

REVIEW

Clinical review: Update on neurally adjusted ventilatory assist – report of a round-table conference

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Report from the Geneva Round Table

Abstract

Conventional mechanical ventilators rely on pneumatic pressure and flow sensors and controllers to detect breaths. New modes of mechanical ventilation have been developed to better match the assistance delivered by the ventilator to the patient's needs. Among these modes, neurally adjusted ventilatory assist (NAVA) delivers a pressure that is directly proportional to the integral of the electrical activity of the diaphragm recorded continuously through an esophageal probe. In clinical settings, NAVA has been chiefly compared with pressure-support ventilation, one of the most popular modes used during the weaning phase, which delivers a constant pressure from breath to breath. Comparisons with proportional-assist ventilation, which has numerous similarities, are lacking. Because of the constant level of assistance, pressure-support ventilation reduces the natural variability of the breathing pattern and can be associated with asynchrony and/or overinflation. The ability of NAVA to circumvent these limitations has been addressed in clinical studies and is discussed in this report. Although the underlying concept is fascinating, several important questions regarding the clinical applications of NAVA remain unanswered. Among these questions, determining the optimal NAVA settings according to the patient's ventilatory needs and/or acceptable level of work of breathing is a key issue. In this report, based on an investigator-initiated round table, we review the most recent literature on this topic and discuss the theoretical advantages and disadvantages of NAVA compared with other modes, as well as the risks and limitations of NAVA.

Introduction

Pressure-support ventilation (PSV) is a widely used mode of assisted mechanical ventilation (MV), notably during the weaning phase [1,2]. Although PSV has been proven valuable in several acute clinical conditions [3,4], pre-defined ventilator settings – for example, airway pressure (Paw) – that remain unchanged from breath to breath are unlikely to provide optimal assistance all of the time.

To improve the match between the patient's needs and the assistance delivered by the ventilator, manufacturers have developed several new modes of MV [5,6]. Among these new modes we identified proportional-assist

ventilation (PAV) and neurally adjusted ventilatory assist (NAVA).

PAV is a mode of support in which the ventilator pressure is proportional to instantaneous flow and volume, and hence to pressure generated by the respiratory muscles [7]. Previous studies have demonstrated that PAV improves the synchrony between patient and ventilator, during several clinical conditions [8-12]. Based on the principles of the equation of motion, software (PAV+; Covidien, Boulder, Colorado, USA) has been developed that automatically adjusts the flow assist and the volume assist so that they always represent constant unloading fractions of the measured values of resistance and elastance loadings of the respiratory system [13-15]. Recent studies demonstrated that PAV+ is a safe and efficient ventilator mode in critically ill intubated patients [16,17]. During PAV the ventilator provides support only during the remaining duration of inspiratory effort,

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which can cause limitation when dynamic hyperinflation is present and when the inspiratory trigger is delayed due to intrinsic end-expiratory pressure.

The other support mode is NAVA, which will be discussed in this article. There are several similarities between PAV and NAVA, but this first round-table meeting focused on NAVA. A vast literature also exists concerning PAV, but this topic would require a whole chapter and will not be discussed in this current paper; hopefully PAV will be the topic of a different round table.

The present article is based on an investigator-initiated round-table meeting. The article aims to review the available knowledge on the physiological rationale and feasibility of the recently introduced NAVA MV modality. Throughout the article, we place emphasis on the most recent findings concerning adjustment of the NAVA settings; on the one hand considering specific issues associated with assisted modes of MV, and on the other considering the expectations placed upon NAVA.

NAVA is an assist mode of MV that delivers a pressure proportional to the integral of the electrical activity of the diaphragm (EAdi) [18], and therefore proportional to the neural output of the patient's central respiratory command. The level of pressure delivered is thus determined by the patient's respiratory-center neural output. With NAVA, the ventilator is triggered and cycled-off based on the EAdi value, which directly reflects the activity of the neural respiratory command. The inspiratory airway pressure applied by the ventilator is determined by the following equation:

$$Paw = \text{NAVA level} \times \text{EAdi},$$

where Paw is the instantaneous airway pressure (cmH₂O), EAdi is the instantaneous integral of the diaphragmatic electrical activity signal (μV), and the NAVA level (cmH₂O/μV or per arbitrary unit) is a proportionality constant set by the clinician.

In February 2011, several European and Canadian investigators with clinical results about NAVA available in publication or in abstract format organized a round-table discussion at the Geneva University Hospital to describe and discuss recent advances regarding NAVA. A representative of the company that commercializes the NAVA machine (Maquet Critical Care SA, Sölna, Sweden) was invited to attend the meeting in order to answer only technical questions. Maquet Critical Care SA agreed to sign a disclosure form before the meeting specifying that neither the minutes of the meeting nor the content of the report could be modified and/or used for commercial purposes. The main purpose of this meeting was for all of the investigators and participants to expose their standpoint and questions about NAVA, and to share the main results of their studies. Maquet

Critical Care SA agreed to provide financial support for organizing the meeting, as detailed at the end of the manuscript, but was not responsible for choosing participants and did not take any part in the writing of this report. We here describe the content of the round-table discussion, focusing on a selection of the most recent studies [19-33] (Table 1).

Main problems with conventional ventilation modalities in the ICU

Assisted modes generally aim at synchronizing the ventilator insufflation to the patient's effort, both to optimize comfort and to minimize the work of breathing. The price to pay for this strategy is a risk of patient-ventilator asynchrony, which can be defined as a mismatch between the patient's neural output and the ventilator's inspiratory and expiratory times [34-37]. Thille and colleagues reported that one-quarter of patients had high rates of asynchrony during assisted ventilation [34]. Frequent asynchrony is associated with a longer duration of MV [34,38].

Compelling evidence accumulated over the last decade also supports the use of tidal volume (V_T) values that are lower than those traditionally used. Lower V_T values than traditionally used have several main advantages: they diminish the risk of ventilator-induced lung injury [39-41]; they preserve spontaneous breathing by avoiding respiratory alkalosis, thus preventing diaphragmatic disuse atrophy associated with MV [42-48]; they diminish several types of patient-ventilator asynchrony [49]; and they may improve the efficiency of gas exchange [50]. Assisted modes of ventilation that maintain at least part of the patient's spontaneous breathing activity contribute to preventing these pulmonary and muscular complications.

