Patient-ventilator interaction during pressure support ventilation and neurally adjusted ventilatory assist*

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Objective: **To compare the effect of pressure support ventilation and neurally adjusted ventilatory assist on breathing pattern, patient-ventilator synchrony, diaphragm unloading, and gas exchange. Increasing the level of pressure support ventilation can increase tidal volume, reduce respiratory rate, and lead to delayed ventilator triggering and cycling. Neurally adjusted ventilatory assist uses diaphragm electrical activity to control the timing and pressure of assist delivery and is expected to enhance patient-ventilator synchrony.**

Design: **Prospective, comparative, crossover study.**

Setting: **Adult critical care unit in a tertiary university hospital.**

Patients: **Fourteen nonsedated mechanically ventilated patients (n = 12 with chronic obstructive pulmonary disease).**

Interventions: **Patients were ventilated for 10-min periods, using two pressure support ventilation levels (lowest tolerable and +7 cm H_2O higher) and two neurally adjusted ventilatory assist levels (same peak pressures and external positive end-expiratory pressure as with pressure support ventilation), delivered in a randomized order.**

Measurements and Main Results: **Diaphragm electrical activity, respiratory pressures, air flow, volume, neural and ventilator respiratory rates, and arterial blood gases were measured. Peak pressures were 17 ± 6 cm H_2O and 24 ± 6 cm H_2O and 19 ± 5 cm H_2O and 24 ± 6 cm H_2O with high and low pressure support ventilation and neurally adjusted ventilatory assist, respectively. The breathing pattern was comparable with pressure support ventilation and neurally adjusted ventilatory assist during low assist; during higher assist, larger tidal volumes ($p = .003$) and lower breathing frequencies ($p = .008$) were observed with pressure support ventilation. Increasing the assist increased cycling delays only with pressure support ventilation ($p = .003$). Compared with pressure support ventilation, neurally adjusted ventilatory assist reduced delays of ventilator triggering ($p < .001$ for low and high assist) and cycling (high assist: $p = .004$; low assist: $p = .04$), and abolished wasted inspiratory efforts observed with pressure support ventilation in six subjects. The diaphragm electrical activity and pressure-time product for ventilator triggering were lower with neurally adjusted ventilatory assist ($p = .005$ and $p = .02$, respectively; analysis of variance). Arterial blood gases were similar with both modes.**

Conclusions: **Neurally adjusted ventilatory assist can improve patient-ventilator synchrony by reducing the triggering and cycling delays, especially at higher levels of assist, at the same time preserving breathing and maintaining blood gases. (Crit Care Med 2010; 38:518–526)**

KEY WORDS: mechanical ventilation; pressure support ventilation; neurally adjusted ventilatory assist; respiratory failure; diaphragm

Modes of partial ventilatory assist provide inspiratory support in tandem with a patient's inspiratory efforts. By assuming a portion of the ventilatory work and unloading the inspiratory muscles, such ventilatory assistance enables the patient to breathe spontaneously at a more comfortable level. Ideally, triggering and cycling-off of such ventilatory assistance should be synchronized to the patient's inspiratory efforts.

Conventional mechanical ventilators control the assist delivered by means of a pneumatic signal, generated by patient effort and measured in the ventilatory circuit, i.e., pressure, flow, or volume. However, such pneumatic controllers can become progressively less effective as the level of ventilatory assist is increased (1–7), thereby contributing to patient-ventilator asynchrony, and an increased work of breathing (7–11). Recent work has demonstrated that patient-ventilator asynchrony can prolong the duration of mechanical ventilation (12). Excessive increases in the assist level can also delay

***See also p. 714.**

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Drs. Beck and Sinderby hold patents for inventions related to neural control of mechanical ventilation. Dr. Spahija is a coinventor on one of these patents. The license for these patents belongs to Maquet Critical Care. Future commercial uses of this technology may provide financial benefit to Drs. Sinderby and Beck through royalties. Drs. Sinderby and Beck each own 50% of Neurovent Research. Neurovent Research is a research and development company that builds the equipment and catheters for research studies. Neurovent Research has a consulting agreement with Maquet Critical Care. Drs. de Marchie, Albert, Bellemare, and Mr. Delisle have not disclosed any potential conflicts of interest.

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pneumatic cycling-off, extending the ventilator breath into neural expiration, prolonging the neural expiratory duration and resulting in a slower neural breathing pattern (2, 9, 13, 14). A low pressure support ventilation (PSV) flow cycling criterion, especially in obstructive lung disease, can excessively delay ventilator cycling, which can increase intrinsic positive end-expiratory pressure (PEEPi) and, in turn, lead to delayed ventilator triggering and wasted trigger efforts (nontriggered breaths) (1, 2, 11, 15). In the latter circumstance, ventilator frequency can underestimate a patient's neural breathing frequency.

Neurally adjusted ventilatory assist (NAVA), a novel mode of partial ventilatory assist, uses diaphragm electrical activity (EAdi) to control the timing and level of assist delivered (16). Because EAdi precedes muscle contraction as well as pressure, flow, and volume generation, the signal is not dampened or delayed by muscle weakness or altered respiratory mechanics. We, therefore, hypothesized that use of the EAdi signal for ventilator triggering and cycling would minimize delays, improve patient-ventilator synchrony, and ultimately preserve breathing pattern when the ventilatory assist is increased. To date, one study has compared PSV and NAVA in intensive care unit patients. That study was, however, conducted in sedated patients, did not assess cycling delays, and NAVA was triggered, using a "first come first serve" algorithm, i.e., triggered on airway pressure, air flow, or EAdi (17).

The present study evaluated the efficacy of NAVA in nonsedated intubated patients recovering from acute respiratory failure. The aim was to compare the effect of increasing levels of assist delivered with EAdi triggered and cycled NAVA vs. PSV on breathing pattern, diaphragm activation, and pressure generation, triggering and cycling-off delays, and gas exchange. Some of the results of the current study have been previously reported in the form of an abstract (18).

