INTRODUCTION

Respiratory failure in children with neuromuscular disease can be divided into two forms, each with different implications for therapy: failure of the lung and failure of the respiratory system pump. Lung failure is often primarily manifested by hypoxemia resulting from intrapulmonary shunting, with or without hypercarbia due to excessive dead space ventilation. Pump failure is reflected in ventilatory failure that is primarily manifested by hypercarbia. Pump failure can further be categorized as arising from central depression of the respiratory controller, mechanical defects in the respiratory pump, and respiratory muscle fatigue. These various forms of respiratory failure are outlined in Fig. 1.1

LUNG FAILURE

Lung failure in patients with neuromuscular disease is most often the result of recurrent pneumonias, usually secondary to chronic aspiration. Aspiration can occur either from above, i.e. during swallowing or from below, i.e. during episodes of gastroesophageal reflux.

Swallowing function is frequently affected in patients with neuromuscular disease, leading to aspiration from above. During a normal swallow, the soft palate elevates, preventing food from coming back out of the nose. The airway elevates during a swallow, thus apposing it against the inferior surface of the epiglottis, largely preventing aspiration into the trachea. The cricopharyngeal muscles dilate allowing the food bolus to pass into the oesophagus, initiating the first peristaltic wave. There are over twenty motor neurons in the brain stem that fire sequentially in order to allow a normal swallow to occur. It is not surprising that in patients with neuromuscular disease, swallowing dysfunction can often lead to aspiration.

Furthermore, when children with neuromuscular disease have gastroesophageal reflux, the re-appearance of a large bolus of food and/or stomach contents from the oesophagus into the pharynx results in a high risk of aspiration. Recurrent aspiration over years or a lifetime can lead to chronic end stage lung disease. This is due to repeated infections that occur when oropharyngeal flora are carried to the lungs with aspirated saliva, solid and liquid food during swallowing, and stomach contents during reflux episodes. In addition, acidic stomach contents cause direct chemical toxicity to the airways. The aspiration of mouth aerobic and anaerobic organisms, and, in patients with artificial airways or recurrent nosocomial exposure, gram negative organisms, can lead to recurrent pneumonias. Eventually, many patients with neuro-
muscular disease develop bronchiectasis and pulmonary fibrosis. Indeed, respiratory failure is the most common reason for early demise in patients with neuromuscular disease.

PUMP FAILURE

The respiratory pump must move air into the lungs, overcoming the elastic and resistive forces of the lungs and chest wall. Pump failure can occur because the respiratory muscles are weak, fatigued, or both. In addition, if the load against which the pump must operate is increased, this can lead to pump, and respiratory, failure as well (Fig. 2). It is useful to consider factors which affect the load and factors which affect the respiratory pump separately.

Factors which increase the respiratory load

If lung compliance is low, the pressures necessary to change lung volume are increased. This presents a substantial load against which the pump must operate. Studies in patients with neuromuscular disease have confirmed low lung compliance. The low lung compliance in patients with neuromuscular disease probably arises from a combination of factors. Recurrent aspiration with resulting fibrosis is one. However, detailed studies by Detroyer and Heilporn have shown that while lung compliance is low in patients with neuromuscular disease, when lung volume changes are expressed as a percent of the total lung capacity of the patient, compliance is actually normal. This would indicate that while loss of alveolar volume leads to decreases in lung compliance, the alveoli that remain have relatively normal elastic properties. Nonetheless, the work of breathing necessary to increase lung volumes for given minute ventilation is greater if lung compliance is low.

In addition to the lungs, the chest wall itself can have abnormally low lung compliance, leading to increased work that the respiratory pump must perform. Studies have shown that in adults with neuromuscular disease, rib cage compliance is substantially reduced while abdominal compliance is slightly elevated. However, the net effect is a reduction of chest wall compliance in patients with neuromuscular disease.

Interestingly, infants with neuromuscular disease have high chest wall compliance. Thus, over the lifespan, the chest wall transitions from a high compliance state to a low compliance state. While the low compliance state of adults causes increased work of breathing, excessively high chest wall compliance leads to problems of its own. A highly compliant chest wall is unable to withstand the negative pleural pressures generated during inspiration, and may collapse inwards causing paradoxical motion of the rib cage and abdomen. This resulting inefficiency of ventilation can actually increase the work of breathing.

