Ther Adv Respir Dis
2019, Vol. 13: 1–13
DOI: 10.1177/1753466619875928

Combined noninvasive ventilation and mechanical insufflator–exsufflator for acute respiratory failure in patients with neuromuscular disease: effectiveness and outcome predictors

Tai-Heng Chen, Wen-Chen Liang, I-Chen Chen, Yi-Ching Liu, Jong-Hau Hsu and Yuh-Jyh Jong

Abstract

Background: To determine the effectiveness of combined noninvasive ventilation (NIV) and mechanical insufflator-exsufflator (MI-E) for acute respiratory failure (ARF) in patients with neuromuscular disease (NMD), and outcome predictors.

Methods: A prospectively observational study of patients with ARF was conducted in a pediatric intensive care unit (PICU). All received combined NIV/MI-E during PICU stays between 2007 and 2017. Pertinent clinical variables of heart rate (HR), respiratory rate (RR), pH, $PaCO_2$, and PaO_2/FiO_2 ratio were collected at baseline and at 2 h, 4-8 h, and 12-24 h after initiating use of NIV/MI-E. Treatment success was defined as avoiding intubation.

Results: A total of 62 ARF episodes in 56 patients with NMD (median age, 13 years) were enrolled. The most frequent underlying NMD was spinal muscular atrophy (32/62, 52%). ARF was primarily due to pneumonia (65%). The treatment success rate was 86%. PICU stay and hospitalization were shorter in the success group (9.4±6.1 *vs.* 21.9±13.9 days and 16.3±7.8 *vs.* 33.6±17.9 days, respectively; both $p<0.05$). HR, RR, pH, and $PaCO_2$ showed a progressive improvement, particularly after 4 h following successful NIV/MI-E treatment. RR decrease at 4 h, and pH increase and $PaCO_2$ decrease at 4-8 h might predict success of NIV/MI-E treatment. The multivariate analysis identified $PaCO_2$ at 4-8 h of 58.0 mmHg as an outcome predictor of NIV/MI-E treatment.

Conclusions: Applying combined NIV/MI-E in the acute care setting is an efficient means of averting intubation in NMD patients with ARF. Clinical features within 8 h of the institution may predict treatment outcome.

The reviews of this paper are available via the supplemental material section.

Keywords: acute respiratory failure, mechanical insufflator-exsufflator, neuromuscular disease, noninvasive ventilation, outcome predictive factors, pediatric intensive care unit

Received: 5 June 2019; revised manuscript accepted: 19 August 2019.

Correspondence to:
Yuh-Jyh Jong
Department of Pediatrics, Kaohsiung Medical University Hospital, No. 100, Tzyou 1st Road, Kaohsiung 80708

Departments Laboratory Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung

Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung

Department of Biological Science and Technology, Institute of Molecular Medicine and Bioengineering, College of Biological Science and Technology, National Chiao Tung University, Hsinchu
yjjong@gap.kmu.edu.tw

Jong-Hau Hsu
Department of Pediatrics, Kaohsiung Medical University Hospital, #100, Tz-You 1st Road, Kaohsiung, 80708

Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung
jhh936@yahoo.com.tw

Tai-Heng Chen
Division of Pediatric Emergency, Department of Pediatrics, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung

PhD Program in Translational Medicine, Graduate Institute of Clinical Medicine, Kaohsiung Medical University and Academia Sinica

Introduction

In patients with chronic neuromuscular disease (NMD), baseline respiratory muscle weakness is typically exacerbated during community-acquired infections, and the risk of repeated respiratory tract infections is high. Such infections are often complicated by congested airway secretions, which are likely to precipitate acute respiratory

Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung

Wen-Chen Liang
I-Chen Chen
Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung

Departments of Pediatrics, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung

Yi-Ching Liu
Departments of Pediatrics, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung

failure (ARF).[1] Indeed, ARF accounts for most unplanned intensive care unit (ICU) admissions and is a common cause of prolonged ICU stay in patients with chronic NMD. Owing to a weakness of inspiratory muscles, inadequate cough, and inability to clear oropharyngeal secretions, a substantial proportion of patients with NMD who undergo invasive mechanical ventilation fail to pass trials of weaning after recovery from the acute illness and are at high risk for extubation failure (postextubation ARF).[2–4]

Over the pasts few decades, noninvasive ventilation (NIV) has been conventionally recognized as a life-prolonging tool for patients with chronic NMD.[1,5–7] However, emerging evidence has underscored the utility of NIV as a first-line intervention of ARF in the general population as well as in patients with NMD to avert intubation.[5,8,9] In addition, the potential benefits of short-term NIV support include facilitation of extubation, shorter ICU stays, and improved survival.[10–15]

In this group of patients, difficulty in clearing airway secretions is considered a major contributor to NIV failure.[16,17] Thus, a combination of mechanical insufflator–exsufflator (MI-E) coughing assistance and NIV has been shown to resolve ARF and facilitate extubation in patients with NMD efficiently.[11,13,18] Our recent pilot study of pediatric patients encompassing various NMDs has demonstrated the feasibility of this combined noninvasive approach.[19] However, there are still some patient requiring intubation after this NIV/MI-E approach, but risk factors predicting failure of averting intubation in these patients remain unclear.[3,17]

Herein we conducted a prospective observational study in a pediatric acute care setting, investigating a cohort of patients with NMD who received short-term continuous NIV/MI-E in combination as treatment of ARF. We aimed to validate the association between outcomes and effectiveness of combined NIV/MI-E treatment and, further, to identify potential outcome predictors.

Methods

Patients

This prospectively designed observational cohort study was conducted in a multidisciplinary 15-bed pediatric intensive care unit (PICU) of a university hospital. From 1 January 2007 to 30 November 2017, we enrolled patients with various NMDs admitted to the PICU due to ARF episodes which were initially managed by noninvasive airway approaches. All cases had a definite NMD diagnosis, confirmed with histopathological, genetic, or both studies at our Department of Pediatric Neurology. Although in our PICU, the majority of enrolled patients were pediatric cases, we also provided multidisciplinary care for adult patients whose NMD diagnosis had been made and received follow-up at our pediatric department. Therefore, even when some adult patients encounter ARF episodes, they would still prefer PICU admission for a consistent care specified to their underlying NMD. This work is an extension of our previous pilot study that has proposed the feasibility of combined noninvasive airway approach in treating ARF of pediatric patients with various NMDs.[19] However, owing to a limited number of patients and relatively shorter time frame of study period, the effectiveness of such treatment in ARF episodes of NMD patients is still unclear and the outcome predictors remain unknown.

