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Neurally Adjusted Ventilatory Assist in Critically Ill Postoperative Patients: A Crossover Randomized Study

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ABSTRACT

Background: Neurally adjusted ventilatory assist (NAVA) is a new mode of mechanical ventilation that delivers ventilatory assist in proportion to the electrical activity of the diaphragm. This study aimed to compare the ventilatory and gas exchange effects between NAVA and pressure support ventilation (PSV) during the weaning phase of critically ill patients who required mechanical ventilation subsequent to surgery.

Methods: Fifteen patients, the majority of whom underwent abdominal surgery, were enrolled. They were ventilated with PSV and NAVA for 24 h each in a randomized crossover order. The ventilatory parameters and gas exchange effects produced by the two ventilation modes were compared. The variability of the ventilatory parameters was also evaluated by the coefficient of variation (SD to mean ratio).

Results: Two patients failed to shift to NAVA because of postoperative bilateral diaphragmatic paralysis, and one patient interrupted the study because of worsening of his sickness. In the other 12 cases, the 48 h of the study protocol were completed, using both ventilation modes, with no signs of intolerance or complications. The Pa_{O_2}/F_{IO_2} (mean ± SD) ratio in NAVA was significantly higher than with PSV (264 ± 71 *vs.* 230 ± 75 mmHg, $P < 0.05$). Pa_{CO_2} did not differ significantly between the two modes. The tidal volume (median [interquartile range]) with NAVA was significantly lower than with PSV (7.0 [6.4–8.6] *vs.* 6.5 [6.3–7.4] ml/kg predicted body weight, $P < 0.05$). Variability of insufflation airway pressure, tidal volume, and minute ventilation were significantly higher with NAVA than with PSV. Electrical activity of the diaphragm variability was significantly lower with NAVA than with PSV.

Conclusions: Compared with PSV, respiratory parameter variability was greater with NAVA, probably leading in part to the significant improvement in patient oxygenation.

What We Already Know about This Topic

- Neurally adjusted ventilatory assist (NAVA) is one of several modes of ventilation that permits variations in breathing patterns and perhaps more patient-ventilator synchrony.

What This Article Tells Us That Is New

- In a prospective, randomized crossover study of 12 surgical patients requiring prolonged ventilation, there was improved oxygenation and increased respiratory variability when the patients were on NAVA for 24 consecutive hours compared with these parameters when they received pressure support ventilation.

PRESSURE support ventilation (PSV) is the most widely used assisted mode of ventilation during the weaning process in medical and surgical critically ill patients.[1] However, PSV provides a fixed end-inspiratory pressure (*i.e.*, level of assistance), regardless of the patient's ventilatory demand or gas exchange, which limits breathing pattern variability.[2–5] Given the high variability in disease processes and states, the application of predefined, uniform values for ventilator parameters, such as a fixed end-inspiratory pressure or tidal volume (VT), is unlikely to provide optimal assist at all times. Compared with the monotonous breathing pattern resulting from the limited variability of end-inspiratory pressure, variations of the breathing pattern may be useful to improve gas exchange.[6]

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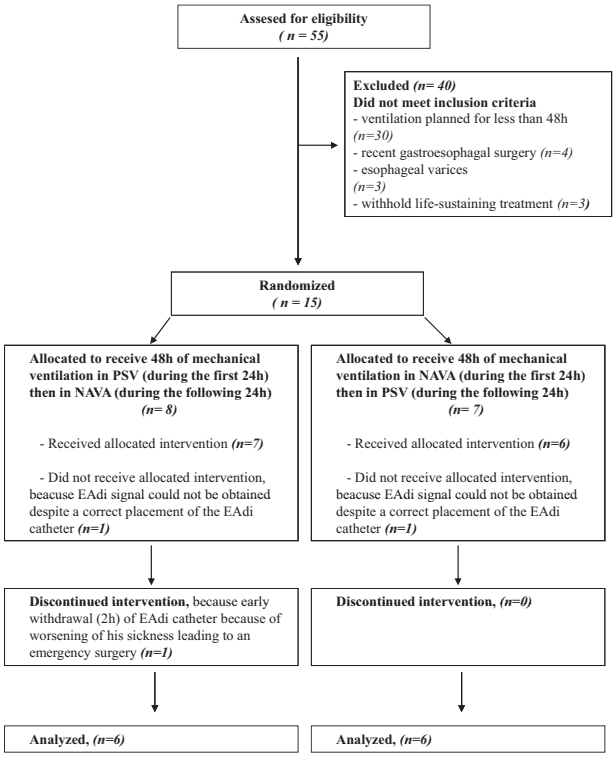

Fig. 1. Trial profile. EAdi = electrical activity of the diaphragm; NAVA = neurally adjusted ventilatory assist; PSV = pressure support ventilation.

This observation was mainly obtained with animal studies,[6–8] which evaluated new ventilatory modes, including variability in their function, and more recently in a human study with the Neurally Adjusted Ventilatory Assist (NAVA) mode.[9,10]

NAVA is a new ventilatory mode wherein the ventilator delivers positive pressure during inspiration in proportion to the electrical activity of the diaphragm (EAdi) obtained by a nasogastric tube covered by electrodes that record and analyze transesophageal electromyography.[11,12] The amount of assistance for a given EAdi depends on a user-gain factor called "NAVA level." Each change in the patient's ventilatory demand can theoretically be rewarded by the ventilator. Like proportional assist ventilation,[2,13,14] NAVA ensures a positive relationship between the ventilator assistance and the patient's effort. Unique to NAVA is the identification of the start of neural exhalation, which is not recognized by assist-control ventilation or PSV. The NAVA characteristics could have clinical implications, such as better patient-ventilator synchrony and a more natural ("noisy") breathing pattern, leading to improved comfort and oxygenation. NAVA has been studied in animals,[15,16] healthy subjects[17], and critically ill patients[9,10,18] but only for 20 min[10] to 3 h.[9] To our knowledge, no physiologic study has been performed to evaluate the use of NAVA for a prolonged mechanical ventilation (MV) period in selected critically ill patients.

