ANESTHESIOLOGY

Neurally Adjusted Ventilatory Assist *versus* Pressure Support Ventilation in Difficult Weaning

A Randomized Trial

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ABSTRACT

Background: Difficult weaning frequently develops in ventilated patients and is associated with poor outcome. In neurally adjusted ventilatory assist, the ventilator is controlled by diaphragm electrical activity, which has been shown to improve patient–ventilator interaction. The objective of this study was to compare neurally adjusted ventilatory assist and pressure support ventilation in patients difficult to wean from mechanical ventilation.

Methods: In this nonblinded randomized clinical trial, difficult-to-wean patients (n = 99) were randomly assigned to neurally adjusted ventilatory assist or pressure support ventilation mode. The primary outcome was the duration of weaning. Secondary outcomes included the proportion of successful weaning, patient–ventilator asynchrony, ventilator-free days, and mortality. Weaning duration was calculated as 28 days for patients under mechanical ventilation at day 28 or deceased before day 28 without successful weaning.

Results: Weaning duration in all patients was statistically significant shorter in the neurally adjusted ventilatory assist group (n = 47) compared with the pressure support ventilation group (n = 52; 3.0 [1.2 to 8.0] days *vs.* 7.4 [2.0 to 28.0], mean difference: –5.5 [95% CI, –9.2 to –1.4], $P = 0.039$). *Post hoc* sensitivity analysis also showed that the neurally adjusted ventilatory assist group had shorter weaning duration (hazard ratio, 0.58; 95% CI, 0.34 to 0.98). The proportion of patients with successful weaning from invasive mechanical ventilation was higher in neurally adjusted ventilatory assist (33 of 47 patients, 70%) compared with pressure support ventilation (25 of 52 patients, 48%; respiratory rate for neurally adjusted ventilatory assist: 1.46 [95% CI, 1.04 to 2.05], $P = 0.026$). The number of ventilator-free days at days 14 and 28 was statistically significantly higher in neurally adjusted ventilatory assist compared with pressure support ventilation. Neurally adjusted ventilatory assist improved patient ventilator interaction. Mortality and length of stay in the intensive care unit and in the hospital were similar among groups.

Conclusions: In patients difficult to wean, neurally adjusted ventilatory assist decreased the duration of weaning and increased ventilator-free days.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Neurally adjusted ventilatory assist is safe and well tolerated by patients
- It improves patient–ventilator interaction

What This Article Tells Us That Is New

- In selected patients difficult to wean from mechanical ventilation, neurally adjusted ventilatory assist improves patient outcome indicated by reduction in duration of weaning
- Such a benefit seems most prominent in tracheostomized patients

Pressure support ventilation is the most widely used mode for partial support in patients weaning from mechanical ventilation.[1–3] However, several studies have demonstrated that poor patient–ventilator interaction is common in pressure support ventilation and that this is associated with adverse clinical outcome.[4,5] Also, in pressure support ventilation the level of inspiratory support is unaffected by patient's effort, which may increase the risk of either ventilator underassist or ventilator overassist, and is associated with diaphragm weakness.[6,7] In addition, high ventilator assist and high tidal volume may result in lung injury.

Neurally adjusted ventilatory assist is a ventilator mode that uses the electrical activity of the diaphragm to control the ventilator.[8] Several studies have demonstrated that neurally adjusted ventilatory assist improves patient–ventilator interaction compared with pressure support ventilation.[9–12] Because support is delivered in proportion to patients' neural effort reflected by electrical activity of the diaphragm, inappropriate ventilator assist should be less common in

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neurally adjusted ventilatory assist modes. Today, few studies have compared neurally adjusted ventilatory assist *versus* pressure support ventilation on clinically relevant endpoints in invasively ventilated patients. A recent French multicenter randomized trial demonstrated that neurally adjusted ventilatory assist was equally well tolerated as pressure support ventilation in the first 48 h after the transition from controlled mode.[11] In addition, this trial demonstrated that ventilation in neurally adjusted ventilatory assist mode improved patient–ventilator interaction, decreased dyspnea sensation, and resulted in less frequent application of postextubation noninvasive ventilation.[11] However, this trial did not detect statistically significant differences in clinically relevant endpoints, such as duration of weaning or mechanical ventilation. This may be explained by the fact that this study did not focus on patients difficult to wean from the ventilator. We reasoned that a ventilator mode that improves patient ventilator interaction and delivers proportional support most likely improves clinical outcome in patients difficult to wean from mechanical ventilation.

Therefore, we hypothesized that neurally adjusted ventilatory assist decreases the duration of weaning in difficult-to-wean patients. The objective of the present randomized controlled trial was to compare neurally adjusted ventilatory assist *versus* pressure support ventilation on weaning outcome in difficult-to-wean patients, defined as failing at least one spontaneous breathing trial, or reintubation after successful spontaneous breathing trial.

Materials and Methods

From October 2011 to September 2017, this randomized study was conducted in a 20-bed general intensive care unit (ICU) of a teaching hospital affiliated with Southeast University in China. Because of study design, blinding was not feasible. The research team and intensive care unit had 3 yr of clinical experience with the neurally adjusted ventilatory assist mode before the start of the study. The protocol was approved by the Institutional Ethics Committee of Zhongda Hospital (approval 2010ZDLL018.0). Written informed consent was obtained from legal primary decision maker, which was the spouse of the patient or if nonexistent a parent or child. The trial was registered at clinicaltrials.gov (NCT01280773, investigator's name: Ling Liu; date of registration: December 28, 2010). The trial was conducted in accordance to the original protocol. A data analysis and statistical plan was written after the data were accessed.