MATERIALS AND METHODS

Intubated intensive care unit patients, mechanically ventilated for management of their acute respiratory failure, were eligible for the study if they were deemed by the intensive care unit treating physician to be ready for ventilator weaning and fulfilled established weaning criteria (19). All continuous sedative infusions were discontinued at least 4 hrs before start of the study. The study was approved by the Ethics Committee of the hospital.

Measurements

EAdi was measured, using a multiple-array esophageal electrode (Neurovent Research, Toronto, Canada) positioned at the level of the diaphragm. Signals from each electrode pair were automatically processed (20–23). The processed EAdi waveform was used to control the ventilator during NAVA application (24) and was acquired at a rate of 2000 Hz into a personal computer for later analysis.

Air flow was measured with a heated pneumotachograph (Fleish, Phipps & Bird, Richmond, VA) positioned between the endotracheal tube and the Y-connector of the ventilator tubing. Esophageal and gastric pressures were measured, using balloons mounted on the esophageal catheter. Mouth pressure was measured from a side port of the endotracheal tube. Flow and pressure signals were acquired at a sampling rate of 100 Hz.

Method for NAVA

The processed EAdi signal was used to control a Servo 300 ventilator (Maquet Critical Care, Solna, Sweden) during NAVA. The pressure assist was initiated when EAdi was detected above an inspiratory trigger threshold set manually above the baseline EAdi noise level to avoid autotriggering during diaphragm inactivity. Ventilator cycling-off was set to occur when the EAdi decreased to 80% of peak inspiratory activity. The intrabreath assist was automatically adjusted in proportion to the amplitude of the processed EAdi signal, multiplied by a proportionality factor (NAVA level), outputted to the ventilator every 16 msecs. Increasing the NAVA level allowed proportionally more pressure to be delivered for a given EAdi signal magnitude, enabling adjustment of the assist level to a given pressure target.

Experimental Protocol

After written informed consent was obtained, the patient's nasogastric tube was replaced with

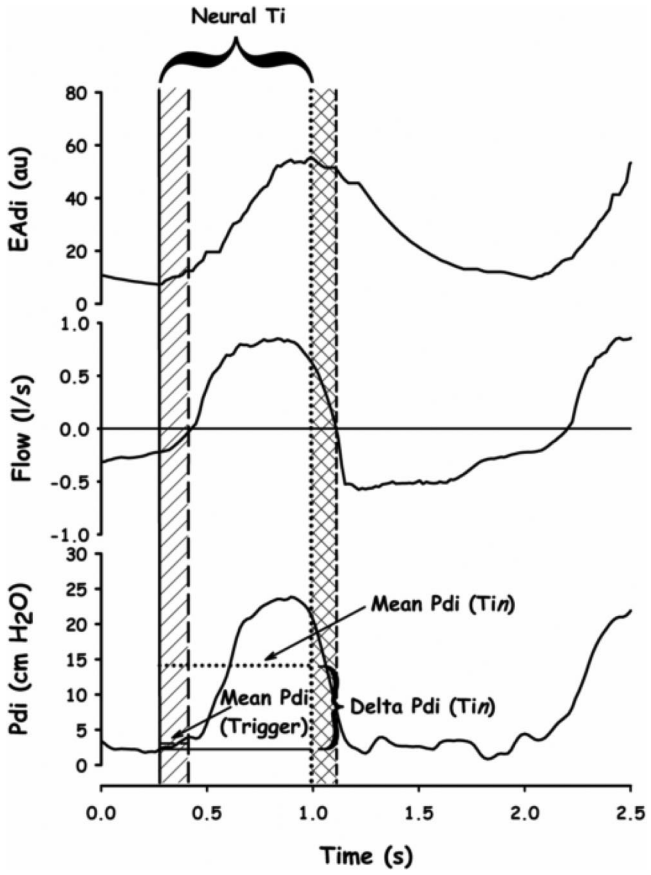

Figure 1. Tracings of diaphragm electrical activity (EAdi), air flow, and transdiaphragmatic pressure (Pdi) from one representative subject illustrating the measurement of ventilator delays and diaphragm pressure-time product (PTPdi). Neural Ti, time difference between the onset of EAdi (*solid vertical line*) and peak EAdi (*dotted vertical line*); trigger delay (*diagonally lined area*), time difference between the onset of EAdi (*solid vertical line*) and the onset of inspiratory flow (*long dashed vertical line*); cycling delay (*hatched area*), time difference between the peak EAdi (*dotted vertical line*) and the end of inspiratory flow (*short dashed vertical line*); PTPdi per breath, delta mean inspiratory Pdi (*dotted horizontal line*) above baseline multiplied by the neural Ti.

Table 1. Patient characteristics

Patient	Gender	Age, yr	Cause of ARF	Pa_{O_2}, Torr	Pa_{CO_2}, Torr	pH	C_{RS}, L/cm H_2O	R_{RSmax}, cm H_2O/L/sec	R_{RSmin}, cm H_2O/L/sec	PEEPi, cm H_2O
1	F	83	COPD, pneumonia	98	44	7.41	0.048	23.7	14.0	8.3
2	F	70	COPD	72	37	7.44	0.087	19.6	15.7	3.3
3	F	65	Post CABG	62	55	7.45	0.072	17.5	16.7	1.5
4	F	69	COPD	88	50	7.50	0.042	30.3	23.6	4.7
5	M	79	Post CABG, COPD	79	37	7.49	0.084	12.6	9.5	4.6
6	M	69	COPD	72	56	7.34	0.091	12.6	10.4	4.8
7	F	72	Vasculitis, COPD	191	45	7.43	0.060	14.2	9.6	2.4
8	F	59	Pneumonia, ARDS	92	42	7.45	0.041	2.1	1.0	1.0
9	M	68	COPD	146	49	7.40	0.060	10.5	9.2	6.1
10	F	75	COPD, pulmonary edema	65	47	7.35	0.053	15.9	13.6	6.0
11	M	54	COPD	62	62	7.38	—	—	—	—
12	F	79	COPD, pneumonia	84	45	7.51	0.042	21.5	18.8	10.5
13	M	48	Sepsis, OSA, asthma	94	44	7.37	0.052	4.7	4.4	11.7
14	M	81	Pneumonia, COPD	100	55	7.32	0.092	17.6	12.8	12.0
Mean (SD)		69 (10)		93 (35)	48 (7)	7.42 (0.06)	0.063 (0.02)	15.6 (7.6)	12.3 (5.9)	5.9 (3.7)