The new challenge in developing ventilation strategies thus consists of minimizing the risk of lung injury, avoiding disuse atrophy of the diaphragm, and improving the match between the patient's needs and the assistance delivered by the ventilator [6]. New ventilation modes have been designed to meet this challenge [5], and NAVA is a pressure-assisted mode in which the pressure delivered by the ventilator is proportional to the electrical activity of the diaphragm recorded continuously through an esophageal probe [18]. NAVA theoretically delivers pressure proportional to the neural output of the patient's central respiratory command. During NAVA, however, reliable positioning of the catheter is mandatory in order to obtain a representative EAdi signal from the diaphragm. Barwing and colleagues have evaluated whether a formula based on the measurement from nose to ear lobe to xiphoid process of the sternum (the NEX distance) modified for the EAdi catheter (NEXmod) is adequate for predicting the accurate position of the esophageal probe [51]. They observed in 18 of 25 patients

Table 1. Main available clinical studies

Study	Diagnosis (number of patients)	Design	Duration	Major findings
Colombo and colleagues, 2008 [21]	Acute respiratory failure (unselected) (n = 14)	Crossover – PSV set to obtain V_T 6 to 8 ml/kg predicted body weight; NAVA vs. PSV increased or decreased by 50%. Effects of modification of assist level	20 minutes x3	NAVA averted the risk of overassistance and improved synchrony
Wu and colleagues, 2009 [19]	ARDS (n = 18)	PSV vs. NAVA – randomized study. Incremental PSV and NAVA run randomly in four steps. The PSV level was gradually increased by 5 cmH ₂ O every 5 minutes from 5 to 20 cmH ₂ O. Incremental NAVA was individually set in steps of 0.2 to 1.0 cmH ₂ O/ μ V every 5 minutes to determine the NAVA level providing an airway pressure in each step equivalent to that with PSV. Evaluation of patient–ventilator synchrony (trigger delay, ineffective effort); effect of assist level	5 minutes x4	Improved synchrony with NAVA
Brander and colleagues, 2009 [20]	Acute respiratory failure (unselected) (n = 15)	NAVA level increased progressively. Method for titrating the NAVA level	30 minutes + 3 hours	Progressive implementation of NAVA may be a method for determining the adequate level – downregulation of EAdi confirmed
Schmidt and colleagues, 2010 [23]	Mainly acute lung injury (n = 12)	Longitudinal observational study – PSV set to obtain V_T 6 to 8 ml/kg predicted body weight; NAVA vs. PSV with increasing assist. Breath-by-breath variability of flow and EAdi-related variables quantified by the coefficient of variation and autocorrelation analysis	10 minutes x4 = 40 minutes	NAVA increases breathing pattern variability
Coisel and colleagues, 2010 [27]	Postoperative patients (n = 15)	Crossover randomized – PSV set to obtain V_T 6 to 8 ml/kg predicted body weight; NAVA vs. PSV. Effects on breathing pattern, gas exchange, and variability of respiratory cycles (evaluated by coefficient of variation)	24 hours	Variability of tidal volume and minute ventilation were significantly higher with NAVA than with PSV. Variability of electrical diaphragmatic activity was significantly lower with NAVA than with PSV. Oxygenation increased during NAVA
Terzi and colleagues, 2010 [25]	ARDS (n = 11)	Crossover randomized – PSV set to obtain V_T 6 to 8 ml/kg predicted body weight; NAVA vs. PSV. Effect of neural trigger vs. flow trigger. Assist level was randomized to be 20%, 40%, or 60% over the basal level. Assessment of the physiological response to varying PSV and NAVA levels in selected ARDS patients and the effect of neural triggering	5 minutes x4 x3 = 60 minutes	Compared with PSV, NAVA limited the risk of overassistance, prevented patient–ventilator asynchrony, and improved overall patient–ventilator interactions. Compared with the pneumatic trigger, the neural trigger (from NAVA) considerably decreased patient–ventilator asynchrony
Spahija and colleagues, 2010 [22]	COPD (14)	Prospective, comparative crossover – PSV set to obtain V_T 6 to 8 ml/kg predicted body weight; NAVA vs. PSV. Patients were ventilated for 10-minute periods, using two PSV levels (lowest tolerable and 7 cmH ₂ O higher) and two NAVA levels (same peak pressures and external PEEP as with PSV), delivered in random order	10 minutes x2	NAVA improved patient–ventilator synchrony by reducing the triggering and cycling delays, especially at higher levels of assist, while preserving breathing and maintaining blood gas exchange
Paspath and colleagues, 2010 [28]	Unselected patients (n = 20)	Longitudinal observational study. Evaluation of effects of PEP on breathing pattern and neuroventilatory efficiency during NAVA. Adequate NAVA level was determined as the NAVA level early after the transition from an initial steep increase in Paw and V_T to a less steep increase or even plateau of Paw and V_T , as described by Brander and colleagues. PEEP was set at 20 cmH ₂ O then decreased to 1 cmH ₂ O. V_T /EAdi was evaluated as an indicator of neuroventilatory efficiency	20 minutes x3	During adequate-assist NAVA, increasing PEEP reduces respiratory drive. Patients adapt their neuroventilatory efficiency such that the individual ventilatory pattern is preserved over a wide range of PEEP levels. Monitoring V_T /EAdi during PEEP changes allows identification of a PEEP level at which tidal breathing occurs at minimal EAdi cost

