INVITED REVIEW

ABSTRACT: Chronic neuromuscular diseases may affect all major respiratory muscles groups including inspiratory, expiratory, and bulbar, and respiratory complications are the major cause of morbidity and mortality. Untreated, many of these diseases lead inexorably to hypercapnic respiratory failure, precipitated in some cases by chronic aspiration and secretion retention or pneumonia, related to impairment of cough and swallowing mechanisms. Many measures are helpful including inhibition of salivation, cough-assist techniques, devices to enhance communication, and physical therapy. In addition, ventilatory assistance is an important part of disease management for patients with advanced neuromuscular disease. Because of its comfort, convenience, and portability advantages, noninvasive positive pressure ventilation (NPPV) has become the modality of first choice for most patients. Patients to receive NPPV should be selected using consensus guidelines, and initiation should be gradual to maximize the chances for success. Attention should be paid to individual preferences for interfaces and early identification of cough impairment that necessitates the use of cough-assist devices. For patients considered unsuitable for noninvasive ventilation, invasive mechanical ventilation should be considered, but only after a frank but compassionate discussion between the patient, family, physician, and other caregivers.

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PULMONARY COMPLICATIONS OF CHRONIC NEUROMUSCULAR DISEASES AND THEIR MANAGEMENT

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The wide variety of chronic neurologic diseases that compromise respiratory function can be categorized into neuropathic (including neurodegenerative diseases) and myopathic disorders.[135]

NEUROPATHIC DISEASES AFFECTING RESPIRATORY FUNCTION

Spinal Cord Injury. Acute spinal cord injury is a devastating event that occurs at a rate of 28–50 injuries per million persons per year in the United States.[40,116] Most injuries are related to motor vehicle, athletic, or industrial accidents.[116] Pulmonary complications are the leading cause of death, with most respiratory deaths attributed to pneumonia.[116]

Acute high cervical spinal cord injury causes profound respiratory compromise. Injuries at or above segments C-3 to C-5 involve the phrenic nerves and cause partial or complete bilateral hemidiaphragmatic paralysis.[98] In addition, intercostal muscle paralysis caudad to cervical lesions limits the normal outward expansion of the middle and upper rib cage, further compromising inspiration.[98,116] The abdominal muscles are also paralyzed, greatly reducing cough effectiveness.[110] Sternocleidomastoid, scalene, and trapezius function persists in high spinal cord injuries, but the efficiency is greatly reduced.[98] High cervical quadriplegics (C-1–3) are unable to generate an adequate vital capacity because of severely reduced inspiratory and expiratory muscle function. Hypoxemia is common and results from both hypoventilation and microatelectasis.[157] In the recum-

Abbreviations: AHI, apnea–hypopnea index; BMD, Becker muscular dystrophy; BMI, body mass index; CPAP, continuous positive airway pressure; DMD, Duchenne muscular dystrophy; EMG, electromyography; ERV, expiratory reserve volume; FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; MG, myasthenia gravis; NPPV, noninvasive positive pressure ventilation; NREM, nonrapid eye movement sleep; Pdi, transdiaphragmatic pressure; PE_{max}, maximum expiratory pressure; PI_{max}, maximum inspiratory pressure; REM, rapid eye movement sleep; RV, residual volume; SNIP, maximal sniff pressure; TLC, total lung capacity; VC, vital capacity.

Key words: mechanical ventilation; neuromuscular disease; noninvasive ventilation; pulmonary complications; respiratory muscles; sleep disorders

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bent position, hypoventilation is exacerbated because abdominal contents push the flaccid diaphragm cephalad, decreasing functional lung volumes.[35] Obstructive sleep apnea and diminished CO_2 responsiveness are also seen with high cervical cord injury and predispose to hypoventilation.[73]

Quadriplegic patients with lesions in the lower cervical cord (C-4–6), whose phrenic nerves are completely or at least partially intact, can contract their diaphragm to a variable extent.[40] Nevertheless, they lack the intercostal muscle activity necessary to stabilize the rib cage.[7] As a result, their inspiratory function is compromised by lack of chest wall motion,[98,116] or the chest wall may even move paradoxically.[98,116] Position may have a profound effect on ventilation in these patients. They may be well saturated with oxygen while supine but become dyspneic and hypoxemic when sitting, because gravity flattens the hemidiaphragms, placing them at a mechanically disadvantageous position and diminishing their ability to develop maximal tension.[40] As with higher-level quadriplegics, these patients lose abdominal and other expiratory muscle function. The combination of expiratory and inspiratory weakness prevents them from coughing and clearing secretions adequately, placing them at high risk for respiratory tract infection.[40,98,116]

Although patients with high cervical lesions (C-1–3) usually require long-term mechanical ventilatory assistance,[10,23] lower-level quadriplegics (C-4–6) do not, unless there is associated chest trauma, pulmonary edema, or pneumonia.[40]

Motor Neuron Disease. ***Amyotrophic Lateral Sclerosis.*** Amyotrophic lateral sclerosis is a relentlessly progressive disease of both upper and lower motor neurons, leading inexorably to death. Although the etiology is unknown, a large number of potential causes have been proposed, including exposure to neurotoxic agents, genetic or autoimmune disease, deficiencies of nerve growth factors, and viral infection.[34,42,151–153] The disease presents with equal frequency in the upper and lower limbs (~40%) and less frequently (~20%) with bulbar muscle involvement.[124] Although the disease has no direct effect on the lung, it has devastating effects on mechanical function of the respiratory system. It affects all the major respiratory muscle groups: (1) expiratory muscles; (2) inspiratory muscles; and (3) upper airway muscles. Dyspnea may occur gradually over time, and this insidious onset may delay the diagnosis. Physicians should seek subtle signs of nocturnal hypoventilation, which can occur even when respiratory muscle function is mildy affected and daytime gas exchange is normal.[34] Symptoms and signs of nocturnal hypoventilation are manifold and include air hunger, snoring, choking, orthopnea, cyanosis, restlessness, insomnia, daytime hypersomnolence, morning headaches, drowsiness, fatigue, depression, and impaired cognition.[6,34,71] With bulbar involvement, which occurs eventually in >80% of patients with amyotrophic lateral sclerosis, swallowing becomes impaired, and ingestion of adequate nutrition becomes impossible. Rapid weight loss can occur, necessitating the placement of a gastric tube.[96] Early bulbar involvement imparts a poor prognosis related to impaired nutrition and the increased risk of aspiration[123,148] Compromised respiratory performance is the main determinant of the limited mean survival in these patients, approximately 4 years after diagnosis.[77]

Postpolio Syndrome. Poliomyelitis, caused by an enterovirus, can affect respiratory function not only in its acute stage but also as a late sequela, many decades later.[146] Poliovirus infection of spinal motor neurons or brainstem nuclei results in a widely variable distribution of weakness of the skeletal or bulbar musculature, leaving affected individuals with variable permanent sequelae after maximal recovery.[146] The continuum of impairment includes minor muscle weakness or deformity in affected limbs, functional deficits in ambulation or self-care, and quadriplegia with the need for continuous respiratory support.[130] Postpolio syndrome affects polio survivors 20–30 years after the acute illness and is characterized by a diffuse symptom complex including fatigue, pain, hot and cold flashes, and slowly progressive loss of function and weakness in previously affected muscles.[56] Respiratory signs and symptoms include dyspnea, morning headaches, daytime hypersomnolence, or frank respiratory insufficiency with daytime hypoventilation and paradoxical abdominal motion.[54,59] The disorder is distinguished from amyotrophic lateral sclerosis by the lack of upper neuron signs, the history of polio, and the very slow progression that permits prolonged survival, even after the onset of respiratory failure.[80] Worsening of respiratory function may occur in patients whose breathing muscles were involved during the initial episode; impairment without initial involvement is uncommon.[56,80]

Spinal Muscular Atrophy. The three classic forms of spinal muscular atrophy, in order of severity, are the infantile form, also known as Werdnig–Hoffmann disease type 1; the childhood type, also called Werdnig–Hoffmann type 2; and the juvenile type (type 3) or Kugelberg–Welander disease.[80,159] Type 1 is a severe form with onset in earliest infancy and

death by the age of 2 years.[135,183] Children with type 2 disease have milder weakness and hypotonia in infancy and develop fairly normally until 6–8 months of age. Most eventually learn to sit, but few walk, and death usually occurs by age 20 years.[135,198] Type 3 is less severe and presents in childhood or early adolescence with proximal weakness similar to that of limb-girdle muscular dystrophies. The ability to ambulate is delayed. Kyphoscoliosis and tongue fasciculations appear late and death usually does not occur until after the third or even fifth decade.[135] Respiratory complications are inevitable in children with type 1 spinal muscular atrophy, occur to a variable extent in type 2, and are rare in type 3.[167] Intercostal muscles are severely involved so that inspiration is dependent on the diaphragm.[167] This causes rib recession and a characteristic chest wall and pectus deformity. Most type 1 children develop chest infections and respiratory distress in the first few months of life, and almost all die of respiratory failure by the age of 2 years unless ventilatory support is provided.[37]

Peripheral Neuropathies. The focus of this review is on chronic neuromuscular disease, so acute inflammatory demyelinating polyneuropathies such as Guillain–Barré syndrome will not be discussed. However, some chronic neuropathies are acquired in the course of critical illness, usually as a consequence of sepsis, probably related to cytokine-induced injury.[93] These can cause phrenic nerve dysfunction and diaphragm weakness, as can cold injury to the phrenic nerves (phrenic frostbite), which may be seen after cardioplegia for open heart surgery. These injuries usually, but not always, resolve over a period of weeks to months.[74] Other causes of phrenic nerve injury and unilateral or bilateral diaphragm paralysis include neck manipulation during general anesthesia, traumatic neck or chest injuries, and tumor invasion; some cases are idiopathic.