The Institutional Review Board (IRB) of Kaohsiung Medical University Hospital had approved this study (KMUHIRB-SV(I)-20180020). The need for informed consent was waived under the agreement of IRB, because according to the relevant regulation, the application of combined NIV/MI-E on NMD patient was based on the well-established guideline of standard care which was not involved in investigating new therapeutic/monitoring technologies and, moreover, the waiver of consents would not jeopardize the patients' right to receive appropriate care.

We recruited study subjects according to whether combined NIV/MI-E used for (1) a first-line treatment as alternative for intubation, as the episodic ARF group; or (2) a rescue means for presenting signs of ARF or respiratory distress observed just after extubation (<12 h), as the postextubation ARF group. All respiratory managements were provided according to the guideline of standard care for NMD patients. The definition of ARF was based on our previously defined criteria,[19] as well as referred to the classifications of ARF types defined by Teague *et al.*,[20] which conformed to the following criteria: oxyhemoglobin saturation (SpO_2) <90% with fractional concentration of oxygen in inspired gas (FiO2) >0.6, arterial blood gas (ABG) showing partial arterial oxygen (PaO_2) <60 mmHg, a ratio

of PaO_2 to FiO_2 <300, or a partial arterial pressure of carbon dioxide ($PaCO_2$) ⩾50 mmHg, or clinical symptoms/signs observed by the attending physicians leading to the decision of ventilatory support. For those with episodic ARF identified at admission, patients have notified the possibility of subsequent intubation if failed to initial NIV attempts, and requesting a waiver of invasive ventilation were categorized 'do not intubate' (DNI) status. We excluded patients if they had: (1) severe bulbar dysfunction (e.g. absence of gag reflex, or vocal cord paralysis) which was evaluated by an attending neurologist, pediatric gastroenterologist, or both who diagnosed clinically through questionnaire of feeding status combined with or without videofluoroscopic swallowing study; (2) cardiopulmonary collapse; (3) recurrent apnea; (4) undrained pneumothorax; (5) multisystem failure; (6) a Glasgow Coma Scale score <10; and (7) uncontrolled seizures.

BiPAP/Mi-E protocol for ARF

Upon admission, patients and their guardians were informed of the availability of NIV and MI-E and the potential contraindications or complications related to its application in the NMD population.[1,5] The procedure of combined NIV and MI-E and required sedative agent selection were delivered according to our pre-established NMD-ARF protocol.[19,21] In brief, NIV was delivered continuously (>18–20 h on the first day) by bilevel positive airway pressure (BiPAP; Respironics®, Murrysville, PA) *via* nasal or facial mask, with pauses without mask of 5–10 min to perform clearance of airway secretions. For infants and children ⩽5 years old, when tolerated and effective (with minimal leak), we applied the Respironics® (Murrysville, PA) pediatric nasal mask with comfort flap and small child headgear. The initial settings of NIV were inspiratory positive airway pressure (IPAP) 8–10 cmH_2O and expiratory positive airway pressure (EPAP) 4–5 cmH_2O. Subsequently, the settings of BiPAP were adjusted following the protocol: (1) IPAP was escalated by an increment of 2 cm H_2O (maximum: 25 cm H_2O) to achieve an appropriate exhaled tidal volume; (2) EPAP was adjusted in a range of 4–12 cmH_2O to maintain SpO_2 >94% with a required FiO_2 <0.6. All patients were set on spontaneous breathing (SB) and/or spontaneous timed (ST) mode of ventilation with a programmed backup rate set at 2 breaths/min fewer than the estimated baseline respiratory rate. On subsequent days, ventilatory assistance was gradually reduced, depending on the clinical status. NIV was discontinued and patients were intubated based on the attending intensivist's clinical decision, including clinical indicators when $PaCO_2$ >65 mmHg, or pH < 7.25, or peripheral SpO_2 <85% despite maximal NIV setting, or when any of the exclusion criteria appeared.

The modality for airway clearance was provided by mechanical cough assist (MI-E; CoughAssist®, Philips Respironics®, The Netherlands). The MI-E was applied either combined with NIV or solitarily used in intubated patients. According to the protocol, the MI-E was applied whenever the patients' oxyhemoglobin saturation decreased <94%, ventilator IPAP increased, or airway secretions increased, as frequently as necessary, up to every 30 min, with a minimum of every 2–4 h around the clock. Initial inspiratory and expiratory pressures of MI-E were set at a low level (+15 and c15 cmH_2O, respectively), and then increased incrementally up to +60 and −60 cm H_2O, respectively, according to the patient's comfort and production of secretions. The positive-pressure breath was delivered to the patient over 1–2 s, while the negative exsufflation was delivered in 1–2 s. Three to five breaths were delivered followed by a period of rest before continuing, for a total of three to five cycles. Manually assisted cough augmentation might be provided intermittently followed by MI-E use based on the patient's tolerance and amounts of expectorated secretions.

