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Non-invasive ventilation in patients with progressive neuro-muscular disorders

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Respiratory failure (RF) is a major cause of morbidity and mortality among patients with progressive neuro-muscular disorders (NMD). Although evidence from controlled trials is lacking, administration of long-term non-invasive mechanical ventilation (NIV) appears to improve physiologic parameters, the quality of life and life-expectancy. A non-invasive approach to the management of tracheobronchial secretions, based on the combination of expiratory muscle aid and NIV, can reduce the need for hospitalisation during chest infection, avoid intubation and facilitate extubation of patients with respiratory exacerbation, leading to significantly better outcomes.

KEY WORDS: Respiratory insufficiency - Neuromuscular diseases - Respiration, artificial.

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Patients with impairment of respiratory function can be distinguished between those with primarily impairment of gas exchange due to intrinsic lung/airways disease, and those with lung ventilation impairment on the basis of respiratory muscle weakness. Patients with neuromuscular disorders (NMD) may develop primarily ventilatory impairment, although the probability of its occurrence can be different, according to the baseline disease (Table I). Once respiratory muscle impairment has become pronounced, patients with NMD can use both inspiratory and expiratory muscle aids to avoid episodes of respiratory failure (RF), have excellent prognoses with long-term home non-invasive mechanical ventilation (NIV) and usually do not require tracheostomy.

TABLE I.—*Probability of respiratory failure in patients with neuro-muscular disorder, according to baseline disease.*

— *Inevitable:*
– Duchenne muscular dystrophy
– Type I Spinal muscular atrophy (SMA)
– Motor Neuron Disease (MND-ALS)
— *Frequent:*
– Limb girdle MD 2C,2D,2F,2I
– Nemaline myopathy
– Int SMA
– Acid maltase deficiency
– X linked myotubular myopathy
– Ullrich congenital muscular dystrophy
– Congenital myasthenia
– Congenital myotonic dystrophy
— *Occasional:*
– Emery Dreifuss MD, Becker MD
– Bethlem myopathy, Minicore, central core myopathy
— *Uncommon:*
– FSH MD
– Mitochondrial myopathy
– Limb girdle MD 1, 2A,B,G,H,
– Oculopharyngeal muscular dystrophy

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Causes, mechanisms and evaluation of respiratory failure

Progressive respiratory muscle weakness

Respiratory muscle weakness, defined as the inability of the rested respiratory muscles to generate normal levels of pressure and flow during inspiration and expiration, is a frequent occurrence in many patients with NMD. As chest wall and pulmonary compliance may be reduced in patients with the disease, the mechanical load on the weakened respiratory muscles (in particular the diaphragm) can be increased. An imbalance between load and capacity leads to muscle fatigue and RF.[1] Ventilatory insufficiency leading to failure can be nocturnal only and result from diaphragm failure, with the patient unable to breathe when supine, or from severe generalised respiratory muscle dysfunction. Due to the inadequacy of inspiratory muscle function, a well-known pattern of restrictive ventilatory defect can be detected by pulmonary function tests (PFT), usually performed by an electrospirometer, with the following characteristics:

— preserved total lung capacity until a far advanced stage of the disease;

— elevated residual volume;

— reduced forced vital capacity (FVC);

— preserved functional residual capacity.

In patients with Duchenne muscular dystrophy (DMD) a characteristic pattern of FVC has been documented, showing an abbreviated period of rising that typically peaks between ages 10 and 12 years, followed by a "plateau" phase and a rapid decline leading inevitably to RF. The maximal FVC recorded and its rate of decline may predict survival time.[2] When FVC falls below 55% of predicted values, the onset of insidiously progressive hypercapnia is likely. A significant difference between upright and recumbent lung volumes has been reported frequently for patients with NMD, suggesting an impaired diaphragmatic function; in particular, a fall in FVC of 25% or more has been considered a sensitive indicator of diaphragmatic weakness.[3]

Impaired cough

Bulbar, inspiratory, and expiratory muscles (predominantly the abdominal and intercostal muscles) are needed for effective coughing. Clearing airway secretions and airway mucus can be a continual problem for patients with generalised muscle weakness, and for those who cannot swallow saliva or food without aspiration. For patients with respiratory muscle dysfunction and functional bulbar musculature it becomes a problem during chest infections, following general anaesthesia, and during any other period of bronchial hypersecretion.