Factors which affect the respiratory pump

Normal pump function

In addition to the above considerations of increased load, patients with neuromuscular disease usually have respiratory muscle weakness leading to weak respiratory pumps. In order to best understand abnormal respiratory muscle function, it is first necessary to understand how the respiratory muscles operate normally. The diaphragm is the major muscle of inspiration in both infants and adults. The most commonly recognized action of the diaphragm is that of a piston, which decreases intrathoracic pressure, thus drawing air into the lungs. The diaphragm, however, has two other important actions. First, a large part of the abdominal contents actually reside within the thoracic cage and a substantial portion of the diaphragmatic area is apposed against the inner rib cage wall. When the diaphragm contracts, there is substantial increase in the intra-abdominal pressure which thus increases lower rib cage transverse dimensions. Second, the area of apposition of the diaphragm has an effect on the lower ribs on which it inserts. When the diaphragm contracts, the area of apposition causes an upward vertical force on the lower ribs. Because the lower ribs are oriented downwards, an upward action on the ribs also causes them to move outward (the so called

apparatus may not be up to the task of increasing minute mechanical system, even if drive were normal, the ventilatory dioxide retention. This does not, however, necessarily imply the output of their ventilation sufficiently to eliminate carbon neuromuscular disease re-breathe CO2, they are unable to increase Respiratory drive in neuromuscular disease

The weak and inefficient respiratory muscles lead to a susceptibility to paradoxic breathing, i.e. asynchronous motion between the rib cage and abdomen. Normally, during inspiration, both the rib cage and the abdominal walls move outwards. In patients with neuromuscular disease, when the abdomen moves out the rib cage often moves in and vice versa. One can use paradoxic motion to assess which muscle groups are primarily being affected by weakness. When the abdomen moves out during inspiration and the rib cage moves in, weakness of the intercostal muscles can be inferred. When the opposite happens, i.e., the abdomen moves in on inspiration and the rib cage moves out, weakness of the diaphragm can be inferred (Fig. 3). Although paradoxic respirations from either cause may look the same, by noting the phase of respiration during which the abdominal and rib cage compartments move either out or in, the diagnosis of either diaphragmatic or intercostal muscle weakness can be made.

Respiratory drive in neuromuscular disease

Most studies have demonstrated that when patients with neuromuscular disease re-breathe CO2, they are unable to increase the output of their ventilation sufficiently to eliminate carbon dioxide retention. This does not, however, necessarily imply abnormal respiratory central drive. Due to the limitations in the mechanical system, even if drive were normal, the ventilatory apparatus may not be up to the task of increasing minute ventilation sufficiently to eliminate the excess carbon dioxide.

Studies that measure a response to hypercarbia other than ventilatory output, i.e. the P100 (pressure measured at the mouth 100 milliseconds following an inspiratory occlusion) have in fact shown that in patients with muscular dystrophy, for example, ventilatory drive is often intact. Although the P100 is a pressure response to carbon dioxide retention, the pressure measured during a P100 is usually substantially below the threshold of weakness that most patients with neuromuscular disease have, and therefore it will increase appropriately during carbon dioxide re-breathing.

Respiratory muscle fatigue

One convenient way to describe the tendency of the respiratory muscles to fatigue is by measurement of the tension time index. Respiratory muscle fatigue is defined as the inability to sustain contractile force in the face of a constant load. Bellemare and Grassino calculated the tension time index of the diaphragm as the ratio of diaphragmatic pressure during a given breath compared to maximal transdiaphragmatic pressure during an occlusion (Pdi/Pdi max) multiplied by the duty cycle, defined as the inspiratory time divided by the total respiratory cycle time (Ti/Ttot). The tension time index is a dimensionless product of these two terms and reflects the likelihood that the respiratory muscles will fatigue. In general, the higher the diaphragmatic pressure as a function of maximal pressure the diaphragm can sustain, the more likely the diaphragm is to fatigue. Similarly, if the inspiratory time (the time in which the diaphragm is operating) is high relative to the total cycle time, this will also lead to a tendency towards diaphragmatic fatigue. Measurement of the tension time index of the diaphragm requires measuring transdiaphragmatic pressures, i.e. with an oesophageal and a gastric catheter. A non-invasive analogue of the tension time index of the diaphragm, the tension time index of the respiratory muscles, has been described by Ramonatxo et al., and yields a similar concept for all of the inspiratory muscles as a whole, rather than just for the diaphragm. In children with neuromuscular disease, the tension time index of the respiratory muscles is elevated, signifying a greater tendency toward respiratory muscle fatigue (Fig. 4). In such children, the increased tendency is almost entirely due to the elevated ratio of mean inspiratory pressure to maximal inspiratory pressure.