The aim of this prospective, randomized, crossover study was to investigate, in a homogenous group of postoperative patients, during the weaning phase of their illness, the 24-h effects of NAVA on ventilatory parameters and gas exchange and to compare these with those observed with PSV. We hypothesized that in this group of patients, characterized by respiratory modifications related to surgery, NAVA would improve oxygenation because it offers a more variable ventilation, which is a more physiologic ventilation.[19,20]

Materials and Methods

The experimental protocol was approved by the Ethics Committee of the Saint-Eloi Teaching Hospital (Comité de Protection des Personnes Sud Méditerranée IV, Montpellier, France), and written informed consent was provided by the patient or next of kin. Our study followed the CONSORT recommendations concerning the report of randomized trials.[21]

Table 1. Characteristics of the 12 Patients Studied

Patient	Sex	Age, yr	Height, cm	Weight, cm	SAPSII	Procedure	Time Between Surgery and Inclusion, Days	Time Between Weaning and Inclusion, Days	Total Duration of Ventilation, Days	Outcome
1	F	43	150	50	68	Laparotomy for hemoperitoneum	6	1	13	D
2	M	76	175	70	36	Pulmonary lobectomy	35	20	43	D
3	M	77	168	58	47	Colectomy	4	3	6	S
4	F	71	155	68	55	Abdominal parietal hematoma	0.5	3	8	D
5	M	70	176	120	80	Peritonitis	6	1	47	S
6	M	73	175	97	33	Rachis surgery	3	1	84	S
7	F	68	160	48	38	Peritonitis	47	42	37	S
8	M	75	160	50	85	Hepatectomy	16	1	12	D
9	M	86	170	85	71	Peritonitis	1	1	4	S
10	F	84	145	90	47	Cardiac surgery	6	1	15	S
11	F	77	170	90	70	Peritonitis	6	1	40	D
12	M	85	180	123	45	Peritonitis	3	1	21	S
	—	76 [71—79]	169 [159—175]	78 [56—92]	51 [43—70]	—	6 [3–9]	1 [1–3]	18 [11–41]	—

Summary data are presented as median [interquartile range].
D = died; F = female; M = male; S = survived; SAPS II = Simplified Acute Physiology Score II.

Table 2. Ventilatory Settings and Main Monitored Ventilatory Parameters Obtained at the Baseline of Each Ventilatory Period for PSV and NAVA

Parameters	PSV (n = 12)	NAVA (n = 12)	*P* Value
Ventilatory Settings	—	—	—
Pressure Support Level, cm H_2O	11 ± 3	NA	—
NAVA Level, cm $H_2O/\mu V$	NA	1.9 ± 1.5	—
Flow Inspiratory Trigger, l/min	2 ± 0	2 ± 0	NS
Neural Inspiratory Trigger, μV	NA	0.5 ± 0	—
Flow Expiratory Trigger, % of maximal peak flow value	30 ± 0	NA	—
Neural Expiratory Trigger, % of maximal peak EAdi value	NA	30 ± 0	—
Inspiratory Rise, %	5 ± 0	NA	—
Oxygen Inspired Fraction, %	49 ± 13	46 ± 13	NS
PEEP, cm H_2O	6 ± 2	6 ± 2	NS
Monitored Ventilatory Parameters	—	—	—
EAdi, μV	7.5 [6.4–12.4]	8.5 [6.3–14.2]	NS
Maximal P_{insp}, cm H_2O	18 [15–21]	19 [15–24]	NS
Mean P_{insp}, cm H_2O	9 [8–10]	9 [7–11]	NS
RR, breaths/min	27.4 [18.1–28.4]	25.1 [21.9–28.8]	NS
VT, ml	460 [376–527]	399 [338–445]	NS
VT, ml/kg PBW	7.5 [5.6–8.4]	6.0 [5.1–8.0]	NS
VE, l/min	10.4 [8.5–11.7]	10.1 [9.2–11.5]	NS
P_{ETCO_2}, mmHg	30.6 [23.3–33.1]	30.4 [24.5–33.0]	NS
$P_{0.1}$, cm H_2O	1.6 [1.1–2.2]	0.9 [0.7–1.1]	NS

Data are presented as mean ± SD for ventilatory settings and as median [interquartile range] for monitored ventilatory parameters.

EAdi = electrical activity of the diaphragm; NA = not applicable; NS = not significant; NAVA = neurally adjusted ventilatory assist; $P_{0.1}$ = occlusion pressure; PBW = predicted body weight; PEEP = positive end-expiratory pressure; P_{ETCO_2} = end-tidal partial pressure of carbon dioxide; P_{insp} = inspiratory airway pressure; PSV = pressure support ventilation; RR = respiratory rate; VE = minute ventilation; VT = tidal volume.

Patients

Fifteen patients were prospectively enrolled from March 2009 to June 2009. They had been mechanically ventilated *via* an endotracheal tube for more than 48 h with PSV levels of 6 to 15 cm H_2O above 2 to 10 cm H_2O of positive end-expiratory pressure. The following inclusion criteria were used: ventilation planned for more than 48 h and patient alert and calm corresponding to a Richmond Agitation–Sedation Scale (RASS) between −2 and 0.[22–24] The following exclusion criteria were mainly related to the clinical contraindication for the use of NAVA: contraindications for an EAdi catheter placement (*e.g.*, esophageal varices, upper gastrointestinal bleeding, gastroesophageal surgery) and clinical instability for any reason. Patients for whom the decision to withhold life-sustaining treatment had been made, pregnant women, and children were also not considered.

Methods

The two ventilatory modes (PSV and NAVA) were delivered by the same ventilator (Servo-I; Maquet Critical Care, Sölna, Sweden) and were set to provide similar MV.[4] In PSV, there was only a flow inspiratory trigger. In NAVA, the ventilator can be cycled on by two different algorithms, based on either EAdi, or Paw or flow, according to a hierarchy that follows the principle that "first-serves-first." There were flow and neural inspiratory triggers that detected first-caused activation of the pressure assist. The fraction of inspired oxygen (F_{IO_2}) was set to achieve oxygen saturation greater than 95%. The positive end-expiratory pressure level was set between 2 and 10 cm H_2O and kept constant throughout the study.