Patients

The investigators screened all the patients under invasive mechanical ventilation each morning (9:00 AM), and selected patients either failed the first spontaneous breathing trial or were reintubated after successful spontaneous breathing trial. Patients receiving invasive mechanical ventilation for more than 24 h were eligible when meeting all the following criteria: failing the initial spontaneous breathing trial or reintubated within 48 h after the first extubation, able to sustain pressure support ventilation more than 1 h with inspiratory support of at most 15 cm H_2O, hemodynamic stable (heart rate less than 140 beats/min, no vasopressors required, or at most 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dopamine/dobutamine, or at most 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ norepinephrine), sedation level Richmond Agitation–Sedation Scale of −2 at the lowest during day time. Patients were excluded if age was less than 18 yr or greater than 80 yr, tracheostomy at time of inclusion, withhold or withdraw life sustaining treatment, contraindication for nasogastric tube insertion (*e.g.*, history of esophageal varices, gastroesophageal surgery in the previous 12 months or gastroesophageal bleeding in the previous 7 days, international normalized ratio of more than 1.5, active partial thromboplastin time of more than 44 s, history of leukemia), neuromuscular disease affecting spontaneous breathing (*e.g.*, history of acute central or peripheral nervous system disorder or neuromuscular disease with irregular spontaneous rhythm), lack of informed consent, and patients included in other intervention study. The details of the spontaneous breathing trial before randomization and the failure criteria are reported in the Supplemental Digital Content (http://links.lww.com/ALN/C274).

Study Design

Enrolled patients were randomly assigned to be ventilated in pressure support ventilation or neurally adjusted ventilatory assist by using sequentially numbered, sealed envelopes by the researchers (Supplemental Digital Content, http://links.lww.com/ALN/C274). In all randomized patients the standard nasogastric feeding tube was replaced by a dedicated 16-F nasogastric tube with nine electrodes that allowed continuous measurement of diaphragm electrical activity (electrical activity of the diaphragm catheter; Maquet, Sweden). All patients were ventilated with the Servo-I ventilator (Maquet; software version 4.01).

Ventilation Strategies

In the pressure support ventilation group, the inspiratory support level was set to obtain a tidal volume (V_T) of 6 to 8 ml/kg of predicted body weight, flow-trigger 1 liter/min, cycle off to 30% of peak inspiratory flow. In the pressure support ventilation group, the catheter which measured electrical activity of the diaphragm was disconnected from the ventilator (except during data acquisition for assessment of patient–ventilator interaction). The signal of the electrical activity of the diaphragm was therefore not available for clinical team. In the neurally adjusted ventilatory assist group, inspiratory assist was titrated to obtain a tidal volume of 6 to 8 ml/kg of predicted body weight, and the trigger of the electrical activity of the diaphragm was set to 0.5 μV. In neurally adjusted ventilatory assist, the software dictates that the ventilator cycles off at 70% of peak electrical activity of the diaphragm, which cannot be modulated by the

clinician. In both groups, the fraction of inspired oxygen (F_{IO_2}) and positive end-expiratory pressure (PEEP) were set by the physician in charge to maintain the oxygen saturation measured by pulse oximetry (S_{pO_2}) ≥ 90%. The level of inspiratory assist was reduced each morning (9:00 AM) in both groups until the tidal volume was less than 6 ml/kg predicted body weight, or the respiratory rate was more than 35 breaths/min, or the S_{pO_2} level was less than 90%. If return to assist-control mode was required, support was titrated to obtain a V_T of 6 to 8 ml/kg predicted body weight and S_{pO_2} of at least 90% were set according to local guidelines.

Weaning Protocol

The patients were screened once daily (9:00 AM) by investigators for possible spontaneous breathing trial from the first day after randomization (day 1). A spontaneous breathing trial was performed if (1) there was improvement of the underlying condition that required mechanical ventilation; (2) P_{aO_2}/F_{IO_2} was at least 200 mmHg; PEEP was at most 5 cm H_2O, F_{IO_2} was at most 50%; and respiratory frequency was less than 35 breath/min; (3) there was hemodynamic stability (heart rate of less than 140 beats/min, no vasopressors required or less than 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dopamine/dobutamine or less than 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ norepinephrine); or (4) there was no sedation or low sedation (Richmond Agitation–Sedation Scale of −2 or higher).

In both groups, a 30-min spontaneous breathing trial was performed with continuous positive airway pressure of 5 cm H_2O or pressure support ventilation with inspiratory pressure of 7 cm H_2O and 5 cm H_2O of PEEP at the prescribed level of F_{IO_2}. Ventilation mode was switched to pressure support ventilation during the spontaneous breathing trial for patients randomized to neurally adjusted ventilatory assist to assure similar conditions during the spontaneous breathing trial for both groups. The trial was interrupted if any of the following signs of poor tolerance were observed: S_{pO_2} of less than 90%; P_{aO_2} less than 60 mm Hg; increase in P_{aCO_2} of more than 10 mm Hg, heart rate changed more than 20%; systolic blood pressure more than 180 or less than 90 mm Hg or changed more than 20%, vasopressors required, respiratory rate more than 35 breaths/min, V_T less than 4 ml/kg, somnolence, coma, agitation, anxiety, diaphoresis, and other onset or worsening of discomfort deemed by the clinical team. Endotracheally intubated patients successfully completing the 30-min spontaneous breathing trial and adequate cough were extubated. Cough was evaluated by placing a white card about 1.5 cm away from the end of the endotracheal tube and asking the patient to cough (three or four times). Cough was considered adequate if wetness appeared on the card.[13] Patients successfully completing the spontaneous breathing trial but without adequate cough strength were reconnected and ventilated in either neurally adjusted ventilatory assist or pressure support ventilation mode according to the randomization. Tracheostomized patients successfully completing the spontaneous breathing trial were immediately disconnected from the ventilator without evaluation of cough strength. Decisions related to tracheostomy were made by the clinical team. Criteria of extubation, noninvasive ventilation, and reintubation based on electrical activity of the diaphragm are reported in the Supplemental Digital Content (http://links.lww.com/ALN/C274).

Patients could be switched to assist-control ventilation (pressure assist control) when they met the criteria reported in the Supplemental Digital Content (http://links.lww.com/ALN/C274). As soon as the criteria for switching to assist-control mechanical ventilation were restored; either neurally adjusted ventilatory assist or pressure support ventilation was reinstituted according to the randomization group.