Figure 3. Paradoxical breathing occurs (A) in the setting of intercostal muscle weakness, in which case the chest wall moves in during inspiration, and (B) in the setting of diaphragmatic weakness, in which case the abdominal wall moves in during inspiration. Adapted from: De Troyer A and Loring SH. Action of the respiratory muscles. In: Macklem PT and Mead J, eds. Handbook of Physiology. The Respiratory System. Mechanics of Breathing. Section 3, Volume III, Part 2. Bethesda, MD, American Physiological Society, 1986.

ASSSESSMENT OF RESPIRATORY FUNCTION IN NEUROMUSCULAR DISEASE

Lung and respiratory system function in patients with neuromuscular disease can be assessed by standard pulmonary function tests, the ability to generate flow transients, and by tests of respiratory muscle function, notably respiratory muscle strength and susceptibility to fatigue. The latter is best measured by the tension time index, described above, and will not be further discussed here.

Pulmonary function tests in patients with neuromuscular disease show characteristic patterns. Notably in the flow volume curve, the peak flow is low due to respiratory muscle weakness. In addition, there is a characteristic “fall off” of flow at residual volume, probably related to expiratory muscle weakness and inability to distort the chest wall inward. Vital capacity in patients with neuromuscular disease is reduced and in patients with Duchenne muscular dystrophy (DMD) the growth of vital capacity is markedly decreased compared to normal controls.10 Vital capacity falls as weakness progresses. Phillips et al. showed that average life expectancy was only three years following the fall of vital capacity to one liter.11

Flow transients are a marker of a patient’s ability to produce an effective cough (Fig. 5). A normal cough requires three phases: a deep inspiration, a period of glottic closure, and a forced expiration. This results in shear forces sufficient to effectively expel the mucus from the airways. The ability to cough is closely mirrored by the ability to produce flow transients, i.e. flow rates which are higher than the maximal flows attained during a forced expiratory manoeuvre. These occur at the beginning of the manoeuvre (cough peak flow) and are also present at lower lung volumes as the subject coughs repeatedly without inspiring. These flow transients are probably related to airway collapsibility and are crucial in producing the shear forces necessary for effective airway clearance. An inability to generate cough flow transients has been associated with increased mortality in adults with neuromuscular disease.12 Studies have shown that flow transients are intimately related to gastric pressures produced during a cough.13

In patients with neuromuscular disease, forced oscillometry may be a useful way of assessing lung function. This technique may be especially useful in those patients who have trouble cooperating with forced expiratory manoeuvres. During input oscillometry, a face mask is attached to the patient’s mouth and nose and low pressure flow oscillations are introduced at the airway opening. By measuring the impedance, Z, of the respiratory system, inferences can be made about the elastic properties, the resistive properties and the inertive properties of the system (See Glossary). There have been few studies of respiratory system impedance in older patients with neuromuscular disease,14 but none in children. However, studies of chest wall strapping, in which chest wall compliance is reduced as it is in adults with neuromuscular disease, may provide a useful model. In such studies, the elastic impedance is increased thereby leading to an increased resonant frequency.15

Respiratory muscle strength

Respiratory muscle strength is, by definition, reduced in patients with neuromuscular disease. Interesting studies in patients with myasthenia gravis have shown successively decreasing maximal pressures in these patients with successive respiratory efforts. Treatment with pyridostigmine can reverse these trends.16

Maximal respiratory pressures can now be measured in infants during crying17 and during occlusions and have been shown to be decreased in infants with neuromuscular disease as well.18

