Journal of Critical Care (2011) **xx**, xxx–xxx

ELSEVIER

Journal of Critical Care

Prevention of extubation failure in high-risk patients with neuromuscular disease☆,☆☆,★

Andrea Vianello MD[a,*], Giovanna Arcaro MD[a], Fausto Braccioni MD[a], Federico Gallan MD[a], Maria Rita Marchi MD[a], Stefania Chizio RRT[a], Davide Zampieri MD[a], Elena Pegoraro MD[b], Vittorino Salvador MD[a]

[a]*Respiratory Intensive Care Unit, City Hospital of Padova, Padova, Italy*
[b]*Department of Neurosciences, University of Padova, Padova, Italy*

Keywords:
Extubation;
Neuromuscular disorder;
Acute respiratory failure;
Noninvasive ventilation

Abstract

Background: A substantial proportion of patients with neuromuscular disease (NMD) who undergo positive pressure ventilation via endotracheal intubation for acute respiratory failure fail to pass spontaneous breathing trials and should be considered at high risk for extubation failure. In our study, we prospectively investigated the efficacy of early application of noninvasive ventilation (NIV) combined with assisted coughing as an intervention aimed at preventing extubation failure in patients with NMD.

Methods: This study is a prospective analysis of the short-term outcomes of 10 patients with NMD who were treated by NIV and assisted coughing immediately after extubation and comparison with the outcomes of a population of 10 historical control patients who received standard medical therapy (SMT) alone. The participants were composed of 10 patients with NMD who were submitted to NIV and assisted coughing after extubation (group A) and 10 historical control patients who were administered SMT (group B), who were admitted to a 4-bed respiratory intensive care unit (RICU) in a university hospital. Need for reintubation despite treatment was evaluated. Mortality during RICU stay, need for tracheostomy, and length of stay in the RICU were also compared.

Results: Significantly fewer patients who received the treatment protocol required reintubation and tracheostomy compared with those who received SMT (reintubation, 3 vs 10; tracheostomy, 3 vs 9; $P = .002$ and .01, respectively). Mortality did not differ significantly between the 2 groups. Patients in group A remained for a shorter time in the RICU compared with group B (7.8 ± 3.9 vs 23.8 ± 15.8 days; $P = .006$).

☆ All authors declare to have no financial or personal relationships with people or organizations that could have inappropriately influenced (biased) the study.

☆☆ No study sponsor was involved in the study design or in the collection, analysis, or interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

★ The authors have no conflicts of interest to declare.

* Corresponding author. Fisiopatologia Respiratoria Azienda Ospedaliera di Padova Via Giustiniani, 2 35128 PADOVA—Italy. Tel.: +39 049 8218587; fax: +39 49 8218590.

E-mail address: avianello@qubisoft.it (A. Vianello).

0883-9441/$ – see front matter
doi:10.1016/j.jcrc.2010.12.008

Conclusions: Preventive application of NIV combined with assisted coughing after extubation provides a clinically important advantage to patients with NMD by averting the need for reintubation or tracheostomy and shortening their stay in the RICU; its use should be included in the routine approach to patients with NMD at high risk for postextubation respiratory failure.

1. Introduction

The onset of acute respiratory failure (ARF), in most cases because of respiratory tract infection, is a crucial event in the advanced stage of most neuromuscular diseases (NMDs) and a major cause of death, unless mechanical ventilation (MV) is used [1-3].

Although noninvasive ventilation (NIV) can be a safer and more effective alternative to endotracheal intubation (ETI) in the treatment of neuromuscular ARF [4,5], 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 [6]. If a contraindication to NIV exists, positive pressure ventilation (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 [2,7,8]. It should be emphasized that extubation failure is an outcome to be avoided because it is independently associated with increased hospital mortality, prolonged intensive care unit (ICU) and hospital stay, higher costs, and greater need for tracheotomy [9]; therefore, strategies preventing this occurrence are required.

To avert extubation failure in patients at high risk, recent studies have evaluated the effectiveness of NIV as a preventive strategy, concluding that its application can reduce the need for reintubation and mortality rate in the ICU and suggesting its early use after extubation in individuals with chronic respiratory disorders (including chronic obstructive pulmonary disease, obesity hypoventilation, sequelae of tuberculosis, chest wall deformity, and chronic persistent asthma), congestive heart failure, and/or hypercapnia [10-12].

Sporadic case reports and small case series in the literature have demonstrated that NIV can be successfully applied to avoid reintubation and tracheostomy in patients with NMD [13-16]. In addition, a recent, large, noncontrolled study showed that the standardized use of NIV and cough assist can lead to effective extubation of almost all "unweanable" patients with NMD who could not pass an SBT, supporting the argument that timely provision of inspiratory and expiratory aids allows for virtual elimination of postextubation failure in patients with neuromuscular disorders [17].