The PSV level was first applied for 5 min to determine the inspiratory pressure level required to obtain a VT between 6 and 8 ml/kg predicted body weight (PBW)[25,26] (as calculated with the following formulas for men and women, respectively: PBW (kg) = 50 + 2.3 [(height (cm)/2.54) − 60] and PBW (kg) = 45.5 + 2.3 [(height (cm)/2.54) − 60]) with a respiratory rate (RR) between 20 and 30 breaths/min; the resulting values of minute ventilation (VE, calculated as the product of VT and RR) were used to set NAVA.[4]

As described previously,[17,27] EAdi was obtained through a nasogastric tube with a multiple array of electrodes placed at its distal end (EAdi catheter; Maquet Critical Care). Correct positioning of the EAdi catheter was assured by means of a specific function of the ventilator ("EAdi catheter positioning"). The

Table 3. Gas Exchange

Parameters	PSV (n = 11)	NAVA (n = 11)
pH	7.45 ± 0.06	7.44 ± 0.06
$Paco_2$, mmHg	41 ± 9	39 ± 7
Pao_2, mmHg	108 ± 27	117 ± 32
HCO_3^-, mM	29 ± 7	27 ± 6
Sao_2, %	98 ± 2	98 ± 2
Pao_2/Fio_2, mmHg	230 ± 75	264 ± 71*

Data are presented as mean ± SD.

* $P < 0.05$ significantly different from the value with PSV.

Fio_2 = oxygen inspired fraction; NAVA = neurally adjusted ventilatory assist; $Paco_2$ = partial pressure of arterial carbon dioxide; Pao_2 = partial pressure of arterial oxygen; PSV = pressure support ventilation; Sao_2 = arterial saturation in oxygen.

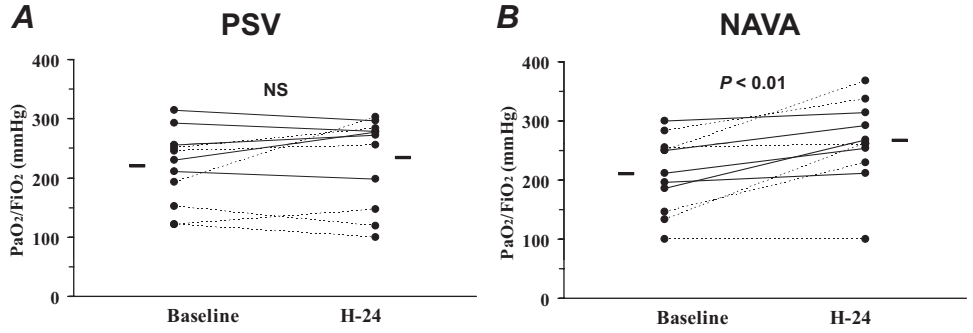

Fig. 2. Individual variations in Pa_{O_2}/F_{IO_2} ratio for 11 of 12 patients after mechanical ventilation with pressure support ventilation (PSV; *A*) and with neurally adjusted ventilatory assist (NAVA; *B*). The *horizontal bars* represent the mean values. The *unbroken line* indicates NAVA then PSV; the *dashed line* indicates PSV then NAVA. F_{IO_2} = inspired oxygen fraction; Pa_{O_2} = partial pressure of arterial oxygen.

EAdi signal was processed according to the American Thoracic Society recommendations[28] and filtered by algorithms designed to provide the highest possible signal-to-noise ratio. To avoid interference secondary to variations in lung volume and chest wall configuration,[28] changes in diaphragm position along the array were also considered.[17,29] EAdi was quantified every 16 ms using the root mean square.[12,17] Portions of signal with residual disturbances were removed and replaced by the values of the previous segment.[15] The amount of pressure instantaneously applied by the ventilator to the airway opening throughout inspiration was determined by the processed EAdi, expressed in microvolts, multiplied by a user-controlled gain factor ("NAVA level") expressed as centimeters of H_2O per microvolt. The amount of assistance depended on the magnitude of both the EAdi signal and the NAVA level. In NAVA, the ventilator can be cycled on inspiration to expiration by two different algorithms, based on EAdi or fluid dynamics (airway pressure or flow), according to a hierarchy that follows the principle of "first-come, first-served." During NAVA, the ventilator was cycled off when the EAdi decreased at 70% of its peak inspiratory value.[10] In the case of a disturbance or a disappearance of the EAdi signal during ventilation in NAVA (*e.g.*, EAdi catheter moving, accidental removal of EAdi catheter), the ventilator automatically converted to PSV (independently of the EAdi signal). When the EAdi signal became valid and useable, the ventilator automatically switched from PSV to NAVA. As mentioned previously, the NAVA level was set to obtain the same amount of assistance (corresponding to the same VE and RR) as determined by prior use of PSV during 5 min.

Protocol

We applied a crossover study design very similar to that previously reported by Dojat *et al.*[30] and Sydow *et al.*[31] Determination of the type of ventilatory mode used was performed weekly using a cluster randomization, the randomized type of ventilatory mode being used during 7 consecutive days. Each patient was consecutively ventilated for 24 h with the PSV mode and with the NAVA mode in random order. At inclusion, the patients were ventilated using settings previously adjusted by the attending physician. In the PSV mode, the physician in charge modified the PSV level by 2 cm H_2O, per the standard of care of the unit. In the NAVA mode,

Table 4. Ventilatory Parameters Obtained during 24 h for Each Ventilatory Period in PSV and in NAVA