Recently, there has been interest in measuring sniff pressures in patients with neuromuscular disease. Since such patients have difficulty maintaining a seal with an oral mask, occluding one nostril and having the patient sniff through the other often leads to pressures that are at least as great as maximal pressures measured at the mouth and may be easier to perform. Studies have shown good correlation between nasal sniff pressures and vital capacity in patients with neuromuscular disease, and good correlations between maximal pressure measured at the mouth and nasal sniff pressures.19

IMPLICATIONS FOR TREATMENT

The above considerations have important implications for treatment of reduced airway clearance, and the roles of respiratory muscle training and ventilatory assistance. Because patients with neuromuscular disease have insufficient respiratory muscle strength to produce adequate cough peak flows, the invention of mechanical in/exsufflators has provided a very useful tool in their therapeutic armamentarium. These devices give positive followed by negative pressures, which allow patients to inhale and exhale more forcefully and simulate a cough manoeuvre.

Respiratory muscle training has been shown to have beneficial effects in terms of maximal inspiratory pressures in patients with myasthenia gravis20 and patients with DMD.21 Patients with myasthenia gravis increased maximal inspiratory and expiratory pressures after periods of training (Fig. 6).22 Furthermore, respiratory muscle training reduces the sense of dyspnoea as measured by the Borg Visual Analogue Scale in patients with DMD.21 Whether or not such improvements in respiratory muscle strength can reduce fatigue and reduce morbidity of chest disease in such patients remains to be determined.

There is some indication that steroid treatment with prednisone or deflazacort may improve respiratory muscle function in

Figure 5. Flow transients: A marker of cough ability. Flow volume curve on the left reflects the absence of cough induced flow transients; curve on the right reflects the presence of flow transients. From: Polkey et al., Am J Respir Crit Care Med, 158:734, 1998.

Figure 6. Myasthenia Gravis. Effects of training. Repetitive maximal respiratory efforts result in decreasing maximal pressures over time. However, training can improve maximal pressures achieved. From: Weiner et al., Can J Neurol Sci 25:236, 1998.
DMD. A Cochrane analysis has shown improved peripheral muscle strength and prolongation of ambulation in children with DMD treated with corticosteroids. Daftry et al. have shown improved respiratory muscle strength, maximal voluntary ventilation and cough peak flow with steroid treatment in DMD patients. In addition, steroid treatment has been shown to cause slower decline in lung function, delayed the onset of the need for mechanical ventilation, and improved sternocleidomastoid muscle (an accessory muscle of inspiration) MRI characteristics. Non-invasive and invasive nocturnal ventilation have been employed as useful measures in treating respiratory muscle fatigue in patients with neuromuscular disease. Nocturnal ventilation can alleviate signs and symptoms of daytime hypercarbia, fatigue, dyspnoea, morning headache, sleep dysfunction, and hypersomnolence. There is an interesting carry-over effect of combined respiratory muscle training and rest also need to be further studied especially in children. The role of combined respiratory muscle training and rest should help reduce respiratory muscle fatigue. Finally, the cellular and molecular bases of respiratory muscular strength need to be better defined in order to devise better treatments, both physical and pharmacologic.

Glossary

**Compliance (C)**: An index of the ease with which a structure can be distended, or, in the case of the respiratory system, can be filled with air. Mathematically, the ratio of the volume change to the distending pressure.

$$C = \frac{\Delta V}{\Delta P}$$

Compliances of each of the parts of the respiratory system can be calculated. Thus:

- Respiratory System Compliance (Crs)
- Lung Compliance (C)

**Chest Wall Compliance (Cw)**, comprised of abdominal compliance (Cab) and rib cage compliance (Crc)

**Equation of Motion**: The equation describing the pressure necessary to distend the respiratory system during inspiration. In order to distend the system, pressure must overcome the elastance (E), resistance (R) and inertance (I) of the system:

$$P = E \times V + R \times V' + I \times V''$$

Where $V$ is volume, $V'$ is flow and $V''$ is acceleration. Taking each of these terms in turn:

**Elastance (E)** is the pressure necessary to overcome the forces opposing volume distortion of the system. $E = \Delta P/\Delta V$. Elastance is the reciprocal of compliance (q.v.), $E = 1/C$. In an oscillatory system, flow swings precede pressure swings in an elastic element by 90° (i.e., the system must be distended before it can develop a back pressure).