In patients with NMD inadequate expiratory muscle function may cause bronchial mucous encumbrance, frequently complicated by pneumonia, atelectasis and, ultimately, Acute Respiratory Failure (ARF). These conditions can result in repeated bronchoscopy-assisted aspirations, hospitalisations, endotracheal intubations, tracheostomy and death.[4]

Cough-peak expiratory flow (CPEF) is a measure of the maximum airflow generated during cough and is normally 360 to 1200 L/min; the CPEF correlates well with the ability to clear airway secretions. Bach et al. have suggested from clinical observations that a CPEF of at least 160 L/min, generated alone or with assistance, is required for effective airway clearance; when the CPEF is<160 L/min, tracheal suctioning is usually required at the onset of respiratory infections.[5]

Sleep-disordered breathing

Sleep-disordered breathing (SDB) refers to the occurrence of central, obstructive or mixed apnea, hypoventilation, or both during sleep. Patients with NMD are vulnerable to SDB, especially during the rapid eye movement (REM) phase, with the commonest form being hypoventilation. Hypoventilation is caused by a reduction in the tidal volume, particularly during REM sleep.[6] In

fact, when patients have severe diaphragm dysfunction REM related inhibition of intercostal and accessory muscles may exaggerate the normal breathing events, leading to hypoventilation and worsening gas exchanges. Over time, sleep-related hypoventilation may become more prolonged, promoting severe hypoxia, bicarbonate retention, and depression of the respiratory drive. This creates a vicious cycle that can result in stable hypoventilation, which is not only nocturnal but also diurnal, right ventricular strain, and acute cardiopulmonary failure.

Obstructive events during sleep have also been reported in patients with NMD due to pharyngeal or laryngeal muscle weakness, which predisposes upper airway collapse. It is suggested that upper airway collapse occurs due to the effect of negative pressure during inspiration acting on hypotonic pharyngeal walls. Because RF may first become apparent during sleep, it is advisable that patients with NMD be monitored carefully for the presence of SDB. Diagnosis of SDB requires clinical suspicion and subsequent polygraphic recording; however, symptoms of SDB may be subtle. The physician should especially be aware of any of the following complaints: broken sleep pattern, nightmares, nocturnal confusion, morning headache, daytime fatigue, mental clouding and somnolence due to hypoventilation and CO_2 retention. Additional symptoms such as fatigue, exertional dyspnoea, orthopnoea, and swallowing difficulties, weakened cough, weight loss, and frequent respiratory infections, could suggest progression of the underlying respiratory muscle disorder and worsening of nocturnal ventilation.

Daytime PFT have typically been shown to correlate poorly with severity of SDB. However, several PFT findings warrant polysomnography: when FEV_1 is below 40% predicted, base excess exceeds 4mmol/L, $PaCO_2$ is above 54mm Hg, and low day time SaO_2 is detected.[7]

Nocturnal oxymetry alone is inadequate at detecting sleep apnea and hypoventilation. In addition, criteria defining significant desaturations remain controversial. Overnight polysomnography (PLSG) or respiratory poligraphy (RP) is suggested for patients who develop symptoms and signs of sleep-wake abnormality or nocturnal RF.[8-10] Nevertheless, it should be noted that recent guidelines have concluded that nocturnal oxymetry alone is an acceptable method of screening for hypoventilation in asymptomatic NMD individuals, assuming that clinically significant hypoventilation of neuromuscular origin is unlikely to occur in the absence of desaturation below 93%.[11]

Long-term non-invasive ventilation for the management of chronic ventilatory failure

Although insidious, ventilatory failure is a major cause of morbidity and mortality among patients affected with NMD, the treatment of neuromuscular respiratory failure was for many years considered to be "most controversial" and "to raise enormous ethical difficulties" due to the lack of effective therapeutic approaches and to the severely impaired quality of life of neuromyopathic patients at an advanced stage of disease.[12]

The proven success of long-term mechanical ventilation administered invasively by an indwelling tracheostomy tube (IMV) in prolonging survival of such patients has not had a substantial impact on this problem, the most frequently cited reason being a lack of improvement in the patient's and family's quality of life. In fact, IMV often restricts the user's lifestyle, requiring a high level of care, and frequently obliges the patient's family to sacrifice personal time and privacy, thus exacerbating depression and anxiety.[13]