Chronic Inflammatory Demyelinating Polyneuropathy. Chronic inflammatory demyelinating polyneuropathy is a sensorimotor polyneuropathy, similar to but more sustained than acute inflammatory demyelinating polyradiculopathy, and is presumed to be autoimmune.[196] It can be severe enough to compromise respiration and lead to respiratory failure, but more often leads to progressive diffuse weakness, sensory loss, ataxia, and pain, with subsequent debilitation and disability, but usually without respiratory failure.[196]

Charcot–Marie–Tooth Disease. Charcot–Marie–Tooth disease is a genetically heterogeneous group of chronic neuropathies that share the same clinical phenotype and occasionally compromise pulmonary function.[138] These are characterized by wasting and weakness of distal limb muscles (especially the peroneal compartment), often with distal sensory loss, skeletal deformities, and decreased or absent tendon reflexes.[138] Onset is usually during the first decades of life, the course is very slowly progressive, and severity is highly variable, even within the same kinship, only rarely leading to severe impairment.[138] Occasionally, respiratory complications occur, including vocal cord paralysis, laryngeal weakness leading to inspiratory stridor, and intercostal muscle and diaphragm weakness progressing to respiratory failure.[66]

DISORDERS OF THE NEUROMUSCULAR JUNCTION

Disorders of the neuromuscular junction, such as myasthenia gravis, may manifest pulmonary complications during acute crises. Such complications are important, but are not the focus of the present review and will not be discussed.

MYOPATHIES AFFECTING RESPIRATORY FUNCTION

Diseases of muscle are numerous and varied. They can be divided into acquired, inherited, and congenital.

Acquired Causes of Myopathy. Among the acquired myopathies are the inflammatory myopathies, polymyositis and dermatomyositis.[57] Pulmonary complications occur in approximately 10% of patients and include restriction due to chest wall and diaphragm muscle weakness and interstitial lung disease.[80] Postparalysis myopathies may be seen in intensive care units after long bouts of respiratory failure treated with paralytics and steroids, and are usually slowly reversible.[68]

Inherited Myopathies. ***Duchenne Muscular Dystrophy.*** Duchenne muscular dystrophy (DMD) is the most common inherited progressive myopathy, affecting up to 1 in 3300 live male births.[135] DMD is caused by the lack of dystrophin.[51] A gene on chromosome X(p21) codes for dystrophin, leading to an X-linked recessive inheritance pattern.[26,51] Features of motor delay prompt the diagnosis in approximately 20% of cases by the age of 2 years and 75% by the age of 4 years.[167] Progressive weakness, loss of ambulation, inability to perform tasks with upper extremities, and occasional involvement of facial muscles, as well as increasing orthopedic, pulmonary, and cardiac complications occur during the elementary school

years, and intellectual impairment may be noted.[135] Loss of ambulation usually occurs by age 10 or 11 years.[135]

Respiratory failure is the major cause of death in patients with DMD.[8,27] Respiratory impairment becomes clinically manifest in the advanced stages of disease, usually in the late teens.[27] Death is brought on by pneumonia, retained secretions, atelectasis, or eventually by respiratory muscle fatigue and failure.[27] Ventilatory abnormalities during sleep resulting from rapid eye movement (REM)–related nocturnal hypoventilation may also be associated with the development of respiratory insufficiency and cor pulmonale.[100,169] Sleep-disordered breathing occurs in up to two-thirds of patients during the early teenage years, associated with transient hypoxemic dips.[100] Although these nocturnal events in younger patients are characterized mainly by obstructive apneas and hypopneas,[100] central hypopneas may occur in older patients.[25] A forced expiratory volume in 1 second (FEV_1) of $<40\%$ predicted, a $PaCO_2$ ≥ 45 mm Hg, and a base excess >4 mmol/L are factors that indicate the development of sleep-disordered breathing in DMD.[92] Numerous studies have shown that, without ventilatory support, the average life expectancy in DMD is around 20 years.[167]

Becker Muscular Dystrophy. Becker muscular dystrophy (BMD) is a late-onset form of X-linked muscular dystrophy.[127] Significant problems may be encountered during childhood for some BMD subjects, but for the majority the disease is relatively mild before adulthood.[135] Early manifestations include proximal lower-extremity weakness and, in some subjects, weakness of the neck flexors.[118] Contractures are usually not a problem until after the transition to a wheelchair, and scoliosis is relatively rare.[44] Restrictive lung disease occurs as a late complication in a small percentage of BMD cases, but the severity of pulmonary disease does not approach that seen in DMD.[118] The cardiomyopathy in BMD tends to be disproportionately severe relative to the degree of restrictive lung disease,[118,173] and rare cases have been reported with symptoms and signs of cardiac insufficiency predating the observed onset of skeletal myopathy.[118] The slowly progressive nature of this dystrophic myopathy, which is compatible with many years of functional mobility and longevity,[135] makes these patients suitable candidates for cardiac transplantation if end-stage cardiac failure occurs.[49]

Facioscapulohumeral Muscular Dystrophy. Facioscapulohumeral muscular dystrophy is a slowly progressive myopathy with autosomal dominant inheritance, remarkable for its early involvement of facial musculature.[192] Muscle weakness is relatively mild, with a slow rate of decline in strength. Lower-extremity proximal muscles are usually also involved.[101] Limb contractures are infrequent, and spine deformity is limited primarily to hyperlordosis.[135] Impairment of pulmonary function also tends to be mild, complicated by a propensity to obstructive sleep apneas related to upper airway muscle weakness.[101] Although respiratory involvement leading to ventilatory decompensation can occur,[167] the prognosis for most affected individuals is quite good, as there is no associated cardiac involvement or learning disability.[63,101,135]

Myotonic Dystrophy. Myotonic dystrophy is an autosomal dominant multisystemic disorder characterized by muscle wasting, myotonia, cataracts, intellectual impairment, and cardiac conduction defects, with a characteristic pattern of temporal wasting and frontal balding.[120] Respiratory involvement occurs during middle age, with a progressive restrictive pattern being the most common pulmonary function abnormality.[167] However, the manifestations are quite variable, with some patients developing diaphragm paralysis and others having mainly sleep disturbances, with obstructive or central apneas, or frank central hypoventilation.[43,186] The apnea–hypopnea index (AHI) and degree of nocturnal desaturation are greater than in nonmyotonic neuromuscular disease for a similar degree of respiratory muscle weakness.[72] Patients tend to be heavier than those with other forms of neuromuscular disease, and the degree of nocturnal desaturation is related to the body mass index (BMI).[72] In most patients with myotonic dystrophy, sleepiness is not clearly attributable to hypercapnia, sleep-disordered breathing, or disturbance of sleep architecture,[187] and central influences have been suggested.[186]

An early congenital form of myotonic dystrophy is accompanied by much more dramatic symptomatology, with mortality (often secondary to pulmonary complications) approaching 25% by 18 months of age.[135] Those who survive the neonatal period demonstrate continued developmental motor delay and often experience significant mental impairment.[80]

Congenital Muscular Dystrophy. Congenital muscular dystrophy describes infants presenting at or within the first few months of birth with dystrophic features on muscle biopsy and associated hypotonia, arthrogryposis, and contractures.[167] Progression of muscle weakness with age is not marked, but ventilation may be compromised in late childhood by a vicious cycle of worsening thoracic scoliosis and nocturnal hypoventilation.[167] Because the disease progresses slowly and bulbar and cardiac involve-

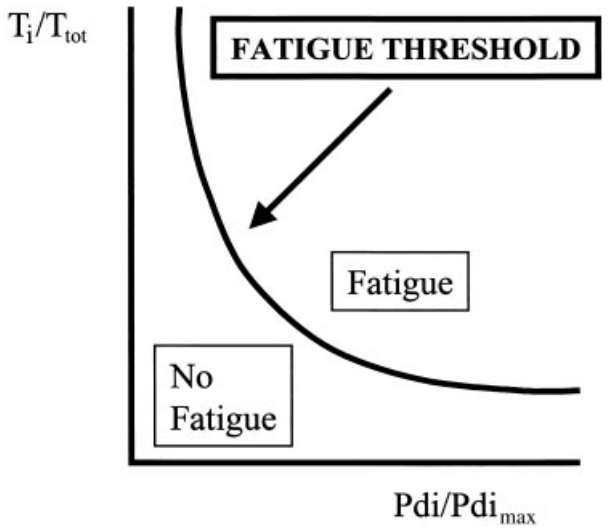

FIGURE 1. Relationship between T_i/T_{tot} and Pdi/Pdi_{max}. Line represents an isopressure–time index value for the diaphragm of about 0.15. Breathing patterns falling to the right of the curve cause diaphragmatic fatigue. Pdi, mean transdiaphragmatic pressure; Pdi_{max}, maximal transdiaphragmatic pressure; T_i, inspiratory time; T_{tot}, total time for respiratory cycle.

ment are rare, the prognosis of patients after starting noninvasive ventilation is relatively good.[166]

CAUSES AND MECHANISMS OF RESPIRATORY FAILURE IN NEUROMUSCULAR DISEASES

Respiratory Muscle Weakness and Fatigue. Respiratory muscle weakness, defined as the inability of the rested respiratory muscles to generate normal levels of pressure and flow during inspiration and expiration,[36,133] is a frequent occurrence in many neuromuscular diseases.[62] Because chest wall and pulmonary compliance are reduced in neuromuscular diseases, the mechanical load on the weakened respiratory muscles is increased.[168] An imbalance between load and capacity leads to muscle fatigue and respiratory failure.[94,188] For skeletal muscles including the diaphragm, muscle fatigue is defined as the inability of a muscle to continue to generate a given tension in response to a steady stimulus.[150] Skeletal muscles may develop fatigue if continuous contraction is driven beyond a given tension threshold.[31,32] In normal subjects, the fatigue threshold for the diaphragm may be reached when the pressure–time index determined by T_i/T_{tot} multiplied by mean Pdi (expressed as a fraction of Pdi_{max}) exceeds a critical value of 0.15, where T_i is inspiratory time, T_{tot} is total time for the respiratory cycle, mean Pdi is mean transdiaphragmatic pressure, and Pdi_{max} is maximal transdiaphragmatic pressure[31,32] (Fig. 1). In other words, because the diaphragm contracts mainly during inspiration, it should fatigue more rapidly if at any given tension, the maximal diaphragmatic pressure decreases or the ratio of inspiratory time over total breathing cycle duration (T_i/T_{tot}) increases.[31]

In neuromuscular diseases, a greater $Paco_2$ has been associated with a decrease in inspiratory time, a lower tidal volume, and an increase in the elastic load of the lung.[108,125] Considering that increasing inspiratory time and Pdi may be very important to maintain a normal $PaCO_2$, the strategies needed to maintain ventilation in patients with neuromuscular diseases increase the risk of respiratory muscle fatigue. It should be emphasized that the fatigue threshold for the diaphragm, calculated by Bellemare and Grassino,[31,32] was obtained in normal subjects and in patients with chronic obstructive pulmonary disease; patients with neuromuscular disease may be different. Indeed, Nava et al. demonstrated that the fatigue threshold for the diaphragm in quadriplegics was around 0.10–0.12, far below the threshold of fatigue of 0.15 described in normal subjects.[131] Thus, these concepts undoubtedly apply to chronic neuromuscular disease, and impairment of nondiaphragmatic muscles may actually predispose to earlier diaphragm fatigue.