ARF, acute respiratory failure; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass graft; ARDS, acute respiratory distress syndrome; OSA, obstructive sleep apnea; C_{RS}, static compliance of the respiratory system; PEEPi, static intrinsic positive end-expiratory pressure; R_{RSmax}, maximum inspiratory resistance of the respiratory system; R_{RSmin}, minimum inspiratory resistance of the respiratory system.

Table 2. Ventilatory parameters

Patient No.	ET Tube Size	F_{IO_2}	Physician Prescribed External PEEP, cm H_2O	Physician Prescribed PSV Level, cm H_2O	Lowest Tolerable PSV Level, cm H_2O	+7 cm H_2O PSV, cm H_2O
1	7.5	0.30	8	16	8	15
2	7.5	0.35	5	10	6	13
3	8.5	0.30	5	16	12	19
4	7.5	0.28	5	20	18	24
5	8.5	0.30	5	20	16	21
6	7.5	0.35	8	14	6	13
7	7.5	0.35	5	18	5	12
8	8.0	0.35	5	8	6	13
9	8.0	0.30	5	18	8	15
10	8.0	0.40	5	18	16	23
11	8.5	0.30	10	16	11	18
12	8.0	0.30	5	16	7	14
13	7.5	0.40	5	21	16	22
14	8.5	0.30	5	20	14	21
Mean ± SD	7.9 ± 0.4	0.33 ± 0.04	5.8 ± 1.6	16.5 ± 3.8	10.6 ± 4.6	17.4 ± 4.3

ET, endotracheal tube; PEEP, positive end-expiratory pressure; PSV, pressure support ventilation.

a modified EAdi catheter. They were then switched to a modified Siemens 300 ventilator (Maquet) capable of delivering PSV and NAVA. Patients were suctioned and positioned comfortably in a semirecumbent position. During the entire protocol, the F_{IO_2} and the external positive end-expiratory pressure (PEEP) were maintained at levels set clinically. From the initial physician prescribed level, the PSV was reduced in steps of 2 cm H_2O every 3 mins, to the lowest level the patient could tolerate, at the same time ensuring a minimum tidal volume (V_T) of 6 mL/kg to 8 mL/kg, breathing frequency <35 breaths/min, oxygen saturation >90%, heart rate <120 beats/min, sustained increase or decrease in heart rate <15%, systolic blood pressure >100 mm Hg and <180 mm Hg, and an absence of diaphoresis or agitation. Patients were subsequently ventilated for 10 mins, using this PSV level; if any of the above described criteria were not satisfied, the assist was increased one step, and the 10-min period was repeated. The inspiratory trigger on the ventilator was set to 1 cm H_2O below the PEEP level and the inspiratory rise time (time to reach the set inspiratory pressure expressed as a percentage of the respiratory cycle time) to 1%. The flow cycle criteria on the SV300 ventilator is fixed at 5% of peak inspiratory flow.

Subjects were subsequently switched to NAVA, which was set to deliver the identical level of assist (peak pressure) and external PEEP as originally prescribed clinically for PSV. The NAVA level was reduced every 3 mins until a peak pressure similar to that observed during low PSV, ensuring that the ventilatory criteria were fulfilled. Subsequently, the NAVA level was progressively increased to a peak airway pressure 7 cm H_2O higher. Thereafter, subjects were randomly ventilated for 10 mins with each of the following four ventilatory strategies: low PSV level (PSVlow); +7 cm H_2O higher PSV (PSVhigh); NAVA with similar peak pressure to the low PSV (NAVAlow); and NAVA with +7 cm H_2O higher peak pressure (NAVAhigh). After each 10-min period, 100 breaths were recorded and an arterial blood gas was drawn.

At the end of the protocol, respiratory mechanics were measured with patients sedated with propofol (1–2 mg/kg in titrating doses) and the ventilator back-up rate in the control mode was gradually increased (25) until complete suppression of the EAdi. Static intrinsic positive end-expiratory pressure (PEEPi stat) was measured, using the end-expiratory occlusion technique (26). Static compliance of the respiratory system was measured by performing end-inspiratory occlusions and calculating the ratio between the end-inspiratory and end-expiratory (PEEPi stat) plateau pressures (27). Resistive properties of the respiratory system were determined from end-inspiratory occlusions (26).

Off-Line Data Analysis

Breath-by-breath analysis was performed on the acquired data (28). Mechanical timing parameters of the breathing pattern were determined from the flow signal and V_T was obtained by digital integration of flow.

For EAdi signal amplitude quantification, the integrated EAdi was measured for each breath from the onset of EAdi to its peak value. Neural inspiratory time (T_{in}) was measured as the interval between the onset of EAdi and its peak value and neural expiratory time (T_{en}) as the remainder of the respiratory cycle.

The trigger delay was measured as the time difference between the onset of the EAdi and the

ventilator inspiratory flow, and the cycling delay as the time difference between the end of neural inspiration and the end of ventilator inspiratory flow. For PSV, the instantaneous flow and volume at the end of T*in* were determined. Ventilator asynchrony was determined as the sum of the triggering and cycling-off delays per breath expressed as a percentage of the total breath duration. For NAVA, because the assist cycles off at 80% of peak EAdi, there is always an inherent delay (from the peak to 80% of peak).