However, in recent years the approach to care of neuromuscular respiratory failure by long-term mechanical ventilation has been revised, due to two new critical developments:

— technology has advanced and several new types of ventilatory aids have been introduced, which deliver effective mechanical ventilation even non-invasively, by way of a

nasal mask or a mouthpiece; non-invasive mechanical ventilation NIV) is characterized by ease of administration, preservation of upper airway function and lower cost;

— the majority of severely disabled ventilator users with neuromuscular disease have expressed satisfaction with their lives, even though they are usually unable to achieve some of the goals associated with acceptable quality of life in the "normal" population.[14]

As a consequence, and thanks to an ethos of optimism, increasing numbers of neuromyopathic patients with advanced respiratory impairment are now being successfully treated by long-term NIV, usually in the home setting.

Indications

Long-term NIV is required when spontaneous respiratory muscle efforts are unable to sustain adequate alveolar ventilation, causing chronic stable or slowly progressive ventilatory failure. If reversible deteriorating factors (*i.e.*, respiratory infection, congestive heart failure, severe electrolyte disturbance, etc.) have been treated successfully, indications for NIV are defined by the following, persisting conditions:[8-10]

1) symptoms attributable to hypoventilation (such as fatigue, dyspnea, morning headache) and one of the following;

2) physiologic criteria:
   - significant daytime CO_2 retention ($PaCO_2$>50 mmHg);
   - nocturnal oxygen desaturation (SaO_2<88% for at least five consecutive minutes);
   - FVC<50% predicted or maximal inspiratory pressure (MIP)<60 cm-H_2O, only for rapidly progressive disease.

Contraindications

The following complications are considered to be contraindications for NIV:

1. severely impaired swallowing, leading to chronic aspiration and repeated pneumonia;

2. ineffective clearing of tracheobronchial secretions, despite the use of non-invasive manual or mechanical expiratory aids;

3. need for round-the-clock (>20h) ventilatory support.

These are conditions usually requiring the application of IMV. It should be noted that the combination of NIV with assisted coughing techniques or crycothyroid "mini-tracheostomy" may avoid tracheostomy-PPV even in subjects with severe inability to cough out airway secretions.[15-17]

NIV is sometimes technically difficult to apply, especially in infants and young children, and requires motivation and cooperation on the part of the patient. If non-invasive techniques are not well-tolerated or unsuccessful, a tracheostomy could be performed electively, before the patient has developed major complications of chronic ventilatory insufficiency. Possible causes of NIV failure and management strategy are reported in Table II.

Mechanism of action

Although there is general agreement that the administration of nocturnal non-invasive positive pressure ventilation (NPPV) to patients with chronic hypoventilation caused by NMD results in increased daytime spontaneous ventilation,[18] there is less consen-

TABLE II.—*Causes of failure of non-invasive positive pressure ventilation and treatment strategy.*

— Interface-related
– Oral air leak → chin strap
– Skin abrasion or rash → customized mask, protective skin covering
– Gastric distension → reduced VT and Peak Inspiratory Pressure
– Nasal congestion or nasal dryness → saline nasal spray or topical nasal steroid preparation
– Difficulty initiating and/or maintaining sleep
— Patient-related
– Anxiety, claustrophobia → small interface, psycotherapeutic approach
– Poor information and motivation → better education
— Disease-related
– Rapid progression
– Bulbar muscle impairment
– Heart failure

V_T: tidal volume

sus regarding the mechanisms by which diurnal symptoms and arterial blood gases (ABG) are improved by night-time PPV. Three theories have been proposed to explain these beneficial effects. According to the "lung mechanics hypothesis", PPV acts by improving the derangement in respiratory mechanics, decreasing stiffness of the respiratory system and reducing the elastic effort of breathing; this theory is based on the observation that short-term administration of PPV may induce an increase in lung compliance and Functional Residual Capacity; however, it requires further investigations.[19] The "rest hypothesis" proposes that nocturnal ventilation rests chronically fatigued ventilatory muscles, thereby improving daytime ventilatory performance and ABG; this theory has been confirmed by the finding of reduced EMG activity of the diaphragm and esophageal pressure swings in patients with chronic hypoventilation during NPPV;[20] however, the relation between muscle fatigue and chronic respiratory failure is not evident.[21] And finally, the "set point hypothesis" argues that, by reducing nocturnal CO_2 retention, night-time assisted ventilation reverses "central fatigue", improves respiratory sensitivity and lowers the CO_2 set-point; as a consequence, daytime ventilation tends to improve progressively. Supportive evidence for this theory derives from studies demonstrating that the reduction in $PaCO_2$ observed after nocturnal NPPV correlates with the increase in the slope of the ventilatory response to the CO_2 curve, although respiratory muscle strength remains unchanged.[22, 23]