**Resistance (R)** is the pressure necessary to overcome the forces opposing flow into the system. $R = \Delta P/V''$

where flow ($V'$) is a volume moved per unit time ($V' = dV/dt$).

In an oscillatory system, pressure swings are in phase with flow swings.

**Inertance (I)** is the pressure necessary to initiate, or accelerate, motion in a system that has mass. In the case of the respiratory system, the tissue mass and the mass of gas in the system both contribute to the inertance. $I = \Delta P/V''$

where acceleration ($V''$) is the change of flow per unit time ($V'' = dV/dt$).

In an oscillatory system, pressure swings precede flow swings by 90° (i.e., pressure must be applied in order to accelerate the mass).

**Fatigue**: The inability of a muscle to sustain the same tension in the presence of a constant load.

**Impedance (Z)**: The entire pressure cost of flow, necessary to overcome the elastic, resistive and inertive elements in a system. During sinusoidal oscillations the impedance is found by dividing the peak-to-peak pressure swings by the peak-to-peak flow swings.

$$Z = \frac{\Delta P}{\Delta V}$$

The elastic and inertive elements of the impedance, in which pressure swings are out of phase with flow swings, together comprise the Reactance (X). The resistive element, in which pressure swings are in phase with flow swings, comprises the Resistance (R).

As frequency increases, for a given minute ventilation, tidal volume falls ($VE = f \times VT$), and elastic impedance decreases. Conversely, as frequency increases, inertive impedance increases due to the increasing frequency of accelerations and decelerations.

**Maximal Inspiratory Pressure (MIP)**: The maximal pressure that can be generated at the mouth during an occluded inspiratory effort, a measure of inspiratory muscle strength. Usually measured at residual volume (RV) or at functional residual capacity (FRC).

**Maximal Expiratory Pressure (MEP)**: The maximal pressure that can be generated at the mouth during an occluded expiratory effort, a measure of expiratory muscle strength. Usually measured at total lung capacity (TLC) or at FRC.

**Maximal sniff pressure (Prn)**: Pressure measured at one nostril (with the other occluded) during a maximal inspiratory effort against an occlusion. An alternative method of measuring inspiratory muscle strength in certain patients, such as those with neuromuscular disease, in whom the ability to maintain a seal around a mouthpiece is compromised.

$$P_{rn}$$: The pressure measured at the mouth 100msec after the onset of an occlusion at the beginning of a normal inspiration. This is an index of respiratory drive. In addition, it has been used as a non-invasive way of measuring the average inspiratory pressure during a breath in order to measure Tension Time Index.
(q.v.), by estimating the mean pressure generated by the inspiratory muscles, assuming a linear fall in mouth pressure during inspiration.

Resonant frequency (fo): During forced oscillations, as the inertive impedance (q.v.) rises and the elastic impedance falls with increasing frequency, there comes a frequency at which they are of equal magnitude. At this point, since their pressure swings are out of phase with each other by 180°, these pressure swings cancel each other out, and the only ones that are left are those through the resistive element. Fo is the frequency at which elastance and inreactance are of equal magnitude and cancel each other out. Impedance is therefore at a minimum at this frequency, and the only impedance left is due to resistance.

Tension Time Index (TTI): A measure of the likelihood that inspiratory muscle(s) will experience fatigue. In the case of the diaphragm, the TTI is a dimensionless number expressed by the following equation:

TTI diaphragm = Pdi/Pdmax x Ti/Ttot

where

Pdi is the mean transdiaphragmatic pressure during inspiration
Pdmax is the maximal transdiaphragmatic pressure that can be generated voluntarily
Ti/Ttot is the duty cycle of the diaphragm, i.e. the inspiratory time during which the diaphragm is contracting, divided by the total respiratory cycle time.

In the case of respiratory muscles as a whole, the TTI is a dimensionless number expressed by the following equation:

TTMus = Pmus/MIPFRC x Ti/Ttot

where

Pmus is the mean pressure generated by all the inspiratory muscles during inspiration, measured at the mouth. This is done by extrapolating the P100 to end inspiration, and finding the time averaged mean
MIPFRC is the maximal inspiratory pressure measured at the mouth at functional residual capacity

REFERENCES