REVIEW

Respiratory management of acute respiratory failure in neuromuscular diseases

F. RACCA [1], L. DEL SORBO [1], T. MONGINI [2], A. VIANELLO [3], V. M. RANIERI [1]

[1]Department of Anesthesiology and Resuscitation, University of Turin, S. Giovanni Battista-Molinette Hospital, Turin, Italy; [2]Department of Neurosciences, University of Turin, S. Giovanni Battista-Molinette Hospital, Turin, Italy; [3]Respiratory Intensive Care Unit, Department of Cardio-Thoracic Surgery, University Hospital of Padua, Padua, Italy

ABSTRACT

Neuromuscular diseases (NMD) can affect all major respiratory muscles, leading to the development of respiratory failure, which is the most common cause of morbidity and mortality in patients affected by those conditions. Based on the clinical onset of acute respiratory failure (ARF), NMD can be classified into two main categories: 1) slowly progressive NMD with acute exacerbations of chronic respiratory failure, and 2) rapidly progressive NMD with acute episodes of respiratory failure. The most common slowly progressive NMDs, such as motor neuron diseases and inherited myopathies, account for the majority of NMD patients developing chronic neuromuscular respiratory failure at risk of acute exacerbations. Conversely, rapidly progressive NMDs, such as Guillain-Barré syndrome and myasthenic crises, are characterized by a sudden onset of ARF, usually in patients with previously normal respiratory function. The patho-physiological mechanisms responsible for ARF in NMD and the variety and complexity of specific challenges presented by the two main categories of NMD will be analyzed in this review, with the aim of providing clinically relevant suggestions for adequate respiratory management of these patients. *(Minerva Anestesiol 2010;76:51-62)*

Key words: Neuromuscular diseases - Respiratory insufficiency - Patient care management - Respiration, artificial - Positive-pressure respiration.

Respiratory failure is the most common cause of morbidity and mortality in patients with slowly or rapidly progressive neuromuscular diseases (NMD).[1-4] In fact, the reduction of inspiratory muscle strength (resulting in ineffective alveolar ventilation) and the weakness of expiratory muscles (leading to inadequate clearance of airway secretions) are causes of chronic respiratory failure as well as potentially life-threatening problems.

The wide variety of NMDs that compromise respiratory function are summarized in Table I.[3]

According to the clinical onset of acute respiratory failure (ARF), NMD can be also classified into two main categories: 1) slowly progressive NMD with acute exacerbations of chronic respiratory failure, and 2) rapidly progressive NMD with acute episodes of respiratory failure.

Motor neuron diseases (*i.e.*, amyotrophic lat-

*On behalf of the "Acute Respiratory Failure in Neuro-Muscular Italian Study Network – ARNeIS".

The members of the ARNeIS are: Ambrosino Nicola, MD, Pisa; Antonelli Massimo, MD, Rome; Appendini Lorenzo, MD, Novara; Banfi Paolo, MD, Milan; Barberis Luigi, MD, Turin; Berta Giacomo, MD, Turin; Bignamini Elisabetta, MD, Turin; Braghiroli Alberto, MD, Novara; Calderini Edoardo, MD, Milan; Capello Elena, Turin; Corrado Antonio, MD, Firenze; Costantino Anna, MD, Alessandria; Del Sorbo Lorenzo, MD, Turin; Fanfulla Francesco, MD, Pavia; Ferreyra Gabriela, RT, Turin; Maspoli Maria, Turin; Mongini Tiziana, MD, Turin; Nava Stefano, MD, Pavia; Navalesi Paolo, MD, Novara; Ottonello Giancarlo, MD, Genova; Racca Fabrizio, MD, Turin; Ranieri V. Marco, MD, Turin; Salvo Ida, MD, Milan; Urbino Rosario, MD, Turin; Vianello Andrea, MD, Padova; Vitacca Michele, MD, Brescia.

TABLE I.—*Neuromuscular diseases affecting respiratory function.*

1. *Motor neuron diseases*
- — Amyotrophic lateral sclerosis (ALS)
- — Poliomyelitis, post-polio syndrome
- — Spinal muscular atrophy (SMA)
- — Spino-bulbar muscular atrophy (Kennedy syndrome)

2. *Peripheral neuropathies*
- — Guillain–Barrè syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP)
- — Critical illness polyneuropathy (CIP)
- — Hereditary motor sensory neuropathies (HMSN)

3. *Disorders of neuromuscular junction*
- — Myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS)
- — Congenital myasthenic syndromes
- — Botulism

4. *Myopathies*

4.1 Acquired myopathies
- — Inflammatory myopathies (polymyositis, dermatomyositis, IBM)
- — Critical illness myopathy (CIM)
- — Toxic myopathies

