CHAPTER 26

RESPIRATORY CONSEQUENCES OF NEUROMUSCULAR DISEASE

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The diaphragm and other respiratory muscles constitute the ventilatory pump upon which the act of breathing depends. In many neuromuscular disorders, muscle weakness involves the respiratory muscles to an equal or even greater extent than other skeletal muscles. The degree of limb muscle weakness cannot be used as a reliable guide to the presence of respiratory muscle impairment since the correlation between the two may be quite poor.[1,2] Respiratory symptoms are often initially minimal because of the inherently large reserve of the respiratory system. Respiratory muscle involvement may also be masked because patients with weak limb muscles spontaneously decrease their overall activity level, thereby reducing the daily physiologic challenge faced by the respiratory system. For all of these reasons, it is not unusual for respiratory muscle weakness to go undetected until overt respiratory failure is precipitated by an acute episode of pulmonary aspiration or infection. Accordingly, the clinician must be vigilant with regard to the possible presence of respiratory muscle weakness in any patient with a known neuromuscular disorder or unexplained exertional dyspnea. Other common symptoms found in patients with neuromuscular disease involving the respiratory muscles include orthopnea, cough during swallowing, weak cough, fatigue, hypersomnolence, morning headaches, insomnia, nightmares, and decreased intellectual performance. Respiratory muscle weakness may be caused by a large and diverse number of diseases affecting the central nervous system, the spinal cord, the nerves, the neuromuscular junction, or the muscle itself. A list of some of the more common or prototypical disorders is shown in Table 26-1, but a comprehensive review of specific disease entities is beyond the scope of this chapter. Instead, our purpose is to discuss general pathophysiologic mechanisms as well as principles of evaluation and treatment that are broadly applicable to most neuromuscular diseases affecting the respiratory system.

OVERVIEW OF PATHOPHYSIOLOGIC MECHANISMS IN CHRONIC VENTILATORY INSUFFICIENCY

Direct Consequences of Respiratory Muscle Weakness

It is not unusual for the pressure produced by the respiratory muscles to be decreased by up to 50% before the appearance of a reduction in vital capacity (VC).[3] Similarly, hypercapnia does not appear in most neuromuscular diseases until the maximum inspiratory pressure (MIP) at the mouth reaches a level below 30% of normal predicted values.[3] These observations underscore the large reserve capacity of the respiratory system, which may, in turn, mask involvement of the respiratory muscles until late in the course of neuromuscular disease.

Respiratory muscle weakness caused by neuromuscular disorders may be associated with increased susceptibility to superimposed respiratory muscle fatigue. The major distinction between simple weakness and fatigue is that the latter is reversible by rest, whereas the former is not. In normal subjects, the diaphragm becomes at risk for the development of fatigue when the pressure–time index (defined as the product of two fractions: inspiratory time/total respiratory cycle time [T_i/T_{tot}] and mean transdiaphragmatic pressure/maximum transdiaphragmatic pressure [P_{di}/P_{dimax}]) exceeds a critical "fatigue threshold" value of 0.15.[4] Based on this calculation, it is apparent that the existence of baseline diaphragmatic weakness (ie, a reduced P_{dimax}) will favor the development of diaphragmatic fatigue. Patients may adopt a breathing pattern that minimizes inspiratory time and transdiaphragmatic pressure (and hence tidal volume) in order to avoid fatigue of the diaphragm, but at the cost of an increase in arterial partial pressure of carbon dioxide (PCO_2).[5,6] In addition, there is evidence that the fatigue threshold value may actually be lower in patients with neuromuscular disorders. Hence, in quadriplegics the fatigue

Table 26-1 Neuromuscular Diseases

Muscular dystrophies
Duchenne muscular dystrophy
Becker muscular dystrophy
Limb-girdle muscular dystrophy
Myotonic dystrophy
Fascioscapulohumeral muscular dystrophy
Congenital muscular dystrophy
Metabolic diseases of muscle
Acid maltase deficiency
Mitochondrial myopathies
Carnitine palmityl transferase deficiency
Other myopathies
Polymyositis or dermatomyositis
Hypothyroidism or hyperthyroidism
Corticosteroid induced
Systemic lupus erythematosus
Diseases of the neuromuscular junction
Myasthenia gravis
Eaton–Lambert syndrome
Botulism
Diseases of peripheral nerve
Charcot–Marie–Tooth disease (also known as hereditary motor and sensory neuropathy)
Friedreich's ataxia
Chronic inflammatory femyelinating polyneuropathy
Guillain–Barré syndrome
Diseases of the motor neuron
Amyotrophic lateral sclerosis
Postpolio syndrome
Infantile progressive spinal muscular atrophy (also known as SMA type 1, Werdnig–Hoffman)
Intermediate spinal muscular atrophy (also known as SMA type 2)
Juvenile spinal muscular atrophy (also known as SMA type 3, Kugelberg–Welander)
Other diseases involving the spinal cord
Traumatic injury
Syringomyelia
Multiple sclerosis

threshold value for the diaphragm is actually reduced (0.10 to 0.12) compared with the value of 0.15 reported for normal individuals.[7] Similarly, a recent study has shown that when the same relative load (expressed as a percentage of maximal strength) is imposed on the respiratory system, the inspiratory muscles of patients with Duchenne dystrophy may be more susceptible to fatigue than those of healthy subjects.[8]