Continued overleaf

Table 1. Continued

Study	Diagnosis (number of patients)	Design	Duration	Major findings
Piquilloud and colleagues, 2011 [26]	Unselected patients (n = 22; COPD n = 8/22)	Prospective interventional study – three consecutive periods of ventilation: PSV–NAVA–PSV, Airway pressure, flow, and transesophageal diaphragmatic electromyography were recorded continuously. To determine whether, compared with PSV, NAVA reduced trigger delay, inspiratory time excess, and the number of patient–ventilator asynchrony events	20 minutes x3	NAVA reduces trigger delay, improves expiratory synchrony (inspiratory time excess was reduced) and reduces total asynchrony events
Rozé and colleagues, 2011 [24]	Unselected patients (n = 15)	To determine the feasibility of daily titration of the NAVA level in relation to the maximal diaphragmatic electrical activity (EAdi _{max} , SBT) measured during a SBT during PSV. EAdi _{max} , SBT was determined daily during a SBT using PSV with 7 cmH ₂ O inspiratory pressure and no PEEP. If the SBT was unsuccessful, NAVA was used and the level was then adjusted to obtain an EAdi of 60% of the EAdi _{max} , SBT. Arterial blood gas analyses were performed 20 minutes after each change in NAVA level	Until extubation	Daily titration of NAVA level with an electrical goal of 60% EAdi _{max} , SBT is feasible and well tolerated

ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; EAdi, electrical activity of the diaphragm; NAVA, neurally adjusted ventilatory assist; Paw, airway pressure; PEEP, positive end-expiratory pressure; PEP, end-expiratory pressure; PSV, pressure-support ventilation; SBT, spontaneous breathing trial; V_T, tidal volume.

(72%) that at NEXmod the EAdi signal was suitable for running NAVA. The NAVA mode was possible at the optimal position in four patients – the optimal position being defined by checking three criteria: stable EAdi signals, electrical activity highlighted in central leads of the catheter positioning tool, and an absence of the p-wave in the distal lead. The authors thus concluded that positioning the EAdi catheter using NEXmod gives a good approximation in most of the patients.

Moreover, the body position, positive end-expiratory pressure (PEEP) and intra-abdominal pressure are factors known to influence the position of the diaphragm. Barwing and colleagues therefore enrolled 20 patients in order to evaluate the effects of these factors on catheter position [52]. They evaluated six different situations regarding the PEEP, body position and intra-abdominal pressure. Their results demonstrated that these factors may modify the EAdi catheter optimal position, although not compromising a stable signal due to the wide electrode array. One can therefore conclude that the optimal catheter position should be adjusted after major changes in ventilator settings, clinical condition or patient positioning.

Management of patient–ventilator synchrony

The time lag between the neural inspiratory input and the occurrence of a ventilator breath affects all steps of the respiratory cycle (initiation, insufflation, and cycling-off for expiration) [53]. Among the different forms of asynchrony, ineffective triggering (also known as wasted effort) is the most common during invasive MV. During noninvasive ventilation (NIV), leaks at the patient–ventilator interface impair the function of the pneumatic trigger and cycling system [54], thus promoting specific asynchronies (autotriggering and prolonged insufflation) [55].

Ineffective efforts are explained both by patients' characteristics and by ventilator settings. The presence of intrinsic PEEP increases the patient effort required to trigger the ventilator, thereby increasing the likelihood that the patient's inspiratory effort will fail to trigger a ventilator breath [36,53,56]. A weak inspiratory effort, which may occur during situations of low respiratory drive such as excessive ventilation, is also a risk factor and is common in patients receiving high assist levels [22] or sedation [38]. An excessive level of pressure support is also associated with prolonged insufflation, thus promoting hyperinflation and intrinsic PEEP. Reduction of ineffective efforts is often possible through a careful optimization of ventilator settings, at least in short-term studies. Reducing V_T during PSV can improve most factors contributing to ineffective efforts [49]. Thille and colleagues showed that wasted efforts could be decreased without increasing the patient's work of

breathing, with the main goal of decreasing the pressure-support level to obtain V_T values of about 6 ml/kg predicted body weight [49]. Because high pressure-support levels are associated with prolonged insufflation beyond the end of the patient's neural inspiratory time, another useful means of decreasing wasted efforts consists of adjusting the inspiratory time by increasing the flow threshold of the cycling criterion [49,57].

Neurally adjusted ventilatory assist and asynchrony

NAVA involves the transesophageal recording of diaphragmatic electrical activity using specifically designed technology to minimize measurement errors. The EAdi signal reliably monitors and controls the ventilatory assist [58]. During NAVA, the EAdi triggers the assist when the patient initiates an inspiratory effort – even during expiration with intrinsic PEEP – and a decrease in EAdi terminates the assist. NAVA does not therefore depend on measurements of airway pressure or flow and keeps the assist synchronous with the inspiratory efforts (independent of the presence of leaks or intrinsic PEEP) [19,21,22,25,29,59]. NAVA thus has two important features: the delivered pressure is, in theory, synchronous with the diaphragmatic activity, and the V_T is completely controlled by the output of the patient's respiratory control center [18].

A frequent form of minor patient–ventilator asynchrony is a long inspiratory trigger delay (time lag between the onset of neural inspiration, then the detection of a breath initiated by the patient and, finally, the onset of ventilator pressurization). Several factors may increase the inspiratory trigger delay during PSV, including the presence of intrinsic PEEP and suboptimal ventilator performance [60]. The cycling-off delay is the time difference between the end of the neural inspiratory ramp and the end of ventilator pressurization. Piquilloud and colleagues compared these delays and their consequences between NAVA and PSV in a group of 22 patients intubated for acute respiratory failure. The inspiratory trigger delay, the excess inspiratory time, and the frequency of patient–ventilator asynchrony were compared between the two modes [26]. Compared with PSV, NAVA substantially improved patient–ventilator synchrony by reducing the inspiratory trigger delay and the total number of asynchrony events, and by improving expiratory cycling-off.