4.2 Hereditary myopathies

3.2.1 *Progressive muscular dysthrophies*
- — Dystrophinopathies, Duchenne (DMD) and Becker (BMD) type
- — Facioscapulohumeral muscular dystrophy (FSHD)
- — Limb-girdle muscular dystrophies (LGMD) and distal myopathies
- — Myotonic dystrophies

3.2.2 *Congenital myopathies* (i.e., central core diseases, myotubular myopathy, nemaline myopathy, myofibrillar myopathies)

3.2.3 *Congenital muscular dystrophies* (i.e., Ullrich's CMD, merosin-deficient CMD, alpha-dystroglycanopathies, Emery-Dreyfuss muscular dystrophy, EDMD)

3.2.4 *Metabolic myopaties* (mitochondrial myopathies, glycogen storage diseases)

eral sclerosis – ALS, and spinal muscular atrophy - SMA) and inherited myopathies (*i.e.*, Duchenne muscular dystrophy) are the most frequent slowly progressive NMDs. When patients with these diagnoses develop chronic respiratory failure, long-term mechanical ventilation (MV) is the main therapeutic intervention to support their respiratory muscle function, increasing life expectancy and health-related quality of life.[5-8] Nonetheless, these patients are at high risk of developing acute exacerbations of respiratory failure.

Myasthenia gravis (MG), Guillain-Barré syndrome (GBS) and inflammatory myopathies are the most common rapidly progressive, and potentially reversible, NMDs. They are characterized by an acute onset of respiratory failure, usually in patients with previously normal respiratory function.[1-9]

This article will specifically review the pathophysiological mechanisms responsible of ARF in NMD patients and the issues concerning their respiratory care, but will not cover non-respiratory management.

All diseases listed in Table I will be taken into consideration with the exception of critical illness myopathy and critical illness polyneuropathy, which are not relevant for the onset of ARF. In addition, SMA type 1 and ALS will be excluded from this review, because the complex ethical and clinical problems arising from their severe clinical evolutions deserve separate remarks.

Mechanisms underlying ARF in NMD

In patients with slowly progressive NMD, ARF is caused by an imbalance between the respiratory load and muscle strength, resulting in ineffective alveolar ventilation and hypercapnia. In particular, in these patients the main determinant of this process is weakness of respiratory muscles.

Respiratory infections are the most frequent cause of acute exacerbation of chronic neuromuscular respiratory failure. During these events the respiratory load increases and the strength of the inspiratory muscles further worsens, resulting in impaired alveolar ventilation. Moreover, weakness of expiratory and bulbar muscles causes ineffective coughing and airway mucus accumulation, further increasing the work of breathing and leading to respiratory distress.[10-13]

In contrast, in patients with rapidly progressive NMD, ARF is generally caused only by an acute and severe decrease in muscle strength, without necessarily the presence of other respiratory diseases as triggers.[1]

Respiratory muscle weakness in NMD

There are three muscular components of the respiratory system: 1) the inspiratory muscles, responsible for ventilation; 2) the expiratory muscles, responsible for coughing; and 3) the bulbar muscles, responsible for airway protection.[2, 3]

