The Pathophysiology of Respiratory Impairment in Pediatric Neuromuscular Diseases

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ABSTRACT
This is a summary of the presentation on the pathophysiology of respiratory impairment in pediatric neuromuscular disorders presented as part of the program on pulmonary management of pediatric patients with neuromuscular disease at the 30th annual Carrell-Krusen Neuromuscular Symposium on February 20, 2008. Pediatrics 2009;123:S215–S218

Children with progressive neuromuscular weakness are at risk of developing significant respiratory morbidity from recurrent infections, and respiratory failure is the most common cause of mortality among patients with neuromuscular diseases (NMDs).1–5 Causes of respiratory failure can be categorized as those resulting from parenchymal disease that lead to hypoxic respiratory failure and those that arise from dysfunction of the respiratory pump that lead to hypercapnic respiratory failure.6 The “respiratory pump” comprises the structural elements of the chest wall, the respiratory muscles, and the respiratory control center. Thus, mechanical disorders of the chest (and abdominal) wall, fatigue of respiratory muscles, or depression of the respiratory control center all can lead to pump failure. Although parenchymal disease (eg, from acute pneumonia or recurrent episodes of aspiration) can cause respiratory embarrassment in children with NMDs, it is pump failure that is more likely to cause chronic respiratory failure. This review, therefore, will concentrate on the various aspects of pump failure and what is currently known about each in children with NMDs. In addition, maturational aspects of the components of the respiratory system as they relate to the development of respiratory failure will be mentioned.

CAUSES OF HYPERCAPNIC (PUMP) FAILURE
Respiratory Center Depression
Assessment of control of breathing in patients with NMDs can be difficult when the responses to hypercapnic or hypoxic challenges are measured. Inadequate responses can result in cases of extreme respiratory muscle weakness, because the mechanics of the respiratory system do not permit a normal response, even when central control mechanisms are intact. In other words, a patient with extreme respiratory muscle weakness may not be able to increase tidal volume or respiratory rate adequately in the face of a hypercapnic challenge, because the respiratory muscles are incapable of increasing their output even in the face of greater input signals. Impaired proprioception of diseased respiratory muscles can impair feedback as well.7

One method of assessing central respiratory drive that is considered to be relatively unaffected by respiratory muscle weakness is the measurement of mouth pressure in the first 0.1 second of inspiration after an occlusion (P0.1). The airway is occluded for the first 0.2 to 0.3 seconds of inspiration, and the mouth pressure over the first 0.1 second is measured. The pressure generated is considerably lower than the pressures generated over the tidal volume or the maximal pressure that one can achieve and, thus, is not limited by the subject’s weakness. In addition, the obstruction is too brief to be sensed by the subject as an increased load. Studies evaluating the P0.1 in subjects with neuromuscular weakness have generally demonstrated normal or near-normal responses. One such study in 9 patients with Duchenne muscular dystrophy (DMD) who were eucapnic at rest demonstrated normal responses to hypercapnia, hypoxia, and hyperoxia compared with age-matched controls.8 The ventilatory pattern, however, differed between the subjects with DMD and controls; in response to hypercapnia and hypoxia, controls increased tidal volume rather than respiratory frequency, whereas those with DMD became tachypnic with little increase in tidal volume.

Alterations in the Mechanical Properties of the Respiratory Pump
Whether a patient with NMD develops respiratory failure is determined by a balance between the load applied to the pump and the ability of the pump to handle the load. The forces that must be taken into consideration for the pump to overcome include the elastic properties of the lung parenchyma and of the pump itself, as well as frictional forces.
related to gas flow. These factors can be measured individually. The elastic load can be described by measurements of lung and chest wall compliances, whereas airways resistance can directly assess the frictional load. Output characteristics of the pump are measured by tests of respiratory muscle strength and endurance.

Lung compliance of adults with neuromuscular weakness is decreased when compared with normal values at a given lung volume. In contrast, when lung compliance is normalized to the subject’s lung volume to yield a specific compliance, those values are normal. The interpretation of these findings is that the reduced compliance of the lung is the result of microatelectasis. Thus, although the existing functional lung parenchyma has normal mechanical characteristics, the result of diffuse airspace collapse is to increase the elastic load on the pump.

