suggest a survival benefit of 6 to 19 months for riluzole. A newer drug, edaravone, has been approved by the Food and Drug Administration in the United States and in some other countries, but also has only limited effect[83]. Tofersen is available in some countries for patients with fALS caused by *SOD1* mutation[84]. Multidisciplinary care with nutritional and respiratory support and good palliative care are very important for quality of life.

Respiratory involvement in post-polio syndrome depends on the distribution of affected lower motor neurons and muscular weakness during acute infection. Typically, weakness improves variably over a long duration after acute infection but may deteriorate with higher age. In those with respiratory involvement in acute infection, involvement of respiratory muscles may occur in about 25%–35%[85].

Myasthenic Syndromes

Myasthenia gravis (MG) is caused by an immune attack against nicotinic acetylcholine receptors (AChR) and other proteins at the neuromuscular junction leading to a defect of transmission. Between 85% and 90% of patients with generalized MG harbour antibodies to AChR originating from the thymus[91]. About 5% of patients have antibodies against muscle-specific kinase (MuSK), which is important for the clustering of AChR at the neuromuscular junction[92]. A smaller percentage have anti-LRP-4 antibodies; other antibodies have been described but not all are of certain significance.

MG is clinically characterized by muscle fatigability on exertion and fluctuating weakness, with a potential for rapid deterioration[93,94]. MuSK antibody positive MG is a clinically distinct variant of autoimmune MG and affects the facial, oropharyngeal, and respiratory muscle more than limbs at onset. MG can present at any age but tends to be earlier in females (mean 28 years) than in males (mean 42 years). Its overall incidence is 0.5–5 cases per 100,000, and its prevalence varies from 1 to 40/100 000[95]. Most cases begin with ocular symptoms (ptosis and diplopia) and then develop generalized fatigable weakness in the limbs, speech and swallowing problems, or dyspnoea or respiratory failure. The severity of the disease can objectively by assessed by Quantitative Myasthenia Gravis score and/or Besinger Score including FVC. However, abnormalities in MIP and PCF are more likely to indicate respiratory dysfunction earlier than changes in FVC in these patients[96]. Myasthenic crisis is the term for MG complicated by respiratory failure or oropharyngeal weakness requiring intubation and/or invasive or non-invasive mechanical ventilation for more than 24 hours and will be discussed in Section 18.14.

Inflammatory Myopathies

Idiopathic inflammatory myopathies (IIM) are a rare heterogeneous group of sporadic muscle diseases and constitute the largest proportion of "myositis". Overall incidence of IIMs is estimated at 7.98 cases per million per year (range 1.16–19), and prevalence at 14 cases per 100,000 inhabitants (range 2.4–33.8). The peak onset in adults is between 30 and 50 years of age, more commonly in women (ratio F/M 2:1). By contrast, inclusion body myositis (IBM) is more common in males over age 50 years[97]. Common characteristics are a mild to severe creatine kinase elevation (5-fold to >50-fold), and an acute to subacute developing symmetric weakness of predominantly proximal and axial muscles, including neck extensors (see Figure 18.5). Weakness can be accompanied by nociceptive pain ("myalgia"), reduced exercise endurance, and increased fatigability[98,99]. Multiple organs, such as lung, heart, and skin can also be involved in some IIMs, and the clinical picture is very variable. IIM encompass dermatomyositis, polymyositis, overlap myositis, necrotizing autoimmune myopathy, antisynthetase syndromes (ASS), and sporadic inclusion body myositis (sIBM). More recently, immune treatments such as immune checkpoint inhibitors for cancer have been observed to cause IIM[100]. Because of its poor response to immune therapies, discussions on the

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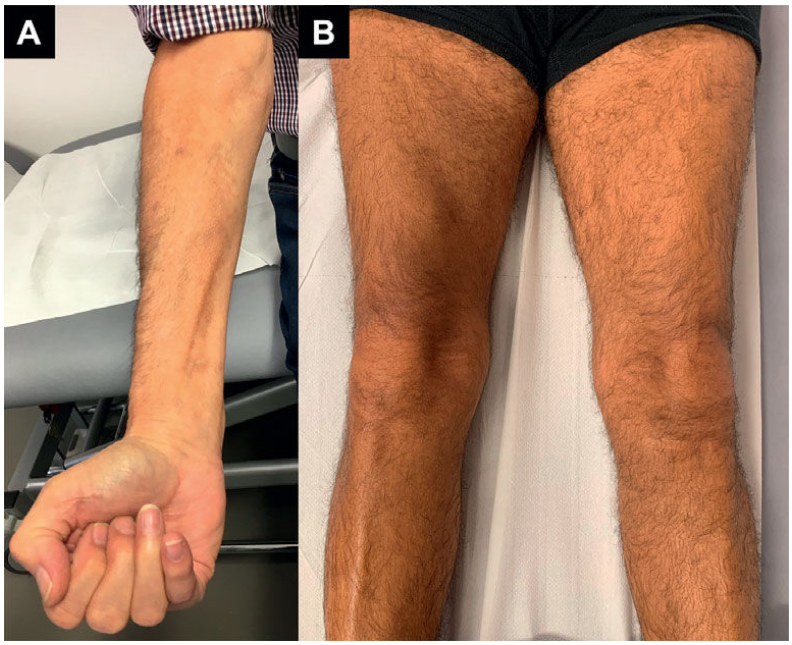


Figure 18.5 A 65-year-old patient with sporadic inclusion body myositis, confirmed by muscle biopsy. Weakness of predominantly ulnar finger flexors along with muscular atrophy (A) and proximal muscular atrophy of lower limbs (B) are characteristic findings. Images provided by S. Wenninger, Friedrich-Baur-Institute, Munich, Germany.

aetiology and pathogenesis of sIBM are ongoing whether this inflammatory process is primary due to an inflammatory process or sIBM should be classified as neurodegenerative disorder with associated inflammation. Moreover, there is also discussion whether polymyositis truly exists or not[101]. Diagnosis is established by clinical phenotype, electromyography, laboratory tests including creatine kinase elevation and myositis-specific and myositis-associated antibodies, organ, and skin involvement. In unclear cases, muscle biopsy is necessary. Over 25 different so-called myositis-specific antibodies and myositis-associated antibodies have been identified during the last decades, some associated with specific clinical features and some also known as paraneoplastic due to malignancy, so neoplasia screening must be performed in every patient[102,103]. Early diagnosis and early treatment are necessary to avoid a severe progression of the disease and irreversible function deficits. Involvement of respiratory or oropharyngeal muscles resulting in alveolar hypoventilation or obstructive sleep apnoea may emerge in all IIM except sIBM, where respiratory muscle involvement is uncommon[104,105]. However, due to bulbar muscle involvement in sIBM, OSA may occur[104–106]. Of note, lung tissue may be affected by interstitial lung disease especially in ASS resulting in impaired respiratory function[107]. Inflammatory myopathies will also be discussed in Section 18.14.

Inflammatory Peripheral Nerve Diseases and ICU-Acquired Weakness

Autoimmune peripheral nerve syndromes include chronic, subacute, and acute diseases. Of those, respiratory involvement is frequent in about one third of acute inflammatory demyelinating poly (radiculo-)neuropathy (Guillain-Barré syndrome [GBS], acute inflammatory demyelinating polyradiculoneuropathy [AIDP]) patients and its variants and in about two thirds of patients with intensive-care acquired weakness (ICU-acquired weakness)[108–110]. Involvement of respiratory and bulbar muscles mainly depends on early and sufficient treatment[109,111–113]. In contrast, respiratory involvement in subacute and chronic forms is rare[114]. AIDP/GBS and ICU-acquired weakness are discussed in Section 18.14.

Respiratory Muscle Training

The diaphragm is a flat skeletal muscle but, compared to skeletal locomotor muscles, contains a slightly higher proportion of type 1 muscle fibres of about 55% ("slow twitch muscle fibres") with high content of myoglobin. This enables the diaphragm to provide high continuous power with almost no fatigability[116,117]. In patients with restrictive ventilatory pattern, several symptomatic treatments are recommended:

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- Exercise for spine mobility and thoracic compliance, usually trained by physiotherapists.
- Breathing and coughing exercises. Several methods are recommended, including focus on deep breathing, pursed lip breathing, belly breathing, and others. Most of them are trained by specialized physiotherapists or nurses.
- Inspiratory muscle training or respiratory muscle training (RMT). Like training of locomotor muscles, the inspiratory muscles can be trained for increased muscle strength and improved endurance. Studies in a variety of NMD patients suggest that RMT can increase respiratory muscle strength[118–122]. RMT focusing on the expiratory muscles (expiratory muscle training) has been investigated in patients with ALS showing an improvement in MEP and swallowing performance[123,124].

Cough Augmentation

Insufficient cough leads to an impaired airway clearance and may result in recurrent respiratory tract infections, especially in combination with aspiration including aspiration of saliva in patients with non-oral feeding. With recurrent respiratory tract infections, probability of acute-on-chronic respiratory insufficiency increases. Moreover, oxygenation is impaired due to dys- and atelectasis of lung tissue and recurrent pulmonary infections. Clearance of secretions is severely impaired when PCF is <160 L/min. Several techniques exist for cough augmentation. They comprise manually assisted cough, mechanical insufflation/exsufflation, and high-frequency chest wall oscillation (HFCWO) for secretolysis[125]. Scientific data for the effectiveness of HFCWO are lacking though, and it is rarely used. Cough augmentation should be initiated once PCF is <270 L/min[125–127]. Mechanical insufflation–exsufflation technique is known to be safe, but to be efficient it needs to be adapted to the individual patient rather than applied according to the manufacturer's manuals[125,128]. Details on cough augmentation and management of tracheobronchial secretions are provided in Chapter 10.

Long-Term Respiratory Support

Patients with NMD often present restrictive respiratory insufficiency in the course of the time. This is particularly the case in severe generalized disease from birth, at early ages, or after the loss of walking ability. Nevertheless, certain diseases have selective diaphragmatic or intercostal involvement and may require ventilation while remaining ambulant. Therefore, achieving diagnosis and performing the correct examinations and tests may significantly guide the respiratory management.

Mechanical ventilation has proven to be a major treatment for NMDs with respiratory failure, and many types of ventilation exist: CPAP, non-invasive positive pressure ventilation (NIPPV), bilevel positive airway pressure (BiPAP), intermittent positive pressure breathing (IPPB), and many more. There is no "one size fits all", thus in every patient mechanical ventilation must be set individually and must be monitored regularly. Even when a "perfect ventilation" in a patient was established, progression of the disease will make changes necessary individually. Overall, CPAP is a common and sufficient therapy in obstructive sleep apnoea, which frequently occurs in patients with weak oropharyngeal muscles, such as DM1, DMD, BMD, and others. But, once respiratory muscle weakness becomes (additionally) apparent, CPAP is no longer sufficient in these patients and must be changed to NIPPV.

Early detection of respiratory dysfunction is vital, and a multidisciplinary approach must be adopted in order to provide the optimum treatment. Ventilation and advanced cough management strategies are currently the standards of care in NMDs because they improve survival, sleep, and quality of life. Managing long-term respiratory support maybe challenging due to the lack of cooperation (children, young adults, patients with cognitive disabilities), mask intolerance and or difficulties to find appropriate ventilation settings. Respiratory management and home ventilation in NMDs may require interaction between the neurologist, the pulmonologist or ICU specialist, the orthopaedic surgeon and spinal rehabilitation experts, and in diseases with cardiac involvement, with the cardiologist. Future need for ventilation should be anticipated and discussed with the patients and – if applicable – caregivers, in order to improve comprehension and future compliance. The need for ventilatory support may not always imply a progression of the disease, in particular in children managed proactively from early stages (e.g. SMA infants treated by innovative therapies), so the objectives have to be tailored for age, profile of disease, and clinical and socioeconomical context. In certain cases, the introduction of a ventilatory support may have ethical implications and its indication will require a multidisciplinary discussion of experts.

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If a precise diagnosis is achieved, the distribution of affected respiratory muscles may be anticipated and appropriate respiratory management may be greatly improved. A better understanding of the course of the disease will also help to identify proactive or preventive interventions and to schedule an adapted follow-up in order to explore and treat expected complications (scoliosis, cardiac dysfunction), which again may impact pulmonary function. In the absence of diagnosis, thorough exploration of the patient to identify the pattern of respiratory muscle weakness (diaphragm, intercostal, accessory, abdominal belt muscles) will be necessary at each visit. In cases with insufficient cough or bulbar involvement, clearance of tracheobronchial secretions will not improve just with mechanical ventilation and cough assistance techniques are often required[41,129]. Spinal deformities or cardiac dysfunction may further impact respiration. In fact, the timing and settings of spinal orthopaedic treatments or surgeries may be impacted by the progression of respiratory symptoms or the results of cardiorespiratory function tests.

Indications for Out-of-Hospital Mechanical Ventilation

The main purpose of mechanical ventilation is to support the ventilatory pump and to correct alveolar hypoventilation. Mechanical ventilation has improved the survival of NMD patients with respiratory failure not only in case of slowly progressive disease, such as DMD[130–132], but also in rapidly progressive diseases, such as SMA in infants or ALS in adults[133–135]. Evidence of alveolar hypoventilation is the main reason for starting ventilation. For a long time, general criteria were used to decide the initiation of ventilation: symptoms of ventilatory pump failure associated with hypercapnia (defined as $PaCO_2$ >45 mmHg or nighttime $tcCO_2$ >45 mmHg), vital capacity below 50% of predicted value, inspiratory maximal pressure below 60 cmH_2O or nocturnal O_2 desaturation below 90% for more than 5 min. Over the past two decades, increasing knowledge of many NMDs has led to better identification of specific clinical presentations and disease courses. Consequently, expert centres have often developed specific criteria for initiating treatment in different diseases. For instance, in DMD, vital capacity <20% of predicted value has proven to be predictive of hypercapnia[136] while preventive ventilation, initiated solely on pulmonary function results, has not improved survival[137]. This evidence has led to more specific criteria for DMD patients[25]. In contrast, proactive ventilation is increasingly recommended in infantile neuromuscular diseases (SMA, congenital myopathies, congenital muscular dystrophies, and some congenital myasthenic syndromes[138]), those with diaphragmatic involvement (Pompe disease), and in ALS, when there is no severe bulbar dysfunction. Early introduction of ventilation has been associated with improved survival in these populations. Even if NIV is applied only during sleep, diurnal cough augmentation techniques are required to compensate cough insufficiency[41,129]. In severe cases, intrapulmonary percussive techniques (Percussionaire®) can be used before cough augmentation manoeuvres are performed in order to enhance clearance of secretions. In patients with prominent bulbar weakness, or those at risk of unexpected respiratory failure (e.g. myasthenic syndromes), NIV may not be sufficient support and tracheostomy should be discussed. Tracheostomy in ALS may prolong survival for decades[133].

Follow-Up of Neuromuscular Patients

As a general rule, frequent surveillance of weight and slow/forced vital capacity in sitting and supine position is mandatory in non-ambulatory neuromuscular patients, or in those with FVC inferior to 60% of theoretical values or in those with fall of supine FVC compared to upright FVC, suggesting diaphragmatic failure (see Chapter 8). Frequency depends on the progression and the severity of the disease and should be individually planned (Table 18.2 and Chapter 8). In children, during growth, the use of certain trunk braces may impair respiratory function, and thus, respiratory function should be assessed regularly with and without braces. Also, home mechanical ventilation and daily use of mechanical insufflation–exsufflation may be recommended proactively or in a peri-operative period in order to optimize the respiratory function, facilitate weaning and overall improve prognosis.

As described in Chapters 6 and 8 and Section 18.2, sleep studies and spirometric measurements in supine and sitting positions are of great help to assess respiratory muscle function[22]. Volitional studies such as FVC or inspiratory and expiratory pressures will not be reliable in young children or non-cooperative patients, although they may at least allow estimating a basal respiratory function while crying[139]. PCF or sniff nasal inspiratory

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pressure is easier to obtain from young children[140,141]. The use of a nasobuccal mask to perform spirometric measures is recommended to prevent air leak in insufficient mouth strength or limited cooperation[142,143].

Progressive restrictive respiratory insufficiency in the course of myopathies is associated with spinal deformities (Figure 18.1). In these cases, diurnal blood gases and poly(somno)graphy combined with measurement of $tcCO_2$ should be performed at least once per year, coupled with spinal X-rays including a lateral view to determine the distance between the airways and the anterior vertebral bodies. The presence of hypercapnia is a straightforward indication to institute a night ventilation and should be identified in any patient with rigid spine syndrome (even in ambulant patients), particularly if FVC is <60% in supine position and always when there is an unexplained loss of weight or when there are clinical signs of hypercapnia (morning headaches, somnolence). In young children, poor recovery of weight after banal infections or recurrent hospitalizations should alert of respiratory fatigue which may remain hidden if explored only in periods without intercurrent infections. Blood gas samples at night or just before awakening allow to detect hypercapnia. Diurnal blood gas analysis may show normal pCO_2, but increased bicarbonate levels as a sign of ventilatory pump failure during the night. Currently, technical improvements in oxycapnographic portable devices allow a quite good quality of night/sleep non-invasive recordings at home, making it easier to regularly survey the presence of hypoventilation in a natural environment. However, these devices do not allow distinguishing the origin of the hypoventilation (ventilatory pump failure, obstructive apnoea, or reduced respiratory drive). In selected patients with unclear results, complete poly(somno)graphic studies will be needed at the hospital facilities.

Innovative Therapies and Technical Developments in NMD

NIV continues to progress, both in terms of machines and ventilation interfaces, allowing the effective assistance of increasingly ventilator-dependent patients. On the other hand, neuromuscular diseases are currently undergoing a true therapeutic revolution. Therapies based on pharmacogenetics and gene therapies are providing convincing results in certain degenerative and lethal diseases (SMA, ALS, DMD, Pompe, thymidine kinase 2 [TK2] mitochondrial myopathy), changing vital and functional prognosis in these patients, particularly when administrated from early stages of the disease. These developments require adjusting respiratory treatments and open the discussion toward more proactive and preventive approaches to global management, including respiratory support.

In a more global clinical approach, growth-friendly fusionless spinal implants have been developed in the last decade and allow spinal stabilization from the prepubertal age. This is a major progress because these implants without vertebral fusion allow a correction or stabilization of the spine as early as five years of life and are the only solution in case of impossibility to control the spinal deformity by other means (fast progression of the scoliosis in spite of orthopaedic treatment, poor tolerance of trunk braces). They are significantly less invasive, less complex technically and therefore reduce the time of recovery and the risk of serious complications compared with previous fusion techniques (vertebral arthrodesis) improving the quality of life of patients and families.

Set-Up and Follow-Up of Home Ventilation

Once the indication for mechanical ventilation is established, repeated visits through a variable time may be required to propose, try, and select the optimum interfaces, devices, and settings. Initiation of home ventilation is mostly performed in a hospital with specialized environment including a multidisciplinary therapeutic team comprising medical expertise in neuromuscular medicine, respiratory medicine, rehabilitation, and palliative care as well as respiratory therapy, nursing, speech and language therapy, physiotherapy, occupational therapy, social service, assistive technologies, and augmented and alternative communication, in a best-case scenario. Educating and training patients and caregivers regarding the use and technical aspects of mechanical ventilation is mandatory in to achieve best possible adaptation of ventilation at home.

NIV is the first-line mode of treatment[25,129,144,145]. The main purpose of mechanical ventilation is to correct hypoventilation. Nocturnal NIV treatment for NMD has been reported to improve symptoms (fatigue, dyspnoea, daytime hypersomnolence, and morning headaches) as well as gas exchange[53,146–148]. Volume-controlled ventilation was the first mode used in the neuromuscular population as it was initially the only ventilation mode available for long-term ventilation. But the development

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and improvement of pressure-controlled or pressure-support modes over the past three decades have led to an increasing use, and they have become the preferred mode upon ventilation initiation[149,150]. Generating a flow curve closer to spontaneous breathing cycles, they are more comfortable during the initiation period even though the delivered volume is not fixed[151]. Over time, volume-controlled ventilation use has been mainly limited to ventilator-dependent patients[152]. While there is only weak evidence comparing both modes, they are both efficient in correcting hypoventilation[153,154]. Ventilatory inspiratory support needs to be titrated to normalize $PaCO_2$ values[25,144,146]. If the patient feels comfortable when hypocapnic, hyperventilation is acceptable, as there is no evidence of dangerous sequalae of hypocapnia. Expiratory pressure will depend on the presence of obstructive sleep apnoea shown in the initial sleep studies or upper airway obstructions persisting or emerging under NIV therapy. Backup respiratory rate will be adjusted to the severity of respiratory failure and the level of dependency of the patient, but generally should respect the physiological range of 12/min to 19/min and respect the comfort of the patient. Monitoring of blood gases will be necessary to assert ventilation efficiency. Overnight transcutaneous capnography is strongly recommended in neuromuscular patients, but, less ideally, oximetry is also useful in monitoring ventilation efficiency at home and its capacity to normalize nocturnal ventilation[155–158]. These monitoring tools may replace poly(somno)graphy, which brings more information but is less accessible. Built-in monitoring programs of ventilation devices are also useful in the evaluation of ventilation efficiency, patient–ventilator synchronization, air leakages, and upper airway obstructions under NIV; their study may help to adjust ventilation parameters[159–161]. However, in case of persistent hypoventilation despite actions to correct ventilation efficiency, full sleep studies may be required to study the underlying mechanisms leading to ventilation failure, which may be, for instance, leaks, insufficient support, or persistent obstruction[159,162].

Different types of interfaces can be considered, although nasal masks are usually preferred upon treatment initiation, especially in patients with severe motor dysfunction[144]. Nasobuccal masks can also be used, especially in case of serious mouth leaks, compromising ventilation efficiency; however, recent evidence suggests that they may promote an increase in apnoeic events[163,164] and should not be used in patients without upper limbs mobility, when there is no constant supervision. In the latter, the patient may not be able to take the mask off in the event of vomiting or intense coughing, which carries a risk of asphyxia.

In case of persistent hypoventilation, for patients who have elevated $PaCO_2$ despite adequate nocturnal therapy, dyspnoea during daytime, and/or hypoxemia due to recurrent respiratory infections, daytime ventilatory support may be needed in order to increase treatment duration[146,165,166]. Often, nasal masks are used, when the patient is awake, as this facilitates nutrition and communication, while nasobuccal masks are used at night. The use of mouthpiece ventilation has been an important alternative in ventilation interfaces, providing efficient ventilation and allowing prolonged efficient ventilation during daytime[166,167]. The availability of various NIV interfaces has enabled the use of NIV in patients, delaying and even avoiding tracheostomy and invasive ventilation. Over the past two decades, the indications for invasive ventilation have declined and have become restricted to failure of NIV, inability to wean invasive ventilation, and situations where bulbar dysfunction impairs NIV modalities or when uncontrolled aspiration is occurring[25,167]. NIV is unanimously considered the first-line treatment of NMDs with respiratory failure. Chapter 11 is dedicated to continuous non-invasive ventilatory support.

Particularities in Home Ventilation at the Paediatric Age

Ventilation in the child is complex for different reasons. The child has a dynamic growing body, and therefore, even for the same disease, clinical pictures and solutions can be very different depending on the age, the period of the disease, and its severity. Any paralytic impairment of the respiratory muscles before four years of age (i.e. during the period of alveolar multiplication) will lead to pulmonary hypoplasia. It is therefore necessary to have a preventive approach in congenital pathologies. Growth of the pulmonary tree continues until the second decade by increasing the diameter of alveoli and bronchi[168]. As a result, proactive ventilation (e.g. in SMA) or daily sessions of thoraco-pulmonary expansion by intermittent positive pressure breathing therapy (IPPB alpha 300 device or similar) are beneficial in the short and long term in children with congenital diseases[169,170]. This is particularly true in cases of flat and stiff thoracic cage due to intercostal muscles contractures, such as congenital muscular dystrophies or spinal muscular atrophy. The

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use of mechanical insufflation–exsufflation is also beneficial to improve coughing[171,172]. Bulbar weakness, gastrointestinal dysfunction, and abdominal weakness or reduced muscle tone are very frequent in infants and lead to cough deficit, gastroesophageal reflux, and swallowing disorders, including aspiration of saliva. These factors can make it difficult to initiate NIV. Recurrent upper airway infections during the first years of life also lead to upper airway obstruction. Finally, development of pulmonary hypotrophy, scoliosis, and stiffness of the thoracic cage may further complicate ventilatory assistance. An abdominal wall support with an elastic belt and relatively high inspiratory pressures may be needed, the latter possibly causing abdominal discomfort due to air leaking to the digestive tube. Enteral nutrition by nasogastric tube can also hamper adequate ventilation. As mentioned, nasobuccal masks are not recommended in young children or if the upper limb function is severely impaired due to the risk of aspiration if they cannot take off the mask in the event of vomiting.

The development of new turbine ventilator machines with different modes, technology, and monitoring comparable to resuscitation ventilators, even if the interfaces for young children remain limited, facilitates ventilation at an early stage. The development of instrumental tools for the elimination of tracheobronchial secretions is also an essential aid in the respiratory care of children with neuromuscular diseases. The objective of the respiratory management of children with NMDs is threefold: (1) ventilatory support, (2) increased coughing, and (3) recruitment of lung volume. The ventilatory support assists the function of weak respiratory muscles and stabilizes gas exchange; increased coughing improves cough flow and promotes the elimination of secretions; and lung volume recruitment aims to avoid functional decline due to atelectasis and contractures of the chest wall[173,174]. Ventilation by tracheostomy was the standard treatment for patients with prolonged or complete dependence on ventilation and for those whose decluttering was impaired due to weak cough. However, the combination of nasal or oral ventilation with cough-increasing strategies has made this option unnecessary for the majority of cases, except for those with advanced bulbar disease or brutal unexpected respiratory failure such as the myasthenic syndromes[175]. It should be noted that in children NIV is generally set with pressure modes because it allows better compensation for air leaks. However, it is essential to reach an exhaled tidal volume of 8–12 ml/kg or to use pressure modes with the possibility of setting a guaranteed volume. Leaks should also be monitored and stabilized. In acute respiratory failure in patients with NMD, NIV and intensified management of secretions with cough augmentation techniques should be initiated. Importantly, NIV should be considered in patients with NMD who present with acute illness and tachypnoea (respiratory rate >20/min), even in the absence of hypercapnia, especially in those with known FVC <1 L or <40% of normal values[176,177]. Adequate hydration should be ensured and the clinician should have a low threshold for administration of antibiotics, especially when there is a high likelihood of underlying lung infection[178]. The role of NIV associated with mechanical insufflation–exsufflation was investigated in a prospective, uncontrolled study of 15 children with NMD with 16 episodes of acute respiratory failure due to pneumonia treated in a paediatric intensive care unit. Intubation could be avoided in 75% of the episodes despite a mean baseline $PaCO_2$ of 73 mmHg[179]. Nevertheless, whenever there is failure of NIV and of secretion management strategies (e.g. due to severe upper airway obstruction, craniofacial abnormalities, or impaired consciousness), invasive ventilation should not be delayed.

Of note, the inhaled equimolar mixture of oxygen and nitrous oxide for minor interventions should be used carefully in children with NMD because it may trigger acute respiratory failure, particularly in those who have diaphragmatic weakness, unless a mechanical ventilatory support is provided with monitoring of vital signs and ICU availability. Also, using oral sedative and muscle relaxant drugs in young children should be discouraged.

Non-neuromuscular causes of respiratory failure should be explored in children suspected of suffering from a neuromuscular disease when abnormal sleep studies are obtained in the context of normal respiratory function during the day. Obstructive apnoea in the paediatric patient may be due to enlarged tonsils or anatomical deformities (facial or maxillary abnormalities, retrognathia, Pierre–Robin sequence, macroglossia) requiring treatment by an otorhinolaryngologist. Central respiratory failure may also occur due to central nervous system abnormalities, including brain stem and cervical spinal cord or upper motoneuron dysfunction. In the presence of central apnoea, an arrest of respiratory drive in sleep (Ondine syndrome) should be ruled out by molecular analysis of the *PHOX2B* gene. Chapter 20 provides further insight into respiratory issues in children with NMDs resulting from different aetiologies.

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Intensive Care of Neuromuscular Patients

Treatment in the ICU may become necessary for severe NMDs for a number of reasons, amongst which progressive focal or generalised weakness requiring ventilatory support is leading. In Chapters 4 and 5, respiratory regulation and the mechanics of the respiratory pump are discussed in depth. The specifics of particular NMDs may affect the way respiratory compromise occurs during the disease course (i.e. as an early presentation or late in advanced disease), which aspects of neuromuscular respiratory function are predominantly affected (i.e. upper airways, diaphragmatic function, or coughing and airway clearance), and prognosis (whether return to the previous level of function can be achieved, or whether long-term respiratory support will be the outcome), and treatment. Understanding both the basic principles of respiratory involvement in NMDs, and the specifics of the individual disorder can help achieve the best possible outcome and quality of life for the patient.

For practical purposes it may be helpful to separate disorders where severe respiratory compromise can occur during the initial manifestation or early during the clinical course (sometimes before the diagnosis is established), from those where respiratory failure is feature of the advanced progression of generalised weakness. A third category comprise NMDs arising as a complication of a critical illness and treatment in the ICU.

The most common representatives of the first group are inflammatory autoimmune NMDs such as GBS, AIDP, MG, and IIMs; toxic neuropathies and myopathies, either through drugs, environmental toxins, or, more frequently in certain geographical regions, envenomation, account for the rest. In the second group, degenerative or genetic disorders such as ALS or various muscular dystrophies such as the dystrophinopathies (DMD/BMD) are leading. Respiratory complications in metabolic NMDs such as the glycogenosis or mitochondrial disorders can occur at various stages of the disease, depending on the exact diagnosis, for example regarding GSD 2, Pompe disease. The third group arise during ICU treatment and include the syndrome of ICU-acquired weakness with critical illness neuromyopathy (critical illness polyneuropathy and critical illness myopathy) and neuropathy or rhabdomyolysis due to toxicity of drugs used in the ICU.

GBS and Its Respiratory Management in the ICU

GBS has an estimated incidence of 1–2 per 100,000 people per year in Europe and North America and possibly higher in other regions[180–182]. Seasonal fluctuations may occur and incidence rates have increased markedly in association with some epidemics, for instance Zika virus in South and Central America[183]. The risk of GBS related to COVID-19 may be elevated, although this is debated; vaccination can also increase the incidence of GBS. The pathogenesis is an immune reaction against Schwann cells or axonal antigens causing demyelination (AIDP) more frequently than axonal damage (acute motor axonal neuropathy or acute motor sensory axonal neuropathy) or damage to the region of the Ranvier nodes (paranodopathy). GBS is frequently triggered by an infectious agent, for instance *Campylobacter jejuni* infections, cytomegalovirus, hepatitis E virus, *Mycoplasma pneumoniae*, Epstein–Barr virus, and Zika virus[182–185].

The main symptom of GBS is weakness, which progresses within two to four weeks most commonly, with areflexia and often accompanied by neuropathic or radiculopathic pain and paraesthesia[186]. Weakness is most often first noticed in large proximal muscles, and facial and ocular weakness develops in more severe cases. Dysphagia and laryngeal weakness carry a high risk of aspiration. Sensory deficits are usually minor or absent. The Miller Fisher syndrome with ophthalmoparesis, ataxia, and areflexia rather than limb weakness is the best-known variant of GBS[187]. Pure motor, pure sensory, paraparetic, pharyngeal–cervical–brachial, and bilateral facial palsy variants occur.

The autonomic nervous system is frequently involved, and particularly in severely affected patients this can cause cardiac dysrhythmia, labile blood pressure, and sensitivity to drugs (e.g. excessive reactions to beta-blockers with bradycardia) as well as gastroparesis, adynamic ileus, urinary retention, and fever. Posterior reversible encephalopathy syndrome is a rare central autonomic complication. Stress due to respiratory failure with sympathetic overdrive can cause life-threatening complications.

The differential diagnosis includes other acute NMDs and causes of the "acute flaccid paralysis" syndrome: neuromuscular transmission disorders (MG, botulism, and organophosphate poisoning or in tropical regions, snake bite), myopathies (particularly rhabdomyolysis, inflammatory muscle disease, toxic and metabolic

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myopathies), spinal cord and anterior horn cell diseases such as West Nile virus infection, transverse myelitis, and spinal cord infarction or compression.

The clinical diagnosis of GBS is supported by cerebrospinal fluid (CSF) findings. CSF analysis typically shows increased CSF protein without significant associated pleocytosis in >80% after seven days. Marked pleocytosis (>50 cells per mm^3) is very atypical for GBS and should prompt thorough investigation for other aetiologies[188,189]. Early electrophysiological testing is primarily important to exclude alternative diagnoses such as vasculitic neuropathy or acute myopathy, and its sensitivity to positively identify demyelination or axonal damage is limited in the first two weeks. MRI scanning of the whole spine is usually performed in order to exclude compressive disease or inflammation of the spinal cord early on.

The initial question in the management of GBS is whether it should be managed on a general ward, or in the ICU. Severe progressive weakness (for instance patients who become unable to walk within 7 days of onset), the presence of oropharyngeal weakness with impaired airway clearance, evidence of significant respiratory weakness, or cardiac dysrhythmia or significant autonomic complication all strongly support ICU admission. The "20-30-40 rule" provides a strong indication for ICU treatment according to respiratory values[182,185,190]. With values <20 ml/kg VC, a MIP <-30 cmH_2O, and MEP <40 cmH_2O, intubation with ventilation will likely be necessary. Intubation must be performed with caution, as autonomic involvement may cause severe vagal reactions. Prolonged ventilation is often necessary, which means that tracheotomy is often required and does not need to be delayed in the hope of an early turnaround unless there is early rapid improvement.

Myasthenic Crisis and Unstable Myasthenia Gravis

In the unstable MG patient, reliable documentation of the patient's trajectory is key for early recognition of the need for ICU monitoring. Use of a pragmatic score such as the Myasthenia Composite Score[191] for assessment of fatiguing may improve reliability, but requires training. Patients with oropharyngeal and neck weakness often also have failure of respiratory muscles, and both neck flexion and extension need to be tested. Bedside respiratory assessment is crucial for recognising impending danger. Testing is similar to respiratory monitoring in GBS as described previously, but it must be stressed that the salient feature in MG is fatiguing, which is not easily captured by typical respiratory tests; retesting may be needed at short intervals, and if in doubt, admission to the ICU is prudent.

Myasthenic crisis was said to occur in 15%–30% of patients with MG but has become much less frequent now[192]; it is more common in the first two to three years of illness but may occur later. If MG crisis is the first presentation of MG, mild symptoms have been present for many years but overlooked and in other cases, the diagnosis comes to light during intercurrent illness or postoperatively. Patients with MuSK MG may be more prone to develop myasthenic crisis because of the predilection for oropharyngeal and respiratory muscles[193]. Myasthenic crisis may develop when diagnosis and treatment are delayed, or despite treatment when there is a specific precipitating cause, such as infection (>30% of cases)[194]. Medication errors such as pyridostigmine dosing mistakes, incautious initiation of drugs with neuromuscular blocking action such as aminoglycosides and some other antibiotics or high-dose IV corticosteroids, surgical procedures (particularly extensive thoracic or abdominal surgeries affecting respiratory mechanics), pregnancy, and sometimes even emotional stress are other precipitating factors[195]. Warning signs of impending myasthenic crisis include rapidly progressive weakness, difficulty with speech and swallow and head drop. If impending crisis is recognized in time, rescue treatment with intravenous immunoglobulins (IVIGs) or plasma exchange (PLEX) may ward off full MG crisis.

In the ICU, the patient should be intubated if in doubt. If oropharyngeal function is preserved, initial non-invasive BiPAP via mask may avoid intubation, as MG crisis may sometimes be controlled rapidly[196]. Medications with the potential to impair neuromuscular transmission should be avoided as far as possible, such as beta blockers given for tachycardia, or numerous commonly used antibiotics such as vancomycin. Usually, the need for ventilatory support in MG follows weakness of diaphragmatic or accessory respiratory muscles, but mechanical ventilation also may become necessary because of airway collapse from oropharyngeal muscle weakness, stridor from vocal cord weakness[197], or the inability to clear secretions. Patients may have been overdosed with cholinesterase inhibitors causing excessive salivation and sweating, abdominal cramps, and urinary

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urgency, and propantheline or glycopyrrolate can be used against cholinergic side effects. Pyridostigmine can be discontinued initially once the patient is ventilated but is reintroduced gradually for weaning. In a ventilated patient it is feasible to start corticosteroids in high doses such as 1 g intravenous methylprednisolone, then 100 mg oral prednisolone. The benefit of thymectomy becomes significant only after months, so it is not commonly performed while the patient is unstable, but when there is an occult thymoma the situation is different, and that must be considered with refractory crises.

