Pulmonary Issues in Patients with Chronic Neuromuscular Disease

Joshua O. Benditt[1] and Louis J. Boitano[1]

[1]University of Washington School of Medicine, Seattle, Washington

Patients with chronic neuromuscular diseases such as spinal cord injury, amyotrophic lateral sclerosis, and muscular dystrophies experience respiratory complications that are cared for by the respiratory practitioner. An organized anatomical approach for evaluation and treatment is helpful to provide appropriate clinical care. Effective noninvasive strategies for management of hypoventilation, sleep-disordered breathing, and cough insufficiency are available for these patients.

Keywords: neuromuscular disease; respiratory failure; noninvasive ventilation; muscular dystrophy; amyotrophic lateral sclerosis

A wide range of progressive neuromuscular disorders lead to dysfunction of the respiratory muscles that in turn can lead to respiratory failure, pneumonia, and death. Breathing disorders are recognized as the leading cause of mortality in neurologic disease (1). Diseases of the cortex, brainstem, spinal cord, motor nerves, neuromuscular junction, and muscles can all lead to dysfunction of the respiratory system. Careful, ongoing evaluation of neurologic patients at risk for respiratory complications is important for management of these at-risk individuals (2–4). An approach to the respiratory system emphasizing evaluation of swallowing, cough, and ventilatory function is helpful to the clinician assessing the respiratory system in patients with neurologic conditions. Many diseases such as myasthenia gravis or amyotrophic lateral sclerosis (ALS) may affect more than one of these functional areas, so that careful attention to all aspects of breathing is critical.

In this concise review we use the term *neuromuscular disease* (NMD) to refer to diseases of the neurologic system including the brain, spinal cord, motor nerves, and muscles. The focus of this article is on chronic neurologic diseases in adults and adolescents. Acute neurologic diseases seen in or as a result of intensive care unit treatment are not covered in this review.

CHRONIC NEUROLOGIC DISEASES AFFECTING THE RESPIRATORY SYSTEM

Chronic neurologic diseases that affect the respiratory system are best analyzed by using an anatomical organization. Table 1 details the location of effect of many of these diseases.

(*Received in original form October 7, 2012; accepted in final form March 6, 2013*)

Correspondence and requests for reprints should be addressed to Joshua O. Benditt, M.D., Pulmonary and Critical Care Medicine, University of Washington Medical Center, Box 356522, Seattle, WA 98195-6522. E-mail: benditt@uw.edu

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

CME will be available for this article at http://ajrccm.atsjournals.org or at http://cme.atsjournals.org

Am J Respir Crit Care Med Vol 187, Iss. 10, pp 1046–1055, May 15, 2013

Originally Published in Press as DOI: 10.1164/rccm.201210-1804CI on April 3, 2013
Internet address: www.atsjournals.org

Central Nervous System Diseases

A number of disorders can affect the pathways (corticospinal tracts) that connect the voluntary respiratory centers of the cortex to the spinal motor neurons and can result in ventilator drive problems. For example, a mid-pontine stroke can cause what is known as the "locked-in syndrome" that results in total muscle paralysis (aside from eye movement) and loss of voluntary breathing control (5). This syndrome is most commonly due to ischemic stroke (6). Extrapyramidal disorders such as Parkinson's disease can also affect voluntary breathing. In these disorders, patients may be unable to voluntarily affect the breathing pattern, and they may also show a Cheyne-Stokes respiratory pattern. Respiratory muscle weakness, restrictive physiology, and upper airway obstruction have been reported in Parkinson's and other extrapyramidal disorders (7). A characteristic "saw-toothed" flow–volume loop in Parkinson's disease has been described (8). Central and obstructive sleep apnea is seen and is more common in patients with Parkinson's who exhibit autonomic dysfunction. Levodopa treatment appears to lead to improvement in FVC but not FEV_1 or upper airway obstruction (9). Hemispheric lesions can also affect breathing. In hemiplegia following stroke, chest wall and diaphragm movements on the contralateral side of the cortical injury can be decreased, resulting in restrictive physiology (10).

The classic disruption of automatic but not voluntary breathing is that of congenital central alveolar hypoventilation (CCAH) or "Ondine's curse" (11). CCAH is now known to result from a defect in the *PHOX2B* gene (12). Injury to the automatic respiratory centers in the brainstem leads to central sleep apnea when the patient falls asleep and loses voluntary triggering of respiration (13). This can also be seen in unilateral and bilateral medullary infarction, bulbar poliomyelitis, and bilateral cervical tractotomy for chronic pain. CNS infection and tumor can result in hyperventilation. A variety of other irregular breathing patterns are also associated with CNS disease, including Cheyne-Stokes respiration and ataxic breathing (14).

Multiple sclerosis (MS) is a primary disorder of the central nervous system and is characterized by recurrent demyelination in regions of the central nervous system. Several causes of respiratory impairment are associated with MS, including respiratory muscle weakness, bulbar dysfunction, obstructive sleep apnea, and respiratory control dysfunction. Two patterns of respiratory failure generally occur in MS (15). First, lesions in the medulla or cervical spinal cord can cause loss of automatic respiratory control and central apnea. The second pattern is associated with the development of bulbar and respiratory muscle impairment resulting in atelectasis, aspiration, and pneumonia. The latter pattern commonly occurs in the advanced stages of MS. Respiratory impairment can occur in the early course of the disease or during acute attacks. There is a correlation between the degree of pulmonary dysfunction and the stage of neurological disability although no correlation has been found between