These encouraging results and the dearth of controlled clinical studies prompted us to prospectively investigate the efficacy of a protocol providing early application of NIV combined with assisted coughing as an intervention aimed at preventing extubation failure in patients with NMD who have required ETI for ARF. To this end, we analyzed the clinical course of 10 subjects with advanced NMD at high risk for reintubation who were extubated after an episode of ARF and were submitted to NIV combined with assisted coughing and compared the results with the outcomes of 10 historical control patients who received standard medical therapy (SMT) after extubation. In particular, we hypothesized that the early use of NIV plus cough assist might outperform conventional treatment in terms of need for reintubation and tracheostomy, mortality, and length of stay in the ICU.

2. Methods

We compared the short-term outcomes of 10 patients with NMD extubated after an episode of ARF who were treated by NIV and assisted coughing after extubation (group A) with the outcomes of a population of 10 historical control patients who received SMT alone after extubation (group B). The patients gave their informed consent to the application of NIV and assisted coughing; those younger than 18 years reached this decision in accordance with their parents. The study was approved by the institutional review board.

2.1. Patients

Ten consecutive patients with NMD admitted to the respiratory ICU (RICU) of the City Hospital of Padova between January 2008 and April 2010 who had been intubated and ventilated for more than 48 hours and who were considered at high risk for developing postextubation respiratory failure were recruited (group A). The diagnoses were based on standard clinical, enzymatic, electromyographic, DNA, and biopsy data.

The ability to cough was assessed using the measurement of peak cough expiratory flow (PCEF) obtained from pulmonary function testing done in stable clinical conditions

within 6 months of admission; an unassisted PCEF level of less than 160 L/min was considered ineffective to clear airway secretions [18].

The degree of swallowing impairment was evaluated by the Gilardeau score (GS), which provides a functional classification of deglutition impairment in patients with NMD, taking into account the type of food involved and ranging from stage 0 ("no difficulty") to stage 4 ("great difficulty") [19]; GS was calculated before intubation.

Inclusion criteria were the following:

1. Diagnosis of NMD
2. MV via ETI more than 48 hours after an episode of ARF
3. Successful SBT plus 1 or more of the following high-risk conditions:
   - More than 1 consecutive extubation failure before the admission to our unit;
   - Ineffective cough defined as PCEF less than 160 L/min;
   - Mild to considerable swallowing impairment defined as stage 1 to 3 at GS;
   - Hypercapnia ($Paco_2$, >45 mm Hg) during the SBT.

Weaning from MV was performed according to standardized protocols, although not specifically designed for patients with NMD, using gradual daily reduction of pressure support. Spontaneous breathing trial consisted of a period of breathing through the endotracheal tube without ventilator support (use of a pressure of less than 8 cm of water) [20]. A weaning trial was done once the patient had reached a phase of clinical stability and met the following criteria: absence of excessive tracheobronchial secretions; resolution of acute-phase disease for which the patient was intubated; stable cardiovascular status; stable metabolic status; absence of hyperthermia, adequate mentation, adequate oxygenation (arterial oxygen saturation [Sao_2] >90% on fraction of inspired oxygen <0.4 or Pao_2/fraction of inspired oxygen >150 mm Hg) with an external positive end-expiratory pressure of less than 5 cm H_2O [20].

In accordance with published criteria, the patients able to tolerate the SBT for 2 hours were extubated [21]. Extubation was contraindicated in the presence of severe swallowing impairment, as expressed by stage 4 at GS, because of the excessive risk of aspiration.

The presence of a facial deformity sufficient to affect mask fitting constituted an exclusion criterion.

The control group (group B) consisted of 10 historical controls consecutively admitted to our RICU between January 2004 and December 2006. Patients admitted in 2007 could not be considered because of the lack of availability of clinical records. Patients in group B were affected with NMD and had developed ARF requiring intubation and prolonged MV; they received SMT alone after extubation. The SMT included the following: (1) oxygen therapy delivered to achieve Sao_2 >92%; (2) conventional chest physical treatments usually consisting of (*a*) postural drainage, (*b*) chest compression and/or abdominal thrust, and (*c*) nasotracheal and/or oral suctioning, when needed; and (3) standard pharmacologic treatment, decided by the attending physicians. Two patients who presented hypercapnia after extubation had been administered NIV during nighttime. None of the control patients were subsequently enrolled as a study patient.

Baseline characteristics of the 2 groups at the time of admission in the RICU are compared in Tables 1 and 2. The following data were recorded: anthropometrics, baseline diagnosis, diagnosis related to ARF, number of chronic nonrespiratory comorbidities [22], severity of illness assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II score [23], degree of swallowing impairment (GS) [19], number of respiratory hospitalizations during the 2 years preceding admission, forced vital capacity (FVC) and PCEF obtained from pulmonary function testing done within 6 months of admission, and arterial blood gas (ABG) tensions from the radial artery by means of a blood gas analyzer (Rapidpoint 405; SIEMENS AG, Munich, Germany) during spontaneous breathing with supplemental oxygen. Supplemental oxygen therapy had in most cases been initiated during transport of the patients to the RICU.

