Assisted Ventilation in Patients with Acute Respiratory Distress Syndrome

Lung-distending Pressure and Patient–Ventilator Interaction

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ABSTRACT

Background: In patients with acute respiratory distress syndrome (ARDS), the use of assisted mechanical ventilation is a subject of debate. Assisted ventilation has benefits over controlled ventilation, such as preserved diaphragm function and improved oxygenation. Therefore, higher level of "patient control" of ventilator assist may be preferable in ARDS. However, assisted modes may also increase the risk of high tidal volumes and lung-distending pressures. The current study aims to quantify how differences in freedom to control the ventilator affect lung-protective ventilation, breathing pattern variability, and patient–ventilator interaction.

Methods: Twelve patients with ARDS were ventilated in a randomized order with assist pressure control ventilation (PCV), pressure support ventilation (PSV), and neurally adjusted ventilatory assist (NAVA). Transpulmonary pressure, tidal volume, diaphragm electrical activity, and patient–ventilator interaction were measured. Respiratory variability was assessed using the coefficient of variation of tidal volume.

Results: During inspiration, transpulmonary pressure was slightly lower with NAVA (10.3 ± 0.7, 11.2 ± 0.7, and 9.4 ± 0.7 cm H_2O for PCV, PSV, and NAVA, respectively; $P < 0.01$). Tidal volume was similar between modes (6.6 [5.7 to 7.0], 6.4 [5.8 to 7.0], and 6.0 [5.6 to 7.3] ml/kg for PCV, PSV, and NAVA, respectively), but respiratory variability was higher with NAVA (8.0 [6.4 to 10.0], 7.1 [5.9 to 9.0], and 17.0 [12.0 to 36.1] % for PCV, PSV, and NAVA, respectively; $P < 0.001$). Patient–ventilator interaction improved with NAVA (6 [5 to 8] % error) compared with PCV (29 [14 to 52] % error) and PSV (12 [9 to 27] % error); $P < 0.0001$.

Conclusion: In patients with mild-to-moderate ARDS, increasing freedom to control the ventilator maintains lung-protective ventilation in terms of tidal volume and lung-distending pressure, but it improves patient–ventilator interaction and preserves respiratory variability. **(Anesthesiology 2015; 123:181-90)**

IN patients with acute respiratory distress syndrome (ARDS), mechanical ventilation with positive-end expiratory pressure (PEEP), limited plateau airway pressure (Paw), and low tidal volume (Vt) is widely accepted as the ventilation strategy of choice to limit ventilator-induced lung injury.[1,2] The use of assisted mechanical ventilation in ARDS is a subject of debate.[3–5] Among other beneficial effects, assisted ventilation preserves diaphragm function and better resembles natural respiratory variability when compared with controlled mechanical ventilation.[3,4] This may be important, as increased variation in breathing pattern improves oxygenation and lung mechanics and enhances tidal distribution to the dependent lung regions.[6,7] However, during assisted ventilation, spontaneous breathing contributes to the transpulmonary pressure (Ptp), potentially increasing the risk of ventilator-induced lung injury if either is excessive.[4]

What We Already Know about This Topic

- Controlled mechanical ventilation (no spontaneous efforts) can be associated with diaphragm weakness and has led to suggestions for more spontaneous breathing efforts with assisted ventilation by patients with acute respiratory distress syndrome (ARDS). However, spontaneous breathing in ARDS can lead to ventilator-induced lung injury by overdistending the lung.

What This Article Tells Us That Is New

- Twelve patients with mild-to-moderate acute respiratory distress syndrome (ARDS) were ventilated in randomized order with three ventilation modes: pressure control ventilation, pressure support ventilation, and neurally adjusted ventilatory assist. Lung-protective ventilation was maintained to a similar degree in all study arms; the results are hypothesis generating for using assisted ventilation in patients with ARDS after the first 48 h of therapy, which might include paralysis.

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Neurally adjusted ventilator assist (NAVA) is a ventilator mode that uses electrical activity of the diaphragm (EAdi) to control timing and level of support during inspiration, thereby introducing inherent feedback loops between patient and ventilator.[8] It has been shown in patients with acute respiratory failure that increasing levels of support with NAVA unloads the respiratory muscles but limits pressure increases due to down-regulation of EAdi.[9–11] This suggests that intrinsic lung-protective feedback mechanisms may limit Vt and lung-distending pressure. Recently, it has been shown in an animal model that not only the magnitude but also the duration of mechanical stress within the respiratory cycle (inspiratory-to-expiratory time ratio) determines the severity of lung injury.[12] This emphasizes the importance of synchrony between neural and mechanical inspiration.

Overall, it is rational to investigate the effects of increased patient freedom to control the ventilator on respiratory mechanics in patients with ARDS. Up to now, data related to these effects are scarce in patients with ARDS.[10,13] Therefore, the aim of the current study was to investigate the effects of three modes of assisted ventilation on lung-distending pressures, Vt, breathing variability, and patient–ventilator interaction in patients with ARDS. The selected ventilator modes cover a wide spectrum of patient freedom to control ventilator assist: (1) pressure control ventilation (PCV): a pressure-limited mode of both mandatory and triggered assist of fixed duration; (2) pressure support ventilation (PSV): a pressure-limited mode with flow-trigger and variable cycling-off, allowing the patient more freedom to time assist delivery to inspiratory effort; and (3) NAVA: a mode where the patient regulates both timing and magnitude of assist *via* neural inspiratory effort. We reasoned that intrinsic lung-protective feedback mechanisms maintain lung-protective ventilation when patient freedom to control the ventilator is increased. Accordingly, the first hypothesis of our study was that with NAVA (maximal "patient freedom") Vt and lung-distending pressure remain within clinically acceptable limits. The second hypothesis was that breathing pattern variability and patient–ventilator interaction in patients with ARDS improve with increased freedom to control the ventilator.

Materials and Methods

Study Design and Population

Twelve adult patients, fulfilling the Berlin definition of ARDS,[14] were studied in a physiological study on the intensive care unit of the Radboud University Medical Center. Exclusion criteria were hemodynamic instability, contraindications to changing a nasogastric tube (*i.e.*, recent nasal bleeding, upper airway/esophageal pathology, or surgery), and previously known neuromuscular disorders.

The protocol was approved by the institutional review board (CMO regio Arnhem-Nijmegen, NL31557.091.10) and is in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Patient surrogate decision makers gave informed consent before study inclusion.

Ventilator and Esophageal Catheter

Patients were ventilated with a Servo-I ventilator (Maquet Critical Care, Sweden). EAdi and esophageal pressure (Pes) were obtained with a multielectrode esophageal catheter with balloon (Neurovent Research Inc., Canada) as described previously.[15,16] Care was taken with correct positioning and inflation of the balloon using the Baydur method.[17] Additional details on catheter positioning are provided in Supplemental Digital Content 1, http://links.lww.com/ALN/B147.