In the postextubation group, patients had to be prepared before extubation, to have no or lowest dosage of sedative medication to maintain appropriate consciousness, to manage airway secretions in endotracheal tube through the MI-E protocol, and were ensured to have no contraindications of NIV use. The rescue NIV/MI-E therapy for postextubation ARF was performed following the protocol: (1) during the transitional period, NIV was delivered by BIPAP with settings of IPAP 10–20 (mean: 13.5) and EPAP 3–6 (mean: 5); (2) supplement fraction of inspired oxygen (FiO_2) should be administered ⩽0.4 to maintain oxyhemoglobin saturation (SpO_2) ⩾94% during the transitional period, and whenever oxygen saturation drops, apply MI-E with or without extra manually assisted cough.[4,18]

Low grade of sedation was occasionally required for patients who could not cooperate well during

the use of NIV. Sedative agents were selected including chloral hydrate (30–40 mg/kg q6–8 h by orogastric tube or per rectal) or midazolam (0.1–0.15 mg/kg q6–8 h iv bolus or 0.5–0.8 μg/kg/min iv infusion).[14,19]

Data collection and outcome measurement

For each ARF episode, we collected the following data including demographic information, underlying NMD, ARF causes, Pediatric Risk of Mortality (PRISM)-III scores (those aged <18 years), NIV/MI-E settings and duration (hours-to-days), administration of sedative agents, and mortality. Upon admission, monitoring for patients' respiratory status was assessed every 2 h (2, 4, and 8 h) including heart rate (HR), respiratory rate (RR), peripheral SpO_2, and oxygen demand (fraction of inspired oxygen; FiO_2). The ABG data were collected before (through single vascular puncture), at 4–8 h, and at 12–24 h (through indwelling arterial line) after NIV-MI-E initiation. The chest X-ray (CXR) was taken before and after NIV/MI-E. Furthermore, we applied an NMD triage scoring system to each ARF episode, which is recently proposed to gauge the clinical severity of respiratory compromise in NMD patients. Briefly, this NMD-specified triage system is an assistive scoring tool specialized for NMD patients with compromised respiration which composes 11 respiratory dimensions (HR, RR, SpO_2, FiO_2, radiographic findings, secretion amount, and physical findings of respiration) with a sum of scores in the range 0–33. Accordingly, these scores guide the health care providers in the frequency of providing noninvasive airway approaches.[22]

Treatment success was defined as free from ETI during the hospitalization. Otherwise, requirement of ETI, or persistent dependence of mechanical ventilation requiring subsequent tracheostomy, or mortalities during the study period were categorized as the failure group.

Statistical analysis

Categorical variables were expressed as a percentage and continuous variables as mean ± standard deviation (SD). Quantitative continuous variables were compared between groups using nonparametric Mann–Whitney *U* test. Variables within either success or failure group and before-and-after NIV/MI-E treatment were compared by the paired Wilcoxon test. Differences between groups for categorical variables were analyzed by Chi-square test (χ^2). Univariate and multivariate analyses of risk factors for NIV/MI-E failure were performed using logistic regression. The ability to predict NIV/MI-E treatment outcome was measured using the area under the receiver operating characteristic curve (AUC). A p value of <0.05 was considered to be statistically significant. The statistical analysis was performed using the statistical analysis system (SAS) version 9.3 (SAS Institute, Cary, NC).

Results

Patient demographics

We enrolled 56 eligible patients with NMD (mean 13.2 ± 11.0 years; range, 2 months to 39 years) who suffered 62 episodes of ARF which had been initially managed by combined NIV and MI-E between 2007 and 2017. Among these ARF episodes, 23 events occurred during postextubation status. Baseline demographics are shown in Table 1. The most frequent NMD diagnosed was spinal muscular atrophy (SMA), accounting for 52% of all patients, followed by Duchenne muscular dystrophy (DMD) at 23%. The most common variant of ARF was type 2 (hypercapnic), confirmed during 53 cases (86%), with a baseline median $PaCO_2$ of 62.8 mmHg. A total of 13 occurrences in 11 patients were stipulated as DNI. The mean time from onset to minimal NIV settings was 40.2 ± 11.8 min. The most common precipitating factor of ARF was pneumonia (65%), which was complicated by atelectasis in 31 instances; and one 33-year-old patient developed acute respiratory distress syndrome (ARDS) based on the Berlin definition. In the 23 episodes of postextubation ARF, reasons for prior mechanical ventilation in 17 cases were scheduled surgeries (largely for spinal correction and gastrostomy feeding tube placement ± fundoplication), whereas six cases with pulmonary compromise were referrals to wean from mechanical ventilation. The median duration of prior mechanical ventilation use before extubation was 4 days (range: 2.5–584 days). In addition to underlying NMD, nine instances of ARF were associated with other comorbidities, including congestive heart failure (six patients with DMD), seizure/epilepsy (one patient with SMA and one with congenital muscular dystrophy), and septic

Table 1. Demographic and main baseline characteristics of cases with ARF.

	Total cases ***n*** **= 62**	**Episodic ARF** ***n*** **= 39**	**Postextubation ARF** ***n*** **= 23**
Age, years	13.2 ± 11.0 (0.17–39)	15.1 ± 11.9 (0.25–39)	10.2 ± 8.7 (0.30–27)
Gender, male	36 (58%)	23 (59%)	13 (57%)
PRISM-III[a]	11.0 ± 2.9 (4–16)	12.0 ± 2.5 (6–16)	9.6 ± 2.9 (6–14)
NMD triage scores	19.6 ± 2.0 (16–24)	20.0 ± 1.9 (16–24)	19.1 ± 2.3 (16–24)
Request DNI	13 (21%)	13 (33%)	
Classifications of NMD, *n* (%)			
SMA	32 (52%)	17 (44%)	15 (65%)
DMD	14 (23%)	13 (33%)	1 (4%)
CM	6 (10%)	2 (5%)	4 (18%)
CMD	4 (6%)	2 (5%)	2 (9%)
Mitochondrial myopathy	4 (6%)	2 (5%)	2 (9%)
Miscellaneous[b]	2 (3%)	2 (5%)	
ARF types, *n* (%)			
Hypoxemic (Type 1)	9 (15%)	6 (15%)	3 (13%)
Hypercapnic (Type 2)	53 (85%)	33 (85%)	20 (87%)
Causes of ARF, *n* (%)[c]			
Pneumonia	40 (65%)	34 (85%)	6 (26%)
Atelectasis	31 (50%)	16 (41%)	15 (65%)
Postextubation	23 (37%)		23 (100%)
ARDS	1 (2%)	1 (3%)	
Prior use of NIV/MI-E at home	29 (47%)	12 (31%)	17 (74%)
Initiating use of NIV/MI-E at ED	7 (11%)	7 (18%)	
Comorbidities other than NMD			
Heart failure	6 (1%)	6 (15%)	
Epilepsy/seizures	2 (3%)	1 (3%)	1 (4%)
Septic shock	1 (2%)	1 (3%)	
Outcome: success *n* (%)	53 (86%)	32 (82%)	21 (91%)