TABLE 1. CHRONIC NEUROMUSCULAR DISEASES THAT CAN AFFECT THE RESPIRATORY SYSTEM

Cerebral Cortex	Brainstem/Basal Ganglia	Spinal Cord	Motor Nerves/Anterior Horn Cell	Neuromuscular Junction	Myopathies
Stroke	Stroke	Trauma	Motor neuron disease	Myasthenia gravis	Muscular dystrophies
Neoplasm	Neoplasm	Infarction or hemorrhage	Postpolio syndrome	Lambert-Eaton myasthenic syndrome	Poly- and dermatomyositis
Cerebral degeneration	Postpolio syndrome	Demyelinating disease	Amyotrophic lateral sclerosis	Drugs	Glycogen storage diseases
Seizures	Central alveolar hypoventilation	Disk compression	Spinal muscular atrophy	Antibiotics	Pompe's
	Progressive bulbar palsy	Syringomyelia	Primary lateral sclerosis	Anticholinesterase inhibitors	McArdle disease
	Multiple system atrophy	Neoplasm	Charcot-Marie-Tooth disease	Corticosteroids	Tarui's disease
	Parkinson's disease		Vasculitides	Quinidine	Thick filament myopathy
	Multiple sclerosis		Metabolic	Lithium	Mitochondrial myopathy
	Chorea		Porphyria	Antirheumatics	Nemaline body myopathy
	Dyskinesias		Diabetes		
			Uremia		

pulmonary dysfunction and the duration of the disease (16). Studies have shown that wheelchair-using patients, especially those with weakened upper extremities, often have severely limited respiratory function (17). Pulmonary function assessment in MS can be difficult because of volitional issues with muscle control.

The potential for central or obstructive sleep-disordered breathing and nocturnal ventilatory dysfunction in MS should prompt a continued assessment of sleep-disordered breathing symptoms and consideration of polysomnography, as patients with MS have been found to have a higher incidence of sleep-disordered breathing than the general population (18).

Diseases of the Spinal Cord

Diseases of the spinal cord often dramatically affect breathing because of their direct impact on control of motor nerves that control respiratory muscles. Although traumatic injury is the major cause of spinal cord pathology, some other causes include tumor, vascular accident, transverse myelitis, and syringomyelia. Cervical spinal cord injury (SCI) often results in a requirement for long-term ventilation. Because the diaphragm is the major muscle of inspiration and ventilation (innervated by C3–C5 spinal nerve roots), the level of the spinal cord injury or pathology determines the effect on ventilatory function. For lesions at C3 and above, ventilatory support is almost invariably required. Injuries between C3 and C5 will vary in the requirement for ventilatory support. Injuries below C5 rarely result in the need for continuous ventilator support. Because cough function largely depends on abdominal and internal intercostal muscle function (spinal nerve roots T1–L1), cervical, thoracic, and even thoracic spinal cord injury can affect the ability to cough and clear secretions. The use of abdominal binders and/or the supine position can improve diaphragm function in those with SCI, resulting in an increase in vital capacity (19).

For patients with spinal cord injury who require chronic ventilator support, tracheostomy is an option although a number of effective noninvasive approaches are available including mouthpiece and mask ventilation. Patients with high cervical spinal cord injury may be candidates for phrenic nerve pacemakers that can be placed to pace the phrenic nerve directly in the thorax (conventional phrenic nerve pacing) (20) or with electrodes placed into insertion points of the phrenic nerve into the diaphragm via a laparoscopic approach (21). In appropriately selected patients tidal volume can be increased after reconditioning of the diaphragm to the point where patients can be liberated from tracheostomy ventilation (22). Only a small amount of data is available on long-term use of phrenic nerve pacing in SCI, but in a report of 12 patients who underwent conventional phrenic nerve pacing 6 were at home and continued pacing fulltime for a mean value of 14.8 years (23).

Sleep apnea is more common in SCI than in the general population and it appears that the higher the level of injury, the more likely it is that the individual will develop sleep apnea (24). The cause of this increased risk is not clear, but possible causes include more time sleeping in the supine position, hypertrophy of neck muscles increasing the risk of obstruction, the use of sedating antispasticity medications, or an as yet undefined central neural effect of SCI. A sleep study should be considered when symptoms of nocturnal hypoventilation such as morning headache, daytime hypersomnolence, or unexplained nocturnal awakenings are present or when daytime hypercarbia ($Pa_{CO_2} >$ 45 mm Hg), unexplained cor pulmonale, or FVC less than 50% predicted are present (19). Almost all patients with SCI will have some cough impairment that requires assistance as described at the end of this review.

Diseases of the Motor Nerves

Amyotrophic lateral sclerosis (ALS) is a disease that can affect upper and lower motor neurons. The disease has a peak incidence in the seventh and eighth decades of life and affects men more than women (25). Most cases are sporadic although 5–10% are familial. The etiology of ALS is unknown although a number of potential mechanisms have been proposed. These include superoxide dismutase-1–mediated toxicity, excitotoxicity, cytoskeletal derangements, mitochondrial dysfunction, viral infections, apoptosis, growth factor abnormalities, inflammatory responses, and disorders of RNA processing (26). ALS often affects all of the respiratory muscles including those for airway protection and cough. Pneumonia and respiratory failure are the leading cause of death in this disease (27). Monitoring pulmonary function in the outpatient clinic is critical to avoid respiratory emergencies. Sleep-disordered breathing is common in ALS, is associated with respiratory muscle weakness and diaphragm weakness in particular, and increases in frequency as the disease progresses. Strong consideration for noninvasive positive-pressure ventilation (NPPV) is suggested for all patients with FVC less than 50% predicted, maximal inspiratory pressure less negative than –60 cm H_2O, sniff nasal inspiratory pressure (SNIP) less than 40 cm H_2O, or sleep evaluation showing desaturation at nighttime or a sleep study showing sleep-disordered breathing (1). As ALS progresses with bulbar involvement, NPPV may cease to be effective and a decision will need to be made concerning the appropriateness of tracheostomy and long-term invasive ventilation. Tracheostomy can prolong life substantially

but does not affect progression of the underlying disease; less than 10% of patients in the United States choose this option (28).