Outcome Measures and Data Collection

The primary outcome is duration of weaning, which was defined as time (recorded by hours) from study enrollment to ventilator liberation (for endotracheally intubated patients this was defined as lack of invasive or noninvasive ventilation for more than 48 h after extubation; for tracheostomized patients this was defined as no ventilator assist for more than 48 h). Weaning duration was calculated as 28 days for patients under mechanical ventilation at day 28 or deceased before day 28 without successful weaning. Duration of weaning and secondary outcomes were also calculated separately for patients with and without tracheostomy after randomization.

Secondary outcomes were the proportion of successful weaning from invasive mechanical ventilation (no need for reintubation within first 48 h after extubation or continuous disconnection of ventilator for more than 48 h in tracheostomized patients); rate of successful extubation (no need for reintubation within 48 h after extubation); ventilator-free days within 7, 14, and 28 days after randomization (if patients died during the 7-, 14-, or 28-day period after enrollment, the number of ventilator-free days was 0); total duration of invasive mechanical ventilation (included the duration of mechanical ventilation before enrollment and after enrollment) in weaned patients, length of stay in ICU and hospital, ICU, hospital, 28-day mortality, and patient–ventilator asynchrony.

The data were collected at the time of randomization to characterize comorbidity, the severity of illness, duration of mechanical ventilation before inclusion (recorded by hours), ventilator settings, respiratory measures, and arterial blood gases. Time spent in each ventilator mode during the first 24 h after randomization was recorded. Ventilatory settings, respiratory measures, and arterial blood gases were also collected at day 1, day 2, and just before first weaning attempt. Adverse events of mechanical ventilation such as pneumothorax and ventilator-related pneumonia, which was diagnosed according to the previous definitions, were also recorded (Supplemental Digital Content, http://links.

lww.com/ALN/C274).[14] The time spent on each ventilation mode during the first 24 h was calculated from the mode conversion record of the ventilator memory card. Estimations of patient–ventilator asynchrony and electrical activity of the diaphragm-derived variables are reported in the Supplemental Digital Content (http://links.lww.com/ALN/C274).

Statistical Analysis

We anticipated weaning duration of 3 ± 1 days[15] and 0.6 days (20%) absolute decrease of duration of weaning in neurally adjusted ventilatory assist group compared with that in pressure support ventilation group. Therefore, 44 patients/group would provide 80% power at a two-sided α-level of 0.05 to detect a 0.6-day absolute decrease in the duration of weaning in neurally adjusted ventilatory assist group. In total, 99 patients were enrolled in the study to manage the dropouts.

Statistical analysis was performed with SPSS 17.0 (IBM, USA) Sigma Stat 3.5 (Systat Software Inc., USA). Mann–Whitney U test was used for comparison of the primary outcome between groups. *Post hoc* sensitivity analysis of primary outcome was performed by the Kaplan–Meier method. This analysis differs from the primary analysis because it does not use imputation and because deceased individuals or those still on mechanical ventilation at 28 days were right censored. Interval data of the baseline variables and secondary outcomes were compared with Mann–Whitney U test between groups and summarized using median (interquartile range). Nominal data of the baseline and secondary outcomes were compared with the chi-square test and summarized using the number of events (percentages). The percentage of patients remaining in mechanical ventilation and successful weaning in 28 days were constructed (Kaplan–Meier method), and differences between groups were compared using the log rank test. *Post hoc* subgroup analysis was performed in tracheostomized and nontracheostomized patients. A two-sided *P* value of less than 0.05 was considered to indicate statistical significance.

Results

Study Population

Among 4,241 patients receiving invasive mechanical ventilation during the study period, 99 patients were enrolled in the intention-to-treat analysis: 52 patients in the pressure support ventilation group and 47 patients in neurally adjusted ventilatory assist group (fig. 1). Enrollment ceased when the target sample size was obtained. Table E1 in the Supplemental Digital Content (http://links.lww.com/ALN/C277) shows volume of patients and enrollment rate per year. The two groups were balanced at baseline with regards to age, Acute Physiology and Chronic Health Evaluation (APACHE) II score, comorbidity, main diagnosis, duration of mechanical ventilation before inclusion,

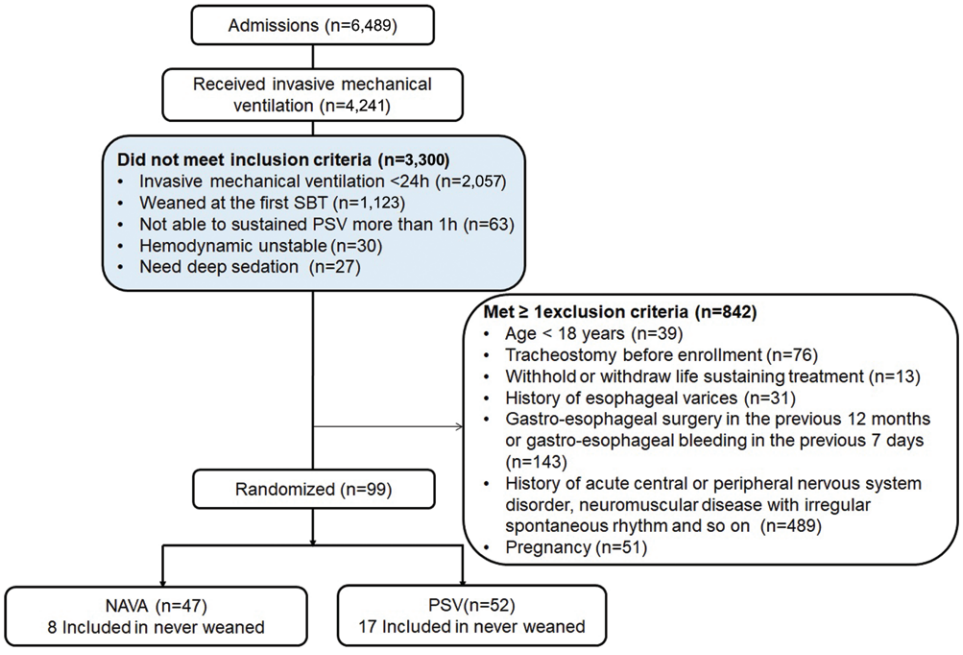

Fig. 1. Flow diagram of the patient enrollment. NAVA, neurally adjusted ventilatory assist; PSV, pressure support ventilation; SBT, spontaneous breathing trial.

ventilator settings, respiratory measures, and blood-gas parameters (table 1). Tracheostomized patients and nontracheostomized patients were balanced at baseline between groups (table E2 in the Supplemental Digital Content, http://links.lww.com/ALN/C275). There were no missing data for primary and secondary outcomes except patient–ventilator asynchrony and electrical activity of the diaphragm–derived variables (details in Supplemental Digital Content, http://links.lww.com/ALN/C275).