Note: data are expressed as mean ± standard deviation (range) or number (%).
ARDS, acute respiratory distress syndrome; ARF, acute respiratory failure; CM, congenital myopathy; CMD, congenital muscular dystrophy; DMD, Duchenne muscular dystrophy; DNI, do not intubate; ED, emergency department; NMD, neuromuscular disease; PRISM-III, Pediatric Risk of Mortality III; SMA, spinal muscular atrophy.
[a]For cases aged <18 years: Total case (*n* = 47), including Episodic ARF (*n* = 27) and Postextubation ARF (*n* = 20).
[b]Miscellaneous including Charcot–Marie–Tooth disease (CMTD) and spinal muscular atrophy with respiratory distress (SMARD).
[c]Total percentage >100 because concurrent and multiple causes related to a single ARF episodes.

shock (one patient with DMD). Nevertheless, most patients ($n = 7$) with these comorbidities were successfully rescued by NIV/MI-E. Only low grade of sedation was required by administrating chloral hydrate or midazolam in 10 cases younger than 5 years old, who were all in the success group. The CXR before and 4–24 h post NIV were completely obtained in only 22 cases. However, neither the level of initial radiograph involvement nor follow-up image findings were significantly related to the NIV outcome. Although NIV/MI-E was usually initiated within the PICU, seven patients (five with SMA, two with DMD) were treated according to need within the emergency department (ED).

Outcomes of study subjects

Owing to the use of NIV/MI-E, the overall success rate was 86%, including avoided intubation in 32 cases (82%) of episodic ARF and weaning from mechanical ventilation in 21 cases (91%) of postextubation ARF. Except for one case, 12 requests of DNI of 10 patients with episodic ARF were successfully rescued by combined NIV/MI-E. The reasons for intubation were persistent/progressive hypercapnia ($n = 4$) and hypoxemia ($n = 2$), and those who met the exclusion criteria of subsequent NIV use, including severe airway bleeding ($n = 1$), hemodynamic instability ($n = 1$), and repeated seizures ($n = 1$). In those who failed treatment, the median time from NIV/MI-E initiation to intubation was 22 h (range, 10–48 h). Two patients in the failure group of postextubation status received subsequent tracheosto-MI-Es, but five patients were later extubated during the same hospital stays. Ultimately, two deaths, including one with DNI status, occurred in type 1 SMA and DMD patients due to necrotizing enterocolitis and severe pulmonary edema complicated by congestive heart failure, respectively. No death seemed to be related or associated with the use of combined NIV/MI-E.

As shown in Table 2, baseline characteristics and clinical variables before NIV/MI-E therapy did not differ significantly according to therapeutic success or failure as well as in subsets of ARF. Furthermore, there were no observed correlations between patient outcomes, and gender, underlying NMD, variants of ARF types, or other comorbidities (χ^2 test). The frequency of MI-E delivery ranged from 8 to 18 times per day among all enrolled patients, which showed no differences between success and failure groups. Of note, the therapeutic success rate in patients who were previously administered at home on NIV/MI-E use (*versus* those who were not) was higher ($p = 0.02$, χ^2 test). In addition, PICU and hospital stays were significantly shorter in those achieving therapeutic success.

All seven ARF interventions initiating NIV/MI-E at the ED produced favorable outcomes, comparable with actions taken within the PICU. Although the duration of hospitalization was similar (13.3 ± 8.1 days *versus* 15.5 ± 8.2 days; $p = 0.31$), we noted that PICU stays were shorter in patients undergoing ED-initiated NIV/MI-E (5.1 ± 1.1 days *versus* 9.8 ± 6.6 days; $p = 0.04$).

The spectrum of clinical and laboratory variables after NIV/MI-E use

Sequential changes in clinical variables, stratified by therapeutic outcomes (success *versus* failure), are illustrated in Figure 1. The clinical variables within and across groups, including HR and RR, and ABG data of pH and $PaCO_2$, showed a progressive improvement following successful NIV/MI-E treatment. The mean HR and RR showed a significant reduction in the success group at 4 h and 8 h after NIV/MI-E use, as well as compared with the failure group. On the other hand, a significant increase in pH and a decrease in $PaCO_2$ were observed at 4–8 h after NIV/MI-E in the success group, whereas these variables showed no changes in the failure group. However, there were no significant changes in PaO_2/FiO_2 ratio and peripheral SpO_2 either within or between the success and failure group.

Predictive factors for NIV/MI-E success

As shown in Table 3, the univariate analysis identified several predictive factors of NIV/MI-E outcome. We found that variables of a significant RR decrease at 4 h (OR 1.40, 95% CI 1.08–1.80; $p = 0.01$), and ABG data at 4–8 h showing progressively pH increase (OR 0.98, 95% CI 0.97–0.99; $p = 0.01$) and $PaCO_2$ decrease (OR 1.11, 95% CI 1.04–1.18; $p < 0.01$) might represent potential predictors of NIV/MI-E treatment success. Furthermore, variables associated with a p value < 0.15 in univariate analysis were subjected to multivariate analysis. The predictive model from a multivariate analysis identified

Table 2. Baseline characteristics and outcomes of the success and failure groups.