Ventilation techniques

While the first ventilators were "volumetric", the more recent ones are "pressuremetric" and therefore more comfortable. Actual ventilation techniques are known as pressure support ventilation (PSV) and combine stable minimum ventilation with greater comfort for the patient. However, there are no data suggesting that one method is better than the others in terms of gas exchange, patient comfort and patient-ventilator interaction (24). Volume-limited ventilators are usually used in the assist-control mode to deliver a relatively large tidal volume (10-15 mL/kg) to compensate for leak around the interface. Portable pressure-limited ventilators cycle between two levels of positive airway pressure using either flow- or time-triggering (bilevel ventilation). Many also offer an assist-control mode that delivers back-up time-cycled inspiratory and expiratory pressures with adjustable inspiratory:expiratory ratios at a preset rate. PSV is a very popular method of providing NIV to stable patients with NMD, as it has been proven to be more comfortable than other modes of NIV, because it allows the patient to control respiratory rate, flow, tidal volume and breathing pattern. However, the tidal volume delivered with this ventilatory mode may be less than expected, due to changes in ventilatory drive or respiratory impedance. To overcome these problems, a new mode of ventilation, termed volume-guaranteed pressure support (PSV-VTG), has been recently developed, with the aim of combining a minimum warranted alveolar ventilation with maximum patient comfort. However, PSV-VTG seems not outperform older modes of ventilation in terms of efficacy on breathing pattern and ABG. In addition, application of PSV-VTG has been associated with a higher rate of patient-ventilator dyssynchrony.[24]

Selection of the interface

Since everyone's face, and especially nose, has different anatomy, one cannot predicted which nasal interface will provide the best seal, least insufflation leakage, or with which interface any particular patient will be most comfortable. For this reason, an adequate assortment of masks (nasal, oral, and oronasal) in both adult and pediatric sizes (if children are being titrated) should always be available. A study comparing a generic nasal "mask" with nasal prongs and full-face interface reported significantly higher minute ventilation and greater decreases in $PaCO_2$ with the full-face interface and concluded that irrespec-

tive of the underlying pathology, the type of interface affects the NIV outcomes more than the ventilatory mode.[25] Patients should be offered a variety of interfaces and, to a large degree, allowed to choose. The alert patient usually prefers non-invasive PPV via nasal route because of its facilitating effect on speech, eating, and comfort since there are no facial straps. In the same study there were no differences in tolerance to ventilation, blood gases, or breathing patterns whether using assist control or pressure-assist modes. In conclusion, there is no definitive consensus about the user interface: nasal masks are more comfortable for night ventilation while oronasal masks reduce air loss from mouth and nose. Mouthpieces can be successfully used in patients subjected to continuous NIV.

Adaptation

Practical experience with NIV may not achieve success rates as high as those reported in the literature. Adaptation to NIV is a critical step for acceptability and efficacy of this treatment during sleep in patients with chronic ventilatory failure Although it can be challenging to initiate outside of hospital environments, possible locations for initiation of NIV may include not only hospitals providing short- or long-term care, but also the sleep laboratory, the physician's outpatient office, or the patient's home, depending on the experience of the clinicians and resources available. Optimal use requires coordination between respiratory therapists, nurses, and physicians to initiate and monitor response to treatment The initial sessions of NPPV should be overseen by experienced personnel, during waking hours, with the patient alert. The objective is to familiarize the patient with the technique, motivate the patient, and to establish initial ventilator settings. Patient comfort and familiarity with NPPV are critical for successful adaptation. Starting at low volumes or pressures (10 mL/kg or 8-10 cm H_2O, respectively) tidal volume or inspiratory pressure is then gradually increased over days or weeks as tolerated until gas exchange targets or the patient's comfort limit are reached.[26] Eventually, an inspiratory pressure of 12–22 cm H_2O is reached, with final settings determined by resolution of symptoms and improvement in gas exchange. For small children, introduction of NPPV during sleep may be advantageous.[27]Hours of use should also be gradually increased. After a few days of "practice sessions" during the daytime, the patient is encouraged to begin nocturnal use for as long as tolerated. The amount of time needed before patients can sleep through the night using the device is highly variable between individuals, ranging from a few days to a few months.[28] During the course of the initialization, the effectiveness of the ventilation should be assessed via $PaCO_2$, both during spontaneous breathing and ventilation, respectively, and supplemented by nocturnal measurements (polygraphy/pulse oximetry, polysomnography, $PTcCO_2$, selective blood gas analyses).[29]