	Absolute Value			Coefficient of Variation, %		
	PSV (n = 12)	NAVA (n = 12)	*P* Value	PSV (n = 12)	NAVA (n = 12)	*P* Value
EAdi, μV	9.4 [6.4–13.8]	8.5 [7.2–13.8]	NS	40 [29–53]	27 [21–37]	0.008
Maximal P_{insp}, cm H_2O	17 [15–22]	23 [16–25]	NS	5 [2–7]	15 [12–18]	0.003
Mean P_{insp}, cm H_2O	9 [8–10]	10 [7–12]	NS	5 [4–6]	9 [8–11]	0.005
RR, breaths/min	24.1 [21.3–25.9]	25.1 [21.6–27.2]	NS	14 [12–18]	13 [11–16]	NS
VT, ml	463 [394–502]	410 [371–457]	0.015	11 [9–11]	16 [14–19]	0.002
VT, ml/kg PBW	7.0 [6.4–8.6]	6.5 [6.3–7.4]	0.015	11 [9–11]	16 [14–19]	0.002
VE, l/min	10.0 [8.5–11.4]	10.7 [9.9–11.9]	0.041	12 [11–15]	17 [14–19]	0.023
P_{ETCO_2}, mmHg	30.2 [24.5–31.5]	29.6 [25.5–31]	NS	7 [5–10]	8 [7–12]	NS
$P_{0.1}$, cm H_2O	1.3 [1.1–1.7]	0.7 [0.6–1.1]	0.005	43 [33–52]	53 [40–70]	NS

Data are presented as median [interquartile range].

EAdi = electrical activity of the diaphragm; NS = not significant; NAVA = neurally adjusted ventilatory assist; $P_{0.1}$ = occlusion pressure; PBW = predicted body weight; P_{insp} = inspiratory airway pressure; P_{ETCO_2} = end-tidal partial pressure of carbon dioxide; PSV = pressure support ventilation; RR = respiratory rate; VE = minute ventilation; VT = tidal volume.

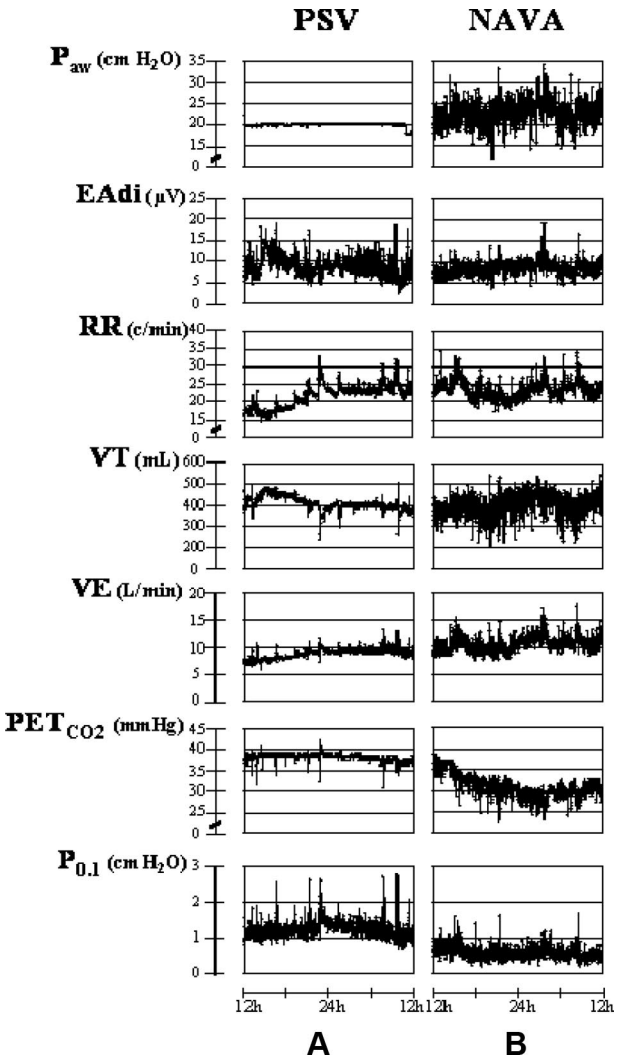

Fig. 3. Experimental records that help illustrate the effects of the two ventilatory modes during 24 h of mechanical ventilation with pressure support ventilation (PSV; *A*) and with neurally adjusted ventilatory assist (NAVA; *B*) in a representative patient. Note that P_{aw}, VT, and VE are more variable in NAVA than in PSV. c/min = breaths per minute; EAdi = electrical activity of the diaphragm; $P_{0.1}$ = occlusion pressure; P_{aw} = airway pressure; P_{ETCO_2} = end-tidal partial pressure of carbon dioxide; RR = respiratory rate; VE = minute ventilation; VT = tidal volume.

physicians could modify the NAVA level by steps of 0.2 cm $H_2O/\mu V$ if signs of respiratory distress were observed. For both modes, the clinician aimed to maintain the patient in the zone defined by the initial settings—to obtain a VT between 6 and 8 ml/kg of PBW with a RR between 20 and 30 breaths/min. Throughout the protocol, suctioning *via* the endotracheal tube was performed as needed.

Measurements

Standard three-lead monitoring electrodes continuously recorded heart rate and rhythm. Oxygen saturation was continuously monitored using pulse oxymetry. Systolic and diastolic arterial blood pressures were continuously monitored through a 20-gauge catheter inserted in a radial or femoral artery. Blood samples were obtained at baseline (in the first hour after MV for each mode) and after 24 h of MV for arterial blood gas analysis (GEM Premier 3000 analyzer; Instrumentation Laboratory, Lexington, MA) through the arterial catheter.

Table 5. Percentage of Time Spent in Inadequate Ventilation Zone in PSV and in NAVA

	PSV (n = 12)	NAVA (n = 12)	*P* value
VT < 5 ml/kg PBW	0.4 [0–1.5]	5.1 [3.6–17.8]	0.002
VT > 12 ml/kg PBW	0 [0–0.4]	0 [0–0.6]	NS
RR < 12 breaths/min	0 [0–0.3]	0 [0–0]	NS
RR > 35 breaths/min	0.4 [0.1–1.8]	0.9 [0.1–2.5]	NS
P_{ETCO_2} > 55 mmHg	0 [0–0]	0 [0–0]	NS
Total Inadequate Ventilation Zone	3.3 [0.7–11.4]	12.6 [6.2–18.9]	0.028

Data are presented as median percentage time of spent in inadequate ventilation during 24 h of the studied period. Inadequate ventilation zone is defined as follows: low VT = VT < 5 ml/kg of PBW; high VT = VT > 12 ml/kg PBW; low RR = RR < 12 breaths/min), high RR = RR > 35 breaths/min): high P_{ETCO_2} = P_{ETCO_2} > 55 mmHg.