Increasing the level of ventilatory assist with standard modes may expose the patient to potentially dangerous levels of volume and pressure, and to uncoupling between the patient's neural output and ventilator assistance. In contrast to PSV, there is good evidence that NAVA offers protection against excessive P_{aw} and V_T values because there is a downregulation of EAdi in response to increasing assistance levels: the net result is a decrease in the

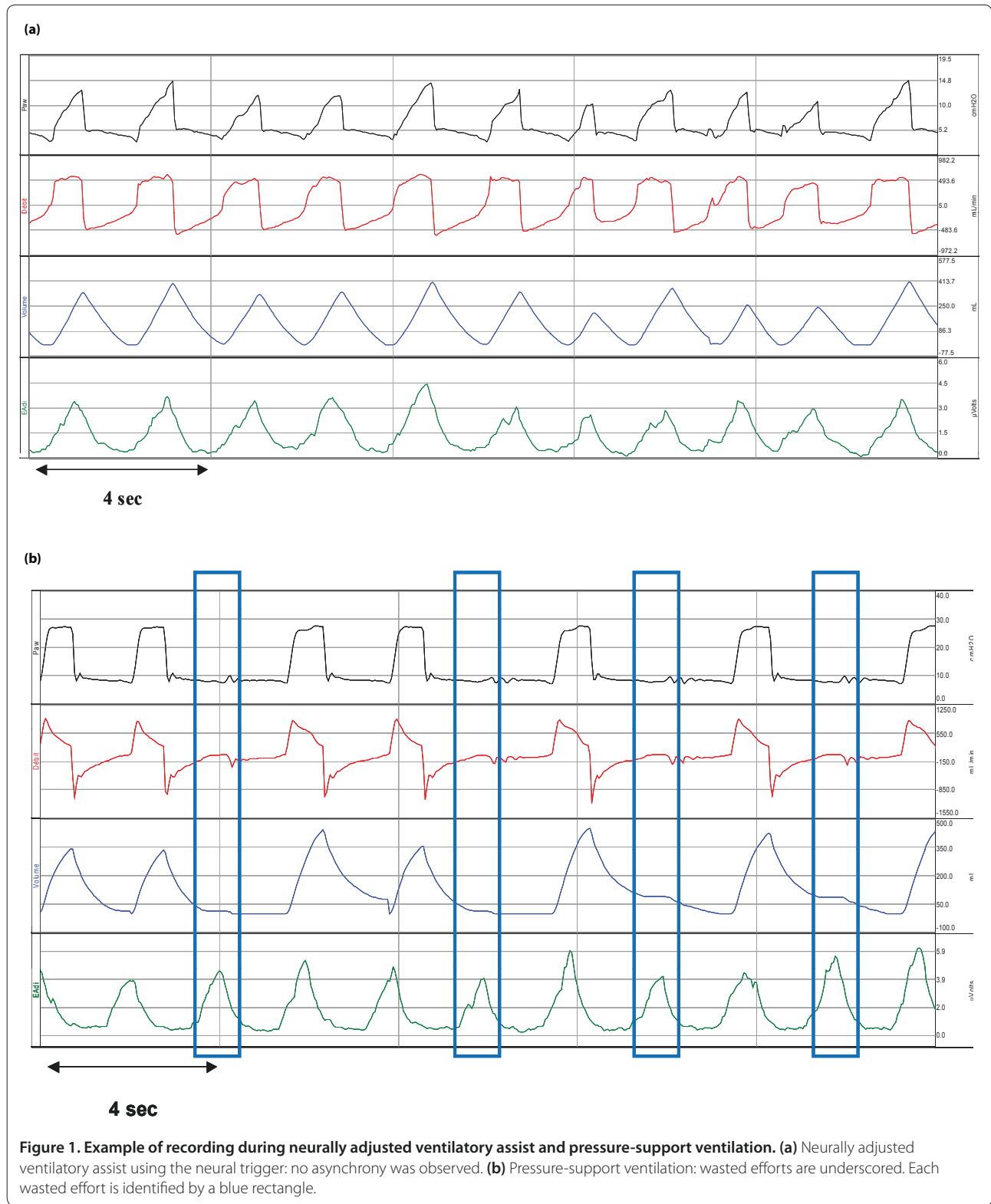
amount of assistance provided [20,21,61–63]. The absence of a V_T increase with increasing NAVA levels suggests that the Hering–Breuer reflex is operative [64], stopping the output from the respiratory control center at the same V_T level, irrespective of the NAVA level. Unloading of the respiratory muscles is always partial, as some level of spontaneous activity is maintained, and patient–ventilator synchrony is improved.

Several studies have evaluated the impact of increasing PSV levels versus NAVA levels using similar methods of setting the ventilator [20–22,25]. Inspiratory pressure support was titrated in order to obtain 6 to 8 ml/kg predicted body weight during active inspiration. During PSV, the ventilator function 'NAVA Preview' estimates the NAVA level that would achieve the same peak inspiratory pressure. All studies performed in the ICU consistently showed that NAVA, in contrast to PSV, averted the risk of overassistance when the assist level was increased gradually. NAVA also improved patient–ventilator synchrony, in contrast to PSV, regardless of the underlying diagnosis. Very high levels of NAVA, however, might result in unstable periodic breathing patterns with delivery of high tidal volume followed by periods of apnea and signs of discomfort [65]. To separate the effects of neural triggering and those of proportional assistance, Terzi and colleagues studied a selected population of patients recovering from acute respiratory distress syndrome, using NAVA with two inspiratory triggers: the EAdi signal and the inspiratory flow threshold used previously for PSV [25] (Figure 1a,b). Not only proportional assistance but also neural triggering improved patient–ventilator synchrony in these patients during the weaning process.

All of the available studies of NAVA in ICU patients have limitations regarding the clinical applicability of the results. Except for two studies [19,25], the patient population was heterogeneous in terms of the cause of respiratory failure. The evaluation time was relatively short in eight studies, but not for two studies [24,27].

Matching alveolar ventilation to metabolic demand: role for the neural controller – variability

Interestingly, and for reasons that are not yet fully understood, NAVA compared with PSV seemed to improve the partial pressure of oxygen in arterial blood in some studies independent of changes in the partial pressure of carbon dioxide in arterial blood (P_{aCO_2}) [25,27]. One hypothesis is that the continuous spontaneous inspiratory activity during NAVA improves the matching between ventilation and perfusion. Earlier studies had established that partial ventilatory support allowing some degree of spontaneous breathing activity using modes of ventilation other than NAVA improved the ventilation/perfusion relationship compared with



fully controlled MV [66]. In addition, NAVA allows a more natural breathing pattern characterized by greater variability, which may also contribute to improve gas exchange [67] (see below).