Chest wall compliance has been measured in both children and adults with NMDs. In children between 3 months and 4 years of age with a variety of NMDs, chest wall compliance normalized to body weight was more than twice that of controls. The result of this finding is that the chest wall deforms during tidal breathing, which makes breathing inefficient. Not only does this increase the work of breathing, but it also predisposes the child to atelectasis and can result in fixed deformation of the chest wall (i.e., pectus excavatum). Therefore, because humans develop most of the gas-exchange surface of the lung in the 2 to 4 years after birth, there is theoretical concern that absence of lung stretch with sigh breaths and the acquisition of chest wall deformities can result in reduced lung growth for children with NMDs.

The chest walls of adults with NMDs have demonstrated the opposite findings. Among 20 adults between 17 and 61 years of age with tetraplegia, chest wall compliance was found to be only 72% of normal. This greater stiffness, which increases the load against which the respiratory pump has to work, is presumed to be the result of ankylosis of costovertebral joints and stiffening of tendons and ligaments of the rib cage resulting from reduced rib cage excursion. It has been postulated that a program of daily maneuvers that provide large chest wall excursions, by either breath stacking or inflation, could minimize the reduction in chest wall compliance that occurs with age and simultaneously improve lung compliance by reversing microatelectasis. Longitudinal studies of lung and chest wall compliance measurements, however, have not yet been undertaken.

Estenne and De Troyer also found that compliance of the abdominal compartment was increased in their subjects with tetraplegia. The combination of a stiffer thorax and more compliant abdominal compartment further reduces ventilatory efficiency by limiting the effectiveness of the diaphragm. The diaphragm not only acts as a piston to lower intrathoracic pressure during its contraction, but it also has 2 other important actions on the lower rib cage. Some diaphragmatic fibers insert directly on lower ribs and cause their elevation and consequent increase in thoracic volume through the “bucket-handle” motion of the ribs as the diaphragm contracts. Caudal movement of the diaphragm also increases intraabdominal pressure. Because a sizable portion of the abdominal contents resides within the lower thoracic cage at end expiration, pressurization of the abdominal compartment creates an outward force on the lower rib cage through the “area of apposition,” at which the diaphragm and chest wall are in close contact. The net result is an outward displacement of the lower rib cage. If the abdominal wall is highly compliant, however, then the increase of abdominal pressure with diaphragm descent will be minimized, as will the effect on the lower rib cage.

**ASSESSMENT OF RESPIRATORY PUMP FUNCTION**

The output of the respiratory pump can be measured by tests of respiratory muscle strength. Normal values of maximal inspiratory (MIP) and expiratory (MEP) pressures have been published from studies in neonates through adults. From infancy onward, the MIP falls within a range of 80 to 120 cm H₂O, whereas the MEP increases with age. Patients with NMDs have reduced respiratory muscle strength. The reduction in muscle strength does not correlate well with global muscle strength but, instead, with the distribution of weakness; respiratory muscle strength is better preserved in those patients with distal muscle weakness than in those with proximal muscle weakness.

One simple method of assessing the interplay between pump function and load is the measurement of the forced vital capacity (FVC) and fractional lung volumes. In boys with DMD, the relationship between the absolute value of FVC and age can be divided into 3 epochs: one of gradual increase coincident with their ambulatory period, followed by a plateau phase at 10 to 12 years when they become confined to wheelchairs, and then a gradual but persistent decline thereafter. When the FVC is described as a percent of the predicted value, however, it is lower than normal and diverges from the normal curve over time. The decline in FVC to a value of <1 L may also predict mortality in patients who do not receive assisted ventilation.

Patients with NMDs demonstrate a restrictive pattern when fractional lung volumes are measured. There is a reduction in total lung capacity, vital capacity, and the expiratory reserve volume. Residual volume (the volume of air that remains in the lungs after a maximal, complete expiratory maneuver), in contrast, can actually be elevated when the respiratory muscles are too weak to deform the chest wall inward to deflate the lungs fully. These patterns will be exaggerated in children with NMDs who also develop scoliosis. Forced expiratory flows are typically reduced in proportion to lung volume so that the ratio of the forced expiratory volume in the first second (FEV₁) to FVC is normal or high.

In the assessment of patients with reversible respiratory failure, respiratory muscle strength (the MIP) has been shown to be a poor predictor of successful liberation from mechanical ventilation, probably because strength reflects an immediate, short-term characteristic of the muscles. The respiratory muscles must generate force repeatedly without a protracted period of rest. Thus, a more important indicator of respiratory pump
output might be the tendency for the muscles to fatigue. The human diaphragm will fatigue in <60 minutes when the pressure it must generate ($P_{di}$) is $>40\%$ of the maximal pressure it can generate ($P_{dimax}$). The time to fatigue also depends on the amount of time the diaphragm must contract ($T_i$) (during inspiration) in relation to the total respiratory cycle time ($T_{tot}$). The product of these 2 ratios, $P_{di}/P_{dimax} \times T_i/T_{tot}$ is the tension-time index of the diaphragm ($TT_{di}$). A $TT_{di}$ value of 0.15 correlates with a time to task failure of 45 minutes; the diaphragm will fatigue even sooner as values of $TT_{di}$ increase above 0.15. Under normal circumstances, the $TT_{di}$ is well below its critical value.