There are few data available concerning the contribution of expiratory muscle weakness to ventilatory failure in neuromuscular disorders. In one study it was found that decreased maximum expiratory pressure (MEP) at the mouth is not an independent predictor of hypercapnia.[9] Nonetheless, in patients with severe expiratory muscle weakness who are unable to generate an effective cough, there is an increased risk of developing atelectasis and pulmonary infection. In patients with neuromuscular disorders, the lowest value of MEP consistent with production of a satisfactory cough is on the order of 50 to 60 cm H_2O.[9,10]

Alterations in Respiratory System Mechanics

The degree of pulmonary restriction found in neuromuscular diseases is frequently greater than would be predicted from the decrement in inspiratory muscle force alone.[11] Increased elastic recoil of both the chest wall and pulmonary parenchyma have been documented.[12] The precise mechanisms underlying these changes are not well understood but are probably multifactorial in nature. For instance, the chronically diminished amplitude of respiratory excursions in patients with neuromuscular weakness may lead to ankylosis of costosternal and costovertebral joints, thereby producing a gradual stiffening of the rib cage. Fibrosis of rib cage muscles (eg, in muscular dystrophy) or connective tissue elements and spinal deformities can also cause a reduction in chest wall compliance.[13] Microatelectasis has been found at autopsy in patients with neuromuscular disorders such as Duchenne dystrophy and spinal muscular atrophy.[14] Once again, it has been hypothesized that this could be related to a lack of spontaneous deep breaths, which normally help re-inflate atelectatic regions of the lung,[15] as well as inefficient cough and clearance of secretions due to expiratory muscle weakness. On the other hand, computed tomography imaging of the lungs failed to confirm the presence of increased atelectasis in a group of patients with Duchenne muscular dystrophy.[16] Impaired activity of surfactant or alterations in the mechanical properties of elastin and collagen fibers within the lungs have also been proposed as possible explanations for reduced lung compliance.[16] Interestingly, in infants and children with neuromuscular disorders, chest wall compliance may actually be increased due to adverse effects on proper development of the chest wall.[17]

Abnormal respiratory mechanics are not limited to the lungs and chest wall but may also involve the upper airway in neuromuscular disorders. In this regard, pharyngeal muscle weakness is observed in neuromuscular disorders such as Duchenne dystrophy,[18] motor neuron disease,[19] and myasthenia gravis.[20] Because weakness of pharyngeal dilator muscles decreases upper airway caliber, there is an increase in upper airway resistance during inspiration. The latter imposes a higher mechanical load on the diaphragm and other inspiratory muscles, thereby increasing the work of breathing.[21] When combined with the decrease in upper airway motor tone normally found during sleep (especially rapid eye-movement [REM] sleep), pharyngeal dilator muscle weakness favors the development of sleep-related hypoventilation and obstructive sleep apnea.

Abnormal Central Control of Breathing

Many neuromuscular disorders that cause respiratory muscle weakness (eg, Duchenne dystrophy, myotonic dystrophy, and Friedrich's ataxia) are also associated with abnormalities of central nervous system function. This raises the question of whether central respiratory control centers within the brain could also be dysfunctional in some of these disorders.[22] Traditional measures of central respiratory drive, such as the ventilatory responses to hypercapnia and hypoxia, or the measurement of inspiratory pressure generated at the mouth 0.1 second after an inspiratory occlusion ($P_{0.1}$),[23] are difficult to interpret in patients with neuromuscular disease. This is because these parameters are affected not only by central ventilatory responsiveness but also by respiratory muscle weakness and abnormal respiratory mechanics. Accordingly, it is often difficult to know what

the "appropriate" values are in such patients, given their other abnormalities of respiratory function.[24] For example, in myotonic dystrophy there is a tendency for carbon dioxide retention that is out of proportion to the degree of respiratory muscle weakness or altered mechanics, suggesting that central respiratory drive is abnormally reduced.[25] In addition, there is a reduction in the ventilatory response to hypercapnia and hypoxia.[26] On the other hand, some studies have reported normal or elevated values of $P_{0.1}$ in these patients,[26–28] suggesting that central drive is not depressed and may even be increased.

There is compelling evidence that sleep-disordered breathing, which is common in patients with neuromuscular disease, can lead to important secondary alterations in central respiratory drive. More specifically, it is postulated that nocturnal hypoventilation and attendant bicarbonate retention lead to a so-called "resetting" of the central carbon dioxide setpoint. Under these conditions, patients with chronic nocturnal hypoventilation develop a reduced central sensitivity to carbon dioxide, which eventually becomes manifest during the daytime. Importantly, it has been demonstrated that such chronic carbon dioxide retention during the daytime can be reversed or ameliorated in many patients by instituting artificial ventilation at night to prevent nocturnal hypoventilation.[29–34] Whether the changes in the carbon dioxide setpoint are due solely to modifications of acid–base status or whether other factors, such as sleep deprivation[35] and hypoxemia, also play a role remains to be determined.