	All cases			ARF group			Postextubation group		
	Success ($n=53$)	Failure ($n=9$)	p value	Success ($n=32$)	Failure ($n=7$)	p value	Success ($n=21$)	Failure ($n=2$)	p value
Baseline features:									
Age (years)	13.5 ± 11.6	11.7 ± 11.4	0.85	15.9 ± 11.8	11.3 ± 12.8	0.45	9.9 ± 9.0	13.0 ± 7.1	0.55
Type of ARF (type 2) (%)	85%	89%	0.75	84%	85%	0.62	86%	100%	0.60
PRISM-III[a]	10.8 ± 3.1	11.9 ± 1.5	0.18	12.1 ± 2.7	11.4 ± 1.3	0.27	9.2 ± 2.8	13.0 ± 1.4	0.08
HR (beats/min)[b]	127.1 ± 19.4	133.9 ± 14.0	0.27	129.9 ± 20.6	133.7 ± 16.1	0.65	122.9 ± 17.0	134.5 ± 3.5	0.19
RR (breaths/min)[b]	31.9 ± 8.1	35.1 ± 7.2	0.21	34.4 ± 7.5	36.4 ± 7.2	0.40	27.9 ± 7.4	30.5 ± 6.4	0.58
pH	7.29 ± 0.08	7.27 ± 0.14	0.97	7.26 ± 0.08	7.23 ± 0.14	0.94	7.35 ± 0.04	7.39 ± 0.01	0.10
$PaCO_2$ (mm Hg)	63.0 ± 19.1	67.4 ± 19.8	0.50	70.2 ± 19.9	71.7 ± 20.4	0.80	52.0 ± 11.1	52.5 ± 7.8	0.74
FiO_2	0.40 ± 0.09	0.38 ± 0.12	0.47	0.41 ± 0.11	0.39 ± 0.13	0.64	0.39 ± 0.06	0.35 ± 0.07	0.39
PaO_2/FiO_2	279.4 ± 99.6	229.1 ± 73.2	0.20	252.0 ± 115.4	204.7 ± 63.7	0.24	321.1 ± 46.2	313.7 ± 8.8	0.55
SpO_2 (%)	93.1 ± 2.9	93.0 ± 2.9	1.00	92.3 ± 3.5	92.6 ± 3.2	0.91	94.3 ± 0.9	94.5 ± 0.7	0.86
Max. IPAP setting (cmH_2O)	17.7 ± 3.0	18.4 ± 2.4	0.31	18.5 ± 3.2	18.6 ± 2.8	0.84	16.4 ± 2.1	18.0 ± 0.0	0.27
Max. EPAP setting (cmH_2O)	6.0 ± 2.4	5.9 ± 1.7	0.92	6.9 ± 2.3	8.0 ± 2.6	0.33	5.2 ± 1.8	4.5 ± 0.7	0.65
Prior NIV/MI-E use at home (%)	52.8%	11.1%	0.02						
NMD Triage Scores	19.5 ± 1.95	20.4 ± 2.4	0.19						
Outcomes:									
NIV duration (d)	7.1 ± 5.5	1.7 ± 1.4	<0.01	8.0 ± 0.5	1.1 ± 0.2	<0.01	5.7 ± 4.7	3.8 ± 1.8	0.66
PICU stay (d)	9.4 ± 6.1	21.9 ± 13.9	0.02	8.8 ± 6.1	22.7 ± 14.5	0.01	10.2 ± 6.2	23.0 ± 7.1	0.04
Hospital stay (d)	16.3 ± 7.8	33.6 ± 17.9	<0.01	15.0 ± 8.1	30.1 ± 19.2	0.04	18.3 ± 7.0	44.0 ± 8.5	0.02

Note: data are expressed as mean ± standard deviation or percentage (%).
ARF, acute respiratory failure; EPAP, expiratory positive airway pressure; HR, heart rate; IPAP, inspiratory positive airway pressure; PRISM-III, Pediatric Risk of Mortality III; RR, respiratory rate.
[a]For cases aged <18 years: ARF success ($n=22$) and postextubation success ($n=18$); ARF failure ($n=5$) and postextubation failure ($n=2$).
[b]The HR and RR were normed for patients' age.

