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REVIEW

Enhancing respiratory function in neuromuscular disease: the role of non-invasive ventilation. A narrative review

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Neuromuscular diseases (NMDs) comprise a heterogeneous group of conditions characterized by extreme progressive muscle weakness leading to respiratory failure. Noninvasive mechanical ventilation (NIV) has emerged as a cornerstone in the management of respiratory complications associated with NMDs. This review aims to elucidate the role of NMV in respiratory function, improving quality of life, and prolonging survival in individuals with NMD. The physiological basis of respiratory impairment in NMDs, principles of NMV application, evidence supporting its efficacy, patient selection criteria, and potential challenges in its application are discussed.

Key words: neuromuscular diseases, non-invasive ventilation, quality of life, survival, respiratory failure

Introduction

Neuromuscular diseases (NMDs) represent a heterogeneous group of disorders acquired or inherited (genetic) affecting the nerves, neuromuscular junctions, and muscles, leading to progressive muscle weakness and respiratory impairment. Neuromuscular diseases occur at different ages and progress at varying rates, making it difficult to provide a single set of guidelines. Respiratory failure is a common and often life-threatening complication of NMDs, contributing significantly to morbidity and mortality [1-5].

The aim of this narrative review is to provide an overview of the effectiveness of non-invasive mechanical ventilation (NVM) as a means to improve respiratory function, enhance quality of life, and reduce long-term mortality in patients with neuromuscular disease. Noninvasive mechanical ventilation has introduced a new management of respiratory dysfunction in people with NMD, offering an effective intervention to support breathing.

Weakness of the respiratory muscles, whether associated with that of the bulbar muscles represents the typical pattern of respiratory impairment in NMDs. Weakness of inspiratory muscles leads to a progressive reduction in total lung capacity and vital capacity, while residual functional capacity appears normal or reduced. Weakness of inspiratory and expiratory muscles, in contrast, leads to an increase in residual functional capacity and residual volume [6]. With the progression of respiratory muscle weakness and the consequent increase in mechanical load, the adoption of rapid, shallow breathing allows a reduction in elastic work, decreasing the muscle tension required to generate an inspiratory act and the perception of dyspnea but leading, over time, to a state of alveolar hypoventilation.

Chronic respiratory failure (CRF) in NMDs generally manifests with initial nocturnal hypoventilation and sleep destructuring. Sleep respiratory disturbances may depend on the

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combined presence of respiratory muscle weakness, reduced supine lung volume, and intercostal muscle tone, while diaphragm tone decreases during NREM sleep but is maintained during REM, consequently, normal ventilation during REM sleep becomes dependent on diaphragmatic function. Finally, the activity of the pharyngeal dilator muscles--particularly the genioglossus decreases gradually during sleep, increasing upper airway resistance that reaches a maximum during REM sleep. Normally, sleep is characterized by a decrease in alveolar ventilation of 1-2 L/min caused mainly by a decrease in tidal volume, while the breathing pattern becomes shallow and irregular. As a result, PaCO2 increases and PaO2 decreases by 2-8 mmHg each, while the ventilatory response to hypoxemia and hypercapnia is reduced. In neuromuscular diseases, these changes become more pronounced during deep sleep and especially during the phasic REM stage. As hypoventilation continues, metabolic compensation through bicarbonate retention contributes to reduced sensitivity of the respiratory drive-in wakefulness, which, together with the progression of muscle weakness and reduced chemosensitivity of the respiratory control center also leads to the appearance of diurnal hypoventilation [7]. The potential benefits of chronic use of the NMV include improvements in gas exchange, sleep, quality of life, and survival [2,8,9].