Tracheostomy should not be performed early, as a rapid recovery is possible. Before attempting to wean from the ventilator, in addition to satisfactory treatment of the myasthenic symptoms, there should be no major pulmonary problem or difficulty handling secretions. Weaning can be initiated once VC reaches 25 mL/kg, and the patient achieves spontaneous tidal volumes of 10 to 12 mL/kg. Weaning methods can include BiPAP with daily small decreases in positive pressure support, or intermittent mandatory ventilation with gradual reduction in the mandatory frequency, or T-piece trials. Extubation success is hard to predict: secretion volume, whether the patient is comfortable with a T-piece trial, and a completely normal chest X-ray, have some predictive value for successful extubation, as does MIP exceeding -50 cmH_2O and VC improvement by 4 mL/kg from pre-intubation to pre-extubation, but nevertheless, repeated extubation failure is common[198]. Repeated failure does not imply "futility" and re-intubation should not be denied.

The mortality rates published for myasthenic crisis have declined to $<5\%$ in the twenty-first century as a result of timely treatment[199]. However, mortality in UK ICUs was still found to be 8.7% overall, and acute hospital mortality after an ICU stay from myasthenic crisis reaches 22%[200], which indicates the importance of continued close monitoring after step-down from the ICU. There must be a strategy for adequate long-term immunosuppression as repeated rescue treatment with IVIG and PLEX will seldom achieve lasting stability. Intermittent scheduled IVIG or repeated PLEX, can be a strategy to bridge until an adequate effect is achieved through second line immunomodulators. The recently introduced complement inhibitor, eculizumab, has been approved for refractory MG and has a more rapid onset of effect, but long-term experience in myasthenic crisis is limited[201]. Its analogue ravulizumab was also approved in several countries with a longer half-life and the advantage of less frequent applications[202]. Efgartigimod, an FcRn antagonist (neonatal Fc receptor antagonist), was also recently approved for myasthenia gravis[203]. Experience of the new drugs in the ICU setting is still limited.

Respiratory Failure in Idiopathic Inflammatory Myopathies

Muscle inflammation can cause weakness of respiratory muscles, leading to dyspnoea and respiratory failure, and has frequently been described in rapidly progressive immune-necrotizing myopathy and immune checkpoint inhibitor associated myositis[100]. Respiratory muscle function should be routinely tested. Interstitial lung disease (ILD) also needs to be considered in patients with IIM and respiratory failure, as well as specifically tested when ASS, MDA5-associated IIM, and overlap myositis are suspected. Broncho-alveolar lavage can help rule out other diagnoses. If ILD is suspected, high-resolution CT of the lungs is needed. ILD features bilateral, predominantly lower field ground glass attenuation and alveolar condensation, lung fibrosis, and mediastinal lymphadenopathies[39].

Immunosuppressive treatment with corticosteroids and a steroid-sparing agent is the cornerstone of treatment in all IIM, except IBM. In addition, PLEX and IVIG can be used. Randomized clinical trials are not available, but there is consensus to start a steroid-saving immunosuppressant drug early on, particularly in the presence of respiratory problems. Mycophenolate mofetil or tacrolimus is initially most often used; azathioprine is less favoured as it has a more delayed onset of effect[204,205]. Methotrexate can cause lung injury, that is, pneumonitis, and this drug should be used with caution[206]. Respiratory weakness, or the presence of ILD often requires an escalation, for instance to high-dose intravenous steroid treatments, as ILD, particularly in anti-MDA5 positive patients, can progress very fast and is often refractory to standard immunosuppressive treatment[204]. With severe respiratory impairment, whether through ILD or purely due to severe weakness as in anti-signal recognition particle related immune-necrotizing myopathy, escalation to cyclophosphamide, or more often, rituximab is required[207].

ILD in ASS most often responds to immunosuppressive therapy, but often recurs in the clinical course. If the pulmonary status is severe, lung transplantation should be considered in consultation with a lung transplant specialist and may be an option when progressive decline in pulmonary function occurs despite adequate immunosuppressive treatment[208].

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Table 18.6 Neuromuscular diseases in adults that can initially present with acute respiratory failure – genetic background and clinical characteristics

Neurogenic disorders that may present with acute respiratory failure	
Variants of CMT	CMT2A (MFN2 mutations), CMT2C TRPV4): stridor and diaphragmatic failure; CMT4A (GDAP1); CMT4B1 (MTMR2); and HMN6-SMARD1 (IGHMBP2)
Acute intermittent porphyria	Rare presentation as acute neuropathy
X-linked SBMA Kennedy	Respiratory failure, laryngospasm, dysphagia, or aspiration pneumonia
ALS	10% of ALS present with respiratory symptoms
Myopathies that may present with acute respiratory failure	
Titinopathy "HMERF"	Type 1 (2q24–31 Titin R279W mutation): FN3 119 domain of exon 343; Type 2 (2q21)
Myofibrillar myopathies	Desmin (cardiac), αB-crystallin (cataracts), Myotilinopathy
Limb-girdle muscular dystrophy	Calpainopathy (LGMDR1/D4); Fukutin-related (LGMDR9); COL6 (LGMDD5/ Bethlem) – respiratory more often late features
Oculopharyngodistal myopathy	OPDM1 (LRP12; 8q22.3)
Congenital myopathies	Nemaline rod (ACTA1 mutations 1q42: Asn115Ser; Gly268Cys; Ile136Met; MYPN); TPM3/SEPN1 centronuclear and cap myopathies; myotubular myopathies (MTM1)
Metabolic neuromuscular diseases	
Glycogen storage disorders	GSD 2 (Acid-α 1,4-glucosidase = Pompe); GSD 3 (Debrancher):
Lipid storage disorders	Rhabdomyolysis with CPT2 deficiency, VLCAD and MCAD
Mitochondrial myopathy	Often multisystemic features, PEO, and CNS involvement

ALS, amyotrophic lateral sclerosis; CMT, Charcot Marie Tooth disease; GSD, glycogen storage disorder; HMERF, hereditary myopathy with early respiratory failure; MCAD, medium-chain acyl-coenzyme A dehydrogenase; PEO, progressive external ophthalmoplegia; VLCAD, very long-chain acyl-coenzyme A dehydrogenase deficiency.

Early Respiratory Failure in Chronic Neuromuscular Diseases

Some chronic NMDs with gradually progressive muscle weakness may have a predilection to involve respiratory muscles early in the course before limb weakness is severe or disabling, as with specific genetic variants of degenerative neuropathies or myopathies. Others can rapidly decompensate in situations such as infection or metabolic compromise, which particularly occurs in the metabolic disorders caused by defects of enzymes involved in muscle energy metabolism. Table 18.6 shows conditions in which this is particularly likely and gives an overview of NMDs in adults that can initially present with acute respiratory failure, or early in the course.

Respiratory Problems in Metabolic NMDs

Respiratory problems may develop in the advanced stages of a metabolic myopathy. However, even before there is marked generalized weakness, emergency situations and in particular respiratory failure may be caused by metabolic decompensation due to intercurrent illness and infection, nutritional compromise (fasting, dietary errors), or unaccustomed physical exertion.

In contrast to muscular dystrophies, metabolic myopathies often do not cause permanent structural muscle damage, at least for a long time during the course, and may respond well to supportive treatment. In some cases, enzyme substitution is available and in future potentially gene treatment. Hence, on the other hand, non-muscular or systemic complications such as renal failure, cardiac decompensation, or central nervous symptoms may occur particularly with certain genotypes. Therefore, expert input into ICU management with knowledge of risks attached to certain mutations is crucial to avoid complications. Many metabolic treatments are experimental and need to be tailored to the specific mutation.

Respiratory Aspects of Mitochondrial Disease

Patients with mitochondrial disease can be at risk of rapid decompensation that occurs without obvious cause or is due to environmental factors affecting metabolism in muscle, CNS, or other organs. In view of this, people with a mitochondrial disease should have an emergency care plan that identifies their underlying disorder and provides management recommendations and be encouraged to carry a medical alert bracelet if they are at risk. Patients may need ICU treatment and mechanical ventilation for respiratory reasons such as infection or weakness of respiratory muscles, but also on account of central nervous system disease such as stroke-like episodes or status epilepticus. ICU treatment and critical care require special knowledge of metabolic pitfalls, including

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potentially toxic medications commonly used in the ICU, and treatment options that may be specific to one individual genotype. The Newcastle Mitochondrial Disease Clinical Guidelines provide expert guidance to health professionals about the management of various aspects of mitochondrial disease using consensus expert opinion, available online[209]. Parikh et al. formulated consensus recommendations and treatment standards for primary mitochondrial disease, including recommendations for management in critical care[210]. Chief among these are precautions to prevent entering catabolism, especially when exposed to medical stressors, including avoiding prolonged fasting with nutritional support within 48 hours after admission, and receiving dextrose-containing IV fluids around procedures and surgeries. Treatment during acute decompensation should include dextrose-containing IV fluids, avoiding exposure to potentially toxic medications such as sodium valproate, and correction of any metabolic derangements. Mitochondrial therapies, including supplements and cofactors, should be continued in the ICU. The risk of renal, cardiac, or central nervous system involvement must be considered, and imaging obtained at admission and when the clinical condition changes.

Acute Respiratory Failure in ALS and Adult Spinal Muscular Atrophies

Emergencies in ALS are most often related to oropharyngeal and respiratory muscle weakness. Anticipation of the potential complications and discussion of preferred treatment options with the patients are crucial. One concern to bear in mind if embarking on invasive treatment is that the rapid overall progression of weakness in ALS makes it very difficult to achieve the previous level of function after intensive care treatment for a complication such as severe pulmonary infection. Advance directives can help guide decision making, even though patients can change their view on treatment options along the course.

Respiratory muscle weakness can present with shortness of breath upon physical activity and later at rest and nocturnal hypoventilation with morning headaches and daytime fatigue. Respiratory monitoring early on may detect the signs of developing respiratory insufficiency and helps to enable an informed discussion of therapeutic options before an emergency arises. NIV has been shown to prolong survival and improve the quality of life in patients with ALS[135,211], but is less well tolerated in the presence of oropharyngeal weakness where secretion management is a particular problem[212]. The decision whether to perform tracheotomy when NIV is not feasible is difficult, and practice varies between countries. The patient's decision whether or not to mechanically assist ventilation, either as NIV or tracheostomy invasive ventilation, should be documented in advance life directives. Ideally, a management plan should be in place before the respiratory complications occur, but respiratory failure cannot always be anticipated.

Laryngeal and oropharyngeal dysfunction can cause aspiration, choking, laryngospasm, and stridor. Vocal cord dysfunction causes stridor and glottic narrowing, which is distressing and may even become life-threatening. Laryngospasm occurs in 2% of ALS patients, causing sudden brief attacks of dyspnoea, often accompanied by inspiratory stridor[213], triggered by aspiration coughing, smoke, cold air, or gastroesophageal reflux. Antireflux therapy and benzodiazepines can be used to reduce the frequency of episodes of laryngospasm. Non-pharmacological techniques to manage such attacks at home are important, and include rapid upright positioning, breathing through the nose, swallowing repetitively, and breathing with slow exhalation through the lips[214]. Vocal cord dysfunction causes stridor and glottic narrowing, which may be distressing or, rarely, even life-threatening. Severe therapy-resistant vocal cord dysfunction can be treated with laser cordotomy, or tracheostomy can be considered.

Respiratory Failure in Advanced Genetic Myopathy and Muscular Dystrophies

Advanced muscular dystrophies and genetic myopathies can affect all major respiratory muscles, and respiratory support is often needed in chronic NMD. Long-term mechanical ventilation is the main therapeutic intervention and increases life expectancy and health-related quality of life[130,215,216]. In principle, this is similar to rapidly evolving conditions such as ALS, but with many muscular dystrophies, muscle weakness and disability have been present for many years or lifelong, and respiratory muscle weakness has developed very slowly. In muscular dystrophy yhis makes it easier for appropriate follow-up to identify when respiratory muscle weakness is developing, and a management plan can be agreed and implemented stepwise. Timely application of techniques for airway clearing, such as air stacking, use of

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cough assist machines, and nocturnal mask breathing, can help substantially extend the time until more invasive techniques such as mask ventilation by day or tracheotomy and invasive ventilation might be needed. If acute treatment in the ICU for intercurrent illness is necessary, there is a reasonable chance for the patient to re-achieve their previous function and quality of life afterwards.

Practical Management of Acute Respiratory Failure

Mechanical ventilation should be considered in a patient with known respiratory muscle weakness at the very latest when dyspnoea, lethargy, or acute respiratory acidosis (pH <7.35 and $PaCO_2$ >45 mmHg) develop[217]. If the patient is already using nocturnal NIV, it may be extended to daytime as well, even to 24 hours if needed and tolerated. Delays in NIPPV implementation increase the likelihood of NIPPV failure[218]. NIV is usually initiated in a specialized unit or high-dependency unit, and knowledge and experience in NIPPV by the staff in mask fitting, minimizing air leaks and providing comfortable initial settings are crucial for success, likewise, patient education and reassurance during the initial process.

Initial settings in most situations are typically in pressure support mode in spontaneous/timed (S/T) setting with a low backup rate of around 10–12 breaths/min. This supports all breaths and provides a minimum respiratory rate. The inspiratory positive airway pressure is usually adjusted upward in increments of 2 cmH_2O as tolerated and needed to improve dyspnoea. A decrease in respiratory rate, increased tidal volume, and good patient–ventilator synchrony indicate the desired effect with reduced work of breathing and improved hypercapnia. Expiratory positive airway pressure may be needed for airways obstruction, but requires caution, starting with an expiratory positive airway pressure of 5 cmH_2O. If it should be increased, one has to take into account that tidal volume will decrease if the inspiratory pressure support remains the same[177].

Emergency department staff unfamiliar with neuromuscular disease sometimes attempt to improve oxygenation by providing CPAP without inspiratory pressure support. This may be tolerated by NMD patients with better preserved respiratory muscle reserves whose admission is due to infection. However, the overall effect is to increase the work of breathing, which may lead to rapid decompensation in a patient with weak inspiratory muscles. Another common mistake is to provide oxygen without respiratory support, which can weaken the respiratory drive and worsen hypoventilation and hypercapnia, which is overlooked when pCO_2 is not monitored. If low O_2 saturation is due to retention of secretions, cough assist techniques or air stacking are a better choice, and Chatwin et al. presented the available airway clearance techniques and discuss their indications[219].

NIPPV is complicated when patients have difficulty swallowing and controlling secretions despite expiratory aids. Invasive ventilation might be the first choice, although the aim must be to reduce to NIV after controlling infection if it proves feasible. There is no clear evidence base when to prefer either method but there is evidence secretion control with NIV can be increased by cricoid mini tracheotomy to improve secretion management[220].

CONCLUSIONS

Mechanical ventilation and cough augmentation are the cornerstones of respiratory management in patients with NMDs and ventilatory pump failure. The occurrence of obstructive sleep apnoea as well as upper airway obstructions under non-invasive ventilation may not be overlooked. NIV improves quality of life and burden of symptoms without necessarily being required for survival. Especially in progressive diseases such as ALS there is a gradual transition from optimizing quality of life towards supporting life as a goal for NIV during the disease course. Whether patients with severe bulbar impairment in ALS should be treated with NIV remains debated. Tracheobronchial retention of secretions, which are not treatable by non-invasive cough augmentation, are the most important indication for tracheostomy. Respiratory management must be embedded in a holistic, interdisciplinary care concept.

Although the principles of respiratory support in neuromuscular conditions in the ICU are similar, the specifics of the individual neuromuscular condition impact on the choice of techniques accompanying treatment, the achievable outcomes, and the long-term outlook. It is therefore important to have detailed knowledge of the pathophysiology and clinical characteristics of the condition that is being treated and experience in its intensive care management. In exceedingly rare genetic and metabolic disease, close cooperation between the ICU team and the specialist neuromuscular service is essential. All decisions must be undertaken with careful consideration of the quality of life achievable through ICU treatment and desired by the patients themselves.

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Chapter 19

Sleep-Disordered Breathing

Thomas Gossard and Erik K. St. Louis

Introduction

Sleep-disordered breathing (SDB) is a highly prevalent condition that affects over one billion people worldwide[1]. As the prevalence of obesity increases in our aging population, the incidence of SDB is also likely to increase in parallel over the next decades[2]. In the nineteenth century, SDB was foreshadowed in literature as Joe, a character in Charles Dickens' *The Pickwick Papers*[3], exhibited symptoms of obstructive sleep apnea (OSA). At first thought to be a moderate disruption in sleep, leading to snoring, intermittent awakenings, and daytime sleepiness, SDB has now been shown to be strongly associated with severe health outcomes such as cardiovascular disease, stroke, pulmonary hypertension, and even death. Most of those with SDB suffer from OSA resulting from upper airway obstruction during sleep, distinct from central sleep apnea in which the control of breathing in the brain is impaired. Diagnosis is primary made by polysomnography (PSG), with increasing application of lower cost and widely scalable home sleep apnea testing. Treatment typically involves lifestyle management changes first, with a noninvasive positive airway pressure ventilation (NIPPV) machine as the gold standard for effective treatment. Other treatment options for refractory sleep disordered breathing include dental appliances and surgical therapies.

Approach to the Patient with Sleep-Disordered Breathing

There are two primary contexts in which sleep-disordered breathing will present. In the outpatient clinic, information is first gathered by a thorough history and physical exam. Patients will often present at the behest of their bedpartner or caregiver, who complains of loud snoring, snorting, sudden gasps, and awakenings from sleep. Patients themselves may often offer no complaints. Those who are symptomatic present with symptoms of daytime sleepiness in which they inadvertently catch themselves dozing or "nodding off," napping, or alternatively manifesting as progressive fatigue, poor focus, or even cognitive decline. Additionally, they may present with morning headaches, insomnia, and nocturia. On physical exam, patients are typically obese, with a thickened neck circumference (>40 cm), with narrowing of the oropharyngeal airway.

SDB may also present in the inpatient acute care setting. If a patient is hospitalized for an acute stroke or cardiovascular event, SDB as a contributing factor should always be considered. Asking questions regarding sleep habits, snoring, and daytime sleepiness may lead to the diagnosis. A useful bedside screening instrument such as STOP-BANG or Berlin questionnaire (to be discussed in later chapters) or portable overnight oximetry are helpful adjuncts in those with minimal symptoms or an unclear history. In those patients with high suspicion for SDB, a sleep medicine referral for a polysomnogram is highly recommended, as SDB is a treatable risk factor for many cardiovascular and cerebrovascular diseases.

Types of Sleep-Disordered Breathing

Obstructive Sleep Apnea

OSA is characterized by partial reductions or complete pauses in ventilation during sleep due to an anatomically narrowed and dynamically collapsible airway. OSA has a 9%–38% prevalence in the general population[4] and has been increasing due to increasing obesity and improved screening tools. Risk factors for OSA include obesity, male sex, and older age. The pathophysiology of this disease is multifactorial[5]. The primary causes of OSA are anatomical disposition, sleep-induced components, sleep position, and a combination of these that leads to an airway collapse and neurochemical breathing instability[6]. These components are exacerbated during sleep, which is why patients with OSA do not experience

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symptoms of airway obstruction during wakefulness. Humans have been theorized to be particularly predisposed to OSA in contrast to other higher primate species as due to an unattached hyoid bone and longer supralaryngeal tract that underlies the capacity for speech[7]. OSA patients and their family members are more likely to have a smaller oral pharyngeal region,[8] increased airway length[9], short mandibles, inferiorly placed hyoid bones, wider uvulas, higher, narrowed hard palates, and an enlarged tongue compared to controls without OSA. There are also several obesity-related structural changes such as reduced lung volumes from increased abdominal fat mass resulting in reduction of "pull" on the trachea and increased thickness of lateral pharyngeal walls. In addition to the structural changes seen with obesity, there is also thought to be neurofunctional changes with fat depots impacting neural respiratory pathways via humoral and inflammatory mediators. Leptin can act as a respiratory stimulant, so impairment of the leptin signaling pathway in obese states may lead to respiratory depression[10]. Neurorespiratory changes during sleep such as decreased tonic and phasic activity of the pharyngeal airway dilator muscles in nonrapid eye movement (NREM) and rapid eye movement (REM) sleep as well as changes in intrabreath regulation of upper airway caliber are also thought to play a role in OSA pathophysiology[6].

Oropharyngeal airway collapse occurs on a continuum, with the mildest form representing an open airway but turbulence of airflow given partial anatomical obstruction and collapse resulting in snoring due to vibratory motion of the soft palate, which may progress to further incomplete obstruction causing respiratory effort related arousals (arousal related to increased work of breathing, yet with preserved ventilation and oxyhemoglobin saturation) and hypopneas (limited airflow and oxygen desaturation with arousal), and ultimately with airway blockage, apnea. The mainstay of therapy for this disorder is continuous positive airway pressure (CPAP) therapy, which counteracts obstruction by pneumatically splinting the airway. Figure 19.1 depicts the continuum of airway obstruction seen clinically in OSA, and the favorable influence of CPAP therapy in counteracting sleep fragmentation and stabilizing oxygenation.

Central Sleep Apnea

Central sleep apnea (CSA) is caused by a dysregulation of the central nervous system centers that control ventilation[6,11]. It is most commonly secondary to another disease such as heart failure or a central nervous system disorder, as CSA occurs as a primary idiopathic condition in roughly 4%–11%[12,13]. The classification of CSA was originally considered as whether characterized by hypercapnic or hypocapnic central apneic events, but a recent reclassification has been proposed according to the physiology of normal breathing[11]. In general, normal ventilation operates as a closed negative loop in which increased or decreased $PaCO_2$ as detected by chemoreceptors will trigger compensatory hyper- or hypoventilation. In healthy individuals, an alteration of $PaCO_2$ caused by a brief apneic event will be quickly adjusted to achieve homeostatic $PaCO_2$ levels. However, in those with CSA, this process is altered, leading to pathological cycling of apnea/hypopnea alternating with hyperpnea. Two principal mechanistic categories for CSA are recognized, hypercapnic and nonhypercapnic. The nonhypercapnic mechanism for CSA results from ventilatory overshoot, with an exaggerated ventilatory response leading to cyclic periodic breathing patterns of alternating hyperpnea and hypopnea known as Cheyne–Stokes respiration (CSR) that is seen primarily in association with heart failure,[14] but can also be seen in atrial fibrillation due to increased left atrial pressures,[15] concomitant cerebrovascular disease, and high altitude settings. A typical polysomnogram fragment demonstrating CSR, with iterative phasic hypopneas/apneas and hyperpneas in a periodic breathing pattern, is shown in Figure 19.2. Other causes include acromegaly and end-stage renal disease due to increased chemoreceptor sensitivity and fluid accumulation.[16] In hypercapnic states, homeostatic control of $PaCO_2$ is much more difficult based on an isometabolic alveolar ventilation curve. Minor changes in ventilation that occur physiologically in sleep can cause major alterations of $PaCO_2$ leading to SDB and can be seen in hypercapnic states due to alveolar hypoventilation such as the setting of morbid obesity or in neuromuscular or restrictive pulmonary disorders. In another etiology of CSA, the neurons responsible for proper rhythmic breathing may be directly affected. These neurons, known as the pre-Bötzinger complex, have receptors for NK1, μ-opioid, and $GABA_B$ and can be altered by medications impacting these receptors such as opioids or benzodiazepines. This region can also be altered in neurodegenerative states such as amyotrophic lateral sclerosis or multiple system atrophy.

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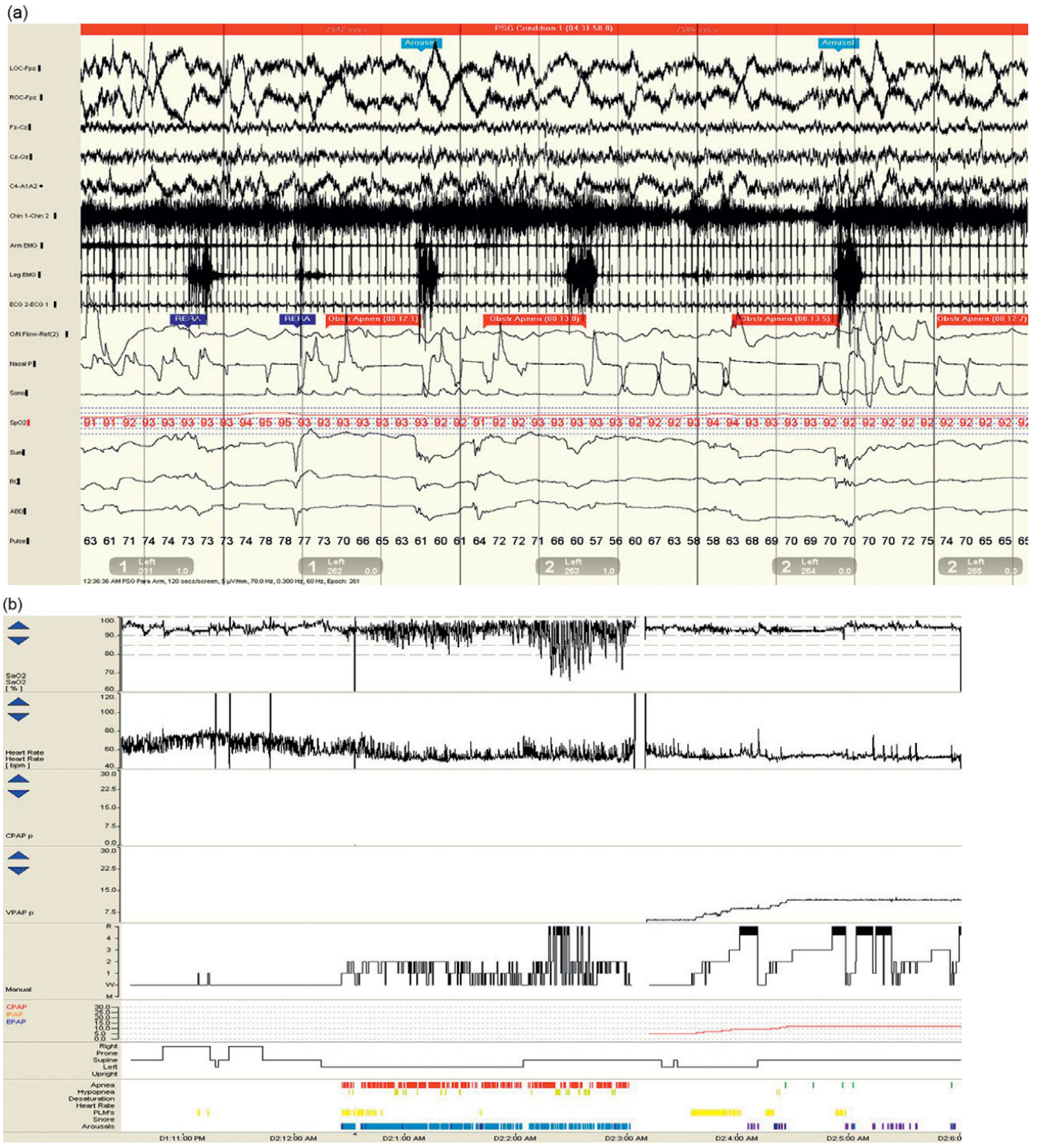


Figure 19.1 (a) 120-second polysomnogram epoch, and (b) hypnogram of a 68-year-old man with severe obstructive sleep apnea during split-night polysomnography. Note in (a) respiratory effort related arousals and obstructive apneas, with features of reduced or absent airflow (channels 10–11) with continued respiratory effort (channels 14–16), before therapy is commenced with nasal continuous positive airway pressure (CPAP). (b) The all-night hypnogram shows the entirety of the split-night polysomnogram. Initially during the diagnostic study portion, there is severe sleep fragmentation, with shallower sleep consisting of unstable N1 and N2 sleep, due to frequent respiratory arousals (as shown in the top panel), with associated frequent oxygen desaturations and heart rate variability. During the subsequent part of the study, nasal CPAP titration was effective in improving the continuity and depth of sleep, with resulting continuous, deeper N3 and rapid eye movement sleep "rebound."

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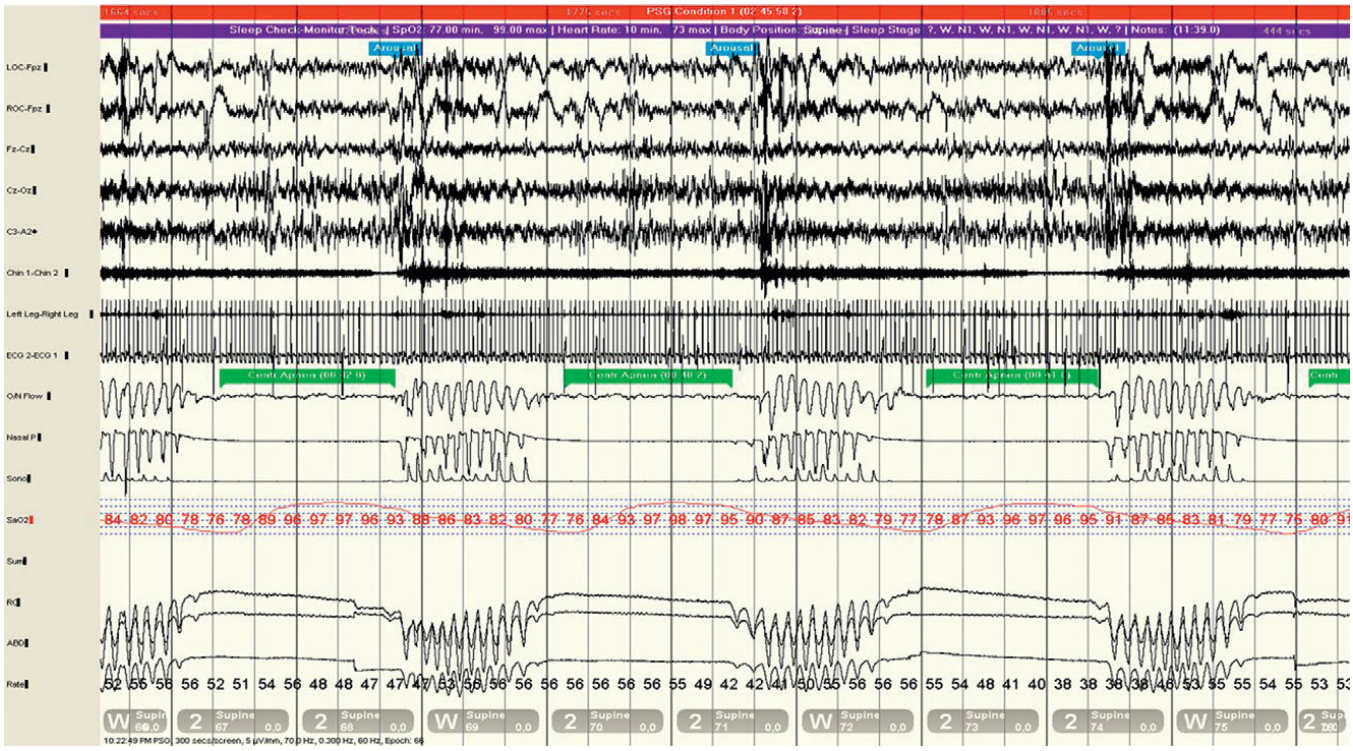


Figure 19.2 Cheyne–Stokes respirations in a 62-year-old man with severe congestive heart failure and central sleep apnea. Note the periodic breathing of phasic apnea and hyperpnea recuring in the airflow channels (9–10) and respiratory effort channels (13–15).

Treatment-Emergent Central Sleep Apnea (Complex Sleep Apnea Syndrome)

Treatment-emergent central sleep apnea (TECA), also known as complex sleep apnea syndrome, was described in 2005[17] as an emergent CSA that appeared following PAP treatment for OSA. In a study of 1286 patients with recently diagnosed OSA who had started PAP, about 6.5% developed TECA[18]. However, most CSA symptoms subsided over the course of 8 weeks, and only 1.5% had TECA after 8 weeks. Risk factors for TECA include severe OSA prior to PAP treatment use of opioids and cardiovascular comorbidity.

Sleep-Related Hypoventilation

Sleep-related hypoventilation (SRH) is described in the *International Classification of Sleep Disorders–Third Edition* criteria by the American Academy of Sleep Medicine[19] as a condition characterized by abnormal gas exchange that worsens with or is present only during sleep[20].

During sleep, especially during REM sleep, there is increased upper airway resistance and decreases in chemosensitivity and skeletal muscle tone, excepting the diaphragm, which may cause hypoventilation with hypoxemia and hypercapnia. Most often, SRH is caused by reduced tidal volume, which may be most prominent during REM sleep, accompanied by oxygen desaturation.

SRH most often erodes sleep quality, has deleterious consequences on normal sleep architecture, and is often associated with decreased sleep quality, nonrestorative sleep, and daytime sleepiness.

A multitude of conditions lead to SRH, including chronic obstructive pulmonary disease (COPD)[21], which when combined with OSA is known as overlap syndrome,[22] Other disorders that may cause SRH include bronchial asthma (which is often worsened at night)[23], respiratory depression caused by polypharmacy (benzodiazepines, barbiturates, etc.)[24], obesity hypoventilation syndrome, and restrictive chest wall disorders. Several neurological conditions that can cause SRH including brainstem tumors, CNS infection, stroke, neurosurgical procedures, spinal cord injury, amyotrophic lateral sclerosis; and neuromuscular disorders such as post-polio syndrome, Lambert–Eaton syndrome, myasthenia gravis and myopathies[25,26]. With progression, neuromuscular disorders

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can lead to compromised ventilatory function during sleep and wakefulness with characteristic abnormalities in waking pulmonary function testing, including decreased forced vital capacity (especially when <50% predicted) and maximal inspiratory and expiratory pressures (with points of concern being thresholds of maximum inspiratory pressure -30 cmH_2O and maximum expiratory pressure 40 cmH_2O, respectively). An awake oxyhemoglobin saturation less than 91% is also suggestive of the need to evaluate for possible SRH. However, neuromuscular weakness may also present with SRH in isolation, so screening portable overnight oximetry and/or PSG to evaluate for possible isolated nocturnal hypoxemia should be considered early in the course of evaluation in a patient with an acute or chronic neuromuscular disorder. Helpful bedside signs of alveolar hypoventilation that may also raise concern for SRH and imminent waking ventilatory failure include orthopnea with tachypnea and abdominal paradox in the supine position, use of accessory respiratory muscles, and brow sweating.

Pulmonary diseases that may lead to SRH include cystic fibrosis, hypersensitivity pneumonitis, and hemoglobinopathies such as sickle cell disease. Finally, congenital central alveolar hypoventilation syndrome, which is likely related to neural crest disorders, may present with varying levels of SRH most often early in life, but rarely in adulthood. Early diagnosis of SRH is key to prevention of morbidity and mortality. Treatment of SRH involves noninvasive positive pressure ventilation, with or without addition of supplemental oxygen.

Screening and Diagnosis of SDB

Questionnaires

Several questionnaires have been shown to be valuable for diagnosing SDB, rapidly confirming suspicion to inform diagnostic testing. The STOP-BANG is among the best rapid SDB screening tools[27], containing eight yes/no questions that address disruptive snoring, tiredness during daytime, observed apneas, high blood pressure, body mass index >35 kg/m2, age > 50 years, neck circumference > 40 cm, and male gender (one point is given for the presence of each positive factor). The initial four factors (STOP) provide excellent sensitivity in detecting OSA, but when adding the other four features (BANG), improved sensitivity with a high negative predictive value for severe OSA was achieved[27,28]. The Berlin questionnaire[29] is slightly more complex and addresses three major categories: presence and frequency of snoring behaviors, waking sleepiness or fatigue, and history of obesity or hypertension. Both scales examine similar clinical characteristics and symptoms. The Epworth sleepiness scale is also available and was developed specifically to determine presence or absence of excessive daytime sleepiness, which can often be a predominant symptom of OSA. A recent meta-analysis comparing all three of these questionnaires determined that STOP-BANG was the most accurate tool for detecting OSA[30].