NAVA = neurally adjusted ventilatory assist; NS = not significant; PBW = predicted body weight; P_{ETCO_2} = end-tidal partial pressure of carbon dioxide; PSV = pressure support ventilation; RR = respiratory rate; VE = minute ventilation; VT = tidal volume.

EAdi was measured with an array of electrodes mounted on a nasogastric tube. Airflow, airway pressure, VT, "estimated occlusion pressure" ($P_{0.1}$, defined as the airway pressure generated 100 ms after the onset of an occluded inspiration, identified as an estimation of the respiratory neuromuscular drive),[32,33] and end-tidal partial pressure of carbon dioxide were obtained from the ventilator. From the flow signal, we obtained ventilatory rate of cycling (RR). The signals for EAdi, airflow, airway pressure, VT, RR, and $P_{0.1}$ were monitored continuously online every 3 s, averaged every minute, recorded by means of a dedicated software (NAVA recording SV1.3; Maquet Critical Care), exported through a card, and analyzed using a customized software.

Every 4 h, according to our local protocol, the nurse in charge of the patient evaluated the pain and comfort using the Behavioral Pain Scale (BPS)[23,34] and the sedation and agitation level using the RASS.[22,23] The BPS evaluates three behavioral domains (*i.e.*, facial expression, movements of upper limbs, and compliance with ventilator). Each domain contains four descriptors that are rated on a 1-to-4 scale, and the total BPS value can range from 3 (no pain and excellent comfort) to 12 (most pain with maxi-

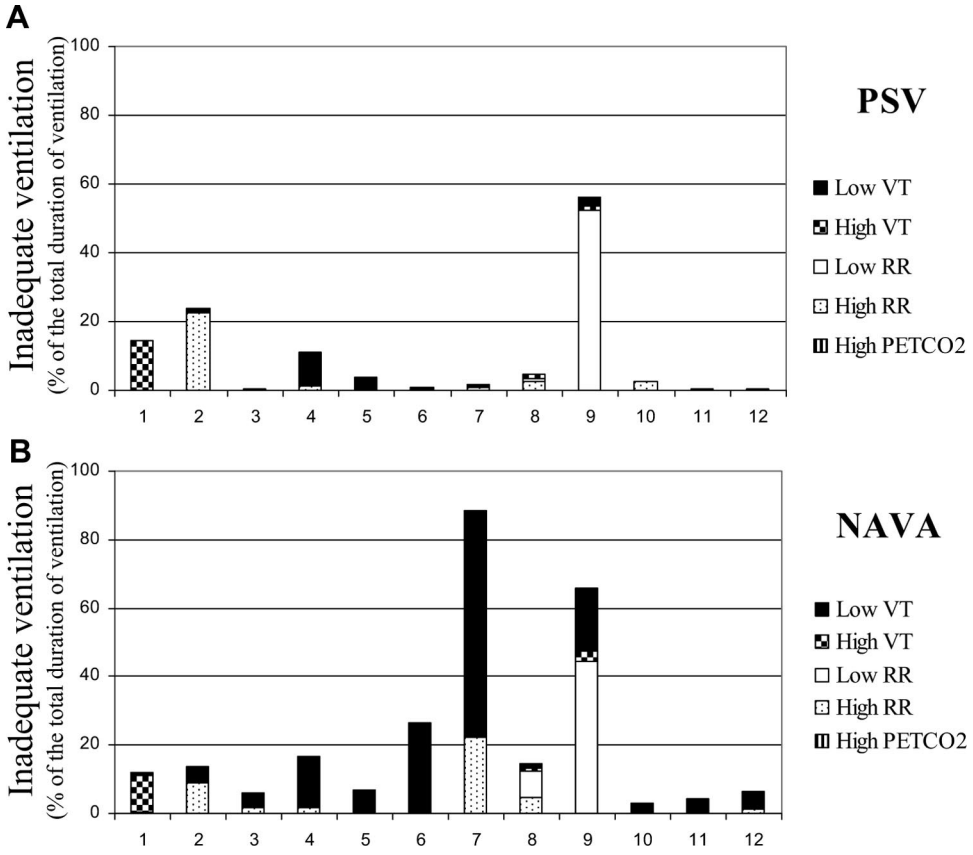

Fig. 4. Contributions to inadequate ventilation of low VT (VT less than 5 ml/kg of PBW), high VT (VT higher than 12 ml/kg PBW), low RR (RR less than 12 c/min), high RR (RR higher than 35 c/min), and high P_{ETCO_2} (P_{ETCO_2} higher than 55 mmHg) during 24 h of pressure support ventilation (PSV; *A*) and neurally adjusted ventilatory assist (NAVA; *B*) in the 12 studied patients. With PSV, inadequate ventilation represented 3% [1–11%] of the total ventilation duration in this mode; with NAVA, inadequate ventilation represented 13% [6–19%] of the total ventilation duration in this mode. c/min = breaths per minute; EAdi = electrical activity of the diaphragm; $P_{0.1}$ = occlusion pressure; P_{aw} = airway pressure; PBW = predicted body weight; P_{ETCO_2} = end-tidal partial pressure of carbon dioxide; RR = respiratory rate; VE = minute ventilation; VT = tidal volume.