Mean transdiaphragmatic (Pdi) swings were calculated for the T*in* and for the trigger delay period. As illustrated in Figure 1, the pressure-time product of the Pdi (PTPdi) during the T*in* and the ventilator triggering period were obtained for each breath by multiplying the corresponding mean inspiratory Pdi signal above the end-expiratory baseline by the T*in* and the trigger delay, respectively.

Wasted inspiratory efforts, identified as inspiratory deflections in EAdi and esophageal pressure failing to trigger the ventilator were computed as a percentage of all inspiratory efforts made (both triggered and nontriggered). The integrated EAdi and the PTPdi corresponding to the trigger delay and to the wasted efforts were calculated.

Breath-by-breath data were ensemble-averaged for each 100-breath data segment in every subject studied and group's mean values were then calculated, using these means.

Statistical Analysis

Variables were compared between NAVA and PSV and the two levels of assist, using two-way repeated-measures analysis of variance (ANOVA) and *post hoc* contrasts of significant effects were performed, using the Student-Newman-Keuls test (SPSS version 12.0, Chicago, IL). Values in the text and figures are mean ± SD, unless otherwise indicated. The level of significance for all statistical tests was set to $p < .05$.

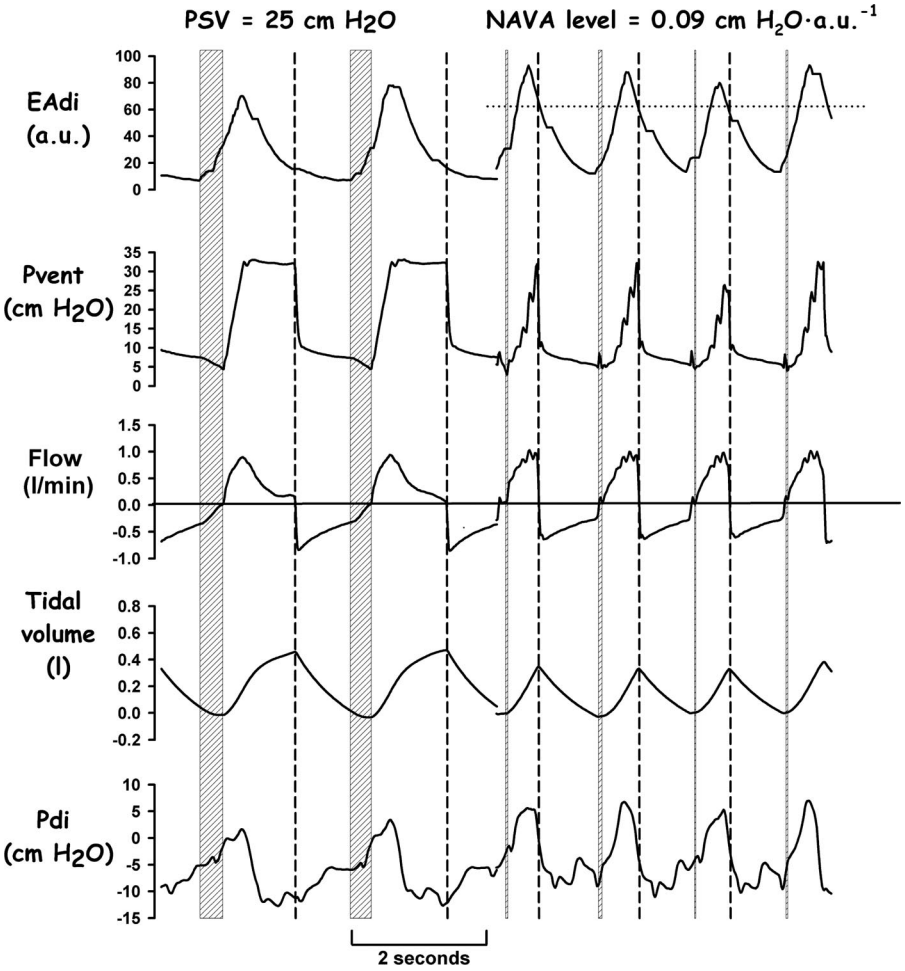

Figure 2. Graphs from one representative subject showing diaphragm electrical activity (*EAdi*), ventilatory pressure (*Pvent*), flow, volume and transdiaphragmatic pressure (*Pdi*) plotted over time during pressure support ventilation (*PSV*) and neurally adjusted ventilatory assist (*NAVA*) delivered at comparable peak pressures. The *vertical shaded bands* highlight the ventilator trigger delays determined from the time difference between the onsets of the EAdi and ventilator inspiratory flow. *Vertical dashed lines* indicate ventilator off-cycling. Trigger delays and the time from peak EAdi to ventilator off-cycling were substantially longer with PSV than with NAVA.

RESULTS

There were 14 patients enrolled in the study. The anthropometric data, etiology of acute respiratory failure, static respiratory mechanics, and baseline blood gas values are presented in Table 1. All patients had orotracheal intubation and were mechanically ventilated on average for 4.9 ± 2.6 days before the study. We were unable to completely suppress inspiratory drive in subject 11 and, thus, could not accurately determine this individual's respiratory mechanics. Ventilatory parameters (dialed into the ventilator) are presented in Table 2.

Representative tracings of EAdi and the corresponding ventilatory pattern from one patient during PSV and NAVA are shown in Figure 2. In general, the airway pressure waveform was square-shaped during PSV and triangular with NAVA. NAVA was successfully administered with the same peak pressure (assist level + external PEEP) as observed during the two levels of PSV delivery (Table 3). However, because of the pressure waveform difference, the mean ventilator pressure was lower with NAVA than with PSV during both assist levels.