Primary Outcome

The primary outcome, weaning duration (recorded by hours) in all patients, was statistically significant shorter in neurally adjusted ventilatory assist compared with pressure support ventilation (3.0 [1.2 to 8.0] *vs.* 7.4 [2.0 to 28.0] days, mean difference: −5.5 [95% CI, −9.2 to −1.4], $P = 0.039$; table 2). *Post hoc* sensitivity analysis also showed that neurally adjusted ventilatory assist group had shorter weaning duration (hazard ratio 0.58; 95% CI 0.34 to 0.98; fig. 2A).

Secondary Outcomes

Secondary outcomes are reported in table 2. The proportion of patients with successful weaning from invasive mechanical ventilation was 70% (33 of 47) in the neurally adjusted ventilatory assist group and 48% (25 of 52) in the pressure support ventilation group ($P = 0.026$, respiratory rate [RR] for neurally adjusted ventilatory assist: 1.46 [95% CI, 1.04 to 2.05]). Weaning duration in tracheostomized patients was shorter in neurally adjusted ventilatory assist compared with pressure support ventilation (table 3). The percentage of patients not weaned from mechanical ventilation at day 28 was 17% (8 of 47) in the neurally adjusted ventilatory

Table 1. Characteristics of the Patients at Randomization

	PSV ($n = 52$)	NAVA ($n = 47$)	*P* Value
Sex, male (%)	36 (69)	30 (64)	0.596
Age, yr	80 (65, 80)	75 (61, 80)	0.385
Predicted body weight, kg	66 (54, 71)	66 (54, 70)	0.909
Actual body mass index, %	27 (21, 29)	26 (22, 29)	0.451
APACHE II	20 (17, 28)	22 (16, 26)	0.894
Comorbidity			
Respiratory system, n (%)	11 (21)	10 (21)	0.988
Cardiovascular system, n (%)	22 (42)	28 (60)	0.130
Others, n (%)	25 (48)	18 (38)	0.327
Duration of MV before inclusion, days	5.9 (3.0, 10.8)	5.0 (2.6, 7.6)	0.065
Main diagnosis			
Pneumonia, n (%)	14 (27)	13 (28)	> 0.999
Extrapulmonary sepsis, n (%)	2 (4)	0 (0%)	0.497
ACS or CHF, n (%)	6 (12)	10 (21)	0.423
AECOPD	5 (10)	5 (11)	> 0.999
Nervous system disease with regular spontaneous breathing, n (%)	9 (17)	5 (11)	0.397
Abdominal surgery, n (%)	5 (10)	4 (9)	0.473
Thoracic surgery, n (%)	1 (2)	2 (4)	0.603
Sever trauma, n (%)	4 (8)	4 (9)	> 0.999
Others, n (%)	6 (11)	4 (9)	0.744
Respiratory mechanics			
Respiratory system static compliance, ml/cm H_2O	35.0 (33.6, 45.7)	36.2 (32.8, 51.4)	0.222
Airway resistance, cm H_2O/liter·s^{-1}	10.0 (8.9, 12.9)	10 (9.0, 11.0)	0.558
Type of difficult weaning			
Failure of first SBT, n (%)	42 (81)	36 (77)	0.632
Reintubation within 48 h after extubation, n (%)	10 (19-)	11 (23)	0.632
Ventilator settings and respiratory parameters			
PEEP, cm H_2O	5 (5, 6)	5 (5, 6)	0.813
PS, cm H_2O	8 (7, 10)	8 (8, 10)	0.112
Fio_2, %	40 (40, 40)	40 (40, 40)	0.919
Tidal volume, ml/kg (ideal body weight)	6.5 (5.7, 7.3)	6.5 (5.8, 7.8)	0.631
Respiratory rate, breath/min	23 (18, 29)	20 (16, 25)	0.107
Minute ventilation, liters/min	8.7 (7.1, 12.1)	8.0 (6.4, 10.5)	0.155
pH	7.43 (7.39, 7.47)	7.44 (7.39, 7.46)	0.869
Pao_2/Fio_2, mmHg	271 (230, 349)	279 (229, 322)	0.649
$Paco_2$, mmHg	35 (29, 41)	36 (32, 41)	0.316

The data are presented as frequency (%) or median (interquartile range).

ACS, acute coronary syndrome; AECOPD, acute exacerbation chronic obstructive pulmonary disease; APACHE II, Acute Physiology and Chronic Health Evaluation II; CHF, congestive heart failure; Fio_2, fraction of inspired oxygen; MV, mechanical ventilation; NAVA, neurally adjusted ventilatory assist; Pao_2, arterial oxygen tension $Paco_2$, arterial carbon dioxide tension; PEEP, positive end-expiratory pressure; PS, pressure support; PSV, pressure support ventilation; SBT, spontaneous breathing trial.