Spinal muscular atrophy (SMA) is a genetic disease that resembles ALS in its effects on the motor neurons but has an onset in infancy. It occurs in several forms, with SMA types 1–4 ranging from most to least severe muscle impairment. Intercostal muscles are more significantly affected and the diaphragm is relatively spared, resulting in paradoxical movement of the chest wall during inspiration with inward movement of the ribcage and outward movement of the abdominal wall. The chest wall in the first year of life is particularly compliant, resulting in distortion of the chest wall and development of a bell-shaped configuration of the chest with pectus excavatum in SMA type 1. Left untreated, there is progressive respiratory failure beginning with anatomical changes that lead to repeated respiratory infections, progressive respiratory failure initially at night but later during the day, and ultimately complete respiratory failure (29).

The reported benefits of NPPV for children with SMA type 1 include the potential for ventilatory support without surgical intervention, amelioration of the chest wall deformity, and improvement in lung development and potentially lung function (30). NPPV is not always effective and so the options of invasive (tracheostomy) ventilation and palliative care need to be discussed with each family individually and carefully, especially for those individuals with SMA 1. Nocturnal support of sleep-disordered breathing may be necessary for those with SMA 2. Invasive ventilation is not required chronically for SMA type 2, 3, or 4 (31). A consensus statement for standard of care in SMA has been developed to aid in standardizing clinical care and also to make uniform study protocols (32).

Acute polio is still exists in the developing world, but in the developed world the major health issue arising from polio is the postpolio syndrome (PPS), in which new weakness develops in survivors of the polio epidemics of the mid-twentieth century. The cause of PPS is unknown although theories of pathogenesis include (*1*) progressive degeneration of reinnervated motor units, (*2*) persistence of poliovirus in neural tissue, and (*3*) induction of autoimmunity with subsequent destruction of neural structures (33). The average time to onset from the time of the initial infection is 35 years but ranges from 8 to 71 years.

PPS effects on the respiratory system include restrictive disease caused by weakness of respiratory muscles and chest wall deformities, obstructive and central sleep apnea and hypercarbic respiratory failure. Although the exact incidence of respiratory system involvement in postpolio syndrome is not known, risk factors for restrictive disease later in life include requirement for mechanical ventilation at the time of acute polio onset, acute polio infection at more than 10 years of age, and time from acute polio episode to development of weakness less than 35 years (34). Sleep-disordered breathing is common and in one series was noted to occur in 65% of patients with PPS (35).

Diaphragm paralysis or weakness can be caused by both motor nerve and muscle problems (Table 2) and may be either unilateral or bilateral. In unilateral diaphragm paralysis, patients may be asymptomatic at rest but have dyspnea with exertion (36). Orthopnea may be present but is not as common or severe as in bilateral paralysis. The diagnosis is often suggested by an elevated hemidiaphragm on chest X-ray and confirmed by fluoroscopic sniff test (37). In this test, an upward or "paradoxical" movement of the paralyzed hemidiaphragm is seen during a vigorous sniff maneuver performed by the patient. The paradoxical motion is the passive movement of a paralyzed hemidiaphragm in response to the increase in abdominal pressure (and decrease in pleural pressure) created by the contraction of the normal hemidiaphragm. Thus, unilateral hemidiaphragmatic paralysis can be recognized readily by the different movement of the two hemidiaphragms. Ultrasonographic imaging of the diaphragm in the zone of apposition provides an alternative means of diagnosing chronic unilateral diaphragm paralysis by demonstrating a thin diaphragm that fails to thicken with inspiration (38) or by showing paradoxical motion of the diaphragm leaflet with a sniff maneuver (39). When disabling symptoms are present and there is significant elevation of the hemidiaphragm on chest radiography, surgical plication of the paralyzed hemidiaphragm to minimize its paradoxical motion has been attempted with some success in improving vital capacity and FEV_1 (especially in the supine position) and in reducing dyspnea (40).

TABLE 2. CAUSES OF DIAPHRAGM WEAKNESS AND PARALYSIS

Neuropathic Causes	Myopathic Causes
Trauma	Muscular dystrophies
Cardiac surgery with cold cardioplegia	Limb-girdle
Blunt trauma	Duchenne and Becker
Spinal cord injury	Myotonic, etc.
Cervical manipulation	Metabolic myopathies
Scalene and brachial nerve block	Hyper- or hypothyroidism
Tumor compression	Acid maltase deficiency
Lung cancer	Rheumatologic
Metastatic mediastinal tumor	SLE
Metabolic	Dermatomyositis
Diabetes	Mixed connective disease
Vitamin deficiency (B_6, B_{12}, folate)	Miscellaneous
Hypothyroidism	Amyloidosis
Inflammatory neuritis	Malnutrition
Idiopathic (neuralgic amyotrophy, Parsonage-Turner syndrome)	Idiopathic
Mononeuritis multiplex	
Vasculitis	
Paraneoplastic	
Miscellaneous	
Cervical spondylosis	
Poliomyelitis	
Amyotrophic lateral sclerosis	

Definition of abbreviation: SLE = systemic lupus erythematosus.