Nonrespiratory Factors Contributing to Chronic Respiratory Impairment

Cardiac involvement occurs in several forms of neuromuscular disease that involve the respiratory system, and is particularly frequent in the muscular dystrophies.[36] In the more advanced stages of Duchenne dystrophy, impaired cardiac function and respiratory insufficiency generally coexist. Left ventricular pump failure with attendant pulmonary venous congestion may cause decreased pulmonary compliance, thereby increasing the work of breathing as well as ventilation–perfusion mismatching and abnormal gas exchange. In addition, there is evidence that respiratory muscle bloodflow is impaired in patients with heart failure, which may further predispose to the development of respiratory muscle dysfunction.[37] As with other conditions characterized by chronic hypoventilation and hypoxemia, pulmonary arterial hypertension and right heart failure may also be present.

Poor nutrition is a common problem among patients with neuromuscular disease.[38,39] Obesity is frequent in patients with neuromuscular disorders because of a variety of factors, including poor dietary habits, sedentary status, and medications (eg, corticosteroids). The presence of obesity places an additional respiratory mechanical burden upon the weakened respiratory muscles and also favors the development of nocturnal hypoventilation and obstructive sleep apnea. Undernutrition may also be a problem, especially late in the disease course, at which time disorders of the alimentary system (impaired swallowing, aspiration, gastroparesis, constipation, etc.) may play an important role. For instance, undernutrition has been reported to occur in approximately half of patients with Duchenne dystrophy.[39] To the extent that undernutrition has also been found to cause atrophy of the diaphragm, particularly within the fast-twitch fiber population,[40] this may also lead to further aggravation of respiratory muscle weakness and dysfunction.

TESTS FOR THE EVALUATION OF RESPIRATORY MUSCLE FUNCTION

Several different tests are currently available to help evaluate the degree of respiratory muscle weakness in patients with neuromuscular disease. Irrespective of the neuromuscular disease in question, the history and physical examination of the patient should serve as the primary guide for determining the nature as well as the frequency of respiratory muscle function testing. A simple measurement of VC with standard spirometry undoubtedly offers the most accessible index of overall ventilatory impairment in neuromuscular disorders, and in many cases it is also the best predictor of survival. Evaluation of respiratory function during sleep (polysomnography) is also important in patients with advanced disease, who are at particular risk for the development of nocturnal hypoventilation and hypoxemia. The more specialized techniques, which specifically measure respiratory muscle function, can be used to confirm a diagnosis of respiratory muscle weakness in uncertain cases. Additional research is needed to determine whether these specialized tests should also be used in following the patient with neuromuscular disease and established respiratory muscle weakness.

Standard or General Tests of Respiratory Function

Spirometry and Lung Volumes As mentioned earlier, spirometry is not a sensitive indicator of respiratory muscle weakness in the early stages of disease, and VC usually remains normal or near-normal until there is a major decline (about 50%) in respiratory muscle strength.[1,3] It should also be noted that in the presence of kyphoscoliosis, it is often preferable to use armspan instead of height to obtain reference values.[41] Despite these limitations, spirometry is the best known predictor of respiratory morbidity and mortality in patients with neuromuscular disease. For example, in Duchenne muscular dystrophy, a VC below 1 L is associated with subsequent mortality,[42] and a VC below 40% of the normal predicted value is significantly correlated with sleep hypoventilation.[43]

Respiratory muscle weakness characteristically induces a restrictive ventilatory defect. The forced expiratory volume in 1 second (FEV_1)/forced vital capacity ratio is generally normal or supranormal, with reductions in total lung capacity and, to a lesser extent, functional residual capacity.[3,14,44] The inspiratory capacity and expiratory reserve volume are typically decreased, reflecting the presence of inspiratory and expiratory muscle weakness, respectively. Significant expiratory muscle weakness, if present, will result in an elevation of residual volume (RV).[3] This may serve as a clue pointing toward a neuromuscular etiology since most other restrictive disorders are associated with reductions in RV.

Another sign of expiratory muscle weakness is when the peak expiratory flow rate, which occurs over the early effort-dependent portion of the forced expiratory curve, is disproportionately reduced in comparison to the FEV_1, VC, and mid-expiratory flows ($MEF_{25–75}$).

Measuring lung volumes with the subject in different body positions is also useful since a large fall in VC upon going from a sitting to a supine posture strongly suggests significant diaphragmatic weakness. In the presence of major diaphragmatic weakness, the weight of the abdominal contents is no longer effectively opposed by the flaccid diaphragm muscle when the patient lies down. Normal subjects demonstrate a mean postural decrease in VC of less than 10% after lying down.[45] In patients with neuromuscular disorders, a postural drop in VC of greater than 25% points to major diaphragmatic weakness with a high degree of sensitivity (79%) and specificity (90%).[46] In addition, it has been reported that the postural fall in VC correlates with respiratory symptoms in amyotrophic lateral sclerosis,[47] as well as the magnitude of oxyhemoglobin desaturation during rapid eye movement (REM) sleep in various neuromuscular disorders.[48]