Study Protocol

Initially, patients were ventilated in PSV mode for 30 min to verify the feasibility of assisted ventilation. Subsequently, in a cross-over design, PCV, PSV, and NAVA were randomly applied for 30 min each. PSV and PCV levels were matched to target a Vt of 6-ml/kg predicted bodyweight. With PCV, mechanical respiratory rate was set just below patient's respiratory rate to allow patient-triggered breaths. NAVA level (cm $H_2O/\mu V$) was set by the use of a dedicated window on the Servo-I ventilator. In brief, in either PSV or PCV, the actual Paw is presented with an overlay of the predicted Paw (as if the patients were in the NAVA mode). The NAVA level was adjusted manually to try to match the predicted peak pressure to the actual peak Paw. PEEP was maintained constant throughout the study period and set according to the higher PEEP/lower inspired oxygen fraction (F_{IO_2}) arm of the ARDSnet consensus.[18] Additional details on the ventilator settings are provided in Supplemental Digital Content 1, http://links.lww.com/ALN/B147. At the end of each mode, arterial blood was sampled for analysis. Drugs, including sedatives and fluids, were unchanged during the entire study period.

Data Acquisition

Flow, Paw, and EAdi were acquired (sampling rate, 100 Hz) from the serial port of the Servo-I and resampled to 2 kHz. Pes was acquired (sampling rate, 2 kHz) by connecting the balloon to a pressure transducer (range ±375 mmHg; Freescale, USA) and A/D converter (DT3004; Data Translation, USA). All signals were acquired synchronously using a dedicated software (Neurovent Research Inc.).

Data Analysis

Data were analyzed offline. All variables were calculated from a stable 5-min period at the end of each mode on a breath-by-breath basis using a software routine developed for

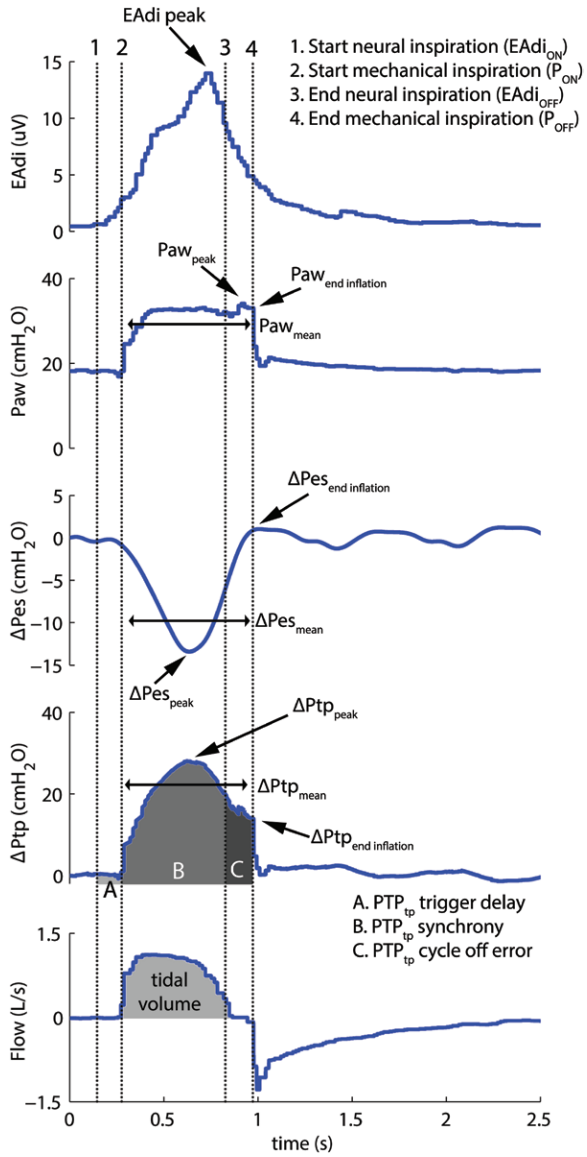

Fig. 1. Representative example of measurements of the main variables studied. The displayed breath is during pressure control ventilation. All variables were calculated on a breath-by-breath basis for each mode and averaged over a 5-min stable respiratory pattern. *Vertical dotted lines* represent neural and mechanical respiratory cycles. *Arrows* indicate the different parameters that are calculated from the waveforms. Tidal volume is calculated as the integral of inspiratory flow over time. Transpulmonary pressure *versus* time product (PTP_{tp}) is calculated as the integral of transpulmonary pressure (Ptp) over time. PTP_{tp} was calculated during the following phases of inspiration: (A) trigger delay; (B) synchronous overlap period between neural and mechanical inspiration; and (C) cycle-off error. P_{ON} – $EAdi_{ON}$ = trigger delay and P_{OFF} – $EAdi_{OFF}$ = cycle-off error. EAdi = electrical activity of the diaphragm; Paw = airway pressure; Pes = esophageal pressure.

MATLAB (MathWorks, USA). For each breath, we defined the following variables during the inspiratory phase (as shown in fig. 1):

- Vt, as the integral of the inspiratory flow over time.
- Peak EAdi.
- Mean, peak, and end-inflation airway pressure (Paw_{mean}, Paw_{peak}, and $Paw_{end\ inflation}$).
- Mean, peak inspiratory deflection, and end-inflation Pes, as change from baseline (ΔPes_{mean}, ΔPes_{peak}, and $\Delta Pes_{end\ inflation}$). Baseline was defined as Pes at the start of neural inspiration.
- Mean, peak, and end-inflation transpulmonary pressure, as change from baseline (ΔPtp_{peak}, ΔPtp_{mean}, and $\Delta Ptp_{end\ inflation}$). Transpulmonary pressure was calculated as the difference between Paw and Pes. Baseline was defined as transpulmonary pressure at the start of neural inspiration.
- Transpulmonary pressure–time product (PTP_{tp}) was calculated as the integral of transpulmonary pressure over time. PTP_{tp} is a measure of duration of mechanical stress within the respiratory cycle. To determine the effect of patient–ventilator dyssynchrony, this variable was also calculated during the following phases of inspiration: (1) trigger delay; (2) synchronous overlap period between neural and mechanical inspiration; and (3) cycle-off error.

Neural respiratory rate was calculated as the number of EAdi peaks per minute and mechanical respiratory rate as the number of Paw peaks per minute. Breath-by-breath variability was assessed by calculating the coefficient of variation (CV; SD/mean × 100) for Vt and EAdi.