Oximetry

Portable overnight oximetry can also be a valuable screening tool for SDB in outpatient or hospital settings. During oximetry, fluctuations of oxygenation are systematically measured by the oxygen desaturation index (ODI), the number of desaturation episodes over the course of an hour. Desaturation episodes are most commonly described as oxygenation decreases of at least 4% from baseline lasting for at least 10 seconds. A representative screening portable overnight oximetry study is shown in Figure 19.3. The ODI strongly correlates with the apnea-hypopnea index (AHI) during PSG, the diagnostic gold standard in patients with OSA[31]. ODI is also a strong predictor of OSA with high sensitivity and specificity when measured by home sleep apnea tests, and for detection of OSA in special populations including children, those with neuromuscular disease, and at-risk surgical populations[31]. One study in hospitalized patients found that ODI was highly specific but not sensitive[32]. The future of oximetry in SDB diagnosis is promising, as oximetry has been utilized in several artificial intelligence models to predict OSA[33,34].

Oximetry may also be particularly helpful for screening for SRH in patients with neuromuscular disease, both in outpatient and inpatient settings. Typical findings of SRH include a borderline or low baseline oxyhemoglobin saturation, and further clustered sustained reductions in saturation indicative of REM-sleep related worsening of hypoventilation; a typical representative example of overnight oximetry in a patient with respiratory insufficiency and SRH in the setting of motor neuron disease (amyotrophic lateral sclerosis) is shown in Figure 19.4. Concomitant features of

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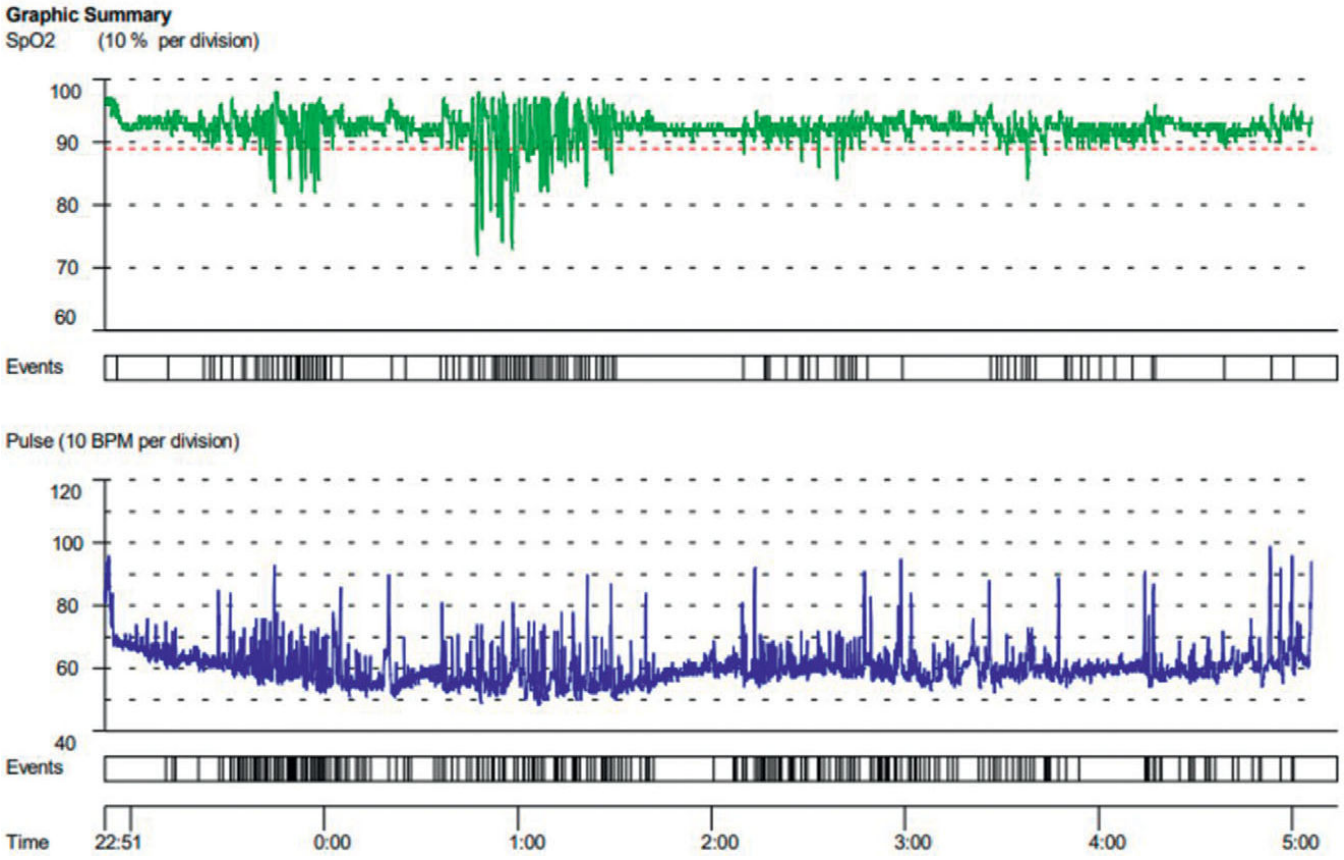


Figure 19.3 Portable overnight oximetry in a 55-year-old man with moderately severe obstructive sleep apnea. The oxygen desaturation index was 18 per hour, consistent with moderately severe obstructive sleep disordered breathing (i.e. estimated stop breathing rate >15 per hour). Note the repetitive oscillatory oxygen desaturations in the top channel (designated SpO_2), while the bottom channel shows corresponding pulse rate instability indicative of likely corresponding repetitive arousal related to untreated sleep disordered breathing. A subsequent home sleep apnea test demonstrated an apnea-hypopnea index also in the moderately severe range at 24 per hour (i.e. >15 per hour, while less than the threshold for severe OSA of 30 per hour). Autotitrating CPAP was prescribed with a pressure range from 5 to 15 cm H_2O, and at one month his sleep quality was improved, and his PAP device demonstrated good control of his apnea (device AHI calculated was 1.1 per hour), with excellent CPAP adherence averaging 7 hours 30 minutes of nightly use. AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.

hypoventilation causing sustained decreases in saturation, combined with oscillatory oxyhemoglobin saturation variability indicative of OSA are frequently seen in patients with neuromuscular disorders.

Polysomnography

PSG is the gold standard for diagnosis of OSA and SDB in general including CSA and SRH, as well as other sleep disorders. PSGs are most often performed in the controlled setting of a sleep laboratory, performed by experienced sleep technicians who affix EEG, electromyography (EMG), electrooculography (EOG), and ECG recording leads, as well as respiratory function measures including airflow (thermistor, nasal pressure sensor), breathing effort (usually determined by chest and abdominal plethysmography), pulse oximetry, and sleep position monitoring. EEG, EOG, and EMG channels are required to determine the correct sleep stage, including NREM sleep (with light sleep stages N1 and N2, and deep or slow wave sleep stage N3) and rapid eye movement (REM) sleep. The staging of sleep is known as "sleep scoring," and this is typically done in 30-second epochs, with the predominant EEG, EOG, and EMG waveform characteristics leading to determination of the stage of sleep. EMG is recorded from the submentalis muscle and the anterior tibialis muscle to determine REM sleep stage, and to measure movements during sleep such as periodic leg movements. Arm EMG leads may also be added to explore REM sleep without atonia as seen in isolated

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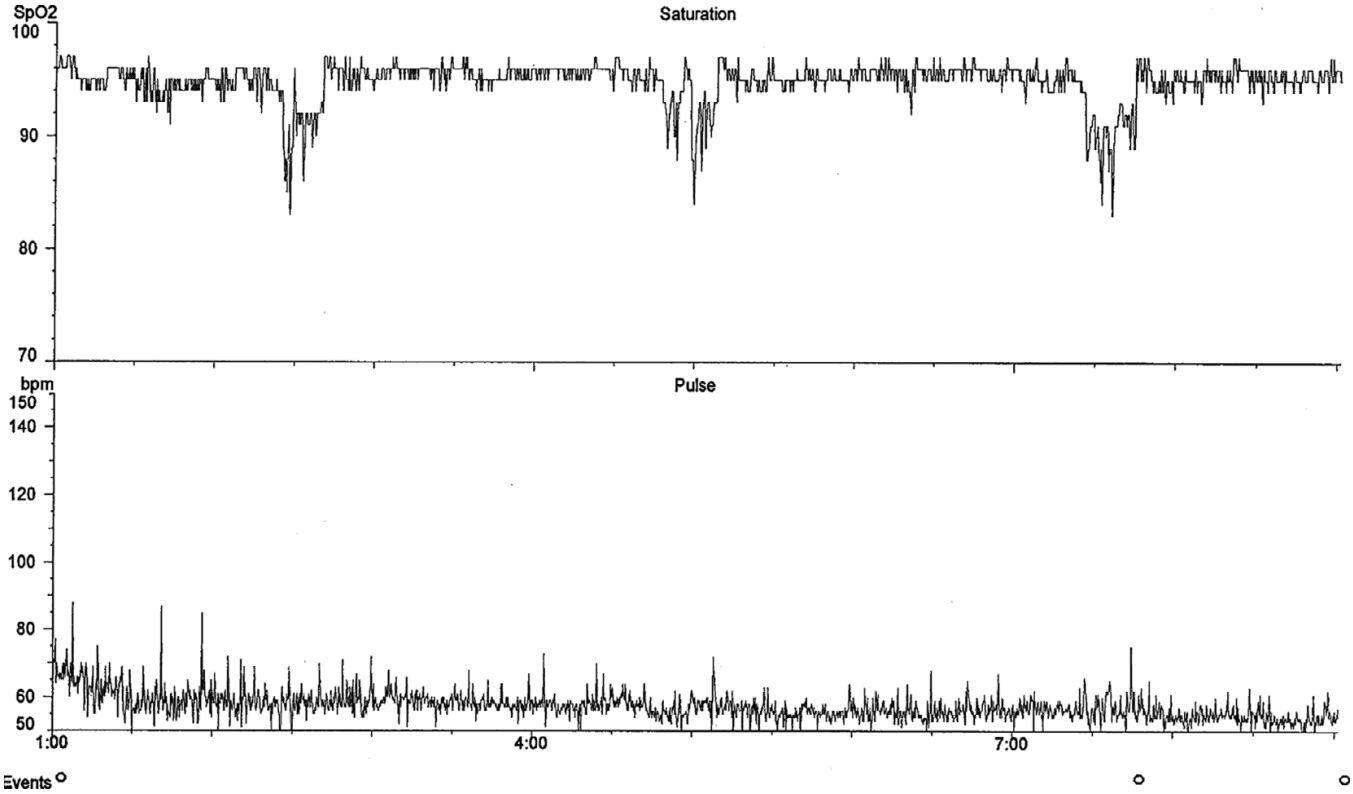


Figure 19.4 Overnight oximetry recording representing a periodic pattern of O_2 desaturation. This overnight oximetry recording (upper trace) over seven hours shows three periodic episodes of O_2 desaturation. The mean O_2 value between episodes is within the normal range. The lower trace represents cardiac frequency. With friendly permission from: de Carvalho M, Costa J, Pinto S, Pinto A. Percutaneous nocturnal oximetry in amyotrophic lateral sclerosis: periodic desaturation. *Amyotroph Lateral Scler*. 2009;10(3):154–61. doi: 10.1080/17482960802382305.

REM sleep behavior disorder which again has a high risk to progress to a neurodegenerative α-synucleinopathy. Respiratory parameters are essential in SDB diagnosis, including oximetry, oronasal airflow measured via the thermistor and nasal pressure sensors and respiratory effort via inductance plethysmography or piezocrystal monitors. Body position can also be monitored, which can be helpful in examining exacerbating positions of SDB, which is typically worse during the supine position. Arousals during sleep can also be determined. Specific patterns of breathing disturbance, oxyhemoglobin desaturation, and arousal can help determine different etiologies of SDB. For SDB, the main parameter of interest is the AHI, the average number of apneas or hypopneas that occur per hour of sleep. Apneas are defined as a complete cessation of breathing or airflow, while hypopnea is a defined reduction in breathing as measured by airflow and oxygenation that occurs in 10-second or longer episodes. The AHI can be used to characterize SDB conditions, such as OSA and CSA. In OSA, an AHI >5 and <15 indicates mild, >15 to <30 indicates moderate, and ≥ 30 indicates severe OSA. PSGs can also assist in the prompt initiation of treatment for SDB, as when criteria for application are met, a PAP trial may be completed during the same night following an initial diagnostic study being completed (known as a "split-night" polysomnogram). In the first half of the study, the patient will sleep per their normal schedule and routine, and the AHI will be determined. If predetermined thresholds for AHI are met sufficiently early in the study (typically, an AHI of 15/hour or greater during first two hours of sleep, with three or more hours remaining to conduct PAP titration), then a PAP treatment trial can be initiated, with titration toward a pressure that eliminates apnea and hypopnea events and snoring to determine treatment efficacy. PSGs can be repeated after periods of treatment to adjust PAP parameters or to evaluate for TECA. PSGs can also assist with characterizing many other sleep disorders such as hypersomnia, REM sleep behavior disorder or other parasomnias, narcolepsy, and many others.

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However, PSGs do have limitations. As the laboratory is an unfamiliar sleeping situation, this may not be the best representation of an individual's normal sleep behavior, limiting sleep opportunity and complicating diagnosis. PSGs are also expensive, and insurance may not always cover this testing. Due to the increased availability and validation of home sleep tests they have begun to replace in-laboratory PSG, particularly when OSA of at least moderate severity is suspected and no significant cardiovascular or neuropsychiatric comorbidity is present.

Home Sleep Apnea Testing

Home sleep evaluation is a rapidly evolving landscape, readily enabling accurate diagnosis of OSA in the home or hospital setting[35,36]. Currently, home sleep testing is typically most efficient and applicable for patients who have a high pretest probability of OSA[37]. Several HSATs are currently available, with differences in terms of the type of data that these provide[38]. Some HSATs provide the same or similar measures as those provided by PSG (EEG, EOG, EMG, ECG, airflow, respiratory effort, oximetry), although most HSATs simply include oximetry and cardiovascular parameters such as ECG, pulse rate, or peripheral arterial tonometry, with or without airflow via oronasal thermal airflow sensor, or respiratory effort. Advantages of HSATs include lower costs, more naturalistic sleep environment, and flexibility of testing. If HSAT is negative for OSA, most often a PSG may then be indicated to evaluate whether mild OSA may be present, since HSAT has a lower yield for detecting mild OSA. Additionally, with HSAT there are several limitations toward comprehensive evaluation for SDB: There are no sleep technicians available to ensure optimal recording conditions or to adjust PAP therapies, and there is no video recording for monitoring of sleep behaviors. HSAT is also not validated for other SDB pathologies beyond OSA, such as in settings of cardiorespiratory disease, neuromuscular disease, suspicion of SRH, chronic opioid medication use, history of stroke, or severe insomnia, so when these comorbidities are present, patients should usually undergo an in-lab PSG[39].

Treatment

Lifestyle Modifications

Lifestyle modifications should be encouraged throughout the diagnostic and treatment process. Weight loss via improving diet and exercise behaviors can help all levels of OSA and at times cure mild cases. Obesity plays a significant role in the pathogenesis of OSA and SRH, both through mechanical obstruction via increased neck circumference as well as hormonal changes from leptin. Interestingly, exercise has been shown to have a moderate treatment efficacy for sleep apnea in sedentary adults regardless of body mass index[40]. Surgical weight loss can also be considered in cases of refractory weight gain; however, SDB may remain despite surgery[41,42]. Emphasizing proper sleep hygiene (i.e. regularity of sleep-wake schedule, ensuring adequate sleep amounts, avoiding caffeine, smoking, and alcohol) can also be effective for management of most sleep disorders.

Positive Airway Pressure

NIPPV is the current first-line treatment for SDB. NIPPV can reduce symptoms such as daytime sleepiness, awakening during sleep, and improved snoring but can also reduce long term future risk from cardiovascular disease. NIPPV can be used in both the acute and chronic care settings. In the acute setting, NIPPV can be used discriminately in the setting of acute respiratory failure to avoid complications of invasive ventilation[43,44] and should be initiated promptly during acute exacerbations of COPD[45] and in the setting of cardiogenic pulmonary edema[46].

Components of a PAP machine include a blower unit delivering designated pressures through tubing that is connected to a snugly fitting mask on the patients face, often held in place by a harness[47]. Most patients with OSA can successfully be treated with CPAP (continuous positive airway pressure), the most common form of NIPPV which provides a constant level of pressure (typically 5–20 cmH_2O) via the oropharyngeal airway during spontaneous breathing[48]. CPAP pressure is typically titrated to the best level for each individual patient during sleep studies. The pressure applied acts as a pneumatic splint to prevent narrowing and collapse of the airway, counteracts end-expiratory pressure reducing respiratory muscle load and work of breathing, and improves lung function, specifically the functional residual capacity[48]. When worn correctly with adequate adherence levels, CPAP can be quite beneficial, eliminating all OSA symptoms. However, patient adherence can be a challenge. Recent developments have helped to make CPAP more user friendly. Examples are adjustable interfaces, pressure relief during exhalation, improved mask frames, and

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autotitrating machines, which may help keep pressures lower during selected sleep positions and stages, helping patient tolerability[47]. CPAP therapy is the most commonly used treatment for OSA. However, CPAP does not offer significant ventilation support, so it may not be helpful for other forms of SDB including CSA or SRH, and the preset pressure may require titration changes over time if patients gain or lose substantial weight, develops other health comorbidities or receives medication changes that can impact disordered breathing type or severity. Auto-CPAP (APAP) is an automatically titrating CPAP device that can be set over a pressure range (typically 5–15 cmH_2O levels), and algorithmic analysis of ongoing patient breathing via airway dynamics leads to changes in pressure levels administered over the pressure range. APAP can help compensate for dynamic factors such as weight loss, body position, sleep stage, or alcohol or sedative medications. It may be beneficial for individuals undergoing significant weight loss such as those anticipated for bariatric surgery, although some studies have found that APAP provides little added benefit over a CPAP[49]. Adaptive servo-ventilation (ASV) was originally developed for treatment of CSA with CSR but can also be applied for TECA. The aim of ASV therapy is to stabilize breathing and reduce apneic events via a specialized bilevel PAP mode offering a set expiratory positive airway pressure to control OSA, and algorithmic adjustment of pressure support during each inspiration within a prespecified range toward maintaining constant minute ventilation[48]. This device is more expensive than CPAP, and ASV should most often not be used in settings of hypoventilation, because given the ASV target of maintaining constant minute ventilation, ASV could worsen hypoventilation in COPD or restrictive thoracic disorders. Bilevel PAP devices are primarily used in cases of SDB associated with hypoventilation, heart failure, neuromuscular disease, restrictive pulmonary disease, CSA, and treatment-emergent sleep apnea[50]. Bilevel PAP functions by establishing a gradient between inspiration and expiration which is key to maintaining alveolar ventilation and reducing $PaCO_2$. The higher inspiration pressure augments patients work of breathing by unloading respiratory muscles, while the lower expiratory pressure maintains upper airway patency and improves functional residual capacity. Downsides of bilevel PAP include cost and, in some cases, ineffectiveness for treatment of central apnea. Another option for treatment of chronic hypoventilation is average volume-assured pressure support, in which the device adjusts the pressure support to reach a target set tidal volume. This allows the device to adapt for disease progression and adjust to nighttime variability and may offer more optimal ventilation assurance for patients having SRH due to neuromuscular disorders or motor neuron disease.

Dental Appliances

For those patients with OSA who are resistant to or intolerant to NIPPV therapies, dental appliances that target widening the upper airway in obstructive sleep apnea may be a suitable option. The most used dental device is a mandibular advancement device (MAD), which advances the mandible to pull the tongue base forward, increasing retropalatal and retrolingual airway patency during sleep. This is best used for patients who have mild-moderate OSA having a strong positional component (i.e. that is particularly worse in the supine position), and MAD has maximal benefit in younger, female, and less overweight patients. While MAD has been shown to decrease AHI, there have been contradicting studies that suggest moderate symptom relief and uncertain change in risk of future cardiovascular complications[50]. There remains a need for further analyses of long-term outcomes of MAD and related dental appliance therapies for OSA.

Surgical Therapies

Surgical approaches can be considered in patients with moderate or severe OSA who cannot tolerate PAP therapies. There are several approaches. Uvulopalatopharyngoplasty (UPP) involves excision of the uvula and soft palate to increase the amount of space in the pharyngeal opening. It has been shown to relieve snoring but may not be as effective in treatment of OSA, particularly when OSA is moderate or severe[47]. Maxillomandibular advancement can be effective in moderate and severe OSA. However, it has rather major morbidity and long-term outcomes remain understudied. Recently, hypoglossal nerve stimulation has proven effective in patients with moderate to severe OSA who cannot tolerate PAP therapy. A large-scale trial has unambiguously confirmed that hypoglossal nerve stimulation is a safe, tolerable, and effective option for moderate-to-severe OSA in carefully selected patients with defined body mass index range and demonstrated mechanism of anteroposterior oropharyngeal airway collapse during drug-induced endoscopy[51].

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Conclusion

SDB will likely continue to increase in prevalence in parallel to the worldwide obesity pandemic. SDB can lead to serious complications including cardiovascular and cerebrovascular diseases. However, treatment with PAP can effectively manage symptoms and alleviate long-term health risks. Accurate diagnosis of SRH type and OSA severity relies upon the gold standard of PSG, yet increasingly HSATs followed by autotitrating PAP devices are supplanting traditional diagnosis and treatment pathways, enabling scalable treatment solutions for community settings that can improve population health. Proper determination of SDB type is necessary to provide the correct therapies for patients with SDB, which include lifestyle changes, NIPPV, dental applications, and surgical options for selected patients.

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Chapter

20 Respiratory Issues in Children with Neurological Disorders

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Introduction

Neurological disease in children can be both congenital and acquired. Congenital diseases include genetic inherited conditions and those acquired during intrauterine development. They may be static or progressive. Some congenital diseases may become apparent only later in childhood – for example, Batten's disease, which is an inherited metabolic condition, but may present only in late infancy with developmental regression. Acquired diseases include brain injury from hypoxia perinatally, central nervous system infections, trauma, and oncological and immune-mediated diseases. Whilst acquired brain injury may result in a static pathological change, the neurological symptoms and sequelae may still progress with age and development through childhood.

Although there are hundreds of neurological diseases that can affect children, the broad phenotypes that affect the respiratory function in children can be summarised as:

- Disorders that affect respiratory drive: these include isolated defects of the respiratory drive, such as in congenital central hypoventilation syndrome, as well as more global encephalopathy syndromes affecting the respiratory drive centres.
- Disorders that affect airway patency and protection: this is a common presentation in several global encephalopathy syndromes, as well as specific conditions affecting bulbar tone and bulbar muscle fatiguability.
- Disorders that affect muscle strength: these are primarily neuromuscular disorders, such as spinal muscular atrophy or muscular dystrophy.
- Disorders that affect muscle tone: tone problems are common to many neurological diseases in children, both increased tone (e.g. cerebral palsy), and low tone (e.g. neuromuscular weakness).

These phenotypes are not mutually exclusive: for example, children with cerebral palsy may have problems with respiratory drive, airway patency and muscle tone, all affecting their respiratory health.

Respiratory issues play a significant role in the quality of life and long-term survival in children with neurological disorders. Respiratory illness is the most common reason for hospital admission amongst children with neurodisability[1]. A survey in the United States on severely neuro-disabled children reported 77% of deaths were a result of pneumonia[2]; another reported 52% of deaths accounted by respiratory problems amongst children and adults with learning difficulties[3].

In this chapter we discuss the respiratory considerations that are relevant in children with neurological disorders. We discuss the pathophysiology of commonly occurring neurological problems that present with respiratory impairment and failure. Although many of these are common to adult diseases, we highlight the evolution of problems with childhood development. We discuss the principles behind long-term management of respiratory function, including monitoring and therapies available to optimise respiratory function. We also discuss the acute management considerations, including mechanical ventilation in the paediatric intensive care unit (PICU). Management of respiratory issues in children with severe neurological impairments are challenging. There is often a lack of high-quality evidence, making it difficult to assess risks and benefits of therapies. Finally, we discuss the ethical dilemmas faced by clinicians treating children with neurological disorders, including those surrounding withholding and withdrawal of life-sustaining treatment.

Pathophysiology of Respiratory Problems in Children with Neurological Disorders

Development of Respiratory Structure and Function through Childhood

Human lung development starts as early as the fourth week of gestation, with the budding of a single airway from the ventral foregut. This airway divides

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progressively, forming two separate lung structures by the sixth week of gestation. As in all mammals, human lung development follows three distinct stages: *the pseudoglandular stage*, where conducting airways with their blood supply form and septal structures and epithelial cells differentiate; *the canalicular stage*, where alveolar ducts appear with the thinning of the blood-gas barrier and surfactant is secreted; and *the saccular-alveolar stage*, where saccules and alveoli are formed. In humans 100–150 million alveoli are formed by birth (compared to 300–600 million in an adult lung). The developmental processes are co-ordinated through a complex interaction of differential genetic transcription, trophic factors, signalling from the extracellular matrix and physical forces exerted by the surrounding tissues and lung fluid[4,5].

Although the greatest rate of alveolar formation occurs in the third trimester of gestational development, alveolar formation continues postnatally, through childhood and into early adulthood[6]. This has implications on developmental disorders in utero and lung insults in early infancy, including premature birth: lung development can continue and function can improve after an early insult. Equally, lung development and function can also be compromised by disorders in childhood that affect any of the developmental determinants – for example, oxidative stress, exposure to trophic factors such as glucocorticoids and the thoracic shape and size.

Changing Mechanical Properties of the Thoracic Cage through Childhood

At birth, ribs are largely cartilaginous. They extend almost perpendicularly from the vertebral column and as such, do not provide a similar degree of thoracic volume expansion as in adults during inspiration (where the ribs can be elevated like a 'bucket handle' to increase the thoracic diameter). The diaphragm in infants is relatively flattened. In adults, the angle of apposition between the diaphragm and the chest wall is small, allowing the diaphragm to move down like a piston creating residual volume. However, in infants, the same angle of apposition is wider. The posterior limb of the diaphragm contracts dorsally to create residual volume like a pair of bellows (a consequence is the appearance of subcostal recession during increased work of breathing). The proportion of fatigable muscle fibres is higher in the paediatric diaphragm compared to an adult. The intercostal muscles are less well developed in childhood. This changes through childhood and puberty, when the ribs ossify and change angle, the diaphragm becomes stronger with a larger proportion of type-I fibres and the chest wall muscles increase in bulk. The result is an increase in lung capacity, a more passive maintenance of lung volumes closer to the functional residual capacity but also a decrease in chest compliance (adaptations evolved to move from the largely supine position to the bipedal upright position)[7,8]. With thoracic expansion, there is also lung growth, with epithelial proliferation, thus expanding the surface for gas exchange.

Cardiovascular Development in Infant Lungs

Alveolar and thoracic development runs hand in hand with cardiovascular development. Pulmonary arterial pressures are high during the first week of life as the neonatal lung adapts to gas exchange across the alveolar blood-gas interface. Pulmonary artery smooth muscle relaxes over the first week of extra-uterine life to allow greater pulmonary blood flow, and in utero intra- and extra-cardiac shunts close (the foramen ovale and the ductus arteriosus, respectively). The alveolar capillary network also increases in area through childhood, keeping up with new alveolarization and lung growth[5]. The result is an overall decrease in pulmonary vascular resistance, with the right cardiac ventricle becoming less dominant over the first year of life. Disorders of lung or thoracic growth therefore may have an impact on pulmonary haemodynamics, leading to pulmonary hypertension and right ventricular failure in extreme circumstances.

Evolution of Breathing Mechanics

Breathing movements start during intrauterine life by the 10th–12th week of gestation in humans. These do not have any function in gas exchange, but the movement of lung fluid is important in lung development. The breathing movements are not constant but show evidence of cyclical change with electroencephalographic activity, with inhibition of breathing activity from cortical structures. Fetal breathing movements can still be modulated by carbon dioxide and oxygen. Hypocapnia may reduce breathing activity, although this develops later in gestation. In fetal life, hypoxia increases the inhibitory drive to breathing movements, possibly to conserve oxygen in low oxygen states. In prematurity and the early neonatal period, this may persist leading to the relatively common response of apneas to hypoxia[9]. In term neonates, the response to hypoxia can be biphasic, with an initial increase in ventilation, followed by hypoxic ventilatory depression if hypoxia continues. The latter phase may be a response to

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hypocapnia from the initial increased ventilation or a central hypoxic depression of the ventilatory drive[10].

Mechanoreceptor feedback mechanisms also mature during early childhood. Immature feedback mechanisms lead to an irregular breathing pattern in newborns. The irregular periodic breathing is more pronounced in preterm neonates – this is due to a combination of a reduced chemoreceptor sensitivity, immature vagal myelination and chest wall instability leading to airway closure and decreased functional residual capacity[10].

Factors Disrupting Normal Lung Development

Some factors, such as inflammation, oxidative stress and glucocorticoid exposure, affect both lung and brain development simultaneously. Whilst inflammation and hyperoxia may increase apoptosis in both lung and brain, and lead to poor organ growth and maturation, glucocorticoid exposure may have differential effects. Glucocorticoids may be used prenatally, or after preterm delivery, to aid lung maturation. However, glucocorticoids may increase brain cell apoptosis and decrease neurogenesis, as evident in animal models and MRI studies, although not translated into follow-up studies in premature children enrolled in glucocorticoid trials[11].

Pathophysiology of Common Childhood Respiratory Problems

The respiratory problems that children with neurological disease present with depend on the underlying disease, and their developmental age and stage. For example, acute presentations with apnoeas are more common in younger infants, while restrictive lung diseases are more likely to become apparent in adolescence when children develop thoracic cage deformities. Next, we discuss the pathophysiology of common respiratory presentations.

Sleep-Disordered Breathing

Sleep-disordered breathing (SDB) refers to a wide spectrum of sleep-related breathing problems including increased resistance to airflow through the upper airway, marked reduction in airflow (hypopnea), and complete cessation of breathing (apnoea). SDB can be either central or obstructive in its nature. Despite the abundant evidence supporting higher risk of SDB amongst children with neurological conditions, SDB is often underdiagnosed[12]. Predisposing factors for SDB amongst children with neurological conditions are shown in Table 20.1.

Central SDB in children can present because of disorders in the respiratory controller centres (pontomedullary centres), the afferent signal sensors (central and peripheral chemoreceptors), the ability to respond to these signals or the effector system (neuromuscular response to the respiratory drive)[13].

Diseases affecting the respiratory control centres could be congenital, such as Arnold–Chiari malformations, or acquired, with posterior fossa tumours, ischaemia or infection. Evolving hydrocephalus may present with a disordered respiratory drive. Congenital disorders of the chemoreceptor pathways can also lead to apnoea

Table 20.1 Predisposing factors associated with sleep-disordered breathing in children with neurological impairment

Predisposing factor	Mechanisms
Brainstem dysfunction	Central sleep-disordered breathing, can be associated with cardiovascular instability and encephalopathy
Epilepsy	Ictal and post-ictal breathing instability Combination of epilepsy and cerebral palsy increase the risk of obstructive sleep apnoea
Upper airway obstruction	Changes in maxillary and mandibular development lead to anatomical features such as retraction of the tongue, causing obstruction Abnormal muscle tone in the upper airways leads to obstruction, for example palatal hypotonia, laryngomalacia, laryngeal dystonia Anti-dystonic and antiepileptic drugs can exacerbate this problem
Chronic aspiration	Recurrent chest infections, atelectasis and bronchiectasis associated with worsening sleep-disordered breathing
Hypotonia	Weakness of the respiratory accessory muscles and diaphragm leads to *pseudo central apnoeas* – intact respiratory drive but inability to initiate beathing due to muscle tone
Thoracic cage deformity	Associated with atelectasis, poor airway clearance, increased work of breathing and nocturnal hypoventilation

Adapted from Grychtol R, Chan EY. Use of non-invasive ventilation in cerebral palsy. *Arch Dis Child*. 2018 Dec;103(12):1170–7.

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and hypoventilation. Classically, gene mutations such as those of the paired-like homeobox 2B gene (*PHOX2B*) give rise to central hypoventilation syndromes, where the chemoreceptor-driven control of breathing during sleep is lost. Acquired diseases of the brainstem or high cervical spine can also mimic this.

Apnoeas occur in neuromuscular disease despite normal respiratory drive pathways because of the loss of effector pathways generating normal respiratory movements. These may be classed as *pseudocentral apnoeas* as they may also occur during rapid eye movement sleep and are not associated with paradoxical changes in the thoraco-abdominal diameter seen in 'classical' obstructive apnoeas.

Respiratory depression may be a secondary phenomenon following drug treatments for neurological disease. Benzodiazepines, commonly used for seizure control and dystonia, can lead to secondary respiratory depression resulting in apnoeas. This is a common reason for the need for intubation and ventilation in children presenting to hospital with status epilepticus.

Obstructive SDB describes a spectrum of upper airway dysfunction (apnoea and hypopnoea) during sleep, characterised by snoring and/or increased respiratory effort secondary to greater upper airway resistance and pharyngeal collapsibility. Obstructive sleep apnoea (OSA) can be common amongst children with cerebral palsy[12]. Patients may present, apart from noisy breathing during sleep, with disturbed sleep, daytime sleepiness, failure to thrive and pulmonary hypertension if severe OSA left untreated[14]. In other syndromic conditions, hypotonic upper airway together with anatomical features can cause severe OSA such as Down syndrome.

Apnoea of prematurity is common and is inversely proportional to the corrected gestational age. It is a combination of central apnoea and obstructive apnoea. The central component is thought to be secondary to the immaturity of both brainstem respiratory centres and the afferent pathways from peripheral chemoreceptors. The delayed maturation of chemoreceptor signals/responses to the upper airway muscles leads to the obstructive element of apnoeas of prematurity, through loss of upper airway patency. Apnoea of prematurity is also associated with gastro-oesophageal reflux disease, possibly due to the stimulation of vagus nerve[10].

Upper Airway Obstruction

Upper airway obstruction may be common in children with neurological disease. This may be present even during awake periods, although obstructive SDB is more common in children with upper airway obstruction.

Obstruction may occur at various levels: (i) at the nasopharynx due to mid-facial hypoplasia; (ii) at the oropharynx due to a combination of hypotonia of palatal muscles, a forward protruding tongue and developmental abnormalities of the temporomandibular apparatus[15]; and (iii) at the level of the larynx, due to inspiratory laryngeal collapse (laryngomalacia), laryngeal dystonia, recurrent gastro-oesophageal reflux and inflammation and loose aryepiglottic folds from disuse of the laryngeal muscles.

The aetiology can be multifactorial. Anatomical changes can occur if there is paucity of movement in utero or early infancy, as seen in neuromuscular disease, or from the use of non-invasive ventilation (NIV) interfaces early in life. In children with severe neurological impairment, dysphagia/bulbar dysfunction, laryngeal inflammation from gastro-oesophageal reflux disease (GORD), kyphoscoliosis, poor muscle tone/dystonia, posture and seizures may all independently or more often, together, cause significant upper airway problems[16]. Adeno-tonsillar hypertrophy, common in childhood, can exacerbate obstructive symptoms.

Some rare diseases, such as sodium channelopathies, can cause a life-threatening episodic laryngeal spasm and stridor in the neonatal period[17]. In those with problems of laryngeal dystonia, the stridor may be more pronounced during periods of agitation, with the stridor getting worse with age (due a combination of muscle strength and air flow through the obstructed airway). Uncontrolled, patients with upper airway obstruction can develop SDB, morning headaches, pulmonary hypertension and right heart failure.

Dysphagia, Gastro-Oesophageal Reflux and Chronic Aspiration

Dysphagia and GORD are common in children with neurological disease. Aspiration from dysphagia occurs in just over a quarter of all children with cerebral palsy based on video-fluoroscopy data[18], whereas GORD occurs in up to three quarters of all children with neurological disease[19].