Flow–Volume Curve Analysis In addition to simple spirometry, a more detailed analysis of the flow–volume curve can provide additional clues to the presence of respiratory muscle weakness. Characteristic features include a delay in reaching peak expiratory flow, truncation of the peak expiratory flow rate, and an abnormally abrupt fall in expiratory flow at the end of expiration (Figure 26-1).[49,50] These changes reflect the fact that the peak expiratory flow rate and flow rates during the final portion of expiration are largely strength dependent. On the other hand, the mid-expiratory flows are less strength dependent and more closely correlated with lung elastic recoil. Accordingly, normal or even supranormal flow rates may be observed in the mid-expiratory portion of the flow–volume curve, consistent with the fact that increased lung recoil contributes to the restrictive ventilatory defect. Inspiratory muscle weakness may be manifested by truncation of the peak inspiratory flow rate.[49] Furthermore, in patients with bulbar or upper airway muscle involvement by neuromuscular diseases (particularly Parkinson's disease), abnormal oscillations of inspiratory and/or expiratory flow may be visible on the flow–volume curve (Figure 26-2).[50] These appear to be the result of dynamic instability of upper airway caliber and in one patient with Parkinson's disease could be largely eliminated by administration of L-dopa.[51]

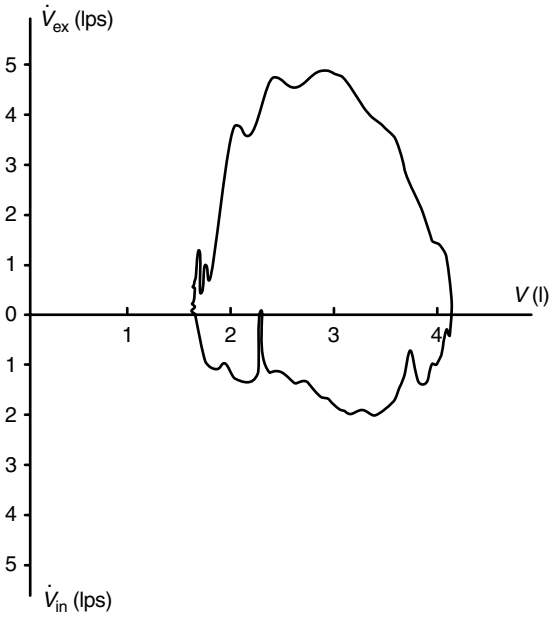

FIGURE 26-1 Flow–volume curve obtained from a patient with neuromuscular disease. Note the abnormal delay in reaching peak expiratory flow as well as the abrupt fall in expiratory flow at end-expiration. Reproduced with permission from Vincken WG et al.[50]

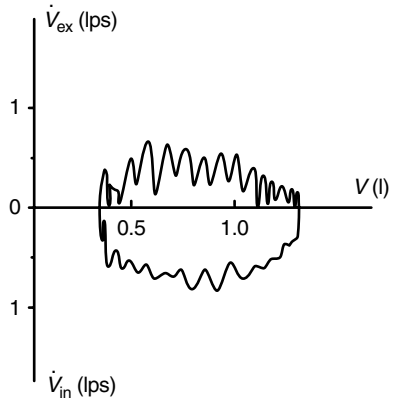

FIGURE 26-2 Flow–volume curve obtained from a patient with an extrapyramidal disorder, demonstrating marked oscillations of both inspiratory and expiratory flow, or so-called "respiratory flutter." Reproduced with permission from Vincken WG et al.[50]

Maximal Inspiratory and Expiratory Mouth Pressures Because of the relative insensitivity of standard spirometry and blood gases to respiratory muscle weakness, it is essential to formally assess respiratory muscle strength in all patients with neuromuscular disorders that potentially affect the respiratory muscles. The simplest direct way of measuring inspiratory muscle strength is to record the pressure generated at the mouth during a maximal inspiratory effort against a closed airway, the MIP.[52,53] Depending upon the neuromuscular disorder in question, the relationship between MIP and outcomes such as nocturnal hypoventilation, mortality, and quality of life is variable. For example, an MIP of approximately 30% predicted has been associated with significantly increased mortality in amyotrophic lateral sclerosis,[54–56] whereas in Duchenne muscular dystrophy a poor correlation was found between MIP values and mortality.[42,43] On the other hand, a significant correlation was reported between reductions in MIP and the fall in VC observed in patients with Duchenne muscular dystrophy.[53] One problem is that, even in normal subjects, there is considerable variability in the MIP measurement.[57] This variability is likely to be even more important in patients with

neuromuscular disease, due to factors such as poor mouth seal caused by facial weakness, or, in some cases, inadequate comprehension of the maneuver because of cognitive impairment associated with the disease.[58] Maximal expiratory mouth pressure measurement against an occluded airway, or MEP, suffers from much the same technical limitations as just described for the MIP. Accordingly, these considerations reinforce the importance of attention to technical details by laboratory personnel, as well as the need for patients to practice the maneuver beforehand, in order to obtain the most reliable results possible.

Arterial Blood Gas Analysis Arterial blood gas analysis is insensitive for either detecting disease or evaluating disease progression in the early to intermediate phases of respiratory muscle weakness. However, blood gas assessment should be performed once the VC has fallen to below 50% of reference values and/or when the MIP is reduced to 30% of normal. It is not unusual to find a mild degree of hyperventilation up until shortly before the development of overt hypercapnic ventilatory insufficiency. Patients may also have normal daytime blood gases despite significant hypoxia and hypercapnia during sleep.