Patient–ventilator interaction was evaluated by comparing Paw and EAdi waveforms with a recently validated automated computer algorithm that reports the timing error between Paw and EAdi.[19,20]

In brief, automatic detection of the start of neural inspiration ($EAdi_{ON}$) was obtained by detecting a 0.5-μV increase in EAdi. The end of neural inspiration ($EAdi_{OFF}$) was automatically detected by finding when the EAdi had decreased to 70% of its peak. The onset of pressure support (P_{ON}) was automatically detected by searching for an increase in Paw of greater than 3 cm H_2O. The termination of pressure support (P_{OFF}) was automatically detected by searching for the decrease in Paw (see fig. 1 for an example of these timings).

Electrical activity of the diaphragm and Paw timings were used to calculate the NeuroSync index as following. The trigger error (P_{ON} – $EAdi_{ON}$) and cycle-off error (P_{OFF} – $EAdi_{OFF}$) were calculated as a percentage of the neural inspiratory detection period and neural expiratory detection period, respectively. Neural inspiratory detection periods were defined as segments from one detected $EAdi_{OFF}$ to the next $EAdi_{OFF}$. Neural expiratory detection periods were defined as segments from one $EAdi_{ON}$ to the next $EAdi_{ON}$. Thus, an early trigger error could range between –100 and 0% and a late trigger error could range between 0 and 100%. In the same manner, an early cycle-off error could range between –100 and 0% and a late cycle-off error could range between 0 and 100%. Breaths with an absolute error of

Table 1. Patient Characteristics at Study Inclusion

Patient	Age (yr)	Sex	BMI (kg/m^2)	RASS	Days on MV	P/F Ratio (mmHg)	ARDS Etiology
1	72	M	25	–3	13	242	Pneumonia
2	71	M	27	–5	4	146	Pneumonia
3	61	F	48	–1	1	116	Urosepsis
4	49	M	26	–1	21	75	Acute pancreatitis
5	64	M	23	–4	1	150	Pneumonia
6	76	M	32	0	4	108	Pneumonia
7	48	M	27	–4	7	143	Acute pancreatitis
8	71	F	32	–4	6	175	Acute pancreatitis
9	68	M	24	–4	32	177	Pneumonia and mediastinitis
10	78	M	18	–3	5	115	Pneumonia
11	45	M	24	–4	11	165	Pneumonia
12	66	M	23	–5	10	120	Pneumonia

ARDS = acute respiratory distress syndrome; BMI = body mass index; F = female; M = male; MV = mechanical ventilation; P/F ratio = Pao_2/inspired oxygen fraction ratio; RASS = Richmond Agitation Sedation Scale.

Table 2. Ventilator Settings

Patient	PCV Level (cm H_2O)	PSV Level (cm H_2O)	NAVA Level (cm $H_2O/\mu V$)	PEEP (cm H_2O)	FIO_2	Inspiratory Time in PCV (s)	Cycle-off in PSV (%)
1	17	17	1.3	14	0.40	0.8	50
2	14	14	1.4	14	0.45	0.5	50
3	12	12	1.0	16	0.65	1.0	50
4	12	10	2.2	16	0.55	0.9	30
5	8	8	1.7	14	0.60	0.7	50
6	12	12	2.5	12	0.60	1.2	30
7	6	6	1.6	16	0.50	0.8	50
8	14	16	4.0	10	0.55	0.9	50
9	16	16	4.1	14	0.43	0.5	30
10	11	11	0.5	16	0.50	0.7	30
11	9	9	2.0	14	0.40	0.8	50
12	12	12	0.8	18	0.80	0.7	30

FIO_2 = inspired oxygen fraction; NAVA = neurally adjusted ventilatory assist; PCV = pressure control ventilation; PEEP = positive end-expiratory pressure; PSV = pressure support ventilation.

more than 33% were defined as dyssynchronous breaths and breaths with an absolute error of less than 33% as synchronous breaths. Asynchronous breaths, defined as a complete dissociation between EAdi and Paw (wasted efforts, autotriggering, and double triggering), were assigned 100% error. The NeuroSync index was then calculated by averaging the errors for all breaths per patient per mode.

Statistical Analysis

To compare modes, one-way ANOVA for repeated measures was performed or the Friedman test as its nonparametric equivalent. *Post hoc* analysis was performed with the Student–Newman–Keuls test or Dunn test, as its nonparametric equivalent, to correct for multiple comparisons. The effect of patient–ventilator dyssynchrony on PTP_{tp} was analyzed using two-way ANOVA for repeated measures with Bonferroni posttest. Linear regression analysis was performed to test associations. For all tests, a two-tailed P value less than 0.05 was considered significant. Data are described as mean ± standard error for parametric data or median (interquartile range) for nonparametric data. Statistical analyses were performed with Prism 5 (GraphPad Software, USA).

Results

Table 1 reports patient characteristics and table 2 reports ventilator settings for PCV, PSV, and NAVA during the study.

Respiratory Variables

Tidal volumes were equal between modes (fig. 2A). One patient having lowest pH of 7.18 revealed excessive Vt both in PSV and NAVA (patient 4, fig. 2A) but not in PCV. There was no difference between modes for neural and ventilator respiratory rates; however, respiratory rates varied widely between subjects (fig. 2B). The coefficient of determination (r^2) between neural and ventilator respiratory rates was high with NAVA (0.99, $P < 0.0001$), 0.70 ($P = 0.0007$) with PCV, and 0.61 ($P = 0.0026$) with PSV. Minute ventilation was equal between modes (table 3).