Immediately before extubation, respiratory rate, heart rate, ABG values, and Sao_2 were recorded. These parameters are listed in Table 3.

If needed, the time and reason for reintubation were recorded. All patients were followed-up until discharge from the RICU. The length of stay in the RICU and the vital status at time of discharge were recorded.

2.2. Protocol

2.2.1. Noninvasive ventilation

Noninvasive ventilation was delivered immediately after extubation by an ICU ventilator using the assist/control mode. At the start of MV, the ventilator was adjusted to obtain a V_T of 10 to 12 mL/kg and a respiratory rate of less than 25 breaths/min; the ventilator setting was then readjusted based on measurements of ABG, with the goal of maintaining satisfactory gas exchange, that is, Sao_2 greater than 92%, with $Paco_2$ less than 45 mm Hg and pH greater than 7.35. Supplemental oxygen was delivered when necessary to raise Sao_2 above 92%; external positive end-expiratory pressure was never added. A full face mask was used on all the patients to start NIV and then, in some cases, substituted by a nasal one after the first few hours of ventilation. Colloid dressings were placed on the major pressure points to minimize skin injury.

Noninvasive ventilation was initially delivered continuously, except for brief periods of "rest" (30-60 minutes), to allow the patients to receive dietary liquid supplements, drink water, and speak. After the first 24 hours, if clinical conditions and blood gas exchange were satisfactory, the application of NIV was interrupted by progressively longer intervals of spontaneous breathing; when necessary, supplemental oxygen was delivered during spontaneous breathing by nasal cannula or a venturi mask, to maintain Sao_2 above

Table 1 Anthropometric, clinical, pulmonary function, and blood gas data at study entry and clinical outcome of patients submitted to NIV plus assisted coughing (group A) and control subjects (group B)

	Patient, n	Type of NMD	Age (y)	BMI (kg/m^2)	Etiology of ARF	APACHE II	Comor, n	Hosp, n	HMV (h/d)	GS	FVC (L)	PCEF, (L/s)	Pao_2 (mm Hg)	$Paco_2$ (mm Hg)	pH	Complications and outcome
	1A	DMD	17	15	Aspiration bronchitis	11	2	0	0	1	0.66	1.27	129 *	94	7.21	TBM, trach, discharged
	2A	CM	17	18	Aspiration pneumonia	14	2	1	7	3	NA	NA	85 *	54	7.36	inhalation, trach, discharged
	3A	MG	46	24.8	Myasthenic crisis	9	3	1	0	1	1.22	2.52	91 *	111	7.21	Success
Group A	4A	SMA	42	12.9	Pneumonia	14	2	1	0	3	0.26	0.66	75 *	44	7.36	Nose abrasion, Success
	5A	LGMD	30	32	Pneumonia	7	0	0	10	0	1.42	4.25	75 *	46	7.32	Nose abrasion, Success
	6A	CM	21	22.2	Pneumonia	24	3	1	8	3	NA	NA	63	82	7.20	Inhalation, trach, discharged
	7A	DMD	14	22	Pneumonia	12	0	2	10	0	0.21	0.59	61	35	7.49	Success
	8A	CM	10	15	Pneumonia	6	1	0	8	1	0.74	0.86	162 *	115	7.05	Success
	9A	DMD	18	24	Bronchitis	11	2	1	0	0	0.66	2.33	135 *	79	7.20	Success
	10A	DMD	16	26	Pneumonia	11	0	1	10	0	0.68	1.86	94 *	79	7.29	Success
	1B	NM	27	11	Pneumonia	8	1	0	0	0	0.69	2.99	31	65	7.32	ETI, trach, discharged
	2B	FSHMD	57	20.3	Heart failure	12	1	0	0	0	NA	NA	36	90	7.20	HF, ETI, died
	3B	DMD	23	18	Bronchitis	8	1	3	12	3	1.14	3.08	69	39	7.36	ETI, trach, discharged
Group B	4B	AMD	35	17	Fever, ARMW	11	0	1	0	2	0.75	0.86	101 *	64	7.32	ETI, trach, discharged
	5B	ALS	78	21.2	Pneumonia	18	1	2	10	3	NA	NA	151 *	107	7.09	ETI, trach, discharged
	6B	DMD	14	16	Bronchitis	20	2	0	8	0	NA	NA	99 *	64	7.32	ETI, trach, discharged
	7B	DMD	14	23.3	Bronchitis	8	1	2	8	2	0.65	1.12	86 *	48	7.34	ETI, trach, pneumonia, died
	8B	DMD	32	24.2	Pneumonia	5	1	0	12	3	1.39	2.40	103 *	31	7.45	Success
	9B	DMD	25	10.2	Pneumonia	10	1	1	9	1	0.29	0.73	55	57	7.45	Success
	10B	MD	44	30	Pneumonia	10	2	1	9	2	0.98	1.55	60	71	7.38	Success