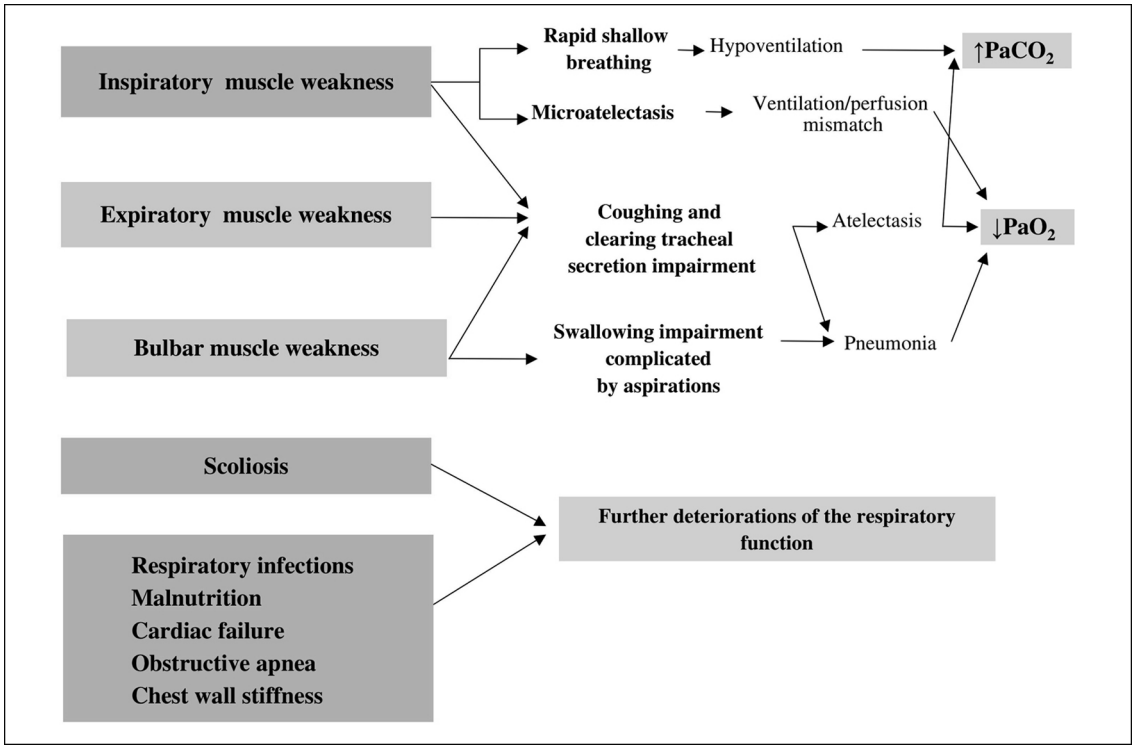

Figure 1.—Respiratory issues in patients with neuromuscular diseases.

Weakness of inspiratory muscles results in inadequate lung inflation, with the consequent derecruitment of alveolar units and formation of microatelectasis, causing ventilation/perfusion mismatch and, hence, hypoxemia. Moreover, the generation of small tidal volumes and the compensatory increase in the respiratory rate (*i.e.*, rapid shallow breathing) results in alveolar hypoventilation, leading to hypercapnia (Figure 1).

Effective cough requires full pre-cough inspiration followed by glottis closure and adequate expiratory muscle strength to generate sufficient intra-thoracic pressures to obtain high peak expiratory flows.[14] Weakness of expiratory muscles combined with inadequate lung inflation prevents effective coughing and airway clearance, altering airway resistance and increasing the risk of developing atelectasis and pneumonia [14, 15] (Figure 1).

Bulbar muscle weakness (facial, oropharyngeal, and laryngeal muscles) can affect the ability to speak, swallow and clear airway secretions, resulting in an increased likelihood of aspiration. Patients with NMD usually experience mild to moderate bulbar dysfunction, with the exception of patients diagnosed with ALS, type 1 SMA and patients with rapidly progressive NMD, who may develop severe glottis functional impairment.

Whereas patients with rapidly progressive NMD develop ARF secondary to an acute and dramatic decrease in respiratory muscle strength, patients with slowly progressive NMD experience a slow reduction in muscular function. They initially suffer from nocturnal respiratory failure and recurrent respiratory infections; subsequently they progress to daytime hypercapnia and eventually to death.[6, 7] Hence, long-term MV is the main therapeutic intervention to support these patients' respiratory muscle function.[6, 7]

Alteration of respiratory mechanics in slowly progressive NMD

In addition to decreased muscle strength, patients with slowly progressive NMD also have a chronically elevated respiratory load, leading to an increased work of breathing.[15-17] Among the

contributors to the increased mechanical load, shown in Figure 1, it is worth mentioning:

— inability to achieve full lung expansion resulting in progressive microatelectasis;[16, 17]

— stiffening of the chest wall caused by muscle atrophy, osteoporosis, and in some cases, extra-articular contractures and intra-articular adhesions, progressing to the irreversible degeneration of the joint cartilage of the rib cage;[18]

— spine deformities contributing to increase the work of breathing [15] and responsible for respiratory muscle misalignment, which impairs their contractile function;[16]

— upper respiratory tract infections [10-12] causing accumulation of mucus in the airways and thus increasing the work of breathing.

Fatigue threshold in slowly progressive NMD

Patients with NMD and severe chronic respiratory dysfunction have a precarious balance between respiratory load and muscle strength even in the stable condition. Therefore, only minor changes in strength or small increments in load (*e.g.*, due to upper respiratory tract infections), are sufficient to precipitate the occurrence of inspiratory muscle fatigue and, hence, ARF.[10-12] Moreover, the muscle fatigue threshold may already be lower in NMD patients as opposed to healthy individuals. Interestingly, Nava *et al.*[19] demonstrated that the fatigue threshold for the diaphragm in quadriplegic patients is reached when the pressure-time index is around 0.10-0.12, which is far below the threshold of fatigue of 0.15 described in healthy subjects.[20] This difference suggests that, in slowly progressive NMD, non-diaphragmatic muscle impairment may predispose patients to earlier diaphragm fatigue.[3]

Diagnosis

Usually, NMD patients requiring intensive care for ARF have been already diagnosed with a specific NMD. However, in patients with rapidly progressive NMD, and in some cases with glycogenosis II or facioscapulohumeral muscular dystrophy, ARF may be the first clinical presentation of their NMD.