Impact of Inspiratory Muscle Weakness. Inspiratory muscles include the diaphragm, external intercostal muscles, and accessory muscles. Weakening of these muscles alters ventilatory mechanics, causing restriction of the respiratory cage and, ultimately, CO_2 retention and frank respiratory failure.[62,168]

Alteration in Respiratory Mechanics. Related to the inability to achieve a full inhalation due to inspiratory muscle weakness, the elastic load of the chest wall gradually increases in neuromuscular disease, contributing to increased work of breathing and eventual ventilatory failure.[33,36,62] Disuse of any part of the musculoskeletal system is accompanied by a number of structural changes, including muscle atrophy, disuse osteoporosis, extraarticular contractures, and intraarticular adhesions, progressing to obliterative degeneration of articular cartilage.[39,70] The additive effects of these processes in adults with neuromuscular disease appear to underlie the stiffening of the chest wall.[137]

Kyphoscoliosis, frequently associated with neuromuscular diseases, also contributes to chest wall stiffness and increases the work of breathing.[33] Kyphoscoliosis is accompanied by deformation of the thoracic cage that further increases chest wall stiffness and produces mechanical misalignment of the respiratory muscles, thus lessening their ability to operate effectively against the increased elastic and

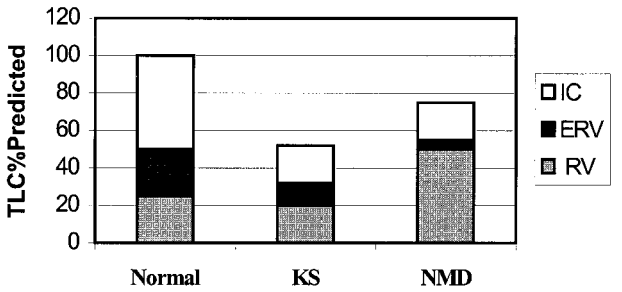

FIGURE 2. Total lung capacity (TLC) and its subdivisions in neuromuscular disease (NMD). The lung volume histograms are compared with figurative normal and kyphoscoliosis (KS) subjects to illustrate the pattern of distribution of the subdivisions within TLC (modified from Bergofsky,[36] with permission). IC, inspiratory capacity; ERV, expiratory reserve volume; RV, residual volume.

resistive loads.[36] Failure to fully inflate also contributes to microatelectasis, decreasing lung compliance and increasing respiratory system elasticity.[36,62]

Restriction of Lung Volume. Diseases of the nerve and muscles alter ventilatory pump function by limiting the ability to lower intrathoracic pressure and inflate the lung,[61] producing the well-established pattern of restriction seen on pulmonary function tests in patients with neuromuscular disease.[45,61,62] Total lung capacity (TLC) and vital capacity (VC) are reduced,[36,45] whereas functional residual capacity (FRC), the resting volume of the respiratory system, is normal or decreased.[36,62] This restriction reflects both direct (loss of distending pressure) and secondary (changes in the passive characteristics of the lungs and chest wall) effects of respiratory muscle weakness on pulmonary function.[62]

When the extent of respiratory muscle involvement varies between muscles, changes in pulmonary function may be helpful diagnostically. For example, a fall in VC of 25% or more between the upright and supine positions has been found to be a more sensitive indicator of diaphragm weakness than upright measures of VC and TLC alone.[75] This change has a specificity and sensitivity of 90% and 79%, respectively, for the diagnosis of diaphragmatic weakness.[75] Lung volume characteristics in normal subjects, kyphoscoliotics, and patients with neuromuscular diseases are presented in Figure 2. Forced expiratory flow rates are reduced in patients with neuromuscular weakness, usually in proportion to the reduction in the FVC, such that the FEV_1 FVC ratio is normal or even high.[84]

Impairment in Gas Exchange. With mild to moderate respiratory muscle weakness, ventilatory drive is increased, leading to hyperventilation, a normal or elevated pH, and a reduced arterial tension of CO_2.[61] The PaO_2 and the alveolar–arterial oxygen tension ($p(A\text{-}a)O_2$) gradient should be normal.[36] Nevertheless, a few processes can increase the $p(A\text{-}a)O_2$ gradient, such as airway obstruction (retained secretions, mucous plugs) or involvement of the pulmonary parenchyma (pneumonia, atelectasis).[61] As respiratory muscles further weaken, the arterial tension of CO_2 increases. However, the degree of chronic hypercapnia may be greater than would be expected from measures of muscle weakness alone.[28,45] This suggests that factors other than muscle weakness contribute to CO_2 retention.[30] Some of these have already been discussed, such as atelectasis and increased chest wall stiffness.[30,62] Increased dynamic elastance (a parameter that reflects elastic load of the lung per unit of maximal inspiratory muscle strength) has been shown to be the strongest predictor of variance in $PaCO_2$.[125] The increased elastic load and respiratory muscle weakness[30] are thought to be responsible for a rapid, shallow breathing pattern.[108,125] Such a rapid, shallow respiratory pattern may reduce elastic work per breath, muscle tension, and perception of dyspnea, despite the cost of increasing dead space ventilation and contributing to CO_2 retention.[108,125]

Gas exchange impairment can be aggravated during sleep (see later) or by activities such as moderate exercise and alterations in the control of breathing.[36,190] The latter may be compounded by blunting of the hypercapnic and hypoxic ventilatory drives by progressive CO_2 retention or other mechanisms.[61] Clinical observations suggest that central neural mechanisms also may play a role in events leading to acute respiratory failure.[3,126,172] Experimental models indicate that a reduction in neural drive or slowing of respiratory frequency may occur after imposing large respiratory loads, and precedes evidence of muscle fatigue.[95,154] Furthermore, the mechanism of this alteration in respiratory drive, sometimes referred to as "central fatigue," appears to be independent of perceived dyspnea, hypercapnia, or hypoxemia.[95,154] This has led to the speculation that, during the development of respiratory failure, it is possible that slower, shallower breaths may limit effort, thus delaying or avoiding frank fatigue of the respiratory muscles, even though minute ventilation is sacrificed and hypercapnia worsens.[95]

Impact of Expiratory Muscle Weakness. A normal cough requires a full pre-cough inspiration, followed by glottic closure, and sufficient expiratory muscle strength to generate intrathoracic pressures that are adequate to obtain high transient expiratory flows (or peak cough expiratory flows).[17,18,170]

In neuromuscular diseases, even when expiratory muscles are severely weakened, adequate flow rates can be generated if inspired volume and elastic recoil of the respiratory system are preserved.[36,143] However, when combined with impaired glottic function or inspiratory muscle weakness, inadequate expiratory muscle function in neuromuscular disease causes severe impairment of the ability to clear airway secretions.[18] Retained secretions then increase airway resistance and alter respiratory mechanics.[33] In addition, because weakened expiratory muscles cannot lower thoracic volume substantially below FRC, the expiratory reserve volume (ERV) is reduced and residual volume (RV) is increased (Fig. 2).[45,84,103]

Clearance of airway secretions is a ubiquitous and potentially life-threatening problem for patients with neuromuscular disease and bronchial hypersecretion, bulbar dysfunction, or severe inspiratory or expiratory muscle weakness, necessitating therapeutic intervention to alleviate this problem.

Impact of Upper Airway Muscle Weakness. Involvement of the upper airway (bulbar) musculature impairs speech and swallowing.[61] With severe bulbar involvement, ingestion of adequate nutrition becomes impossible and weight loss ensues.[34] Swallowing impairment is a major cause of sialorrhea (drooling) in patients with upper airway dysfunction.[123] In these subjects, as the swallowing mechanism deteriorates, speech is invariably affected, and patients may require assistive technology to communicate effectively. Choice boards and computer-assisted speech devices are available for patients with neuromuscular speech difficulties.[96]

Furthermore, dysfunction of the lips, tongue, and pharyngeal and laryngeal muscles increases the risk of aspiration and causes difficulty with the glottic closure that is necessary for effective cough function.[34] Upper airway muscle weakness also contributes to airway obstruction during sleep and predisposes to sleep-related breathing disorders during use of negative-pressure body ventilators.[14,43,90]

Inadequate Airway Protection as a Consequence of Respiratory Muscle Weakness. A normal cough requires an intact sensory pathway to detect airway irritation and secretions, and the integrity of all major respiratory muscle groups.[17,18,34] In neuromuscular disease, cough may be impaired by involvement of any of the major respiratory muscle groups, including: (1) inspiratory muscles, leading to a reduction in the force necessary to generate a deep inspiration; (2) bulbar muscles, causing inability to close the glottis completely during the compressive phase; and (3) expiratory muscles, causing inability to compress and expel intrathoracic gas.

Laryngeal weakness and ineffective cough complicate impaired swallowing function.[135] Uncoordinated laryngeal function or weakness may lead to penetration of oral contents (liquids and solid foods more than semisolids, along with nasopharyngeal and oral secretions) into the airway, which predisposes to aspiration pneumonia.[168] Choking episodes are common and may be triggered by saliva. Secretion management may be a particularly vexing problem in neuromuscular disease because secretions become more viscous when hydradion is inadequate.[34] In addition, poor orofacial muscle tone and weakness contribute to drooling that is often regarded as socially unpleasant.[55] Drooling is an indicator of a poorly coordinated swallowing mechanism that exposes patients to the more serious problem of aspiration.[55,168]

Chest Infections. In patients with neuromuscular disease, over 90% of pneumonias are triggered by upper respiratory tract infections.[20] Chest infections pose a serious threat to vulnerable patients with muscle weakness and a poor cough.[168] Prompt treatment is required with physiotherapy, postural drainage, antibiotics, and appropriate assisted ventilation.[167,168]