Dysphagia can occur because of disorders in any or all phases of swallowing. Lip closure may be affected due to weakness and discoordination of facial muscle movements. Both sensory and motor problems may affect tongue movements – this can lead to problems in bolus

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formation and movement of food through the oral cavity. Children with oral sensory problems may hold food under their tongue to avoid swallowing. Key to swallowing is the complex co-ordinated contraction of tongue base muscles and pharyngeal muscles with simultaneous activation of airway protective reflexes. Many children with neurological disorders may struggle to co-ordinate this complex action. Children with posterior fossa disorders may not have an intact gag reflex or a powerful cough. In children with neuromuscular disorders these airway protective reflexes may be too weak or absent. In children with cerebral palsy, dystonia and poor coordination can make them prone to dysphagia[20]. Finally, the upper oesophageal sphincter needs to open to allow food bolus to move down the oesophagus via peristalsis, which may also need co-ordination of muscle contraction[21].

GORD occurs due to loss of lower oesophageal sphincter tone, loss of co-ordination of oesophageal motility and delayed gastric emptying. Other contributory factors include supine position, constipation, dystonia of abdominal muscles, scoliosis, seizures and antiepileptic and anti-dystonia medication[22,23].

The combination of dysphagia and GORD increases the risk of recurrent aspiration. Dysphagia alone can lead to the silent aspiration of oral secretions (i.e. without obvious coughing or choking). GORD can lead to the aspiration of gastric content, causing greater upper airway and pulmonary inflammation and infection. Ultimately, it may lead to bronchiectasis and lung parenchymal damage. It is worth noting, however, the relationship between aspiration and lung damage is not linear, implying other factors may be involved.

Recurrent Infections

Hospital admissions with respiratory failure in children with neurological diseases are often ascribed to infection. Prospective studies of hospitalised children comparing those with neurological disease, non-neurological diseases and children without comorbidities indicate pathogens are less likely to be detected in those with neurological disease, compared to children without comorbidities[24]. This suggests that many children with neurological disease hospitalised with clinically suspected infection may have alternative pathophysiological explanations, such as aspiration events, and atelectasis from respiratory pump failure and an ineffective cough. Children with cerebral palsy needing mechanical ventilation are often colonised with bacteria associated with the digestive tract. Whilst this may support aspiration as a likely causal explanation, there may be other explanations linking gut and respiratory tract microbiomes. An association between poor diversity of the gut microbiome and the incidence of chronic lung disease of prematurity and childhood wheeze has been shown[25]. Children with neurological disease remain at risk of an early dysfunction of the gut–lung axis through repeated exposure to antibiotics, poor gut motility and poor nutrition. The use of gastric acid suppression may also contribute: in ICU, proton-pump inhibitors have been linked to an increase incidence of ventilator-associated pneumonias.

Respiratory Pump Failure

Respiratory pump failure can occur due to muscle weakness, muscle fatigue and abnormal tone – these can all occur within the same patient. Infants need post-inspiratory diaphragm tone and contraction of upper airway muscles to control the rate of expiration, thus maintaining functional residual capacity (FRC). Respiratory pump failure leads to inadequate maintenance of FRC in children with neurological disease.

Neuromuscular diseases in childhood can vary in severity and may progress with age. For example, spinal muscular atrophy (SMA), a degenerative disease of the anterior horn motor neurons, starts as a predominantly proximal muscle disease, with weakness of the intercostal muscles, but relative sparing of the diaphragm. As a result, there is paradoxical inward movement of the chest wall during inspiration-as the diaphragm contracts, the intercostal muscles are unable to stop the chest wall from collapsing inwards; the abdomen moves out, seen as thoraco-abdominal asynchrony, and later reflected by a bell-shaped chest (Figure 20.1). In other neuromuscular diseases such as in SMARD (spinal muscular atrophy with respiratory distress, a disease genetically unrelated to SMA) the diaphragm is primarily affected. The addition of an ineffective cough and aspiration due to bulbar weakness contributes to respiratory failure in neuromuscular diseases.

In spinal lesions, depending on the level and extent of the lesions, presentations may differ. Upper thoracic lesions may cause poor cough and secretion retention due to abdominal muscle paralysis; mid-cervical lesions cause intercostal weakness; high cervical lesions cause paralysis of all respiratory muscles.

Muscle fatigue may be seen in myasthenic syndromes such as congenital myasthenia or acquired autoimmune myasthenias. Respiratory muscles may be affected in severe disease, needing ventilatory support.

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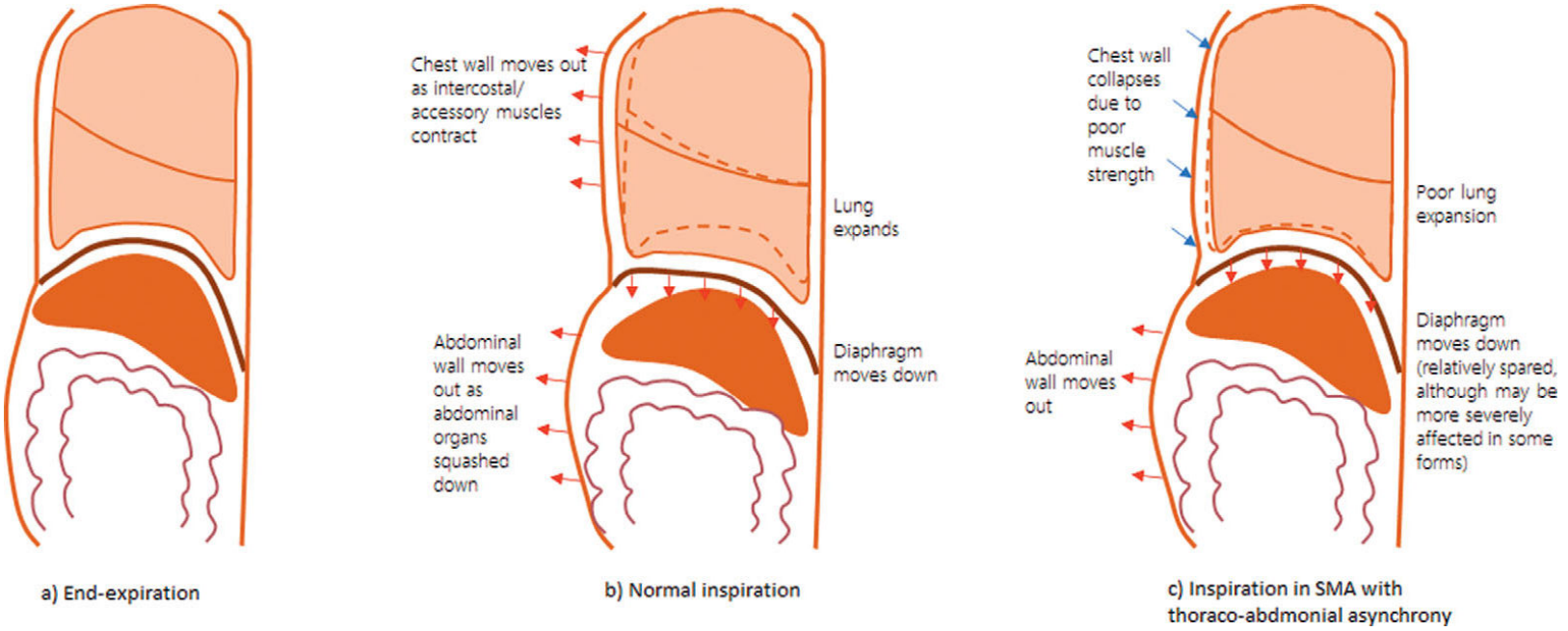


Figure 20.1 Thoraco-abdominal asynchrony or 'paradoxical breathing' seen in infants with spinal muscular atrophy (SMA). As the diaphragm is relatively spared compared to other respiratory muscles, the abdomen moves outwards, and the ventral part of the chest wall collapses inwards during inspiration. While subcostal recession indicates an increase in respiratory effort in children without neuromuscular disease, in infants with SMA, this pattern of breathing can be seen at rest without an increase in respiratory load.

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Increased muscle tone can also affect respiratory mechanics. Myotonic syndromes may not affect respiratory muscles commonly but in certain cases infants may need early respiratory support. Children with spastic cerebral palsy, however, may have significant dystonia of their intercostal and thoracic muscles leading to poor chest excursion and loss of lung volume. In extremis, status dystonicus can lead to complete chest rigidity and respiratory arrest. Conversely, loss of tone due to treatment may also result in the need for respiratory support.

Impact of Kyphoscoliosis

Spinal curvature frequently occurs in all types of neurological disorders because of imbalances of muscle tone and gravity. This, in turn, causes chest wall deformities and reduces chest wall compliance, as reflected by the restrictive respiratory pattern on lung function. The effect on the underlying lungs includes unequal lung expansion with atelectasis/overexpansion, ventilation/perfusion mismatch and asymmetrical lung growth[26]. It is important to note that neuromuscular scoliosis can continue to progress even after growth has stopped. This can lead to what has been termed a thoracic insufficiency syndrome, whereby the thorax becomes unable to support normal growth and respiratory function in growing children[27].

Management of Chronic Respiratory Problems in Children with Neurological Disorders

Respiratory problems are the leading cause of hospitalisations in children with neurological impairment. Day-to-day management is aimed at reducing infections and respiratory failure needing hospital treatment, improving longer term respiratory health and quality of life. In this section we discuss management strategies needed, as undertaken by parents and carers day at home under the oversight of respiratory paediatricians with a multidisciplinary team of physiotherapists, speech and language therapists, dietitians and occupational therapists.

Secretion Management

Secretion management in children is highly variable and patient specific. The key part of the eventual management is related to an adequate assessment of coughing, which can be affected by oro-bulbar function, muscle strength and tone, and secretion load and viscosity.

The four stages of a cough are shown in Figure 20.2. Oro-bulbar function and muscle strength are both vital to coughing effectiveness, along with intact sensory pathways that trigger coughing.

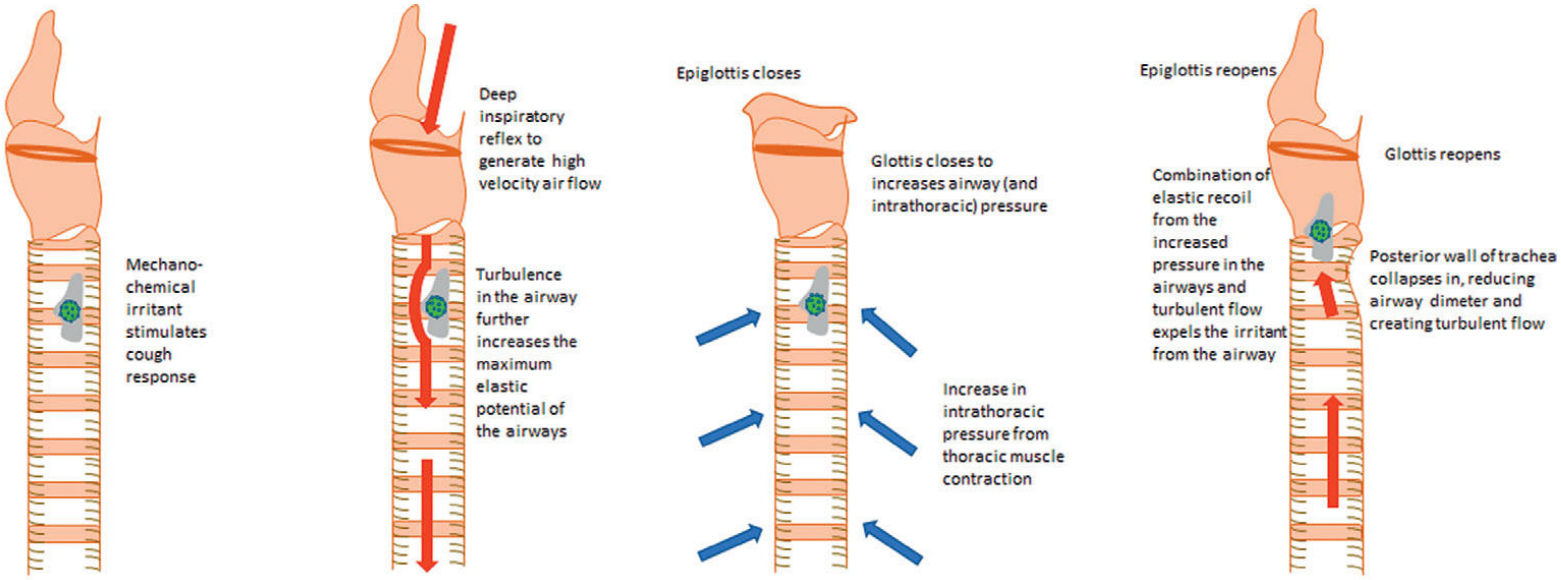
In children with neurological disease, one or more of the stages of the cough may be affected. The sensory pathways that lead to the cough being generated may be impaired – in children with cerebral palsy, recurrent aspiration and chemical irritation can reduce airway sensitivity. Poor co-ordination of the oro-bulbar muscles may lead to ineffective inspiratory effort and timed closure of the glottis. Poor airway tone may lead to the collapse of airways, without the intake of air. Chest wall deformities or respiratory muscle weakness may not enable the patient to generate adequate compression for air expulsion. Finally, any expelled material could be aspirated back down the airway if swallowing is disco-ordinated.

Both increased secretion load and viscosity can impair the mucociliary escalator. Mucous plugs can block smaller airways, leading to distal airway collapse and eventually atelectasis and distal infection. Drooling is common because of oro-bulbar dysfunction and poor swallowing. Control of secretion load can be achieved using antisialogogues such as hyoscine bromide or glycopyrronium. While these can be titrated, it is important to strike a balance between reducing load but not increasing mucous viscosity so that it cannot be cleared, particularly in the morning. Longer lasting procedures such as salivary gland Botulinum toxin injection may be more difficult to adjust. Nevertheless, the use of Botulinum toxin injection of salivary glands has been reported to reduce the incidence of number of pneumonia episodes[28].

Assisted secretion clearance is commonly needed in children with neurological disorders. Manual secretion clearance techniques include passive postural drainage along with airway suctioning. Suctioning of oral secretions will be needed in those without intact oro-bulbar function or with an ineffective cough. Airway adjuncts such as naso-pharyngeal airways or tracheostomy tubes may be needed to maintain airway patency (or for tracheostomy tubes, to facilitate long-term ventilation) Suctioning will be required to keep the airways patent. Although suctioning to the end of the tracheostomy tube is recommended to avoid airway injury, deep suctioning may occasionally be necessary when coughing is ineffective – this can be uncomfortable and may be reserved when shallow suctioning is ineffective[29].

Percussive techniques can help in mobilising secretions when passive methods may not be enough. This can

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Stage 1: Cough stimulus initiated by an irritant in the airway. Children with neurological impairment may not have airway responses that are able to sense and initiate coughing

Stage 2: Maximum inspiratory airflow is generated by a deep inspiratory effort. Children with neurological impairment may not have poor pharyngeal and laryngeal tone, leading to reduced airflow. The effort is generated by the respiratory muscles (diaphragm, intercostal and accessory muscles) – poor tone and power can impair this

Stage 3: Compression occurs, when the epiglottis and glottisc closes and the respiratory muscles contract. Poor oro-bulbar co-ordination may impair a co-ordinated closure of the larynx. Impaired muscle tone and power can reduce compression forces leading to a weak and ineffective cough.

Stage 4: Expulsion of air at high velocity, along with the irritant. Impaired oro-bulbar co-ordination can lead to an ineffective cough response. Poor airway tone and muscle weakness can lead to inadequate expiratory airflow. Poor swallowing co-ordination can also mean that the expelled material is aspirated back into the airway.

Figure 20.2 The stages of coughing. Each stage can be affected in children with neurological impairment, due to sensory dysfunction, poor muscle tone, muscle weakness or impaired co-ordination of muscle function.

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be provided manually by caregivers with gentle percussion of the chest wall. However, mechanical devices can be used for high frequency percussion. High-frequency chest wall compression (HFCWC) using a close-fitting mechanical vest can be used, providing percussive compression at 10–12 Hz. This has been shown to be effective in reducing the number of hospital episodes in children with neurological impairment[30]. In older children who are able with more preserved oro-bulbar function, intrapulmonary percussive ventilation is similarly effective[31]. Intrapulmonary percussive ventilation involves delivery of bursts of air and aerosol at 200–400 cycles per minute, and 20–40 cm H_2O pressure via a mouthpiece to mobilise secretions. However, to be effective, an effective seal needs to be developed around the mouthpiece, making HFCWC a more pragmatic alternative.

When coughing is ineffective due to muscle weakness, cough assistance may be needed. This can be provided manually, with a caregiver providing manual thoracic or abdominal compression timed during the expiratory phase of coughing. Mechanical assistance can be provided via mechanical insufflation–exsufflation. Coughing is induced by providing positive pressure to fill the lungs (either via a mask, or tracheostomy/endotracheal tube if present) followed by a rapid switch to negative pressure to augment the expiratory flow, thereby simulating a cough (Figure 20.3). Mechanical insufflation–exsufflation has been reported to reduce the number of hospital episodes in children with neuromuscular and central nervous system disorders, with parents and carers expressing a high degree of satisfaction[32].



Figure 20.3 Use of mechanical insufflation–exsufflation (MI-E). A child using MI-E to assist secretion clearance at home using a face mask.

Treatment and Prevention of Infections

Proactive management of respiratory infections and vigilance to its complications are vital. The factors predisposing children with neurological diseases to respiratory infections are listed in Box 20.1.

The most common and severe infection threats to severely neurologically impaired children are respiratory viruses, although secondary opportunistic bacterial infections should be taken equally seriously. Children (and their carers) should be offered annual influenza vaccination. Handwashing and other infection control to reduce viral spread measures should be widely used in schools and other institutions especially during flu seasons.

Recurrent hospital admissions for respiratory exacerbation or repeated courses of antibiotics could indicate introduction of antibiotic prophylaxis. There is a risk of promoting antibiotic resistance in prolonged usage,

Box 20.1 Contributing factors to recurrent respiratory infections amongst children with neurological disorders

- Infective cough and poor secretion clearance due to respiratory muscle weakness for instance, in children with neuromuscular weakness, cerebral palsy
- Restrictive respiratory pattern secondary to kyphoscoliosis, thoracic/spinal deformities
- Upper airway muscle dysfunction leading to sleep-disordered breathing
- Recurrent aspiration from above due to swallowing dysfunction and/or below from gastro-oesophageal reflux. Aspiration can be silent or present with overt symptoms such as coughing
- Other compounding factors, for example prematurity, chronic lung disease – leading to higher incidence of poor lung function/lower respiratory reserve, reactive airway disease
- Limited mobility
- Poor nutritional status
- Propensity to bacterial colonisation due to pooling of secretions
- Vicious cycle of respiratory infection, impaired mucociliary clearance and chronic inflammation can lead to structural damage to the lungs such as bronchiectasis

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hence regular/annual review of prophylactics need/choices is recommended. For those children with recurrent respiratory exacerbations who are colonised with *Pseudomonas aeruginosa*, nebulised antibiotics (for example, Colomycin) may be advocated in reducing bacterial load[16]. However, unlike its use in the cystic fibrosis patient population, specific data on children with severe neurological impairment are not available.

Prevention of aspiration 'from above' is an important component of reducing respiratory infections. Secretion management techniques, as outlined previously, help with this. Assessment by speech and language therapists is essential to prevent the aspiration of food/drink in patients with neurological disorders, presenting with symptoms of persistent coughing or choking on eating/drinking. Video-fluoroscopy is performed to examine the patient's swallowing function when given liquid or solids orally. Feeding advice can then be clarified including the type, consistency of feed that can be safely administered; thickeners may be needed with liquid intake. Often an alternative feeding route (e.g. naso-gastric, naso-jejunal, gastrostomy) may be required. More drastic intervention such as laryngotracheal separation, though rarely needed, has been used, although it is important to consider the pleasure the child derives from oral feeding.

Aspiration 'from below' following GORD can also cause significant respiratory morbidity from aspiration pneumonia, although its prevalence is difficult to quantify. Multichannel intraluminal impedance and pH monitoring is the standard diagnostic test; other supportive evidence may be in the form of increased lipid-laden macrophage index on bronchoalveolar lavage or video-fluoroscopy capturing reflux episodes. Proton pump inhibitors are used as the first-line treatment. Surgery such as Nissen fundoplication may be needed in severe intractable cases not controlled by medical treatment, even though it is associated with an increased rate of complications[33]. A pragmatic approach of performing anti-GORD surgery at a later stage when GORD has failed to respond to maximal medical treatment has been advocated[34]. In children with intractable GORD but reliant on feeds via gastrostomy, gastrostomy–jejunal feed is an option to mitigate risk of reflux in those children where fundoplication is not feasible.

Nutrition

The impact of malnutrition on respiratory health should not be overlooked. Dysphagia and GORD could contribute to malnutrition. This could lead to respiratory muscle catabolism and muscle atrophy. This can further muscle weakness, and an increased susceptibility to infections[35]. Dietetic and/or speech therapy advice on feeding strategies, supplementation and alternative routes of feeding would be appropriate. Conversely, inactivity and treatment such as steroids could contribute to overweight which may compromise respiratory function and increase risk of SDB[36].

Management of Upper Airway Obstruction and SDB

Direct fibre optic laryngoscopy can be used to assess upper airway obstruction. Overnight oximetry is used as a screening tool to indicate the severity of desaturation secondary to OSA. The more detailed sleep studies (cardio-respiratory polygraphy/formal polysomnography) further differentiate different types of apnoeas (obstructive versus central) and help to direct treatment.

Tonsillectomy, adenoidectomy and aryepiglottic surgery are often used as treatment for airway obstruction and SDB in neurologically impaired children when medical treatment GORD, dystonia and allergic rhinitis has failed to make significant improvement. Long-term ventilation (LTV) has been used in this population (see Section 20.3.6) with variable success.

Home Oxygen

Supplemental oxygen is sometimes used in this cohort long term to prevent chronic hypoxaemia leading to a progressive rise in pulmonary artery pressures. Its use should be cautioned in neuromuscular patients who also have hypoventilation because their blunted sensitivity to hypercapnia (secondary to chronic hypoventilation) makes them vulnerable to respiratory arrest if the hypoxaemia is corrected and the hypoventilation undetected.

Long-Term Ventilation

Long-term ventilation encompasses (i) NIV via a mask interface, and (ii) invasive ventilatory support via tracheostomy (tr-LTV). Both forms of ventilation can support children with severe neurological impairment presenting with respiratory failure.

NIV is indicated in three main scenarios: (i) airway obstruction can be improved by continuous positive airway pressure (CPAP), which prevents airway collapse either during inspiration (in upper airway disorders) or

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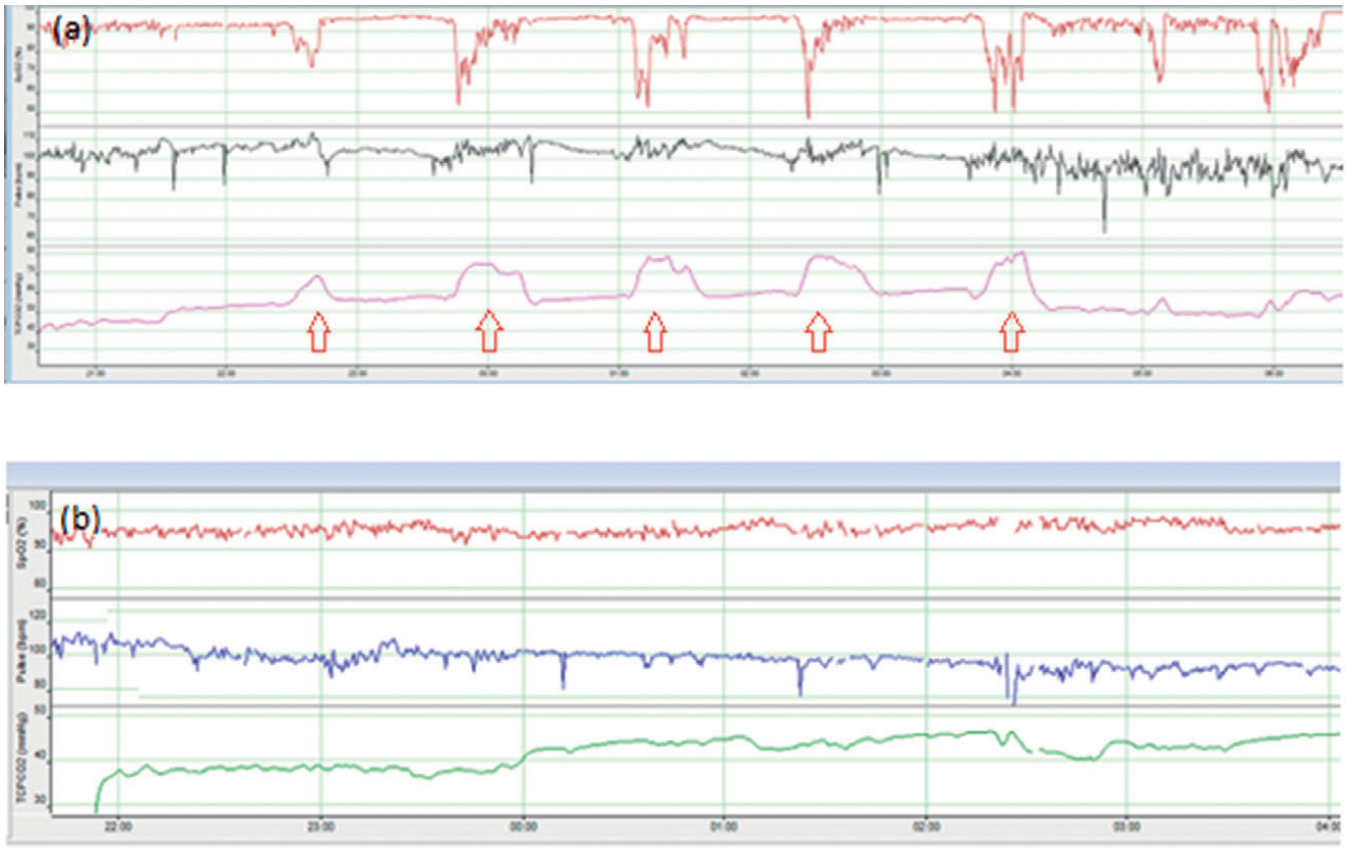


Figure 20.4 Hypnograms (from sleep studies) of a teenager with Duchenne muscular dystrophy (a) before and (b) after initiation of non-invasive ventilation. (a) Baseline sleep study showing *severe obstructive hypoventilation* with mean SpO_2 93% (nadir 47%); mean $TcCO_2$ 60 mmHg (Max 80 mmHg); his obstructive apnoea-hypopnoea index = 21.7 events/hr = significantly raised (scored events not shown here). (b) After initiation of bi-level positive airway pressure (BiPAP) – gas exchange improved – CO_2 normalised; desaturations due to obstructive episodes disappeared.

expiration (in lower airway problems), as well as improving FRC and oxygenation; (ii) chronic respiratory failure resulting from muscle weakness (central cause or muscle fatigue due to increased respiratory load, e.g. chronic lung disease), parenchymal lung disease (e.g. recurrent aspiration) or chest wall disorders (e.g. kyphoscoliosis) is more appropriately supported by a bi-level (i.e. positive pressures set for inspiration and expiration) positive airway pressure (BiPAP); and (iii) reduced respiratory drive causing central apnoea/hypoventilation requires BiPAP with a mandatory set rate, which will be delivered if there are no patient-delivered breaths.

Tr-LTV is used when there is intractable upper airway obstruction, or the airway is unprotected, for instance, due to vocal cord paralysis or absence of airway protective reflexes. It is also used if ventilation is required throughout the day (e.g. if there is a complete loss of respiratory drive), as NIV mask use without breaks can lead to pressure area breakdown. Tr-LTV requires a greater level of care and monitoring at home to ensure tracheostomy patency and position.

Evidence of outcome benefit of long-term ventilation amongst children with neurological disorders is limited/unavailable, except amongst children with neuromuscular conditions. The benefits of LTV in children with neuromuscular conditions include improved survival, slowing functional decline and reduced respiratory morbidities[37–39] (Figure 20.4). It is less clear amongst children with other severe neuro-disabilities[40].

Management of children on home ventilation requires expertise of a multidisciplinary team (consisting of respiratory paediatricians, neurologists, nurse specialists, physiotherapists, palliative care team). The imposition of home ventilation (non-invasive or invasive) should be weighed against the benefits the child receives in terms of quality of life. This includes the

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presence of monitoring and home carers, which can be intrusive. For example, NIV may be instituted for SDB but the use of a mask or monitoring equipment may paradoxically hamper sleep quality. A balanced decision therefore must be made when considering home ventilation – the ethical aspects of this are explored in Section 20.5.

Monitoring of Respiratory Function

Respiratory muscle weakness can be monitored by measuring vital capacity and maximal inspiratory and expiratory pressures. This is not easy in practice due to difficulties in cooperation, coordination or difficult seal around the mouthpiece. More often, oximetry and cardio-respiratory sleep studies are used as surrogate measures of respiratory function.

Other Considerations

Thoracic deformities can cause restrictive respiratory failure. Postural management using special seating may be helpful. Bracing may be useful but may be used for only limited periods due to the risk of pressure sores and pain, as well as potential impact upon GORD. Surgical spinal fixation may be an alternative – although children with multiple morbidities may face greater operative risks, quality of life can improve following surgery with improvement in posture, ambulation and pain. Multidisciplinary input is recommended in the preoperative planning stage to assess the risks and benefits.

Seizures are commonly associated with neurological impairments. Its control, or lack of, may cause apnoeas and desaturation. There is also potential risk of aspiration during seizures. However, antiepileptic drugs may have adverse side effects: acutely, benzodiazepines can lead to respiratory depression. Older antiepileptics, such as phenobarbital, may be sedative, and further add to respiratory morbidity through aspiration risk.

Currently, respiratory stimulants are not widely used for respiratory drive problems in children with neurological disease. Caffeine is used widely as a respiratory stimulant in children with apnoea of prematurity with evidence of earlier liberation of respiratory support in those given caffeine compared to those who were not[41]. There are case reports of the beneficial effects of caffeine in disorders such as central congenital hypoventilation syndrome post anaesthetic[42], which warrant further exploration.

Acute Respiratory Problems in Children with Neurological Disorders

Acute presentations of respiratory problems in children with neurological disease are commonly manifested as cyanosis, or an increase in the work of breathing. The latter will be due to the response of the respiratory drive centres to hypercapnia or hypoxia. However, in specific neurological diseases this may not be the case. For example, as outlined is Section 20.2, in early infancy or those with neuromuscular disease, the presentation of respiratory disease may be in the form of apnoeas.

Next, we discuss the acute management of respiratory symptoms in children with neurological disease according to the setting in which they present: pre-hospital, hospital and the PICU. For all presentations of acute respiratory problems, the neurological basis/aetiology of the disease that precipitates the problem also must be addressed. For example, for children with apnoeas due to hydrocephalus, cerebrospinal fluid may need to be drained; for children with respiratory failure from status dystonicus, muscle tone will need to be addressed.

Pre-Hospital Management

Pre-hospital management may begin at home, with parents/carers undertaking steps at the first signs of any respiratory distress and deterioration. Some children may be given respiratory plans in advance for times when they have early signs of an infection, for example, increasing LTV pressures.

Secretion Clearance Techniques

Secretion load may increase with infections. Secretions may also become thicker, which may also occur if the child becomes dehydrated due to poor intake or gastrointestinal losses. The ability to cough may be impaired further in children with acute illnesses due to fatigue. Normal secretion clearance techniques may therefore need to be escalated at the earliest sign of an acute illness.

Adjustment of Respiratory Support

Intermittent ambulatory use of supplemental oxygen in the absence of any further monitoring and support in an unwell child is rarely recommended. Even with home oxygen monitoring, it will be important to understand the cause of hypoxia, and this will normally require medical input. However, children who are long-term

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ventilated at home, whether non-invasively or via a tracheostomy, may have agreed escalation processes for when they are unwell. This may include extending the duration of ventilation for example, from nocturnal use to diurnal use of ventilator, using a higher support preset programme (often referred to as 'sick settings', with ventilator pressures) or the addition of oxygen to the ventilator circuit. However, even if these may be well managed by parents and carers at home, there must be safety nets in place for them to seek medical advice if the child fails to improve or continue to deteriorate. For those who are long-term ventilated, this is likely to be from the long-term ventilation team, who may be able to provide an outreach service or facilitate assessment and admission to the local hospital or long-term ventilation inpatient unit.

Early Antibiotics

The risk of recurrent pneumonias is high in children with neurological disorders for the reasons outlined previously. Children with recurrent infections or bronchiectasis may need longer courses of antibiotics.

Pre-ICU Hospital Management

Many children with neurological disease will need hospital management for acute respiratory presentations because of their low respiratory reserves, the rarity of individual diagnoses leading to clinical unfamiliarity and the complexity of each child, necessitating more specialised input.

Oxygen

A primary reason for admission to hospital often is hypoxia, needing supplemental oxygen. There is uncertainty about the oxygen saturations to target in children needing supplemental oxygen, and may depend on their comorbidities, as well as the baseline oxygen saturations they may be adapted to. Supplemental oxygen without ventilatory support to offload respiratory muscles to children with neuromuscular disease may blunt the hypoxic respiratory drive and may be dangerous in the absent of other monitoring. This should therefore be avoided or used with caution[43].

Anti-Sialogogues and Mucolytics

One of the difficult balances that need to be struck, particularly in the acute phase of a respiratory presentation, is the reduction in secretion load whilst not increasing the risk of producing inspissated secretions which cannot be cleared easily by coughing. Acutely, the dose of anti-sialogogues may need to be carefully titrated – inspissated secretions can commonly block smaller airways, especially if the child has a weak or ineffective cough, posing added risk to children with relatively narrow bore tracheostomy tubes which can get obstructed. Vigilance is needed to safeguard against this in hospital, with shorter acting drugs like glycopyrronium, and dose-titrated to effect. One strategy may be to use a combination of anti-sialogogues for reducing the oropharyngeal secretion load but sodium chloride nebulisers to prevent thickening of secretions in the lower airways.

Mucolytics such as N-acetylcysteine and DNAse are widely used in the context of children with bronchiectasis. In children with neurological disease and an ineffective cough, the use of mucolytics has not been well studied because of the heterogeneity of this population. However, these could be trialled with assessment of their effect if smaller airways are obstructed by mucous.

Bronchodilators

Children with evidence of recurrent aspiration may present with wheeze. This may be due to the aspiration events themselves, with partially obstructed airways from aspirated content or mucosal inflammation. However, recurrent aspiration may also trigger to reactive airway disease[23]. Therefore, bronchodilators may be trialled in children with neurological disease presenting with wheeze and the effect can be assessed.

Feeding

Although feeding problems including reflux and aspiration are likely to be long-standing and should be tackled as part of chronic respiratory management, intercurrent infections and an increased work of breathing may exacerbate both. Feeds (oral/nasogastric/via gastrostomy) may be held acutely if there is an imminent risk of needing to escalate to intubation and invasive ventilation. However, once the child is stabilised, feeds should be restarted – nasogastric or gastrostomy feeds may need to be given continuously or more frequently than normal. Gastric feeds could be converted to jejunal feeds during acute illness to reduce the risk of aspiration.

Non-Invasive Respiratory Support

Humidified high-flow nasal cannula oxygen may offload the respiratory muscles by reducing airflow turbulence,

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whilst providing pharyngeal dead space washout and providing air flow generated positive pressure through the respiratory cycle (estimated to be approximately 4 cmH_2O)[44]. CPAP aims to maintain FRC, which is important in children as the closing volume for alveoli can be very close to the FRC. CPAP is usually delivered via nasal prongs or a mask in infants and via a full-face mask in older children. Both can be used to escalate from low-flow oxygen where available. Both may also be used in apnoeas of infants, with the intention of providing oropharyngeal stimulation whilst maintaining FRC. As with low-flow oxygen, however, concerns remain regarding their use in children with neuromuscular diseases: neither may provide adequate ventilatory support, whilst also blunting the hypoxic respiratory drive. Where possible therefore, BiPAP with a set rate in children is preferred in neuromuscular disease[43]. This can adequately support the respiratory muscles, including if the muscles fail to generate a response to the central respiratory drive.