Any perturbation that would increase either the $P_{di}/P_{dimax}$ or $T_i/T_{tot}$ will also increase the likelihood for the development of diaphragm fatigue. Patients with NMDs are at risk for diaphragm fatigue for multiple reasons: the increased elastic load resulting from low pulmonary and chest wall compliance will increase $P_{di}$, whereas respiratory muscle weakness will lower the $P_{dimax}$. Because the response of patients with NMDs to hypercapnia or hypoxia is one of tachypnea, the $T_{tot}$ will be reduced. If patients with bulbar weakness develop upper airway obstruction (for instance, during rapid eye movement [REM] sleep), $T_i$ will be prolonged.

The tension-time index of all of the respiratory muscles ($TT_{mus}$) is analogous to the $TT_{di}$, but it is obtained noninvasively and includes all of the muscles of inspiration. Here, the pressures used are mean inspiratory pressure at the mouth ($Pi$) and MIP, in place of $P_{di}$ and $P_{dimax}$, respectively. The $TT_{mus}$ has been shown to be abnormally elevated in children with NMDs, chiefly because of a reduction in the MIP. The critical value of the $TT_{mus}$ that predicts respiratory muscle fatigue is not known, but the measurement is an integrated index that reflects load, output, and breathing pattern. It may be useful when performed serially to predict impending respiratory muscle failure before it is clinically evident.

**CLINICAL SEQUELAE OF IMPAIRED RESPIRATORY MUSCLE FUNCTION**

There is a typical progression of respiratory symptoms in patients with NMDs. Initially, because of respiratory muscle weakness and chronic low-volume breathing, patients have impaired airway clearance and develop atelectasis. A normal cough requires a precough inspiratory effort to 60% to 90% of total lung capacity followed by glottic closure and compression of the thoracic gas. The glottis then opens, and expiratory muscles expulse air from the lungs at high flow rates. The high pleural pressures also briefly compress the airways, resulting in short flow “spikes” or supramaximal flow transients that help shear mucus from airway walls. Respiratory muscle weakness and bulbar dysfunction can reduce cough effectiveness by limiting the precough inspiration, impairing glottic closure, and reducing peak cough flows. Expiratory muscle weakness can also reduce or eliminate supramaximal cough transients. Adults who cannot generate peak flows during assisted cough of at least 270 L/min when well or 160 L/min when ill are considered to be at risk for recurrent pneumonias. In addition, absence of cough transients has been associated with increased mortality rates in adults with NMDs.

Cough peak flows, however, are age and size dependent, and the cutoff values of cough peak flow for adequate secretion removal in children are not known. Furthermore, there is a maturational stiffening of the central airways; younger children may still be able to generate supramaximal flow transients even at lower pleural pressures, because their airways are more compliant than those of adults.

Patients with progressive neuromuscular weakness will eventually develop sleep-disordered breathing. Most commonly, patients will hypoventilate because of their weakness and low tidal volume breathing. This problem will likely be accentuated during REM sleep, when intercostals and accessory muscles do not contribute to ventilatory effort. Those patients with upper airway muscular weakness or bulbar dysfunction can also demonstrate obstructive apneas during REM sleep. Both hypoxemia and hypercapnea result from these breathing derangements during sleep. These disturbances result in frequent arousals, reduced sleep efficiency, and eventual sleep deprivation. Once nocturnal hypercapnea is present, if ventilatory support is not introduced, diurnal hypercapnea inevitably will follow.

**CONCLUSIONS**

Abnormalities of the static and dynamic properties of the respiratory system have been well described for both children and adults with NMDs. These abnormalities, when untreated, result in stereotypical and interrelated clinical problems including impaired airway clearance, abnormal nocturnal ventilation, and, ultimately, diurnal respiratory failure. There are important physiologic differences between children and adults with NMDs, and those differences lend insights into possible causes of progression of respiratory dysfunction. Importantly, recognizing those maturational differences can also lead to interventions that could limit or prevent some of the respiratory complications described in patients with NMDs.

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