Ongoing monitoring

Since monitoring is essential to verify the efficacy of NIV, during the early adaptation period home-care providers should regularly visit the patient at home to reinforce proper use of the equipment and to make further adjustments to optimize fit and comfort. Immediately after discharge from the hospital (usually for the first week), all individuals administered long-term NIV should be followed closely by the members of the home care team. Although the frequency of follow-up visits may vary from patient to patient, a daily visit of the nurses is recommended for all patients until the situation stabilizes and the caregivers become accustomed to their role. After the initial period, the time between visits can be increased as the situation dictates.[30] Proper use of the equipment by the patient and family should be verified on a regular basis: this includes checking patients, their compliance with the ventilator, fit of interfaces, adverse effects, and equipment hygiene. In some instances, evaluation of the patient/equipment interface may also

include the monitoring of nocturnal SaO_2 during assisted ventilation.[31] The nursing staff should provide the primary physician with regular and timely reports of the visit findings. Technical supervision needs to be provided at home on a regular basis by the technicians of the commercial companies. Due to technological advances in communication, medical monitoring at home has been increasingly linked via telemedicine to health professionals for data exchange and interactive communication.[32]

Results

Administration of NIV to NMD patients with chronic hypoventilation may be expected to improve physiologic function and quality of life as well as decrease the frequency of episodes requiring acute care facilities. In particular:

— physiological indices: although physiological outcomes of NIV remain conflicting in NMD patients, MIP and FVC may transiently increase or stabilize (33,34). Night-time (direct effect) and daytime (indirect effect) ABG values tend to normalize promptly after initiation of NPPV;[35]

— pulmonary morbidity: NIV decreases the risk of respiratory complications and hospitalizations and postpones the last-resort necessity of performing a tracheostomy by months to years, depending on the rate of progression of bulbar muscle dysfunction;[36, 37]

— quality of life: NIV users usually report an alleviation of symptoms related to CO_2 retention; in addition, they have been proven to be comparable to other age-matched groups in terms of health perception and social integration;[14, 38]

— survival: NPPV has been demonstrated to prolong life in DMD, the mean survival in hypercapnic DMD patients without ventilatory support being only 9.7 months.[39] In DMD patients, NPPV is generally considered to provide an additional life's expectancy of 5–10 years.[40, 41] The 5-year survival rates among patients with post-polio syndrome and other slowly progressive NMD using nocturnal NPPV are nearly 100%.[42]

Although restricted to uncontrolled series of patients due to obvious ethical reasons, the results of our experience suggest that the administration of NPPV in DMD may not only increase survival, but also have a dramatic impact on the causes of death. In fact, whilst unventilated DMD patients have been reported to die as a result of respiratory insufficiency in 70% of cases,[43] the great majority of our patients submitted to long-term ventilatory treatment die of a cardiomyopathy: as a final effect, the natural history of the disease is significantly changed. NPPV appears to improve the quality of life and survival of patients with Amyotrophic Lateral Sclerosis (ALS), even those with bulbar involvement. Not surprisingly, however, the survival of those in the latter group is poorer than in those with intact bulbar function.[44]

Complications

Well-recognised difficulties related to the long-term use of NPPV include skin pressure from the interface (70%), allergy to the plastic lipseal or silicone interfaces (13 *vs.* 5% for non-silicone interfaces), dry mouth (65%), eye irritation from air leakage (about 24%), nasal congestion (25%) and dripping (35%), sinusitis (8%), nose bleeding (4% to 19%), gum discomfort (20%), maxillary flattening in children, and aerophagia.[45]