BMI indicates body mass index; DMD, Duchenne muscular dystrophy; ALS, amyotrophic lateral sclerosis; SMA, spinal muscular atrophy; MG, myasthenia gravis; LGMD, limb girdle muscular dystrophy; NM, nemaline myopathy; FSHMD, facioscapulohumeral muscular dystrophy; AMD, acid maltase deficiency; CM, congenital myopathy; MD, myotonic dystrophy; ARMW, acute respiratory muscle weakness; trach, tracheostomy; comor, comorbidity; hosp, hospitalization; NA, not available.

* Supplemental oxygen therapy.

Table 2 Anthropometric, clinical, pulmonary function, and blood gas data at admission to RICU in patients submitted to NIV plus assisted coughing (group A) and to SMT (group B)

	Group A	Group B	*P*
No. of subjects	10	10	–
Age (y)	23 ± 12.19	35 ± 20	.12
BMI (kg/m^2)	21.9 ± 5.87	19.1 ± 6.0	.30
Sex (male; female)	5; 5	7; 3	.240
Diagnosis related to ARF, n			
Pneumonia	7	5	.64
Bronchitis	2	3	.64
Heart failure	–	1	1
Other	1	1	1
APACHE II	12 ± 4,99	11 ± 5	.659
Comorbidities, n	1.5 ± 1.17	1 ± 0.42	.219
GS	1.2 ± 1.31	1.6 ± 1.26	.56
Hospitalizations in 2 y, n	1 ± 0.63	1 ± 1.05	1
Patients previously administered HMV, n	6	7	.74
HMV use (h/d)	5.3 ± 5.1	6.8 ± 6.1	.35
FVC (L)	0.73 ± 0.41	0.84 ± 0.36	.53
PCEF (L/min)	1.79 ± 1.23	1.81 ± 0.99	.96
Pao_2 (mm Hg)	97 ± 33.83	79 ± 36.33	.26
$Paco_2$ (mm Hg)	74 ± 28.22	64 ± 26	.42
pH	7.27 ± 0.12	7.34 ± 0.13	.22
Oxygen saturation (%)	95 ± 2.58	95 ± 3	1

Values are expressed as mean ± SD.

Table 3 Clinical and blood gas data at the time of extubation and outcomes of patients submitted to NIV plus assisted coughing (group A) and to SMT (group B)

	Group A	Group B	*P*
Reason to be considered at risk for reintubation, n			
>1 consecutive extubation failure	3	5	.48
Ineffective cough	4	5	.61
Swallowing impairment	5	3	.65
Hypercapnia ($Paco_2$ >45 mm Hg)	7	2	.07
Respiratory rate (breaths/min)	17.0 ± 4.1	17.6 ± 4.6	1
Heart rate (beats/min)	104.7 ± 11	117.3 ± 8.7	.01
Pao_2 (mm Hg)	88 ± 31	97 ± 44	.60
$Paco_2$ (mm Hg)	50 ± 13.5	41 ± 13	.14
pH	7.43 ± 0.04	7.43 ± 0.09	1
Oxygen saturation (%)	96 ± 3.8	96 ± 3	1
Reintubation, n	3	10	.002
Tracheostomy, n	3	9	.010
Death, n	0	2	.235
ICU stay (d)	7.8 ± 3.9	23.8 ± 15.8	.0061

Values are expressed as mean ± SD.

92%. In all cases, nocturnal ventilation via nasal mask was continued until discharge from the RICU.

2.2.2. Assisted coughing

The following techniques were used to improve ability to clear secretions, depending on the patient's clinical status and level of cooperation:

1. Manually assisted coughing, to provide an optimal insufflation followed by an abdominal thrust in conjunction with the patient's coughing efforts. The ICU ventilator was used for delivering the deep insufflations. Patients were taught to maximally expand their lungs by "air stacking" (retaining consecutive) ventilator delivered volumes; once air stacked, the abdominal thrust was provided [24].

2. Mechanically assisted coughing (Mech-AC), delivered in the presence of stiffness of the chest wall (ie, severe thoracic deformity or obesity) and to uncooperative patients unable to fully perform air stacking. A mechanical device (Pegaso Cough; DIMA Italia, Bologna, Italy) was applied via a face mask, based on the simple principle of releasing alternating positive and negative pressure across the airway opening. It consists of a 2-stage axial compressor that provides positive pressure to the airway then rapidly shifts to negative pressure, thereby generating a forced expiration. The insufflation and exsufflation pressures and timing were independently adjusted according to efficacy and patient tolerance; generally, pressures between +30 and−40 cm H_2O were applied [25]. Although the Pegaso device has not been widely studied, its comfortable and successful application has been reported in the scientific literature [26].