Table 2. Outcomes

	PSV (n = 52)	NAVA (n = 47)	RR for NAVA or Mean Difference between Groups (95% CI)	*P* Value
Primary outcome				
Duration of weaning in all patients, days*	7.4 (2.0, 28.0)	3.0 (1.2, 8.0)	–5.3 (–9.2,–1.4)	0.039
Other outcomes				
Successful weaning, n (%)†	25 (48)	33 (70)	1.46 (1.04, 2.05)	0.026
Patients not weaned at day 28, n (%)	17 (33)	8 (17)	0.52 (0.25, 1.09)	0.073
Reasons for not being weaned at day 28				
Died before ventilator liberation, n (%)	9 (17)	7 (15)	0.86 (0.34, 2.13)	0.791
Unsuccessful weaning process, n (%)	8 (15)	1 (2)	0.14 (0.02, 1.07)	0.033
Successful extubation, n (%)‡	17 (33)	21 (44)	1.37 (0.83, 2.26)	0.221
Total duration of IMV in weaned patients, days§	10.0 (6.1, 26.9)	7.1 (5.0, 12.5)	–9.5 (–20.2, –1.5)	0.056
Patients tracheostomized, n (%)	21 (40)	13 (28)	0.69 (0.39, 1.21)	0.183
Ventilator related pneumonia, n (%)	3 (6)	2 (4)	0.74 (0.13, 4.22)	0.731
Patients receiving postextubation NIV, n (%)	9 (17)	9 (19)	1.11 (0.49, 2.55)	0.813
Duration of postextubation NIV, hr	15 (9, 24)	8 (3, 8)	–11 (–26, 2)	0.092
Invasive ventilator-free days, day 28	21.0 (0, 26.0)	25.0 (20.0, 27.0)	5.3 (1.00, 9.6)	0.028
Ventilator-free days, day 7	0 (0, 5.0)	4.0 (0, 5.8)	1.0 (–0.1, 1.9)	0.064
Ventilator-free days, day 14	6.6 (0, 12.0)	11.0 (6.0, 12.8)	2.7 (0.5, 4.6)	0.027
Ventilator-free days, day 28	21.0 (0, 26.0)	24.0 (20.0, 27.0)	5.3 (1.2, 9.7)	0.039
Length of stay in ICU, days	27 (13, 40)	19 (12, 32)	–7 (–21, 7)	0.266
Length of stay in ICU in survivors, days	19 (10, 33)	24 (12, 35)	–4 (–23, 13)	0.894
Length of stay in hospital, days	32 (19, 58)	29 (19, 44)	–7 (–26, 13)	0.437
Length of stay in hospital in survivors, days	30 (17, 44)	35 (26, 47)	9 (–7, 26)	0.481
ICU mortality, n (%)	17 (33)	8 (17)	0.52 (0.25, 1.09)	0.073
28-day mortality, n (%)	14 (27)	14 (30)	1.11 (0.59, 2.07	0.752
Hospital mortality, n (%)	25 (48)	16 (34)	0.71 (0.44, 1.15)	0.157
Modes of SBT				
CPAP, n (%)	35 (67)	34 (72)	N/A	> 0.999
PSV, n (%)	17 (33)	13 (28)	N/A	> 0.999

The data are presented as frequency (%) or median (interquartile range).

*Duration of weaning was defined as time from study enrollment to extubation or disconnection of the ventilator continuously for 48 h in patients tracheostomized. Weaning duration was calculated as 28 days if patients could never be weaned. Duration of weaning in all patients included the patients who end up with and without tracheostomy within the 28 days after enrollment. †Successful weaning (from invasive mechanical ventilation) included both successful extubation (no need for reintubation within 48 h after extubation in endotracheal intubation patients) and continuous disconnection of ventilator for more than 48 h (for patients who were tracheostomized after enrollment). ‡Successful extubation was defined as no need for reintubation within 48 h after extubation (for endotracheal intubation patients). §Including mechanical ventilation time before enrollment.

CPAP, continuous positive airway pressure (5 cm H_2O); ICU, intensive care unit; IMV, invasive mechanical ventilation; N/A, not applicable; NAVA, neurally adjusted ventilatory assist; NIV, noninvasive mechanical ventilation; PSV, pressure support ventilation (with inspiratory pressure of 7 and 5 cm H_2O of PEEP); RR, respiratory rate; SBT, spontaneous breathing trial.

assist group and 33% (17 of 52) in the pressure support ventilation group ($P = 0.073$, RR for neurally adjusted ventilatory assist: 0.52 [95% CI, 0.25 to 1.09]). The percentage of patients successfully weaned was significantly higher in the neurally adjusted ventilatory assist group (fig 2B). The percentage of patients receiving postextubation noninvasive ventilation were not different between neurally adjusted ventilatory assist and pressure support ventilation groups (9 of 52, 19% *vs.* 9 of 47, 17%, $P = 0.813$). Neurally adjusted ventilatory assist was associated with an increased number of ventilator-free days on days 14 and 28 (table 2). Table 3 reports the secondary outcomes in tracheostomized and nontracheostomized patients.

Patient–Ventilator Asynchrony and Electrical Activity of the Diaphragm–derived Variables

The asynchrony index, ineffective efforts, and premature cycling were statistically significant higher in the pressure support ventilation group than that in the neurally adjusted ventilatory assist group (fig. 3, A and B). However, double triggering was more frequent in the neurally adjusted ventilatory assist group than in the pressure support ventilation group. Trigger error and cycle-off error were much higher in the pressure support ventilation group compared with the neurally adjusted ventilatory assist group. Peak electrical activity of the diaphragm and mean inspiratory electrical activity of the diaphragm were statistically significant higher in the neurally adjusted ventilatory assist group compared with the pressure support ventilation group (fig. 3C). Detailed analysis of patient–ventilator interaction is shown in the Supplemental Digital Content (http://links.lww.com/ALN/C274).