Sleep Study Evaluation (Polysomnography) Sleep-disordered breathing is frequent in patients with neuromuscular disorders.[59] Not only are such patients at increased risk for developing nocturnal hypoventilation with attendant hypoxemia, but there is also an increased prevalence of obstructive sleep apnea. The latter can be related to pharyngeal dilator muscle weakness as well as the presence of significant obesity, which is fairly common given the sedentary status of most neuromuscular patients.[60] Patients with neuromuscular disease are especially prone to develop hypoventilation and oxyhemoglobin desaturation during REM sleep (Figure 26-3).[48] This is because REM sleep is associated with neurally mediated inhibitory mechanisms that greatly reduce the activity level of respiratory muscles other than the diaphragm.[61,62] Accordingly, the impact of REM-associated reductions in intercostal and accessory muscle activation is particularly severe in patients with underlying diaphragmatic weakness since the diaphragm is no longer able to effectively compensate for the loss of the other inspiratory muscles under these conditions. Interestingly, there is evidence that the inhibitory influences of REM sleep on nondiaphragmatic respiratory muscles are blunted in certain patients with diaphragmatic weakness, possibly as a compensatory protective mechanism.[63] In patients with neuromuscular disorders, it can also be difficult to distinguish between hypoventilation and obstructive sleep apnea since the diaphragm and other inspiratory muscles may be too weak to generate the negative suction forces needed to produce the classic signs of obstruction. Under these conditions, direct assessment of respiratory effort during sleep with an esophageal balloon catheter (see below) may be necessary to differentiate between the two entities.[59]

Although attempts have been made in a number of studies to use pulmonary function tests (spirometry, MIP, MEP) and daytime blood gases in order to predict the need for polysomnography in neuromuscular patients, the results have been mixed and seem to vary with the specific disease in question. In Duchenne muscular dystrophy, an FEV_1 $<$40% was found to be a sensitive (91%) but not specific (50%) indicator of sleep hypoventilation, whereas a base excess of $>$4 mmol/L was highly specific (100%) but less sensitive (55%).[43] As a general guideline, one should strongly consider performing a sleep study to rule out significant sleep-disordered breathing when (1) the VC has fallen to below 50% of reference values and/or when the MIP is reduced to 30% of normal; (2) significant abnormalities of daytime blood gases are present; or (3) there are symptoms suggestive of sleep-disordered breathing, such as morning headaches, hypersomnolence, nocturia, insomnia, nightmares, and decreased intellectual performance.

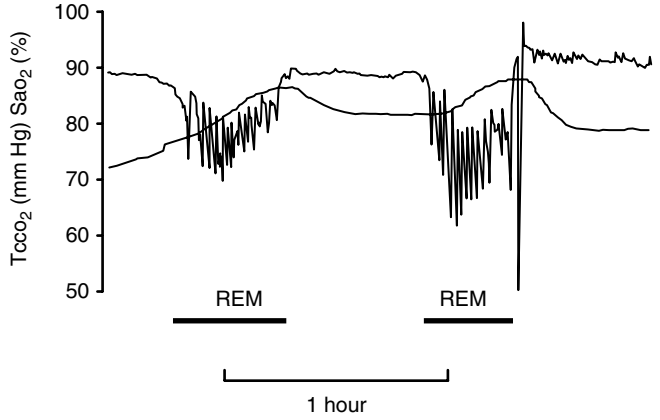

FIGURE 26-3 Polysomnographic tracing showing marked oxyhemoglobin desaturation (SaO_2) along with increases in transcutaneous carbon dioxide ($TcCO_2$) during REM sleep in a patient with neuromuscular weakness. Reproduced with permission from Bye PT et al.[48]

Specialized Tests of Respiratory Muscle Function

Maximal Sniff Nasal Pressure Maximal sniff nasal pressure (sniff P_{imax}) is a relatively new test of inspiratory muscle strength and involves measurement of the pressure generated within an occluded nostril during a maximal sniff maneuver through the contralateral, unoccluded nostril (Figure 26-4).[64] Because the technique does not require a mouthpiece and the sniff is a very familiar maneuver for most individuals, it avoids some of the technical difficulties encountered with the classic MIP measurement. In patients with neuromuscular disorders, it has been reported that sniff P_{imax} values are statistically equivalent to the classic MIP measurement, but with the advantage of being easier to obtain in patients with neuromuscular disorders.[64,65] Furthermore, the correlation between VC and sniff P_{imax} appears to be higher than that between VC and MIP in neuromuscular patients.[65] The technical limitations of sniff P_{imax} include the need for an airtight nasal plug, sufficient pressure generation to cause airflow limitation in the contralateral nostril, and the absence of major nasal congestion.

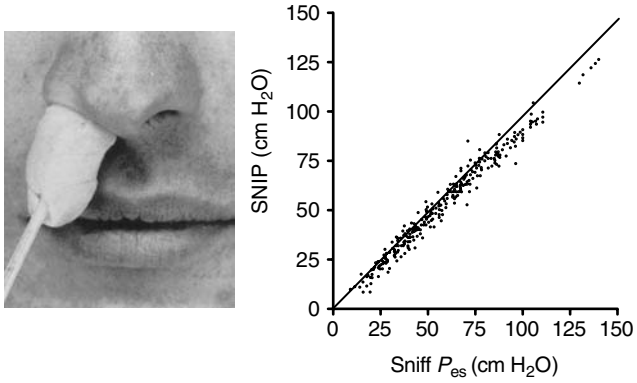

FIGURE 26-4 Measurement of sniff nasal inspiratory pressure (SNIP). *Left*: A nasal plug fitted around the tip of a catheter is inserted into one nostril. *Right*: Relationship between SNIP and sniff esophageal pressure (sniff P_{es}) in normal subjects. Reproduced with permission from Heritier F et al.[64]