Barotrauma has been reported as a complication of invasive and non-invasive ventilation. While its incidence has been cited as 0.5 to 40% for invasive ventilation users with primarily respiratory impairment,[46] its occurrence is very rare for non-invasive ventilation and pneumothorax has been reported to be "a virtually non-existent complication" in hundreds of ventilator users with neuromuscular disease, all of whom perform regular daily ventilatory treatment.[47] Nevertheless, in our experience we reported the development of pneumothorax associated with long-term NIV administered to DMD patients; given the wide scale utilization of chronic NPPV, we suggested that care-givers and patients be made aware of this serious complication.[48]

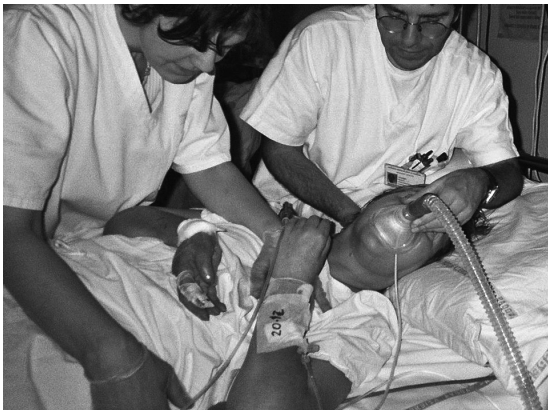

Figure 1.—Combined application of manually and mechanically assisted coughing on a patient with neuromuscular acute respiratory failure.

NIV in the acute setting

The onset of ARF in patients with advanced stage NMD may be caused by airway encumbrance with mucous, as a result of weakened respiratory muscles and an inability to cough effectively. A non-invasive approach to the management of tracheo-bronchial secretions in patients with advanced NMDs, based on the combination of expiratory muscle aid and NIV, has been proposed (Figure 1). This treatment strategy may result in a reduced need of nasal suctioning and conventional intubation, and/or tracheostomy.[49] Among non-invasive expiratory aids, manually assisted coughing techniques, such as anterior chest compression and abdominal thrust, have been shown to be effective in facilitating the elimination of airway secretions. Mechanically Assisted Coughing (MAC) can be delivered by a device (Cough-Assist™, J.H. Emerson Co., Cambridge MA, or Pegaso Cough, DIMA Italia, Bologna, Italia) that assists patients in clearing bronchial secretions. It consists of a two-stage axial compressor that provides positive pressure to the airway, then rapidly shifts to negative pressure, thereby generating a forced expiration. It is usually applied via a facemask. It commonly produces a decrease in pressure by approximately 80 cmH2O in 0.2 s; the insufflation and exsufflation pressure and time are independently adjustable. The device can deliver maximum positive and negative pressures of about 60 cmH2O. Mechanical insufflation-exsufflation (MI-E) has been reported to effectively mobilize mucous secretions and has been proposed as a complement to manually assisted coughing in the prevention of pulmonary morbidity in NMD patients during upper respiratory tract infection.[4, 50]

The safety, tolerance and effectiveness of MI-E in the home setting has been examined in the paediatric population. In a paper by Miske et al, the outcome of 62 young patients with NMD and impaired cough who experienced the use of MI-E at home has been retrospectively analysed.[51] Diagnoses included the following: DMD (17 patients); Spinal Muscular Atrophy (SMA), types I and II (21 patients); myopathy (12 patients); other nonspecific NMD (12 patients). The use of MI-E was recommended for those patients who had experienced a decrease in respiratory muscle strength or those who had an acute lower respiratory tract infection or atelectasis unresolved by conventional means. Chronic atelectasis resolved in four patients after beginning MI-E therapy, and five patients experienced a reduction in the frequency of pneumonias. Complications were reported in two subjects, but ultimately they regularly used the device. Based on these results, the Authors conclude that the use of MI-E is safe and effective in the paediatric population.