Typically, a session of assisted coughing was provided whenever the Sao_2 level decreased, ventilator peak inspiratory pressure increased, or the patient had an increase in dyspnea or sense of retained secretions. Treatments were usually repeated until 1 or more of the following were observed: reduction in dyspnea, reduction in respiratory rate, sputum elimination, improved breathing sounds, increased percussion resonance, and increased Sao_2 level. Manually assisted coughing and Mech-AC were usually administered by a respiratory therapist except during weekends, when only trained nonprofessional caregivers (ie, patient's home care attendant, a family member, residents) were available. The daily treatment frequency was recorded on a diary by nurses.

2.2.3. Criteria for reintubation

The decision to perform ETI was made by the patient's treating physician, according to the criteria usually used for patients developing postextubation respiratory failure; in particular, patients were reintubated if they met at least 1 of the following criteria: (*a*) respiratory acidosis (pH <7.35 with a $Paco_2$ >45 mm Hg or, in the presence of hypercapnia at the time of extubation, a $Paco_2$ increase of >15%); (*b*) hypoxemia (ie, Sao_2 to <85%, despite the use of a high fraction of inspired oxygen); (*c*) a significant increase in respiratory rate; (*d*) changes in mental status, rendering the patient unable to tolerate NIV; (*e*) clinical signs of respiratory muscle fatigue (use of accessory muscles, inward movements of the abdomen

during inspiration); (*f*) severe dyspnea; and (*g*) copious secretions that could not be adequately cleared or that were associated with acidosis, hypoxemia, or changes in mental status [27]. Endotracheal intubation was also promptly performed in emergency situations such as coma, cardiac or respiratory arrest, or severe hypotension despite adequate volume challenge, the use of vasopressors, or both.

The treating physician recorded the single most relevant cause of reintubation and the total days of RICU stay.

2.2.4. Study end points and statistical analysis

The primary end point was need for reintubation in the RICU. Secondary end points were tracheostomy, death, and length of stay in the RICU.

A sample size estimation with a type I error of 0.05 and a power of 90% determined that a significant clinical difference in need for reintubation would be detected with a minimum of 10 subjects per group based on an expected difference in clinical outcome of 0.7 between the study and the control groups. The Fisher exact test was used to compare categorical variables (need for reintubation, tracheostomy, and death), and the Student *t* test was used to compare continuous variables (anthropometric data, degree of dysphagia, pulmonary function and blood gas data at study entry and at the time of reintubation, and length of stay in the RICU).

3. Results

Sixteen patients with NMD were considered to be at high risk for postextubation respiratory failure and, therefore, eligible for the study. Six of the patients were excluded because of severe swallowing impairment contraindicating extubation, and the remaining 10 patients were recruited. All of the excluded patients were affected by amyotrophic lateral sclerosis.

Table 1 lists diagnoses, anthropometrics, etiologies of ARF, APACHE II score, number of comorbidities, GS, number of hospitalizations, previous use of noninvasive home mechanical ventilation (HMV), FVC and PCEF (obtained 5.6 ±1.2 months prehospitalization), ABG obtained before intubation, and complications and outcomes of the individual subjects. All of the subjects (except for case 4B) were wheelchair bound. Severe respiratory tract infection (bronchitis or pneumonia) was the most common cause of acute decompensation in both groups; subject 2B presented with heart failure at admission. Supplemental oxygen therapy initiated during transport to our RICU might have contributed to the worsening of respiratory acidosis in 8 of the patients in group A and 5 in group B. There were no significant differences between groups A and B in any of the parameters noted in Table 2.

The response to NIV plus assisted coughing in comparison with SMT is reported in Table 3. In group A, all of the patients tolerated the application of NIV as required by the protocol; patients 4A and 5A developed nose-skin abrasion but did not discontinue therapy. The number of assisted coughing sessions per day ranged from 2 to 6 (mean, 4 ± 1.1), including treatments administered by nonprofessional care providers. Mechanically assisted coughing was administered to patients 2A, 4A, and 6A because of inability to perform the air-stacking maneuver. In group B, patients 4B and 9B received NIV during nighttime in addition to SMT.

Patients receiving the treatment protocol showed a significantly reduced need for reintubation and tracheostomy compared with those who received SMT alone (reintubation, 3 vs 10; tracheostomy, 3 vs 9; Fisher exact *P* value = .002 and .01, respectively). Mortality did not significantly differ in the 2 groups (0 vs 2; Fisher exact *P* value = .235). In addition, patients in group A stayed for a shorter time in the RICU compared with group B (7.8 ± 3.9 vs 23.8 ± 15.8 days; *P* = .006).