Impaired Control of Breathing. When neuromuscular diseases impair respiratory muscle function, the ventilatory response to either hypercapnia or hypoxemia is reduced because of respiratory muscle weakness and altered chest wall mechanics.[168] Nevertheless, the sensitivity of chemoreceptors is well preserved, and the central drive, as measured by the occlusion pressure, $P_{0.1}$ (mouth pressure measured 0.1 second after the interruption of airflow at the start of inspiration)[191] is normal or slightly increased.[28] The breathing pattern is usually rapid and shallow because of the abnormal respiratory mechanics and muscle physiology, as previously discussed.[29] For example, in muscular dystrophy, respiratory muscle weakness is accompanied by degenerative changes in the muscle spindle.[179,180] Electrophysiologic studies have demonstrated impaired stretch reflexes from muscle spindles, and decreased or absent tendon reflexes.[28] Disturbances in feedback from respiratory muscle receptors may impair modulation of respiratory muscle contraction and cause disturbances in the regulation of breathing in muscular dystrophy.[28] However, a component of central hypoventilation re-

lated to abnormal respiratory control has long been suspected in myotonic dystrophy, on the basis of the tendency toward CO_2 retention that is inappropriate for the degree of respiratory muscle dysfunction.[30,168,186]

Sleep and Breathing in Neuromuscular Diseases. ***Normal Breathing Events during Sleep.*** During nonrapid eye movement sleep (NREM), ventilation falls abruptly and is associated with a more rapid, shallow, and regular breathing pattern, resulting in a rise in the partial pressure of CO_2.[65] Ventilation shows only a slight further decline once sleep becomes established.[43] In contrast to ventilation, upper airway resistance increases abruptly at sleep onset due to reduced activity of the pharyngeal dilator muscles and rises further in association with increasing delta activity in the electroencephalogram during slow-wave sleep.[97] Subjects with a tracheostomy have changes similar to normal subjects during sleep.[129] Thus, the changes in ventilation during sleep are most likely related to a reduction in ventilatory drive due to blunted chemosensitivity[53,128] rather than to the increase in upper airway resistance. A rise in genioglossus activity during NREM sleep, after the initial fall at sleep onset, may be important in maintaining airway patency.[182]

During REM sleep there is a marked generalized reduction in the tone of skeletal muscles, with the exception of the diaphragm and extraocular muscles.[65] Thus, a further fall in tidal volume (due to rib cage contribution), minute ventilation, and mean inspiratory flow occur during the transition from NREM to REM sleep.[65]

In normal subjects, these changes in ventilation and breathing pattern cause only minor changes in gas exchange. However, changes in gas exchange are augmented in those with underlying respiratory muscle weakness, especially if the diaphragm is significantly involved.

Sleep-Disordered Breathing in Neuromuscular Diseases. Sleep-disordered breathing is frequently encountered in chronic neuromuscular diseases such as amyotrophic lateral sclerosis, muscular dystrophies, and myotonic dystrophy.[43] Respiratory muscle weakness, rib cage and spinal deformities, upper airway muscle weakness, obesity, craniofacial abnormalities, and abnormalities of ventilatory control all occur in neuromuscular disorders and serve to enhance the likelihood of sleep-disordered breathing.[43,141] Strong evidence now underlines the importance of diagnosing and treating sleep-disordered breathing in the management of patients with neuromuscular diseases to improve quality of life[115] and possibly longevity.[21,134,165]

The nature of sleep-disordered breathing in patients with neuromuscular disease reflects the distribution of respiratory muscle involvement.[141] When patients have severe diaphragm dysfunction, suppression of intercostal and accessory muscles during REM sleep leads to hypoventilation.[6,190] However, if diaphragm strength is intact, but the upper airway or intercostal muscles are weak, then obstructive apneas or hypopneas are more likely to occur.[141] In some forms of neuromuscular disease, such as poliomyelitis and myotonic dystrophy, primary abnormalities in ventilatory control may also contribute to sleep-disordered breathing, often complicated by nocturnal or even diurnal hypoventilation.[141,186]

Nocturnal hypoventilation. The commonest form of sleep-disordered breathing in patients with respiratory muscle weakness is hypoventilation due to reduced tidal volume, particularly during REM sleep, and has been well described in isolated diaphragmatic paralysis, amyotrophic lateral sclerosis, and myotonic dystrophy.[71,72,77,190]

Neuromuscular weakness exaggerates the normal breathing events that occur during REM sleep, worsening gas exchange abnormalities, particularly in patients with diaphragm weakness.[43,92] The hypoventilation contributes to frequent arousals, reducing sleep time and sleep efficiency,[71] and results in daytime symptoms and sleep deprivation.[71,190] The arousal response limits the magnitude of the drop in SaO_2 and rise in CO_2 tension by changing the sleep state, increasing postural muscle tone, recruiting upper airway and respiratory muscle activity, and permitting ventilation to be restored.[6,190] Thus, arousals may represent a protective mechanism to minimize alterations in blood gases.[43,141] However, the arousals also contribute to poor sleep quality and the typical daytime symptoms of hypersomnolence and fatigue.

Over time, the ventilatory chemosensitivity may accommodate to the changes in blood gases, permitting not only longer periods of REM sleep, but also longer periods of hypoxia.[140,189] Hypoventilation may also become more prolonged, promoting bicarbonate retention, and further depression of respiratory drive.[83,87,139] This creates a vicious cycle that eventually leads to severe hypoventilation, not only during REM sleep but also diurnally (Fig. 3).[141] and, if uninterrupted, to eventual death.

Obstructive sleep apnea. Obstructive events during sleep are common with neuromuscular disorders, particularly in patients who snore, have a high body mass index (BMI), or have anatomic abnormal-

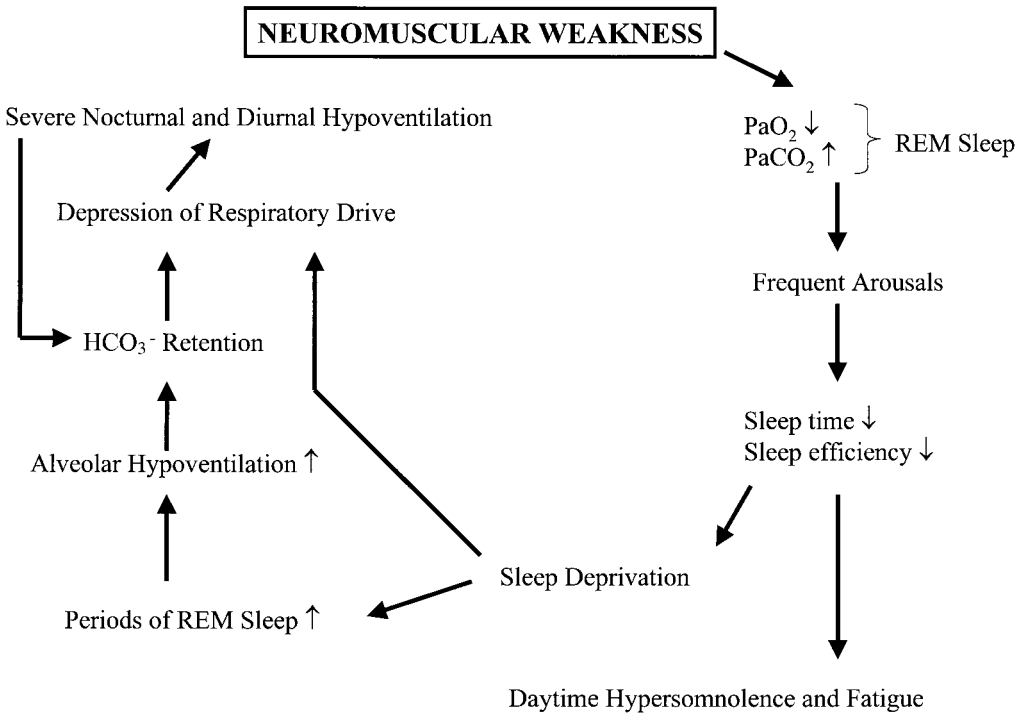

FIGURE 3. Circular events leading to severe hypoventilation in neuromuscular disease.

ities such as retrognathia or macroglossia.[25,106] Such abnormal sleep events have been reported mainly in patients with Duchenne muscular dystrophy, amyotrophic lateral sclerosis, or myotonic dystrophy.[72,77,100] Even in the absence of frank apneas, increased upper airway resistance during REM sleep may contribute to obstructive hypopneas.[100] Pharyngeal or laryngeal muscle weakness adversely affects the normal stabilizing function of the pharyngeal muscles as well as the local reflex mechanisms that prevent upper airway collapse during inspiration.[60]

Large discrepancies between studies have been reported in the prevalence of obstructive events during sleep in patients with the same underlying conditions and similar respiratory function.[43] These discrepancies may arise from differences in how events are classified or in how sleep is monitored.[169] Normally, obstructive events are distinguished from central ones by the continued or increased chest wall movement in the absence of airflow. In patients with severely weakened inspiratory muscles, chest wall motion may not be detectible during obstructive events, at least by standard plethysmography techniques, causing the event to be interpreted as central despite continued inspiratory effort.[169] Although not done routinely in most U.S. sleep laboratories, esophageal manometry is a more sensitive way to detect these diminished inspiratory efforts.

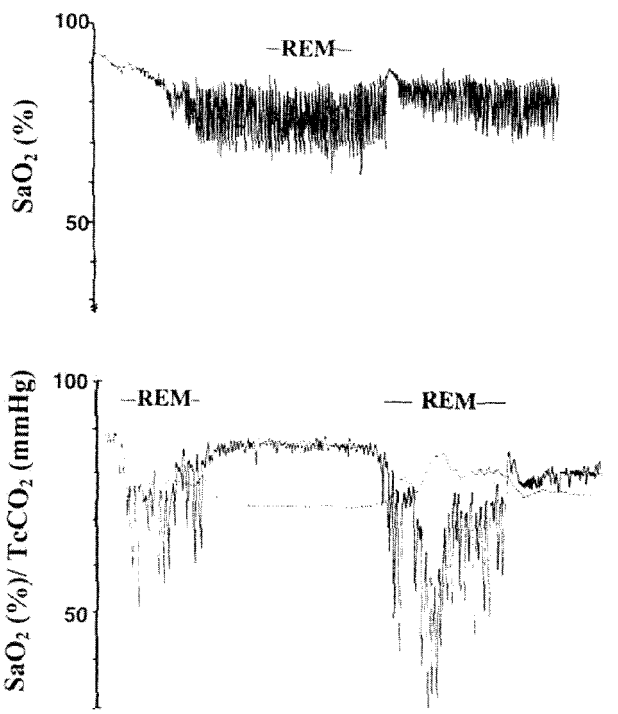

FIGURE 4. Overnight oximetry recordings illustrating the differing patterns of nocturnal oxygen saturation (SaO_2) associated with sleep-disordered breathing in neuromuscular disease. (**Top**) Repetitive episodes of oxyhemoglobin desaturation typical of obstructive sleep apnea. (**Bottom**) Typical severe REM hypoventilation (reproduced with permission from Piper[141]).