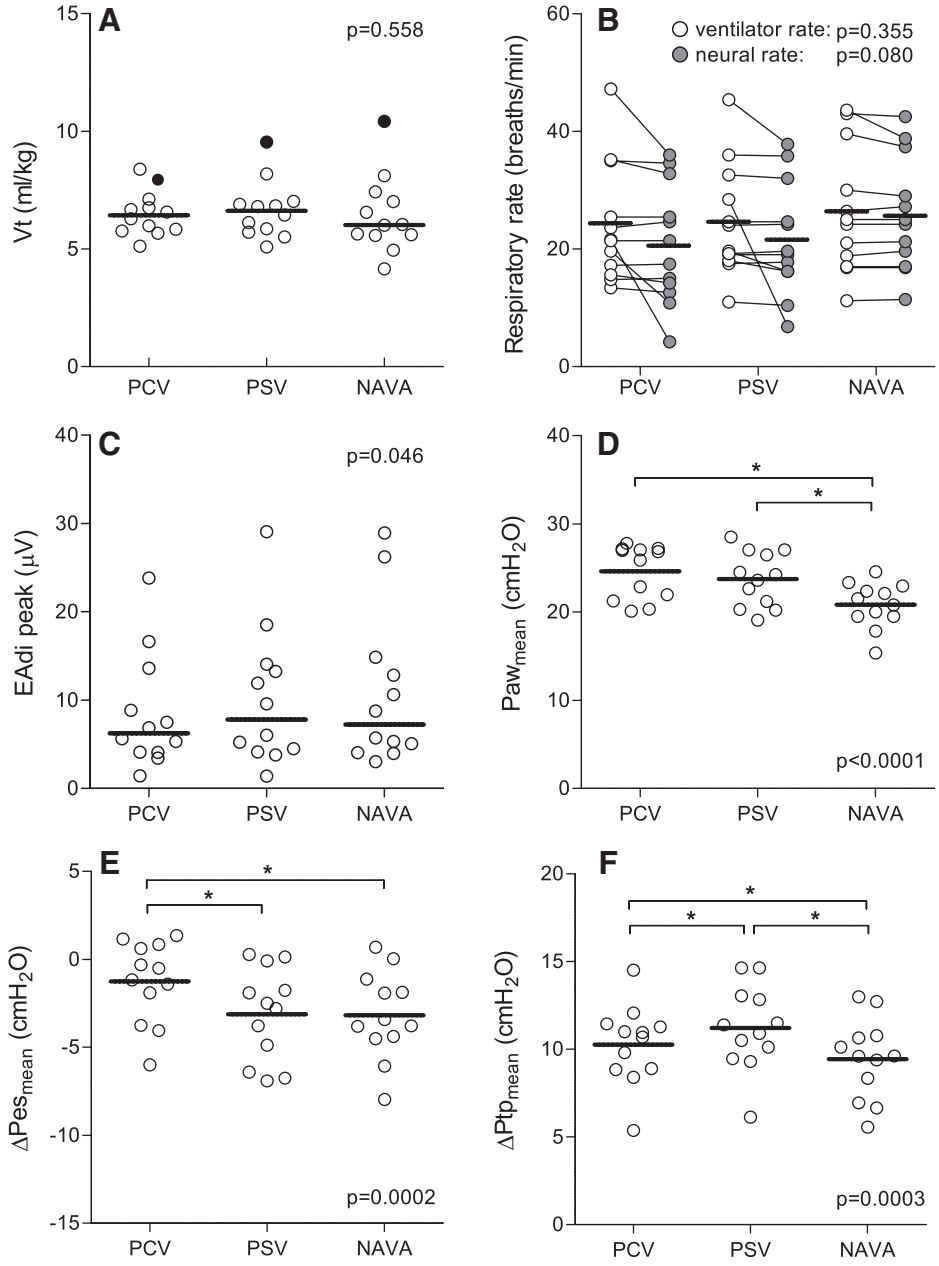

Fig. 2. (*A*) Tidal volume (Vt), (*B*) ventilator and neural respiratory rate, (*C*) electrical activity of the diaphragm (EAdi), (*D*) mean airway pressure (Paw$_{mean}$), (*E*) mean esophageal pressure (ΔPes$_{mean}$), and (*F*) mean transpulmonary pressure (ΔPtp$_{mean}$) for each ventilation mode. *Filled circle symbol* in *A* represents patient 4. *Horizontal bars* represent mean values (*B*, *D–F*) or median values (*A*, *C*). *P* values in each panel represent the result of one-way ANOVA for repeated measures (*B*, *D–F*) or Friedman test (*A*, *C*). * Significant difference ($P < 0.05$) between indicated modes after *post hoc* analysis with Student–Newman–Keuls test. NAVA = neurally adjusted ventilatory assist; PCV = pressure control ventilation; PSV = pressure support ventilation.

Peak EAdi ranged from near-zero to 30 μV between patients (fig. 2C). *Post hoc* analysis did not reveal any significant differences between modes for EAdi. Mean Paw (Paw$_{mean}$) during inspiration was lower with NAVA compared with both PCV and PSV (fig. 2D). Changes in pleural pressure during inspiration are expressed by ΔPes$_{mean}$ and ranged from positive to high negative values. Group mean values for ΔPes$_{mean}$ were higher during PCV, that is, less negative swing, compared with PSV and NAVA (fig. 2E). Lung-distending pressure, expressed by ΔPtp$_{mean}$, was highest during PSV, lower during PCV, and lowest during NAVA (fig. 2F). Peak and end-inflation ΔPes and ΔPtp during inspiration were slightly lower during PCV compared with PSV and NAVA, whereas these values were equal for Paw (table 3).

The CV of EAdi was equal between modes, whereas the CV of Vt was higher with NAVA (table 3). Linear regression analyses between CVs of EAdi and Vt are presented in

Table 3. Breath Parameters and Variability

	PCV	PSV	NAVA	*P* Value
Minute ventilation (l/min)	10.8 (7.2 to 13.2)	9.9 (8.7–12.9)	10.3 (9.0 to 12.6)	0.779
Paw_{peak} (cm H_2O)	28 ± 1	27 ± 1	29 ± 1	0.170
$Paw_{end\ inflation}$ (cm H_2O)	24 ± 1	25 ± 1	25 ± 1	0.684
ΔPes_{peak} (cm H_2O)	−5 ± 1*†	−6 ± 1	−7 ± 1	0.027
$\Delta Pes_{end\ inflation}$ (cm H_2O)	3 (2 to 4)*	1 (−5 to 2)	0 (−2 to 2)	0.039
ΔPtp_{peak} (cm H_2O)	16 ± 1*†	17 ± 1	17 ± 1	0.016
$\Delta Ptp_{end\ inflation}$ (cm H_2O)	8 ± 1 *†	11 ± 1	11 ± 1	0.014
CV of Vt (%)	8.0 (6.4 to 10.0)†	7.1 (5.9 to 9.0)‡	17.0 (12.0 to 36.1)	0.0005
CV of EAdi (%)	27.7 (22.5 to 40.5)	28.2 (23.8 to 8.6)	29.3 (22.7 to 39.5)	0.920

Data are described as mean ± standard error for parametric or median (interquartile range) for nonparametric data. *P* values represent the result of one-way ANOVA for repeated measures for parametric data or the Friedman test as its nonparametric equivalent. Annotations represent the significant difference ($P < 0.05$) between indicated modes after *post hoc* analysis with Student–Newman–Keuls (parametric data) or Dunn (nonparametric data) tests.

* PCV *vs*. PSV; † PCV *vs*. NAVA; ‡ PSV *vs*. NAVA.

CV = coefficient of variation; EAdi = electrical activity of the diaphragm; NAVA = neurally adjusted ventilatory assist; $Paw_{end\ inflation}$ = end inflation airway pressure; Paw_{peak} = peak airway pressure; PCV = pressure control ventilation; $Pes_{end\ inflation}$ = delta end inflation esophageal pressure; Pes_{peak} = peak esophageal pressure; PSV = pressure support ventilation; $Ptp_{end\ inflation}$ = delta end inflation transpulmonary pressure; Ptp_{peak} = delta peak transpulmonary pressure; Vt = tidal volume.