Acute-on-chronic neuromuscular respiratory failure

Patients with slowly progressive NMD may need intensive care because of progressive respiratory muscle dysfunction. However, their admission to the intensive care unit (ICU) is usually prompted by precipitating factors, the identification of which is essential because these factors are more amenable to therapy than the NMD itself. A list of the potential precipitating factors of ARF in these patients is summarized in Table II.[21-25]

In particular, ARF most often occurs in NMD patients during otherwise benign upper respiratory tract infections [10-12] or as a result of more severe respiratory complications such as pneumonia and atelectasis.[26]

Additionally, several myopathies are associated with cardiac dysfunctions (dilated cardiomyopathy and/or abnormalities of the conduction system) (Table III),[27, 28] that may also contribute to the development of ARF.[7]

Finally, pneumothorax is a rare but serious and life-threatening complication in NMD patients. Therefore, in case of a suspected pneumothorax, the execution of a computed tomography (CT) scan is mandatory because it can be particularly difficult to detect on a conventional chest X-ray.[25]

The overall diagnostic process is summarized below.

TABLE II.—*Causes of acute exacerbations of chronic respiratory failure in patients with slowly progressive neuromuscular disease.*

Common causes	• Upper respiratory tracts infections/acute bronchitis • Pneumonia • Atelectasis
Rare causes	• Cardiac failure (in particular in patients with myopathies) • Abuse of sedative drugs • Aspiration • Pneumothorax • Pulmonary embolism • Tracheal hemorrage (patients with tracheostomy) • Acute gastric distension due to non invasive ventilation

TABLE III.—*Causes of acute exacerbations of chronic respiratory failure in patients with slowly progressive neuromuscular disease.*

Disorder	Cardiac effects
Dystrophinopathies, Duchenne (DMD) and Becker (BMD) type	Dilated cardiomyopathy (very common; broad spectrum of severity including severe cardiac failure); arrhythmias and conduction defects (<10% of patients)
Limb-girdle muscular dystrophies (LGMD)	Arrhythmias and conduction defects (common); dilated cardiomyopathy (rare in LGMD type 2A, 2D)
Myotonic dystrophies	Arrhythmias and conduction defects (common); dilated cardiomyopathy (rare)
Emery-Dreifuss muscular dystrophy (EDMD) and laminopathies	Arrhythmias and conduction defects (common); dilated cardiomyopathy (rare in EDMD type 1)
Myofibrillar myopathies and other congenital myopathies	Arrhythmias and conduction defects; dilated cardiomyopathy
Mitochondrial myopathies	Arrhythmias and conduction defects; dilated cardiomyopathy
Glycogen Storage Diseases (Pompe disease, infantile type)	Dilated cardiomyopathy

HISTORY

Rule out abuse of sedative drugs and aspiration.

PHYSICAL EXAMINATION

Rule out signs and symptoms of:

— heart failure (pulmonary crackles, peripheral edema, elevated jugular venous pressure, pleural effusion, hepatic congestion);

— pneumonia, aspiration or atelectasis (rales or consolidation on auscultation);

— pneumothorax.

LAB-TESTS

— Serum B-natriuretic peptide and D-dimer (good negative predictive values for heart failure and pulmonary embolism, respectively);

— blood and sputum culture with gram stain if pneumonia is suspected.

IMAGING

— Electrocardiogram to rule out arrhythmias and conduction defects;

— chest X-ray to rule out cardiomegaly, pulmonary congestion, any new pulmonary infiltrates and pneumothorax (mandatory CT scan in case of suspected pneumothorax and non-conclusive chest X-ray);

— echocardiogram to evaluate ventricular function if heart failure is suspected.

Rapidly progressive NMD with ARF

GUILLAIN-BARRÉ SYNDROME

GBS is an acute, immune-mediated polyneuropathy, usually presenting with ascending muscle weakness following a recent infection. The cardinal clinical features are progressive, symmetric muscle impairment with or without sensory involvement and absent or depressed deep tendon reflexes. The weakness can vary from mild difficulty with walking to nearly complete paralysis of all extremity, facial, respiratory and bulbar muscles. Lumbar puncture and clinical neurophysiology studies (*i.e.*, electromyography with nerve conduction studies) must be performed in all patients with suspected GBS in order to confirm the diagnosis. The typical finding on lumbar puncture is an elevated cerebrospinal fluid protein content with a normal white blood cell count (*i.e.*, albuminocytologic dissociation). This finding is present in 80 to 90% of patients with GBS one week after the onset of symptoms.[29, 30]

MYASTHENIC CRISIS

The cardinal feature of MG is fluctuating skeletal muscle weakness in ocular, bulbar, limb and respiratory muscles, often with generalized muscle fatigue, due to the presence of autoantibodies against the post-synaptic acetylcholine receptor.