Respiratory Variables and Time Spend in Different Ventilatory Modes

Ventilator settings, respiratory physiologic variables, and blood-gas parameters on day 1 and on the day of weaning are reported in table E3 in the Supplemental Digital

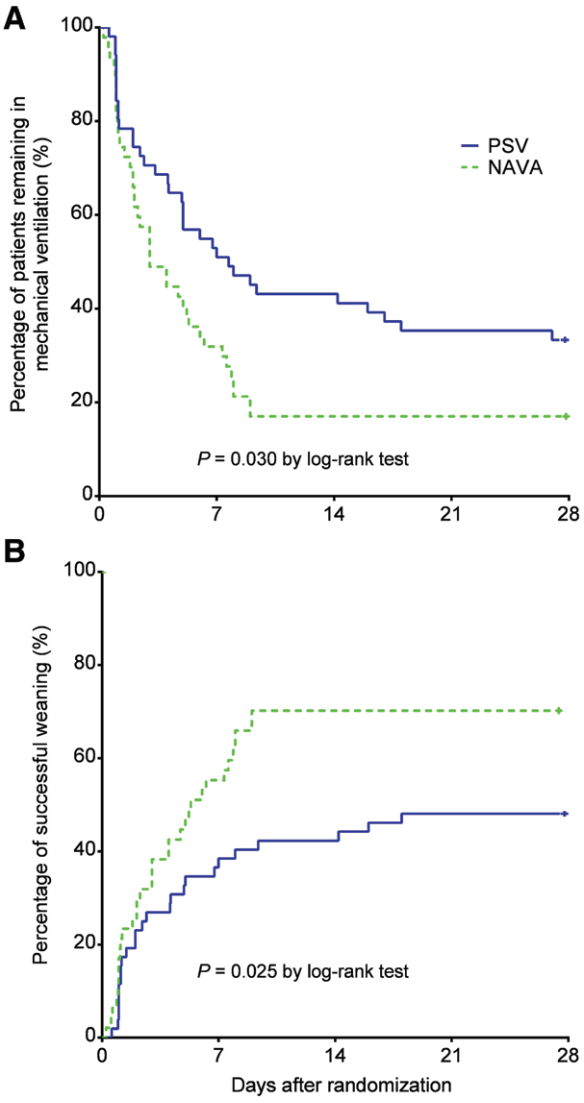

Fig. 2. Kaplan–Meier estimates for the percentage of patients remaining in mechanical ventilation (*A*) and for the percentage of successful weaning (*B*). NAVA, neurally adjusted ventilatory assist; PSV, pressure support ventilation.

Content (http://links.lww.com/ALN/C276). The time spent in the assist-control ventilation was similar between the neurally adjusted ventilatory assist and pressure support ventilation groups (table E4 in the Supplemental Digital Content, http://links.lww.com/ALN/C278).

Adverse Events and Survival

Nasal bleeding possibly related to the neurally adjusted ventilatory assist catheter occurred in one patient in the neurally adjusted ventilatory assist group. Ventilator-related pneumonia was comparable in the neurally adjusted ventilatory assist (2 of 47, 4%) and pressure support ventilation (3 of 52, 6%) groups ($P = 0.731$). No adverse events related to the neurally adjusted ventilatory assist mode were recorded. The differences between groups were not significant for ICU mortality (RR for neurally adjusted ventilatory assist, 0.52 [95% CI, 0.25 to 1.09]), 28-day mortality (RR for neurally adjusted ventilatory assist, 1.11 [95% CI, 0.59 to 2.07]), and hospital mortality (RR, 0.71 [95% CI, 0.44 to 1.15]) (table 2). Length of stay in the ICU and in the hospital were similar in the two groups, both for all the patients or restricted to survivors (table 2).

Discussion

This is the first randomized controlled trial to compare neurally adjusted ventilatory assist with pressure support ventilation in patients difficult to wean from mechanical ventilation. The major finding of our study is that in these patients, neurally adjusted ventilatory assist compared with pressure support ventilation improves clinical outcome, in particular decreasing the duration of weaning, increasing ventilator-free days at days 14 and 28, and increasing the probability of successful weaning. Finally, this study shows that neurally adjusted ventilatory assist is very well tolerated in these patients and confirms that neurally adjusted ventilatory assist improves patient–ventilator interaction as reported previously.[9–12]

Neurally Adjusted Ventilatory Assist for Invasive Ventilation

Neurally adjusted ventilatory assist is the only ventilator mode that uses electrical activity of the diaphragm to control the ventilator.[8] This results in a more physiologic breathing pattern, because the inspiratory assist is in proportion to patient's neural effort.[8] Several studies have compared neurally adjusted ventilatory assist to pressure support ventilation during invasive ventilation, and most studies demonstrated that neurally adjusted ventilatory assist improves short-term physiologic effects such as patient–ventilator interaction and gas exchange.[9,10,16] In a recent multicenter randomized controlled trial, Demoule *et al.*[11] compared neurally adjusted ventilatory assist to pressure support ventilation in patients (n = 128) early after the transition from controlled mode to partially supported ventilator mode. They demonstrated that neurally adjusted ventilatory assist is feasible and safe in these patients. In addition, neurally adjusted ventilatory assist improved patient–ventilator interaction and reduced the use of postextubation noninvasive ventilation. However, that study did not find a difference in the duration of weaning or duration of invasive mechanical ventilation. This is in apparent contrast to the current study, which is the first to demonstrate that neurally adjusted ventilatory assist reduces the duration of weaning and increases the chances of successful weaning.

Important differences in design and population between the current trial and the study of Demoule *et al.*[11] should