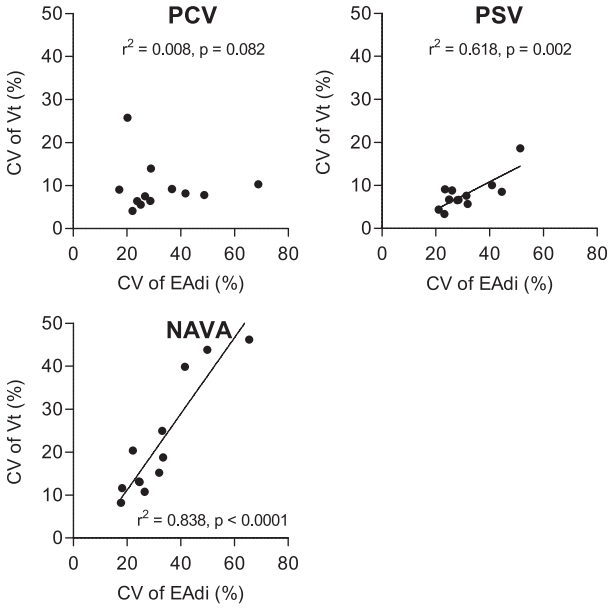

Fig. 3. Linear regression analysis between coefficient of variation of electrical activity of the diaphragm (CV of EAdi) and coefficient of variation of tidal volume (CV of Vt) for each ventilation mode. NAVA = neurally adjusted ventilatory assist; PCV = pressure control ventilation; PSV = pressure support ventilation.

figure 3, which shows no relation with PCV, a poor relation with PSV, and a good relation with NAVA.

There was a significant difference in PTP_{tp} between modes (one-way ANOVA, $P = 0.0018$). *Post hoc* analysis showed that PTP_{tp} was significantly lower ($P < 0.05$) with NAVA (6.9 ± 0.8 cm H_2O s) compared with PSV (8.3 ± 0.7 cm H_2O s) and PCV (9.5 ± 0.8 cm H_2O s).

Patient–Ventilator Interaction

The percentage of synchronous breaths were higher and trigger delay shorter with NAVA compared with PCV and PSV (table 4). Cycle-off error was higher with PCV compared with PSV and NAVA (table 4). Wasted efforts and double triggering were overall uncommon and equal between modes, whereas the rate of autotriggering was different between modes (table 4). The latter is explained by the fact that during PCV, 87.6 ± 16.8% of the breaths were patient triggered and 12.4 ± 16.8% were ventilator controlled. The NeuroSync index, depicted in figure 4A (0% error = perfect patient–ventilator interaction and 100% error = zero patient–ventilator interaction), indicated more than 20% error in seven patients during PCV, which improved during PSV and was less than 20% in all patients during NAVA. The higher cycle-off error with PCV resulted in an increased PTP_{tp}, as depicted in figure 4B.

Blood Gases

Table 5 shows arterial blood gas values at the end of each 30-min interval. Pao_2 and $Paco_2$ were significantly higher with NAVA compared with PCV (table 5).

Discussion

The current study reports the effects of different modes of assisted ventilation on lung-distending pressure, Vt, breathing pattern variability, and patient–ventilator interaction in patients with ARDS. The three selected modes allow for different degrees of patient freedom to control the ventilator. The main findings of this study were that with increasing freedom to control the ventilator (1) Vt remains within the limits of lung-protective ventilation; and (2) lung-distending pressures remain similar between modes. Even with NAVA, when the patient has a high degree of freedom to control the amount of support, Vt and lung-distending pressures were similar to assist control ventilation, whereas breathing pattern variability and patient–ventilator interaction improved compared with PCV and PSV. Furthermore, prolonged inspiratory time during PCV resulted in a longer duration of mechanical stress.

Table 4. Effect of Different Ventilation Modes on Patient–Ventilator Interaction

	PCV	PSV	NAVA	*P* Value
Synchrony (% breaths)	60 (15–89)*†	89 (71–99)	93 (79–99)	0.005
Dyssynchrony (% breaths)	16 (6–36)*†	2 (0–14)	4 (0–14)	0.004
Trigger delay (ms)	107 ± 20†	96 ± 16‡	48 ± 11	0.0005
Cycle-off error (ms)	265 (143–401)*†	36 (18–134)	8 (2–16)	<0.0001
Wasted efforts (% breaths)	0 (0–2)	0 (0–1)	0 (0–0)	0.093
Autotriggering (% breaths)	2 (0–16)	1 (0–12)	0 (0–4)	0.046
Double triggering (% breaths)	0 (0–1)	0 (0–0)	1 (0–2)	0.065

Data are described as mean ± standard error for parametric or median (interquartile range) for nonparametric data. *P* value represents the result of one-way ANOVA for repeated measures for parametric data or the Friedman test as its nonparametric equivalent. Annotations represent significant difference ($P < 0.05$) between indicated modes after *post hoc* analysis with Student–Newman–Keuls (parametric data) or Dunn (nonparametric data) tests. Values are given as median and interquartile range.

* PCV *vs*. PSV; † PCV *vs*. NAVA; ‡ PSV *vs*. NAVA.

NAVA = neurally adjusted ventilatory assist; PCV = pressure control ventilation; PSV = pressure support ventilation.

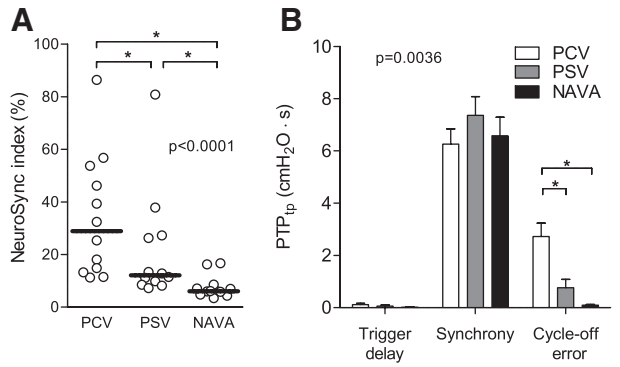

Fig. 4. (*A*) NeuroSync index[16] of each ventilation mode. The NeuroSync index is an overall indicator of patient–ventilator interaction, where 0% error = perfect and 100% error = zero patient–ventilator interaction. *Horizontal bars* represent median value and *P* values represent result of Friedman test. * Significant difference ($P < 0.05$) between indicated modes after *post hoc* analysis with Dunn test. (*B*) Transpulmonary pressure–time product (PTP_{tp}) during different phases of patient–ventilation interaction. *Bars* represent mean ± standard error. *P* values represent result of two-way ANOVA for repeated measures. * Significant difference ($P < 0.05$) between indicated modes after *post hoc* analysis with Bonferroni test. NAVA = neurally adjusted ventilatory assist; PCV = pressure control ventilation; PSV = pressure support ventilation.