The fatigue is manifested by worsening contractile force of the muscles. Patients typically have fluctuating weakness of the specific affected muscle groups. The weakness may fluctuate throughout the day, but it is most commonly worst in the evening or after exercise. The diagnosis of MG should be confirmed by serologic testing for autoantibodies and electrophysiologic studies.[31] Myasthenic crisis may be precipitated by a variety of factors including infection, surgery, medications and tapering of immunosuppressive drugs. However, the crisis often occurs as a spontaneous event.

Clinical management

The respiratory management of NMD patients with ARF includes five different issues: 1) evaluation of the need for respiratory support; 2) respiratory support; 3) weaning; 4) indications for long-term respiratory support; 5) anticipatory respiratory care.

Evaluation of the need for respiratory support

Acute-on-chronic neuromuscular respiratory failure

In patients with an acute exacerbation of respiratory failure, techniques to improve airway clearance and MV should be always considered.

Need for airway clearance techniques

During acute illness, assisted coughing techniques should be used in cases of: 1) oxygen desaturation; 2) increased dyspnea; 3) sense of retained secretions; 4) presence of auscultatory rhonchi; and 5) increased ventilator peak airway pressures.[11, 22-24]

Need for mechanical ventilation

Mechanical ventilation should be considered in patients with acute exacerbation that have at least one of the following issues: 1) dyspnea, as referred by the patient; 2) lethargy; and 3) acute respiratory acidosis (*i.e.*, arterial pH <7.35 with $PaCO_2$ >45 mmHg).[23] These patients benefit the most from non-invasive positive pressure ventilation (NIPPV). For patients already using nocturnal NIPPV, daytime NIPPV may be needed during acute exacerbations.[6-33] Only if the non-invasive approach is contraindicated or ineffective may these subjects undergo intubation and invasive MV.

NIPPV is contraindicated in patients with a severe inability to swallow, uncontrollable airway secretions despite the use of noninvasive aids, life-threatening hypoxemia, severely impaired mental status, hemodynamic instability, recent facial, upper airway or upper gastrointestinal tract surgery, or bowel obstruction.[22, 23, 34, 35]

NIPPV failure is defined as the inability to reduce dyspnea or lethargy, decrease the respiratory rate or improve blood gas exchange (*i.e.*, arterial pH <7.30 or below the value on admission or failure to maintain a PaO_2 >65 mmHg with a FiO_2 ≥0.6) within the first 6-12 hours of application, despite optimal ventilator setting.[23, 34]

Rapidly progressive NMD with ARF

Supportive care with intubation and MV is necessary in 25-50% of GBS patients [36] and 15-27% of MG patients.[37] In addition, ICU monitoring is needed in about 20% of GBS patients developing severe dysautonomia.

The frequently insidious onset of ARF increases the risk of life-threatening complications such as respiratory arrest or aspiration pneumonia.[38] Currently, there are insufficient data to recommend the extensive use of NIPPV in patients with rapidly progressive NMD syndromes presenting with ARF.[1, 2] In fact, NIPPV can prevent intubation in patients in myasthenic crises, but it may be considered only in patients without hypercapnia.[39, 40]

In patients with GBS, the act of intubation may be associated with severe complications due to dysautonomia (*i.e.,* bradycardia, blood-pressure shifts, profound hypotension with sedatives) and fatal hyperkalemia induced by the heightened chemosensitivity of the denervated muscles in cases of succinylcholine usage. These potential complications support the need to prospectively identify patients in imminent need of intubation. The decision to intubate these patients should be made earlier rather than later to avoid emergency intubation and cardiorespiratory arrest.

Absolute criteria for intubation include impaired consciousness, respiratory or cardiac arrest, shock,

severe arrhythmias, blood-gas alterations and bulbar dysfunction with confirmed aspiration.

The decision to intubate is more challenging in those patients who do not meet these criteria but whose weakness is gradually progressing. These patients need to be followed carefully and assessed regularly for clinical signs of respiratory muscle fatigue and aspiration (*i.e.*, cough after swallowing), combined with pulmonary function testing to guide the decision for endotracheal intubation.[1, 2] Progression toward MV in patients diagnosed with GBS is likely to occur in those patients with bulbar dysfunction (*i.e.*, dysarthria, dysphagia, or impaired gag reflex), bilateral facial weakness, inability to cough, or dysautonomia.[41, 42] Other prognostic parameters to be considered are vital capacity (VC) <20 mL/kg, maximum inspiratory pressure (PI_{max}) <30 cmH_2O, maximum expiratory pressure (PE_{max}) <40 cmH_2O (the "20/30/40 rule"), or a reduction of >30% in VC, PI_{max} or PE_{max}. Interestingly, Rieder *et al.* found VC to be a poor predictor of the need for MV in patients with MG exacerbations,[43] due to the fluctuations in VC generated by the erratic nature of MG. However, in clinical practice, given the lack of studies on ARF in MG, the same predictors of the need for MV in GBS may be applied to patients with MG.[1]