Among patients in group A, the treatment protocol failed in cases 1A, 2A, and 6A. Patient 1A initially remained stable but, after 24 hours, began to rapidly deteriorate, showing clinical signs of respiratory muscle fatigue, and was intubated because of worsening respiratory acidosis. Bronchoscopic examination performed immediately after ETI showed a narrowing of the airway lumen in the sagittal diameter and an excessive expiratory collapse of the trachea and mainstem bronchi consistent with tracheobronchomalacia (TBM). He was then tracheostomized. Patients 2A and 6A experienced persistent inhalation of saliva and sputum retention within 24 hours of extubation, resulting in severe oxyhemoglobin desaturation and the need for repeated bronchoscopic assisted aspiration. Both patients were intubated to protect their airways and subsequently underwent placement of both a gastrostomy tube for enteral feeding and a tracheostomy. The remaining 7 patients in group A had an uncomplicated clinical course and were discharged from the RICU on nocturnal-only NIV.

All the patients in group B had to be reintubated. Five patients (1B, 4B, 6B, 9B, and 10B) underwent ETI because of worsening respiratory distress, as indicated by severe dyspnea, clinical signs of respiratory muscle fatigue, and derangement of ABG; after intubation, they failed to wean from MV and were tracheostomized. Patient 2B was reintubated because of severe hypotension and died on the ninth day after intubation as a consequence of cardiac failure. Patients 3B and 5B were reintubated and then tracheostomized because of inability to adequately protect the upper airway with repeated aspiration of saliva causing severe oxyhemoglobin desaturation. Patients 7B and 8B were administered ETI within a few hours after extubation because of difficulty in breathing, agitation, and anxiety and were tracheostomized; patient 8B subsequently died as a consequence of unresolved pneumonia, complicated by irreversible septic shock.

4. Discussion

This is the first time, to our knowledge, that the efficacy of early application of NIV combined with assisted coughing in preventing postextubation respiratory failure in patients with

NMD who passed SBTs has been prospectively evaluated in a controlled study. Our results demonstrate that this treatment protocol is effective in averting the need for reintubation or a tracheostomy and reducing the duration of ICU stay. Although the use of historical controls is a scientific limitation of our study, it is important to note that, except for the application of NIV plus cough assist to group A, there were no significant changes in personnel or treatment protocols in our RICU during the study period that might have influenced the outcomes of the 2 groups.

Once patients with NMD have been intubated, they are at risk for a series of complications, including ventilator-associated pneumonia, respiratory muscle atrophy, and bacteremia [2,28]; for this reason, efforts should be done to limit the duration of invasive PPV and remove the endotracheal tube as soon as the patient is capable of sustaining spontaneous breathing. Unfortunately, extubation intolerance is a common occurrence among patients with NMD who have been stabilized on PPV because of weakness of the inspiratory muscles, leading to incomplete lung expansion and rapidly progressive hypoventilation, poor cough strength, and inability of patients to protect their upper airway with the need for airway suctioning and an increased risk of aspiration and pneumonia [1,2,7,29]. In particular, impaired ability to expel secretions is a crucial component of extubation failure: in fact, Bach and Saporito [18] have reported that all 43 postextubation patients with NMD with effective cough, as expressed by PCEF (unassisted or assisted) of more than 160 L/min remained successfully extubated, whereas all 15 with PCEF under this level had to be reintubated within 48 hours, the most likely reason being airway congestion because of the lack of adequate cough assistance. In addition, patients who had passed SBT, as in our case, but presented PCEF of 60 L/min or less were nearly 5 times more likely to fail extubation compared with those with PCEF higher than 60 L/min [30].

Noninvasive ventilation is increasingly being used to prevent extubation failure, with recent trials also having included patients with NMD. In particular, Mayordomo-Colunga et al [31] delivered "elective" or "rescue" NIV to a series of 36 children deemed at high risk for 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 [31]. In comparison with this data, the lower incidence of extubation failure found in our group (3/10 vs 8/14 cases) supports the view that the combination of NIV plus cough assist may be more effective than NIV alone. In fact, 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 oxyhemoglobin desaturation [32].

Although our protocol has shown the potential to reduce the need for reintubation and expedite weaning time for NMD individuals, our success rate was significantly lower compared with the recent, large experience published by Bach et al [17]. In our experience, the ventilator-delivered volumes and the frequency of assisted coughing treatments were significantly lower than those reported in the study of Bach et al. Thus, our less aggressive regimen could explain why our outcomes were less favorable, particularly if we consider that a number of patients showed baseline Sa_{O_2} less than 95% at the time of extubation; in fact, such a condition might have been caused by residual airway secretions and has been reported to increase the rates of extubation failure [33].