Bilateral diaphragm paralysis is most often seen in the setting of a disease producing severe generalized muscle weakness. The most common causes are diffuse muscle diseases or motor neuron disease such as ALS. In bilateral diaphragm paralysis orthopnea, dyspnea with exertion and dyspnea on immersion in water, due to water pressure on the abdominal wall and upward displacement of the diaphragm, are notable symptoms (41). Sleep-disordered breathing with hypoventilation and hypoxemia is common (42). Pulmonary function is impaired with an associated reduction in vital capacity, with a significant drop in vital capacity in the supine position of up to 50% (43). The maximal inspiratory pressure is reduced in most cases. Disability can be quite pronounced. Physical examination may reveal paradoxical breathing in a resting or sleeping supine patient. Bilateral diaphragmatic paralysis can be difficult to diagnose as there is no normal hemidiaphragm to use for comparison with an abnormal one. As a result, chest radiography and fluoroscopic sniff testing can yield false negative results. Two-dimensional ultrasound to assess the movement of the diaphragm dome shares the same limitations as fluoroscopy (44). Phrenic nerve conduction studies can be useful in diagnosing a neuropathic cause of diaphragmatic paralysis but can have technical limitations (45). Diaphragm electromyographic measurement may be useful but technical issues such as "cross-talk" from adjacent muscles, electrode placement, or variable muscle-to-electrode distances due to subcutaneous fat limit its usefulness. The "gold standard" diagnostic test is the measurement of transdiaphragmatic pressure (Pdi) using thin balloon-tipped polyethylene catheters placed in the esophagus and stomach to demonstrate the lack of ability to generate transdiaphragmatic pressure (46). Bilateral diaphragmatic

paralysis is not often reversible unless the underlying disease is treatable. However, recovery has been noted in more than 50% of individuals with unilateral idiopathic diaphragmatic paralysis, with recovery taking an average of 15 months from the onset of symptoms (45). The sleep-related hypoventilation and orthopnea commonly seen in individuals with diaphragmatic paralysis can be treated with noninvasive positive-pressure ventilation (47). Phrenic nerve pacing is not applicable in most cases of diaphragm paralysis because it requires intact phrenic nerves and normal diaphragmatic motor function.

Diseases of the Neuromuscular Junction

Myasthenia gravis (MG), the most common chronic disease affecting neuromuscular transmission, is an autoimmune disease characterized by an antibody-mediated immune attack directed at acetylcholine receptors and/or receptor-associated proteins in the postsynaptic membrane of the neuromuscular junction. It results in weakness of many muscle groups including the respiratory muscles. An acute crisis can result in intensive care unit admission, respiratory failure, and death (48). Dysphagia and aspiration are common in MG. MG can also occur as a paraneoplastic syndrome in association with thymoma. It has been estimated that approximately 15% of all patients with thymoma will exhibit myasthenia gravis. Removal of the thymoma may result in amelioration of the myasthenia symptoms. Outpatient management of MG with corticosteroids, cholinergic agents, and immunosuppressants is aimed at relieving symptoms and preventing acute crises. Increased secretions from cholinergic drugs used to treat MG may make treatment of cough insufficiency and secretion management more difficult.

The Lambert-Eaton myasthenic syndrome (LEMS) is associated with small-cell lung cancer that can affect the respiratory muscles in a fashion similar to myasthenia gravis. LEMS differs from MG in that it affects the presynaptic neuromuscular junction rather than the postsynaptic membrane as in MG. In patients with small-cell lung cancer, LEMS is present in approximately 3% of cases (49). In patients with LEMS, the small-cell lung cancer may also be occult and should be sought for up to 5 years after the diagnosis of LEMS. Although respiratory involvement is often a late finding, frank respiratory failure can be a manifestation of LEMS and this disorder should be considered in individuals with unexplained neuromuscular weakness. Although LEMS shares a similar pathophysiological mechanism with myasthenia gravis, the clinical presentation is different and is characterized by (*1*) an increase in the compound muscle action potential with repetitive nerve stimulation, a feature not seen in myasthenia, (*2*) more common proximal leg weakness that is worse in the morning, (*3*) greater autonomic dysfunction, (*4*) areflexia, and (*5*) frequent association with malignancy (50).

Diseases Affecting the Respiratory Muscles

There are many causes of chronic muscle disease resulting in respiratory muscle dysfunction including genetic muscular dystrophies, myopathies, and myotonias as well as inflammatory myopathies and those associated with systemic diseases.

Duchenne and Becker muscular dystrophies are both progressive myopathies caused by mutations of the dystrophin gene on chromosome Xp21 (51). Dystrophin is a protein on the cytoplasmic face of the plasma membrane of muscle fibers, functioning as one component of a large, tightly associated glycoprotein complex. It provides mechanical reinforcement to the sarcolemma and stabilizes the glycoprotein complex (52). In Duchenne muscular dystrophy (DMD), dystrophin is absent whereas, in Becker dystrophy, a milder variant, dystrophin is reduced in quantity or quality. Both disorders are inherited as X-linked traits and are characterized by progressive muscle wasting and weakness of all skeletal and ultimately cardiac muscle in males.

Respiratory effects of muscle weakness result in restrictive pulmonary deficit, and inspiratory and expiratory muscle weakness predisposes these individuals to developing respiratory complications such as atelectasis and pneumonia. As the respiratory muscles further weaken and the restriction becomes severe, patients often need nocturnal ventilatory assistance because of hypoventilation and obstructive sleep apneas (53). Daytime NPPV may be provided to individuals with DMD as the disease progresses. If individuals with Duchenne or Becker muscular dystrophy require surgery, they may be at higher risk of respiratory complications and a preventive team approach has been suggested (2).