According to the principle of homeostasis, the closed loop that regulates PaCO₂ comprises: sensors (or detectors), which are chemoreceptors; a controller (or comparator), which is the central respiratory command; and

effectors, which are the respiratory muscles. Each component controls the next component in the loop, and the effectors change their activity (that is, adapt) to keep the PaCO₂ value relatively constant. In other words, EAdi and therefore the breathing pattern must adapt to a variety of conditions to maintain PaCO₂ within the normal range. Another regulatory mechanism is optimization of the work of breathing. For example, the rate and/or the depth of breathing can be adjusted to minimize the energy expenditure at a given respiratory effort and/or to minimize the stretch on the lungs.

Any strategy based on automated feedback control of ventilatory support should ideally require neural information on the lung volume, rate of lung volume change, and transpulmonary pressure, which are provided by mechanoreceptors in the lungs and chest wall. Finally, the variability and complexity of the breathing pattern are influenced by several factors, including the load–capacity relationship of the respiratory system [68–70], vagal afferent traffic to the brain [71], and the activity of the central pattern generators [72].

Ventilatory activity is nonlinear in nature and exhibits chaos-like mathematical complexity [72,73]. Variability is a mathematically complex notion, often expressed using the coefficient of variation, which is the ratio of the standard deviation over the mean. However, the complexity of flow and EAdi variability can also be described using noise titration, the largest Lyapunov exponent, Kolmogorov–Sinai entropy, and three-dimensional phase portraits [74,75]. Schmidt and colleagues used these methods to compare respiratory variability and complexity during PSV and NAVA [23]. Compared with PSV, NAVA increased breathing pattern variability and flow complexity without changing EAdi complexity. Accordingly, when the NAVA level was increased from zero to a high level in healthy individuals, they adapted their inspiratory activity to the NAVA level in order to control V_T and to regulate PaCO₂ over a broad range of NAVA settings [63]. In contrast, during high-level PSV, V_T became almost entirely determined by the ventilator and hypocapnia developed as previously shown in healthy subjects [76,77]. These differences between NAVA and PSV establish that with NAVA, even at a high level of assistance, V_T is not imposed by the ventilator but remains under the control of the patient's central respiratory command. NAVA therefore decreases the risk of over-assistance. The extent to which the preserved variability associated with NAVA is beneficial remains to be established. Whether variability restoration could be used to adapt NAVA settings also warrants further studies, as well as the development of specific tools for assessing variability at the bedside.

Patients with respiratory failure probably adjust their breathing activity to achieve the best compromise

between the muscular effort needed to breathe and the sensory cost of tolerating elevated PaCO₂ levels. NAVA acts as an additional external cost-free muscle controlled by the central respiratory command. NAVA therefore does not seem to alter the closed loop that controls the PaCO₂ and respiratory pattern optimization. Accordingly, when introducing NAVA in patients with respiratory failure, progressively increasing the NAVA level allows the PaCO₂ (that is, V_T) to improve to the optimal value. Further NAVA level increases then lead to respiratory effort adjustments aimed at maintaining this optimal PaCO₂ value, but do not change V_T [20].

Moreover, Karagiannidis and colleagues intended recently to evaluate the physiological effect of extracorporeal membrane oxygenation on the pattern of breathing in patients with severe lung failure treated with NAVA [78]. They demonstrated that a downregulation of extracorporeal exchange gas transfer caused an immediate upregulation of ventilation. Eucapnia under NAVA was preserved because the patients adjusted their minute ventilation to their needs. These interesting data highlighted once again that the ventilatory adaptation to maintain normocapnia remains under NAVA.

How can the optimal NAVA level be determined?

Determining the optimal NAVA level remains challenging, and several methods have been suggested. Contrary to PSV and as already described, NAVA generates V_T levels that can remain constant independent of the assist level once the patient's ventilation needs appear to be satisfied [20]. Consequently, NAVA settings cannot be adjusted based solely on V_T (and/or the corresponding PaCO₂ target).

Brander and colleagues tried to find the best NAVA level using breathing pattern analysis during a titration procedure [20]. Titration consisted of starting at a minimal assist level of around 3 cmH₂O and then increasing the NAVA level every 3 minutes in steps of 1 cmH₂O per arbitrary unit (the amount of microvolts recorded from the EAdi signal). The response in terms of V_T and Paw was biphasic. During the first phase, V_T and Paw increased while the esophageal pressure–time product (that is, inspiratory muscle effort) and EAdi decreased. Further increases in the NAVA level (second phase) did not significantly change Paw or V_T but continued to decrease the esophageal pressure–time product and EAdi. The first phase may thus indicate an insufficient NAVA level to supplement the patient's weak breathing effort, while the beginning of the second phase may correspond to the minimal assist level that satisfies the patient's respiratory demand. The optimal (or adequate) NAVA level may thus be indicated by the inflection point of the airway pressure trend graph during a stepwise increase in the NAVA level (Figure 2). In this

study the patients were ventilated with these settings for 3 hours without experiencing adverse hemodynamic or respiratory events [20]. Interestingly, the optimal NAVA level occurred at about 75% of the highest EAdi obtained with the minimal NAVA level and PEEP [20].

As suggested, titration of the NAVA level may be performed by systematically increasing the NAVA level to determine the optimal setting with regard to unloading patient's respiratory muscles [20,61,79]. During a recent observational study, transferring patients to NAVA was uneventful and the NAVA level contributed to adjustments of the preset NAVA level [80]. Interpretation of several interacting physiological parameters might be difficult in cases in which there is no marked decrease in EAdi during NAVA titration [80]. An automated approach enabled faster identification of the best NAVA level with a good accuracy [81].