In children who are long-term ventilated, the ventilator settings may need to increase to 'sick settings' during admission, or the ventilator may be needed continuously or with more oxygen. With all forms of NIV, there is a risk of aerophagia and stomach distension. This could splint the diaphragm and cause basal atelectasis, particularly in smaller children. It may also increase the risk of vomiting and aspiration. This needs to be monitored closely and steps taken either to reduce this risk (through feeding measures mentioned previously) or by invasively ventilating.

PICU Management

The admission criteria for PICU may vary according to healthcare context – some centres may be able to manage NIV outside PICUs in a ward/high-dependency unit environment. Those approaching the need for intubation and ventilation however will need admission to the PICU.

Thresholds for Intubation

The threshold for intubation will often be subjective but requires careful thought. NIV may be used preferentially, in anticipation of the likelihood that extubation may be difficult. At higher pressures (e.g. inspiratory pressure >20 cmH_2O), the leak around the mask interface may become problematic, and pressure delivery may be uncomfortable. Pressure sores on face from the mask interface are a risk, especially when higher pressures are used or continuous NIV is needed. In PICU environments full-face (covering the whole face) or oro-nasal (covering the nose and mouth) masks may be preferred, as nasal mask interfaces are likely to allow for pressure leak from the mouth. Full face masks will need to incorporate provision for CO_2 ventilation if used with a circuit without an expiratory limb. Mask types may be alternated to reduce pressure area sores. If secretion clearance is a particular problem, then the mask may need repeated removal for airway suctioning – hampering the effectiveness of NIV.

Hypoxia and severe encephalopathy with loss of airway protective reflexes may be absolute indications for intubation and ventilation. Children with worsening respiratory failure despite optimisation of NIV would also need intubation. Fatigue following prolonged increased work of breathing should be judged clinically; however, in children with neuromuscular disease, this may be difficult. In these children, the risk of fatigue leading to an apnoea or respiratory arrest remains high.

Sedation and Neuromuscular Blockade

Following the initial anaesthesia for intubation, sedation is likely to be needed for endotracheal tube tolerance. The risk of respiratory depression due to sedation accumulating in children with neurological disease is high, especially in those with a poor respiratory drive at baseline. If possible, agents causing minimal respiratory depression such as alpha agonists, should be used. Patients may benefit from sedation breaks, where continuous infusions are stopped for a period of time each day to allow for drug elimination across compartments (mixed results are reported in a general PICU population with this strategy). Safeguards also must be in place against a child being distressed by the endotracheal tube but being unable to express this – for example, in severe neuromuscular disease when traditional signs of pain such as facial grimacing may be absent. Sedative drugs, such as benzodiazepines, may be needed in children with status dystonicus as well, especially where the abnormal muscle tone impedes chest wall movement.

Continuous neuro-muscular blockage may be needed for patient–ventilator dyssynchrony and/or poor respiratory gas exchange. As children with neurological disease will often have decreased muscle strength (either because of the primary condition or disuse atrophy), accumulation of neuromuscular blockade can contribute to a critical illness myopathy. This may make extubation difficult. Where possible therefore continuous neuromuscular

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blockade should be limited, and if used continuously, breaks in neuromuscular blockade or dose titration with neurophysiological monitoring (e.g. the use of Train-of-Four devices) should be used. Reversal of neuromuscular blockade with agents like sugammadex prior to extubation could be considered.

Ventilation Strategies

Ventilation strategies may need to be specific to the problem causing respiratory failure. Children with a central respiratory drive problem and neuromuscular weakness will require a mandated respiratory rate. In children with disorders of chemoreception, resulting in a poor hypercapnic respiratory drive (e.g. central congenital hypoventilation syndrome), permissive hypercapnia ventilation strategies may not help with liberation from the ventilator. Children with restrictive chest walls may require higher pressures for adequate gas exchange.

Neurally adjusted ventilation assistance (NAVA) may provide a useful mode of ventilation in some children with neurological disease. This mode senses the electrical activity of the diaphragm using an oesophageal probe and provides proportional support. In children with reversible diseases of muscle strength (e.g. autoimmune neuromuscular diseases, Botulinum toxicity, critical illness myopathy) this mode may allow for ventilator weaning while avoiding ventilator asynchrony during recovery of neuromuscular function. Beyond the ventilator functioning, diaphragm electrical activity measurements from the NAVA catheter may also provide important diagnostic information to help understand the respiratory mechanics, and tailor further ventilator weaning[45]. NAVA may also be used alongside NIV.

Ventilation strategies are important in regulating intracranial pressure in children with encephalopathy and concerns about intracranial hypertension. As in adults, CO_2 is tightly regulated within normal limits (4.5–5.3 kPa), with hypocapnia causing cerebral vasoconstriction, and hypoperfusion and hypercapnia causing cerebral vasodilation and raised intracranial pressure. However, this should be balanced against the need to reduce the intrathoracic pressure to allow venous drainage[46]. Normal oxygen levels should be the aim, with hypoxia likely to cause cerebral hypoxia, while hyperoxia can be associated with worse neurological outcomes.

Extubation Readiness

Extubation readiness testing using spontaneous breathing trials are commonly used in the PICU. However, in children with neuromuscular disease and muscle weakness, spontaneous breathing trials with or without supported breaths may not be successful as the respiratory muscles may not be able to generate the flow needed to trigger breathing support. Therefore, in these children extubation directly onto NIV with a set ventilatory rate may be a preferred strategy. Extubation directly to NIV may also be a strategy in children where oversedation may need to be avoided to preserve respiratory drive.

Tracheostomy Insertion

Unlike in adult ICUs, tracheotomy insertion to facilitate longer term ventilation weaning in the PICU is uncommonly carried out. This is because the relative risks and benefits of ventilation via an endotracheal tube and a tracheostomy tube often favour the former: tracheostomy formation can be associated with a higher incidence of complications in children – reversal may leave residual stoma-related problems, airway reconstruction surgery may be needed, and tracheostomy care may still require management within a high dependency or a PICU environment. In comparison, endotracheal tubes, particularly nasally placed endotracheal tubes, can be well tolerated by children with minimal sedation requirements.

However, in those where extubation is repeatedly unsuccessful or recovery is expected over months, a tracheostomy may need to be considered. Disease- and child-specific considerations must be made before deciding this: for children with poor baseline function and those with progressive neurodegenerative diseases, tracheostomy and long-term ventilation may add to the child's healthcare burden, and therefore may not be in their best interests (see the next section).

Ethics of Escalation of Care

Supporting respiratory failure in children with neurological disease can lead to situations where the level of care needs to be escalated, such that the healthcare-related burdens to the child may increase. This may occur, for example, when an ICU admission may be needed, or when long-term ventilation needs to be established. The burdens from the healthcare intervention/s will add to the existing disease-related burdens to the child and may reach the point where the appropriateness of the intervention may be questioned. This can be a commonly occurring scenario in children with neurological diseases. Children may be fully dependent on parents and carers with no prospect of ever reaching

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independent living. They may struggle to communicate. Some diseases may progress. Other diseases, although static in nature, will have sequelae that develop as the child grows, for example, progressive scoliosis and contractures in children with cerebral palsy.

The ethical question primarily is one of the appropriateness of withholding or withdrawing treatment which may otherwise prove life-sustaining. Unlike with adults, children have proxy decision makers in those with parental responsibility in matters relating to their health. The degree to which this is observed may depend on the legal jurisdiction: in the United Kingdom, children may consent to their own treatment even under the age of 16 years if they demonstrate the capacity to understand the risks and benefits of the proposed treatment. However, if they lack the capacity to consent, then parents are expected to provide consent with the view to maintain the best interests of the child.

The ethical and legal constructs to help decision making in the United Kingdom are outlined by the Royal College of Paediatrics and Child Health document *Making Decisions to Limit Treatment in Life-Limiting and Life-Threatening Conditions in Children: A Framework for Practice*[47]. Briefly, the following ethical considerations may help with decision making.

Expected Benefits

All treatments offered in medicine must have an intended clinical benefit. However, as often the case with children, the evidence base to justify treatment is extrapolated from adult data or relies on observational studies. In a heterogenous subgroup of children such as those with neurological disorders, the evidence is even more difficult to apply. The benefit of many of the interventions may be difficult to fully quantify.

Demands of Treatment

Whilst benefits are often sought, the demands of treatment may have a more dominant impact on the child's life. This is particularly true if the child is already suffering from significant burdens of their disease. In respiratory care, this may include interventions such as the unpleasantness of frequent airway suctioning, the discomfort from a tight-fitting NIV mask if worn for most of the day, and invasive procedures like insertion of venous and arterial lines as part of intensive care. As well as the demands of treatment, the burdens of ongoing survival may be considered where treatment would sustain life.

Locus of Choice and Autonomy

In children with neurological disease, it may not always be possible to seek consent to treatment due to lack of capacity. Parents will largely decide for the child in partnership with the medical teams. In most cases this will ensure that a child's best interests are maintained. However, on rare occasions, the parents' interests may not match those of the child. Clinical teams have a duty to safeguard the best interests of the child. Where there are disagreements between the medical teams and parents, processes must exist to resolve these. Conversely, consensus may also not ensure ethical validity of decision making.

Cultural and Religious Values

Ethics are not agnostic to wider cultural and religious societal values. Therefore, what may seem appropriate for a child in one country may not translate to another. Equally, the values of minority populations should be protected to avoid discrimination. Common ground should always be sought with an attempt to respect cultures and religions, while holding the best interests of children in primacy.

Justice

Although rarely spoken about, justice will always form the backdrop to decisions made particularly in publicly funded healthcare services. Intensive care and long-term ventilation services are expensive. Whilst they may bring benefit to individual patients, this may need to be balanced against the cost to other patients and services that cannot be provided when resources are limited. These arguments are rarely expressed when dealing with individual patients but may form part of the conversation when setting up services such as long-term ventilation units for children with neuromuscular disease.

Whilst there may not be a single formula by which to make the most ethically valid decision, a robust and consistent decision-making process is likely to help with this. Decision making should involve the clinical team, the child where possible and the family. An honest account should be presented by the clinical team about what any treatment entails, without making judgements about the child and family's life. Understanding should be checked. Alternative treatments should also be discussed. Evidently, decision making is a process rather

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than something to be achieved in a single meeting. Equally, when there is a long-term change in treatment, such as the institution of long-term ventilation, regular reviews should take place to make sure the burdens to the child have not exceeded the benefits.

If there is disagreement between clinical teams and the family, then second opinions should be sought. In the United Kingdom, formal mediation should be sought to try and reach common ground. As a last resort, courts of law may have to arbitrate where life-sustaining treatments are involved.

Transition to Adult Care

Respiratory diseases are the most common reason for death in childhood for many children with neurological disease. Good respiratory health, aided by good-quality respiratory care, may increase the number of children who will survive to adulthood. The care of these children needs to be handed over to adult teams to continue this during adolescence – the exact timing will depend on the health service. For some adolescents, the respiratory problems will be the same as in childhood, whereas for some new problems will evolve as the disease progresses or the sequelae such as scoliosis or contractures deteriorate.

There may not be a single model of transition for paediatric to adult care that works best across health services – each local service may have to adopt its own model; however, there are examples of best practice. The National Institute of Health and Care Excellence in the United Kingdom suggests the following overarching principles for transition of care in its guidance[48]:

- Involvement of young people in the design, delivery and evaluation of transition services to ensure smooth transition between paediatric and adult services.
- Transition support must be developmentally appropriate: This is of relevance for children with neurological disease who are likely to have development that does not match their chronological age. In addition, the expected trajectory of disease and future needs must be considered.
- Transition should focus on the positives, to emphasise what is possible and available to the young person, rather than what is not.
- Person-centred approaches should be used in transition planning. This should ensure that the young person is included in the transition planning, including planning support for education and employment, independent living and housing, community inclusion and well-being and mental health.
- Health and social care would need to work together in ensuring that the transition planning is integrated.
- Transition planning must be proactively managed by service managers in healthcare and social care sectors. In addition, a single named person may be best at co-ordinating the process.
- Safeguarding information must be shared amongst organisations: This has relevance in children with neurological disease as they may be particularly vulnerable. Child and adult safeguarding services will need to work for effective protection of young people.
- Each child must have a registered general practitioner (family doctor).

Further specific support has been developed for specific diseases in the United Kingdom, such as epilepsy, disability and children with special educational needs.

Conclusions

In this chapter we have highlighted the respiratory problems that can result in children with neurological impairment, the problems they can cause and strategies for effective management. Whilst many of the problems can be common to adults, childhood development can lead to an evolution of problems in the individual child. Good care may require anticipation of problems with possible prevention for instance, effective management of tone early to prevent more severe thoracic deformities. However, challenges remain in adopting evidence-based approaches, whilst also tailoring to individual needs.

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Chapter 21

Respiratory Therapy

Donatha Hornemann, with contributions from Regina Lomako and Martin Groß

Respiratory therapy and respiratory therapists are a quintessential part of the care of ICU patients. Respiratory therapy covers diseases of the airway, lungs and the respiratory muscle pump. In particular, respiratory diagnostics (e.g. spirometry), non-invasive and invasive ventilation, management of secretions, nebulization, oxygen therapy and other drug and non-drug therapies are included[1].

Respiratory care covers diseases from the field of pulmonary, cardiorespiratory, and critical care medicine. Respiratory therapists (RTs) are professionals who provide diagnosis and therapy care for respiratory impairments. They are experts for issues related to respiratory diagnostics, mechanical ventilation, weaning and pulmonary rehabilitation[2] and other mechanical, pharmacological and manual therapy methods. While RTs originated in pneumology about 70 years ago[3], their field of activity extended to a variety of medical disciplines such as neurology, pediatrics, critical care medicine and sleep medicine[4]. RTs also coordinate and monitor patient care and equipment, perform advanced respiratory care and evaluate the treatment. They educate patients and family caregivers about health conditions, equipment or community support groups and programs. RTs are considered consultants in all topics of ventilatory support. This includes all technical aspects of mechanical ventilation, ventilation strategies based on the pathomechanisms, airway management, pharmacotherapy, especially nebulized therapy, and research acquaintance with the latest guidelines, standards and important studies. RTs must be able to interpret laboratory data that affect the care of the mechanically ventilated patient and communicate with other professional groups[5]. Depending on the place of work RTs need special knowledge in critical care, pediatric or neurology, home ventilation or sleep medicine. RTs thus bear a considerable degree of responsibility for their patients and must be experts in their field. The American Association of Respiratory Care has defined levels of education[5]. RTs are largely absent in ICUs in the United Kingdom and European Union countries with some notable exceptions.

Respiratory Therapy Worldwide

The profession of respiratory therapist originated in the United States in 1947 with the establishment of the Inhalation Technician Association[6]. The current form emerged over time, with the organization eventually being renamed the American Association for Respiratory Care (AARC), a nonprofit organization that advocates for respiratory care[6]. The AARC has been particularly active in promoting recognition of the respiratory care professions. It was the AARC that worked to spread the profession outside the United States, finally resulting in RTs working in more than 50 countries[7]. The International Council for Respiratory Care (ICRC) was founded in 1991 with the aim to achieve high-quality respiratory therapy on an international level by establishing evidence-based standards. According to the ICRC, the following countries and areas are members: Argentina, Bahrain, Brazil, Canada, Chile, China, Colombia, Costa Rica, Finland, France, Ghana, Guatemala (Candidate status), India, Italy, Japan, Jordan, Liberia, Mexico, Nepal, Norway, Oman, Pakistan, Palestine, Philippines, Russia, Saudi Arabia, Singapore, South Korea, Spain, Taiwan, Turkey, United Arab Emirates, United Kingdom, United States and Yemen. According to Data USA there are 121,000 RTs employed in the United States, the majority in clinics, hospitals and inpatient facilities[8].

The countries mentioned are also those where RTs or similar professionals are established in the healthcare system. In addition to the ICRC, there are numerous other national organizations dedicated to respiratory therapy or respiratory care.

Overall, the penetration of RTs is still heterogeneous: “The presence of dedicated respiratory therapists is common in North America (85%), Middle East (85%), and Latin America (84%) but less common in Europe

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(26%) and Oceania (7.7%)"[9]. Also, there are no internationally accepted regulations for responsibility at the interface between RTs and other professions, and there are significant differences in training between countries.

Education of Respiratory Therapists

The profession of a respiratory therapist is regulated diversely in different countries. In some countries it is an independent education, in others it is based on a qualifying profession such as nursing or physical therapy. The duration of education in general is approximately 1.5–4 years, depending on the country and the form of training. Depending on the country and the training system, the overall duration of the basic training and advanced qualifications varies, as well as the duration of the theoretical and practical parts of the training.

Bachelor's and master's degree programs in respiratory care are offered[7,10]. In some countries like the United States more advanced degrees are strongly preferred.

A survey of RTs in the United States showed that most of them prefer to raise the academic standard to minimum of a bachelor's degree[11]. In other countries such as Germany, on the other hand, training continues to be largely without an academic degree.

Advanced Qualifications

In the United States, board-certified or registered RTs may later acquire specialty credentials as pulmonary function technologists, adult critical care specialists, neonatal/pediatric specialists, sleep disorders specialists or asthma educator specialists through the National Board for Respiratory Care[12]. Patients in neurological critical care often develop respiratory complications, which means that the collaboration with skilled RTs is essential for treatment[13]. Due to an increasing number of treatment slots for ventilator weaning in institutions offering early neurological-neurosurgical rehabilitation in Germany RTs are required to have expertise in this area[14]. Consequently, in Germany there is an additional qualification to train RTs in specific neurological aspects, comprising neurological diseases and their respiratory sequelae, neurogenic dysphagia, management of secretions and tracheal cannulas, weaning in neurological patients and neurorehabilitation[4]. Also in the United States it is promoted that RTs should have expert knowledge when working with neurological ill persons[13].

Work Locations

While hospitals are the primary place where RTs work, there are numerous other locations including doctors' offices, educational institutions, patient homes, nursing homes, rehabilitation facilities, weaning centers and sleep laboratories. These areas of work are highly dependent on national structures.

RTs are involved in assessing patients' symptoms, carrying out targeted diagnostics and initiating appropriate therapy together with the treating physician. In the best case, the decision-making process takes place in an interdisciplinary team consisting of physicians, RTs, nurses and therapists. The tasks of RTs vary greatly depending on the field of activity and specialty. Major differences exist between clinical and out-of-hospital settings, between pediatric and adult patients, or between neurology, pulmonology, critical care and sleep medicine. Whereas in the acute care sector it is often about maintaining and restoring vital functions, in the home sector it is more about maintaining the state of health. In the field of neurology, it is primarily neurological ICUs, intermediate care units, weaning centers or neurological early rehabilitation units where RTs are deployed.

RTs working in the industry are specialists in respiratory therapy-related products. RTs will then be involved in the further development of ventilators, tracheostomy tubes or other products. They may also be the contact person on site in clinical and non-clinical care to provide instruction on new products or to solve device-specific problems. In the United States RTs have the following tasks: adjustments of mechanical ventilator, regular checks of mechanical ventilator and recording of basic parameters (such as plateau pressures), identification of patient–ventilator asynchronies, assistance with resuscitation and intubation and placement of arterial lines, among others.

Respiratory Therapists' Benefit for Institutions

The healthcare system is facing change in very many countries around the world. Improving quality while reducing costs are universal goals. To reach these goals, adherence to standardized protocols and guidelines and the use of new therapeutic methods are required. RTs are competent to monitor adherence to protocols and guidelines and to introduce novel treatment methods[15]. RTs work at the interfaces between doctors, nurses, therapists

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and other disciplines, as well as at the interface between hospital and outpatient setting. RTs often retain contacts with the medical device industry and are aware of new products and innovations.

If there are RTs working in the team, complications are reduced and costs are lowered by shortening the duration of hospital treatment[16]. Also, unnecessary arterial blood draws and bronchoalveolar lavage are reduced, and unnecessary oxygen therapy or excessive flow rates are avoided[17].

Implementing RTs fosters training within the team or institution. This optimizes treatment standards and raises the overall level of expertise. A member of the team or institution RTs can optimally address existing challenges in training sessions.

Special Tasks of Respiratory Therapists in Neurology

The treatment of neurological patients with ventilation is very challenging and requires good monitoring of ventilation and neurological parameters alike[18]. Neurological disorders may involve the brain, the spinal cord, the peripheral nervous system and the muscles. Cough insufficiency, dysphagia and tracheobronchial retention of secretions are found in any of those categories and are thus ubiquitous problems in severe neurological diseases. While ventilatory muscle pump failure is found in spinal cord injury and neuromuscular disease, acquired hypoventilation syndrome and respiratory pattern abnormalities are found in brain diseases. Ventilatory pump failure can further result in impaired thoracic compliance, which again aggravates ventilatory pump failure[4].

Also, acute neurological diseases may lead to respiratory complications. Patients after stroke often need mechanical ventilation, and they are prone to pneumonia. Risk factors for stroke-associated pneumonia are well established and comprise mechanical ventilation, neurogenic dysphagia, severity of neurological disease and disorders of consciousness, cough insufficiency and chronic obstructive pulmonary disease (COPD) as a comorbidity[16,20].

If ventilation must be initiated in the acute phase of the illness, the goal of the RT is generally to wean those affected from mechanical ventilation. Progressive neuromuscular diseases and amyotrophic lateral sclerosis (ALS) form an exception, as trying to wean patients off the ventilator may be harmful or outright impossible. Weaning from mechanical ventilation or initiation of noninvasive or invasive out-of-hospital ventilation are thus common areas of activity for RTs in neurological disorders[4]. RTs also control out-of-hospital ventilation, adjust the parameters to the needs of the patients and adapt them to changes in the course of the disease. With respect to ventilation interfaces RTs adapt masks and mouthpieces, and they advise on tracheal cannula type and model.

Respiratory therapy aims to find a solution for cough weakness for example by using a mechanical insufflation-exsufflation (cough assist), by using manual techniques or by specifying storage and inhalation strategies.

RTs have profound knowledge regarding inhalation therapy including devices, selection of inhalers and patient education[21]. Patients who have been trained in the use of inhalers by RTs show better results[21]. COPD, as a highly significant comorbidity, can be treated more effectively and exacerbations can be prevented.

Respiratory Therapy in a Patient with Genetic Amyotrophic Lateral Sclerosis

The female patient, born in 1971, first visited our outpatient department in September 2022.[1] She received life-supporting invasive ventilation (IV), used a mechanical insufflator-exsufflator regularly and was capable of using an electric wheelchair with residual hand function. The cuff of the tracheal cannula was continuously deflated, and there were no signs of dysarthria or dysphagia. In 2015 a pathologic mutation in the superoxide dismutase 1 (*SOD1*) gene had been diagnosed. A sister of the patient died due to ALS in 2010, and the mother of the patient had died young at the age of 52; there was no information on the cause. The son was an asymptomatic carrier of the *SOD1* mutation, and the daughter did not undergo genetic diagnostics.

The patient started to receive tofersen 100 mg every four weeks via intrathecal bolus injection from January 2023. The intrathecally administered antisense oligonucleotide tofersen reduces synthesis of the SOD1 protein. In a recent phase 3 trial with an open-label extension design, tofersen had not reached the primary end point of decelerating the decline of the ALS-functional rating scale at week 28, but in the open-label extension, there was significantly less decline of slow vital capacity in the group, which started earlier with tofersen than in the delayed start group at week 52[22].

The patient was seen by an RT every four months to control mechanical ventilation and mechanical insufflation. This comprised taking the patient's history,

[1] This section was written by Regina Lomako and Martin Groß.

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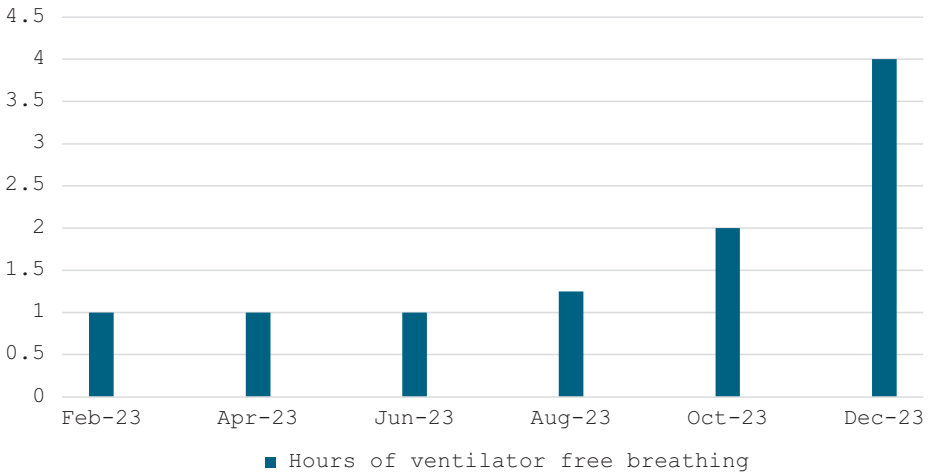


Figure 21.1 Capacity of ventilator-free breathing per day.

perfoming blood gas analysis and analyzing home ventilation data and alarm history. As the mechanical insufflator-exsufflator had initially been used with the tracheal cannula's cuff deflated, the RT advised using it with an inflated cuff. Additionally, the patient was advised by the RT on ventilation management including a cautious weaning strategy, adapted to the subjective capacity of the patient to breathe without the ventilator. Additionally, speech and language therapists performed flexible endoscopic evaluation of swallowing and tracheoscopy via the existing tracheostoma every 12 months,

The patient's history and data saved in the home ventilator showed that the spontaneous breathing capacity considerably improved from January 2023 to December 2023. For the reported ventilator-free breathing ability per day see Figure 21.1.

In summary, RTs as part of the interdisciplinary team not only controlled home ventilation and mechanical insufflation–exsufflation and advised the patient and her caregivers, but also helped document a possible positive effect of tofersen in a patient with lack of alternative to measurements.

Diagnostics

The following are particularly relevant for the diagnosis of respiratory complications in neurological diseases and can be performed and evaluated by RTs:

- Blood gas analysis. Blood gas analysis (arterial or capillary) provides information on respiratory (SpO_2, $SpCO_2$) and metabolic (BE, HCO_3^-) parameters and is a valuable tool for adjusting ventilation.
- Spirometry. Spirometry is used to measure the moving respiratory volumes. However, it is heavily dependent on the patient's cooperation. The method is performed at rest – sitting or supine – or under stress, as in spirometry.
- Peak cough flow. Peak cough flow is measured as a part of spirometry or using a peak flow meter. The device measures the maximum speed of the cough impulse. Active cooperation of the patient is required.
- Peak expiratory flow. As with peak cough flow, peak expiratory flow is measured as a part of spirometry or using a peak flow meter. The maximum expiratory flow is measured. Here, too, active participation is necessary.
- Polygraphy and polysomnography. Poly(somno)graphy is used to collect various parameters for sleep diagnostics. In polysomnography, brain waves (EEG) are also recorded, but not in polygraphy. These are the standard diagnostic procedures to identify sleep-related disorders of breathing. To detect hypercapnia, poly(somno)graphy is combined with transcutaneous capnometry.
- Diaphragm ultrasound diagnostics. Ultrasound diagnostics is a simple, non-invasive way to evaluate current diaphragmatic function and can be performed by trained RTs.
- Flexible endoscopic evaluation of the swallowing act is a safe and effortless way of assessing swallowing function.

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- Tracheoscopy: Tracheoscopy can be used to assess the trachea endoscopically. This involves, for example, injuries or deformities that can make decannulation difficult or imply a change in the management of tracheostoma or tracheal cannula.

The following measurements are not part of the diagnostic routine in clinical care but are used extensively for research on the respiratory muscle pump.

- Pi_{max}. The maximum static inspiratory pressure (Pi_{max}) is used to estimate inspiratory muscle strength. During this measurement, the valves are closed briefly during the inhalation effort. The ventilator can now measure the maximum pressure.
- Occlusion pressure. The occlusion pressure is the maximum pressure generated during the first 100 ms of inspiration. It reflects the central respiratory drive and the load on the respiratory muscle pump.
- Sniff pressure. For sniff pressure measuring, a measuring device is placed in one nostril of the patient. The pressure is measured during a quick, short, and sharp breathing maneuver ("sniff"). The sniff is a non-invasive way to assess inspiratory muscle force[23]. Measurement of nasal "sniff" pressure (SnPna) has higher diaphragm specificity compared with PI_{max}.
- Twitch pressure. The gold standard for assessing phrenic muscle function is pressure recordings after electromagnetic stimulation of the phrenic nerve, called twitch pressure[24].

Treatment for Insufficient Cough

Impaired tussive and mucociliary clearance increases morbidity and mortality in neurological and neurosurgical patients. Patients often cannot generate an effective cough to mobilize and evacuate secretions. Most often, the problem is weakened respiratory muscles[25].

To generate an efficient cough thrust, inspiratory muscles are needed to provide sufficient breath volume, glottic closure is needed to build thoracic pressure and expiratory muscles are needed to provide sufficient expiratory flow. Respiratory muscle training and manual and mechanical cough assistance can be effective for patients with cough insufficiency[25]. Implementation of these methods is a typical task of RTs.

Respiratory Muscle Strength Training

Respiratory muscle strength training is targeted to improve inspiratory or expiratory muscle force. Thus, there are expiratory muscle strength training (EMST) and inspiratory muscle strength training (IMT). The respiratory muscles can be exercised just like any other muscle in the body. Resistances during inspiration are used for IMT and resistances during exhalation are used for expiratory muscle strength training. RTs must adjust the resistance so that effective training can take place while avoiding overtraining. Respiratory muscle strength training is useful only if the respiratory muscles can be built up. Special knowledge of the pathology of the underlying disease is thus essential.

There are some studies that have investigated the effect of respiratory muscle training on pulmonary parameters in neurological patients. For multiple sclerosis an expiratory muscle training increased maximum inspiratory and expiratory pressure[26–29]. Similar effects have been shown for Duchenne muscular dystrophy[30–32]. In patients with spinal cord injuries at level C3 to C8, inspiratory respiratory muscle training has been shown to be a useful therapeutic option to improve cough thrust[33]. In post-stroke respiratory muscle weakness, IMT may also be useful. IMT has been shown to increase maximal inspiratory and maximal expiratory pressures and reduce the risk of respiratory complications. Respiratory muscle training should be performed for 30 minutes five days per week[34].

Bagging

Bagging is a useful option to increase thoracic volume, reduce atelectasis and generate an effective cough thrust. During bagging, additional air is insufflated into the patient synchronously during inspiration using a hand-held resuscitator. Breathing frequency must also be individually adapted to the patient. The method can also be used for tracheostomized patients. The breathing stroke via the handbag is delivered at the end of the patient's inspiration. This technique achieves an increase in inspiratory volume. The air can be moved past existing secretions in inspiration and can support the transport of secretions toward the larynx during expiration. Following the bagging, the patient is asked to cough. It is usually useful to provide additional manual support for the cough. Manual cough support can be provided either by compressions on the thorax or by pressure below the

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epigastric angle. Bagging should be used with caution in patients with COPD, which is often a secondary diagnosis of neurological disease[35]. The reason for this is that patients with COPD may develop dyspnea or pneumothorax when bagging is applied.

Air Stacking

Air stacking is a step up from bagging. Several inspirations are provided in succession with the handbag, without an expiration occurring in between. The air is thus stacked in the lungs. At the beginning only two inspirations are stacked. The number is then increased in consultation with the patient. Air stacking can be used for both cooperative non-tracheotomized patients and tracheotomized, independent of their capability to cooperate. A one-way valve between the bacterial filter and the resuscitator bag can be used to prevent intermittent exhalation in tracheostomized patients. During air stacking, a lifting of the chest should be observed[7,35].

Active Humidification and High-Flow Therapy

High-flow therapy is used by RTs primarily when there is either hypoxemia, inefficient respiratory gas conditioning or increased viscosity of the tracheal secretions. High-flow therapy can also be used to prevent tracheal cannula obstruction. By setting a higher flow, patients can be additionally supported in their respiratory work.

Aerosol Delivery Devices

RTs can provide the optimal devices for inhalation therapy. For example, the measurement of inspiratory muscle force can be used to decide between a dry powder inhaler and a metered dose inhaler. RTs must choose the correct device for nebulizing. The type of nebulizer determines the size of aerosols and thereby the location of the deposition. Inhalation drugs can be administered using either a mouthpiece or a face mask. RTs have to keep in mind pathology, best place for deposition and patients themselves – for instance level of consciousness, individual preferences and individual training in the use of inhalants – to determine the best device[36]. The use of prechambers to improve aerosol deposition at the target site, as well as general recommendations on inhaled substances are also within their remit.

Vibration and Oscillation Therapy

High-frequency oscillation vests can be used to improve secretion mobilization, depending on the underlying condition, called high-frequency chest wall oscillation (HFCWO).

For HFCWO, vests are put on the patient and mechanically generate high-frequency vibrations. These in turn are transmitted to the chest. The oscillations generate gravitational forces and change the viscosity of the secretion. This results in easier mobilization of secretions[37]. Ventilated patients may benefit from twice-a-day application[38,39].

While HFCWO has been shown to be effective in acute respiratory failure or COPD, there is insufficient evidence to support its use in neurological and neurosurgical patients[40].

Intrapulmonary Percussive Therapy

An alternative to HFCWO is intrapulmonary percussive ventilation (IPV). In this form of therapy, air blasts with high gas flow rates are applied via the mouth in spontaneously breathing patients. IPV is also applicable in neurological and neuromuscular diseases. Studies show that pulmonary infections and hospitalizations can be reduced by the therapy method[25,41]. IPV can also be used in tracheostomized patients to improve gas exchange and expiratory lung function or to specifically prevent pneumonia[42].

Autogenic Drainage/Active Cycle of Breathing Techniques

Manual chest compressions to assist expiration can improve secretion mobilization in both ventilated and non-ventilated patients (Figure 21.2). This technique involves placing the hands on the bony thorax and manually assisting expiration. This results in a greater exhalation flow rate and secretions are moved toward the larynx. They can then either be coughed up and swallowed or aspirated endotracheally.

Mechanical Insufflator-Exsufflator

The mechanical insufflator-exsufflator is a respiratory therapeutic aid that is intended to support or imitate the physiological coughing through positive pressure during inspiration and negative pressure during expiration (see Chapter 10). For the first treatment, it is

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Figure 21.2 Manually assisted autogenic drainage. © D. Hornemann.

recommended to choose lower pressures to get better patient compliance for the therapy. In most cases, higher pressures can then be applied in the following therapy units. In addition to the pressures, insufflation time and exsufflation time are also decisive for efficient secretion mobilization.

Specific Positioning Techniques

To support manual and mechanical techniques, specific positioning techniques can also be used. The aim of the positioning techniques is to mobilize secretions, improve ventilation and oxygenation and prevent atelectasis and dystelectasis. Drainage bearings with head down position and torsional stretch position are examples.

Inhalation with Capsaicin

To promote sensitivity in the pharynx and to induce coughing, RTs use inhalation with capsaicin, which triggers a coughing stimulus[43]. It is used both to promote sensitivity and to strengthen the coughing force.

Pharyngeal Electrical Stimulation

Neurogenic dysphagia is a common symptom of neurological disabilities. Stroke, Alzheimer's disease, traumatic brain injury, critical illness polyneuropathy, Guillain–Barré syndrome, multiple sclerosis or ALS are just some of the diseases that are often associated with dysphagia. In some diseases, neurogenic dysphagia is not progressive, while in others it increases as the disease progresses.

Pharyngeal electric stimulation (PES) can be used to promote sensitivity by neurogenic dysphagia. In PES, a nasogastric tube equipped with two electrodes is inserted through the nose. The two electrodes are located at the level of the upper esophageal sphincter and stimulate the pharynx and the cranial nerves involved in swallowing with low currents. People after a stroke show significant improvements in swallowing through PES. Furthermore, the time until decannulation can be reduced[44,45].

eHealth

eHealth is an ever-growing part of healthcare systems. Its importance is steadily increasing due to lack of qualified personnel and time and general digitalization. Telemonitoring, mHealth and telemedicine are all part of eHealth. *Telemonitoring* describes the possibility of directly transmitting digital data such as ventilation or vital parameters. The major benefit is that deteriorations can be detected earlier and adjustments to current therapies can be made more quickly. For example, if the tidal volume is not reached, ventilation pressures can be adjusted directly via remote access. *mHealth* comprises mobile health applications for smartphones that are designed to promote and support health. *Telemedicine* can take place in acute situations as well as in the care of the chronically ill. In the form of televisits it serves as a digital variant of regular care, while teleconsultations can be provided by an expert in acute situations.