Respiratory support

Airway clearance

Effective secretion clearance is critical for patients with slowly progressive NMD to prevent atelectasis, pneumonia, ARF and hospitalization. The use of airway clearance techniques, which includes techniques for manually or mechanically assisted coughing and secretion mobilization, is strongly recommended and should be always included in the noninvasive approach to treat respiratory tract infections in these patients.[6, 7]

Manual assisted coughing techniques include inspiratory assistance followed by augmentation of the forced expiratory effort. An improvement of the inspiratory capacity can be achieved by a series of tidal breaths without exhalation between them (*i.e.*, air stacking), obtained with the application of positive pressure with self-inflating bags or mechanical ventilators. Forced exhalation is augmented by pushing on the upper abdomen (*i.e.*, abdominal thrust) or chest wall (*i.e.*, anterior chest compression) in synchrony with the subject's own cough effort.[7] Nevertheless, manually assisted coughing requires significant patient cooperation.

The mechanical insufflator-exsufflator (MI-E) is a device that generates deep insufflation by a positive pressure (*i.e.*, +30-40 cmH_2O) blower followed immediately by a forced exsufflation in which high expiratory flow rates are determined by a deep negative pressure (*i.e.*, -30-40 cmH_2O).[14] The MI-E may be applied via a full-face mask or via the endotracheal or tracheostomy tube with the cuff inflated. Cough flow rates by MI-E have been shown to be superior to those generated by manual assisted coughing techniques alone.[44] However, its use is recommended in combination with manually assisted coughing in order to further increase cough flows. Treatment with the MI-E can be necessary as frequently as every few minutes around the clock until no further secretions are present.[22-33]

Secretion mobilization techniques that induce more efficient airway secretion clearance are also helpful and include manual chest percussion and postural drainage.[6] Provision of MI-E in combination with standard chest physical treatments may improve the management of airway mucous obstruction in NMD.[22]

Bronchoscopy should be considered only in cases of persistent atelectasis after all noninvasive airway clearance techniques have proven to be unsuccessful.[7]

NIPPV

Acute-on-chronic neuromuscular respiratory failure

NIPPV combined with mechanically assisted coughing has been established as standard practice in slowly progressive NMD patients without severe bulbar impairment, but requiring for ARF. In fact, this strategy may represent an effective life support measure that serves as an alternative to invasive MV, both in the outpatient patient and in the ICU.[11, 12, 22-24, 45, 46]

Admission to the hospital for ARF can be very disruptive for these patients,[47] who can be successfully managed at home by experienced and

TABLE IV.—*In hospital use of non-invasive positive pressure ventilation for patients with slowly progressive NMD with acute exacerbations of chronic respiratory failure.*

Study	Design	N. of patients (age)	Interventions	Main results	Limit
Vianello 2000 [23]	Prospective case-control	14 patients (38.8+23 yrs) *versus* 14 historical controls	E=NIPPV+CM C=MV via ETI	Mortality and treatment failure significantly lower in the NPPV group	Severe bulbar involvement
Servera 2005 [22]	Prospective cohort study	17 patients (48.7+20 yrs)	NIPPV + MI-E	Successful in averting death and ETI in 79.2% of the acute episodes	Severe bulbar involvement
Vianello 2005 [24]	Prospective case-control	11 patients (34.9+17.3 yrs) *versus* 16 historical controls	E=NIPPV + MI-E+ CPT; C= NIPPV+ CPT	Treatment failure was significantly lower in the experimental group	
Padman 1994 [52]	Retrospective study	11 NMD patients (+ 4 cystic fibrosis patients) with acute on chronic respiratory failure (4-21 yrs)	NIPPV	Treatment failure only 6.6% Significant RR and $PaCO_2$ improvement Number of patients needing intubation only 1	
Niranjan 1998 [53]	Retrospective study	10 patients (13-21 yrs)	NIPPV + MI-E	Avoidance of ETI in all patients	
Bach 2000 [55]	Retrospective study	11 children suffering from SMA type 1 (6–26 months) 28 distinct episodes of ARF	Immediately upon extubation the patients received NIPPV + MI-E	NIPPV was largely successful even in very young children with severe skeletal and bulbar muscle weakness	
Piastra 2006 [55]	Retrospective study	10 children (3 month-12 yrs)	NIPPV + CPT	The treatment was successful in eight out of 10 patients	