Instead of stepwise titration, Rozé and colleagues tried to find the best NAVA level using an EAdi target of 60% of the highest EAdi value recorded during spontaneous breathing [24]. This measurement was reassessed daily using a spontaneous breathing trial with a pressure-support level of 7 cmH₂O and no PEEP. This method proved feasible and well tolerated until extubation (Figure 3). The 60% of the highest EAdi value threshold was based on a muscular rehabilitation protocol developed using data on diaphragmatic electromyogram activation during exercise [82]. Whether this approach is also optimal during assisted ventilation needs further evaluation. It is worth noting that EAdi measured during the daily spontaneous breathing trial increased steadily over time in all patients until successful extubation [24]. This improvement probably originated in multiple factors, including discontinuation of sedative agents and gradual restoration of the functional electrophysiologic activity of the diaphragm. Monitoring diaphragmatic activity may be of clinical interest and could be achieved using the NAVA electrode.

Using EAdi analysis to titrate NAVA is an interesting approach that could potentially be easier to use than the breathing pattern analysis method of Brander and colleagues (V_T change during titration) [20]. The EAdi target of 60% of the highest EAdi value with 7 cmH₂O of PSV proposed by Rozé and colleagues should be used cautiously [24], as Brander and colleagues found that the EAdi at the optimal NAVA level was equal to 75% of the highest EAdi value recorded with minimal NAVA (inspiratory P_{aw} above PEEP = 3 cmH₂O) [20]. Further studies are clearly needed to better determine the optimal EAdi target.

Noninvasive ventilation, sleep and NAVA

NIV is a specific clinical situation during which the occurrence of leaks may greatly affect patient-ventilator

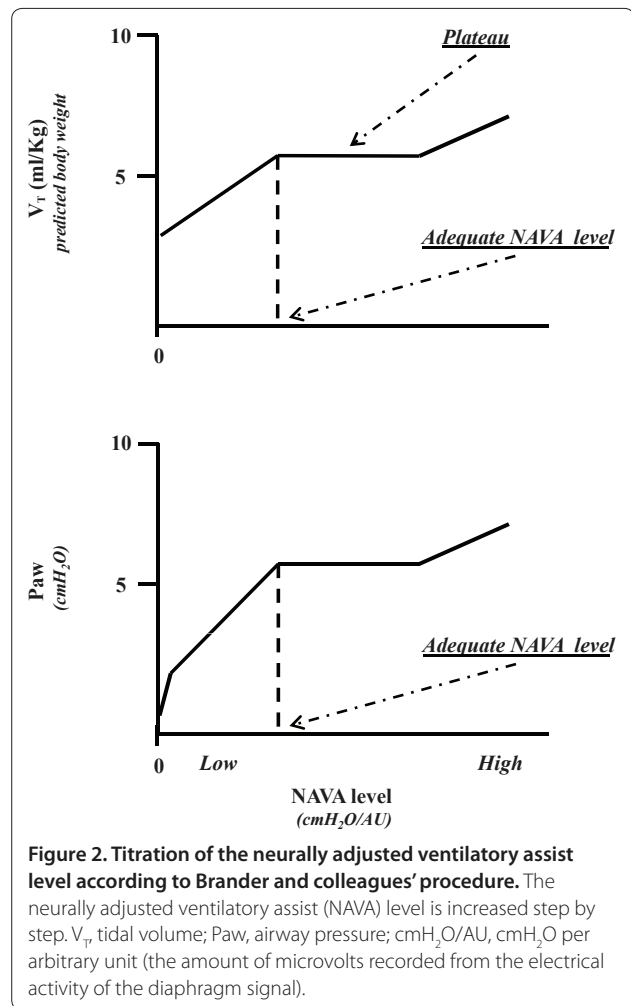
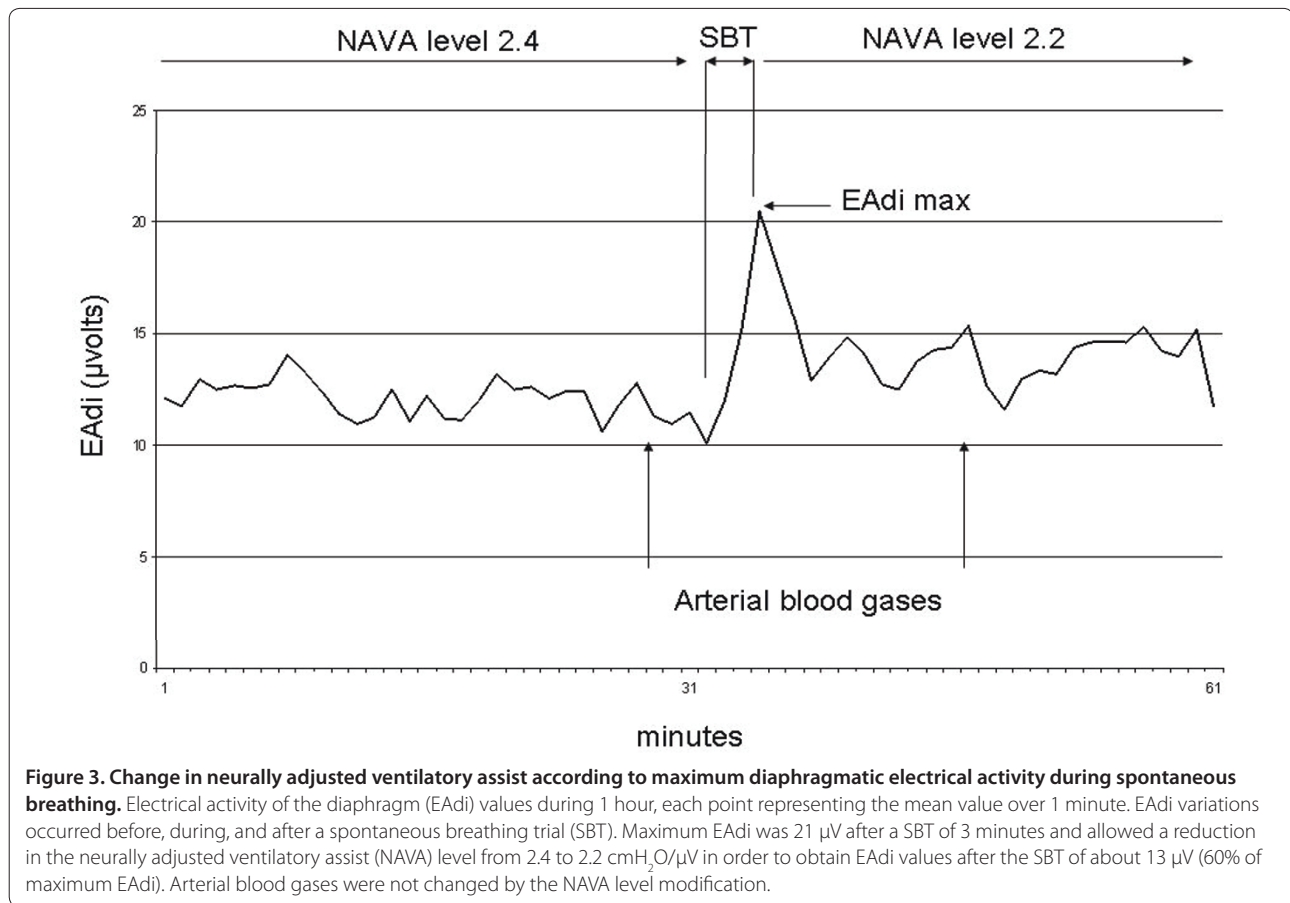