Myotonic dystrophy (DM) is an autosomal dominant disorder that is genetically heterogeneous with variable phenotypic expression. It is caused by mutations in the dystrophia myotonic protein kinase gene (54). The disease results from processing defects involving the mRNAs of several genes affecting skeletal muscle chloride channel function, the insulin receptor, and cardiac troponin T (55). There are two major classifications including DM1, formerly known as Steinert's disease, and DM2, a more mild disease form. DM differs from other muscular dystrophies with multisystem effects including cardiac conduction abnormalities, cataracts, infertility, and insulin resistance. DM1 presents at birth through adulthood in its milder form. Only adult onset has been seen in DM2. A characteristic phenotypic feature of skeletal muscle weakness is facial muscle weakness. Limb weakness is associated with weakness of thigh, hip flexor, and extensor muscles. Cardiac abnormalities include both conduction disturbances and structural defects (56). Respiratory muscle weakness is common in DM1, resulting in variable restrictive pulmonary impairment and alveolar hypoventilation. Oropharyngeal muscle weakness can result in dysphagia and risk of chronic aspiration but is more commonly associated with sleep-disordered breathing. Sleep-disordered breathing with a prominent central apnea component and nocturnal hypoxemia has been shown to be common in myotonic dystrophy. Diaphragm weakness is common in DM and contributes to hypoventilation. Daytime hypercapnia has also been observed (57). Sudden death in DM is associated with ventricular arrhythmias, and nocturnal hypoxemia secondary to sleep-disordered breathing is a significant risk factor for cardiac arrhythmia. Patients with DM with severe oropharyngeal muscle weakness may develop chronic upper airway airflow restriction or aspiration. A tracheotomy may be indicated to better support patients with upper airway issues.

Although NPPV has been associated with improved survival there are limitations in the use of this therapy for patients with DM (58). The characteristic facial muscle weakness in this patient population often limits the ability to successfully apply positive-pressure mask ventilation. Cognitive impairment also has been associated with a significant limitation in the patient's compliance with the nightly use of positive-pressure mask ventilation (59). Other muscular dystrophies such as limb-girdle muscular dystrophy and fascioscapulohumeral dystrophy can affect the respiratory muscles but do not generally cause respiratory impairment until later in the course of the disease.

Inflammatory myopathies such as dermatomyositis, polymyositis, and inclusion body myositis are systemic inflammatory diseases of unknown etiology that cause profound skeletal muscle weakness. Symptoms related to respiratory muscle weakness usually are not the presenting complaints; however, respiratory muscle weakness can occur in 5–10% of the patients with dermatomyositis and polymyositis (60) and may be found in as many as 75% of individuals if respiratory muscle function is

carefully evaluated (61). Interstitial lung disease may occur in up to 70% of patients with dermatomyositis or polymyositis (62). Individuals diagnosed with dermatomyositis or polymyositis should be evaluated for the presence of restrictive pulmonary disease, which may be due to respiratory muscle weakness as well as interstitial lung disease. If respiratory muscle weakness is pronounced (maximal inspiratory pressure [$P_{I_{max}}$] < 30% of predicted), ventilatory failure may ensue (60).

A number of genetic metabolic myopathies can affect the respiratory muscles including glycogen storage diseases and lipid metabolism disorders. Acid maltase deficiency (type II glycogenosis or Pompe disease) is a disease that involves respiratory muscles and may come to the attention of the respiratory practitioner. It is due to the deficiency of acid α-glucosidase, an enzyme responsible for the degradation of glycogen polymers to glucose. A simple dried blood spot assay of absent or reduced acid α-glucosidase enzyme activity is now available (63). Deficiency of this enzyme leads to accumulation of glycogen within cardiac and skeletal muscle lysosomes, resulting in myopathy. Although typically involving infants, this disease can manifest in adulthood. Complete enzyme deficiency results in cardiorespiratory failure and death usually in the first year of life (64). Initially, subjects develop symptoms related to muscle weakness; those with a later onset of symptoms have a better prognosis. With respiratory muscle involvement, there may be restrictive ventilatory limitation and, in severe cases, respiratory failure. Results from trials of enzyme replacement therapy with recombinant acid α-glucosidase show improvements in motor status, function, and survival (64). Other metabolic myopathies can be caused by defects of lipid metabolism or disorders involving the mitochondria directly (65).

Precise diagnosis of the wide range of neurologic diseases discussed is outside the scope of a concise review such as this but is complex and relies on clinical history and neurologic examination as well as many different types of testing ranging from magnetic resonance imaging and computed tomographic imaging studies to electrodiagnostic testing to serum blood testing (including genetic testing).

RESPIRATORY APPROACH AND TREATMENT OF NEUROMUSCULAR DISEASE

The respiratory physician, nurse, or therapist is often called on for therapeutic management of the patient with neuromuscular disease. One helpful way to think about the functional neuromuscular respiratory system is to divide it into three main areas of function (Figure 1) (66, 67): (*1*) Ventilatory function determined predominantly by the inspiratory muscles; (*2*) cough function, which is determined by inspiratory, expiratory, and glottic function; and (*3*) swallowing and airway protection determined by glottic muscles.

Each one of these three functional parts of the system may show evidence of impairment and contribute to neuromuscular respiratory failure, although dysfunction in each area is not always present at the same time. For example, isolated bilateral diaphragm weakness would be expected to affect ventilatory function although swallowing function would be normal and cough function perhaps only mildly impaired. ALS, on the other hand, often affects all three areas in significant ways because of the presence of both upper and lower motor neuron involvement. Evidence for dysfunction in each of the three areas should be sought at each clinic visit by eliciting historical data, performing a thorough physical examination, and laboratory testing. Several respiratory society statements have underscored the need for regular and thorough evaluation in this manner (1, 3, 4).