Mechanical and Neural Breathing Pattern

At low levels of assist, the VT and frequency of breathing was similar with PSV and NAVA (Fig. 3). Increasing PSV increased the VT on average by 250 mL ($p < .001$) compared with 30 mL with NAVA ($p = .005$), whereas the fB decreased by 8 breaths/min with PSV ($p < .001$) and by 2 breaths/min with NAVA ($p = .04$). The larger reduction in frequency of breathing with PSV was due to significant prolongation of both ventilator inspiratory and expiratory durations (Table 3).

Increasing the assist with either PSV or NAVA had no effect on T*in*, whereas T*en* was prolonged with both, and to a greater extent with PSV (Table 3). The PTPdi ($p < .001$, repeated-measures ANOVA) and the integrated EAdi per breath ($p = .005$, repeated-measures ANOVA) were both significantly reduced when the assist was increased (Fig. 4*C* and *D*); there was no difference between modes at a given level of assist.

The instantaneous flow at the end of the neural Ti was 82 ± 13% of the peak value during low PSV and 79 ± 15% of

Table 3. Breathing pattern parameters

	PSV Low	PSV + 7 cm H_2O	NAVA Low	NAVA + 7 cm H_2O	*p* ANOVA Low Level vs. + 7 cm H_2O	*p* ANOVA NAVA vs. PSV
Pmo peak, cm H_2O	18.2 ± 4.8	24.3 ± 4.8[c]	19.0 ± 4.6	24.1 ± 5.9[h]	<.001	NS
Pmo mean, cm H_2O	14.4 ± 3.7	20.7 ± 4.4[c]	10.7 ± 2.9[b]	13.6 ± 2.8[e,h]	<.001	<.001
Ti *m*, sec	1.05 ± 0.53	1.60 ± 0.89[b]	0.89 ± 0.21	0.86 ± 0.17[e]	.003	.021
Te *m*, sec	1.83 ± 0.86	3.39 ± 2.49[a]	1.81 ± 0.93	2.09 ± 1.29[e,f]	.017	.005
Ti/Ttot *m*	0.37 ± 0.07	0.35 ± 0.08	0.36 ± 0.06	0.33 ± 0.07[h]	.048	NS
VE, L/min	11.7 ± 4.2	11.1 ± 3.7	12.1 ± 4.3	12.0 ± 4.0	NS	NS
VT/Ti, mL/sec	540 ± 202	542 ± 204	560 ± 144	608 ± 129[d]	NS	NS
Ti *n*, sec	0.85 ± 0.24	0.83 ± 0.23	0.84 ± 0.25	0.80 ± 0.19	NS	NS
Te *n*, sec	2.10 ± 1.13	3.32 ± 2.30[b]	1.84 ± 0.90[a]	2.13 ± 1.22[e,f]	.010	.003
Ti/Ttot *n*	0.32 ± 0.09	0.24 ± 0.11[c]	0.33 ± 0.07	0.30 ± 0.08[e,g]	<.001	.005

PSV, pressure support ventilation; NAVA, neurally adjusted ventilatory assist; ANOVA, analysis of variance; Pmo, mouth pressure; Ti, inspiratory breath duration; Te, expiratory breath duration; Ttot, total breath duration; VT, tidal volume; VE, minute ventilation; VT/Ti, mean inspiratory flow; *m*, mechanical; *n*, neural; Ti/Ttot, duty cycle.

Post hoc contrast vs. PSV low: [a]$p < .05$, [b]$p < .01$, [c]$p < .001$; *post hoc* contrast vs. PSV + 7 cm H_2O: [d]$p < .05$, [e]$p < .01$; p*ost hoc* contrast vs. NAVA low: [f]$p < .05$, [g]$p < .01$, [h]$p < .001$. Values are mean ± SD.

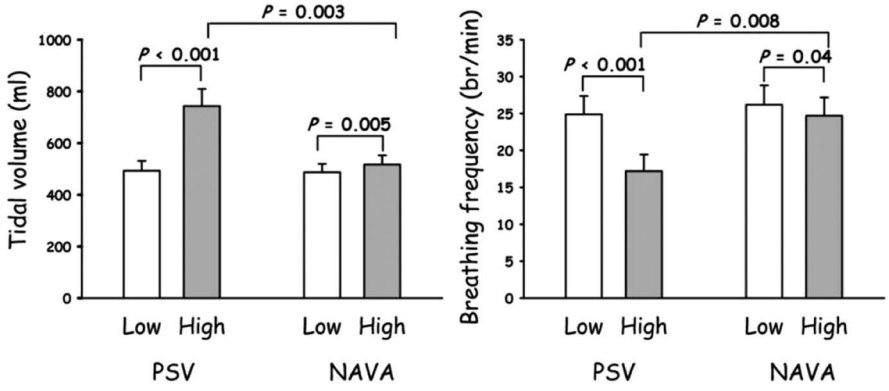

Figure 3. *Bar plots* showing group mean ± SEM values showing the mechanical breathing pattern during the two levels of pressure support ventilation (*PSV*) and neurally adjusted ventilatory assist (*NAVA*). At low levels of assist, the tidal volumes and breathing frequencies were similar with PSV and NAVA. Increasing the level of assist resulted in a slower and deeper breathing pattern with PSV, whereas significantly smaller changes were observed with NAVA.

peak during high PSV. The respective volumes delivered at those points were 331 ± 145 mL and 340 ± 219 mL, which corresponds to 64 ± 18% and 48 ± 17% ($p < .001$) of the VT delivered.

Ventilator Triggering

As shown in Figure 4*A*, the trigger delays were significantly larger with PSV compared to NAVA, during both low ($p < .001$) and high assist ($p < .001$). The trigger delays with PSV corresponded to 29 ± 15% and 35 ± 20% of the Ti*n* during low and high assist ($p = .015$), respectively, whereas they were 13 ± 3% and 14 ± 4% for the corresponding levels of NAVA ($p = .001$ at both levels for PSV vs. NAVA). Increasing the ventilatory assist had no effect on the trigger delays in either mode.

