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Neuromuscular disorders and chronic ventilation

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A B S T R A C T

Morbidity and mortality have decreased in patients with neuromuscular disease due to implementation of therapies to augment cough and improve ventilation. Infants with progressive neuromuscular disease will eventually develop respiratory complications as a result of muscle weakness and their inability to compensate during periods of increased respiratory loads. The finding of nocturnal hypercapnia is often the trigger for initiating non-invasive ventilation and studies have shown that its use not only may improve sleep-disordered breathing, but also that it may have an effect on daytime function, symptoms related to hypercapnia, and partial pressure of CO_2. It is important to understand the respiratory physiology of this population and to understand the benefits and limitations of assisted ventilation.

1. Introduction

Neuromuscular disorder (NMD) may result from injury or metabolic, or genetic abnormalities of the central or peripheral nervous system. Cardiac and respiratory complications continue to be the most frequent causes of morbidity and mortality. Early initiation of non-invasive ventilation (NIV) and therapies to improve cough and manage secretions may preserve muscle function, alter the natural progression of the disease [1] and reduce hospitalizations [2]. Mechanical ventilation is used in patients with neuromuscular disorders to treat extrathoracic and central intrathoracic airway obstruction, correct existing respiratory failure, and to prevent impending respiratory failure. Technologic advances in invasive and non-invasive ventilation and airway mucus clearance augmentation have led to reduced morbidity and mortality in these patients over the last several decades. This article describes the physiologic mechanisms for pulmonary complications of neuromuscular disease and the rationale for utilizing mechanical ventilation in these patients.

2. Pulmonary sequelae of neuromuscular disease

Infants presenting with hypotonia and/or unexplained delay in gross motor skills development require diagnostic evaluation to determine the etiology. The rapid expansion in the knowledge of genetic disorders, underlying gene mutations, and availability of DNA-based diagnostic tests have facilitated early diagnosis of spinal muscular atrophy, congenital muscular dystrophies, several forms of congenital myopathies, congenital myotonic dystrophy, and other less frequently occurring diseases without the need for muscle biopsy [3]. Whereas the impairment in some neuromuscular conditions is transient (congenital myasthenia gravis and infantile botulism), it is sustained or progressive in the majority. For those whose neuromuscular weakness is progressive, it is expected that over time their respiratory status will become compromised. They develop an ineffective cough, placing them at risk for recurrent infections and atelectasis [3,4]. Weak accessory respiratory muscles and reduced upper airway tone lead to sleep-disordered breathing and hypoventilation [5]. These disturbances create fragmented sleep because of frequent arousals and decreased sleep efficiency, leading to sleep deprivation [6]. Once nocturnal hypercapnia develops, diurnal hypercapnia typically follows within two years if mechanical ventilatory support is not initiated [7]. Thus, nocturnal hypercapnia is often the precipitating event for initiation of non-invasive ventilation.

3. Respiratory dysfunction

Respiratory failure occurs when the lungs and respiratory pump are unable to meet the metabolic demands of the body. The respiratory pump comprises the thoracic wall, respiratory muscles, and the central nervous system respiratory control center. Thus, mechanical limitations of the chest and abdominal wall, respiratory muscle fatigue, and depression of the respiratory control center

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may lead to pump failure [8]. In patients with NMD, hypercapnic respiratory failure often results from pump dysfunction; however, this is often exacerbated by parenchymal lung disease leading to concomitant hypoxemia. Parenchymal disease frequently develops as a consequence of acute or recurrent lower respiratory infections and/or aspiration of feeds or gastroesophageal refluxate.

Similar to preterm infants, the difference between the compliance of the chest wall and that of the lung is amplified in infants with muscle weakness [9]. Neonates, however, are normally able to overcome this disadvantage by contracting their intercostal muscles in order to stabilize the chest wall and prevent inward movement of the thorax with each contraction of the diaphragm. In patients with NMD, their ability to compensate for this discrepancy is limited as a consequence of sub-optimal contractility of their diaphragm and intercostal muscles.

Studies measuring the P100 (pressure measured at the mouth 100 ms following an inspiratory occlusion) in patients with NMD suggest that their respiratory drive is normal, but their altered mechanics do not allow them to respond adequately to hypercarbia [10]. In one study, patients with Duchenne muscular dystrophy increased their respiratory rate compared with age-matched controls who increased their tidal volumes in response to hypercapnea and hypoxia [11]. This shortcoming increases their risk for hypoventilation and muscle fatigue, especially in the setting of an increased respiratory load. Over time, hypercarbia and respiratory failure ensue.