Vt and Lung-distending Pressures

In the current study, Vt could be considered lung protective in the majority of patients and was not affected by ventilator mode. Peak and end-inflation Paws (table 3) were equal between modes, whereas mean Paws were lower during NAVA than during PCV and PSV (fig. 2D). Lower mean ventilator pressures with NAVA could be explained by the slower rate of pressurization with NAVA compared with a squared pressure waveform with PSV and PCV. These lower mean Paws do not necessarily reflect a too low level of assistance during NAVA. The latter is supported by the similar levels of EAdi with the three modes (fig. 2C), and the similar level of mean Pes compared with PSV. The lower level of mean Pes during PCV mainly reflects a too long inspiratory time during PCV. Although there were statistical differences in ΔPtp_{mean}, $\Delta Ptp_{end\ inflation}$, and ΔPtp_{peak} between modes, these were small in absolute values. Based on a *post hoc* analysis of the low Vt ARDSnet study,[1] Hager *et al.*[21] concluded that no safe plateau pressure exists. It can be derived from the first figure in their article that reduction in plateau pressure from 30 to 25 cm H_2O is associated with reduction in mortality of approximately 4%. In our study, differences in airway and transpulmonary pressures among modes were 3 cm H_2O or less and therefore probably of limited clinical significance.

Protection against excessive Ptp and Vt is likely mediated by vagal afferents sensitive to lung distension.[22,23] Indeed, our data demonstrate similar Vt and lung-distending pressures during PCV, PSV (both delivering fixed pressure), and NAVA (proportional control of pressure). Prevention of high Vt and Ptp may be mediated by the Hering-Breuer inspiratory-inhibiting (vagal) reflex, where lung inflation at critical volume (*i.e.*, lung stretch) terminates inspiration.[24] However, in the current study in one patient, a Vt greater than 9 ml/kg was observed during PSV and NAVA. This patient had the lowest blood pH (7.18), consistent with the view that acid–base homeostasis is the primary goal of the respiratory centers in the brain stem and may be achieved at the expense of high Vt or Ptp.[25] On the basis of this observation, we suggest to be very cautious with the use of assisted breathing modes in patients with a very low pH.

Breathing Pattern Variability

Preservation of natural breathing variability and complexity during mechanical ventilation is considered important, as it may improve oxygenation, lung mechanics, and gas distribution to the more dependent regions.[6,7] Breath-by-breath variability of Vt with NAVA was higher in comparison with PCV and PSV, whereas EAdi variability was similar. Accordingly, the ventilator output responded to the patient's neural breathing effort during NAVA and not during pressure-targeted assist (fig. 3), which is in accordance with previous findings.[9,26] By definition, a larger respiratory variability with

Table 5. Effect of Different Ventilation Modes on Blood Gas Values

	PCV	PSV	NAVA	*P* Value
pH	7.40 (7.33–7.44)	7.40 (7.33–7.44)	7.39 (7.31–7.44)	0.378
Pao_2 (mmHg)	78(68–84)*	80 (69–97)	81 (69–91)	0.022
Pao_2/Fio_2 (mmHg)	153 ± 12	163 ± 16	163 ± 13	0.341
$Paco_2$ (mmHg)	46 ± 3*	48 ± 3	49 ± 3	0.008
HCO_3^- (mmol/l)	27.4 ± 2.1	27.5 ± 2.0	27.8 ± 2.0	0.235

Data are described as mean ± standard error for parametric or median (interquartile range) for nonparametric data. *P* values represent the result of one-way ANOVA for repeated measures for parametric data or the Friedman test as its nonparametric equivalent. Values are given as mean ± standard error.

* The significant difference ($P < 0.05$) between PCV and NAVA after *post hoc* analysis with Student–Newman–Keuls (parametric data) or Dunn (nonparametric data) tests.

Fio_2 = inspired oxygen fraction; NAVA = neurally adjusted ventilatory assist; PCV = pressure control ventilation; PSV = pressure support ventilation.

NAVA increases the incidence of breaths with a high Vt.[9] It is unknown whether this periodic delivery of breaths with a higher Vt during assisted mechanical ventilation is harmful. It could also be regarded as a type of sigh or recruitment maneuver, which have been shown to have moderate success for improving lung mechanics and gas exchange.[27–29] In the current study, oxygenation improved slightly with NAVA compared with PCV, but not compared with PSV. This might be explained by better lung recruitment of the dependent regions with NAVA.[6] $Paco_2$ was slightly lower during PCV compared with NAVA. This might have resulted from small differences in Vt, respiratory rate, and Vt distribution, nevertheless blood pH was unaffected.

Patient–Ventilator Interaction

With NAVA patient–ventilator interaction was with minimal error, whereas prevalence of patients with poor patient–ventilator interaction increased during PSV and PCV. This is consistent with recent findings in patients with ARDS[10,13] and in other patients with acute respiratory failure.[30,31] This is of potential clinical relevance, as patient–ventilator asynchrony has been associated with adverse clinical outcome, including prolonged mechanical ventilation.[32,33] For example, reversed triggering or breath stacking in assist-control mode may contributing to ventilator-induced lung injury[34,35] (see figure, Supplemental Digital Content 1, http://links.lww.com/ALN/B147, for an example of breath stacking caused by reversed triggering in the current study). Experimental animal data suggest that not only the magnitude but also the inspiratory cycle duration of lung-distending pressure during PCV is associated with lung injury of increased severity.[12,36] In the current study, late cycling-off resulted in prolonged and unnecessary lung-distending pressures with PCV and to a lesser extent with PSV (fig. 4B). Thus, our results support the notion that poor patient–ventilator interaction and fixed duration of assist during spontaneous breathing is less lung protective than synchronized assist delivery in proportion to neural inspiratory effort.