Telemonitoring can bring experts digitally on site or obviate the need for long travel times for checkups. In the form of email chats, telephone and video calls and application-based monitoring a wide range of options is available[46,47]. Teleconsultations, telerehabilitation, telediagnostics and telemetry belong to telemedicine services[48]. Telemedicine is a possibility to optimize healthcare services. Overall, eHealth produces copious amounts of data (Big Data). The potential of Big Data is enormous and can make medicine more individualized. Artificial intelligence should make it possible in the future to link many more parameters together to make better prognoses.

RTs can evaluate digitally transmitted data and intervene promptly. Despite the many positive aspects of the digital transformation in health care, the practitioners must be vigilant to ensure that the users are not overwhelmed by the large amount of data and interpret changes in parameters incorrectly. Comprehensive training is incredibly important to avoid hasty hospital

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admissions based on uncertainties of those who interpret the data and placing an additional burden on hospitals.

The COVID-19 pandemic has contributed to more widespread use of telemedicine in health systems in many countries than before, or to optimization of the functioning of existing systems. Nevertheless, there often is a lack of resources and knowledge to utilize the technology[49].

RTs can telemedically train patients in the use of pulse oximeters, inhalation, ventilation and oxygen equipment or other medical devices. Symptom queries or instructions for symptom relief are also possible. RTs can provide counseling on dealing with shortness of breath or teach breathing techniques[49].

Patients with neurological diseases often have mobility restrictions. Thus, telemedical consultations are a great relief.

In some countries, the term teleneurology has become established. This refers to information and communication systems for neurological care when healthcare professionals and patients cannot be in the same place at the same time[48]. RTs can perform telemedicine tasks independently, thereby participating in improving patient health care and relieving the burden of inpatient facilities[49]. In the United States, RTs are already telemedical monitoring the respiratory parameters of patients with ALS. There, under the guidance of RTs, the results of the telemedical functional tests are similar to the traditional approach. In the future, RTs could perform telemedicine monitoring in addition to working in clinical and out-of-hospital sites[50].

Conclusions

Respiratory therapy is an important cornerstone of care of neurologically ill patients with respiratory impairment. RTs working in a neurological setting must be experts in respiratory aspects of neurological disease and intensive care and in management of pulmonary comorbidities and complication. RTs are not only required from a professional point of view, but having RTs as team members likely reduces costs through shorter hospital stays and improved documentation (e.g. weaning protocols). In future, they should be consequently involved in the treatment of neurological patients with respiratory impairment. They also should contribute their expertise to the development of new eHealth technologies.

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Chapter

22 Quality of Life in Mechanically Ventilated Patients

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Since 1907, when Johann Heinrich Dräger introduced the first device for mechanical emergency ventilation ("Pulmotor"), there have been substantial changes with regard to technical advances on the one hand and indications and outcome targets on the other hand. The rationale for implementation of mechanical ventilation has gradually been amended. Initially, the primary goal was to merely safeguard survival in emergency cases, whereas in recent years, the goal of long-term ventilation with primary outcome of survival has been gradually shifted to patients' quality of life (QoL), especially when usage may last for days, months, and years. Accordingly, the impact for patients and their surroundings is much more controversial. For long-term ventilation, the impact on patients' and caregivers' QoL may be diverse, and a fine-tuned discussion on pros and cons may be primarily driven by the question of securing QoL under mechanical ventilation.

In neurology in industrialized countries, mechanical ventilation is regarded as standard therapy for progressive neurodegenerative diseases (e.g. amyotrophic lateral sclerosis [ALS]; spinal muscular atrophy) and neuromuscular diseases (e.g. Duchenne muscular dystrophy). This chapter reviews our current understanding of QoL under long-term mechanical ventilation, especially in ALS, as this is often regarded a model disease for this setting. In these patients, it is usually meant to be a long-term therapy and increases survival for months with non-invasive ventilation (NIV) via mask[1,2] to years with invasive ventilation[3]. Across most Western countries, NIV is regarded the gold standard and only 1%–3% receive IV, with most of these cases in emergency tracheostomy[4,5]. Over the last decade, NIV in ALS has been improved as a result of application of measures such as cough assist techniques, control of excess salivation, and nutrition, avoiding the need for tracheostomy in the majority of cases[6]. Data concerning the long-term adjustment of NIV in ALS show that correction of leaks, management of obstructive sleep apnea, and adaptation to the patient's degree of ventilator dependence improve the prognosis[6]. Since then, ventilation has become an essential part of the treatment of ALS with considerable insights, including evidence of efficacy, indication criteria and time of initiation, ventilation parameters and adaptation strategies, treatment of complicating factors, transition from NIV to invasive ventilation, termination of NIV, and end-of-life management[7]. Accordingly, there have been reports of highly successful long-term ventilation via masks[8]. However, patients benefit from ventilation to varying degrees[9] and patients with bulbar symptoms show an increased risk of complications. The success of the measure in bulbar patients is strongly dependent on the physician's experience and the efficiency of symptom control using optimal equipment, especially the choice of mask[10].

Clinically, alveolar hypoventilation leads to sleep disturbances, motor restlessness during the night and fatigue and lack of concentration during the day[11]. The use of positive pressure ventilation can thus not only increase survival but also control these symptoms[9]. It may also have positive impact on secondary effects of chronic oxygen deficiency, including cognitive performance[12,13]. So overall, the physical benefit of ventilatory support is multifactorial and mostly undisputed. However, its use may have much more complex implications for patients and their families, including interaction with patients' QoL, which will be reviewed in the following discussion. The interaction of ventilation and patients' QoL is highly complex and depends on many factors, which may eventually again interact and interfere. Some patients decline ventilation, including NIV, due to the fear of losing autonomy, dignity, and QoL[14]. But those who opt for it consider QoL to be among the most important factors[15].

We hereby review some of the factors which may be considered in the clinical evaluation of short-term and long-term use of mechanical ventilation in the context of QoL.

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As physicians have a proactive role in the decision-making process[16,17] and physicians' depth of knowledge and professional experience mainly determine patient's preferences on ventilation[18], an in-depth knowledge of the complexity of decision making is essential.

Quality of Life

The diagnosis of a fatal disease such as ALS puts severe constraints on patients and their caregivers. Accordingly, the patient's depressiveness may increase and QoL may decrease shortly after diagnosis[19]. If patients survive long enough, QoL usually increases and depressiveness declines[20]. Contrary to popular belief[21], long-term ventilation therapy such as mask ventilation may not necessarily have a negative effect on the patient's well-being with increase of depressive symptoms[22] and may instead positively influence QoL[2,23]. Whereas some studies provide evidence for the lack of positive effect on QoL shortly after initiation of mechanical ventilation in ALS patients[24], other studies provide evidence that those subjects who survive long enough to adapt may benefit by using long-term ventilation: Compared to other approaches of standard care treatments, it probably improves both median survival and QoL[25]. Accordingly, patients on mask ventilation sometimes show a similar or even higher QoL than those without ventilation[22]. Whereas long-term mask ventilation is regarded as an appropriate measure by many clinicians in ALS, the extent to which patients benefit from early use of a tracheostoma is still heavily discussed. Many physicians regard the circumvention of tracheotomy the primary goal of ventilatory support for fear of a "locked-in syndrome"[26]. Accordingly, current practice in Switzerland and France tends to discourage the use of IV. However, it must be questioned whether this fear of IV is justified. In long-term invasive ventilation, 18% of patients develop totally locked-in state and 33% develop minimal communication state[27]. For those who preserve cognitive function to communicate via technical devices[28,29], there have been reports of preserved QoL[8,30]. In fact, invasive mechanical ventilation for patients who accept tracheostomy allows life prolongation and their QOL is not necessarily reduced; instead, QoL was similar in subjects with and without IV[31]. Also, long-term invasive ventilation has repeatedly been shown to have a positive effect on patients' QoL despite severely limited physical functions[32]. Accordingly, patients in the locked-in state, who were under ventilation, reported moderate to high levels of QoL[33]. And even patients in the locked-in state under long-term invasive ventilation reported mostly satisfactory QoL[8,30].

Factors in Patients' Psychosocial Adjustment

Although frequency of initiation of different ventilation measures should be determined by medical condition in ALS, attitude towards ventilation measures varies between centers[34] and countries[35,36]. Accordingly, frequency of initiation and termination of therapeutic means including mechanical ventilation show a broad variety across the world[37]. In Japan, for example, there is a strong preference for invasive methods[38], whereas in many Western countries these methods are rarely used. Legal and medical frameworks may partly explain these differences[39], including cost coverage of ventilation and of caregiver support. Decisions on ventilation may also partly be explained by personal preferences and cultural differences[35]. Personal satisfaction with the financing, healthcare provision, and medical infrastructure may all interfere with personal preferences regarding therapeutic measures including mechanical ventilation[40]. Finally, regulations may significantly impact therapeutic decisions, especially with regard to assistive devices, medical interventions and exit strategies to terminate measures[40] The right to withdraw ventilation may facilitate the decision to start ventilation in the first place[35] and the possibility of exit strategies, including do not attempt to rescusciate orders, are closely linked to favorable decision regarding ventilation[41].

A common reason for the lack of use of mechanical ventilation is the fear of a loss of QoL under these measures[42]. In line with this, healthy people significantly underestimate the QoL of patients with ALS under ventilation therapy[43]. This is also true for primary caregivers who are in close contact with ALS patients on an everyday basis[35]. Even doctors with little experience with these patients cannot imagine that the QoL under ventilation can be satisfactory; however, the more experience doctors have with ventilation therapy, the more their assessment matches the patients' self-assessment[44]. There is a general inability to anticipate the mental state and decisional preferences of another person and even of oneself, unless one has experienced the transitional state and the coping process in the course of a disease. Accordingly, many patients cannot imagine ever using ventilation before the onset of respiratory symptoms[45].

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However, as soon as the first respiratory crisis occurs, ventilation then suddenly appears to be an acceptable therapy for patients and relatives. Once patients have decided in favor of it, they very rarely revise this decision again[45]; they are usually very satisfied with the decision[46,47] and would almost always opt for it again[8].

Understanding Quality of Life under Ventilation

If QoL is defined as a purely health-related aspect, as it is often done in the literature and in questionnaires, then lower QoL is associated with greater physical limitation. However, if QoL is understood as a subjective, hedonic concept, then it can be maintained independently of physical symptoms, as has been described for various diseases by Herschbach in 2002 as the *well-being paradox*[48]. In this context, QoL, like affect status, can be seen as a measure of successful psychosocial adjustment during the course of an illness[49].

The prognosis of mandatory ventilation (and nutritional support) in combination with progressive immobility is a shock for patients and presents them with a maximum emotional challenge as life plans must be rewritten[50]. Shortly after diagnosis, many patients show reactive depressive episodes accordingly[20,45]. Those patients who already had depressive episodes in the course of their lives are also those who react to the diagnosis with depression[22]. Depressed ALS patients may present with depressive symptoms in the year before diagnosis already[51]. In the weeks, months, and years following diagnosis, well-being and anxiety have to be managed[50]. Ventilation, in particular, confronts patients and their families with a distinct challenge in terms of physical, mental, and financial stress[52]. However, this burden can have a variable influence on the QoL of patients and their relatives, depending on the subjective evaluation of the situation[53]. Each patient shows a highly individual way of dealing with this situation with possible dynamics throughout the disease course[20]. However, there are also general tendencies, such as the fact that the loss of physical integrity does not necessarily have to be associated with a loss of well-being[54]. Accordingly, physical function and time since diagnosis are not predictors of poor psychosocial adjustment per se even in most severe neurological diseases such as ALS[8,30,55]. In locked-in ALS patients with no or minimal residual physical function and invasive ventilation, the majority had a positive QoL[8]. Also, in the study by Hermann and colleagues, similar phenomena were found[30]. In other diseases, too, where patients are in the complete locked-in syndrome and thus in complete physical dependence (e.g. on technical devices such as ventilators), there are repeated indications of a satisfactory QoL despite physical restrictions[56].

Time to Adapt

Such positive phenomena in the context of ventilation are partly, but not solely, due to the physical effects of ventilation[9]. Among others, time to adapt may be an extrinsic factor which strongly interferes with patients' QoL under ventilation. Even if shortly after diagnosis well-being initially drops[19], people with severe neurological diseases may report QoL scores that in the long term adjust to an individual level of QoL that corresponds to that before the disease. Accordingly, patients simply need time to cope with the challenges and obstacles they must face in the context of severe physical restriction and physical dependency on people and interventions (including mechanical ventilation). If this time is granted, psychosocial adaptation may be possible. Among other variables, this process is driven by the leveling of outlier values according to the principle of *regression to the mean*[57]. Accordingly, there is a certain selection bias in such studies reporting on high QoL in locked-in state for instance, as they mainly include patients who have survived for a long time. Such studies only very rarely include so-called rapid progressors, in whom the rapid physical deterioration makes a psychosocial adaptation to the disease and the circumstances of the disease impossible[20]. Accordingly, there was a negative linear relationship of average speed of physical decline per months and patient's well-being, indicated by decreased QoL and increased depressiveness[43]. Long-term ventilated patients and their families participating in studies have often had sufficient time to come to terms with the situation, which is associated with a higher QoL. In this context, good timing is mandatory in the discussion for the implementation of ventilatory support. Making the decision to use ventilation shortly after the patient and family are first confronted with the diagnosis is an almost insurmountable task given the multiple consequences for the patients and their social environment[58]. The slower the physical symptoms progress, the more time the patient and the relatives have to emotionally adapt to the changing living conditions and to come to terms with profound decisions on mechanical ventilation. Patients

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prefer to be living in the moment and the notion of "right thing, right time"[59]. Yet, granting too much time may lead to the initiation of ventilation in a respiratory crisis[60] which is true for 81% of those cases treated via tracheostomy in the United Kingdom[4,5]. Especially when acute medical indications for invasive ventilation suddenly arise, patients and families often lack the much-needed time to come to terms with the situation. In clinical practice, social competency and professional experience of the treating clinician are mandatory for a timely discussion on appropriate therapeutic measures including ventilation.

Social Inclusion

Another important extrinsic factor that may determine good QoL in long-term ventilated patients is sufficient social support[43,55]. Good social support is a prerequisite for good psychosocial adjustment[35] and may be provided by families, friends, and professional multidisciplinary teams[61]. Patients with children also have a higher QoL[62]. Family and social contacts are the most important and most frequently mentioned factors for a good QoL for patients with a fatal diagnosis[49,63]. Satisfaction with these social aspects is also often high, so that the conditions for a good QoL are given in many long-term ventilated patients[58]. On the other hand, the QoL of relatives who are mostly the primary caregivers is massively endangered by the burden of invasive ventilation[53]. Patients' and caregivers' QoL are closely interrelated and close attention to social surroundings is required when discussing insertion of ventilation[64]. Overall, family functioning may be the most important predictor of QoL and mental health under ventilation[65].

Finally, as an extrinsic factor, communication should be mentioned as an important key to a good QoL under ventilation therapy, as it can give the patient a subjective feeling of autonomy, independent of physical limitations[66]. Therefore, patient communication should be enabled through the use of partner-assisted scanning, eye-tracking devices or brain–machine interfaces (including brain–computer interfaces), even in the advanced state of the disease[67]. Communication is an essential factor for social interaction so that patients can express themselves as human beings with thoughts, wishes, and needs even under ventilation therapy[68]. Thus, these devices allow for social inclusion which is mandatory for patients[69]. Overall, QoL also under mechanical ventilation may be secured if communication is restored[67].

Intrinsic Factors of Quality of Life under Ventilation

In addition to these extrinsic factors, there are also intrinsic factors that explain the well-being of many ventilated patients. Accordingly, the fact of using mechanical ventilation can have a positive psychological effect which again facilitates QoL[70]. This effect can be explained by an internal locus of control, that is, the feeling of being at the mercy of an acute respiratory crisis can be controlled by the use of ventilation, which provides reassurance for the patient and their relatives[11]. Thus, the patient is no longer at the pure mercy of nature and thus, mechanical ventilation may facilitate the patient's feeling of autonomy. Another important intrinsic factor of successful psychosocial adjustment is successful coping strategies such as response shift, that is, a change in the focus of attention of what is regarded to be important[71]. This is a strategy used by ALS patients with successful psychosocial adjustment[55,72]. Accordingly, more advanced patients mentioned communication and medical care as important factors determining QoL, whereas patients in the early stage of the disease did not mention these areas[22]. Another important coping strategy for successful psychosocial adjustment is reappraisal and reframing[55,73]. This involves reinterpretation of a situation or event by trying to see the situation in a different context (frame). Those patients who regarded themselves as not defined by physical restraints in the context of ALS for instance, but rather relied on intrinsic strengths not affected by the illness, such as spiritual well-being, had a significantly higher chance of good psychosocial adjustment[22]. Patients can train this focus on areas of life that are important to them and actively change their focus of attention in the sense of mindfulness, which can lead to a significant improvement in QoL regardless of physical status which may require ventilatory support[74].

Cultural Factors

As mentioned before, the appraisal of ventilatory support is strongly associated with cultural context[37]. Cultural context may define general beliefs and attitudes with regard to the question of whether a life under mechanical ventilation is regarded to be worth living or not and medical and legal frameworks are adapted accordingly. Especially more collectivistic thinking societies with strong concepts of family obligations would require that family members be kept alive at all costs[75]. Accordingly, in countries such as

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Japan, where technical extensions of possibly limited physical functions is regarded to be a positive and most favorable approach within the society, invasive mechanical ventilation is much more favored than in other countries of the world and received by 33% of subjects[37,38]. In other countries in Europe, there are heterogeneous preferences observed, with usages of 1%–11%[76–78]. In Germany, invasive ventilation rate is around 9% and even NIV with 20.8%[79] is less frequently used compared to IV in Japan. In general, Europeans and European Americans show a trend to be more negative in both their general attitudes and their personal desire for life-supporting measures, including ventilation; they mention "I do not want to live as a vegetable" and "I do not want to be a burden" in addition to the lack of autonomy as a feared outcome of life-sustaining measures[75]. For North American ALS patients autonomy remains the core basis of respiratory management[37,80]. This shows how much personal decisions on mechanical ventilation may be adapted according to cultural context[35,81]. In a transnational comparison between Sweden, Poland, and Germany, there was evidence of increased frequency of mechanical ventilation, the more liberal the society was regarding beliefs and values. More conservative and traditional values were associated with a reduced likelihood to decide for any therapeutic intervention which may prolong survival, including mechanical ventilation[35]. When patients are faced with fatal illness, they also often become more philosophical about their life, including dealing with questions of spiritual beliefs and meaning of life. In this process they many seek comfort in spiritual or religious philosophies, which may provide comfort in these insecure times[82]. Accordingly, religious well-being was shown to be positively associated with QoL or vice versa[83]. There may also be other protective factors which may be associated with higher well-being, including higher education status which may facilitate the retrieval of protective coping strategies such as active coping ("where do I get support from?") and spiritual resources ("I am more than my physical existence")[22].

Personal Factors to Consider in the Context of Patient QoL

When the initiation of mechanical ventilation is considered to improve the patient's QoL or when preferences regarding mechanical ventilation are discussed, the families' emotional/physical stress and financial burden must be taken into account.[47]. This is especially true for countries where financial support of therapeutic approaches, including ventilation and the follow-up costs, is not fully covered by the health insurance system[18,39]. Home ventilation required service provision by a specialized multidisciplinary team[85], with financial costs of about $153,252 in 1993[86]; nowadays it is estimated to be more than 200,000 Euros per year.

Further, ventilation requires large personal resources, including 24-hour care, which in many countries is mostly granted by family members, and thus imposes a significant burden on families. It requires a constant change of caregivers and equipment and produces limitations in many respects[87]. Accordingly, patients' decisions on ventilation are strongly influenced by the concern for care demands placed on their families[15]. Those with higher income and more resources are more prone to decide for IV, even in highly socialized health systems[88]. Although a patient's QoL may improve, it is nevertheless a highly individualistic question to promote ventilation, especially in low-income countries, where families may lack financial and personal resources to support the patient under ventilation. But especially in these countries, where the financial burden for families is high, there is possibly also a very high family obligation to sustain a patient's life at all costs, as mentioned previously[75] and families may be ready to bear the financial burden for decades to reach this goal. In the end, it is their personal decision to do so. But doctors nevertheless may want to provide a finely tuned discussion on these factors, especially when personal resources are limited.

There are also disease-associated factors, including severe cognitive impairments such as dementia, which greatly interfere with patients' decisions. They may hamper decision-making capacity and affect acceptance or refusal of interventions, whereas mild cognitive impairment does not interfere[62]. Lack of executive capacities may attenuate the ability of introspection and insight into both illness and the consequences of long-term ventilation. Also, the use of other devices, including percutaneous endoscopic gastrostomy and prior NIV, strongly predicts the use of more invasive techniques such as IV[89]. So, decisions on mechanical ventilation and IV are closely linked to the general question of medical decision making. Interestingly, patients make a sharp distinction between non-invasive and invasive techniques[35]. NIV is viewed as a means to relieve symptoms of respiratory

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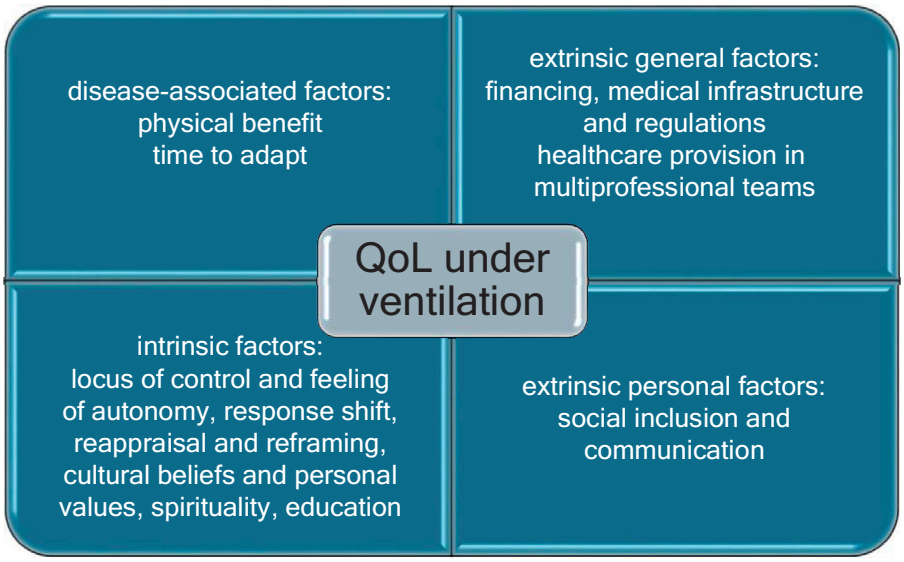


Figure 22.1 Summary of multiple factors which facilitate quality of life under mechanical ventilation. QoL, quality of life.

failure[90], but IV is rather viewed as taking over their breathing and thereby saving their life when they otherwise would die[91]. In this context, decisions, especially on IV, are determined by personal factors[35] and the main themes influencing decision making on invasive ventilation are mostly patient-centric[92]. It is usually a specific subgroup of patients who opt for IV, so it's usually a highly motivated, young, male patient[3], who has younger children and a spouse[38] and who is engaged in the family and/or the community; these patients usually have a thorough understanding of the alternatives to IV, also attributed to higher educational level[87]. So, personal factors play a major role in decision making on ventilation, especially on IV. If most of these personal factors are favorable, mechanical ventilation including IV may be a good way to secure QoL in these patients.

Figure 22.1 summarizes the factors that facilitate patient QoL.

Conclusions

In conclusion, current evidence suggests that good QoL can be maintained regardless of physical limitation in ventilated patients and is facilitated by extrinsic factors and intrinsic factors. Thus, not only the question of when but also the context need to be taken into account in the decision-making process for mechanical ventilation. Regarding long-term ventilation, it is a delicate decision process which must be patient centred and family oriented, and which must follow the principles of medical ethics: (1) beneficence, (2), non-maleficence, (3) autonomy, and (4) justice[93]. Severe neurological conditions requiring ventilation affect all areas of daily life of patients and their families. Despite the physical limitations and the dependence on medical measures such as ventilation, the patient's perception must not be reduced to physical symptoms, because QoL does not necessarily depend on the question of physical integrity and freedom from ventilation. Ideally, Decisions for or against ventilation should never be driven by pure medical or financial considerations. Instead, patients 'preferences must be regarded in personal, social, and cultural context. Simply providing (invasive) ventilation is by far no sufficient measure to secure QoL in patients, but ventilation may be a first and important step to secure QoL and preserve patients' feeling of the meaning of life.

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Chapter

23 The Caregivers

Victoria Kuhna

The underlying disease and the individual clinical picture determine decisions on long-term respiratory care. Patients may depend on intermittent or continuous mechanically ventilation but may also simply carry a tracheal cannula for endotracheal suctioning. In any of these situations patients need out-of-hospital intensive care by professional or family caregivers. Long-term respiratory care may comprise the possibility of weaning from mechanical ventilation or decannulation in non-progressive disease, when the condition of the patient improves, or may focus on participation and quality of life, when mechanical ventilation is a permanent requirement. For many families, the realization that mechanical ventilation is permanently necessary is an impetus to proceed with comfort care. Decisions can be different in chronic neuromuscular conditions where non-invasive ventilation can support life and promote quality of life for the time being.

Respiratory impairment not only affects patients but also their families and social interactions, particularly when patients are stuck at home. While long-term ventilated patients are often placed in nursing homes, there is an increased transition from in-hospital ventilation to home mechanical ventilation (HMV)[1], especially in high-income countries[2].

In low-, mid-, and high-income countries, family members who function as caregivers experience enormous burdens and a wide spectrum of fundamental challenges. Some of them are environment and culture dependent. For example, the fear of stigmatization in Nigeria[3] or lack of ventilators in Somalia[4]. Others, such as the lack of trained personnel[5], a negative impact on the physical and mental health of relatives[6], or the impact of the disease on the dyadic relationship between patient and caregiver are universal. In addition, a study conducted in Germany on amyotrophic lateral sclerosis patients and their caregivers showed that a significant number of caregivers must adjust their work commitments to care for home ventilated patients. According to Kaub-Wittemer et al.[7] about 69% of working caregivers change their work schedule, reduce hours, or take unpaid leave. Female caregivers are disproportionately affected, with 12% quitting their jobs compared to 3% of male caregivers[7].

This chapter explores the multifaceted challenges caregivers of home mechanical ventilated patients have to face and highlights the basic skills, challenges, and support systems that are essential for the care experience of patients ventilated at home. The chapter is divided into four pivotal sections, each delving into a specific dimension of home care for mechanically ventilated patients. Continuous learning and adaptation are crucial to keep abreast of the latest technologies and best practices in home ventilation care. Only caregivers who are equipped with the most current knowledge and skills can provide the best possible care. Additionally, training and education are equally important. Actively participating in training sessions and workshops not only enhances caregivers' skills and knowledge but also ensures that they are up to date with the latest advancements and methodologies in the field.

Basic Requirements for Home Ventilation

Operating and maintaining home ventilation equipment requires a diverse set of skills, particularly for caregivers who may not have a formal medical background. A detailed description of these skills covers technical, medical, and practical aspects:

- Technical skills involve understanding the functions of different types of ventilators and familiarity with settings like ventilation mode, tidal volume, respiratory rate, inspiratory time, end expiratory pressure, driving pressure, and oxygen flow as well as the resulting measured parameters. Additionally, it is required to safely start, stop, and adjust the ventilator and to have the ability to change modes and settings according to the patient's needs and healthcare provider's instructions. Also, there is a necessity of

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troubleshooting skills for identifying and resolving common issues like alarms, disconnections, air leaks, or power failures. In home ventilation management, certain key medical and health skills are critical. First, patient monitoring is crucial. It involves understanding and interpreting vital signs such as monitoring oxygen saturation, respiratory rate, heart rate, and blood pressure and signs of distress or changes in the patient's condition. Airway management is another critical skill, requiring basic knowledge of airway anatomy and physiology as well as practical skills in managing the airway, including techniques like suctioning, positioning, and ensuring that the airway remains open and clear. Additionally, maintaining hygiene and preventing infection are paramount. This includes employing techniques to keep the equipment clean and carrying out regular cleaning and disinfection of ventilator components and accessories. Together, these skills form a comprehensive approach to ensuring the safety and well-being of patients on home ventilation.

- Key practical skills are essential for managing home ventilation. Regular maintenance is vital, encompassing routine checks and upkeep of the equipment, such as changing filters and checking batteries. It includes maintaining schedules and tracking service needs for optimal equipment function. Emergency preparedness entails knowing procedures for ventilator failure. This involves skills in manual ventilation with a resuscitation bag and understanding when it's necessary to seek emergency medical assistance. Moreover, effective communication and meticulous recordkeeping are essential skills, involving clear dialogue with medical staff and detailed documentation of ventilator use and patient status. Together, these practical skills ensure a comprehensive and safe approach to the management of home ventilation systems.
- Emotional and psychological skills are integral for managing both the patient-caregiver and personal relationships in home ventilation care[8]. The quality of the relationship before the illness impacts the current caregiver–patient dynamics[9].
  A compassionate approach that acknowledges emotional needs and supports the personal relationship is key, as is effective communication – potentially including augmentative methods (augmentative and alternative communication) – to foster trust and understanding, ensuring care meets the patient's desires[10]. In addition to these interpersonal skills, stress management is crucial for caregivers. They must have access to and be proficient in techniques that help manage personal stress, thereby preventing caregiver burnout. This aspect of caregiving is often overlooked, but it's vital for maintaining the mental and emotional well-being of caregivers, which in turn affects the quality of care they provide. Reducing the burden of care by seeking help from others, maintaining social networks and participation as well as psychological counseling are important strategies to reduce distress.
- Coping strategies of these caregivers may vary from person to person and are based on the relationship to the patient, the educational background as well as psychological factors (e.g. emotions)[11]. Cultural background and societal influences also have a tremendous effect on coping mechanisms[12] and the implementation of care for a person in need. Therefore, there is no general answer available to the question of how relatives who function as caregivers deal with a ventilated family member. Each culture deserves special attention in this regard. Nevertheless, the provision of technical implementation, education of the caregivers at the initiation of treatment as well as follow-up services at home are crucial[2] and needed worldwide.
- 24/7 availability of technical assistance on site or through a technical support call center is essential to minimize potential risks for patients[13] and may decrease the stress family members experience.

Caregivers of home-ventilated patients encounter a range of threats and challenges that span physical, emotional, and environmental aspects. Physically, they are prone to musculoskeletal injuries from activities like lifting or repositioning patients, leading to back injuries, muscle strains, and other related issues. The continuous nature of care for ventilated patients often results in caregiver fatigue, impacting their physical health.

Emotionally, the demanding nature of their work may result in significant stress, potential burnout, and psychological strain, often causing sadness, anxiety, or depression. The intensive care required can also cause social isolation as caregivers become disconnected from their social networks.

From an environmental standpoint, caregivers in home care environments face environmental risks like poor ergonomics due to limited space and inadequate

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lighting and safety hazards from using medical equipment like ventilators. Systemic challenges include the financial cost of home care, loss of income, and lack of training and support, which may lead to mistakes and feelings of inadequacy, as well as legal and ethical issues around end-of-life decisions and patient autonomy.

Addressing these threats demands a comprehensive approach that encompasses proper training, physical and emotional support for caregivers, and a conducive home care environment. The implementation of supportive policies and systems is also crucial in mitigating these risks, ensuring the well-being of both caregivers and patients in home-ventilated care settings.

Support Levels for Caregivers of Home-Ventilated Patients

There are large variations in the organization and financing of local healthcare systems, making it impossible to point out every country's approach to HMV. Nevertheless, a review of the relevant literature has revealed the following offers of support around the world.

In-house nursing staff. Many countries offer in-house care services provided by specialized nurses. This can range from several hours per week to around-the-clock care. The extent of services provided by professional home care assistants mainly depend on health insurance coverage, the financial situation of the involved families, personal preferences, and availability. While all costs are covered in countries such as Finland, where a team of registered nurses continuously attends the patient[14], countries such as Germany, Bulgaria, Serbia[2], Spain[15], and Canada[16] mostly require copayments. No reimbursements can be claimed in other European countries such as the Ukraine, Bosnia, and Herzegovina[2]. In most Asian, African, and South American countries, inhouse nursing remains a privilege of the high-income population and is not supported by insurance. Due to this imbalance of support, many families are dependent on non-governmental organizations which go beyond the spectrum of what health insurances offer.

Spirituality and religious support

In many countries, spirituality and religious support groups have an enormous impact on the care of patients and their families, often shaping their emotional and mental well-being during challenging times. These groups provide a sense of community and understanding, offering comfort and guidance. Moreover, religious belief can play a crucial role in medical decisions. This can range from encouraging aggressive treatment in the hope of a miracle or assuming that it is forbidden to withhold or withdraw medical therapies, to the acceptance of long-term suffering as a part of the spiritual journey and finally to acceptance of death as part of God's plan. Notably, even followers of the same religion may interpret the implications of their religion with respect to decision making differently. This dynamic interplay between faith and medical choices underscores the profound impact of spirituality in health care.

A systematic review of the experiences of caregivers and parents of children with intellectual disabilities in Africa by Mkabile[3] in 2021 pointed out the poignant reality of daily struggles faced by caregivers. These included shattered expectations, difficulties in adjustment, the search for meaning in the context of the diagnosis, and challenges regarding the lack of specialized services (including educational, health, and social services). There is hardly anything else than religion and spirituality on which people can rely[3].

The fear of stigmatization and/or the lack of financial resources, as well as the lack of trained personnel, often leads to resignation to the situation and acceptance of death either because of forced inaction or as a punishment of the gods, for example, as in Nigeria[3]. Endorsement and support through clergymen are thus highly important for affected families to withstand this "outsider role" and to ensure health care for the patients.

Many churches have created private support groups. These are particularly present in Italy as well as in certain regions in the United States. This service is essential for most low-income families.

Governmental support for caregivers of home-ventilated patients. This support varies greatly. In countries like the Netherlands and Germany it may include financial aid for equipment and supplies, training for proper care techniques, respite care for temporary relief, counseling, and support groups to manage emotional stress[17]. Other countries, like Taiwan and Finland, have also been highlighted for their publicly funded, universal systems that are open to all residents and provide a broad choice of at-home or facility-based care, treating it as a human right and administered at the municipal level[18].

Social care/community services. Professional social work with people who are affected by impairments in the broadest sense is becoming increasingly important.

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Inclusion, in the sense of participation of people in the life of society, is anchored as a human right (United Nations Disability Inclusion Strategy) and thus defines the goal of professional social pedagogical activity. In addition to social work that is decidedly geared to the situation of the individual, its purpose is also to minimize social barriers and enable disabled people to participate in daily life activities. Though being a human right, this fact is predominantly implemented only in Western-oriented countries.

While certain community services are embedded into, for example, the German law (*Zivildienst*), which creates support possibilities for families of HMV patients financed by the government, the majority of non-high-income countries are dependent on donations and private charity programs and do not offer any government (subsidized) support programs.

Telemedicine. Patients on HMV are dependent on frequent visits of specialist care consultants to verify the proper function of their ventilator devices and to monitor the patient's physiological parameters[19,20]. Either several parameters are monitored and transmitted to a central control through a telemonitoring system[21] or simply digital consultations (audio or visual) with the involved physicians can take place. In both cases, this approach helps to decrease hospitalizations[22]. Nevertheless, a stable internet connection as well as confidence in the use of this technology is a prerequisite[19].

Supporting caregivers of home-ventilated patients involves addressing their emotional needs, providing education, and practical support. They must learn to operate medical equipment like ventilators, handle emergencies, and know when to seek professional help. Ongoing training is essential to keep them up to date with new practices and equipment.

Yet, the intensity of caregiving can lead to burnout, making respite care a critical service. This temporary relief allows caregivers to rest and recharge, ensuring that they can continue to provide care without compromising their well-being. Access to counseling and support groups where experiences and coping strategies are shared can provide a lifeline. These groups can be forums for emotional support but also places to exchange practical advice and information.