Figure 2. Titration of the neurally adjusted ventilatory assist level according to Brander and colleagues' procedure. The neurally adjusted ventilatory assist (NAVA) level is increased step by step. V_T , tidal volume; P_{aw} , airway pressure; cmH₂O/AU, cmH₂O per arbitrary unit (the amount of microvolts recorded from the electrical activity of the diaphragm signal).

interactions, thereby complicating the determination of optimal ventilator settings. In a study by Vignaux and colleagues, more than 40% of patients experienced various types of asynchrony during conventional NIV and the asynchrony rate correlated with the level of leakage [83]. With NAVA, assistance is delivered based on neural triggering, which is not affected by leakage. NAVA may thus, in theory, diminish asynchrony events, thereby improving the tolerance of NIV. New software for NIV has been developed using NAVA technology. With this specifically designed algorithm, NIV assistance is triggered and cycled-off by the neural diaphragmatic activity, which would be expected to improve patient-ventilator synchrony during NIV. This hypothesis has not yet been fully investigated.

A study of NIV-PSV with a helmet interface in healthy volunteers compared asynchrony with a neural trigger and a conventional pneumatic trigger [59]. Increasing PSV levels and respiratory rates applied with neural triggering and cycling-off produced significantly less impairment of synchrony, trigger effort, and breathing



comfort, compared with conventional pneumatic triggering and cycling-off.

Camarrotta and colleagues recently compared NAVA and NIV-PSV delivered through a helmet interface in postextubation hypoxemic patients [32]. Ten patients underwent three 20-minute trials of helmet NIV in PSV, NAVA, and PSV again. The authors demonstrated that there was less asynchrony during NAVA than during PSV and no difference in gas exchange, although there were more leaks during NAVA. Moreover it is important to underline that the PSV mode chosen was specifically dedicated to NIV, whereas the NAVA mode dedicated to NIV that is now currently available did not exist at the time of this study.

Recent data obtained in low-birth-weight infants indicate that NAVA can maintain synchrony – both in terms of timing and proportionality – even after extubation in patients with an excessively leaky interface under NIV (all infants in this study were ventilated using a single nasal prong) [29].

Another consideration for NIV that deserves attention in the near future is the impact on swallowing, phonation, and sleep quality, most notably when NIV is used for several days. Improvements in swallowing performance

have been reported in neuromuscular patients receiving MV compared with spontaneous breathing [84,85]. The close relationship between the muscles involved in swallowing and those contributing to inspiration was evidenced by Orlikowski and colleagues using an original method of tongue-strength measurement. The significant tongue weakness observed in 16 weak patients with Guillain-Barré syndrome correlated with the alterations in respiratory parameters [86]. Additional physiological studies are required to document the potential benefits of NAVA on swallowing-breathing interactions during NIV.

Sleep quality during NIV has been shown to be a predictor of success or failure [87]. Sleep quality can also be improved compared with standard NIV settings by careful physiological titration of the ventilator settings [88]. Patient-ventilator asynchrony can cause sleep disruption. Bosma and colleagues demonstrated that PAV, a mode of partial ventilatory support in which the ventilator applies pressure in proportion to the inspiratory load, was more effective than PSV in matching the ventilatory requirements to the level of ventilator assistance, thereby resulting in fewer patient-ventilator asynchronies and better quality of sleep [11]. Delisle and colleagues recently obtained sleep recordings during a

crossover study comparing NAVA and PSV in 14 mechanically ventilated patients [89]. Each condition was studied for 4 hours, and recordings were obtained over 19 consecutive hours in all. Patient–ventilator asynchrony varied significantly across sleep stages, and no asynchrony occurred with NAVA. Overassistance occurred only with PSV, which probably explained the improvements in physiological indices of sleep quality observed with NAVA.

Neurally adjusted ventilatory assist in children and infants

MV in children and in low-birth-weight infants is more difficult to apply than in adults and has several specificities. First infants take a very small tidal volume, have a rapid respiratory rate, have a limited chest wall musculature, and have variable and fluctuating lung compliance. Second, most neonatal units use uncuffed tracheal tubes for fears of pressure necrosis and air leak is always present, making reliable measurements and triggering problematic. Third, ventilators that are efficient in adults are not systematically efficient in children and infants, mainly because the inspiratory triggers are not sufficiently sensitive for early detection of infants'/children's inspiratory effort [90].