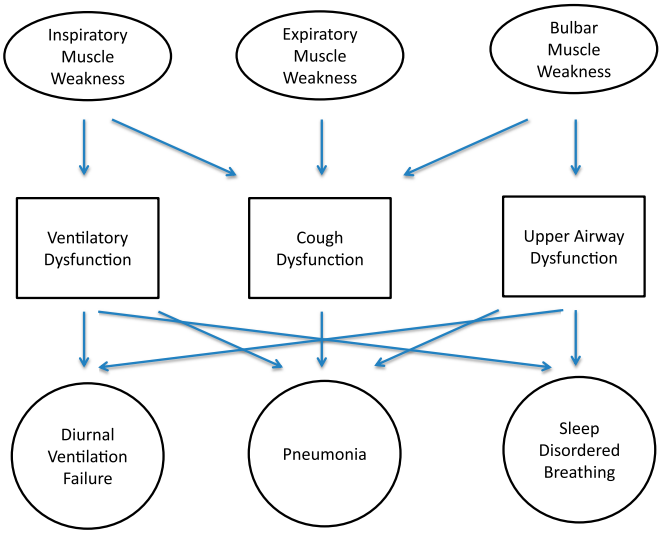

Figure 1. Pathogenesis of respiratory dysfunction in patients with neurologic disease.

Ventilatory Muscle Dysfunction

A number of different clinical measurements of ventilatory muscle function have been used. Maximal inspiratory pressure and maximal expiratory pressure have been traditional measures for respiratory muscle strength. FVC has also been used as a measure of global respiratory muscle strength in that both inspiratory and expiratory muscles are used to perform the maneuver. Supine vital capacity appears to be more sensitive than upright vital capacity in revealing diaphragm weakness (68). Sniff nasal inspiratory pressure (SNIP) appears to be a reproducible and accurate measure of inspiratory muscle strength. SNIP has been shown to be an accurate predictor of the presence of nocturnal desaturations and respiratory failure in patients with ALS (69). Because no one test accurately predicts clinical sequelae of NMD, it has been suggested that ongoing testing with multiple modalities is important to identify those at risk for sleep-disordered breathing and hypoventilation (70).

Hypoventilation in neuromuscular disease often first presents at night during sleep, particularly the REM stage (71). This is thought to occur because of the decrease in respiratory drive, relative excess loading of the diaphragm during sleep atonia, as well as instability of the upper airway due to muscle weakness of the bulbar muscles. Symptoms consistent with sleep-disordered breathing include more frequent nocturnal awakenings, nocturia, vivid nightmares, night sweats, daytime hypersomnolence, morning headaches, nausea, depression, decreased concentration, and diminished daytime performance. Polysomnography can be used to evaluate sleep in patients with neuromuscular disease but an overnight stay in a sleep laboratory may be especially difficult for such individuals if they require a personal care attendant, position changes, or help with toileting. Thus, ensuring a high pretest probability before ordering a sleep study is important. Baseline values of daytime Pa_{CO_2} of at least 45 or base excess of at least 4 mEq may correlate with sleep hypoventilation (70). An unattended sleep study in the home or overnight oximetry and exhaled end-tidal CO_2 levels ($P_{ET_{CO_2}}$) monitoring (3) may substitute for a full laboratory polysomnogram; however, the sensitivity and specificity of these portable tests are unclear in this population (72). For patients who have elevated Pa_{CO_2} despite adequate nocturnal therapy, dyspnea during the daytime or hypoxemia due to recurrent respiratory infections associated with atelectasis, daytime ventilatory support may be needed as well.

NPPV is becoming the preferred method of treatment for patients with NMD, including daytime ventilator support (73, 74). Tracheostomy ventilation may be necessary when bulbar dysfunction prevents use of noninvasive modalities or when uncontrolled aspiration is occurring (74). However, tracheostomy ventilation is associated with many potential complications and may be less desirable for the patient (75). There are currently three ways in which noninvasive positive airway pressure ventilation may be delivered: (*1*) via mouthpiece with or without a lip-seal, (*2*) via nasal mask, and (*3*) via full face mask. On occasion, more than one method may be used in the same patient. Most often mouthpiece ventilation (Figure 2) is used during the day and mask positive-pressure ventilation at night (76).

Nocturnal NPPV treatment for NMD has been reported to improve symptoms of fatigue, daytime hypersomnolence, and morning headaches as well as gas exchange in a multitude of observational studies as summarized previously in this journal (77). In more recent literature, NPPV in DMD and ALS has been studied extensively. In a study of full-time NPPV in DMD, 42 patients aged 15–33 years had survival rates of 88, 77, 58, and 51% at 1, 3, 5, and 7 years, respectively, after addition of the daytime use of mouthpiece ventilation (76). With this protocol treatment, the mean survival was 31 years of age. Symptoms of hypoventilation improved as did daytime Pa_{CO_2}. Although these are uncontrolled data, survival without mechanical ventilator assistance has previously been reported to be approximately 20 years of age (78).

In ALS, a number of nonrandomized studies have suggested improved survival in this disease with the use of NPPV (79–81). In one small randomized study of ALS, 22 patients randomized to receive NPPV for muscle weakness and hypercapnia survived 205 days longer than 19 patients who received the same medical care but no NPPV (82). A Cochrane review of this topic suggested that NPPV in ALS significantly improves quality of life and prolongs survival (83). Withdrawal studies in which patients successfully treated with nocturnal NPPV had devices removed for short periods of time have been published (84, 85). In both of these studies withdrawal of NPPV resulted in deterioration of blood gases, worsening sleep quality, and return of nocturnal hypoventilation, which reversed with reinstitution of therapy.

On the basis of available data a number of expert panel statements have been issued suggesting the use of NPPV in DMD (3, 86) and ALS (1). Far fewer data are available for NMDs other than ALS and DMD; however, it appears that NPPV is effective (77). Although limited numbers of randomized controlled trials of NPPV compared with "medical" treatment alone are available, it should be noted that many experts have expressed concerns over randomization when the outcome of untreated hypercarbic respiratory failure is known.