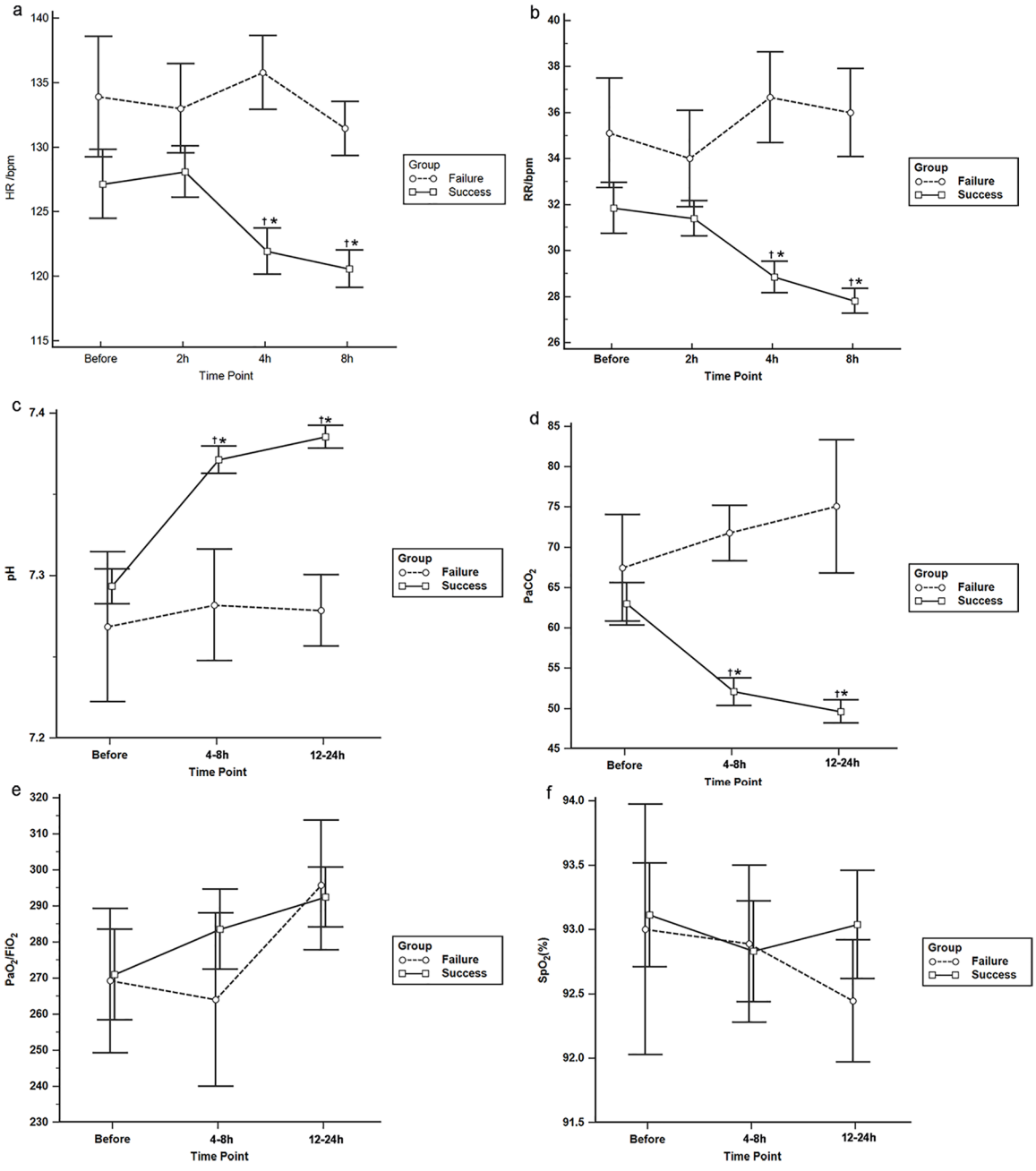

Figure 1. Evolutions of clinical variables within and between success and failure groups after NIV/MI-E use: (a) mean heart rate (HR); (b) mean respiratory rate (RR); (c) mean pH; (d) mean $PaCO_2$; (e) mean PaO_2/FiO_2 ratio; (f) mean peripheral SpO_2.
*$p < 0.05$ comparison between success and failure groups; †$p < 0.05$ compared with baseline (within groups analysis).

$PaCO_2$ value at 4–8 h (adjusted OR 1.09, 95% CI 1.00–1.18; $p = 0.056$) as potential predictor of NIV/MI-E treatment outcome (AUC 0.946). The optimal cutoff value of $PaCO_2$ (at 4–8 h) suggested to detect NIV/MI-E treatment failure was 58.0 mmHg, with 100% of sensitivity and 24.5% of specificity.

NIV/MI-E complications

There was no major complication such as pneumothorax or gastric distension in either group. The most commonly reported complication was the dermatological problem associated with compression of NIV interfaces, including dermal breakdown or irritant dermatitis over the nasal bridge in

Table 3. Univariate and multivariate analysis for risk factors of NIV/MI-E failure.

	Univariate analysis	*p* value	AUC	Multivariate analysis[a]	*p* value	AUC	Cutoff value	Sensitivity	Specificity		
	OR	95% CI			AOR	95% CI					
Decrease of HR at 4h	1.12	1.00–1.24	0.049	0.688	1.03	0.87–1.21	0.753	0.946			
Decrease of RR at 4h	1.40	1.08–1.80	0.010	0.804	1.51	0.97–2.36	0.068		2.0	66.7%	18.9%
pH at 4–8h[b]	0.98	0.97–0.99	0.011	0.767	0.98	0.96–1.00	0.094				
$PaCO_2$ at 4–8h	1.11	1.04–1.18	0.001	0.887	1.09	1.00–1.18	0.056		58.0	100%	24.5%
NMD Triage score	1.28	0.89–1.84	0.193	0.633	–	–	–				
PRISM-III scores	1.14	0.85–1.55	0.386	0.589	–	–	–				

NIV/MI-E combined noninvasive ventilation and mechanical insufflator-exsufflator.
AUC, area under the curve; AOR, adjusted odds ratios; CI, confidence interval; HR, heart rate; NMD, neuromuscular disease; OR, odds ratio; PRISM-III, Pediatric Risk of Mortality III; RR, respiratory rate.
[a]Only variables associated with a *p* value <0.15 in the univariate analysis were subjected to multivariate analysis.
[b]Multiply by 1,000 due to extremely low value for rendering statistic analysis.

12 cases. Six cases reported epigastric discomfort and chest tightness that were resolved after adjusting the NIV pressure setting. All the above reversible adverse events did not interfere with the utility of NIV/MI-E during the study period.

Discussion

The evidence that non-invasive airway approaches help avoid intubation during ARF episodes in children and young people with chronic NMD comes from six observational, noncontrolled studies of 71 subjects, age range 3 months to 69 years, 64 known to be under 25 years.[10–14,19] However, in most cases, the methods applied for airway clearance are poorly described, and the impact of effective airway clearance, for example, with mechanical cough assist devices, on the success rate of NIV in the management of ARF is not clear. To the best of the authors' knowledge, the present study addresses the largest cohort of patients with NMD to receive combined NIV and MI-E in an acute care setting as treatment of ARF. We have demonstrated that upon the timely institution of NIV/MI-E, intubation or re-intubation was avoided in 86% of ARF events, eliminating risks of long-term dependence on ventilation. Moreover, PICU and hospital stay in patients successfully rescued by NIV/MI-E were shorter than those requiring intubation. As in our pilot study, we thus validated the effectiveness of managing ARF in patients with NMD using a limited and exclusively noninvasive airway approach.[19] Furthermore, this is the first study showing outcome predictors of NIV/MI-E in treating ARF due to chronic NMD.

In nonspecialty PICUs caring for heterogeneous patient populations, there are several known predictors of NIV failure in the treatment of ARF.[5,9,16] However, the predictive factors of NIV failure in the specific NMD population is still undefined. In contrast to past studies, we found that neither PRISM-III scores nor NMD triage scores at admission can predict NIV/MI-E failure in our cases.[23,24] This NMD-directed triage scoring system might guide the frequency of NIV/MI-E use in these circumstances but unreliably predicts NIV failure.[22] Moreover, regardless of changes of SpO_2/FiO_2 ratio and SpO_2, ABG showing progressively increasing pH and decreasing $PaCO_2$ during the first few hours after NIV/MI-E may signal NIV/MI-E success. It reemphasizes that oxygen supplementation should not be provided empirically in the absence of NIV with augmented secretion clearance or without monitoring CO_2 exchange.[25] In line with previous observations, our study suggested that the outcome of NMD patients with hypoxemic ARF might be less positive to noninvasive airway managements compared with those with CO_2 retention, namely hypercapnic ARF.[1,5,19]

It is also worth noting that in patients who received at-home NIV/MI-E training, the therapeutic success rate was high. Hence, proactive efforts may be beneficial in this regard.[26] Similar to a previous study, and we found that patients with NMD and postextubation ARF achieved a high rate of therapeutic success (91%).[27] Moreover, this modality is of particular effective in those with scheduled postoperative status.[15,28] This evidence implies that a more comprehensive discussion complemented by this information should be conveyed to the NMD patients and their parents who may stipulate DNI during an episode of ARF. They should know that temporary intubation may not always mean long-term dependence on invasive ventilation or an inevitable tracheostomy.