Clinical Implications

The role of assisted ventilation in ARDS has been extensively debated in recent years.[4] The most striking evidence in opposition to assisted ventilation is the effect of muscle paralysis in the first 48 h in patients with ARDS with Pao_2/Fio_2 less than 150 mmHg, which has been associated with improved outcome.[37] Our findings may have implications for mechanical ventilation in mild-to-moderate ARDS after these first 48 h. First, our results suggest that it is reasonable from a physiological point of view to use an assisted ventilation mode with good patient–ventilator interaction without increasing the risk of excessive Vt and lung-distending pressure. Our data are supported by recent findings in a pig model of ARDS that higher levels of spontaneous breathing reduce global stress and strain.[38] Second, in terms of the patient's inspiratory drive and effort, the current study revealed a high variability in EAdi and Pes values, ranging from overassist to strenuous efforts (fig. 1). Also, a great dispersion in neural respiratory rate implies a large variety in respiratory drive in patients with ARDS. These findings suggest that adjusting ventilator assist to target low Vts resulted in different levels of neural drive in each study patient, probably due to a complex interaction between sedation, ventilatory mode, and level of assist. Accordingly, monitoring Vt in conjunction with EAdi and/or Pes can aid to optimize ventilation in ARDS to prevent overassist or insufficient assist and improve patient–ventilator interaction.[39] The capabilities of EAdi for monitoring purposes were recently well demonstrated in a trial to monitor the dynamic intrinsic PEEP.[40]

Critique of the Method

Several limitations of the current study should be addressed. First, Pes was used as an estimate of pleural pressure. The validity of Pes for this purpose has been discussed before in the literature.[41,42] Second, the real lung-distending pressure is transpulmonary pressure obtained under static conditions (zero-flow) to eliminate the resistive component in the equation of motion. Achieving and verifying static conditions in spontaneous breathing under assisted ventilation in critically ill patients is very cumbersome. Therefore, our measurements of lung-distending pressures were performed during dynamic conditions and cannot directly be compared with static transpulmonary pressures. As peak pressure is highly influenced by airway resistance and is not a reliable estimate of lung-distending pressure, mean transpulmonary pressure

during inspiration may be a better estimate under dynamic condition. Last, it should be recognized that our study is a single-center, physiological study, conducted in a heterogeneous group of patients with ARDS with a wide range of sedation scores. Different conditions leading to ARDS, such as pulmonary *versus* extrapulmonary, might influence the effect on lung-protective ventilation while changing ventilator modes, when studied in large subgroups. In our study, each mode was studied for a period of 30 min. This allows for physiological comparisons and improves our understanding in the effects of these different modes on respiratory mechanics, patient–ventilator interaction, and gas exchange. Large clinical trials that evaluate these different ventilator modes for several days in large groups of patients are needed to determine whether one mode is superior in outcome compared with the other modes.

In conclusion, in patients with mild-to-moderate ARDS, increasing patient freedom to control the ventilator maintains lung-protective ventilation in terms of Vt and lung-distending pressure but improves patient–ventilator interaction and preserves respiratory variability.

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Competing Interests

Drs. Sinderby and Beck have made inventions related to neural control of mechanical ventilation that are patented. The license for these patents belongs to Maquet Critical Care, Sölna, Sweden. Future commercial uses of this technology may provide financial benefits to Drs. Sinderby and Beck through royalties. They each own 50% of Neurovent Research Inc. (NVR, Toronto, Ontario, Canada). NVR is a research and development company that builds the equipment and catheters for research studies. NVR has a consulting agreement with Maquet Critical Care. Drs. Sinderby and Beck are married. St. Michael's Hospital has a research agreement with Maquet Critical Care AB and receives royalty and overhead from this agreement. The other authors declare no competing interests.

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References

1. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000; 342:1301–8
2. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, Austin P, Lapinsky S, Baxter A, Russell J, Skrobik Y, Ronco JJ, Stewart TE; Lung Open Ventilation Study Investigators: Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. JAMA 2008; 299:637–45
3. Marini JJ: Spontaneously regulated *vs.* controlled ventilation of acute lung injury/acute respiratory distress syndrome. Curr Opin Crit Care 2011; 17:24–9
4. Gama de Abreu M, Guldner A, Pelosi P: Spontaneous breathing activity in acute lung injury and acute respiratory distress syndrome. Curr Opin Anaesthesiol 2012; 25:148–55
5. Fan E, Villar J, Slutsky AS: Novel approaches to minimize ventilator-induced lung injury. BMC Med 2013; 11:85
6. Blankman P, Hasan D, van Mourik MS, Gommers D: Ventilation distribution measured with EIT at varying levels of pressure support and neurally adjusted ventilatory assist in patients with ALI. Intensive Care Med 2013; 39:1057–62
7. Spieth PM, Carvalho AR, Güldner A, Kasper M, Schubert R, Carvalho NC, Beda A, Dassow C, Uhlig S, Koch T, Pelosi P, Gama de Abreu M: Pressure support improves oxygenation and lung protection compared to pressure-controlled ventilation and is further improved by random variation of pressure support. Crit Care Med 2011; 39:746–55
8. Sinderby C, Navalesi P, Beck J, Skrobik Y, Comtois N, Friberg S, Gottfried SB, Lindström L: Neural control of mechanical ventilation in respiratory failure. Nat Med 1999; 5:1433–6
9. Patroniti N, Bellani G, Saccavino E, Zanella A, Grasselli G, Isgrò S, Milan M, Foti G, Pesenti A: Respiratory pattern during neurally adjusted ventilatory assist in acute respiratory failure patients. Intensive Care Med 2012; 38:230–9
10. Terzi N, Pelieu I, Guittet L, Ramakers M, Seguin A, Daubin C, Charbonneau P, du Cheyron D, Lofaso F: Neurally adjusted ventilatory assist in patients recovering spontaneous breathing after acute respiratory distress syndrome: Physiological evaluation. Crit Care Med 2010; 38:1830–7
11. Brander L, Leong-Poi H, Beck J, Brunet F, Hutchison SJ, Slutsky AS, Sinderby C: Titration and implementation of neurally adjusted ventilatory assist in critically ill patients. Chest 2009; 135:695–703
12. Spieth PM, Silva PL, Garcia CS, Ornellas DS, Samary CS, Moraes L, Bentes M, Morales MM, Kasper M, Güldner A, Huhle R, Koch T, Pelosi P, Gama de Abreu M, Rocco PR: Modulation of stress *versus* time product during mechanical ventilation influences inflammation as well as alveolar epithelial and endothelial response in rats. Anesthesiology 2015; 122:106–16
13. Mauri T, Bellani G, Grasselli G, Confalonieri A, Rona R, Patroniti N, Pesenti A: Patient-ventilator interaction in ARDS patients with extremely low compliance undergoing ECMO: A novel approach based on diaphragm electrical activity. Intensive Care Med 2013; 39:282–91
14. ARDS Definition Task Force; Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS: Acute respiratory distress syndrome the Berlin definition. JAMA 2012; 307:2526–33
15. Doorduin J, Sinderby CA, Beck J, Stegeman DF, van Hees HW, van der Hoeven JG, Heunks LM: The calcium sensitizer levosimendan improves human diaphragm function. Am J Respir Crit Care Med 2012; 185:90–5