Transdiaphragmatic Pressure The ability of the diaphragm to effectively generate negative pressure in the thorax during inspiration can be assessed directly by measuring the pressure difference across the diaphragm, or P_{di}. Pressure changes on either side of the diaphragm in the abdominal (P_{ab}) and pleural (P_{pl}) spaces, respectively, are measured by placing balloon catheters into the stomach and midesophagus. During a maximal inspiratory effort, maximal P_{di} can then be calculated as $P_{dimax} = P_{ab} - P_{pl}$ (Figure 26-5).[66] However, depending upon the particular maneuver employed to generate the maximal inspiratory effort, both the magnitude and the variability of normative values will differ. For example, absolute values obtained during maximal sniff and Müller (through the mouth against a closed glottis) maneuvers are similar (approximately 120 cm H_2O), but the coefficient of variation is substantially lower with a sniff.[67,68] When complete diaphragmatic paralysis is present, the diaphragm is sucked up into the chest during inspiration, so that both P_{ab} and P_{pl} become negative during inspiration and effectively cancel each other out (ie, $P_{di} = 0$). This pattern of pressure generation also gives rise to paradoxical inward motion of the abdominal wall during inspiration, which can be detected clinically when the patient is placed in the supine body position or quantified using respiratory inductance plethysmography and related techniques for measuring thoracoabdominal motion.[69]

Additional information can be gained by combining measurements of P_{di} with phrenic nerve stimulation. Direct electrical stimulation of the phrenic nerves removes the need for patient cooperation in the performance of a maximal inspiratory effort. In addition, the time between imposition of the stimulus and appearance of the compound action potential at the level of the diaphragm (normally about 6 to 10 ms, recorded from surface EMG electrodes placed over the lower rib cage) can be measured, thereby providing an index of phrenic nerve conduction time.[70] In normal subjects, bilateral phrenic nerve twitch (ie, a single impulse) stimulation results in P_{di} values that are approximately 20% of maximal sniff P_{di} values.[67] Similar values are obtained with cervical magnetic stimulation of the phrenic nerve, which is technically easier and also better tolerated by most patients than conventional electrical stimulation[71] since the current intensities required for the latter are often painful.

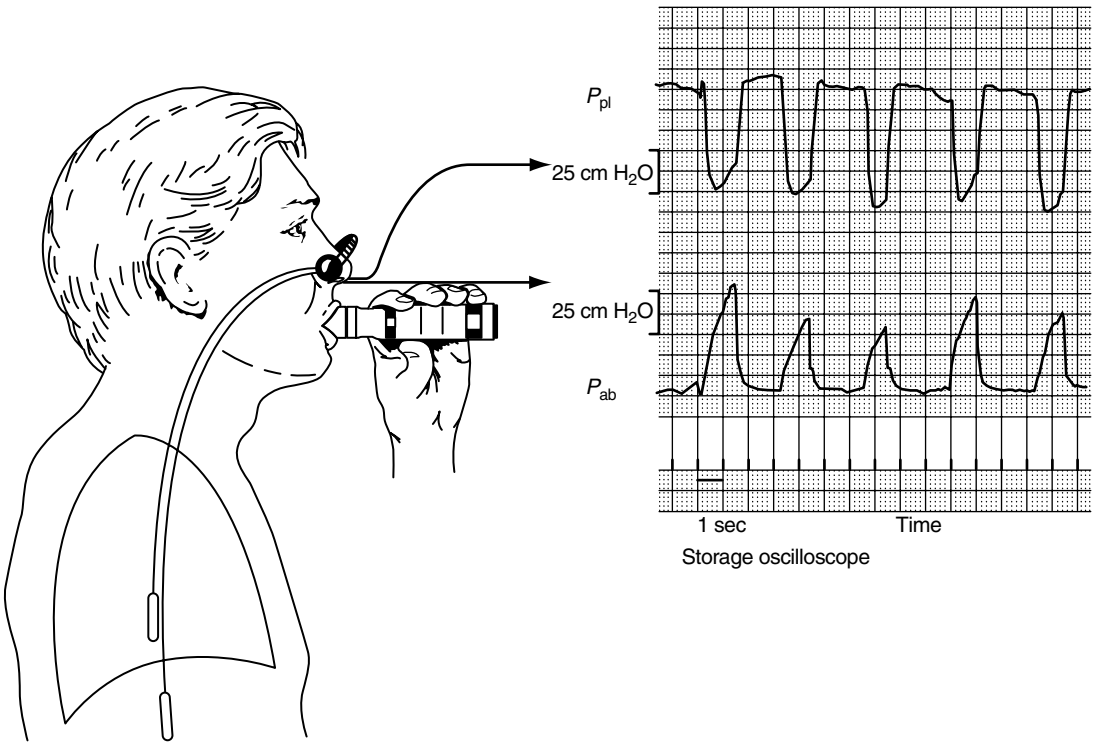

FIGURE 26-5 Method for determining maximal transdiaphragmatic pressure in humans. Balloon catheters placed into the esophagus and stomach are used to measure pleural (P_{pl}) and abdominal (P_{ab}) pressures, respectively. Reproduced with permission from Laporta D and Grassino A.[66]