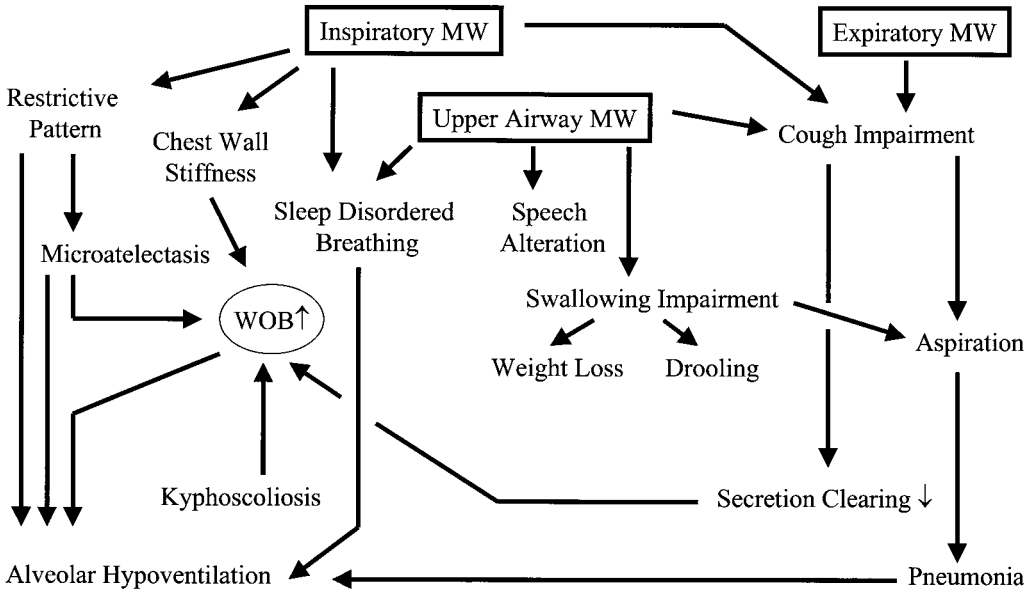

FIGURE 5. Schematic representation of pathologic links in neuromuscular disease. Inspiratory MW, inspiratory muscle weakness; Upper Airway MW, upper airway muscle weakness; Expiratory MW, expiratory muscle weakness; WOB, work of breathing.

Overnight oxygen saturation profiles exemplifying hypoventilation and obstructive apneas are shown in Figure 4.

Other causes of breathing disorders during sleep. In certain disorders such as myotonic dystrophy, daytime somnolence, hypercapnia, nocturnal desaturations, and diurnal hypoventilation are all common and may not be explained by sleep-disordered breathing or disturbances of sleep architecture.[43,186] These patients may have an irregular breathing pattern during wakefulness and light sleep that does not persist during slow-wave sleep, suggesting that there may be a brainstem abnormality affecting respiratory control.[186]

Besides breathing abnormalities disrupting sleep, other factors may be responsible for the poor sleep and daytime sleepiness often seen in patients with neuromuscular disease. The inability to alter position can produce pain and discomfort, causing frequent disruptions during sleep.[141] Also, difficulty clearing secretions, anxiety, and depression may further impair sleep quality.[71]

Orthopedic Abnormalities in Neuromuscular Diseases. Progressive neuromuscular disorders, particularly the juvenile muscular dystrophies and spinal muscular atrophies, predispose to the development of serious and devastating spinal deformity.[38,79] Initially, weakness of the spinal extensors places the ligamentous structures supporting the posterior elements of the spine under constant tension. During rapid trunk growth, the unopposed stress of gravity causes posterior tilting of the pelvis and decreases the ability of the column to withstand vertical loads.[5] The progressive kyphoscoliosis opens posterior facet joints, facilitating lateral bending and rotation of the spine. Inequalities in the lateral forces acting on the kyphotic spine then produce lateral collapse. In the final stages, severe axial rotation of the spine and sometimes the pelvis occur, creating more severe deformities and more complex problems than in patients with idiopathic scoliosis alone.[38] Spinal deformities in patients with neuromuscular disorders may be difficult to control with bracing, and may progress even after skeletal maturity has been reached.[24] The pelvic obliquity predisposes to dislocations of the hip; limited balance or ability to sit; back pain; and, when kyphoscoliosis is advanced, severe restriction of pulmonary function.[178]

A schematic representation of the pathologic consequences of progressive neuromuscular weakness affecting the three major respiratory muscle groups and chest wall is shown in Figure 5.

DETECTION OF RESPIRATORY FAILURE

The development of respiratory failure in patients with neuromuscular diseases is often insidious, particularly when inability to ambulate occurs in tandem with respiratory muscle weakness. Thus, clinicians must have a knowledge of subtle indicators and a high index of suspicion.[144] Nonspecific symptoms such as fatigue, lethargy, or difficulty in concentrating may be the first indicators of respiratory insuffi-

ciency.[144] Dyspnea may be absent, particularly in quadriplegic patients, although orthopnea is typical of isolated diaphragm paralysis, as is breathlessness on immersion in water.[58] Involvement of the upper airway musculature may produce additional symptoms, such as difficulties with speech or swallowing, and aspiration associated with dysphonia.[168] Because muscle weakness contributes to sleep-disordered breathing, symptoms such as poor sleep, daytime somnolence, and morning headache are common, and often reflective of CO_2 retention.[30,91,190]

As the disease progresses, tachypnea at rest may be an early manifestation, associated with a decrease in tidal volume.[62] Nonetheless, the respiratory muscle problem is often clinically inapparent until respiratory insufficiency is advanced because of the paucity of clinical signs that are specific for respiratory muscle weakness. Some patients have disproportionate weakness of the diaphragm or the intercostal muscles that may lead to paradoxical breathing. However, when both major inspiratory muscle groups are affected equally, breathing movements will be synchronous.[85] Compensatory recruitment of other muscles may be a useful sign and is detected by inspecting and palpating the accessory and abdominal muscles.[85]

A more complete list of presenting symptoms and signs for respiratory failure in neuromuscular disease is found in Table 1.

Table 1. Symptoms and signs of respiratory impairment in neuromuscular disease.

Symptoms
Constitutional
Generalized fatigue
Weakness
Cardiopulmonary
Dyspnea
Lower extremity edema
Orthopnea
Secretion retention
Central nervous system
Early morning headaches
Daytime hypersomnolence
Mood disturbances
Psychiatric disorders
Sleep
Restless sleep
Nightmares
Enuresis
Frequent arousals
Signs
Vital signs
Tachypnea
Tachycardia
Respiratory
Accessory chest and abdomen muscle use
Paradoxical breathing pattern
Diminished excursion
Cardiac
Distended neck veins
Edema
Increased P2
Cyanosis

EVALUATION OF NEUROMUSCULAR PATIENTS WITH SUSPECTED RESPIRATORY FAILURE

Pulmonary function studies, including spirometry and lung volume, are routinely obtained in the evaluation of patients with neuromuscular disease and have the advantages of being noninvasive and readily available. However, the strength of the respiratory muscles must be severely impaired (by as much as 50%) before any significant reduction in VC or TLC can occur.[45] Thus, VC and TLC are insensitive measures of respiratory muscle weakness and, for this reason, maximum inspiratory and expiratory pressures are often used to assess respiratory muscle strength.[61,114]

The most widely used tests of global inspiratory and expiratory muscle strength are the static maximum pressures measured at the mouth (PI_{max} and PE_{max}).[47,111] These tests have the advantage of being noninvasive, and normal values have been established in both adults and children.[47,76,111] A high negative PI_{max} (80 cm H_2O) or a positive PE_{max} (90 cm H_2O) on a properly performed test excludes clinically important inspiratory or expiratory weakness.[142]

PI_{max} and PE_{max} are influenced by age, gender, posture, lung volume, and the type of mouthpiece.[47,181] They are measured preferably in the sitting position using a standard flanged mouthpiece.[142] Conventionally, PI_{max} is measured from residual volume, and PE_{max} from TLC, with a noseclip. The highest recorded pressure maintained for 1 second represents PI_{max} or PE_{max}. Values of PI_{max} and PE_{max} are reduced in patients with advanced neuromuscular disease.

Factors such as submaximal effort or air leaks around the mouthpiece may cause erroneous measurements, especially in individuals with orofacial muscle weakness. For these reasons, simplified maneuvers or measures that require no subject effort have been proposed as alternative means of measuring inspiratory muscle strength. The maximal sniff pressure test is easier to perform than the PI_{max} maneuver for most subjects.[121] Thus, inspiratory muscle strength is often better reflected by maximal

sniff pressure (SNIP) than by the PI_{max} maneuver. SNIP is measured through a plug occluding one nostril during sniffs performed through the other nostril.[121] Nasal leaks are eliminated by using waxed plugs hand-fastened around the tip of a polyethylene catheter. SNIP is measured from functional residual capacity rather than from residual volume.[105] Normal values of SNIP have been established in one large study (men $\geq$70 cm H_2O, women $\geq$60 cm H_2O).[185] Although SNIP tests appear to be more reliable in assessing respiratory strength in patients with neuromuscular disease than maximal static inspiratory efforts,[174] these tests measure global respiratory muscle function and do not give specific information about diaphragm strength.

Transdiaphragmatic pressure (Pdi), the pressure difference between esophageal and gastric pressures, reflects the tension developed by the diaphragm, and is viewed as a specific measure of diaphragmatic inspiratory action.[162] Esophageal and gastric pressures are measured by manometric balloons placed in the midesophagus and stomach during a PI_{max} maneuver.[181] Although measurements of Pdi have the advantage of specifically assessing diaphragm function, the technique is invasive and may be poorly tolerated or even hazardous in patients with swallowing impairment.

The reliability of Pdi measurements can be improved by direct transcutaneous phrenic nerve stimulation, either by electric or magnetic impulses.[163] A major advantage of this technique is that it requires no patient effort, a particularly attractive feature for patients with neuromuscular disease. However, a drawback is that the magnitude of twitch Pdi depends on the impedance of the abdomen and rib cage.[61]

In patients with acute respiratory failure requiring intubation and mechanical ventilation, assessment of neuromuscular function may be challenging.[98] Clear signs such as paradoxical abdominal movements are nonspecific and, even in the presence of phrenic neuropathy, are often absent or overlooked.[160] Motor and sensory nerve conduction studies, in combination with needle electromyography, may provide useful diagnostic information regarding the presence and localization of neuropathic processes, particularly in the acute setting, to evaluate phrenic nerve function[160] in, for example, Guillain–Barré syndrome and myasthenia gravis, and also sepsis and traumatic damage to the phrenic nerves.[199] In patients with amyotrophic lateral sclerosis who present with respiratory insufficiency, these techniques may be not only of diagnostic but also of prognostic value, by differentiating between acute and chronic denervation.[41,136]

Table 2. Indications for a polysomnogram in neuromuscular disease.