16. Sinderby C, Beck J, Spahija J, de Marchie M, Lacroix J, Navalesi P, Slutsky AS: Inspiratory muscle unloading by neurally adjusted ventilatory assist during maximal inspiratory efforts in healthy subjects. Chest 2007; 131:711–7
17. Baydur A, Behrakis PK, Zin WA, Jaeger M, Milic-Emili J: A simple method for assessing the validity of the esophageal balloon technique. Am Rev Respir Dis 1982; 126:788–91
18. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network: Higher *versus* lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004; 351:327–36
19. Sinderby C, Liu S, Colombo D, Camarotta G, Slutsky AS, Navalesi P, Beck J: An automated and standardized neural index to quantify patient-ventilator interaction. Crit Care 2013; 17:R239
20. Doorduin J, Sinderby CA, Beck J, van der Hoeven JG, Heunks LM: Automated patient-ventilator interaction analysis during neurally adjusted non-invasive ventilation and pressure support ventilation in chronic obstructive pulmonary disease. Crit Care 2014; 18:550
21. Hager DN, Krishnan JA, Hayden DL, Brower RG; ARDS Clinical Trials Network: Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med 2005; 172:1241–5
22. Allo JC, Beck JC, Brander L, Brunet F, Slutsky AS, Sinderby CA: Influence of neurally adjusted ventilatory assist and positive end-expiratory pressure on breathing pattern in rabbits with acute lung injury. Crit Care Med 2006; 34:2997–3004
23. Lecomte F, Brander L, Jalde F, Beck J, Qui H, Elie C, Slutsky AS, Brunet F, Sinderby C: Physiological response to increasing levels of neurally adjusted ventilatory assist (NAVA). Respir Physiol Neurobiol 2009; 166:117–24
24. Hering E, Breuer J: Self-steering of respiration through the nerves vagus (circa 1868), Breathing: Hering-Breuer Centenary Symposium. Edited by Churchill PR, London, United Kingdom, 1970, pp 359–64
25. Karagiannidis C, Lubnow M, Philipp A, Riegger GA, Schmid C, Pfeifer M, Mueller T: Autoregulation of ventilation with neurally adjusted ventilatory assist on extracorporeal lung support. Intensive Care Med 2010; 36:2038–44
26. Schmidt M, Demoule A, Cracco C, Gharbi A, Fiamma MN, Straus C, Duguet A, Gottfried SB, Similowski T: Neurally adjusted ventilatory assist increases respiratory variability and complexity in acute respiratory failure. Anesthesiology 2010; 112:670–81
27. Patroniti N, Foti G, Cortinovis B, Maggioni E, Bigatello LM, Cereda M, Pesenti A: Sigh improves gas exchange and lung volume in patients with acute respiratory distress syndrome undergoing pressure support ventilation. Anesthesiology 2002; 96:788–94
28. Pelosi P, Cadringher P, Bottino N, Panigada M, Carrieri F, Riva E, Lissoni A, Gattinoni L: Sigh in acute respiratory distress syndrome. Am J Respir Crit Care Med 1999; 159:872–80
29. Pelosi P, Bottino N, Chiumello D, Caironi P, Panigada M, Gamberoni C, Colombo G, Bigatello LM, Gattinoni L: Sigh in supine and prone position during acute respiratory distress syndrome. Am J Respir Crit Care Med 2003; 167:521–7
30. Spahija J, de Marchie M, Albert M, Bellemare P, Delisle S, Beck J, Sinderby C: Patient-ventilator interaction during pressure support ventilation and neurally adjusted ventilatory assist. Crit Care Med 2010; 38:518–26
31. Bertrand PM, Futier E, Coisel Y, Matecki S, Jaber S, Constantin JM: Neurally adjusted ventilatory assist *vs* pressure support ventilation for noninvasive ventilation during acute respiratory failure: A crossover physiologic study. Chest 2013; 143:30–6
32. Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L: Patient-ventilator asynchrony during assisted mechanical ventilation. Intensive Care Med 2006; 32:1515–22
33. de Wit M, Miller KB, Green DA, Ostman HE, Gennings C, Epstein SK: Ineffective triggering predicts increased duration of mechanical ventilation. Crit Care Med 2009; 37:2740–5
34. Chanques G, Kress JP, Pohlman A, Patel S, Poston J, Jaber S, Hall JB: Impact of ventilator adjustment and sedation-analgesia practices on severe asynchrony in patients ventilated in assist-control mode. Crit Care Med 2013; 41:2177–87
35. Akoumianaki E, Lyazidi A, Rey N, Matamis D, Perez-Martinez N, Giraud R, Mancebo J, Brochard L, Marie Richard JC: Mechanical ventilation-induced reverse-triggered breaths: A frequently unrecognized form of neuromechanical coupling. Chest 2013; 143:927–38
36. Casetti AV, Bartlett RH, Hirschl RB: Increasing inspiratory time exacerbates ventilator-induced lung injury during high-pressure/high-volume mechanical ventilation. Crit Care Med 2002; 30:2295–9
37. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal JM, Perez D, Seghboyan JM, Constantin JM, Courant P, Lefrant JY, Guérin C, Prat G, Morange S, Roch A; ACURASYS Study Investigators: Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010; 363:1107–16
38. Güldner A, Braune A, Carvalho N, Beda A, Zeidler S, Wiedemann B, Wunderlich G, Andreeff M, Uhlig C, Spieth PM, Koch T, Pelosi P, Kotzerke J, Gama de Abreu M: Higher levels of spontaneous breathing induce lung recruitment and reduce global stress/strain in experimental lung injury. Anesthesiology 2014; 120:673–82
39. Doorduin J, van Hees HW, van der Hoeven JG, Heunks LM: Monitoring of the respiratory muscles in the critically ill. Am J Respir Crit Care Med 2013; 187:20–7
40. Bellani G, Coppadoro A, Patroniti N, Turella M, Arrigoni Marocco S, Grasselli G, Mauri T, Pesenti A: Clinical assessment of auto-positive end-expiratory pressure by diaphragmatic electrical activity during pressure support and neurally adjusted ventilatory assist. Anesthesiology 2014; 121:563–71
41. Talmor D, Sarge T, O'Donnell CR, Ritz R, Malhotra A, Lisbon A, Loring SH: Esophageal and transpulmonary pressures in acute respiratory failure. Crit Care Med 2006; 34:1389–94
42. Akoumianaki E, Maggiore SM, Valenza F, Bellani G, Jubran A, Loring SH, Pelosi P, Talmor D, Grasso S, Chiumello D, Guérin C, Patroniti N, Ranieri VM, Gattinoni L, Nava S, Terragni PP, Pesenti A, Tobin M, Mancebo J, Brochard L: The application of esophageal pressure measurement in patients with respiratory failure. Am J Respir Crit Care Med 2014; 189:520–31