Table 3. Outcomes in Tracheostomized and Nontracheostomized Patients

	Tracheostomized Patients			Nontracheostomized Patients		
	PSV (n = 21)	NAVA (n = 13)	*P* Value	PSV (n = 31)	NAVA (n = 34)	*P* Value
Primary outcome						
Duration of weaning	14.2 (4.1, 28.0)	5.2 (3.0, 7.9)	0.046	5.1 (1.2, 28)	2.7 (1.1, 8.6)	0.193
Other outcomes						
Successful weaning, n (%)*	15 (71)	12 (92)	0.210	17 (55)	21 (62)	0.621
Patients not weaned at day 28, n (%)	7 (24)	0 (0)	0.370	10 (32)	8 (24)	0.580
Reasons for not being weaned at day 28						
Died before entering weaning process, n (%)	3 (14)	0 (0)	0.270	6 (19)	7 (21)	0.526
Unsuccessful weaning process, n (%)	4 (19)	0 (0)	0.144	4 (13)	1 (3)	0.184
Time from the randomization to tracheostomy, days	3.6 (1.8, 4.5)	3.7 (1.9, 4.8)	0.944			
Total duration of IMV in weaned patients, days†	7.0 (4.8, 15.4)	6.0 (4.3, 8.2)	0.252	22.5 (9.9, 27.0)	12.5 (9.9, 18.0)	0.134
Ventilator related pneumonia, n (%)	3 (14)	2 (15)	1.000			
Invasive ventilator-free days, day 28	16.0 (0, 24.0)	25.0 (20.4, 26.0)	0.035	23.0 (0, 26.9)	25.3 (19.4, 26.9)	0.184
Ventilator-free days, day 7	0 (0, 2.9)	1.8 (0, 4)	0.317	1.9 (0, 5.8)	4.3 (0, 5.9)	0.193
Ventilator-free days, day 14	0 (0, 9.9)	8.8 (6.1, 11.0)	0.043	8.9 (0, 12.8)	11.3 (5.4, 12.8)	0.175
Ventilator-free days, day 28	13.8 (0, 23.9)	22.8 (21.0, 25)	0.046	22.9 (0, 26.8)	25.3 (19.4, 26.9)	0.165
Length of stay in ICU, days	34 (25, 74)	35 (28, 47)	0.800	15 (10, 33)	14.0 (11, 24)	0.737
Length of stay in ICU in survivors, days	34 (24, 70)	34 (21, 47)	0.742	14 (19, 30)	14 (11, 25)	0.843
Length of stay in hospital, days	52 (27, 73)	44 (34, 58)	0.795	26 (16, 40)	25 (17, 37)	0.772
Length of stay in hospital in survivors, days	44 (29, 64)	48 (37, 69)	0.536	26 (17, 37)	31 (21, 43)	0.460
ICU mortality, n (%)	7 (33)	1 (8)	0.116	10 (32)	7 (21)	0.398
28-day mortality, n (%)	4 (19)	2 (15)	1.000	10 (32)	12 (35)	> 0.999
Hospital mortality, n (%)	11 (52)	2 (15)	0.067	14 (45)	14 (41)	0.805

The data are presented as frequency (%) or median (interquartile range).

*Successful weaning (from invasive mechanical ventilation) included both successful extubation (no need for reintubation within 48 h after extubation in endotracheal intubation patients) and continuous disconnection of ventilator for more than 48 h (for patients who were tracheostomized after enrollment). †Including mechanical ventilation time before enrollment.

ICU, intensive care unit; IMV, invasive mechanical ventiliation; NAVA, neurally adjusted ventilatory assist; PSV, pressure support ventilation.

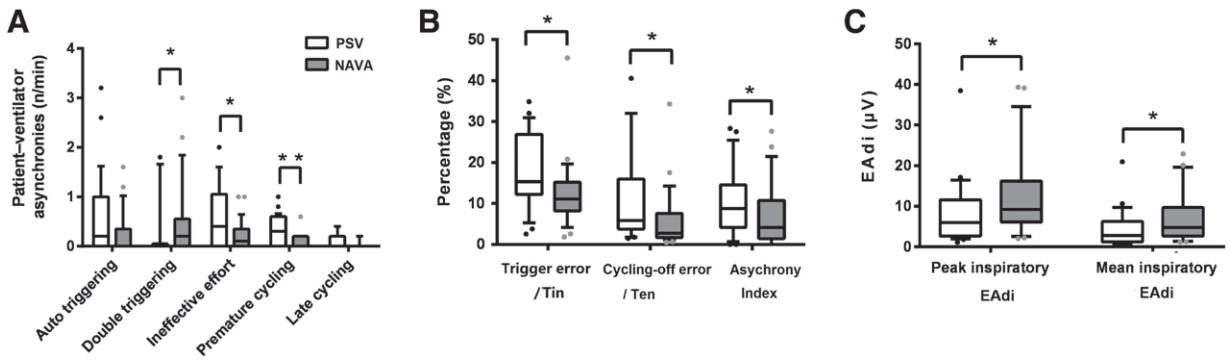

Fig. 3. Box plots showing the median and interquartile range of patient–ventilator asynchronies and electrical activity of the diaphragm (EAdi). (*A*) Rates of the autotriggering, double triggering, ineffective effort, premature cycling, and late cycling showed as numbers per minutes. (*B*) Asynchrony index and the trigger error and cycle-off error showed as the occupation of neural inspiratory and expiratory time, respectively. (*C*) Peak and mean inspiratory EAdi showed as μV. NAVA, neurally adjusted ventilatory assist; PSV, pressure support ventilation; Ten, neural expiratory time; Tin, neural inspiratory time. **P* < 0.05; ***P* < 0.01.

be acknowledged. First, regarding patient selection, in the study by Demoule *et al.*,[11] patients were enrolled early after the transition from controlled to a partially supported mode (able to sustain pressure support ventilation for at least 30 min), whereas in our study only patients with failed weaning were recruited. In fact, the beneficial effects of neurally adjusted ventilatory assist on weaning duration in our study were mainly driven by patients tracheostomized after randomization (table 3). It is likely that a ventilator mode that improves patient–ventilator interaction has more

clinical impact in difficult-to-wean patients. Second, in contrast to the study by Demoule *et al.*,[11] electrical activity of the diaphragm in pressure support ventilation group was not available for clinicians in our study. This is important, because clinicians in the study of Demoule *et al.*[11] may have adapted ventilator settings in pressure support ventilation group based on electrical activity of the diaphragm to limit inappropriate inspiratory assist (overassist or underassist) and to improve patient ventilator interaction. This may result in better outcome than pressure support ventilation without monitoring the electrical activity of the diaphragm. Our trial better reflects the use of pressure support ventilation in today's clinical practice, and under these conditions neurally adjusted ventilatory assist appears to improve weaning outcome. The reduction in 4.4 days in all patients and even 9.0 days in tracheostomized patients should be considered clinically relevant. Moreover, the absolute difference in successful weaning of 22% between neurally adjusted ventilatory assist and pressure support ventilation is important from patient perspective and economical perspective, although the latter was not formally evaluated in the current study.