E: experimental; C: control; NIPPV: non-invasive positive pressure ventilation; CM: cricothyroid-mini-tracheostomy; MV: mechanical ventilation; ETI: endotracheal intubation; CPT: chest physical treatments; MI-E: mechanical insufflations-exsufflation; NMD: neuromuscolare disease; RR: respiratory rate; ARF: acute respiratory failure; SMA: spinal muscular atrophy; YRS: years.

well-trained family members.[48] Bach *et al.*[11, 12, 45, 46] described a regimen for managing acute-on-chronic neuromuscular respiratory failure at home. The patients receive 24-h NIPPV during the exacerbation. Pulse oximetry is monitored continuously and when oxygen saturation on room air falls below 95%, secretions are aggressively removed with MI-E until oxygen saturation returns to the 95% range. Although no controlled studies have established the efficacy of this approach, authors [11, 12, 45, 46, 49, 50] report dramatic reductions in the need for hospitalization and a prolongation of life expectancy.

NIPPV and assisted coughing techniques have also become standard therapy for the treatment of acute-on-chronic neuromuscular respiratory failure in the critical care setting.[22-24, 34, 35, 48] This increased utilization of NIPPV has been driven in large part by the desire to reduce patient discomfort and to avoid the sedation and complications of invasive MV.[51] Table IV summarizes the clinical studies on NIPPV in these patients.

In particular, in the study by Vianello *et al.*,[23] in-hospital mortality (14% *vs.* 57%), treatment failure (29% *vs.* 79%) and duration of ICU stay (13.6±9.7 *vs.* 47.1±51.9 days) were lower in the NIPPV group than in the invasive MV group. Interestingly, superimposed or unresolved pneumonia with septic shock was absent in individuals receiving nasal NIPPV. In contrast, these complications represented the reason for failure in six of the 11 subjects unsuccessfully treated via translaryngeal tube. In addition, the results of another prospective cohort study evaluating only NMD patients treated with a non-invasive approach (NIPPV and MI-E) showed a low mortality rate (8.3%) and a short hospital stay (12.05±7.04 days).[22] Moreover, the role of NIPPV as a reliable alternative to intubation finds indirect confirmation in the results of two other clinical investiga-

tions conducted in NMD patients treated with invasive MV for ARF.[47-50] In these studies, the mortality rate was 29% and 33%, respectively. Moreover, Bradley *et al.* reported a median weaning time period before being discharged to the community of ten weeks among survivors.

Patient selection remains important to the success of this ventilatory strategy. In fact, bulbar dysfunction increases the patient's risk for aspiration, hampers the elimination of airway secretions and increases resistance to airflow.[51, 56] This dysfunction can impede the successful use of NIPPV and MI-E.[52] In addition, patient training in NIPPV and assisted coughing before hospitalization is very important to the success of this therapeutic approach.[57]

In conclusion, only a few prospective studies on the management of slowly progressive NMD with acute-on-chronic respiratory failure have been performed,[22-24] perhaps because it is difficult to recruit NMD patients presenting with ARF.[51] These trials and other retrospective studies [11, 12, 45, 46, 52-54, 58, 59] have reported the success of NIPPV in improving gas exchange abnormalities and avoiding intubation in these patients. Therefore, a non-invasive approach (*i.e.*, NIPPV combined with assisted coughing) is preferred where feasible. If it fails or is contraindicated (*e.g.*, severe bulbar impairment), patients can be intubated as a short-term measure.

After recovery from the acute illness, patients without severe bulbar impairment should be promptly extubated and started immediately on NIPPV.[6, 48, 54]

The presence of indications for tracheotomy can be evaluated, but tracheotomy should not be considered in the acute phase.[6]

Rapidly progressive NMD with ARF

Bulbar dysfunction in these patients is often challenging. NIPPV is clearly inappropriate in patients with ARF unless upper airway function is well preserved. In addition, the use of NIPPV in patients with GBS or MG has not been extensively evaluated; only three small studies have been published [39, 40, 55] on the use of NIPPV in patients with MG and only two case reports on the use of NIPPV in patients with GBS.[60, 61] These studies have shown that NIPPV may prevent intubation in patients in myasthenic crisis while awaiting the effect of plasmapheresis or IVIG, but only in patients without hypercapnia.[39, 40] Therefore, there are insufficient data to date to recommend the widespread use of NIPPV in patients with rapidly progressive NMD syndromes presenting with ARF. If NIPPV is used, patients need to be carefully selected and treated in a monitored environment.[1]

Early tracheotomy should be encouraged if it appears that the patient will require endotracheal intubation beyond the first three weeks.[62]

Weaning

Withdrawal of NIPPV

NIPPV is initially delivered continuously, except for brief periods of rest to allow patients to speak and receive nutritional support. As the patient's physical condition improves, NIPPV becomes intermittent and assisted coughing is used more sparingly. Moreover, it is recommended that diurnal ventilation be reduced before nocturnal ventilation.[23, 57]