Financial concerns often weigh heavily on caregivers. Information on government benefits, subsidies for caregiving supplies, and potential tax relief can alleviate some of this stress. Moreover, home adaptations, such as lifts or ramps, can be financially demanding, so knowledge of funding sources for these modifications is invaluable.

Professional home healthcare services provide expert care to complement caregivers and offer them breaks. Legal advice on guardianship and patient rights is crucial for navigating healthcare and legal matters. Clear information on the patient's condition and care requirements supports informed decision making and advocacy. Community programs that offer services like meal delivery and medical transport reduce caregivers' daily load. Additionally, technology aids support through telehealth and organizational apps for care schedules and patient monitoring.

Networking with healthcare professionals and other caregivers can open doors to additional resources, advice, and emotional support. Connecting with these networks can help caregivers feel less isolated and more empowered.

Lastly, advocacy for policies that recognize, and support caregivers' roles can lead to long-term systemic changes. This includes pushing for legislation that provides financial support, professional training, and formal recognition of the caregiver's vital role in the healthcare system.

By ensuring that caregivers have access to the support they need, the critical role they play in the healthcare system is recognized and the invaluable service they provide to home ventilated patients is honored.

Conclusions

Concerning the complexity of diseases HMV patients are confronted with and the burdens that their relatives must face on a daily basis, it quickly becomes apparent that there are not enough support services providing help to and/or relief for caregiving families.

It is imperative to expand support programs worldwide and to acknowledge the effort and burdens family caregivers experience on a day-to-day basis. We must acknowledge that caregivers often work without adequate resources and recognition.

Society has a duty to alleviate this burden by providing appropriate support programs that not only offer practical assistance but also recognize and honor the significant emotional and physical efforts that these caregivers endure on a daily basis.

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Chapter 24

Palliative Care

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All human beings are born free and equal in dignity and rights, particularly the right to live, according to the Universal Declaration of Human Rights, proclaimed by the United Nations General Assembly on December 10, 1948[1]. The United Nations Convention on the Rights of Persons with Disabilities (CRPD), set up to guarantee that persons with disabilities enjoy all human rights, entered into force on May 3, 2008. The CRPD obliges participating countries to ensure equal participation and access to health care for people with disabilities[2].

Care of progressive disease which can rapidly lead to substantial disability, total dependency and loss of dignity is a completely different matter. Health care goals remain targeted to improving quality of life – a quality that is determined by the patient. Neurological patients with respiratory symptoms may require extensive technical and financial resources. Especially in low- and mid-income countries resources for optimum care are absent. The dilemma between optimizing care for one individual patient or providing basic care for multiple other patients has no universal solution.

Palliative Care and Neuropalliative Care

According to the World Health Organization (WHO), "Palliative care is an approach that improves the quality of life of patients (adults and children) and their families who are facing problems associated with life-threatening illness. It prevents and relieves suffering through the early identification, correct assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual."[3] This definition focuses on the severity of the illness and is applicable to life-threatening neurological diseases. Recently, a redefinition by the International Association for Hospice and Palliative Care has been published: "Palliative care is the active holistic care of individuals across all ages with serious health-related suffering due to severe illness and especially of those near the end of life. It aims to improve the quality of life of patients, their families and their caregivers."[4] As neurological diseases may be severe and associated with serious health-related suffering, but not necessarily leading to demise, the focus on end-of-life care makes this definition less suitable for a variety of life-threatening neurological diseases. In the context of neurological disease, the definition of the WHO is thus more suitable. Based on the WHO definition, a definition of "neuropalliative care" would be straightforward: "Neuropalliative care is palliative care in neurological disease." The rising interest of neuropalliative care has been reflected not only by recent research activities but also by the implementation of a medical guideline in Germany[5,6]. Current practice in the emerging field of neuropalliative care is mainly focused on outpatient care, while neuropalliative care on the ICU is still to be broadly implemented with palliative care currently in most institutions not being provided by neurologists but by other medical disciplines.

Specific Characteristics of Neurological Diseases with Respiratory Impairment

Neurological diseases with respiratory impairment can be stabilized by adequate care and life-supporting technologies for years or even decades. Even tracheostomized and mechanically ventilated patients may have a reasonable quality of life and a high degree of participation and they may genuinely feel their care is not extraordinary[7]. Nevertheless, respect for autonomy as a basic principle of medical ethics implies that a patient capable of judging has the right to reject life-supporting technologies. The patient's choice is again highly dependent on professional advice. Therefore physicians patients and their relatives are to balance rehabilitation, intensive and palliative care throughout the lifespan of the patient. Their common goal is to optimize quality of life by stabilizing physiological parameters, fostering participation and relieving suffering, without solely focusing on the number of days remaining.

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Palliative Care, Demographic Changes, Epidemiological Developments and Medical Progress

Several developments will strongly impact the need for palliative care and the scope of palliative care on an international level: aging societies and the rising prevalence of noncommunicable diseases, multimorbidity, neurological diseases and disability (see Chapter 2). Consequently, patients with a combination of neurological disease, cardiopulmonary comorbidity or older age will be more commonly seen. These changes in patient profiles directly point towards a rising need for neuropalliative care.

Medical progress and the evolution of healthcare structures also bring new areas into the focus of palliative care: Complex care models for severely affected patients such as early neurological-neurosurgical rehabilitation (ENNR) or out-of-hospital intensive care, where also a significant portion of patients suffers from neurological disease, each have their specific ethical and palliative aspects of treatment. In the context of neurointensive care, ENNR or out-of-hospital intensive care patients are often dependent on life-supporting technologies like tracheal cannulas or mechanical ventilation, either temporarily or persistently. Especially the long-term use of life-supporting technologies implies a specific need for ethical reflection and palliative care.

Palliative Care and Neurological Disease

People with progressive neuromuscular diseases and amyotrophic lateral sclerosis (ALS) are surviving longer and longer due to improved respiratory care[8], and neurointensive medical treatment options reduce the mortality of severe acute neurological-neurosurgical diseases[9]. These patients may suffer from fluctuating attention , awareness and a major deficit of storing short term memories, language, communication, higher brain performance, perception and mobility as well as from depression, anxiety, abdominal symptoms, pain, spasticity and social isolation. Many of these symptoms are amenable to palliative treatment[10]. Furthermore, there may be chronic disorders of swallowing, coughing and respiration with a permanent need for life-supporting technologies as stated in the last paragraph. This serious debilitating state has been seen as a chronic critical illness by some authors[11]. After intensive care treatment has been completed, self-care is often compromised and out-of-hospital intensive care may be required.

Palliative Care and Rehabilitation

Rehabilitation has been defined by the WHO as follows: "Rehabilitation is a set of interventions designed to optimize functioning and reduce disability in individuals with health conditions in interaction with their environment. Health condition refers to disease (acute or chronic), disorder, injury or trauma"[12]. This implies that even patients with chronic progressive neurological diseases as ALS or Duchenne muscular dystrophy, which inevitably result in respiratory impairments and finally the need for life-supporting therapies, are to be addressed by rehabilitation. Other neurological conditions such as upper cervical spinal cord injury or locked-in syndrome are not progressive but are comparable in terms of respiratory impairment and rehabilitative needs. All these patients need assistive technologies which may facilitate mobility and communication, such as electric wheelchairs and gaze-controlled communication devices, specific adaptations to their workplaces and multidisciplinary treatment. With the help of rehabilitation, they may be capable of substantially contributing to the societies they live in. The physicist Stephen Hawking is possibly the most prominent example, but there are many others such as Dinah Radtke, who participated in negotiating the CRPD[13], or Nathalie Scheer-Pfeifer, who edited a book on nursing and therapy in ALS together with one of the authors of this chapter[14]. These extreme examples of long term care could become far less extreme when palliative care and rehabilitation are synergistic concepts in neurological disease, and do not contradict each other. Therefore., some patients require both palliative care and rehabilitation at the same time. Every patient with a strong death wish deserves a comprehensive discussion on rehabilitation options. and expected limitations.

Palliative Care and Intensive Care

Today, palliative aspects are becoming increasingly important in intensive care medicine[15–17]. This is particularly important as physicians and relatives overestimate the prognosis of intensive care patients and underestimate mortality[18]. Clinicians perform poorly in predicting future cognition among ICU survivors[19]. Mortality in intensive care units is around 20%, but differs depending on a variety of factors as geographic region, structural aspects, specialist area and patient characteristics[20–25].

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Studies from different European countries, Australia, New Zealand, the United States, and Singapore[26–36] and a study from 16 Asian countries[37] showed that death in the ICU can be preceded by either full intensive care treatment, a waiver of cardiopulmonary resuscitation only, a waiver of escalation of intensive care therapy ("withholding") or termination of intensive care therapy ("withdrawal"). There is significant variability between different countries but also between different intensive care physicians in the same ICU concerning the extent to which withdrawal of therapy is practiced[38].

Intensive care patients may suffer from distressing symptoms such as delirium, traumatic stress, anxiety and depression[39]. Dyspnea and pain also play a major role in ventilated patients[40]. It is therefore necessary to integrate palliative medicine into intensive care as early as possible in order to correctly define therapeutic goals, avoid unnecessary suffering and provide emotional support for patients and their relatives[41–44]. Proactive palliative interventions in the ICU also reduce length of stay in the ICU and the hospital and do not increase or maybe even decrease mortality[45].

Palliative Care, Neurointensive Care and Early Neurological-Neurosurgical Rehabilitation

Neurological intensive care patients often present special challenges: The patients and their families often experience a sudden deterioration not only of bodily functions but also cognition and the treating physicians are confronted with a complex and uncertain prognosis[41]. It is estimated that around 14% of all intensive care patients and around 62% of patients in a neurointensive care unit need palliative care[46,47]. Palliative care treatment is also important for survivors after neurointensive care treatment and stroke[48,49].

In Germany, ENNR is preferably applied to patients with severe neurological and neurosurgical disease, who do not recover quickly, in specialized institutions, even if patients are still on mechanical ventilation. Oehmichen et al. reported a mortality rate in ENNR for ventilated patients of 23% in 2012[21]. In addition to diseases generally common in neurointensive care such as intracranial hemorrhages, hypoxic encephalopathies, severe traumatic brain injuries and cerebral infarctions, patients with so-called critical illness polyneuropathy and/or myopathy (CIP/CIM) are also cared for in ENNR[50]. CIP/CIM results from severe diseases requiring intensive care in any medical discipline, for example internal medicine and surgery. Affected patients are often elderly and suffer from multimorbidity, including chronic multiorgan failure. They may require life-supporting technologies such as mechanical ventilation, dialysis or left ventricular support procedures, often combined with delirium and disorders of higher brain performance[51].

Palliative Care and Mechanical Ventilation

Correctly indicated noninvasive or invasive ventilation therapy prolongs life and maintains quality of life in ALS[52,53], and the majority of patients with Duchenne muscular dystrophy have a good or very good quality of life and are satisfied or very satisfied with their health, even when being noninvasively or invasively ventilated[53,54]. Furthermore, noninvasive ventilation can be used to treat dyspnea, to enable transfer from the ICU to the palliative care unit and in patients who do not require intubation. However, this option often fails due to the regulations in the palliative care unit and hospice, as the possibility of ventilation is generally excluded in both places. While noninvasive ventilation might reduce dyspnea, the feasibility and benefits of noninvasive ventilation in palliative medicine have not yet been sufficiently studied[44,55–57].

Medical Indication and Informed Consent

A medical indication can be defined as "the reasonable professional judgement that a medical procedure is suitable and useful to reach a specific therapeutic goal with a certain probability"[58]. A given medical indication is the primary prerequisite for the application of medical therapies. If there is no medical indication – as is the case in mechanical ventilation of a dying patient – a medical therapy must not be applied and a current medical therapy must be stopped. Any medical therapy that is not medically indicated should not be proposed to patients or their legal representatives for consideration. Communicating, if therapies are not indicated, relieves the patient and family members and facilitates the decision-making progress. Also, a request of a patient or legal representatives to apply a therapy that is not medically indicated should not be followed by the physician.

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Finally – apart from emergency situations – the application of a medical therapy requires an informed consent by the patient or legal representatives. This means, that the benefits and risks of any therapy must be explained to the patient or legal representatives and have to be understood. The principle of autonomy implies that the patient or legal representatives ultimately decide about the application or nonapplication of a medical therapy.

Therapy Restriction ("Withholding") and Therapy Termination ("Withdrawal")

Therapy restriction means that if the patient's condition worsens, new therapies are not initiated and ongoing therapies are no longer escalated. In *therapy termination*, on the other hand, ongoing therapies are ended[59]. This may mean, for example, stopping catecholamine therapy, nutrition, fluids or mechanical ventilation. Removing an artificial airway access such as an endotracheal tube or a tracheostomy tube also constitutes termination of therapy. Restricting therapy is perceived by doctors and relatives as less psychologically stressful and ethically less problematic than terminating therapy[60]. Ethically there is no crucial difference between withholding a medical intervention and stopping an ongoing medical therapy.[61] All types of therapies must be examined equally to determine whether their implementation represents a benefit or a burden for the patient[62].

24.11 Euthanasia, Physician-Assisted Suicide and Letting Die

"*Euthanasia* refers to the act of intentionally ending the life of a patient by a healthcare practitioner through medical means at that patient's explicit request while *physician-assisted suicide* involves the provision or prescribing of drugs by a health care practitioner for a patient to end their own life"[63]. *Euthanasia* has been legalized in a minority of countries, representing a mere fraction of the global population[63,64]. Patients capable of making decisions and their legal representatives have the right to demand that life-sustaining therapies be stopped. In these cases the cessation of medical interventions that prevent death, such as mechanical ventilation, artificial nutrition and fluid administration, is *letting die* and not *euthanasia*[62]. *Letting die* is a passive process with continuation of comfort care while euthanasia is a sudden act.

The Medical Prognosis and the Patient's Wishes

Although the accurate communication of prognoses is ethically imperative, there is a lack of sufficient data for many of the diseases in neurological intensive care[65]. The prognosis and decision making in hypoxic encephalopathy are particularly well understood[66]. A study from Taiwan showed that patients with a history of cardiopulmonary resuscitation received palliative care team consultation more often than other intensive care patients[67]. The patient's age is another negative prognostic factor regarding the neurological outcome of various serious neurological diseases[68–71] and the outcome of intensive care treatment in general[72]. Rocker et al. showed as early as 2004 that the intensive care physician's assessment that a patient had a $<10\%$ chance of survival was a stronger predictor of mortality in the ICU than the severity of the disease, organ failure or the need for vasopressors[20]. Older neurointensivists also rate patients' prognoses as worse than younger ones do[73]. The establishment of additional high-quality decision aids is necessary[74,75].

The therapy goal should be changed to palliative therapy as early as possible if intensive therapy no longer meets the patient's wishes. Even if the general prognosis cannot yet be estimated with certainty, it may be possible to estimate whether the patient is expected to achieve a functional level that is acceptable to them. For this purpose, the wishes of the patient has to be recorded as early as possible. Patients who can give consent generally communicate their wishes. In many other, a loving will or prior expressed wishes are guides. If the patient's wishes cannot be determined, physicians and proxy must come to a reasonable consensus what is acceptable to their loved one. The truth of the matter is that families know very well and can use good judgment. For patients who have never been able to give consent (for example due to a congenital severe cognitive impairment), the course of action must be specifically determined based on the presumed benefits and potential harm.

Integrating Palliative Care into Intensive Care Medicine

Many practical approaches to integrating palliative care into intensive care medicine have now been examined[45]. The use of an end-of-life symptom management protocol

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is likely to be effective in ensuring patient comfort and in reducing distressing symptoms without hastening death[34,76]. Palliative care training for intensive care physicians, nurses and therapists improves communication skills and the ability to recognize the need for palliative care[77]. The use of a palliative care consultation service and the participation of a palliative care physician in daily rounds reduce the length of stay in the ICU without being associated with increased mortality[78–80]. The integration of a palliative medicine consultation service also reduces treatment costs[79] and promotes acceptance as well as decision making[81]. The use of specific screening tools regarding the indication for palliative care consultation in the intensive care unit is recommended in order to reduce the utilization of intensive care resources and to provide patients and their families with the optimal palliative care support[82,83]. Clinical ethics advice, for example in the form of a clinical ethics committee, reduces the length of stay in the ICU and increases the satisfaction of families and practitioners[84]. With an early family conference (<72 hours), a decrease in the length of time spent in the ICU was shown without an increase in mortality[45]. Structured communication tools reduce the duration of ventilation and intensive care stay as well as treatment costs[85]. A structured communication tool is listed in Box 24.1. When communicating the prognosis to family members involved in the decision-making process, forthrightness is needed from all parties involved. Time should be permitted to verify their understanding of the condition of their loved one and goals of care[86]. Cultural religious and spiritual aspects must also be taken into account in communication with patients and their relatives[87–89].

Box 24.1 Suggested structured communication tool

Introduction and role clarification

- Participants of the conference and their profession (in the case of team members) or their relationship to the patient (in the case of family members or friends)

Legal framework

- decision by the patient or legal representatives living will and advance directives

Prognosis

- probability of survival, disorders of consciousness, dependency on nursing, assistive technologies and life-supporting technologies

Patient´s description

- personal preferences, level of activity, mental well being, isolation

Patient´s wishes

- communicated at family conference, living will, treatment wishes communicated in the past, presumed wishes

Limitations of therapy

Cultural, Religious and Spiritual Issues in End-of-Life Planning

While it is not possible to cover such a complex topic in this book, we will mention cultural, religious and spiritual differences that are relevant on a national and international level. The concept of spirituality is currently undergoing discussion, while the fundamental aspects are that spirituality is "a human and individual aspect" "related to the connectedness and meaning of life." Spirituality and religiosity are overlapping concepts, and spirituality is applicable to nonreligious individuals. Spirituality is associated with quality of life in ALS patients and their caregivers[90,91]. A spiritual approach also fosters coping in stroke survivors[92] and is associated with the quality of life of their caregivers[93]. Spiritual care as the appropriate intervention reduced fear of death and helped develop hope in Iranian Muslims[94,95].

With respect to data and reflections on diverse ethnical identities, they are not meant to be discriminatory but intended to sensitize for the cultural aspects of palliative care. Studies of end-of-life planning from the United States reveal that African American and Hispanic individuals are less likely than White individuals to engage in any type of end-of-life planning activities[96]. Religious minorities groups are less likely to have an advance directive or a healthcare proxy and less likely to engage in end-of-life planning activities; they may consider pain and suffering as something to be endured, not avoided, and feel that only God has the power to make decisions about ending life. African American individuals are more likely to believe they would be given less-quality medical care if they had an advance care directive on file.

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A review with an international perspective pointed out that Islam values the sanctity of human life which may lead to unnecessary invasive treatments and protracted painful deaths for many Muslim patients[97]. Considering fundamental differences in the concepts of personhood, dying and death between the world religions, especially between Judaism, Christianity and Islam versus Hinduism and Buddhism, and fundamentally different perspectives on withholding and withdrawal of treatment, these differences must be taken into account in palliative care. Notably, a worldwide increase secularism is expected. Their views are is understudied with respect to end-of-life care since a 2007 landmark publication[98].

Culture, religiosity and spirituality must be addressed in palliative care. Spiritual care is part of the role of the neurologist and other disciplines and professions caring for neurological patients with respiratory impairment.

Basic Principles of Decision Making

Decision making in neurological diseases with respiratory impairment is complex in acute, subacute and chronic settings alike. Shared decision making (SDM) as the current standard concept is performed by the patient and the physician together, yet a general definition for SDM is lacking[99]. Additionally, patients with severe neurological diseases are often not capable of participating in decision making. Actually, the concept has been broadened, with caregivers being involved in SDM or with physicians responsible for most major decisions[100]. Additionally, the treatment team of a patient must be informed and involved in all aspects of decision making.[101]. Nevertheless, the complex process of decision making can be facilitated by using the following principles:

- If there is no medical need, medical therapies are not initiated or are discontinued if previously initiated.
- If there is a medical indication, but the informed patient or legal representatives refuse, medical therapies are not initiated or are discontinued.
- If there is a medical indication and informed consent of the patient or legal representatives, medical therapies are instituted.
- If an emergency or if the patient´s wishes cannot be clarified, therapy can proceed.

Patients and caregivers might be involved in SDM, but in this process they are influenced by the prognostic information they get from the physician. This information again is dependent on the knowledge, experience and personal attitudes of the physician. The physician is obliged to foster patient-centered decision making.

Critical Palliative Care Choices in the ICU

Critical palliative care is a fraught topic. Opinions are split when it comes to (1) when to approach patients, (2) how to honor a persistent wish to die, (3) which method of withdrawal from the respirator is the most humane and palliative, and (4) how to interpret the law of the state (or land).

We can look at this critical juncture from two major angles. First, patients with acute catastrophic brain injury, who are respirator dependent and comatose (or stuporous at best), will need a tracheostomy and percutaneous gastrostomy approximately two weeks after admission. For many families, this surgical procedure is a so-called “fork in the road.” Proceeding with it entails long-term care; not proceeding with it implies a transition to comfort measures and withdrawal of all supportive care. These decisions take time and require conversations with proxy. But in our experience these decisions are seldom problematic and occasionally palliative care teams and chaplain service become involved to provide further support, explanation and therapeutic and supportive listening with the aim to allow family expression of emotions, hopes and worries regarding the current medical condition and life stage. We often reframe the current situation and identify coping strategies during these tough times. By necessity, the attending intensivist is often the sole orchestrator of these conversations, and this requires skill and experience. We recognize this could be critically insufficient if such attributes are absent.

Second, it is much different if a fully alert and *compos mentis* patient repeatedly requests removal of ventilatory support. These situations occur not infrequently in patients with advanced ALS and occasionally after a recent severed spinal cord leading to tetraparesis and ventilator dependency. Whether to honor the request to turn off the ventilator requires further analysis by an ethics and palliative care committee. It is difficult to judge whether the patient’s request is a rational choice and whether the patient is capable of autonomous choice. Psychiatric evaluation may be needed but seldom, if ever,

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is a treatable mental illness diagnosed. Reactive depression is expected and not necessarily a mental breakdown. Once this request to die surfaces, the patient should be presented with all relevant facts and rehabilitation options. Postponing the decision is paramount if the patient is young and has not had severe additional brain injury or other major systemic organ failure, but some patients with a complete transection may continue to forcefully reject any such suggestion to delay. The ventilator can be withdrawn if the patient refuses to reconsider, because any patient may exercise the right to refuse life-sustaining treatment. These decisions can be incredibly stressful to caregivers who may disagree with the decision and long deliberations may be needed. Documentation of any decision made should be imperative and detailed, but we need better methods to document the issues at hand, the patient's understanding and the specific elements of what matters most to them.

Ventilator-Dependent ALS

Hearing that patients with advanced ALS were not aware that respiratory failure was going to develop is a cause of exasperation for intensivists. We estimate that fewer than half of these patients had such a decision discussed with their physician or neurologist. Even so, once informed, few make their decision before the emergency of respiratory failure even when suffering with the disorder for years. This causes immediate difficulty with obtaining consent in an emergency. Many neurointensivists have had patients with ALS triaged to the neuroICU with no prior family discussion or family understanding of the severity of illness. Physicians have a major responsibility to discuss the illness and its expectant prognosis in time[102], which is welcomed by most patients, but some patients postpone or avoid any discussion[103]. It has been shown that European neurologists including those specialized in the treatment of ALS are comfortable with responding to patients' requests concerning end-of-life practices but rather reluctant to play an active role with respect to end-of-life decisions. This could be overcome by palliative care training[104]. Although many patients choose life-sustaining measures at least initially, approximately one in five want to actively withdraw support. A Dutch cohort observed that in 2000–2005 14.8% of patients with ALS died during continuous deep sedation while 16.8% chose euthanasia or physician-assisted suicide. The proportion of patients choosing euthanasia or physician-assisted suicide was 20.2% in 1994–1998[105].

Acute Severe Spinal Cord Trauma with Ventilator Dependency

Another major problem is sudden devastating traumatic quadriplegia. Complete cervical transection with apnea usually precludes recovery, but up to 60% of the patients with injuries at the C3 level or lower may recover. The ethical questions in patients with traumatic quadriplegia and ventilator dependency are exceedingly difficult. It is unusual for a patient with full knowledge of the consequences to ask emphatically to have the ventilator removed. In follow-up interviews at rehabilitation centers, assessments were positive, with 92% of the patients following high spinal cord injury reportedly "glad to be alive"[106]. Although many patients express some degree of hopelessness and despondency, many also change their mind with the passage of time. Nevertheless, already during initial hospital treatment end-of-life decisions may be taken, with a study from the Netherlands reporting, that in the majority of deaths after traumatic spinal cord injury, end-of-life decisions had been taken, 89.5% of which were decisions to withdraw treatment[107]. A major retrospective multicenter observational cohort study using data derived from the American College of Surgeons Trauma Quality Improvement Program database was recently published and included patients with complete cervical spinal cord trauma. In 5070 patients with the age range of 16–90 years with complete cervical spinal cord injury treated across 477 hospitals, 960 (18.9%) had the respirator removed[108]. Major factors that were associated with this decision were advanced age, male gender, White race, prior dementia, reduced consciousness at presentation and a prehospital cardiac arrest and concurrent severe injury to the head or thorax. Other factors associated with significantly decreased likelihood of withdrawal of the ventilator included being African American or Asian.[109] There was significant variability across hospitals. Medicare or Medicaid insurance status increased the probability of withdrawal suggesting economic factors play a role but also comorbidity.

Socioeconomic disparities and insurance status thus clearly require attention and study.

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Medications for Symptom Control

Symptom control in neuropalliative care does not generally differ from the processes introduced elsewhere in this book (see Chapters 10 and 17). Dyspnea can be treated with opioids. When an adequate dosage of opioids is used, the risk of shortening the life of the patients through depression of the respiratory drive is negligible in cancer as well as in ALS[110,111]. The different opioids (e.g. morphine or hydromorphone), different ways of application (e.g. p.o., s.c., i.v.), different dosages (as for patients pretreated with opioids for pain) and different schedules of titration can be found in published recommendations. We think that sustained release morphine in doses as low as 10 mg–30 mg p.o. is effective for treating breathlessness in opioid-naïve patients. It is important to monitor for nausea and vomiting, which are the most common side effects[112]. Oxygen insufflation to treat dyspnea, in contrast, is ineffective and potentially harmful, as it can result in severe hypercapnia and ultimately hypercapnic coma. The risk of oxygen-induced hypercapnic coma is higher in neuromuscular disease than in chronic obstructive pulmonary disease[113,114]. If dyspnea is accompanied by anxiety or restlessness, treatment with benzodiazepines is beneficial, and if dyspnea is refractory, palliative sedation may be required[115,116]. Death rattle is a symptom that may trouble relatives of dying patients. While it is regularly treated with anticholinergics like glycopyrrolate or hyoscine butylbromide, there is still insufficient evidence for this treatment[117].

Termination of Mechanical Ventilation and Removal of Artificial Airways

According to most authors, ventilated intensive care patients die on average within the first hour after cessation of ventilation[118–120] and usually within one day[67,121]. Extubated patients die more quickly than nonextubated patients[118–120]. Data from neuroscience-ICUs are scarce. One study reported only one third of the patients surviving more than 24 hours after terminal extubation and the level of consciousness not predicting the duration of survival[122]. In particular, if an artificial airway is to be removed, it is advisable to have a benzodiazepine, an opiate and an anesthetic such as propofol on hand[123,124].

There is ample experience with the discontinuation of mechanical ventilation in ALS. The proportion of patients undergoing tracheostomy and consecutively receiving invasive ventilation in ALS strongly differs between countries worldwide. Drug therapy has been specifically described for the elective termination of noninvasive and invasive ventilation therapy[125,126]: In patients with residual spontaneous breathing under noninvasive ventilation drug symptom control with morphine and lorazepam i.v. resulted in a terminal phase with an average of 32 hours. In patients without residual spontaneous breathing under noninvasive ventilation or with invasive ventilation, deep sedation with lorazepam or midazolam and morphine led to a terminal phase with a rapid course of <1 hour.

Termination of life-supporting ventilation can lead to acute dyspnea, and the removal of an artificial airway can result in acute airway obstruction, tracheobronchial retention of secretions and consecutively acute dyspnea, too. In both procedures a high symptom burden is expected, and they share key requirements: First, the attending physician should have a detailed discussion with the patient and relatives or legal representatives, preferably involving a second member of the treatment team. This discussion should review the method of stopping mechanical ventilation, use of compassionate sedation and a general focus on comfort and relief of suffering; patients do not die gasping for air. The presence of a physician at the patient's bedside or in the immediate vicinity when implementing the measure is obligatory[127,128]. Relatives can be present when the procedure is performed. Haste must be avoided at all costs. The administration of opiates is quintessential in both termination of life supporting ventilation and the removal of an artificial airway with additional application of benzodiazepine or propofol, if needed. Also, the physician should remain in the room or in the immediate vicinity to monitor symptom control when the patient is dying. After the patient has died, there could be another conversation with the relatives, and the doctor finally offers to leave the room, so that the relatives can mourn in peace. Later, a debriefing should take place within the treatment team. The following two subsections suggest specific procedures for intubated patients and patients depending on life-supporting noninvasive ventilation and tracheostomy invasive ventilation.

Mechanically Ventilated Patients

The preferred method is compassionate palliative sedation. Short acting benzodiazepines (midazolam or lorazepam) are used for sedation, and opiates are applied

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i.v. to treat dyspnea. Doses should be slowly titrated to achieve desired palliative effect. Ketamine may be additionally used and best given as a continuous infusion. Again, once the patient is adequately sedated the *ventilator can be withdrawn* while continuing other palliative care measures.

Another possibility is to reduce FiO_2 to room air and positive end-expiratory pressure to zero. Sedation with opioids is titrated upwards if this leads to discomfort. This is then followed by weaning to pressure support, and its effect is assessed for at least 1 hour. The patient is placed on a T-piece or extubated. Once extubated the patient is calm and breathes with low frequencies until apnea.

Patients on non- invasive mechanical ventilation

After establishing a venous access, a dose of 5–10 mg of midazolam is administered in a bolus or via a short infusion (depending on body weight: body weight <40 kg = 5 mg; body weight >40 kg = 10 mg). An additional dose of 5 mg of midazolam can be administered if sedation is insufficient. The goal is sleep and quiet breathing.

In opioid-naïve patients, morphine in a dose of 10 mg is administered. If the patient is already receiving opiates, the sedation dose must be adjusted.

Propofol should be kept on hand as an additional sedative, but administration is rarely necessary.

With noninvasive ventilation, the doctor removes the ventilation mask from the patient's face.

If, contrary to expectations, the patient becomes restless and visibly uncomfortable. administration of 5 mg midazolam is sufficient. If the breathing pattern changes or hyperventilation occurs, then administration of morphine in combination with midazolam is necessary, both at a dose of 5 mg, and if necessary another administration at the same dosage.

Patients often breathe spontaneously, but very shallowly and peacefully, for a few minutes to several hours. Spontaneous breathing then suddenly stops. It is necessary to explain that changes in respiratory rhythm is part of natural dying.

What to Avoid in Palliative Care for Mechanically Ventilated Patients

Sufficient symptom control by palliative medication is an indispensable requirement to achieve adequate palliation. Some measures are best avoided.

- Midazolam preferably should be combined with morphine as severe respiratory distress can result from the administration of midazolam alone.
- It is poor practice to discontinue one life-supporting therapy while continuing another in the same patient. Some family members may object to discontinuation of fluids and nutrition even knowing that death will be imminent.
- A method at times practiced in intensive care units of gradually reducing oxygen saturation and ventilator support and subsequently allowing the patient to die over days is not advisable, as this prolongs the patient's suffering.

The Role of the Neurologist

Critics may find compassionate sedation and extubation are nearly identical to active euthanasia. In 2017, after years of legal and professional warring, the American College of Physicians concluded that "on the basis of substantive ethics, clinical practice, policy, and other concerns articulated in this position paper, the American College of Physicians does not support legalization of physician-assisted suicide. It is problematic given the nature of the patient-physician relationship, affects trust in the relationship and in the profession, and fundamentally alters the medical profession's role in society"[129]. The American Academy of Neurology emphasizes the patient's right to refuse life-sustaining treatment. Neurologists are obligated to honor requests for withdrawal or withholding of care and to provide palliative care. The American Academy of Neurology supports discontinuation of treatments that provide no benefit to the patient including nutrition and hydration. But, pushing the envelope even further, it is not the neurologists' duty to provide assisted suicide or active euthanasia at the request of their patients or proxy. In the United States and most other countries, the neurologist must insistently deny euthanasia to any (competent or incompetent) person when requested. Therefore, one should try not to blur the line between active euthanasia (physician's intent to cause death) and aggressive pharmaceutical treatment to provide comfort (physician's intent to relieve perceived suffering) using escalating extremely high doses of opioids. If there is no written or discussed medical justification, high doses can be easily misconstrued as a concealed attempt to induce death.

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Conclusions

Neurological patients with respiratory impairment may have a good quality of life and a high degree of participation, even in cases of permanent dependency on life-supporting therapies as mechanical ventilation or tracheal cannulas. We recently reported a longitudinal cohort study of patients with ALS and their caregivers in the surroundings of Munich, Germany. This would provide patients with personalized care, enabling them to be cared for at home for as long as possible. Patients were regularly visited at home by a multiprofessional team and we were able to demonstrate feasibility and satisfaction[130,131]. The medical concepts of palliative care, intensive care and rehabilitation are not contradictory, but complementary in these patients. A variety of concepts to optimize the intersection between palliative and intensive care have been introduced in this chapter. It is of particular importance to record the patient's preference as early as possible. If life-supporting technologies no longer meet the patient's wishes, they can be discontinued. In our recent cohort, 20% of all deceased patients died from assisted suicide or termination of non invasive mechanical ventilation. Whatever method is used, our ultimate goal is relief of suffering and this can be compassionately accomplished.

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Chapter

25 Organizational Settings of Respiratory Care throughout the World: A Bird's-Eye View and Sample

Martin Groß, Donatha Hornemann and Thomas Platz*

Systems and frameworks have been constructed to allow short-term and long-term care. Because the need for respiratory care can result from acute, chronic and chronic-progressive neurological conditions, continuity of care is expected.The trajectory of care for neurological patients with respiratory impairment can roughly be subdivided into the three stages of acute, postacute and long-term care (see Figure 25.1).

Patients with acute neurological illness and respiratory impairment are treated in stroke units, intermediate care units or ICUs, depending on the severity of their condition. Patients with respiratory impairment due to chronic or chronic progressive neurological conditions are treated in variable settings, comprising outpatient clinics, sleep medicine departments and hospital wards as well as medical and neurosciences intermediate and ICUs.

The disciplines of neurology and pulmonology both strongly contribute to the postacute setting of neurorespiratory care. Postacute treatment facilities, where neurological patients with tracheostomy or mechanical ventilation are treated, have been established in high-income countries. These facilities can be part of acute care hospitals or function as stand-alone institutions. Examples are units and centers for weaning, early neurological-neurosurgical rehabilitation and spinal cord injury. These specialized units or centers work with the presumption of improving care of neurologic patients with respiratory needs through (1) serious attempts at weaning from mechanical ventilation, if indicated; (2) achieving the positive effects of noninvasive and invasive mechanical ventilation on quality of life which often are attributed to improved hypoventilation and alleviation of associated symptoms; and (3) applying rehabilitative strategies to reduce disability, and to foster participation. Postacute treatment facilities may also comprise outpatient clinics, outreach treatment or telemedicine and may offer the full spectrum of neurorespiratory care, ranging from diagnostic procedures and initiation of noninvasive ventilation (NIV) to regular controls of patients with tracheal cannulas or invasive ventilation.

Finally, long-term care takes place in-community nursing care or in-community intensive nursing care settings. However, clinically worsening patients may have to be transiently transferred back to acute care settings. When clinical improvement occurs or is expected patients can be transferred from the in-community setting to postacute treatment facilities to be weaned, decannulated or further rehabilitated.

Nevertheless, healthcare structures and centers for neurological patients with respiratory impairment have been comprehensively organized for only a few countries. To explore differences (and detect needs) this chapter provides some insights into healthcare structures and their variability between regions and countries – the disparity is obvious.