In patients with NMD, the vast majority of ARF episodes results from mechanical failure, which is worsened by ineffective coughing during intercurrent chest infections.[16] It is thus essential is to normalize gas exchange, primarily through augmented coughing for better clearance of airway secretions.[1] Among the various coughing-assist techniques, MI-E represents the most potent tool, promoting effective peak flow to resolve mucus plugging and subsequent atelectasis.[13,29] Early combined application of NIV and MI-E is known to prevent postextubation ARF and facilitate extubation in patients with NMDs.[4,18] However, the availability of MI-E in acute care settings as the first-line therapeutics is not always certain.[30] Emerging evidence nevertheless indicates that adding MI-E to NIV during episodes of ARF episodes may prevent intubation/reintubation, perhaps decrease hospital mortality, and shorten ICU or hospital stays.[4,11,13,19] Nevertheless, it should be kept in mind that severe bulbar dysfunction may not only increase risk of aspiration but result in an inability to clear the airway of secretions despite augmented cough techniques.[1] Therefore, a careful evaluation of deglutition ability should be performed when deciding to adopt a noninvasive approach in NMD patients with ARF and that patients with profound bulbar muscle compromise should be excluded from this strategy.

There has been increasing interest in initiating NIV in the treatment of ARF at ED admissions to reduce intubation rate, and length of ICU stay.[31] However, there are remarkably few studies regarding initiation of NIV within the ED for pediatric ARF.[32,33] Our present findings, drawn from a larger NMD-specific cohort, validate the hypothesis of our pilot study that early initiation of NIV/MI-E in the ED does help avert intubation and may potentially shorten ICU stays.[21] Despite relatively few experiences in this study, we still believe that any capable emergency medical services should include certified staff members (possibly an arm of the neuromuscular team) to provide the most appropriate level of ventilation support for patients with NMD. If available, the patients and family should also be encouraged to bring home-based NIV and cough-assist devices for use during transport and ED admission.[6]

There are several acknowledged study limitations, the first being a lack of a control group. To date, only one randomized controlled study has addressed the efficacy of NIV in childhood ARF, and subjects with underlying NMD were excluded.[8] However, more than a few patients with NMD or their guardians may request DNI during ARF episodes, so the prospect of a randomized study in this setting may be ethically and practically infeasible. Another issue is that data on lung functions at baseline, which may serve to predict NIV outcomes, were not fully recorded in our patients.[11] A previous study suggested that chest radiographic findings after 24 h up to 72 h of NIV use might represent a prognostic factor of NIV outcome.[34] We only obtained partial CXR data up to 24 h post-NIV that was hard to conclude its predictive value. Finally, although blood gas analysis as early as 1–2 h after NIV may help predict NIV failure,[8,27] we only monitored blood gases after 4–8 h (earliest point). Our reason for such delay was to minimize vascular punctures, which provoke irritability/crying and patient–ventilator asynchrony, interfering with NIV/MI-E treatment effectiveness. Continuous transcutaneous PCO_2 monitoring, as a surrogate of blood CO_2 level, may remedy this problem when designing future studies.

Conclusion

A combination of NIV and MI-E should ideally be available in acute care settings to avert intubation and potentially shorten PICU or hospital stays for ARF in patients with NMD. Early institution of NIV/MI-E in the ED may further shorten PICU stay. Clinical features within 8 h of admission can predict the suitability of this non-invasive approach.

Acknowledgements

The authors would like to thank the Statistical Analysis Laboratory of the Department of Medical Research, Kaohsiung Medical University Hospital, for its help, and Prof. Yi-Hsin Yang for advice and review regarding this study.

Author contributions

TH Chen contributed to conception and design, acquisition of data, or analysis and interpretation of data, and drafting the manuscript for intellectual content. WC Liang contributed to acquisition and interpretation of data. IC Chen contributed to acquisition of data. YC Liu contributed to acquisition of data. JH Hsu contributed to conception and design, acquisition of data, or analysis and interpretation of data, and final approval of the version to be published. YJ Jong contributed to conception and design, acquisition of data, revising the manuscript critically for important intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study received a research grant from Kaohsiung Medical University Hospital, Kaohsiung, Taiwan (grant numbers KMUH-106R76 and KMUH-107-7R80).

Conflict of interest statement

On behalf of all authors, the corresponding author states that there is no conflict of interest.

ORCID iD

Tai-Heng Chen https://orcid.org/0000-0001-7713-3627

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplemental material

The reviews of this paper are available via the supplementary material section.