Cough Insufficiency

Cough insufficiency may be suspected if the patient describes an inability to bring secretions to the mouth for expectoration or if there is a history of frequent respiratory infections. Cough function is best assessed by measuring peak cough flow rate (PCF). This can be easily measured with an asthma peak flow meter or office spirometer connected to a facemask or mouthpiece (Figure 3). Normal values range from 360 to 960 L/minute (87); a value below 160 L/minute puts individuals at high risk for cough insufficiency and ventilator dependence. During a respiratory infection, PCF may drop substantially and a PCF less than 270 L/minute during a healthy period can drop below 160 L/minute during infection and so should trigger cough augmentation procedures (88).

Cough augmentation methods include manually assisted cough or "quad" cough, which can improve cough flows and secretion removal. Manually assisted cough is performed by having an assistant compress the lateral ribs or gently thrusting into the epigastrium to increase airflow out of the lungs. Lung volume

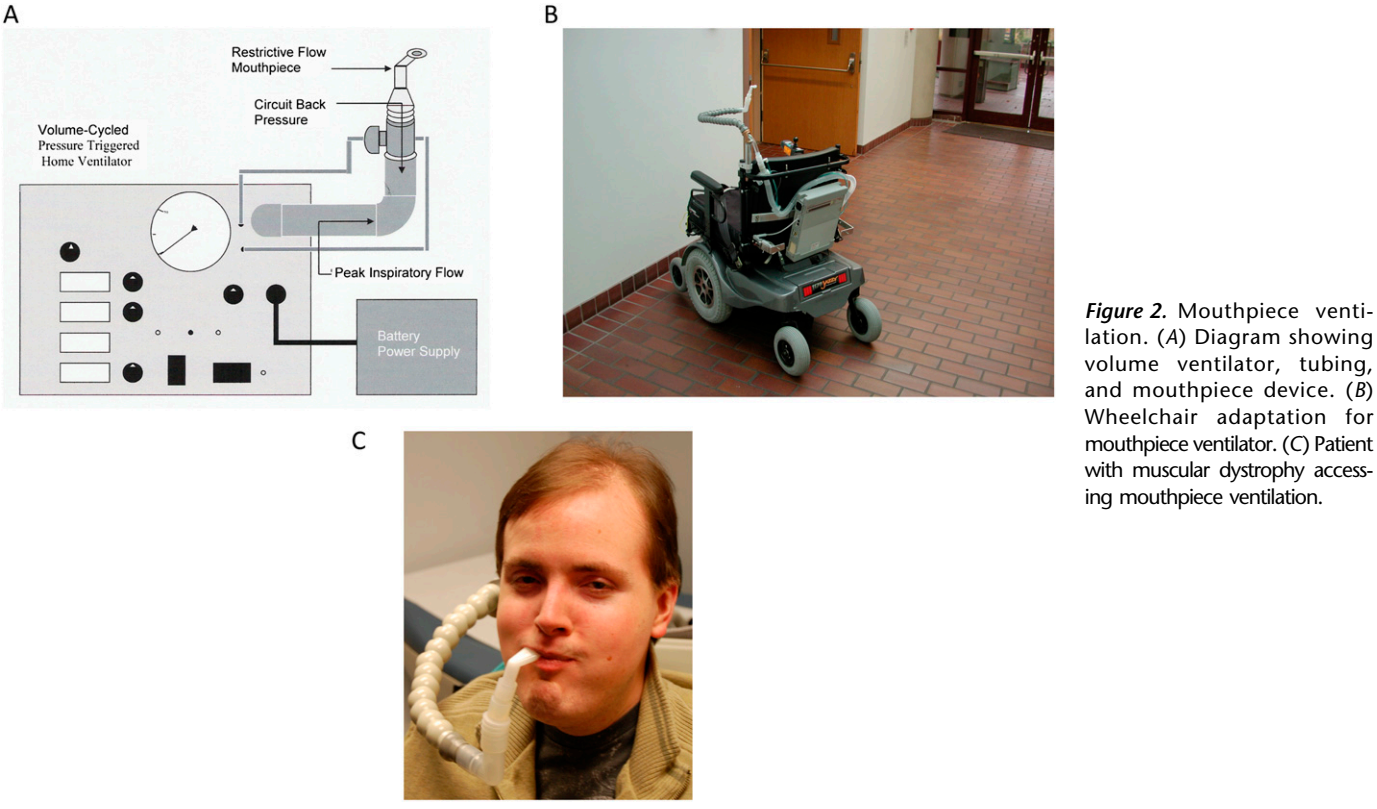

Figure 2. Mouthpiece ventilation. (*A*) Diagram showing volume ventilator, tubing, and mouthpiece device. (*B*) Wheelchair adaptation for mouthpiece ventilator. (*C*) Patient with muscular dystrophy accessing mouthpiece ventilation.