In the hospital setting MI-E has been utilized in combination with NIV in order to avoid endotracheal intubation and tracheotomy during episodes of acute respiratory failure in patients with NMD. In our experience, we evaluated the short-term outcomes of 11 consecutive NMD patients with respiratory tract infections and tracheo-bronchial mucous encumbrance who were administered MI-E and conventional chest physical treatments in our intensive care unit in comparison with the outcomes of 16 historical matched controls who had received chest physical treatments alone. Treatment failure (intubation and/or tracheotomy) was significantly lower in the MI-E group than in the conventional chest physical treatment

group (2/11 *vs.* 10/16 cases). In addition, MI-E did not produce serious side effects and was well tolerated by all subjects.[17]

The most severe NMD presenting at birth is SMA, type 1. These patients are floppy at birth and 90% are dead by 12 months of age. One hundred percent of typical type 1 patients are dead by age 2, virtually always of ARF due to inability to cough effectively during intercurrent respiratory tract infections. It has been reported that type 1 patients were extubated using an extubation protocol specifically designed to support inspiratory and expiratory muscles, using oximetry as feedback.[52] By comparison to type 1 patients who underwent tracheotomy for prolonged survival, these patients had more hospitalizations until age 3 but significantly less subsequently. Whereas 16 of 17 patients with tracheostomy tubes lost all ventilator-free breathing tolerance post-tracheotomy and could not speak, 85% of the 41 patients managed noninvasively or extubated to high span bi-level positive airway pressure and aggressive MAC weaned to nocturnal-only nasal ventilation and subsequently developed the ability to speak. In spite of these favourable results, there is a wide variation in which kind of ventilatory support is actually offered to families of SMA children, depending on physician training and attitude.[53]

The most common and rapidly progressive NMD is DMD; although the use of nocturnal-only inspiratory aid can relieve symptoms and ameliorate hypercapnia early on, it does not always prolong survival, due to the onset of ARF; however, the institution of a protocol based on the use of oximetry and respiratory aid can significantly reduce respiratory morbidity and mortality.[5] This protocol involves using oximetry as feedback to maintain normal SaO_2 (greater than 94%) by appropriately using NPPV and manually assisted coughing (MAC), especially during intercurrent respiratory tract infections. In many cases patients may become continuously dependent on ventilatory support for years without ever requiring hospitalization. Prolongation of survival for DMD was quantitated with and without access to the home acute care protocol. The patients were trained to use mouth piece and nasal Intermittent NPPV and MAC as needed to maintain SaO2 greater than 94%. Survival was considered prolonged when NPPV was required more than 16 hrs/day (full-time) indefinitely and with little breathing tolerance. Ninety-one of 125 patients used NPPV 8 to 16 hrs/day (part-time) for 1.9±1.3 years, beginning at 19.1±3.3 years of age. They had a mean VC of 411±252 ml when beginning ongoing daily NPPV. Survival was prolonged for 51 of these 91 patients as they used full-time NPPV for 6.3±4.6 (range =6 months to 18) years. Of the 31 NPPV users who died without access to the protocol, 20 died from respiratory causes. Of the 91 patients, none of the 34 with access to home oximetry, MAC, and NPPV underwent tracheotomy or died from respiratory complications over a 5.4±4.0 year period of full-time NPPV whereas 3 of these patients died from heart failure. Five patients with no breathing tolerance were extubated/decanulated to continuous NPPV and used MAC as needed to maintain normal SaO_2 in ambient air postextubation/decanulation. Thus, noninvasive respiratory aids can permit extubation/decanulation of patients with no breathing tolerance and can prolong survival for patients with DMD.

The same oximetry and respiratory aid protocol has been administered to a population of 101 patients with ALS;[54] they were trained in mouth piece and nasal PPV when symptomatic for hypoventilation and MAC with oximetry feedback when assisted PCF decreased below 270 L/m. Survival was considered to be prolonged when full-time NPPV was required with limited ventilator free breathing tolerance. Of the 101 patients, 15 had not yet used NPPV or MI-E and 11 severe bulbar patients died without ever successfully using them. Three patients used nasal PPV full-time, oximetry, and MI-E episodically but do not yet require ongoing NPPV. Eighteen used NPPV part-time for 3.8±4.1 months. Nineteen others underwent tracheotomy after 4.7±4.5 months of part-time NPPV. Sixteen used part-time NPPV for 17.5±13.0 (maxi-

mum 25) months then full-time NPPV for 14.1±12.6 (maximum 40) months before undergoing tracheotomy. Nineteen used part-time and full-time NPPV for 25.2±19.8 (maximum 114) and 17.5±13.3 (maximum 87) months, respectively, without undergoing tracheotomy. Ten of these NPPV users died once bulbar dysfunction became severe. Thus, up to continuous use of NIV along with MAC when needed can also permit prolonged survival and delay the need for tracheotomy for a significant minority of ALS patients by over 1 year.