Extubation

The principles guiding the decision to extubate patients with ARF are also applicable for patients with NMD.[63] After recovery from an acute illness, NMD patients considered for extubation should have an adequate cough reflex, minimal secretions, and tolerate a low level of pressure support for a prolonged period of time without signs of respiratory fatigue.[1, 2] Moreover, some authors have recommended that extubation in NMD occur only when arterial oxygen saturation on room air has normalized.[54] There is a general agreement that, if not contraindicated (*e.g.*, severe bulbar impairment), patients with slowly progressive NMD should be extubated directly to NIPPV combined with assisted coughing.[6, 48, 54]

Extubation failure is relatively common in patients with MG (44% of extubation attempts), and atelectasis is the strongest predictor of this complication.[64]

Indications for long-term ventilation beyond the ICU

Patients with slowly progressive NMD who develop hypercapnic ARF should be referred to a

TABLE V.—*Key points for the clinical management of acute respiratory failure in patients with neuromuscular diseases.*

Slowly progressive NMD with acute exacerbations of chronic respiratory failure	Rapidly progressive NMD with acute episodes of respiratory failure
These patients frequently depend on long term mechanical ventilation	The acute onset of respiratory failure usually occurs in patients with a previously normal respiratory function
For patients, who do not have severe bulbar impairment, use of NIPPV in combination with assisted coughing is an effective alternative to invasive ventilation	Most often a generalized worsening of muscle function causes ARF without necessarily the presence of other respiratory diseases as triggering factors
For patients already using nocturnal NIPPV, daytime NIPPV may be needed during acute illness	NIPPV plays a small role in the management of these patients because bulbar dysfunction is often a challenge. NIPPV can avoid ETI in Myasthenic crisis, but only in patients without hypercapnia
If a non-invasive approach fails, patients can be intubated and mechanically ventilated as a short-term measure	The decision to intubate these patients should be made earlier rather than later, to avoid emergency intubation
After recovery from the acute illness, patients without severe bulbar impairment should be promptly extubated and treated with NIPPV combined with assisted coughing	Regular assessment for clinical signs of respiratory muscle fatigue and aspiration, and monitoring of VC, PImax, and PEmax are essential to determine the appropriate timing for intubation and mechanical ventilation
Tracheotomy can be considered, but it is not an acute intervention. A non-invasive approach is preferred where feasible	Early tracheostomy must be encouraged if intubation is still required after the first three weeks of invasive mechanical ventilation
Patients with SMA type 1, ALS, or other NMD in advanced stages of the disease require special attention for the complex ethical problems arising in case of irreversible endotracheal intubation need	

ARF: acute respiratory failure; NIPPV: non-invasive positive pressure ventilation; MG: myasthenia gravis; GBS: Guillain Barrè syndrome; ETI: endotracheal intubation; VC: vital capacity; PImax: maximum expiratory pressure; PEmax: maximum expiratory pressure; SMA 1: spinal muscular atrophy type 1; ALS: amyotrophic lateral sclerosis; NMD: neuromuscular diseases.

specialized center for assessment for long-term MV.[34] Generally, after recovery from the acute illness, NMD patients should have long-term ventilatory assistance if symptomatic nocturnal hypercapnia or daytime hypercapnia persists.[65]

Anticipatory respiratory care

Since slowly progressive NMDs are characterized by progressive clinical deterioration, these patients must be involved in the decision-making process regarding treatment escalation, such as endotracheal intubation, tracheotomy and eventually the option of palliative care.[66] Providing patients and their families with information about treatment options and anticipating possible future needs are crucial steps to appropriately tailor the management of respiratory issues in NMD patients. Advance discussion of a treatment plan should be standard of care for these patients, especially in patients diagnosed with type 1 SMA, ALS and other NMDs in the advanced stages of the disease, as these patients are the most fragile. When ARF occurs in these patients, special attention must be paid to the regulatory laws in each country and to the complex ethical issue of providing these patients with a permanent artificial airway (irreversible endotracheal intubation).

NIPPV is often the only way to maintain life in NMD patients who decline endotracheal intubation and invasive MV.[6, 67]

Conclusions

The variety and complexity of specific problems presented by different NMDs necessitate separate remarks on the adequate clinical manage-

ment of the two main types of ARF occurring in these patients (acute-on-chronic neuromuscular respiratory failure and rapidly progressive NMD with sudden respiratory failure (Table V). Although these suggestions can significantly improve patient outcomes and quality of life, they must be integrated with individualized clinical judgment at the bedside.

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Corresponding author: F. Racca, MD, Department of Anesthesiology and Resuscitation, S. Giovanni Battista Hospital, corso Dogliotti 14, 10126 Turin, Italy. E-mail: fabrizio.racca@gmail.com