This said, we believe that the adverse outcome of a number of patients also suggests that there are clinical conditions in which ventilatory and cough assistance may still be ineffective. In particular, an unsuccessfully treated child in group A (case 1A) was intubated as a consequence of TBM causing respiratory distress and acute respiratory acidosis: according to prior experience, this outcome points out that TBM can be an unexpected cause of failed extubation, rendering NIV ineffective and requiring tracheostomy or the insertion of an airway stent [34].

In addition, although patients with a clinical history of substantial deglutition impairment were excluded from our treatment protocol, patients 2A and 6A had to be reintubated because of a complete inability to swallow with aspiration of saliva causing persistent oxyhemoglobin desaturation; this is similar to published data, which reported the need for a tracheal tube in patients with NMD showing severe, irreversible dysphagia causing baseline Sa_{O_2} to be less than 95% [35].

On this basis, we can hypothesize that tachypnea, dyspnea, and continuous NIV after extubation may hamper swallowing efforts and exaggerate preexisting swallowing difficulties. Thus, deglutition disorders, although limited, may compromise this treatment protocol, particularly in patients who are unable to fully adhere to assisted-coughing techniques, and careful evaluation of deglutition ability should be recommended when deciding to make an extubation attempt in patients with NMD [36]. It should be emphasized that switching to mouthpiece NIV during meals has been proposed to minimize the risk of aspiration: in fact, providing high tidal volumes (1-1.5 L) by a mouthpiece at a reduced respiratory frequency could leave the patients enough time to manipulate food boluses and trigger swallowing between inhalations [37].

Finally, it is noteworthy that our noninvasive approach allowed most patients to avoid resorting to a tracheostomy. Given that life satisfaction may be poor for individuals with NMD who are administered a tracheostomy at the time of a respiratory crisis and that tracheostomized patients are also likely to experience greater difficulty in returning home [38,39], we believe that our protocol also has a positive impact from an ethical point of view.

In conclusion, the findings of our investigation provide support for considering preventive use of NIV plus assisted coughing an effective means to avert the need for

reintubation in patients with NMD and for including its application in the routine approach to NMD individuals at high risk for postextubation respiratory failure. Nevertheless, we believe that a significant proportion of patients with NMD, namely, subjects with substantial swallowing dysfunction and inadequate cooperation such as the case of advanced bulbar amyotrophic lateral sclerosis and some spinal muscular atrophy type 1, may still encounter particular difficulties although being liberated from the endotracheal tube and that patient selection and close monitoring remain important for successful discontinuation of invasive MV.