Table 6. Time Spent with an Acceptable Ventilation during PSV and NAVA

	Duration of Ventilation[45]		Periods with Acceptable Ventilation, %		Periods with Acceptable VT, %	
Patient	PSV	NAVA	PSV	NAVA	PSV	NAVA
1	1,374	1,504	86	88	86	88
2	1,462	1,436	77	87	99	95
3	748	1,436	100	95	100	96
4	1,496	1,462	90	82	90	83
5	1,708	1,459	95	93	96	93
6	1,481	1,449	99	74	100	74
7	602	1,090	99	12	99	12
8	1,448	1,309	96	87	99	98
9	1,310	1,414	45	35	96	69
10	1,438	1,660	97	97	100	97
11	1,404	1,487	100	96	100	96
12	1,529	1,434	99	94	100	95
	1,443 [1,358–1485]	1,443 [1,429–1468]	97 [89–99]	88 [80–94]*	99 [96–100]	94 [81–96]**

Acceptable ventilation is defined as VT between 5 and 12 ml/kg of predicted body weight, RR between 12 and 35 breaths/min, and $P_{ETCO_2} < 55$ mmHg. Periods are expressed as the percentage of the total duration of ventilation with the corresponding mode. Summary data are expressed as median [interquartile range].

* $P < 0.05$ between PSV and NAVA; ** $P < 0.01$ between PSV and NAVA.

NAVA = neurally adjusted ventilatory assist; P_{ETCO_2} = end-tidal partial pressure of carbon dioxide; PSV = pressure support ventilation; RR = respiratory rate; VT = tidal volume.

mal discomfort). Setting changes made by the attending physician were also recorded.

Statistical Analysis

The primary endpoint was oxygenation, estimated by calculation of the Pa_{O_2}/F_{IO_2} ratio obtained after 24 h of MV in each mode. We used data from studies performed by our group.[3,4] In these studies, in the subgroup of postoperative patients, Pa_{O_2}/F_{IO_2} ratio was 202 ± 48 mmHg. Assuming an α risk of 0.05 and a β risk of 0.20, we calculated that at least 12 patients would be required to identify an increase of 25% Pa_{O_2}/F_{IO_2} ratio with NAVA. Therefore, we decided to include 15 patients. The secondary endpoints were the variability of the ventilatory parameters and the ventilatory comfort. The variability of the ventilatory parameters was evaluated by the coefficients of variation for airway pressure, EAdi, RR, VT, VE, end-tidal partial pressure of carbon dioxide, and $P_{0.1}$, which were calculated (SD to mean ratio multiplied by 100) as described previously.[10,20,35] The ventilatory comfort of the patient was evaluated by time spent in acceptable ventilation, defined as 12 less than RR less than 35 breaths/min, 5 less than VT less than 12 ml/kg of PBW, and end-tidal partial pressure of carbon dioxide less than 55 mmHg.[25,30] Then, we chose to define inadequate ventilation zone as low-tidal volume (VT less than 5 ml/kg of PBW), high VT (VT more than 12 ml/kg of PBW), low RR (RR less than 12 breaths/min), high RR (RR more than 35 breaths/min), and high end-tidal partial pressure of carbon dioxide more than 55 mmHg. Time spent with $P_{0.1}$ higher than 4 cm H_2O was also calculated.[30]

Values are expressed as mean ± SD or median [interquartile range], according to the type of variable distribution. Normality of the distribution was assessed with Kolmogorov-Smirnov test. For the ventilatory variables (EAdi, airflow, airway pressure, VT, RR, and $P_{0.1}$) recorded every minute, the averaged values obtained during the 24 h of MV were used for comparisons between PSV and NAVA. Data were analyzed by paired Student *t* tests or Wilcoxon tests, according to their distribution. All *P* values were two-tailed and a *P* value less than 0.05 was considered significant. Statistical analysis was performed using SAS/STAT software version 8.1 (SAS Institute, Cary, NC).

Results

During the 3 months of the study, we screened 55 patients and enrolled 15 consecutive postoperative patients, 3 of whom did not complete the study and could not be included in the data analysis (fig. 1). For two of the excluded patients, we could not obtain an EAdi signal despite a correct placement of the EAdi catheter; the third excluded patient dropped out of the study because of worsening of his sickness leading to an emergency surgery. The causes of respiratory failure of the 12 patients who concluded the study were abdominal postoperative acute respiratory failure (n = 9), cardiothoracic postoperative acute respiratory failure (n = 2), and neurosurgical postoperative acute respiratory failure (n = 1). No patients were tracheotomized. Clinical characteristics of the 12 patients who concluded the 48 h of the study protocol are shown in table 1. Five (42%) patients died, reflecting the selected postoperative population. No significant differences between PSV and NAVA were observed at baseline for all studied parameters (table 2). The main characteristics of the ventilatory settings of the two modes are summarized in table 2. Gain level changes made

Table 6. Continued

Periods with Acceptable RR, %		Periods with Acceptable P_{ETCO_2}, %		Changes in Pressure Assist, no. of Events	
PSV	NAVA	PSV	NAVA	PSV	NAVA
100	100	100	100	1	1,499
77	91	100	100	1	1,433
100	98	100	100	2	1,433
99	98	100	100	0	1,461
99	100	100	100	1	1,457
99	100	100	100	2	1,445
99	70	100	100	0	1,087
97	87	100	100	1	1,302
48	54	100	100	1	1,405
97	100	100	100	1	1,655
100	100	100	100	1	1,487
99	99	100	100	3	1,433
99 [97–99]	99 [90–100]	100	100	1 [1–1.25]	1,439 [1,426–1468]**