Pressure titration when initiating NPPV
To evaluate for obstructive sleep apnea (obese, snorer, or hypersomnolence)
To seek sleep-disordered breathing or hypoventilation in a:
Symptomatic patient without daytime hypercapnia or severe pulmonary function defect
Asymptomatic patient with daytime hypercapnia or severe pulmonary function defect

NPPV, noninvasive positive-pressure ventilation.

Frequency of Pulmonary Function Monitoring. The frequency of monitoring depends on the rapidity of progression of the neuromuscular syndrome and may range from every 1–2 months to yearly.[91] Once the vital capacity drops below 40–50% predicted, or maximal inspiratory pressure (or SNIP) below 30% predicted, daytime arterial blood gases should be checked.[91]

Unlike patients with generalized respiratory muscle disease, those with isolated complete diaphragm paralysis and normal lungs may develop ventilatory failure before manifesting severe restriction on pulmonary function tests, at least in the sitting position.[144] In such cases, a significant reduction in supine VC is helpful in detecting severe or predominant diaphragmatic weakness.[75] If in doubt, measurement of transdiaphragmatic pressure is the most reliable way to document the nature and severity of the problem.[109]

Possible aggravating conditions that may contribute to hypercapnia, such as obstructive sleep apnea, hypothyroidism, congestive heart failure, or electrolyte disturbances (K^+, Ca^{++}, Mg^{++}, PO_4^{3-}), should also be considered.[175] Because of the common association between neuromuscular disease and sleep-disordered breathing, sleep studies are often useful in the evaluation. Indications for polysomnography are listed in Table 2.

TREATMENT OPTIONS

Diet. Weight control is often necessary in patients with myopathy or postpolio syndrome.[168] Not only do obese patients put extra loads on already weak skeletal muscle, but they also suffer from the deleterious effects of obesity on respiratory function.[168] Many patients with neuromuscular diseases become overweight through a combination of inactivity, reduced energy turnover in wasted muscle, and a mis-

guided desire to improve muscle bulk by overeating.[168] Conversely, some patients lose excessive weight because of swallowing difficulty or a desire to facilitate transfers for their caregivers. This is no better strategy than being overweight, because of the adverse effect of undernutrition on muscle function.

Patients are usually advised to maintain a high-protein, low-calorie diet, aiming to achieve their ideal weight, which will be lower than that of persons of a similar height who have a normal muscle mass.[67] Patients with impaired swallowing, such as those with amyotrophic lateral sclerosis, may develop severe nutritional depletion. Gastric tubes (usually inserted percutaneously) are recommended for such patients when weight loss becomes significant, but ideally before respiratory impairment is severe.[37] Constipation is also a common problem in patients confined to wheelchairs, especially if their ability to perform a Valsalva maneuver is compromised by expiratory muscle weakness. This may cause considerable distress and, if severe, may further compromise ventilatory reserve by diaphragm splinting.[168] Thus, a routine bowel regimen is advisable, consisting of a high-roughage diet supplemented with stool softeners and laxatives as necessary.

Management of Oral Secretions. Troublesome and persistent drooling is a common problem when bulbar function is impaired. Programs intended to improve oral motor skills should be utilized initially, but surgery has proven necessary in over half of pediatric patients with this problem.[55]

Oral motor skills can be strengthened through therapy programs administered by speech or occupational therapists.[135] Goals include improved tongue position, lip closure, and jaw position.[55] Various anticholinergics, such as transdermal scopolamine delivered through a patch that is replaced every 3 days, or oral preparations, such as benztropine mesylate, have been of some benefit in decreasing drooling[55,135]; the role of botulinum toxin therapy is unclear.

Surgical intervention is recommended for children with persistent moderate to severe drooling unresponsive to at least 6 months of conservative treatment, or any child with at least moderate drooling and cognitive impairment who would be unable to participate in a conservative treatment program.[55] The surgical procedures are intended to reduce salivary production by: (1) dividing the parasympathic secremotor fibers (transtympanic neurectomy); (2) excising saliva-producing tissue (submandibular gland excision); or (3) blocking the flow of saliva into the mouth (parotid duct ligation). Other procedures, such as submandibular duct relocation or parotid duct fistulization, facilitate the swallowing of saliva by moving the entry point of the salivary gland to the pharynx.

These surgical procedures are sensible only for slowly progressive neuromuscular disorders in which a prolonged benefit might be anticipated, and are rarely used in more rapidly progressive conditions such as amyotrophic lateral sclerosis.

Physiotherapy. ***General Physiotherapy.*** General physiotherapy is of great value in children with neuromuscular disease for maintaining posture and preventing contractures, as well as for building morale.[1]

A program of deep-breathing exercises, assisted coughing, and forced expiratory maneuvers can improve symptoms and perhaps temporarily preserve VC in children with muscular dystrophy, but documentation of this latter benefit awaits systematic assessment.[1]

Inspiratory Muscle Training. One of the main problems in the treatment of patients with neuromuscular disease is the progressive impairment that occurs in inspiratory muscle function.[188] Because chest wall and pulmonary compliance are reduced in neuromuscular disease, the mechanical load on the weakened respiratory muscles is increased.[168] Imbalance between load and the capacity of the respiratory muscles may lead to fatigue and respiratory failure.[133] Therefore, the treatment of diseased respiratory muscles to improve their strength and endurance presents a great challenge.[188] Pharmacologic therapy with theophylline has been reported to strengthen the respiratory muscles and make them less susceptible to fatigue,[156] but this is a minor effect. Periodic respiratory muscle rest using noninvasive ventilation has been recommended to prevent decline in respiratory muscle function,[27,64] although this effect has never been demonstrated in controlled studies.

Prior studies suggest that strength and endurance of the respiratory muscles can be improved through specific training programs.[86,102,188,195] Using a double-blind protocol, Topin et al. showed that low-intensity inspiratory muscle training at home may improve respiratory muscle endurance in children with DMD, and that the effectiveness of training appears to be dependent on the quantity of training.[184] Similar controlled studies have not been reported in adults, and concerns have been raised that overzealous attempts at inspiratory muscle training in severely impaired patients could actually accelerate fatigue by overworking already weak respiratory muscles.

However, as long as these techniques are used in the less severely impaired patients, increased force

and endurance can be achieved through a variety of methods, including repetitive respiratory efforts against a closed glottis, voluntary hyperpnea, voluntary hyperventilation, or a combination of these techniques with exercise.[117,188]

Although discrepancies among studies are numerous, perhaps related to differences in the patient populations studied and in the training stimulus used, several studies have suggested that training with an inspiratory threshold load (70–80% of the maximal inspiratory mouth pressure) provides a stimulus that increases both the pressure- and flow-generating capacities of the respiratory muscles, and therefore may provide a practical approach to inspiratory muscle training in both children and adults with neuromuscular disease.[102,117,135,184]

Surgical Therapy of Scoliosis. Treatment of spinal deformity secondary to neuromuscular disease presents a great surgical challenge.[38] The techniques have varied considerably and include Harrington distraction rods, alar hooks, Luque instrumentation, and sublaminar wiring.[122] Use of intraspinous rather than sublaminar wiring has reduced time spent in the operating room as well as blood loss.[122] The surgical/anesthetic complication rate of surgery to correct the deformity is ~16% in patients with neuromuscular disease.[135] A forced vital capacity of <35% predicted has been associated with a risk of complications that approaches 50%.[122]

Correction or prevention of kyphoscoliosis would seem intuitively to preserve pulmonary function and reduce morbidity.[135] However, observations on the effect on vital capacity are conflicting.[168] In addition, even when studies show a statistically significant improvement in measured vital capacity after spinal surgery,[104] the overall rate of decline in the patient's clinical course is not necessarily reduced.[168] While debate continues as to whether surgery to correct or at least arrest the progression of scoliosis improves the long-term outcome, enhanced physical comfort, preservation of the ability to sit, and cosmetic benefit are other appropriate considerations that should be balanced against the risks of surgery.[122] In addition to the question of whether spinal surgery should be performed, that of the timing of surgery is also debatable. If it is undertaken, the surgery is usually performed after substantial scoliosis has developed, but before pulmonary restriction has become severe (i.e., VC >50% predicted).

Oxygen and Other Medical Therapy. Because alveolar ventilation is the main cause of respiratory insufficiency in neuromuscular disorders, the use of oxygen therapy alone to treat acute or chronic ventilatory failure is usually inappropriate and may be hazardous.[78,161] The addition of oxygen therapy to ventilatory support is sometimes required during episodes of acute pneumonia, but because oxygenation should be normal in uncomplicated neuromuscular disease, it is unlikely to be required in the long term. Close monitoring of $PaCO_2$ is indicated if oxygen therapy is used.[161]

Central respiratory stimulants may occasionally be of value in neuromuscular diseases associated with central hypoventilation. For example, the progesterone agent, megestrol, may temporarily reverse hypercarbia in patients with myotonic dystrophy and moderate restriction (N. Hill, unpublished observation).

Mechanical Ventilation. ***Rationale for Mechanical Ventilation in Neuromuscular Diseases.*** In most neuromuscular diseases, respiratory drive is intrinsically normal, but it may become secondarily blunted in the face of mechanical abnormalities causing restriction and eventual hypoventilation.[161] An imbalance created by the increased work of breathing and reduced respiratory muscle capacity leads to hypercapnia, initially during REM sleep but eventually during all stages of sleep and, ultimately, during wakefulness.[140] The appearance of daytime alveolar hypoventilation heralds a progression to death unless interrupted by therapeutic measures.[149] As the central physiologic defect is respiratory muscle weakness, the main therapeutic intervention is to provide mechanical assistance to aid respiratory muscle function.