Germany

Differentiated subacute care and high numbers of patients in in-community intensive care[1]

In Germany, postacute care for neurological patients with respiratory impairment is well organized with clear understanding where to route patients. Moreover, certifications for specialized centers have been established by different professional societies. The German Society for Pulmonology and Mechanical Ventilation certifies weaning centers, the German Society for Neurorehabilitation certifies centers for weaning in neurological-neurosurgical early rehabilitation[1] and the German Anesthesiological Society certifies weaning units. Patients with mechanical

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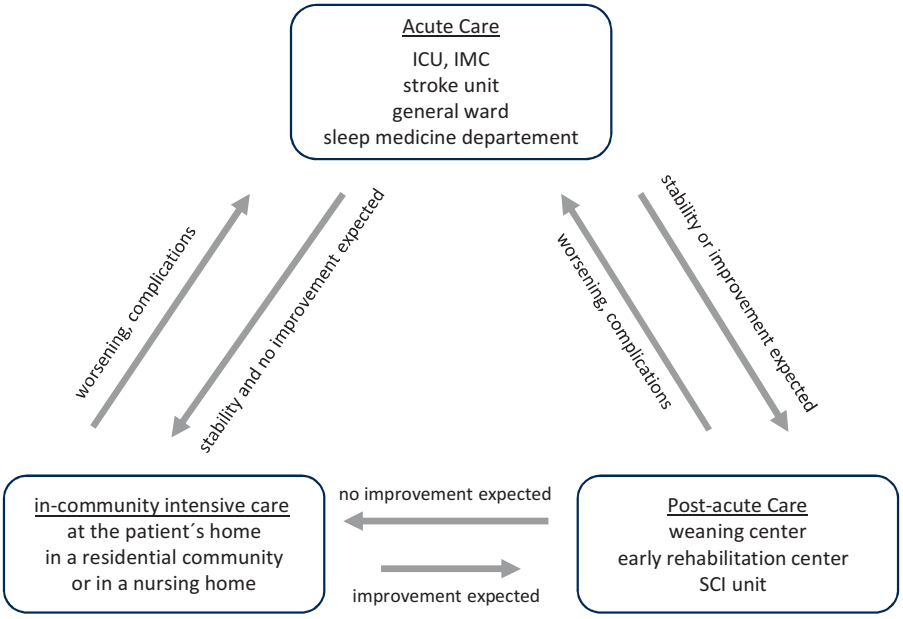


Figure 25.1 Acute, postacute and long-term care settings for neurological patients with respiratory impairment. Patients may be transferred from one care structure to another, due to their current or prognosticated clinical condition: clinical improvement, stagnation, worsening or occurrence of complications (e.g. pneumonia). ICU, intensive care unit; IMC, intermediate care unit; SCI, spinal cord injury.

ventilation are also treated in paraplegic centers, neuromuscular centers and sleep laboratories, which are all certified by their professional societies[2]. Guidelines for prolonged weaning[3], prolonged weaning in early neurological-neurosurgical rehabilitation[4], noninvasive ventilation in chronic respiratory failure[5] and breathing, breathing support and mechanical ventilation in acute and chronic spinal cord injury[6] been published accordingly. Long-term care for patients with tracheostomy and life-supporting mechanical ventilation is mostly provided at home, in residential communities or in specialized nursing homes, of which some have a focus on long-term neurological rehabilitation. Care is provided by specialized nurses, but also by family caregivers and trained laypeople. While NIV is routinely used for chronic obstructive pulmonary disease (COPD) and neuromuscular diseases, most of the approximately 23,000 patients in an in-community intensive care setting are tracheotomized, and a large minority of those tracheotomized patients additionally need invasive ventilation. Most of those 23,000 patients are affected by neurological diseases[2].

Certain patient registries have also been established. A weaning registry has been established by the WeanNet, where weaning centers certified by the DGP collect patient characteristics and outcomes[7].

The Netherlands

Unique organization by four academic centers covering the entire country.[2]

Home mechanical ventilation in the Netherlands is transmurally organized by four centers for home mechanical ventilation (HMV), which are located at university hospitals[8]. These centers are not only responsible for the initiation of HMV, but also for long-term monitoring and for supporting the patients at home. Initiation of HMV mostly happens in an inpatient setting, but the centers for HMV aim at initiation of HMV in the home of the patient more often, as this is equally safe, effective and cost-efficient. All patients have been entered into a HMV registry since 1992. Over the years there has been a rise among the total number of patients and among the proportion of patients older than 60 years, who now constitute about 50% of patients with HMV. About 90% of patients with HMV live at home, and neuromuscular patients are the majority. (This contrasts with Switzerland, where patients with COPD form the majority of patients with HMV.) In the Netherlands the

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indications for HMV are strictly defined and comprise rapidly and slowly progressive neuromuscular disorders, spinal cord injury, thoracic restrictive disorders, obesity hypoventilation syndrome, COPD and sleep-disordered breathing with failure of regular treatments [9]. In contrast to Germany, weaning failure is not considered an indication for home ventilation per se, so that indication for HMV depends solely on the primary diagnosis. All HMV patients are supervised by specialized nurses from the center from the start until the end, including regular house visits. This means that the centers can be contacted 24/7 for troubleshooting. Maintenance of the ventilators will be done yearly by a certified company.

Luxembourg

Improving care structures with impetus from a patient's organization[3]

In the Grand Duchy of Luxembourg, medical treatment of patients with respiratory impairment due to neurological diseases usually is provided in ICUs, pulmonology departments or sometimes in palliative care units of acute care hospitals. In-community care for these patients takes place in nursing homes. However, the capacity of these institutions is severely restricted. Long-term home care for invasively ventilated patients is very limited, too, as long-term care insurance does not provide for round-the-clock care, which must be specifically requested and approved. In long-term care insurance, only personal hygiene, excretion, nutrition, clothing and mobility are recognized as activities of daily living, but assistance with ventilation is not. Thus, there is no comprehensive long-term care concept for neurological patients with tracheostomy or life-sustaining mechanical ventilation currently, and the needs of the patients and their families are not addressed. While the Ministry of Health and the Ministry of Family advertised measures to improve the care of palliative patients in the "National Plan on End of Life and Palliative Care 2023–2026," long-term home care including assistance for patients with tracheostomy and life-sustaining ventilators is still neglected. Consequently, patients are isolated due to a lack of coordination and inappropriate care, and patients with neurodegenerative disorders are the second largest group requesting euthanasia or assisted suicide in Luxembourg, following cancer patients[10].

The association "Wäertvollt Liewen" (translated as "living life is precious") is the initiator of home-based in-community intensive care in Luxembourg. With the help of doctors and a nursing service, several invasively ventilated patients have since been able to live a life of dignity at home amid their families. Assistance and care are provided by specially trained laypersons, so-called confidants. Due to the ever-growing shortage of nursing staff, this concept should be further expanded.

In the "National Plan for Rare Diseases" of the Ministry of Health, different actors are currently working together and a project titled "ALS [amyotrophic lateral sclerosis] and related neuro-degenerative pathologies care chain" has been launched, aiming to better meet the expectations of the patients and to guide, coordinate and structure all actions in the field of severe neurodegenerative diseases. One of the first objectives is to organize the medical care and optimize it. In a further phase of the project, the in-community care of the patient is to be improved. The paramount objective is to increase in the quality of life of the patient and their families.

Switzerland

Connecting in-hospital with out-of-hospital care[4]

The initial treatment of severely ill or traumatized patients with mechanical ventilation takes place in ICUs. Specialized units exist for neurological and pneumological disorders as well as spinal cord injuries. Patients with weaning failure or prolonged weaning are preferably transferred to a dedicated weaning center, as for instance the Swiss Paraplegic Center in Nottwil. Pediatric patients are taken care of in children's hospitals.

Home ventilation is managed by the Swiss Society of Pneumology with their Home Ventilation Working Group and other partners. The technical support of the respiratory devices is provided by the manufacturers with their authorized service centers. Patients with spinal cord injuries are managed by the spinal cord injury units in collaboration with dedicated nursing teams like the Respicare-Team of the Swiss Paraplegic Center (see Figure 25.2). Organizations like Parahelp support the

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[4] Michael Baumberger and Luca Brendebach

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Figure 25.2 The Swiss Paraplegic Center. @ Swiss Paraplegic Center, kindly provided by the center.

patients with specially trained staff at their homes or in nursing institutions (Figure 25.3). The management of tracheotomized patients outside specialized units is challenging and difficult to organize due to lack of specific knowhow.

United States

Noninvasive ventilation at home as a key strategy[5]

As would be the case in most countries, the cost containment and payment reimbursement process for all medical expenses has a major impact on the ultimate design of patient care. This is especially true for those requiring advanced respiratory support and multispecialty attention. The capitated payment system in the United States for acute care in the hospital makes it necessary to move the patient quickly to outpatient status. The availability of equipment is less demanding than the very cumbersome regulatory and legislative barriers to obtaining reimbursement.

When the patient with neuromuscular disease requires hospital admission for hypercapnic respiratory failure, this most frequently triggers the delivery of an HMV-style device unless the patient responds very easily to the more conventional bilevel positive airway pressure device. This is known as a respiratory assist device (RAD) as designated by the Centers for Medicare and Medicaid Services (CMS). The CMS payment provider is responsible for the majority of patients enrolled in the national Medicare and Medicaid payment systems. The vast majority of patients will be dismissed with a device using an NIV interface. This process most frequently will require at least an attempt to trial a RAD device and otherwise prove this to be shown as "tried and proven ineffective." If the prescription for the HMV is successful,

[5] Peter Gay

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Figure 25.3 While a third person recites the alphabet, Nathalie Scheer-Pfeifer picks a correct letter by raising an eyebrow. Her assistant writes down the letters. Spelling a whole sentence this way takes time. © Henri Goergen.

then a respiratory therapist must be available to the patient from the home vendor under the category of "frequent and substantial servicing." This does not, however, necessarily require ready availability or home visits for the patient.

It is on very rare occasions that patients choose to undergo tracheostomy unless they are intolerant of NIV or have such profound secretion management difficulties that they require very frequent suctioning through a protected airway. It is also rare in the United States when patients become completely paraplegic or "locked in" that they choose invasive mechanical ventilation as this often requires transfer to a permanent skilled nursing facility far from home.

The majority of patients who need treatment for hypercapnic chronic respiratory failure will most often be seen by a pulmonary or sleep physician and be introduced through laboratory study with polysomnography. There are Centers of Excellence for neuromuscular disease in the country, and patients are seen locally. In either case, they must meet the criteria of a reduced vital capacity $<50\%$ predicted, an abnormal oximetry with mild hypoxemia $\leq 88\%$ for at least 5 minutes during an overnight oximetry study or mild hypercapnia at ≤ 45 mmHg at rest.

These patients do not require polysomnography and can actually be directly prescribed an RAD. The device is usually set with a modest inspiratory pressure level >10 cmH_2O, minimal expiratory pressure and a backup rate >10 breaths per minute. The options to consider a volume assist pressure support or pressure control are also available and are usually determined by the

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prescribing physician. When a patient receives an RAD, the CMS reimbursement is initiated for up to 90 days and will continue for a total of 13 months if the patient is proven to be compliant with nightly therapy. After this capped rental period, the patient will own the RAD but continue to have reimbursement for additional accessory equipment.

The vast majority of patients choose NIV treatment in their home and do not generally transition to invasive ventilation for permanent care. There are alternative options for either outpatient or inpatient physical rehabilitation services, but these are only on a short-term basis and then must be sustained by the patient and family members.

Canada

Specialized home mechanical ventilation programs by academic centers and need to expand facilities for patients on tracheostomy invasive ventilation[6]

While health care in Canada is governed by the Canada Health Act adopted in 1984 and some federal funding supports health care across the country, health services are a provincial responsibility, resulting in a patchwork of care provision. Services provided in one province may be unavailable in another, based on provincial priorities and health budgets. All basic health care in Canada is universally available but can be enhanced, particularly in the community by private insurance. There are no national registries of neurological or neuromuscular (neuro/NMD) patients specifically receiving respiratory support. There is however, a very robust Canadian Neuromuscular Disease Registry but respiratory data are limited[11]. Databases, limited to HMV, exist in those provinces with provincially funded HMV programs. These are quite informative, indicating diagnosis, respiratory supports (bilevel devices, one or two), mechanical cough assistance, ventilators (one or two) and interface (mouthpiece ventilation, mask, tracheostomy). A recent Canadian survey indicated a prevalence of 12.9/100,000 and reported that more than half of individuals had neuromuscular disease[12]. However, this is very likely an underestimate since the latest data indicate that in Ontario, which has a population of 14.5 million, there are 6700 patients served by the provincial ventilator equipment pool. This would be a prevalence of 46/100,000 population, 4.5% of whom are invasively ventilated.

Respiratory care and ventilatory support of neurological/NMD patients vary throughout the provinces but most often are provided by dedicated HMV programs (e.g. Ontario: five specialized HMV programs, British Columbia: one, Alberta: two), only in university centers. These programs monitor at-risk patients for airway clearance and development of respiratory failure, focusing on elective airway management and NIV. One representative program is the CANVent (Canadian Alternatives in Noninvasive Ventilation) program at the Ottawa Hospital Rehabilitation Center[13] (Figure 25.4). There is a close liaison with critical care units to facilitate weaning and discharge from ICU for stable patients. HMV programs follow and monitor both patients with NIV and TIV in the community. They regularly perform overnight oximetry testing, and many provide remote monitoring and adjustment of bilevel devices and ventilators. Almost all provinces have funded HMV equipment and support, but a few do not, such as New Brunswick and Nova Scotia, providing either no funding or supporting only those on social assistance.

Elective NIV is initiated in patients' homes, outpatient clinic settings, rehabilitation centers and much less commonly in sleep laboratories (where available) or in ICU. Invasive ventilation is initiated in ICU and decannulation may occur in ICU, stepdown units, rehabilitation centers and much less commonly on inpatient units.

There is only a small number of specialized postacute rehabilitation programs for neuro/NMD (GF Strong in British Columbia, Lindhurst in Ontario), and some do not accept patients with tracheostomy ventilation. Most provinces incorporate such patients into general rehabilitation centers. Long-term TIV patients who cannot be weaned may unfortunately spend a significant time awaiting transfer in ICU where rehabilitation efforts may be minimal. Though not limited to neuro/NMD patients, a recent Canadian report indicated that 11% of ICU beds were occupied by stable TIV patients[12,14]. Uncommonly, such patients may be transferred to ventilator-capable beds on other acute inpatient services[15], but most await transfer to chronic assisted ventilatory care beds where available. TIV in the home is also possible and all efforts are made to transfer home directly from ICU, where human and financial resources are available. These patients will be followed by HMV programs.

[6] Douglas McKim

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Figure 25.4 Measuring maximum insufflation capacity with mouthpiece ventilation in C2 tetraplegia around an (uncuffed) tracheal cannula. The Ottawa Hospital, General Campus ICU @ CANVent, used with permission. URL: www.youtube.com/@CANVentOttawa.

Russia

Regional differences with respect to healthcare structure, and rehabilitation taking place in palliative care centers[7]

Financing of the public healthcare system is dependent on regional tax revenues. Therefore, in large cities, especially in Moscow, elaborate care supply structures have been established, while in rural areas resources are much more limited. In this section the Moscow model is highlighted as a model for the further development of healthcare structures throughout the country (see Figure 25.5).

Acute neurological care often starts in combined *stroke and neurological ICUs* (*NICUs*). From the NICU the patient can be routed to the neurosurgical unit or neurosurgical intensive care unit of the same hospital for neurosurgical treatment. After 14 days of treatment on the NICU, a decision should be taken on the further medical pathway. Patients with tracheostomy or invasive mechanical ventilation are routed to *long-term respiratory support units* that are normally part of *palliative care centers*. In palliative care centers there are units providing medical treatment and rehabilitation (comparable to early neurological-neurosurgical rehabilitation in Germany), as well as *palliative units proper*. The patients are transferred from the acute care hospital to palliative units proper after the decision for an exclusively palliative treatment concept has been made by a palliative care doctor together with the patient's relatives.

Patients with low-flow oxygenation respiratory support are normally transferred from NICUs to *neurological units*, where they get rehabilitation treatment. Further on they can go to *rehabilitation centers* where both outpatient and inpatient care can be provided. Patients in need of long-term care with respiratory support (e.g. oxygen concentrator) can be treated at home, mostly supervised by a nurse specialized in palliative care.

Weaning is initiated and coordinated by a doctor in charge. In NICUs doctors are normally certified as neurologists and anesthesiologists. Palliative care centers employ doctors with palliative care certification as well as anesthesiologists for long-term respiratory support units. *Rehabilitation* is provided by doctors specialized in physiotherapy and rehabilitation as well as speech and

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Figure 25.5 Modern equipment on the Stroke and Neurological Intensive Care Unit, Moscow City Clinical Hospital 31.

language therapists. There are no specialized respiratory therapists in Russia.

Specialized outpatient departments and centers exist for tetraplegia (spinal cord injury), ALS and multiple sclerosis. There patients can receive further medical treatment and rehabilitation.

There is also a specialized Center of Intensive Care and Rehabilitation where mechanically ventilated patients with good recovery prospects, can be routed for rehabilitation.

Ukraine

Rehabilitation services in Ukraine[8]

The rehabilitation sector in Ukraine is reforming while facing major challenges according to an assessment published by the World Health Organization in November 2021. Public financing for rehabilitation is primarily through the National Health Service of Ukraine, Ministry of Social Policy and Ministry of Health.

Recent changes include the introduction of professional qualifications for physical and rehabilitation medicine, physical therapy and occupational therapy. While licensing and regulatory structures apply to physicians, continuing educational demands are not requisite for other therapists working in the rehabilitation context. Speech and language therapy for adults is not formally recognized as a healthcare profession and largely associated with the educational system and oriented towards children. Similarly, orthotics and prosthetics are not recognized healthcare professions in Ukraine.

The profession of respiratory therapist is not yet established, restricting the possibilities for successful rehabilitation. There is no uniform data collection on

[8] Regina Lomako

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rehabilitation outcomes on a national level. In the regional Mechnikov hospital 70% of all patients in need of mechanical ventilation could eventually successfully undergo the process of weaning, which takes place at the ICU. It is important to note that rehabilitation services are currently largely absent at the community and primary healthcare levels, which may have a negative impact on functional gains achieved within rehabilitation facilities.

Assistive products are funded through social budgets for persons with disabilities and are not part of health financing. Assistive products are provided without the involvement of rehabilitation professionals, which may restrict the utility of the assistive product due to unsuitability for patient needs or lack of training in the use of the product.

Iran

Necessity of prioritizing ICU capacities, provision of stepdown in-hospital care, but need for establishing in-community care structures.[9]

In Iran, critical care was first recognized as a fellowship in 2014 and was later changed into a subspecialty with board certification. Both anesthesiologists and specialists in internal medicine can enter this two-year training program. There are more than 4500 ICU beds in the country, which reflects a shortage of available beds for a population exceeding 80 million. ICUs are now run by intensivists who provide a 24/7 coverage in a closed format.

There are some general ICUs, which serve mainly medical patients with a variety of conditions ranging from shock to respiratory failure. These ICUs also admit trauma patients. There are also some more specialized ICUs, mainly for neurology/neurosurgery patients, patients undergoing open-heart surgery, or thorax surgery. Most common neurological diseases requiring intensive care include stroke, multiple sclerosis and brain masses.

Admission is often arranged through emergency departments, where initial care is provided, but patients may also be transferred to ICU from hospital wards in case of deterioration. Shortage of ICU beds mandates being very selective in prioritizing patients. Most patients admitted suffer from respiratory insufficiency and require mechanical ventilation and respiratory support. After partial recovery and being weaned from a ventilator, patients are moved to stepdown units where the less acute care such as respiratory therapy and neurological rehabilitation is provided by a team of physicians, nurses and respiratory therapists as well as physiotherapists. Physiotherapists with a bachelor's or master's degree often provide rehabilitation and respiratory care.

A worsening shortage of ICU beds as well as increasing preference of patients and families have made critical care outside the hospital an evolving demand. Some healthcare organizations now provide this care through providing equipment such as supplemental oxygen machines and suctions and specialized mattresses at home. These institutions are often managed by the private sector and this type of care is still in its infancy and not fully established.

China

The emerging role of respiratory therapists and respiratory rehabilitation[10]

In China, the acute and the majority of postacute respiratory treatments for neurological patients with respiratory impairment are still mainly undertaken by medical physicians and nurses in hospitals, with a significant shortage of respiratory therapists. Although undergraduate students majoring in respiratory therapy have been recruited for decades, the number is still small and most of them are assigned to the respiratory department or ICU/respiratory ICU in large top-tier teaching hospitals. The West China Medical Center of Sichuan University has recruited four-year undergraduate students majoring in respiratory therapy since 2000 and awarded a bachelor of science degree after graduation. During the coronavirus pandemic, respiratory therapists have been extensively engaged in the front line of treatments and respiratory support and have made an outstanding contribution.

Many large hospitals have developed their own respiratory rehabilitation center and some of them provide certified respiratory rehabilitation training for physicians and nurses. These centers deliver respiratory rehabilitation during hospitalization through senior

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[10] Hongcai Liu

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physicians, rehabilitation nurses, respiratory therapists and cardiopulmonary physiotherapists and follow-up outpatient treatment for various of respiratory diseases, including patient education, home respiratory rehabilitation and long-term monitoring for patients with non-invasive home mechanical ventilation.

Nepal

Weaning and rehabilitation in the acute care setting and no established structures for home mechanical ventilation[11]

The treatment of neurological disorders with respiratory insufficiency is largely limited to acute and postacute care in Nepal, cerebrovascular accident and epilepsy being the most common causes for hospital admission. Endovascular treatment of stroke was introduced in 2019[16], and in 2023 data from two institutions providing endovascular treatment of stroke were published[17]. Acute care takes place – like all over the world – in an inpatient setting, in intensive and intermediate care units (ICU/IMC) and general wards. But contrary to many Western countries the postacute care in Nepal follows acute care in the same hospital. Doctors and nurses stand as front-liners in every step of acute and postacute care. They are supported by physiotherapists, who engage in management of secretions to reduce the risk of airway infections and mobilization. The profession of respiratory therapists is not established in Nepal. The management of mechanical ventilation is provided by anesthesiologists. Speech and language therapy, on the other hand, takes place mainly in an outpatient setting.

HMV has not been established in Nepal to date, as lack of trained professionals and financial resources hinder its initiation and continuation. The only long-term care known to be practiced until now is the use of nebulizers and long-term oxygen therapy, for patients with COPD. However, one may find many rehabilitation centers or nursing homes in Nepal aiming to improve mobility and thus quality of life of neurological patients. However, monitored units of neurological rehabilitation do not exist in Nepal. With intensive care medicine and long-term care in developing stages, there are nonetheless hopes for improvement in health care in the future in Nepal.

Conclusions

Future challenges are to understand healthcare structures on a global level, to establish a "continuum of care" from the ICU to community-based care, to harmonize such efforts across as many countries as possible and to identify multiprofessional and interdisciplinary synergisms and best practices care concepts. Medical disciplines, such as neurology, pulmonology, anesthesiology, oto-rhinolaryngology, pediatrics, physical medicine and rehabilitation; nursing specialties; different therapeutic professions, such as respiratory therapy, speech and language therapy, occupational and physiotherapy and (neuro)psychology; as well as medical device providers will have to be integrated in care models for neurological patients with respiratory impairment.

Improvement can come from a mindset that takes nothing for granted. Ideally a patient outcome should not be determined by resources and the country where the patient lives. The development of guidelines and scientific statements will identify major deficiencies that can be corrected or tested in prospective studies.

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Chapter

26 Future of Neurorespiratory Medicine

Martin Groß, Eelco F. M. Wijdicks, Donatha Hornemann, Maxwell S. Damian and Oliver Summ

What does the future hold for neurorespiratory medicine and can it establish itself as a field? Treatment of acute brain diseases involves acute respiratory care, support systems and technology, and decisions on when to intervene with tracheostomy. An urgent question is what is needed to support a patient with a neuromuscular respiratory failure and what resources must be provided? To agree on a subset of principles of care, to define proficiency and qualifications needed to care for patients with respiratory impairment due to neurological disease, and to strive for further medical and technological progress, will be a challenge if not a potential road block. We leave the future with the future, but here are some thoughts.

Principles of Care

Care can best be organized if basic principles are agreed upon. People with respiratory impairment due to neurological disease often suffer from a variety of other severe and often chronic neurological deficits. Comorbidities may add to the complexity of their health impairment. Consequently, relatives and caregivers experience a considerable burden. But, has been well established that patients with severe disabilities may experience a good or even excellent quality of life and their quality of life is systematically underestimated by laypeople and health professionals. People with new disabilities should have the same level of treatment as much less affected patients, but they do face barriers, prejudice, and even discrimination with respect to healthcare access. Another great challenge concerning patients with respiratory impairment due to neurological disease is their considerable and often unmet need for rehabilitation and palliative care. Care for these patients should be patient centered, family oriented, multiprofessional, interdisciplinary, lifelong, and non-discriminatory. Furthermore, it should closely interconnect inpatient and out-of-hospital care and integrate neurorespiratory care, rehabilitation, and palliative care according to the need of the patient[1]. These are not empty words. All that is needed to guide a patient to a better life.

Patient-Centered and Family-Oriented Care

The intellectual roots of the concept of patient-centered care can be traced as far back as Hippocrates: "It is more important to know what sort of person has a disease than to know what sort of disease a person has"[2]. Balint first described "patient-centered medicine" as a counterpart to "illness-centered medicine". In patient-centered medicine the patient must be understood as "a unique human being"[3]. Today the concept is better known as "patient-centered care". While there is no consensus on the definition of "patient-centered care", it is widely agreed that patient-centered care "fully integrates the patient's perceptions, needs and experiences" throughout the healthcare journey[4]. Nevertheless, family orientation is a highly important aspect of care, as a stable psychosocial network improves participation, quality of life, and even survival of the patient[5].

Multiprofessional and Interdisciplinary Teams

While "multiprofessionality" implies that different professions work together in a team, "interdisciplinarity" describes a set of principles, how the team works together. Multiprofessionality comprises medical and non-medical professions. neurology, pulmonology, anesthesiology, pediatrics, Otorhinolaryngology intensive care, and palliative care are core medical disciplines, while respiratory therapy, speech and language therapy, physiotherapy, occupational therapy, nursing, (neuro)psychology, and social work are core non-medical therapies.

"Interdisciplinarity" refers to aspects of organization, communication, and cooperation. "Interdisciplinary" teams are characterized by flat hierarchies, where the

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physician shares responsibility for the treatment of the patient with other professions and acts as a coordinator rather than as a team leader. Team meetings are held regularly to approve the goals of therapy for each individual patient. Cooperation is taking place multilaterally and the treatment strategy is constantly discussed and optimized[6].

Lifelong Care

Although the expression "lifelong care" emerged in medical literature in the late 1980s, a comprehensive definition is still lacking. Nevertheless, "lifelong care" refers to care that is designed for and delivered during the whole lifespan of the patient. Lifelong care is propagated as a care concept for chronic and disabling conditions, noncommunicable diseases, and multimorbidity. The number of patients needing lifelong care will thus be constantly rising in future, and this is especially true for neurological patients with respiratory impairment and chronic need for life supporting technologies. Key concepts of lifelong care have recently been described[7].

Reconciliation of Neurorespiratory Care, Rehabilitation, and Palliative Care

In the next decades neurological patients with chronic respiratory impairment will increase with respect to number, severity, and complexity of illness and comorbidities, degree of suffering, need for assistive and life-supporting technologies, and monitoring. While during the twenty-first century effective pharmacological treatment strategies for genetic and autoimmune diseases may be established, this will not reverse this process: More and more patients will need neurorespiratory care to support their health, rehabilitation to optimize participation, and palliative care to relieve suffering. All these efforts will have to be directed at optimizing quality of life. Ideally, medical disciplines must develop their concepts to fit their patient's needs. Neurorespiratory physicians, while being experts in neurology, will have to be generalists with respect to provision of neurorespiratory care, rehabilitation, and palliative care, if they want to be helpful for them.

Equity

Even in industrial countries patients with chronic severe neurological illness do not have equal access to health care. There are many barriers. Some of these are part of the physical environment like lack of accessibility by wheelchairs, some of these are caused by lack of adequate assistive devices, some are caused by communication barriers, and some are rooted in the minds of the caregivers. Professional caregivers might underestimate a patient's quality of life or might even be reluctant to treat chronically ill or disabled patients for distinct reasons, such as the patient's condition is not worth the effort. The United Nations Convention on the Rights of Persons with Disabilities has long clarified their right for equal access, not only to health care but also to the job market and other aspects of life. All efforts must be made to achieve this goal. A major issue is to recognize that patients with progressive diseases have the same rights to receive rehabilitation as do patients after an acute disease or trauma: to reduce disability and to optimize participation are the general objectives of rehabilitation and these are applicable for both groups of patients. Also, involvement of patients and families in the development of medical supply structures, assistive technologies, and scientific projects will have to be strengthened further.

Providers of Care

Medical progress and lack of specialized doctors will foster the need for respiratory therapists and physician assistants and the professionalization of these disciplines[8]. Furthermore, speech and language therapists will establish their role in diagnostics and therapy of dysphagia and management of tracheal cannula. Tasks originally performed by doctors will be delegated to these professions – management of home mechanical ventilation or endoscopic procedures (e.g. flexible endoscopic evaluation of swallowing). Delegation again necessitates structured training, practical supervision, and regular refreshers.

Trained caregivers can deliver sophisticated care, even for patients dependent on life-sustaining therapies like tracheostomy invasive ventilation[9]. Their role increasingly important in ageing societies. Lack of trained nurses will drive this development.

Technical Aspects of Home Ventilation

Over the last two decades there has been considerable research to identify the optimum ventilation mode for noninvasive home ventilation, especially in amyotrophic lateral sclerosis[10,11]. Evidence is still lacking for the superiority of any mode, may it be volume-controlled versus pressure controlled, pressure controlled versus

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pressure assisted, or "intelligent" versus "conventional" modes. Factors such as the experience of the staff, the choice of the ventilation interface, and consulting and training the patients, their families, and their caregivers are probably more important than marginal technical improvements in home ventilators. Attention will have to be paid not only to ventilatory pump failure but also to insufficient cough, dysphagia, and tracheobronchial retention of secretions. The use of devices combining mechanical ventilation and mechanical insufflation-exsufflation especially for patients with tracheal cannulas might be a major step forward.

Telemedicine

Although telemedicine already existed before the COVID-19 pandemic, it is undeniable that, as a result, there has been a strong push to make it available to overcome difficulties in patient care[12,13]. Usage and performance data from ventilators can be transferred to a cloud-based web server using newer technologies. Remote access not only makes it possible to view the data but also to directly adjust certain parameters[14]. This enables prompt and direct adjustment to problems without having to wait for an on-site checkup, which is often possible only with a significant delay.

Telemedical monitoring can be a great relief, especially for people with disabilities or in rural areas, to avoid or reduce long journeys[15]. This form of therapy and monitoring is therefore particularly suitable for people with neurological and neuromuscular diseases, which are often associated with a high degree of physical impairment[16].

Obstacles include the different software from the manufacturers, with which doctors and other professions must familiarize themselves and the lack of reimbursement for telemedical treatments. Another limitation is monitoring and keeping track of large amounts of data, which are generated by telemedicine. This again may require additional staffing. License issues when crossing boundaries may need to be clarified.

Neurocritical Care

David Eggerton's illuminating 2007 book *The Shock of the Old* warned against the notion that despite all the failures of technologies, people (and for our purposes neurointensivists) believe the future will be bright and technologically advanced. New does not necessarily mean better and technology may not be transformative, and he emphasized the continued importance of the old[17]. In medicine "the old" is the physician's skill in diagnosing and judging the state of the patient, and in this book, the patient in respiratory distress. In neurocritical care, we have seen significant strides but not in early ICU respiratory care. The clinical syndromes of acute neurologic conditions (at presentation and when deteriorating) are now well documented and have been taught. Neurologists with these skills know what to expect.

The establishment of societies such as the Neurocritical Care Society or the Neurocritical Care section in the European Society of Intensive Care Medicine (ESICM), dedicated to the scientific advancement of the field, has provided strong impetus towards evidence-based management, including respiratory problems in neurological disease. The recent recommendations of ESICM for respiratory management of acute brain injury are an important step in this direction but are still based on literature review of a small number of papers and clearly showed that the evidence for most approaches was not there[18]. Strong recommendations could be given only for general (accepted) ICU approaches. However, an ambitious program of research was proposed. The ICU management of respiratory problems in rarer neurological disorders is wide open for the development of an evidence base.

Yet, clear criteria for extubation remain elusive and extubation failure is frequent. Systematic trials are needed, including evaluation of the advances in ventilation technology. The goal is that modes of ventilation that automatically adapt to the patients' requirement of support can better individualize mechanical ventilation and may facilitate smoother and earlier weaning.

Beside the technicalities of ventilation itself, transformative advances in neurological therapy will have an impact on criteria for admission to ICU and on the way severe complications are managed. Examples are gene therapy for 5q spinal muscular atrophies or dystrophinopathy and advanced immunomodulation or immune reset cell therapy for severe autoimmune disorders[19,20]. These advances are radically changing the prognosis of these disorders and thus the rationale for invasive respiratory support in disorders hitherto lacking effective treatment.

The better integration of intensive care in the entire care package means that critical care-relevant aspects are being covered better in pre-ICU assessment, although there is considerable room for progress. For example, the recent Guillain–Barré syndrome (GBS) guideline

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provides insufficient clinical information other than the modified Erasmus GBS Respiratory Insufficiency Score (mEGRIS) and uses unvalidated tests for lung mechanics[19]; mEGRIS has no clinical assessment of respiratory function. On the other hand, ICU treatment will look towards post-ICU care as an extension, using telemedicine and remote monitoring options more frequently, potentially involving ICU in the post-discharge management[21].

Further Research Perspectives

The pathophysiology of ventilator pump failure in neuromuscular diseases and spinal cord injury and therapeutic strategies in these conditions are well understood. In contrast, the pathophysiology of disorders of respiratory regulation in cerebral illness is a black box and should be investigated in the coming decades along with corresponding therapeutic strategies[22].

As the motor patterns of respiration, swallowing, and coughing are coordinated in the medulla and pons, research on any of these topics has the potential to foster understanding of the system of respiration, coughing, and swallowing. Best practice in management of cough insufficiency and retention of secretions will also have to be established by clinical research. Particularly the role of tracheostomy in long-term care must be clarified and optimized proceedings regarding management of tracheal cannulas must be consented.

The most prominent issue for research in the field of medical ethics is undoubtedly to create a model to handle the dilemma between optimizing care for severely affected individuals and limited resources. Also, optimizing participation in chronic conditions and integration in the labor market are highly relevant topics.

The contribution of different professions and trained laypeople to care for the neurological patient with respiratory impairment must also be the subject of scientific research. This is crucial to conceptualize interdisciplinary teamwork, to define the practice profiles of the different professions, and to optimize their educational curriculum.

Also, healthcare supply research is to play an increasingly important role in future. Understanding care structures and evaluating their performance is of fundamental importance to develop them further and to create an environment of mutual learning on an international level. The integration of telemedicine in healthcare structures should also be evaluated. Telemedicine is expected to generate a huge amount of data. Big data analytics may help in establishing earlier detection of complications and avoiding hospital admissions.

Conclusions

Despite economic restrictions in poorer countries acute, subacute, and long-term care (Chapter 25) for neurological patients with respiratory impairment should be organized according to the principles discussed in this chapter. The role of respiratory therapists and trained caregivers will gain importance in the provision of care for neurological patients with long-term respiratory impairment, and thus their role should be further developed. There also is considerable potential for development of more sophisticated medical devices to support respiration and coughing. Telemedicine might help to sustain high-quality care despite substantial demographic changes across the globe and to optimize the patient's journey. Research is needed on a wide range of topics: physiology and pathophysiology, clinical methods, quality of life, participation, ethics, the role of different professions and patients' family members, and healthcare supply. By picking up these tasks neurorespiratory medicine as an evolving discipline may play a key role in mastering demographic and epidemiological challenges and contribute to sustainable development goal 3 of the United Nations: "Ensure healthy lives and promote well-being for all at all ages". We owe it to our patients with neurorespiratory disease and their families.

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