The PTPdi ($p = .021$, ANOVA) and EAdi ($p = .005$, ANOVA) for triggering was lower with NAVA (Fig. 4*C* and *D*). The integrated EAdi required to trigger the ventilator during low and high PSV was 17% and 23% of that measured over the entire inspiratory phase, respectively; the corresponding values were 5% ($p = .004$) and 6% ($p = .009$) for NAVA.

Wasted inspiratory efforts were observed in 6 of the 14 subjects during PSV. In such individuals, 5 ± 4% of all generated inspiratory efforts failed to trigger the ventilator during low PSV and 31 ± 26% during high PSV. Neural Ti, EAdi, and PTPdi between the triggered and wasted efforts observed in 6 of 14 patients studied were not significantly different (Fig. 5). No wasted efforts were observed during NAVA.

Ventilator Cycling-Off

PSV was associated with significantly larger cycling-off delays compared with NAVA, during both low ($p = .049$) and high assist ($p = .004$) (Fig. 4*B*). Increasing the assist resulted in an almost 3-fold increase in the mean delay of ventilator cycling-off with PSV ($p = .003$), whereas the delay was not altered with NAVA. The expiratory asynchrony (continuation of ventilator inflation after cessation of neural inspiratory activity) was 14 ± 16% and 26 ± 23% of the neural Te for low and high PSV, respectively ($p = .012$), whereas it was 4 ± 2% for both NAVA levels ($p = .024$ and $p = .003$ for low and high PSV vs. NAVA).

Total asynchrony was 18 ± 13% during low PSV and 23 ± 12% during high PSV, in contrast to 7 ± 2% for both corresponding levels of NAVA.

Gas Exchange

Table 4 shows the mean arterial blood gases obtained at the end of each experimental period. There were no differences observed when PSV was compared with NAVA at a given level of assist.

DISCUSSION

Our results show that, in a predominantly chronic obstructive pulmonary disease (COPD) group of patients with acute respiratory failure, NAVA compared with PSV (5% flow-cycling criteria) improves patient-ventilator synchrony, especially at higher ventilatory assist. The results also demonstrate that NAVA results in smaller breathing pattern changes and maintains similar gas exchange, when the level of ventilatory assist is increased.

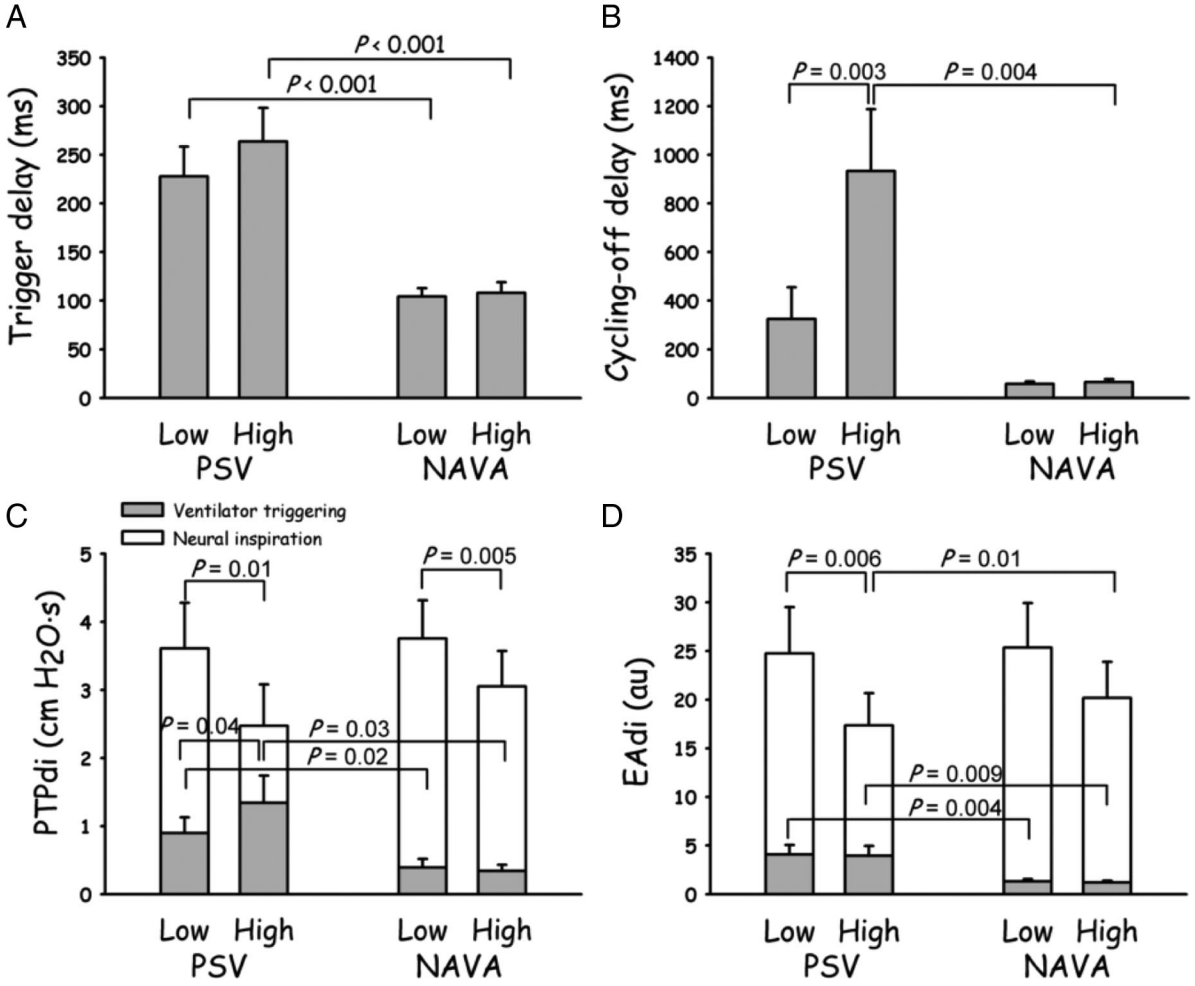

Figure 4. *Bar graphs* showing the group mean ± SEM values for ventilator triggering (*A*) and cycling-off delays (*B*), as well as the diaphragm pressure-time product (*PTPdi*) (*C*) and corresponding diaphragm electrical activity (*EAdi*) (*D*) involved in ventilator triggering (*gray shaded area*) relative to the neural inspiration (*white area*). Neurally adjusted ventilatory assist (*NAVA*) was associated with significantly lower trigger and cycling delays during both levels of assist. Increasing the level of assist reduced the PTPdi and EAdi per breath during both pressure support ventilation (*PSV*) and NAVA, whereas the PTPdi and EAdi associated with triggering were lower with NAVA.