The age of onset of respiratory impairment may vary depending on the rate of disease progression, whether congenital or acquired. Some diseases, such as Guillain Barré Syndrome (GBS) and Myasthenia Gravis (MG) are characterized by the sudden onset of acute respiratory failure. Amyotrophic Lateral Sclerosis (ALS) has unavoidable respiratory involvement, with a chronic-progressive course, sometimes very rapid. Diseases with variable or slowly progressive respiratory involvement are, for example, Myotonic Dystrophy type 1 (DM1), with onset of respiratory impairment in adolescence or adulthood. The congenital or myofibrillar myopathies, cingulate muscular dystrophy (LGMD), Becker's dystrophy (BMD), Facio-Scapulo-Humeral Dystrophy (FSHD), and Spinal Muscular Atrophy type 2 (SMA2) have a respiratory impairment with variable age of onset. In SMA2, only 40% of patients manifest respiratory failure, usually at school age. Developmental age diseases with rapidly progressive or fatal chronic respiratory failure include Spinal Muscular Atrophy Type 1 (SMA1), childhood classic Pompe disease, and congenital Myotonic Dystrophy. In these diseases, respiratory failure usually arises between 1-6 months of age. In Duchenne muscular dystrophy (DMD), respiratory failure presents a chronic-progressive course and generally follows the loss of ambulation. Post-polio syndrome (PPS), mitochondrial myopathies (MM), Charcoth-Marie-Tooth (CMT) and late-onset Pompe's disease present less frequently respiratory involvement at a variable age of onset [10]. Sullivan et al. [11] reports the effectiveness of CPAP via nasal mask for the treatment of obstructive sleep apnea as an effective alternative to tracheostomy, the treatment used until then. This new model of treatment also encouraged the market introduction of new ventilators that could be used outside the hospital. Invasive ventilation via tracheostomy was used traditionally, but if the upper airway is adequate, a wide variety of new devices and new interface models have been introduced. Since the 1990s, NMV has also been progressively used in intensive care for all types of acute respiratory failure as well as at home for cases of chronic respiratory failure e.g. for neuromuscular patients [12]. Since then, non-invasive mechanical ventilation (NMV) has been increasingly used to treat chronic hypercapnic respiratory failure in NMDs. Studies conducted in neuromuscular patients suggested an alleviation of symptoms of chronic hypoventilation in the short term and prolongation of survival. A recent Cochrane review stated that "long-term mechanical ventilation should be offered as a treatment option to patients with chronic respiratory failure due to neuromuscular diseases[1]. Recurrent episodes of nocturnal desaturation, often associated with hypercapnia, due to periods of hypoventilation especially during REM sleep, can profoundly affect the prognosis of patients with neuromuscular disorders (e.g., DMD, SMA, ALS) [13-16]. Several randomized controlled trials show that in ALS without severe bulbar dysfunction, NMV improves survival with maintenance and improvement in quality of life, including sleep quality. The survival benefit of NMV in this group is much greater than that of currently available neuroprotective therapy, such as riluzole [17,18]. DMD patients have a more predictable natural history than other neuromuscular disorders [19]. We observe a loss of lung volume especially when they begin to sit in a wheelchair; we observe desaturations during sleep first in the REM period in later adolescent years, until the onset of respiratory failure. Vianello highlighted that life expectancy without ventilatory support is about 9-10 months when DMD patients develop daytime hypercapnia [20]. In addition, without the use of cough assistance, many acute episodes of respiratory failure are precipitated by lung infections, as the progression of weakness of expiratory muscles and inspiratory muscles reduces the effectiveness of coughing and respiratory pump.

Another relevant type of NMD are Spinal Muscle Atrophies (SMA). Respiratory problems are the main cause of death in children with forms 1 and 2, and in a small percentage of those with SMA 3. In children with the severe form, bulbar involvement is also constant, and therefore swallowing also becomes problematic, with the risk of ab-ingestis pneumonia. From an etiopathological point of view, in SMA type 1 and 2, several key components lead to respiratory problems in SMA: the deficit in muscle pump function and the mechanical effect of scoliosis on the chest wall, paradoxical breathing determining impaired lung development, lead to a state of hypoventilation at first at night and then during the day, resulting in hypercapnia. The difficulty in expectoration also causes recurrent lung infections that can further aggravate the muscle strength deficit. Furthermore, swallowing deficits and gastroesophageal reflux, along with difficulty in coughing, can lead to aspiration of gastric contents directly into the lungs. Airway clearance through cough assistance, non-invasive or invasive ventilation, and adequate nutritional assistance are associated with longer survival in SMA1, 2 and 3. However, the choice of long-term ventilation in SMA1 patients is still debated. The discussion also concerns ethical issues, i.e., whether to undertake a care pathway aimed at prolonging survival by using either non-invasive ventilation or invasive ventilation via a tracheostomy.

Studies showed that NMV with airway clearance therapy, and cough assistance represent a standard practice for patients with neuromuscular respiratory failure. In patients with chronic respiratory failure and positive pressure, NMV is the preferred mode of ventilation. Specifically, Assisted-Pressure Controlled Ventilation (APCV) is the most used, with target tidal volume and inspiratory times set according to a defined range [24,25].

Among neuromuscular diseases, ALS plays a role of considerable importance. It is characterized by a degeneration of the first and second motor neurons, resulting in progressive paralysis of all body muscles, including those involved in important vital functions such as phonation, swallowing, and breathing. In ALS, life expectancy is generally between 2 and 5 years after the diagnosis and the most common cause of death is respiratory failure whose development slowly leads to increased arterial carbon dioxide partial pressure [26]. The association between sleep apnea and nocturnal hypoventilation causes compromising clinical symptoms like sleep disturbances, daytime fatigue, cognitive impairment, and depression [15,27,28]. In later stages, dyspnea and orthopnea may appear as well. In these cases, the use of non-invasive ventilation thanks to its non-invasiveness and good tolerability is regarded as an essential therapeutic component in ALS.

Search strategy

There were no restrictions on dates or study design. Literature selected for this narrative review was identified using the following terms in Pubmed/Medline and Embase: non-invasive ventilation, non-invasive ventilatory support, chronic respiratory failure, home ventilation, moto-neuron diseases and neuromuscular diseases. Retrospective, prospective, controlled, and non-controlled studies were included. Abstracts and/or clinical cases were excluded.