Tests of Respiratory Muscle Endurance Respiratory muscle endurance has been evaluated by a number of different methods in patients with neuromuscular disorders. Although not a pure test of respiratory muscle endurance alone, the classic maximal voluntary ventilation (MVV) maneuver was found to be reduced in neuromuscular diseases, even when the VC was normal.[24,72,73] Others have measured the maximal sustainable ventilation or pressure produced by the respiratory muscles over various predetermined periods of time[74,75] or the maximal time for which a subject is able to sustain a predetermined percentage of the MVV or P_{dimax}.[76,77] The proper role of respiratory muscle endurance testing for patients with neuromuscular disorders remains to be determined. One potential application is in evaluating the effectiveness of therapeutic interventions. An important technical issue is that, for satisfactory reproducibility of respiratory muscle endurance test results, the subject must learn to adopt a standardized breathing pattern.[78] In addition, there is a theoretical risk of precipitating respiratory muscle fatigue and failure in severely affected patients. Therefore, it is probably only feasible to perform tests of respiratory muscle endurance in a subset of neuromuscular patients who do not suffer from significant cognitive dysfunction or severe respiratory muscle weakness.

RESPIRATORY MANAGEMENT

General Measures

An impaired ability to cough and clear airway secretions places patients with neuromuscular disease at particularly high risk for the development of pulmonary infections. In many cases, there is also an increased propensity to aspirate food or pharyngeal secretions, due to weakness or a lack of coordination of the upper airway muscles. Moreover, it appears that even relatively mild upper respiratory tract infections can lead to major additional reductions in respiratory muscle strength.[79] Therefore, any respiratory tract infection in the patient with severe neuromuscular disease has the potential to trigger an episode of full-blown respiratory failure requiring mechanical ventilatory assistance. For this reason, it is imperative that aggressive measures be taken to both prevent and treat respiratory infections in such patients. This includes the appropriate use of vaccinations against influenza and pneumoccocal pneumonia, aggressive antibiotic treatment of suspected bacterial infections of the respiratory tract, and chest physiotherapy for removal of airway secretions. In addition, either manual or mechanically assisted expulsive maneuvers can be successful in increasing cough efficiency.[80]

Orthotic devices to brace the spine have not been demonstrated to be effective in improving pulmonary function in neuromuscular patients with kyphoscoliosis and may, in fact, worsen pulmonary restriction. Surgical procedures to correct scoliosis are similarly unhelpful in slowing the decline of pulmonary function, at least in patients with Duchenne muscular dystrophy, in whom this issue has been specifically addressed.[81–83] Nonetheless, spinal stabilization may improve comfort and quality of life if instituted early after the loss of ambulation and before the onset of severe scoliosis or contractures. It is important to recognize, however, that surgical stabilization of the spine is associated with a substantial risk of perioperative pulmonary and cardiac complications in such patients and may even be fatal. In one study, approximately half of the patients with a preoperative FVC value of less than 35% suffered from postoperative complications.[83] Therefore, candidates for such surgery should be carefully evaluated in order to exclude those with significant cardiomyopathy, and if undertaken, the intervention should ideally be performed before the VC has fallen to below 50% of its predicted value.[83]

Ventilatory Muscle-directed Measures

Respiratory Muscle Training The rationale for respiratory muscle training is that by increasing strength and endurance, it could help improve exercise tolerance, reduce dyspnea, augment cough efficiency, and increase the ability of the respiratory muscles to tolerate acute increases in respiratory mechanical load associated with pulmonary infections. On the other hand, there is at least a theoretical risk of increasing the rate of disease progression by overtraining, particularly in those disorders (eg, Duchenne dystrophy, postpolio syndrome) in which overuse has been implicated in disease pathogenesis.[84,85] To date, the majority of studies evaluating the effectiveness of respiratory muscle training in neuromuscular disorders have been heavily weighted toward patients with Duchenne muscular dystrophy, although benefits in multiple sclerosis,[86,87] postpolio syndrome,[88] and quadriplegia[89] have also been reported. Most investigations in Duchenne patients,[76,77,90–93] but not all,[74,75] have shown improvements in respiratory muscle strength or endurance after periods of training ranging from approximately 6 weeks to 24 months. Another study also showed a significant reduction in respiratory load perception after training,[94] and it was suggested that this might translate into reduced dyspnea. In general, the reported improvements in respiratory muscle function after training were not associated with changes in VC. In addition, respiratory muscle training appears to offer little or no benefit in Duchenne muscular dystrophy patients with very severe baseline ventilatory impairment (VC $<$ 25% predicted).[76,90] Another potential application of respiratory muscle training, which differs conceptually from those outlined above, is to selectively train nonaffected muscles capable of playing a compensatory role. Hence, in patients who have lost the use of expiratory abdominal and intercostal muscles due to lower cervical spinal cord injury, it is possible to restore a degree of expiratory muscle function by selectively training the clavicular portion of the pectoralis major muscle, which retains innervation under these conditions.[95]

At the present time, there is no clear consensus regarding the role of respiratory muscle training in the management of patients with neuromuscular disorders. Indeed, it should be noted that a similar situation exists even with respect to training of nonrespiratory skeletal muscles in this patient population.[84] Although the overall approach appears promising, questions remain regarding the degree to which the

observed improvements represent true training effects versus learning. Furthermore, it will be important to ascertain whether any improvements in respiratory muscle function induced by training translate into decreased respiratory morbidity or mortality. Finally, given the great heterogeneity of the target diseases in question, future research will need to better identify the most effective training parameters (stimulus intensity, duration, inspiratory versus expiratory, etc.) for specific neuromuscular disorders.