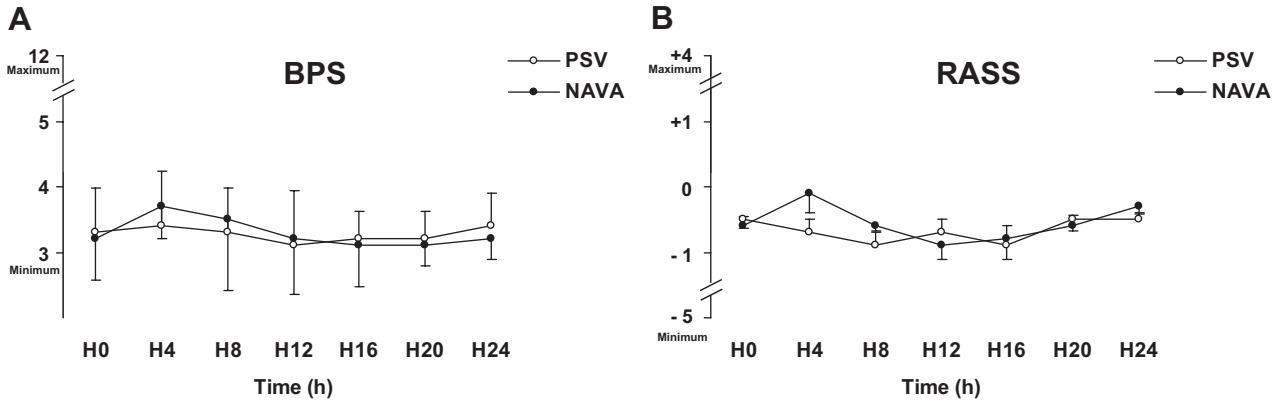

Fig. 5. (*A*) Time courses of pain and comfort evaluation performed every 4 h using the Behavioral Pain Scale (BPS) within 24 h of mechanical ventilation in pressure support ventilation (PSV) and neurally adjusted ventilatory assist (NAVA). No significant difference was observed between the two modes at any time. The total BPS value can range from 3 (no pain and excellent comfort) to 12 (most pain with maximal discomfort). (*B*) Time courses of sedation and agitation evaluation performed every 4 h using the Richmond Agitation Sedation Scale (RASS) within 24 h of mechanical ventilation in PSV and NAVA. No significant difference was observed between the two modes at any time. The RASS value can range from −5 (unarousable) to +4 (combative).

by the attending physician in NAVA were never necessary in seven patients and were performed three, five, and nine times in three, one, and one patients, respectively. Among the 12 studied patients, 5 patients have never presented a switch from NAVA to PSV during the 24 h of NAVA ventilation period. For the remaining seven patients, NAVA was automatically switched (safety back-up) in PSV mode 7 [3–11] times, and the duration of each PSV use before a new automatic switch to NAVA lasted 28 [22–57] s, which corresponds to less than 0.5% of the total period of ventilation in NAVA.

Arterial blood samples were obtained in 11 of the 12 studied patients. In subject 12, arterial blood samples were not available for logistical reasons. The Pa_{O_2}/F_{IO_2} ratio was similar at baseline between the two modes and it was significantly higher with NAVA than with PSV after 24 h of mechanical ventilation (table 3 and fig. 2).

Ventilatory parameters are reported in table 4. VT and $P_{0.1}$ were significantly lower with NAVA than with PSV. VE was significantly higher with NAVA than with PSV. Variability of airway pressure, VT, and VE were all significantly higher with NAVA than with PSV. EAdi variability was significantly lower with NAVA than with PSV (table 4). Typical tracing of main ventilatory parameters obtained during 24 h of MV in a patient (patient 11) with PSV and NAVA are shown in figure 3.

The time spent with inadequate ventilation was broken down into periods of low VT, high VT, low RR, high RR, and high end-tidal partial pressure of carbon dioxide, according to the definitions in the method section. The percentage of time spent with inadequate ventilation was significantly higher with NAVA than with PSV, related mainly to a low VT (table 5 and fig. 4). Table 6 shows individual time spent with an acceptable ventilation and number of changes in pressure assist during PSV and NAVA. The time spent with a $P_{0.1}$ higher than 4 cm H_2O was significantly lower with NAVA than with PSV (1 [0–5] min *vs.* 11 [1–56] min, $P <$ 0.05). No significant differences were observed between the two modes for the BPS and RASS scores over the study period (fig. 5).

Discussion

The present study demonstrates that (1) the use of NAVA for a long period of 24 h of mechanical ventilation was feasible for selected postoperative critically ill patients; (2) oxygenation with NAVA was improved in comparison to PSV; and (3) variability of main ventilatory parameters (airway pressure, VT, and VE) was significantly higher with NAVA than with PSV, likely because of a more physiologic patient/ventilator adaptation.

Feasibility of Prolonged Mechanical Ventilation in NAVA

When introducing a new ventilatory mode, it is necessary to compare it with the standard of care treatment, which in our unit is PSV. To our knowledge, this is the first study to report NAVA use for 24 consecutive h in postoperative critically ill patients and to compare the ventilatory behavior with that observed with PSV. The two published studies on NAVA performed in intensive care unit patients report durations of only 20 min[10] and 3 h.[9] Moreover, our population consisted of only surgical patients (mainly abdominal surgery), whereas in the previous studies, populations were heterogeneous (medical and surgical patients). In contrast to previous studies, which included mixed medical and surgical patients, we chose to evaluate NAVA only in postoperative patients, the majority after abdominal surgery procedures, because we also wondered if NAVA worked satisfactorily in patients at risk for postoperative diaphragmatic dysfunction. We found that with two patients, one operated on for liver transplantation and one for a colectomy, the EAdi signal necessary for NAVA was absent or too weak, despite the correct positioning of the EAdi catheter. For these two patients, NAVA

allowed us to diagnose postoperative severe diaphragmatic dysfunction. The incidence of diaphragmatic dysfunction varies from 10% to 30% in postabdominal surgery.[36,37] This is the first study to report limitations for the use of NAVA postoperatively with patients having diaphragmatic dysfunction (no EAdi signal or EAdi signal too weak to be interpreted). Nevertheless, for these two patients, the NAVA algorithm immediately implemented a security process by switching to the PSV mode (safety back-up), without any complication for the patients. It is noteworthy that patients could trigger the ventilator in PSV, not with their diaphragm, which was too weak, but with their accessory inspiratory muscles.

Aside from these two patients and a third, who did not complete the study for independent reasons of NAVA (worsening of his initial disease leading to an emergency surgery with EAdi catheter withdrawal), all other patients were able to complete the study, confirming that prolonged use of NAVA is satisfactory and safe in critically ill postoperative patients.