Trends in the Use of Mechanical Ventilation. During the first half of the twentieth century, poliomyelitis was responsible for most cases of respiratory dysfunction caused by neuromuscular disease.[193] These patients were treated with a variety of so-called "body" ventilators, beginning with "iron lungs" or tank ventilators and subsequently weaned, if possible, to more user-friendly devices such as rocking beds or jacket ventilators, or from mechanical ventilation entirely.[119] With the increasing popularity of positive-pressure ventilators during the 1960s, patients with neuromuscular disease were increasingly managed with tracheotomies if they desired ventilator support.[119]

Noninvasive positive-pressure ventilation (NPPV), administered nocturnally and as needed during the daytime, was used successfully to treat patients with neuromuscular disease at a few centers as early as the 1960s.[2] However, these centers used mainly mouthpiece interfaces that failed to gain wide acceptance

elsewhere.[119] Face masks were also available, but these likewise failed to gain wide acceptance for the long-term administration of noninvasive ventilation, largely because of poor patient tolerance.[119] The signal change that led to the recent proliferation of noninvasive ventilation came in the early 1980s with the introduction of the nasal continuous positive airway pressure (CPAP) mask for the treatment of obstructive sleep apnea.[177] In 1984, Rideau and colleagues proposed that such masks should be used with positive-pressure ventilators to achieve nocturnal respiratory muscle rest in patients with DMD, thus retarding disease progression.[147]

Soon thereafter, the success of nocturnal nasal ventilation was reported in ameliorating gas exchange disturbances and symptoms in patients with chronic respiratory failure caused by a variety of neuromuscular diseases.[69,99] Since then, NPPV has become the preferred ventilator modality for the long-term management of patients with neuromuscular disease and respiratory failure because of its greater ease of administration, portability, and lower morbidity and cost compared to invasive ventilation.[119] However, not all patients with neuromuscular disease are good candidates for NPPV.[119] Selection of patients is likely to remain of critical importance to optimize the likelihood of success,[161] which is discussed later.

Noninvasive Positive-Pressure Ventilation. NPPV, the most common noninvasive method presently used, consists of a ventilator that delivers airflow to the lungs through a mask or mouthpiece that is affixed to the nose, mouth, or both. Technical aspects are best considered under two headings.

Masks or interfaces. The nasal mask is the most widely used interface for administration of CPAP or NPPV to patients with chronic respiratory failure.[119] The standard nasal mask is a triangular or cone-shaped, clear plastic device that fits over the nose and utilizes a soft cuff to form an air seal over the skin.[119] Nasal masks are available from many manufacturers in multiple sizes and shapes. Because skin irritation is a common problem, nasal masks with gel seals that may enhance comfort have recently been introduced. Also, "mini-masks" have been developed that minimize the bulk of the mask as well as feelings of claustrophobia.[119]

Except during emergency situations (when there is insufficient time), masks may be custom-molded. These masks may be made from facial impressions or moulages, a technique that requires time and technical skill.[149] Custom-molded masks are now rarely used because of the plethora of commercially available mask types and sizes. In addition to skin reactions, nasal ventilation is limited by air leaking through the mouth, a problem that may be ameliorated by use of chin straps.

Oronasal or full-face masks cover both the nose and the mouth. Mainly used for acute respiratory failure, newer oronasal masks have become available that are suitable for long-term use. Some patients have difficulty in tolerating masks that cover both the nose and the mouth, and asphyxiation may be a concern in patients with neuromuscular disease who are unable to remove the mask in the event of ventilator malfunction or power failure.[119] Furthermore, interference with speech, eating, and expectoration; claustrophobic reactions; and the theoretical risk of aspiration and rebreathing are greater with oronasal than nasal masks. Oronasal masks should be equipped with anti-rebreathing valves and rapid removal straps to minimize the risks of asphyxiation in the event of ventilatory failure or aspiration due to vomiting.[119] However, oronasal masks may be preferred in patients who have excessive air leaking through the mouth during nasal ventilation,[132] particularly in those with bulbar dysfunction.

Mouthpieces held in place by lipseals have been used since the 1960s to provide NPPV for as much as 24 hours per day to patients with postpolio respiratory insufficiency.[9] The mouthpiece has the advantages of being simple and inexpensive. Custom-fitted mouthpieces that may enhance comfort and efficacy are also available at some centers.[2] During the daytime, patients receive ventilatory assistance via a mouthpiece attached to their wheelchair controls or held by a gooseneck clamp.[119] During sleep, some patients use strapless custom mouthpieces, and others use strapped-on lipseals. Although air leaking through the mouth can be minimized with lipseals, air leaking through the nose may still pose problems and may compromise the efficacy of mouthpiece ventilation.

Ventilators. Portable pressure- or volume-limited ventilators are available for home use by patients with neuromuscular disease. Volume-limited ventilators are usually used in the assist-control mode to deliver a relatively large tidal volume (10–15 ml/kg) to compensate for leak around the interface.[149]

Portable pressure-limited ventilators cycle between two levels of positive airway pressure using either flow- or time-triggering (bilevel ventilation).[176] Many also offer an assist-control mode that delivers back-up time-cycled inspiratory and expiratory pressures with adjustable inspiratory:expiratory ratios at a preset rate. These ventilators are best suited for patients requiring part-time ventilatory assistance, such as only at night, and are unsuitable

Table 3. Indications for noninvasive positive-pressure ventilation in chronic neuromuscular disease (adapted from a Consensus Conference[52]).

1. Symptoms (such as fatigue, dyspnea, morning headache) and one of the following:
2. Physiologic criteria (one of the following):
(a) $PaCO_2$ >45 mm Hg (6 kPa)
(b) Nocturnal oximetry demonstrating oxygen saturation <88% for >5 consecutive minutes
(c) For progressive neuromuscular disease, maximal inspiratory pressure <60 cm H_2O or FVC <50% predicted

FVC, forced vital capacity.

for patients requiring continuous ventilation unless adequate alarms and back-up batteries are also provided.[119] Controlled data are lacking to guide pressure-preset ventilator settings, but inspiratory pressures between 12 and 22 cm H_2O are often used. Higher pressures are sometimes used for patients with high respiratory impedance, such as those with advanced scoliosis or obesity. Expiratory pressure, usually 3–6 cm H_2O, is also applied during pressure-limited ventilation, because many of these ventilators have a single tube ventilator circuit, and some end-expiratory flow is necessary to exhaust CO_2 and avoid rebreathing. Higher expiratory pressures may be needed in patients with underlying obstructive sleep apnea. However, it is important to remember that if expiratory pressure is increased, inspiratory pressure must be raised equally to maintain the same level of inspiratory resistance (or pressure support).

Pressure-limited ventilators are most commonly used for long-term ventilatory support of patients with neuromuscular disease because they are inexpensive, well tolerated, and highly portable. However, volume-limited ventilators may be preferred in patients with advanced disease because of their greater monitoring capabilities, back-up batteries, and ability to "stack" breaths to assist with coughing.

Patient selection for noninvasive positive-pressure ventilation. The first episode of ventilatory insufficiency or failure ($PaCO_2$ ≥45 mm Hg, pH ≤7.35) in patients with neuromuscular disease may be precipitated by an acute chest infection. Acutely, NPPV may be used to reduce the need for intubation or facilitate weaning.[165] However, these patients usually have problems in clearing secretions, so initial intubation may be necessary to control secretions, followed by extubation to noninvasive ventilation.

The current consensus recommends that NPPV be used in symptomatic patients with one of the following: (1) diurnal $PaCO_2$ >45 mm Hg (6 kPa); (2) nocturnal SaO_2 ≤88% for >5 consecutive minutes; or (3) severe pulmonary dysfunction (FVC <50% predicted or maximal inspiratory pressure <60 cm H_2O)[52] (Table 3).

The third consideration, however, is not an evidence-based guideline[91] and, in the authors' experience, patients with very slowly progressive conditions, such as limb-girdle muscular dystrophy, may not become symptomatic or hypoventilate until FVC falls well below 50%. Furthermore, the authors' experience is that, unless patients are motivated by the desire for symptom relief, they are unlikely to adhere to a noninvasive ventilatory regimen. However, these pulmonary function criteria may be sensible for patients with rapidly progressive neuromuscular disease such as motor neuron disease, allowing time to adapt to NPPV before impairment becomes severe.[91]

Patients should be queried about symptoms of nocturnal hypoventilation (daytime somnolence, morning headaches, decreased attention span, fatigue).[25,149] Some patients develop obstructive sleep apnea/hypopnea syndrome before the appearance of overt nocturnal hypoventilation.[25] In this subgroup, CPAP alone may be effective initially, but a subsequent transfer to NPPV is usually required, and the need for this should be ascertained by periodic follow-up studies.[161]

Contraindications to noninvasive positive-pressure ventilation. Because NPPV leaves airway protection to the patient, those with overwhelming secretions or severe swallowing dysfunction respond poorly. In this case, clinical judgment must be exercised when deciding whether secretions are excessive or cough impairment is too severe for NPPV management.[91] Home management of noninvasive ventilation is generally much simpler than that of invasive mechanical ventilation, particularly if the need for ventilatory support is part-time. However, patients must still have adequate financial resources and caregiver support to be successful. The lack of these and other contraindications to NPPV are listed in Table 4.

Table 4. Contraindications to noninvasive ventilation for neuromuscular disease.

Absolute contraindications
Upper airway obstruction
Uncontrollable secretion retention
Inability to cooperate
Inability to achieve adequate peak cough flow, even with assistance
Inability to fit interface or other noninvasive device
Relative contraindications
Swallowing impairment
Inadequate financial resources
Inadequate family/caregiver support
Need for full-time ventilatory assistance

Initiation of noninvasive positive-pressure ventilation. The goals of using NPPV are to alleviate symptoms, improve alveolar ventilation, improve sleep quality, enhance quality of life, and decrease the risk of pulmonary complications, and, in so doing, decrease the number of hospitalizations, postpone the need for a tracheotomy, and prolong survival.[91,155]

Possible locations for initiation of NPPV include hospitals providing short- or long-term care, the sleep laboratory, the physician's outpatient office, or the patient's home. The choice of location depends on the experience of the clinicians and resources available. The initial sessions of NPPV should be overseen by experienced personnel, during waking hours, with the patient alert. The initial objective is to familiarize the patient with the technique, motivate the patient, and to establish initial ventilator settings. Patient comfort and familiarity with NPPV are critical for successful adaptation.