Although NIV can be a safer and more effective alternative to endotracheal intubation (ETI) in the treatment of neuromuscular ARF, contraindications still remain to the application of NIV in the acute setting, including respiratory arrest, severe inability to protect the airway, uncontrollable airway secretions despite use of noninvasive aids, life-threatening hypoxemia, severely impaired mental status or agitation, hemodynamic or electrocardiographic instability, and bowel obstruction. If a contraindication to NIV exists, PPV via ETI constitutes the approach for treating patients with ARF who require ventilatory support. Unfortunately, because of weakness of the inspiratory muscles, inadequate cough, and inability to handle oropharyngeal secretions, a substantial proportion of patients with NMD who undergo invasive PPV fail to pass spontaneous breathing trials (SBTs) after recovery from the acute illness and should be considered at high risk for extubation failure.[55, 56] In particular, impaired ability to expel secretions is a crucial component of extubation failure, as confirmed by the fact that NMD patients who have passed SBT but present PCEF of 60 L/min or less are nearly five times more likely to fail extubation compared to those with PCEF higher than 60 L/min.[57] NIV is increasingly being used to prevent extubation failure, with recent trials also having included patients with NMD. In particular, Mayordomo-Colunga et al. delivered "elective" or "rescue" NIV to a series of 36 children deemed at high-risk of extubation failure, including 14 patients with underlying neurologic conditions. As a result, a remarkably high proportion of neurologic patients required reintubation, so that this subgroup was considered to be at increased risk for extubation failure.[58] In our experience, we demonstrated that the combination of NIV plus cough assistance may be more effective than NIV alone in averting the need for reintubation or a tracheostomy and reducing the duration of ICU stay. This can be explained by the fact that although prophylactic use of NIV may unload the weakened respiratory muscles and augment alveolar ventilation, thereby reducing the work of breathing and preventing progressive hypoventilation, it does not substantially enhance airway clearance; as a consequence, additional provision of expiratory aids may become critical to avoid complications that evolve from retained secretions, including atelectasis, secondary infection and abrupt oxyhaemoglobin desaturation.[59]

Conclusions

The long-term use of NIV can alleviate symptoms for NDM patients with chronic ventilatory failure; in addition, NIV combined with assisted coughing can avoid tracheostomy, and prolong survival for some patients. The effects of NIV are almost certainly multifactorial and further studies are necessary to clarify the most important mechanisms of action, and thereby facilitate more rational use.

Riassunto

Ventilazione non invasiva in pazienti con malattie neuromuscolari progressive

L'insufficienza ventilatoria a sviluppo insidioso e tardivo rappresenta la principale causa di morbidità e mortalità tra i soggetti affetti da Malattie Neuro-Muscolari (MNM). Nonostante ciò, il trattamento dello scompenso ventilatorio di origine neuromuscolare per molti anni è stato considerato come una procedura estremamente controversa e tale da sollevare notevoli dubbi di carattere etico, a causa della mancanza di una strategia terapeutica realmente efficace e della severa compromissione della

Qualità di Vita (QoL) riscontrata nei soggetti neuromiopatici in stadio avanzato di malattia. In anni recenti, tuttavia, l'approccio alla cura dell'insufficienza ventilatoria di origine neuromuscolare ha subito una notevole revisione, in seguito all'introduzione della Ventilazione Meccanica Non-Invasiva applicata a Lungo Termine. Infatti, seppure manchino le evidenze derivanti da studi controllati, non eseguibili per ragioni di carattere etico, tale modalità di trattamento risulta in grado di correggere il deficit della pompa ventilatoria, ridurre i sintomi correlati alla ritenzione di CO_2 e migliorare l'aspettativa e la QoL dei pazienti. Essa si caratterizza per semplicità di utilizzo, mantenimento dell'integrità funzionale delle vie aeree superiori e basso costo. In combinazione con le manovre di assistenza alla tosse, l'applicazione di VMNI consente inoltre di diminuire la necessità di ospedalizzazione, il ricorso all'intubazione e alla tracheotomia in caso di infezione del tratto respiratorio che determini ingombro secretivo tracheo-bronchiale

PAROLE CHIAVE: Insufficienza respiratoria - Malattie neuromuscolari - Respirazione artificiale.

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