Gas Exchange, Ventilatory Parameters, and Variability

In contrast to previous publications,[9,10] our study is the first to report oxygenation improvement with NAVA. This can be explained by the short length of NAVA trials in two studies[9,10] and by the absence of differences in breathing pattern, ventilator assistance, and respiratory drive in two of the three sequences performed by Colombo *et al.*[10] Variable ventilation during 24 consecutive h can lead to oxygenation improvement by allowing sighs in NAVA. We can speculate that this indicates a progressive alveolar recruitment over time during ventilation with NAVA as reported in other modes, such as noisy PSV[8,38] or airway pressure release ventilation.[31] Several studies have reported that ventilatory variability promotes improved oxygenation in healthy and injured lungs.[7,8,20,39,40]

Like Colombo *et al.*,[10] we found that variability of EAdi was higher with PSV than with NAVA (40 *vs.* 27% for our results, 29 *vs.* 22% for Colombo *et al.*[10]), whereas VT variability was higher with NAVA than with PSV (16 *vs.* 11% for our results, 17 *vs.* 10% for Colombo *et al.*[10]). On the other hand, we did not find any difference in RR variability, contrary to results shown by Colombo *et al.*[10] obtained when a high NAVA level was applied. This is probably linked to the fixed NAVA level used in our study, whereas Colombo *et al.*[10] tried three different NAVA levels. Compared with noisy PSV,[8] which imposes to the patient a desired variability value of pressure assist, in proportional assist ventilation[2,5,13,14] and NAVA,[9,10] breathing pattern and pressure assist variability are imposed by the patient, which is probably a more physiologic respiratory behavior.

We found that VT was significantly higher in PSV than in NAVA, confirming that the ideal tidal volume dose and ventilatory support during assisted ventilation, in general, and PSV, in particular, is difficult to determine.[41,42] Thille *et al.*[43] recently reported that high VT and high PSV levels were not only associated with ineffective triggering but also with more respiratory alkalosis, suggesting that patients with high rates of ineffective triggering received excessive pressure support. Studies in animals[15,16] and healthy volunteers[17] have demonstrated that NAVA protects against excessive airway pressure and VT by a down-regulation of EAdi at high NAVA levels, unloads the respiratory muscles, and improves subject-ventilator synchrony. In our study, three patients were ventilated in NAVA with a VT less than 5 ml/kg of PBW for a period ranging from 16% to 75% (fig. 4) with no signs of discomfort or respiratory distress, which suggests that some patients need fewer VT because of lung volume reduction related to their pulmonary illness. These results suggest that, overall, compared with PSV, NAVA has the potential in some patients to limit the risk of over-assistance, as suggested by the Colombo study.[10]

In summary, oxygenation improvement observed with NAVA in the present study is probably due to more complex association of different features of NAVA, such as increased variability of respiratory variables, neuromechanical coupling improvement of the respiratory system associated with a better patient-ventilator synchronisation, presence of more alveolar auto recruitment (assimilated to more physiologic sigh), and limitation of excessive tidal volume[9,44,45] and/or over-assistance, which may limit ventilation-induced lung injury, especially in a nonhealthy lung.[44] However, the fact that mean airway pressure and $Paco_2$ did not change significantly does not mean that changes in these variables are not responsible (in some patients) for changes on oxygenation (with NAVA mean airway pressure increased by 11% and $Paco_2$ decreased by 5%). It can be speculated that, at least in some patients, the level of assist is not comparable between the two modes.

Patients receiving MV require sedation and analgesia for anxiety and pain during the time they are intubated, but we stopped administration at the beginning of the weaning to improve it. In the Colombo study,[10] patients were under light-to-moderate sedation, which may have influenced the respiratory pattern behavior. Except patient 9, who suffered from chronic kidney failure and was treated for a prolonged period with fentanyl (explaining in part the time spent with a low RR), none of our patients received either sedation drugs or morphine. In this way, their neural drive was not depressed, as shown by the variability of ventilatory parameters. Although it is difficult to specifically evaluate the respiratory comfort during a prolonged period of MV, and even more so continuously, we did not observe any significant differences in BPS and RASS scores recorded every 4 h between the two modes (fig. 5), suggesting that the two modes were equivalent in terms of impact on sedation and agitation adaptation.

This study has some limitations. First, we could not evaluate all parameters of the breathing pattern (*i.e.*, inspiratory and expiratory times, inspiratory flow) and breath-to-breath asynchrony between ventilator and patient, which should normally be uncommon with NAVA, according to previous studies.[10] Second, although we evaluated the agitation and

sedation-analgesia levels each 4 h (using RASS and BPS scores), there was no specific auto-evaluation of the ventilatory comfort. Third, we did not calculate the work of breathing, but we evaluated the estimated $P_{0.1}$ as a surrogate of inspiratory effort. Fourth, NAVA is not the only ventilatory mode that increases the variability of breathing.[7,8,27,46] Studying the effects of other modalities of assisted ventilation, such as proportional assist ventilation or noisy PSV, based on the variability of respiratory variables, would thus provide an interesting way of comparing it with NAVA. Finally, because none of the patients included in the present study was affected by moderate or severe chronic obstructive pulmonary disease, we can reasonably rule out the presence of increased levels of intrinsic positive end-expiratory pressure. Thus, no information on the impact of NAVA in patients with chronic obstructive pulmonary disease may be drawn from our results.

In conclusion, our findings show that NAVA could be used, once there was satisfactory contact and reporting between the nasogastric tube with electrodes and the ventilator. We reported that prolonged MV with NAVA in critically ill postoperative patients is satisfactory, once diaphragmatic dysfunction is eliminated. Variability of respiratory parameters, such as VT, VE, and airway pressure, are increased, probably participating in part to the significant improvement in oxygenation of patients ventilated with NAVA. Although the present study principally provides evidence of improved respiratory variability and oxygenation with NAVA, future studies are required to better evaluate for what duration the oxygenation may improve during the ventilation and better evaluate the patient/ventilator adaptation with quantification of ineffective efforts and their effects on the length of MV and intensive care unit stay in critical ill postoperative patients ventilated with NAVA. Although NAVA is not developed to explore diaphragmatic dysfunction, in the present study, it allowed diagnosis of severe diaphragmatic dysfunction.

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