Principles of NIV Application and patient selection criteria

Several authors and scientific societies have established algorithms to determine the most suitable condition and timing of NIV initiation in ALS patients given the patient's clinical state along with their pulmonary function tests. The European Federation of Neurological Societies (EFNS) recommends initiation when symptoms and/or signs of respiratory insufficiency are present such as FCV < 80%, SNIP < 40cmH2O, nocturnal desaturation, or pCO2 > 45mmHg [29]. The American Academy of Neurology (AAN), on the other hand, recommends initiation when FVC < 50% and orthopnea [30]. However, in no case is it specified how spirometry should be performed i.e. whether supine or sitting, and this already may result in a bias in the result. We often find spirometry still normal if performed in a sitting position but pathological if performed in a supine position [31].

In patients with bulbar involvement and frontotemporal symptoms, poor compliance with NMV has been reported, and especially in frontotemporal patients survival does not change [32,33].

Guidelines have established how night-time evaluation should be included in the initial assessment of the patient since the early stages of the disease begin to manifest during the sleep phases.

Other authors [34–37] demonstrated how the ventilation start-up setting (out-patient, in-patient, or domiciliary) also implemented by the telemonitoring service, does not affect its effectiveness.

NMV requires the titration of the correct interface and ventilation mode, both patient-dependent. Nasal masks are generally well tolerated allowing easier interaction. However, given the nature of the disease, impairment of facial muscles is not rare, and an oro-nasal mask might be the best interface [38]. Alternatives to this kind of mask are the Mouthpiece Ventilation (MPV) and the Intermittent Abdominal Pressure Ventilation (IAPV).

Mouthpiece ventilation (MPV) is a modality that uses an interface mouthpiece that the patient holds with his lips when he wants to be supported during inspiration. Nasal and/or oronasal interfaces are the most used, but they can cause nose skin injury and claustrophobia. Mouthpiece ventilation avoids these problems and can be used for daytime ventilation in patients who use the ventilator for more than 16 hours a day. MPV is used as daytime ventilatory support in combination with other effective ventilation interface modalities for night ventilation by many neuromuscular patients. In some patients, the mouthpiece may cause gastric distension (no more than nasal interface), increased salivation, and sometimes vomiting [39-41].

Intermittent Abdominal Pressure Ventilation is indicated for neuromuscular disease a narrative review by Pierucci et al. underlined the advantages of IAPV as a useful alternative for daytime support. Intermittent Abdominal Pressure Ventilation contributes to improve gas exchange, reduce symptoms, and improve quality of life by reducing the incidence of pneumonia and avoiding the need for intubation and tracheostomy. This type of home ventilation consists of a portable ventilator and a comfortable, easy-to-wear abdominal corset with Velcro closures. Its operation is based on the cyclic inflation of a rubber bladder inside the corset that moves the diaphragm upward to expel air from the residual volume. In this way, air enters the lungs through the upper airway while gravity returns the diaphragm to its resting position [42-44].

These modalities allow a rotation of interfaces reducing the risk of facial pressure ulcers These modalities allow a rotation of interfaces reducing the risk of pressure ulcers on the face, the phenomenon of claustrophobia, and improving patients' quality of life and sense of autonomy.

Caregivers and decision-making

As previously outlined, neuromuscular diseases rapidly progressive such as ALS led to a rapid loss of crucial functions from both the motor and respiratory points of view. As a result, patients inevitably become dependent on the care provided by their caregivers, often made up of family members. It is therefore essential, in our opinion, to involve these people in decision-making processes and overall patient management. The use of NMV offers significant benefits in care, as it is easier to manage than invasive ventilation [45,46.]

Even though there is still no consistent evidence in the literature about telemonitoring, from a clinical point of view, its advantages have emerged. This system offers the possibility to check a patient's ventilation constantly and to promptly identify any problem. This approach will represent an important step forward in assisting patients with chronic respiratory diseases, enabling more efficient and personalized treatment management.

Conclusions

By providing effective ventilatory support, NMV improves respiratory function, enhances quality of life, and prolongs survival in individuals with NMDs. It aims also to compensate for diaphragm weakness,

alleviate hypercapnic symptoms, and improve patients' general condition and quality of life prolonging patient's survival of more than 13, 11, or 15.5 months in ALS patients.

Despite its efficacy, the widespread adoption of NMV in NMDs faces several challenges, including patient adherence, mask intolerance, air leaks, and device-related discomfort. Long-term use of NMV may also necessitate periodic adjustments in settings, mask fittings, and patient education to optimize therapeutic outcomes. Additionally, the availability of specialized respiratory equipment, home healthcare support, and caregiver training are critical factors influencing the successful implementation of NMV in the community setting.

Further research and clinical initiatives are warranted to refine the patient's selection criteria, optimize NMV strategies, and promote long-term adherence in individuals with NMDs.

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Author PB and AAMDB have given substantial contributions to the conception or the design of the manuscript, author EC, MP, AL, and author AAMDB to acquisition, analysis, and interpretation of the data. All authors have participated to drafting the manuscript, authors PB, AL and MM revised it critically. All authors read and approved the final version of the manuscript.

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