The tension time index (TTI) was first calculated by Bellemare and Grassino to describe the tendency of the diaphragm to fatigue [12]. The formula was described as follows:

$$TTI = P_{di}/P_{di\ max} \cdots T_i/T_{tot},$$

where P_{di} is the mean diaphragmatic pressure calculated during a mouth occlusion, $P_{i\ max}$ is the maximal transdiaphragmatic pressure, T_i is the inspiratory time, and T_{tot} is the total time of the respiratory cycle. The higher the diaphragmatic pressure and the longer the inspiratory time relative to total time of the respiratory cycle, the more likely the diaphragm is to fatigue. In children with neuromuscular disease, the tension time index is elevated, suggesting that they are more likely to experience respiratory muscle fatigue [13]. This may be attributed to the elevated ratio of mean inspiratory pressure to maximum inspiratory pressure [14].

Non-invasive and invasive nocturnal ventilation have been used to treat respiratory muscle fatigue in patients with neuromuscular disease. It may also improve daytime hypercarbia, morning headaches, fatigue, and hypersomnolence (Box 1), reducing morbidity in this population [14,15]. It may also improve daytime alertness, promoting growth and development [16]. Nocturnal ventilation may also lower diurnal partial pressure of CO_2 (PCO_2) by allowing rested muscles to work more efficiently during the day and by reducing carbon dioxide levels which allow the kidneys to excrete bicarbonate, preventing metabolic alkalosis and lowering the PCO_2 set-point in the central nervous system's respiratory control center [14]. If given intermittently during the day, it may reduce muscle fatigue and improve endurance [17].

Box 1
Benefits of mechanical ventilation in patients with neuromuscular disease.

- Improves sleep-disordered breathing
- Stabilizes the chest wall
- Prevents atelectasis
- Improves daytime function
- Decreases morbidity and mortality
- Improves patency of the upper airways
- Normalizes gas exchange
- Reduces symptoms due to chronic hypoventilation
- Resets the sensitivity of central chemoreceptors
- Reduces frequency of hospitalization
- Slows chest wall deformity and decline in lung function
- Improves quality of life
- Reduces daytime somnolence
- Improves airway clearance

4. The evolution of mechanical ventilation in patients with neuromuscular disorders

The need for mechanical ventilation emerged during the outbreak of the poliomyelitis epidemic in the early-to mid-twentieth century. The development of a negative pressure ventilator, often referred to as an “iron lung,” decreased mortality by about 50% [18]. Patients were placed inside a cylindrical tank and a pump was used to generate a vacuum within the vessel. This negative pressure facilitated expansion of the chest wall, resulting in decreased intrapulmonary pressure and a pressure gradient causing air to flow into the lungs. Elastic recoil of the lung and chest wall resulted in passive exhalation when the vacuum pressure was released. Biphasic cuirass ventilation is an updated version, where a shell is worn over the chest, and a bi-directional pump augments both inspiration and exhalation. This type of ventilator also has the ability to assist with airway mucus clearance by way of a “secretion clearance mode.” During the vibration phase, shear forces are generated and secretion viscosity is reduced. In the cough phase, sustained inflation (negative pressure) is alternated with positive pressure that compresses the thorax, producing a forced exhalation maneuver.

In 1910, Green and Janeway introduced the “rhythmic inflation apparatus,” in which a patient's head was placed into the device and sealed at the neck via positive pressure applied to the patient's head. This was one of the earliest forms of NIV and used to provide support for a short period of time. By the early 1980s, case reports indicated that NIV could be used to chronically ventilate patients with diseases such as NMD. This type of support initially only provided volume control–intermittent mandatory ventilation, but over time newer machines were able to provide pressure control–intermittent mandatory ventilation. Today, ventilators can provide more sophisticated modalities of ventilation both invasively and non-invasively, while optimizing patient–ventilator synchrony.

4.1. Non-invasive positive pressure ventilation

Patients with NMD often have normal lung parenchyma, so the elastic recoil of the lung (P_{el}) and airway resistance (P_{aw}) are normal [18]. However, their muscular pressure (P_{mus}) is reduced, resulting in decreased maximal airflow and lower lung volumes. The application of continuous positive airway pressure (CPAP) may alter chest wall mechanics and reduce a patient's work of breathing by stabilizing the chest wall and preventing inward collapse during inspiration. It does not help to maintain ventilation in patients with underlying muscle weakness and is therefore usually not a sufficient form of support in patients with neuromuscular disorders.

4.2. Non-invasive positive pressure ventilation

One of the main goals of non-invasive positive pressure ventilation (NIPPV) is to provide ventilatory support and avoid the need for an artificial airway. Similar to CPAP, bi-level positive airway pressure (B_LPAP) supplies a baseline supra-atmospheric pressure,

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