Starting at low volumes or pressures (10 ml/kg or 8–10 cm H_2O, respectively) tidal volume or inspiratory pressure is then gradually increased over days or weeks as tolerated until gas exchange targets or the patient's comfort limit are reached.[91] Eventually, an inspiratory pressure of 12–22 cm H_2O is reached, with final settings determined by resolution of symptoms and improvement in gas exchange. For small children, introduction of NPPV during sleep may be advantageous.[149]

Hours of use should also be gradually increased. After a few days of "practice sessions" during the daytime, the patient is encouraged to begin nocturnal use for as long as tolerated. The amount of time needed before patients can sleep through the night using the device is highly variable between individuals, ranging from a few days to a few months.[88]

Clinical evaluation, nocturnal oximetry, and daytime arterial blood gas testing are used to assess the efficacy of NPPV.[107] Polysomnography is necessary for certain patients in whom obstructive apnea is suspected, or when there are problems adapting (Table 2).

Some patients find it impossible to sleep using NPPV and, for them, daytime use should be encouraged because it may be as effective as nocturnal ventilation for improving gas exchange.[158] If the patient is unable to adapt at all, alternative noninvasive ventilators such as negative-pressure devices or abdominal displacement ventilators can be tried. If these are not considerations or fail, and if the patient desires prolongation of survival, invasive mechanical ventilation with tracheostomy should be proposed.

Ongoing monitoring. Patients require close monitoring during the early adaptation period. Home-care providers should visit the patient at home to reinforce proper use of the equipment and to make further adjustments to optimize fit and comfort, ideally weekly for the first few weeks. Routine physician follow-up is usually performed after the first few weeks and then every 1–6 months, depending on outcome and ease of adaptation. At each visit, patients should be queried about symptoms and problems. A daytime arterial blood gas during spontaneous breathing should be obtained, and if symptomatic control is suboptimal or the arterial blood gas demonstrates increased CO_2 retention, nocturnal oximetry or polysomnography should be performed, ideally on room air. If patients are reluctant to undergo studies of arterial blood gases (especially children), a blood sample can be obtained from an ear lobe.

Occasional adverse effects occur with the use of NPPV, including skin and eye irritation, drying of mucous membranes, air leaks, aerophagia, and possible colic when abdominal distension is severe.[112] Air leaks from the mouth and around the mask can limit the efficacy of NPPV. The problem can be ameliorated by refitting of the mask, use of chin straps, or swiching to an alternative interface.

Outcome. Significant improvements in nocturnal and diurnal arterial blood gas tensions, mortality, and quality of life have been reported in patients with postpolio syndrome and other slowly progressive neuromuscular conditions using NPPV.[113,164] The 5-year survival rates among these patients using nocturnal NPPV are nearly 100%.[161]

Most patients with DMD receiving ventilatory support judge their quality of life as satisfactory.[11] A 1-year survival of 85% and 5-year survival of 73% have been reported in patients with DMD using NPPV as the sole means of ventilatory support.[165] However, other centers have reported lower survival rates,[113] perhaps reflecting more advanced disease at initiation or less aggressive efforts to assist with secretion clearance.

Although no controlled trial has been performed, NPPV appears to improve the quality of life and survival of patients with amyotrophic lateral sclerosis,[115,145] even those with bulbar involvement. Not surprisingly, however, the survival of those in the latter group is poorer than in those with intact bulbar function.

Other Techniques of Noninvasive Ventilatory Assistance in Neuromuscular Disease. *Negative pressure ventilation.* Several types of negative pressure ventilators can assist or support ventilation,[119] including iron lungs, chest shell ventilators, and pulmowraps. These de-

vices create an intermittent subatmospheric pressure around the chest and abdomen and assist chest wall expansion.[155] The iron lung is the most efficient and comfortable of these ventilators, but it is heavy and bulky. Except for the chest shell ventilator, substantial time may be required to apply these ventilators and includes the adjustment time needed to minimize air leakage around the iron lung cervical collar or pulmowrap seals.[155] Negative-pressure ventilators can also exacerbate or even induce obstructive apneas and oxygen desaturations during sleep, necessitating periodic nocturnal oximetry or polysomnography in order to properly monitor patients using these devices.[14,90]

With decreasing pulmonary compliance or airway stability, these ventilators become less effective and their use can be associated with the development of systemic hypertension.[155] Users almost invariably benefit from switching to the more effective NPPV.[9] Because of their limitations compared to NPPV, the use of body ventilators is rarely warranted,[22] being reserved for patients who are not responding well to NPPV.

Adjunctive respiratory aids for patients with neuromuscular disease. (1) Abdominal displacement ventilators. The rocking bed and pneumobelt both rely on displacement of the abdominal viscera to assist diaphragm motion and, hence, ventilation.[119,197] Although these ventilators may be useful in patients with bilateral diaphragmatic paralysis,[89] they are relatively ineffective ventilators. Also, efficacy depends on abdominal and chest wall compliance, so that patients with severe spinal deformity, excessive thinness, or obesity may not be ventilated adequately.[119] Thus, these ventilators are rarely used today, although some patients with quadriplegia due to high spinal cord lesions use the pneumobelt during the daytime because it assists ventilation while the patient sits in a wheelchair, freeing the face and hands.

(2) Diaphragm pacing. Diaphragm pacing consists of a radiofrequency transmitter and antenna that send stimulatory signals to internal receivers placed subdermally in the subclavicular region bilaterally, and electrodes placed surgically near the phrenic nerve, usually in the supraclavicular region.[81] Although nerve reimplantation techniques have been described, the technique usually requires intact phrenic nerves and diaphragm function. Thus, its main use has been in patients with high spinal cord lesions, particularly in children who may have trouble adapting to NPPV. Limitations of diaphragm pacing include high cost, a lack of alarms despite the potential to fail abruptly, and induction of obstructive apneas that necessitates retention of the tracheostomy in most patients.[13] Nonetheless, diaphragm pacing has convenience advantages over invasive positive-pressure ventilation, may provide ventilatory assistance for many years, and still has a role in selected patients.

(3) Glossopharyngeal breathing. Glossopharyngeal breathing provides a nonmechanical way for individuals with weak inspiratory muscles and minimal tolerance for spontaneous breathing to maintain normal alveolar ventilation. It also provides a safety mechanism for ventilator transfers or in the event of sudden mechanical ventilator failure.[12] It can be used to provide a deep breath to improve cough effectiveness, increase speech, maintain pulmonary compliance, and prevent atelectasis.[22] The technique involves the use of tongue muscles and closure of the glottis to supplement inspiratory effort by bolusing (gulping) air into the lungs. The glottis is closed with each "gulp" to retain the air. One breath usually consists of 6–9 gulps of 40–200 ml each.[22] Successful application requires patients with sufficient bulbar function, and even then some patients may have difficulty learning the technique.

(4) Techniques to assist cough. Numerous approaches are available to increase cough expiratory flows in patients with neuromuscular disease, and include manually assisted coughing, use of mechanical insufflator/exsufflators, and others such as oscillation or percussion.[18]

Manually assisted coughing applies positive pressure to the abdomen in synchrony with the patient's cough effort, leading to enhanced expiratory flow rates.[15] A number of different techniques allow an attendant to apply rapid abdominal thrusts that result in effective clearance of secretions.[15] Patients can assist the attendant by taking a maximal inspiration before the abdominal thrusts are applied.

Mechanical in/exsufflators deliver a deep insufflation using positive pressure (+20–40 cm H_2O) followed immediately by an equal negative pressure that produces a forced exsufflation.[18] Mechanical in/exsufflation enhances expiratory flows and assists with tracheobronchial secretion clearance without the discomfort or airway trauma caused by tracheal suctioning.[18] The positive pressures can be provided via an oronasal mask, a mouthpiece, or even a translaryngeal or tracheostomy tube (with an inflated cuff).[18]

First described by Beck in 1966, the use of high-frequency chest wall oscillation can facilitate bronchial secretion clearance. These techniques appear to be most useful in patients with cystic fibrosis or bronchiectasis.[18] Effectiveness in patients with neuromuscular disease has not been established. Oscil-

lation can be applied externally to the chest wall or abdomen or directly to the airway as high-frequency positive-pressure ventilation, jet ventilation, or oscillation in which there are rapid small-amplitude pressure swings above and below atmospheric pressure.[50]

Invasive mechanical ventilation. Invasive mechanical ventilation for patients with neuromuscular disease should be used only if noninvasive approaches are contraindicated or have failed and the patient desires aggressive support.[91] Invasive mechanical ventilation should be considered also in patients requiring continuous or nearly continuous ventilatory support,[161] although some clinicians advocate noninvasive ventilation even for these patients to avoid the complications and greater care burden of invasive techniques.[16]

If long-term invasive mechanical ventilation is unavoidable, every effort should be made to simplify the invasive regimen. If at all possible, patients should be weaned to nocturnal ventilation only. Also, when upper airway function is intact, speech and swallowing should be preserved. Patients should be allowed to talk with the cuff deflated, compensating for the leak by increasing ventilator tidal volume, and encouraged to eat by mouth. They should be taught to suction themselves and administer as much self-care as they can to minimize the burden on caregivers.[91]

Invasive mechanical ventilation can cause hemorrhage, tracheoesophageal fistulae, or upper airway obstruction by granulation tissue or stenosis, but fortunately these complications are infrequent if the above principles are followed.[171]

END-OF-LIFE ISSUES IN INDIVIDUALS RECEIVING MECHANICAL VENTILATION

Patients with severe neuromuscular disease who receive mechanical ventilation (whether noninvasively or via a tracheostomy) may reach a stage where they find their quality of life intolerable.[19,145] Under these circumstances, the patient may request discontinuation of mechanical ventilation.[19] This situation is often very stressful for the patient, relatives, and staff and must be handled with great sensitivity, prioritizing patient autonomy and dignity.[19] However, mechanical ventilation is a medical therapy and, if a mentally competent patient so desires, there is no ethical reason not to discontinue it, either immediately or at a later date determined by the patient.[82] Before mechanical ventilation is withdrawn, the attending physician, nurse, and other involved staff members should discuss the procedure, strategies for assessing and ensuring comfort, and the patient's expected length of survival after withdrawal with the family (and the patient, if possible).[46] Essentially, the choice lies between an abrupt discontinuation of ventilatory support or a gradual withdrawal (sometimes called terminal weaning).[46,48,145]

If the patient is to have ventilatory support removed suddenly, the clinician has a responsibility to satisfy the patient's request in a compassionate and humane manner.[4] Specifically, frequent assessment of the patient's comfort during and after withdrawal of the ventilator is mandatory, and intravenous opioids and benzodiazepines should be used liberally to relieve dyspnea and other discomfort.[194] In such a situation, oxygen may also be useful.[145] Coming off the ventilator slowly (by decreasing the efficacy of the ventilator) may allow gradual development of hypercapnia and provide terminal coma.[48]

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