Whether or not the respiratory drive of the preterm infant is suitable to control MV is unknown. Beck and colleagues first evaluated patient–ventilator interaction with NAVA in seven very-low-birth-weight infants [29]. As suggested by previous animal studies [91], they demonstrated that NAVA could be implemented for a short-term period, both invasively and noninvasively, in infants with body weight as low as 640 g up to 3 years old. During invasive ventilation with NAVA, EAdi and ventilator pressure were correlated and patient–ventilator synchrony was improved compared with the other mode. Moreover, this synchrony persisted after extubation while ventilating the patient with an excessively leaky interface. After this first physiological demonstration, Bengtsson and Edberg demonstrated the clinical feasibility and safety with use of NAVA in pediatric patients [30]. Similarly, Breatnach and colleagues compared NAVA (with a neural trigger) and PSV (with a pneumatic trigger) in 16 ventilated infants [31]. This prospective crossover comparison demonstrated that ventilation with NAVA improved patient–ventilator synchrony.

Furthermore, Alander and colleagues recently compared NAVA with pressure-controlled ventilation for newborns and with pressure-regulated controlled ventilation for children older than 3 months (with conventional trigger modes: pressure and flow trigger) [92]. In this prospective cross-over study, 18 patients requiring MV were randomized for 10 minutes with the different modes. During NAVA, the peak airway pressure was lower, the

respiratory rate was 10 breaths/minute higher than in the pressure group, and patient–ventilator synchronization was improved. However, there were no differences in tidal volume and in oxygen saturation.

To evaluate the effects of the neural trigger on trigger delay, ventilator response time, or work of breathing, Clement and colleagues conducted a study in 23 pediatric patients aged 0 to 24 months with a diagnosis of bronchiolitis presenting respiratory failure requiring MV [33]. The authors compared the neural trigger and the pneumatic trigger using similar NAVA assistance, and observed that the trigger delay, the ventilator response time, and the work of breathing were reduced by the neural trigger.

Finally, all of these studies seem to demonstrate the feasibility of and a potential advantage for NAVA in children compared with the other assisted ventilatory modes. Because patient–ventilator synchrony is improved with NAVA, the children may require lower doses of sedation with this mode of MV [93], which could reduce the time of MV.

Future research

Clinical studies obtained in critically ill patients confirm many of the expected short-term physiological benefits associated with NAVA, as discussed above.

Particularly, NAVA seems to markedly improve the problems of nonsynchronization between the patient and the ventilator and the problems of risk of overventilation – including the risk of ineffective or missed inspiratory efforts due to intrinsic PEEP observed in chronic obstructive pulmonary disease patients, or to a rapid breathing frequency with a very small tidal volume observed in pediatric patients.

In addition, NAVA minimizes the risk of overinflation because the duration and level of pressurization remain under respiratory-center control, and minimizes the risk of diaphragmatic inactivity because the presence of pressure assistance requires the presence of this inspiratory activity.

A preserved respiratory muscle function is pivotal for weaning from MV [44]. By using NAVA, which outperforms the previous modes of MV for adequately assisting the patient's inspiratory effort without inducing patient/ventilator dyssynchrony, a reduction in the duration of MV could be expected. Studies are needed to evaluate the best time to begin the weaning process with NAVA.

The NAVA setting is an important question not yet fully resolved. If clinicians are accustomed to set a PSV level, this is not the case for NAVA. Furthermore, because the breathing pattern is less modified by the NAVA setting than during PSV, it is much less informative for NAVA adjustment. As described above, the literature

suggests that the adjustment should consider the electromyographic activity of the diaphragm, but this method is not simple. As recently proposed, a direct evaluation of patient comfort and sense of dyspnea for the NAVA setting should be evaluated [23].

Finally, the next research step will be to evaluate NAVA over longer periods, in order to know whether this mode can replace the modes usually used during MV and the weaning period, like PSV. Appreciating the safety, the feasibility and the constraints of this technology will be useful. It is therefore necessary to test, during the total weaning period, the effectiveness of the esophageal probe and to know whether it is regularly necessary to adjust the probe position. One of the most difficult questions to address, however, is in which situations it is not desirable to let the respiratory centers drive the ventilation. Situations of severe metabolic acidosis, of high respiratory drive and of high catecholamine levels may induce situations of extreme hyperventilation, which may be dangerous for the lungs. When sedation and/or paralysis become necessary is therefore an important question to address before widespread use of this mode [94].

Conclusion

NAVA, which is based on an original physiological concept, adds new knowledge on patient-ventilator interactions during spontaneous breathing, thus helping to unravel the complex mechanisms involved in breathing control during MV. There is compelling evidence that NAVA, as well as the PAV+ software, improves patient-ventilator interactions and increases respiratory variability in comparison with PSV. This advantage holds potential for many applications. The short-term and long-term experience with NAVA, however, remains scant. Further clinical studies are needed to assess the feasibility and safety of NAVA. A key challenge is how to determine the best NAVA settings according to the patient's ventilatory needs and the acceptable level of work of breathing.

Abbreviations

EAdi, electrical activity of the diaphragm; MV, mechanical ventilation; NAVA, neurally adjusted ventilatory assist; NEXmod, nose to ear lobe to xiphoid process of the sternum distance modified for the EAdi catheter; NIV, noninvasive ventilation; PaCO₂, partial pressure of carbon dioxide in arterial blood; PAV, proportional-assist ventilation; Paw, airway pressure; PEEP, positive end-expiratory pressure; PSV, pressure-support ventilation; V_T, tidal volume.

Competing interests

SJ received a grant from Maquet Critical Care SA in 2009 and 2010 for clinical research. PJ's research laboratory received grants from Maquet Critical Care SA Drager, Res-Med, Hamilton, for clinical research over the last 5 years. LB's research laboratory received a grant from Maquet Critical Care SA in 2009 and 2010 for clinical research. LB's research laboratory has also received research grants from Drager, Covidien, General Electric and Fisher Paykel over the last 5 years. J-CMR and AM received grants from Drager, Covidien, and General Electric over the last 5 years for their research group. AD's research laboratory received a grant from Maquet Critical Care SA in 2008 and 2009 for clinical research. AD coordinates a multicenter clinical study on NAVA. The remaining authors declare that they have no competing interests.

Author contributions

NT, J-CMR and LB initiated and wrote the manuscript; all authors contributed to the revision of this. All authors read and approved the final manuscript.

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