Mechanical Ventilation There is considerable evidence that patients with chronic and progressive ventilatory failure due to neuromuscular diseases benefit from the use of noninvasive ventilatory support, particularly during sleep.[34] Such therapy can consist of either negative pressure (eg, cuirass, body suit or poncho, tank respirator) or positive pressure (eg, via a mask or mouthpiece) delivery methods. Although negative pressure ventilation popularized the use of noninvasive ventilatory support for neuromuscular disease during the poliomyelitis epidemics, this approach has fallen out of favor due to the somewhat cumbersome nature of the devices (ie, difficulty getting into and out of the devices, limited access to the patient during treatment), as well as the increased risk of upper airway obstruction during sleep.[30,96] Positive pressure ventilation is generally delivered via a tight-fitting nasal or full-face (eg, to prevent mouth leak) mask. Potential complications of noninvasive positive pressure ventilation (NIPPV) include facial pressure sores, eye irritation from air leaks, mouth dryness, and gastric distention. As a general rule, the more invasive tracheostomy is reserved for specific circumstances, such as severe bulbar dysfunction, excessive oropharyngeal or pulmonary secretions that require frequent suctioning, or an essentially continuous 24-hour need for ventilatory support.

Several investigations have shown that nocturnal ventilatory support can improve daytime arterial blood gases[29–33] (Figure 26-6), as well as quality of life or survival.[97–99] The use of NIPPV may also decrease pulmonary morbidity and hospitalization rates.[98,100–102] On the other hand, there is no convincing evidence that NIPPV is able to mitigate the progressive loss of respiratory muscle strength or otherwise slow the rate of decline of pulmonary function. In fact, a reduction in respiratory muscle strength was reported after a median period of only 42 hours on NIPPV,[100] suggesting that NIPPV could lead to deconditioning of the respiratory muscles in some patients.[103] Such a concern argues against the use of NIPPV as a prophylactic measure, that is, before the actual onset of alveolar hypoventilation. Indeed, in one study that specifically addressed the issue of prophylactic NIPPV in Duchenne dystrophy, not only was a lack of benefit for this intervention found, but, for unclear reasons, there was actually increased mortality in the group treated with preventive ventilation.[104]

As discussed earlier, hypoventilation often begins during sleep and may manifest itself as insomnia or nightmares as well as more classic symptoms such as fatigue, daytime hypersomnolence, and morning headache. The clearest indication for the institution of NIPPV is when such symptoms are present and associated with documented

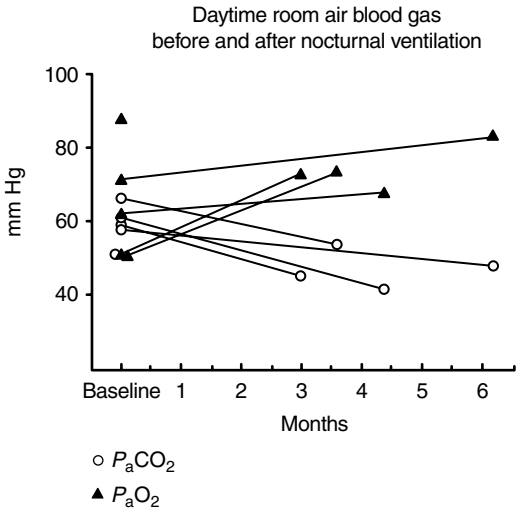

FIGURE 26-6 Daytime arterial blood gas measurements on room air before and after treatment with noninvasive positive pressure ventilation (NIPPV) in a group of patients with neuromuscular disease. Circles = arterial partial pressure of carbon dioxide. Triangles = arterial partial pressure of oxygen. Reproduced with permission from Kerby GR et al.[32]

hypoventilation. A recent consensus conference has suggested that NIPPV be offered in symptomatic patients with at least one of the following: (1) daytime arterial PCO_2 greater than 45 mm Hg; (2) nocturnal level of oxyhemoglobin saturation less than 88% for over five consecutive minutes; or (3) severe underlying pulmonary function abnormalities (MIP < 60 cm H_2O or FVC $< 50\%$ predicted).[34] There is no consensus for specific threshold values of spirometric or blood gas measurements after which NIPPV should be offered in asymptomatic patients, and this will undoubtedly be influenced by the particular disease entity in question and other components of the overall clinical context.

Finally, research suggests that physicians' perceptions of quality of life on NIPPV, and hence their attitudes in offering such therapy to patients, are frequently more negative than reported by patients actually undergoing NIPPV.[105,106] Therefore, an overly negative attitude to ventilatory support on the part of the physician, even in the face of progressive neuromuscular disease, is not appropriate. However, it is imperative that the issue of NIPPV be discussed with patients and their families well before the need for such therapy arises, and these decisions need to be reevaluated on a periodic basis.[107]

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