Ventilator Triggering

Ventilator triggering in conventional ventilators is controlled by pneumatic sensors that detect changes in pressure, flow, or volume in the ventilator circuitry (29). As a result, the inherent characteristics of each ventilator's pneumatic and electronic systems contribute to the different trigger delays observed among ventilators (30). To eliminate such an effect on our results, the same Servo 300 ventilator was used to deliver NAVA and PSV in the current study. In bench test studies, the Servo 300 was found to have one of the most rapid trigger responses among the ventilators tested (30–32).

We chose pressure triggering over flow triggering, with the trigger set to −1 cm H_2O below the PEEP level. This choice was motivated by previous reports having associated flow triggering with autocycling due to leaks (33) and cardiogenic oscillation (34) as well as a lack of evidence demonstrating any clear superiority of flow triggering over pressure triggering with PSV (29, 31, 35, 36).

Trigger Delays and Inspiratory Effort With PSV

The average delay for triggering with PSV in our study was 228 msecs and 264 msecs with low and high PSV, respectively. These values fall within the 80-msec to 550-msec range of values previously reported for pressure-triggered PSV (13, 17, 31, 35, 37, 38). This wide variability can be ascribed to different ventilators used, varying levels of assist provided, the method used to assess trigger delays, and the different etiologies of respiratory failure. Our finding that increasing the PSV level did not significantly alter the observed trigger delays is consistent with previous studies, which likewise used crural EAdi to assess patient-ventilator synchrony (13, 17). Although others have reported increased trigger delays with increased PSV (1, 38), use of pleural pressures instead of direct EAdi measurement for the evaluation of trigger delays could conceivably have contributed to errors in estimating the onset and duration of inspiratory T*in* in such studies (39).

The trigger delays in the current study were marginally greater than those reported by Beck et al (13) and Colombo et al (17); however, in contrast to the mixed patient populations in those studies, the majority of our patients had COPD. Factors, such as dynamic hyperinflation and PEEPi, associated with COPD, have been

shown to contribute to ineffective trigger efforts and trigger delays (1, 2). Increasing the PSV level resulted in wasted inspiratory efforts in 43% of our patients. Although patient-ventilator asynchrony tends to be more pronounced in patients with COPD (40), increased ineffective efforts and double triggering at higher PSV levels have also been reported in patients with acute respiratory failure of varying etiology (38, 40). PEEPi stat did not significantly correlate with the trigger delays observed with PSV in our study. However, the external PEEP, which was clinically set and thus not individually optimized at each level of assist, could have influenced dynamic hyperinflation and the trigger delays from patient to patient (41, 42).

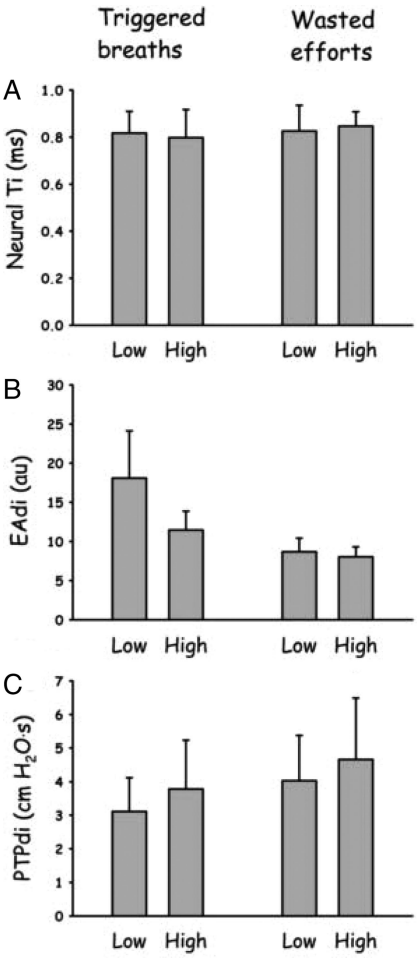

Figure 5. *Bar graphs* showing mean ± SEM values from the 6 of the 14 subjects who exhibited wasted inspiratory efforts during pressure support ventilation. The neural inspiratory duration (*Ti*), diaphragm electrical activity (*EAdi*), and diaphragm pressure-time product (*PTPdi*) of the triggered vs. the wasted efforts were not significantly different.

Similar to the findings of Beck et al (13), patients in the present study spent on average about one third of their T*in* triggering the ventilator with PSV. Aslanian et al (31) revealed that the corresponding breathing effort associated with trigger delays could be 10% to 30% of the total breathing effort, a finding likewise supported by our study. Others have also shown that delays and/or failure to trigger the ventilator represent an increase in the energy expended by the respiratory muscles (1, 43–45). Similar to others (1, 13, 28, 46, 47), we found that increasing the PSV level reduced the EAdi and PTPdi per breath. However, despite this, the breathing effort expended on ventilator triggering was not reduced; rather, a larger proportion of the inspiratory effort per breath was expended on ventilator triggering.