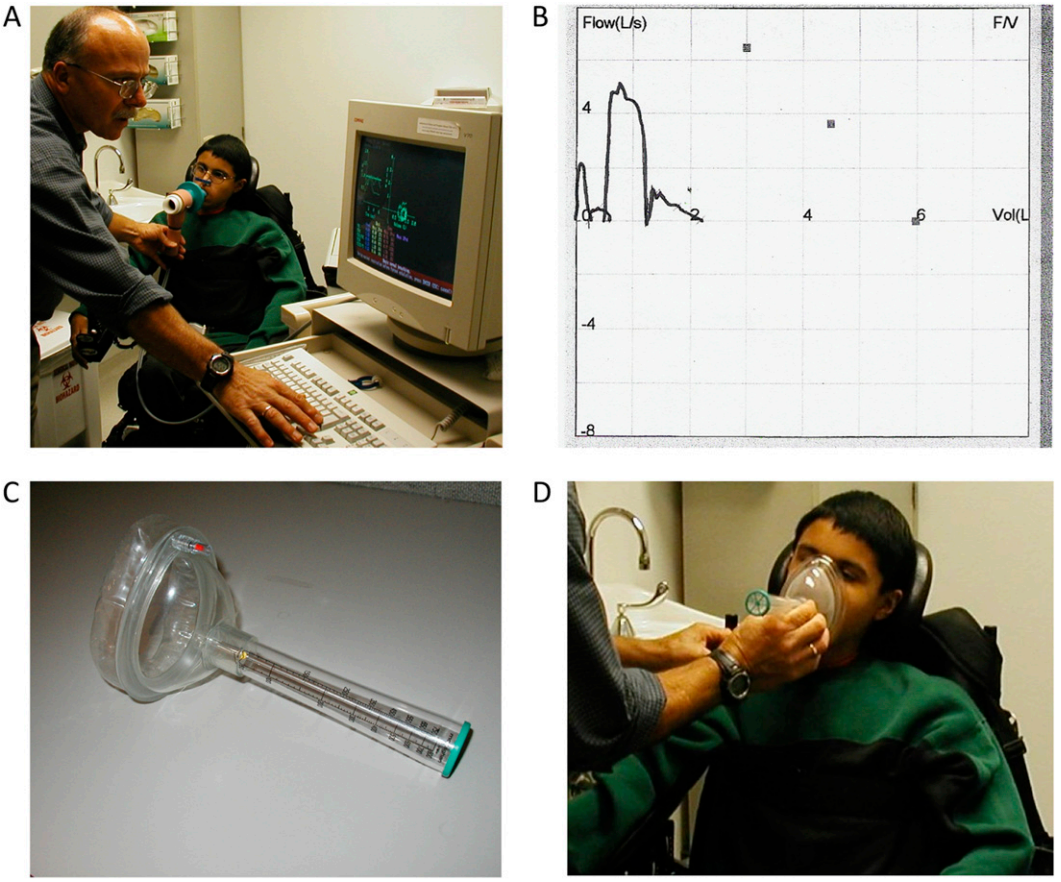

Figure 3. Measurement of cough peak flow. (*A*) Measurement of peak cough flow, using portable clinic spirometer. (*B*) Peak cough flow tracing from spirometer showing flow rate of approximately 300 L/minute (5 L/s). (*C*) Simple peak cough flow meter using mask and asthma peak flow meter. (*D*) Patient performing peak cough flow measurement with simple peak cough flow meter.

recruitment maneuvers that inflate the lung to the maximal insufflation capacity above the patient's vital capacity can be performed by "breath stacking," which delivers extra breaths with a resuscitator bag, mouthpiece volume ventilator, mechanical insufflator–exsufflator (MIE), or glossopharyngeal breathing. These maneuvers take the lung to a supramaximal volume and have been shown to result in improved lung compliance (89). In addition, lung volume recruitment increases PCF by increasing lung elastic recoil pressure and the gas volume available for cough flow (90). It has been recommended that these maneuvers be performed on a daily basis when the spontaneous PCF drops below 270 L/minute (4). The techniques become invaluable during episodes of infection and increased secretion and can prevent the need for intubation (91).

The MIE is a device that assists cough by delivering through a facemask or mouthpiece a brief positive inspiratory pressure to the airway followed by a negative pressure resulting in expiratory "cough" flows that can be substantial and enough to clear airway secretions (Figure 4; and see video in the online supplement). A substantial amount of literature supports the use of these devices (92–94). An official statement of the American Thoracic Society suggests that MIE be routinely considered for use in the treatment of patients with DMD with impaired PCF (3).

Devices that vibrate or oscillate the respiratory system to loosen but not remove secretions include intrapulmonary percussive ventilation and high-frequency chest wall compression. One randomized study showed that intrapulmonary percussive ventilation decreased hospitalization and antibiotic use in pediatric-aged patients in a residential facility (95). High-frequency chest wall compression has not been well studied and showed only minimal effects in patients with ALS (96).

Swallowing Dysfunction

Swallowing dysfunction is seen in patients with neuromuscular diseases such as ALS. Weakness of the lips, tongue, and pharyngeal and laryngeal muscles can result in an increased risk of aspiration as well as difficulty with generating adequate glottic closure for effective cough function. Swallowing may be impaired and ingesting adequate nutrition can be challenging for the patient. Choking is common and may even be triggered by aspiration of saliva. Malnutrition or rapid weight loss should

Figure 4. Illustration of use of the mechanical insufflator–exsufflator (MIE) to remove secretions.

signal the clinician to assess the swallowing mechanism. Swallowing may be tested by barium swallow or direct visualization of swallowing endoscopically (97).

Treatments for swallowing muscle dysfunction are limited. The risk of aspiration and development of pneumonia in patients with neuromuscular diseases such as ALS is due primarily to problems with upper airway function and cough. Other than surgical diversion of the airway or tracheostomy no treatment directly targeted to laryngeal and glottic muscle weakness is available. When patients develop significant dysphagia and aspiration of solids or liquids, many experts recommend placement of a percutaneous endoscopic gastrostomy tube to reduce transit of foreign material across the at-risk airway opening (98).

CONCLUSIONS

Patients with neuromuscular diseases of many types are at risk for respiratory complications related to hypoventilation both at night and during the day as well as cough impairment and aspiration. Careful assessment and treatment of respiratory issues can improve both quality and length of life.

Author disclosures are available with the text of this article at www.atsjournals.org.

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