Explanations for Improved Outcome in Neurally Adjusted Ventilatory Assist

Possible explanations for the beneficial outcome in neurally adjusted ventilatory assist groups should be discussed. First, the current trial confirms earlier observations that neurally adjusted ventilatory assist improves patient ventilator interaction.[9–11,17,18] It is recognized that poor patient–ventilator interaction is common in ICU patients and is associated with adverse clinical outcome.[4,19] Second, ventilation in neurally adjusted ventilatory assist mode and especially monitoring the electrical activity of the diaphragm may facilitate "diaphragm-protective mechanical ventilation," in which the level of assist is titrated to patients' neural effort,[7,20] and therefore both ventilator underassist and ventilator overassist are less likely to occur. In neurally adjusted ventilatory assist mode, the ventilator will reduce inspiratory support when respiratory drive (electrical activity of the diaphragm) is low as the ventilator will vice versa. Interestingly, the electrical activity of the diaphragm in the neurally adjusted ventilatory assist group was 9.1 μV (6.1 to 16.2), exactly the level that was associated with preserved diaphragm thickness in a recent study by Goligher *et al.*[6] The statistically significant lower electrical activity of the diaphragm in the pressure support ventilation group suggests that ventilator overassist and may be associated with diaphragm thinning. Interestingly, in a physiologic study, Di Mussi *et al.*[21] investigated diaphragm muscle contractile efficiency in patients randomized to pressure support ventilation or neurally adjusted ventilatory assist. Remarkably, the values of electrical activity of the diaphragm for pressure support ventilation group and neurally adjusted ventilatory assist group during assisted ventilation were almost identical to the values reported in our trial. They demonstrated that neurally adjusted ventilatory assist was associated with improved diaphragm neuromuscular contractile efficiency within 48 h of randomization. This may be a reasonable explanation for the beneficial effects on clinical outcome in the neurally adjusted ventilatory assist group in our study. Third, quality of sleep may play an important role in the success of ventilator weaning.[22,23] neurally adjusted ventilatory assist has been reported to improve the quality of sleep over pressure support ventilation in mechanical ventilation patients.[24] However, in our study we did not monitor sleep quality, and this therefore remains speculative.

Although neurally adjusted ventilatory assist decreased the duration of weaning, it did not affect the length of ICU stay. It should be noted that length of stay is determined by other factors then weaning, including airway management in tracheostomized patients. In addition, about a fourth of patients in our study were not weaned at day 28 (patients dying or transferred to other hospital), and duration of ICU stay was counted as 28 days.

Strengths and Limitations

This is the first randomized clinical trial that to compare neurally adjusted ventilatory assist and pressure support ventilation in patients difficult to wean from mechanical ventilation. In contrast to the previous randomized trial investigating neurally adjusted ventilatory assist, electrical activity of the diaphragm was not available to clinicians in the pressure support ventilation group, allowing real comparison of pressure support ventilation as used in clinical practice with neurally adjusted ventilatory assist.

There are some limitations that should be noted. For sample size calculation, we predicted a reduction in weaning time of 20% in patients randomized to neurally adjusted ventilatory assist. This value is more or less arbitrarily chosen, because no data are available to predict the effects of neurally adjusted ventilatory assist on weaning duration in difficult-to-wean patients. However, a larger reduction in weaning time with a novel ventilator mode appears unlikely, because the pathophysiology of difficult weaning is complex, and several contributing factors cannot be modified by a ventilator mode. In line with our reasoning, in an ongoing randomized trial comparing neurally adjusted ventilatory assist and pressure support ventilation, the proposed reduction in ventilator-free days is ±10%.[25] Because of the design of the study, blinding was not feasible. This might be a potential source of bias. However, strict criteria for initiation and discontinuation of weaning trials were formulated. In addition, data for patient–ventilator interaction were not available for all patients because of limited resources. However, patient–ventilator interaction was not the primary outcome of this study, and many previous studies have already demonstrated that neurally adjusted ventilatory assist improves patient–ventilator interaction. It should also be acknowledged that patients in our study were 12 to 16 yr older compared with recent weaning

studies.[11,26] This may also explain the rather high mortality and high percentage of failed weaning patients in our study. In this study we did not exclude patients that were tracheostomized after randomization, and we did not provide a specific weaning protocol for tracheostomized patients. This may make interpretation of the data more complex, because the approach of clinicians to weaning and ventilator liberation may be different for tracheostomized *versus* nontracheostomized patients. Therefore, *post hoc* subgroup analysis was performed for these groups (table 3), obviously reducing the number of patients and therefore the power. The results of subgroup analysis should be interpreted with great caution. Another limitation is that decisions related to tracheostomy were not protocolized and decided by the clinical team. Interestingly, 21 patients ended up with tracheostomy in the pressure support ventilation group *versus* 13 patients in the neurally adjusted ventilatory assist group. As mentioned above the benefit of neurally adjusted ventilatory assist is more prominent in the patients with tracheostomy than those without in term of ventilator-free days, by days 14 and 28. Because in this study more patients in the pressure support ventilation group ended with tracheotomy than in the neurally adjusted ventilatory assist group, our results likely underestimated, not overestimated, the benefit of the neurally adjusted ventilatory assist. Finally, it should be emphasized that this study was conducted in an ICU with extensive clinical experience using the neurally adjusted ventilatory assist mode. The results of the present study should be confirmed in centers less skilled in neurally adjusted ventilatory assist during the weaning phase.

Conclusions

We demonstrate that in patients difficult to wean from mechanical ventilation, neurally adjusted ventilatory assist improves clinical outcome, especially the duration of weaning compared with pressure support ventilation. We confirmed that neurally adjusted ventilatory assist improves patient–ventilator interaction and is feasible and safe for a prolonged period of time in clinical centers with extensive experience using this mode.

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Competing Interests

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Full protocol available at: liulingdoctor@126.com. Raw data available at: liulingdoctor@126.com.

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