References

1 Metha S. Neuromuscular disease causing acute respiratory failure. Respir Care 2006;51:1016-21.
2 Hill NS. Neuromuscular disease in respiratory and critical care medicine. Respir Care 2006;51:1065-71.
3 Racca F, Del Sorbo L, Mongini T, Vianello A, Ranieri VM. Respiratory management of acute respiratory failure in neuromuscular diseases. Minerva Anestesiol 2010;76:51-62.
4 Vianello A, Bevilacqua M, Arcaro G, Gallan F, Serra E. Non-invasive ventilatory approach to treatment of acute respiratory failure in neuromuscular disorders. A comparison with endotracheal intubation. Int Care Med 2000;26:384-90.
5 Servera E, Sancho J, Zafra MJ, Català A, Vergara P, Marin J. Alternative to endotracheal intubation for patients with neuromuscular diseases. Am J Phys Med Rehabil 2005;84:851-7.
6 Hill NS, Brennan J, Garpestad E, Nava S. Noninvasive ventilation in acute respiratory failure. Crit Care Med 2007;35:2402-7.
7 Bradley MD, Orrell RW, Clarke J, Davidson AC, Williams AJ, Kullmann DM, Hirsch N, Howard RS. Outcome of ventilatory support for acute respiratory failure in motor neurone disease. J Neurol Neurosurg Psychiatry 2002;72:752-6.
8 Simonds AK. Streamlining weaning: protocols and weaning units. Thorax 2005;60:175-82.
9 Epstein SK. Extubation failure: an outcome to be avoided. Crit Care 2004;8:310-2.
10 Nava S, Gregoretti C, Fanfulla F, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med 2005;33:2465-70.
11 Ferrer M, Valencia M, Nicolas JM, et al. Early noninvasive ventilation averts extubation failure in patients at high risk: a randomized trial. Am J Respir Crit Care Med 2006;173:164-70.
12 Ferrer M, Sellarés J, Valencia M, et al. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. Lancet 2009;374:1082-8.
13 Restrick LJ, Scott AD, Ward EM, French R, Cornwell WE, Wedjicha JA. Nasal intermittent positive-pressure ventilation in weaning intubated patients with chronic respiratory disease from assisted intermittent positive pressure ventilation. Respir Med 1993;87:199-204.
14 Birnkrant DJ, Pope JF, Eiben RM. Management of the respiratory complications of neuromuscular diseases in the pediatric intensive care unit. J Child Neurol 1999;14:139-43.
15 Reddy VG, Nair MP, Bataclan F. Role of non-invasive ventilation in difficult-to-wean children with acute neuromuscular disease. Singapore Med J 2004;45:232-4.
16 Plant N, Walker R. Immediate extubation to noninvasive ventilation can reduce postoperative morbidity and need for PICU in children with neuromuscular disorders. Paediatr Anaesth 2009;19:549-50.
17 Bach JR, Gonçalves MR, Hamdani I, Winck JC. Extubation of patients with neuromuscular weakness: a new management paradigm. Chest 2010;137:1033-9.
18 Bach JR, Saporito LR. Criteria for extubation and tracheostomy tube removal for patients with ventilatory failure: a different approach to weaning. Chest 1996;110:1566-71.
19 Willig TN, Gilardeau C, Kazandjian MS, et al. Dysphagia and nutrition in neuromuscular disorders. In: Bach JR, editor. Pulmonary Rehabilitation. The obstructive and paralytic conditions. Philadelphia: Hanley and Belfus; 1996. p. 353-69.
20 Esteban A, Anzueto A, Frutos-Vivar F, et al. Mechanical Ventilation International Study Group. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA 2002;287:345-55.
21 Boles JM, Bion J, Connors A, et al. Weaning from mechanical ventilation. Eur Respir J 2007;29:1033-56.
22 Charlson ME, Pompei P, Ales KL, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
23 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.
24 Bach JR. Mechanical insufflation-exsufflation: comparison of peak expiratory flows with manually assisted and unassisted coughing techniques. Chest 1993;104:1553-62.
25 Tzeng AC, Bach JR. Prevention of pulmonary morbidity for patients with neuromuscular disease. Chest 2000;118:1390-6.
26 Toussaint M, Steens M, Soudon P. Mechanical insufflation-exsufflation (cough-assist and Pegaso): background, indications and recommendations for clinical practice. Reanimation 2009;18:137-45.
27 Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med 2004;350:2452-60.
28 Henderson RD, Lawn ND, Fletcher DD, McClelland RL, Wijdicks EF. The morbidity of Guillain-Barre' syndrome admitted to the intensive care unit. Neurology 2003;60:17-21.
29 Kurachek SC, Newth CJ, Quasney MW, et al. Extubation failure in pediatric intensive care: a multiple-center study of risk factors and outcomes. Crit Care Med 2003;31:2657-64.
30 Salam A, Tilluckdharry L, Amoateng-Adjepong Y, Manthous CA. Neurologic status, cough, secretions and extubation outcomes. Intensive Care Med 2004;30:1334-9.
31 Mayordomo-Colunga, Medina A, Rey C. Non invasive ventilation after extubation in paediatric patients: a preliminary study. BMC Pediatrics 2010;10:29-36.
32 Mellies U, Dohna-Schwake C, Voit T. Respiratory function assessment and intervention in neuromuscular disorders. Curr Opin Neurol 2005;18:543-7.
33 Goncalves MR, Bach JR. Mechanical insufflation-exsufflation improves outcomes for neuromuscular disease patients with respiratory tract infections: a step in the right direction. Am J Phys Med Rehabil 2007;84:89-91.
34 Murgu SD, Cherrison LJ, Colt HG. Respiratory failure due to expiratory central airway collapse. Respir Care 2007;52:752-4.
35 Bach JR, Bianchi C, Aufiero E. Oximetry and indications for tracheotomy for amyotrophic lateral sclerosis. Chest 2004;126:1502-7.
36 Willig TN, Paulus J, Lacau ST, et al. Swallowing problems in neuromuscular disorders. Arch Phys Med Rehabil 1994;75:1175-81.
37 Bach JR, Gonzalez M, Sharma A, Swan K, Patel A. Open gastrostomy for noninvasive ventilation users with neuromuscular disease. Am J Phys Med Rehabil 2010;89:1-6.
38 Moss AH, Oppenheimer EA, Casey P, Cazzolli PA, Roos RP, Stocking CB, Siegler M. Patients with amyotrophic lateral sclerosis receiving long-term mechanical ventilation: advance care planning and outcomes. Chest 1996;110:249-55.
39 Oppenheimer EA. Amyotrophic lateral sclerosis: care, survival and quality of life on home mechanical ventilation. In: Robert D, Make BJ, Leger P, Goldberg AJ, Paulus J, Willig TN, editors. Home Mechanical Ventilation. Paris: Arnette-Blackwell; 1995. p. 249-60.