References

1. Panitch HB. Respiratory implications of pediatric neuromuscular disease. *Respir Care* 2017; 62: 826–848.
2. Yates K, Festa M, Gillis J, *et al.* Outcome of children with neuromuscular disease admitted to pediatric intensive care. *Arch Dis Child* 2004; 89: 170–175.
3. Cabrera Serrano M and Rabinstein AA. Causes and outcomes of acute neuromuscular respiratory failure. *Arch Neurol* 2010; 67: 1089–1094.
4. Vianello A, Arcaro G, Braccioni F, *et al.* Prevention of extubation failure in high-risk patients with neuromuscular disease. *J Crit Care* 2011; 26: 517–524.
5. Hull J, Aniapravan R, Chan E, *et al.* British Thoracic Society guideline for respiratory management of children with neuromuscular weakness. *Thorax* 2012; 67(Suppl. 1): i1–i40.
6. Finkel RS, Mercuri E, Meyer OH, *et al.* Diagnosis and management of spinal muscular atrophy: part 2: pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscul Disord* 2018; 28: 197–207.
7. Mercuri E, Finkel RS, Muntoni F, *et al.* Diagnosis and management of spinal muscular atrophy: part 1: recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord* 2018; 28: 103–115.
8. Yanez LJ, Yunge M, Emilfork M, *et al.* A prospective, randomized, controlled trial of noninvasive ventilation in pediatric acute respiratory failure. *Pediatr Crit Care Med* 2008; 9: 484–489.
9. Najaf-Zadeh A and Leclerc F. Noninvasive positive pressure ventilation for acute respiratory failure in children: a concise review. *Ann Intensive Care* 2011; 1: 15.
10. Padman R, Lawless S and Von Nessen S. Use of BiPAP by nasal mask in the treatment of respiratory insufficiency in pediatric patients: preliminary investigation. *Pediatr Pulmonol* 1994; 17: 119–123.
11. Niranjan V and Bach JR. Noninvasive management of pediatric neuromuscular ventilatory failure. *Crit Care Med* 1998; 26: 2061–2065.
12. Vianello A, Bevilacqua M, Arcaro G, *et al.* Non-invasive ventilatory approach to treatment of acute respiratory failure in neuromuscular disorders. A comparison with endotracheal intubation. *Intensive Care Med* 2000; 26: 384–390.
13. Servera E, Sancho J, Zafra MJ, *et al.* Alternatives to endotracheal intubation for patients with neuromuscular diseases. *Am J Phys Med Rehabil* 2005; 84: 851–857.
14. Piastra M, Antonelli M, Caresta E, *et al.* Noninvasive ventilation in childhood acute neuromuscular respiratory failure: a pilot study. *Respiration* 2006; 73: 791–798.
15. Khirani S, Bersanini C, Aubertin G, *et al.* Non-invasive positive pressure ventilation to facilitate the post-operative respiratory outcome of spine surgery in neuromuscular children. *Eur Spine J* 2014; 23(Suppl. 4): S406–S411.
16. Demaret P, Mulder A, Loeckx I, *et al.* Non-invasive ventilation is useful in pediatric intensive care units if children are appropriately selected and carefully monitored. *Acta Paediatr* 2015; 104: 861–871.
17. Rabinstein AA. Noninvasive ventilation for neuromuscular respiratory failure: when to use and when to avoid. *Curr Opin Crit Care* 2016; 22: 94–99.
18. Bach JR, Goncalves MR, Hamdani I, *et al.* Extubation of patients with neuromuscular weakness: a new management paradigm. *Chest* 2010; 137: 1033–1039.
19. Chen TH, Hsu JH, Wu JR, *et al.* Combined noninvasive ventilation and mechanical in-exsufflator in the treatment of pediatric acute neuromuscular respiratory failure. *Pediatr Pulmonol* 2014; 49: 589–596.
20. Teague WG. Noninvasive ventilation in the pediatric intensive care unit for children with acute respiratory failure. *Pediatr Pulmonol* 2003; 35: 418–426.
21. Chen TH, Hsu JH and Jong YJ. Noninvasive airway approaches for acute neuromuscular respiratory failure in emergency departments. *Pediatr Pulmonol* 2017; 52: E55–E57.
22. Wampole A, Schroth M and Boriosi J. Survival of a child with spinal muscular atrophy and acute respiratory distress syndrome. *Pediatr Pulmonol* 2015; 50: E29–E31.
23. Lum LC, Abdel-Latif ME, de Bruyne JA, *et al.* Noninvasive ventilation in a tertiary pediatric intensive care unit in a middle-income country. *Pediatr Crit Care Med* 2011; 12: e7–e13.
24. Mayordomo-Colunga J, Medina A, Rey C, *et al.* Predictive factors of non invasive ventilation failure in critically ill children: a prospective epidemiological study. *Intensive Care Med* 2009; 35: 527–536.

25. Chiou M, Bach JR, Saporito LR, *et al.* Quantitation of oxygen-induced hypercapnia in respiratory pump failure. *Rev Port Pneumol* 2016; 22: 262–265.

26. Lemoine TJ, Swoboda KJ, Bratton SL, *et al.* Spinal muscular atrophy type 1: are proactive respiratory interventions associated with longer survival? *Pediatr Crit Care Med* 2012; 13: e161–e165.

27. Dohna-Schwake C, Stehling F, Tschiedel E, *et al.* Non-invasive ventilation on a pediatric intensive care unit: feasibility, efficacy, and predictors of success. *Pediatr Pulmonol* 2011; 46: 1114–1120.

28. Graham RJ, Athiraman U, Laubach AE, *et al.* Anesthesia and perioperative medical management of children with spinal muscular atrophy. *Paediatr Anaesth* 2009; 19: 1054–1063.

29. Chatwin M, Ross E, Hart N, *et al.* Cough augmentation with mechanical insufflation/exsufflation in patients with neuromuscular weakness. *Eur Respir J* 2003; 21: 502–508.

30. Chatwin M, Toussaint M, Goncalves MR, *et al.* Airway clearance techniques in neuromuscular disorders: a state of the art review. *Respir Med* 2018; 136: 98–110.

31. Merlani PG, Pasquina P, Granier JM, *et al.* Factors associated with failure of noninvasive positive pressure ventilation in the emergency department. *Acad Emerg Med* 2005; 12: 1206–1215.

32. Yeow ME and Santanilla JI. Noninvasive positive pressure ventilation in the emergency department. *Emerg Med Clin North Am* 2008; 26: 835–847, x.

33. Hostetler MA. Use of noninvasive positive-pressure ventilation in the emergency department. *Emerg Med Clin North Am* 2008; 26: 929–939, viii.

34. Ignacio Munoz-Bonet J, Flor-Macian EM, Brines J, *et al.* Predictive factors for the outcome of noninvasive ventilation in pediatric acute respiratory failure. *Pediatr Crit Care Med* 2010; 11: 675–680.