Trigger Delays and Inspiratory Effort With NAVA

We used crural EAdi to assess delays in ventilator triggering and cycling as well as for controlling the ventilator during NAVA. It should be pointed out, however, that these two processes are distinct: NAVA was delivered automatically based on preestablished algorithms and on-line threshold adjustments, whereas ventilator triggering and cycling delays were assessed off-line by manually positioning reference cursors on the corresponding signals used for analysis of patient-ventilator synchrony.

Trigger delays with NAVA were ~105 msecs, a >50% reduction of those observed with PSV. Similar trigger delays have been reported with NAVA for both animals (7) and humans (17). Increasing the NAVA level had no effect on trigger delays, and unlike PSV, did not elicit any wasted efforts. Our results indicate that, due to a more efficient triggering, less EAdi and PTPdi were required for ventilator triggering with NAVA than with PSV.

Ventilator Cycling-Off With PSV and NAVA

Conventionally, ventilator cycling-off is achieved by terminating the assist at a point when inspiratory flow has declined to some value relative to its peak inspiratory level. Synchrony between neural and mechanical breath termination is dependent on such factors as the level of assist delivered (peak airway pressure), patient inspiratory effort, neural inspiratory time, as well as the time constant of the respiratory system (4). Consequently, the optimum flow cycling-off level varies from person to person and can range from very low levels (5% of peak flow) in patients with acute lung injury (10) to ≥50% in patients with severe COPD (6, 11). The SV300 ventilator used in the present study had a fixed cycling-off criterion of 5% of peak inspiratory flow, which could be considered low for patients with COPD. The present study shows that cycling-off on average at 80% of peak flow during PSV would have been required to match the EAdi off-cycling, a cycling criterion that is even higher than that previously proposed by Tassaux et al (11) and not readily available on current ventilators. How actual cycling-off at 80% of flow would have altered neural timing and modified patient-ventilator interaction is, however, unknown.

Increasing the PSV level produced an approximate 3-fold increase in the cycling-off delays, confirming previous theoretical work of Yamada and Du (4). The delayed cycling during the increased PSV clearly affected breathing pattern by decreasing breathing frequency and increasing V$_T$. This breathing pattern effect, which could be clinically interpreted as a response to efficient unloading, however, is simply a reflex-induced prolongation of the neural expiratory period caused by

Table 4. Arterial blood gases

	PSV Low	PSV + 7 cm H_2O	NAVA Low	NAVA + 7 cm H_2O	*p* ANOVA Low Level vs. + 7 cm H_2O	*p* ANOVA NAVA vs. PSV
Pa_{O_2}, torr	87.4 ± 19.3	92.7 ± 21.4[a]	87.1 ± 20.7	91.3 ± 21.5[a]	0.005	NS
Pa_{CO_2}, torr	48.4 ± 8.3	47.4 ± 9.4	48.7 ± 9.2	47.1 ± 8.1	0.01	NS
pH	7.42 ± 0.07	7.43 ± 0.07	7.42 ± 0.06	7.44 ± 0.07[a]	0.016	NS

ANOVA, analysis of variance; NAVA, neurally adjusted ventilatory assist; PSV, pressure support ventilation.

Values are mean ± SD.

Post hoc contrasts low vs. high assist: [a]$p < .05$.

impaired patient-ventilator synchrony (15, 48). Our results show that the duration of neural Ti and the volume delivered within that time period remained unaltered when the level of assist was increased; essentially, the increased VT was produced by a prolongation of assist delivery secondary to delayed ventilator cycling-off. Because NAVA cycles-off relative to the neural effort that it detects, cycling delays and breathing pattern were unaffected by changes in the NAVA level. Similar findings have been reported in animal studies (7). Recent studies in healthy subjects and in rabbits with acute lung injury have also shown that VT and respiratory rate remain stable with NAVA, even at assist levels high enough to eliminate inspiratory esophageal pressure and Pdi deflections (24, 49). Of special note is the fact that the EAdi could not be eliminated at those high NAVA levels. Despite the significantly lower VT delivered during the high NAVA compared with high PSV, acid-base balance was still effectively maintained.

Despite the improved patient-ventilator interaction, there was still a 7% asynchrony observed with NAVA. This asynchrony can be ascribed to delays intrinsic to the ventilator, i.e., ventilator internal processing, valve response, as well as delays inherent to NAVA, i.e., trigger threshold setting, 16-msec signal EAdi sampling, recursive filtering, ventilator cycling at 80% of peak EAdi.

Clinical Relevancy

The majority of our patients had COPD; thus, the effect of reduced delays observed with NAVA could conceivably have been less pronounced had it been applied to another patient population. Conversely, because patient-ventilator synchronization is most difficult in patients with COPD (12, 40), such patients are the most likely to benefit from use of NAVA. Studies have shown that patient-ventilator asynchrony is associated with sleep disruption (50), prolonged duration of mechanical ventilation, and an overall poorer prognosis (12, 51), which suggests that improvement in patient-ventilator synchrony has the potential of significantly improving such clinical outcomes.

Although our patients were not sedated or paralyzed, it should be pointed out that an EAdi signal is required to control the ventilator with NAVA; excessive sedation or diaphragm paralysis may, therefore, preclude NAVA application.

Certain similarities can be drawn between NAVA and proportional assist ventilation, i.e., both modes deliver ventilatory assist in proportion to a measurement of respiratory effort. Although no studies to date have directly compared the two modes, a recent review has compared their underlying principles (52).

CONCLUSIONS

The present study, conducted predominantly in patients with COPD, shows that compared with PSV with flow cycling criteria fixed at 5% of peak flow, NAVA improves patient-ventilator synchrony by reducing the triggering and cycling-off delays and abolishing wasted efforts, especially at higher levels of ventilatory assist. Furthermore, patient-ventilator synchrony and breathing patterns are maintained when the level of NAVA assist is increased. The results also demonstrate that NAVA is able to unload the diaphragm at the same time maintaining acid-base balance as effectively as PSV.

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