



Neurally adjusted ventilatory assist

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Purpose of review

Compared with the conventional forms of partial support, neurally adjusted ventilatory assist was repeatedly shown to improve patient–ventilator synchrony and reduce the risk of overassistance, while guaranteeing adequate inspiratory effort and gas exchange. A few animal studies also suggested the potential of neurally adjusted ventilatory assist in averting the risk of ventilator-induced lung injury. Recent work adds new information on the physiological effects of neurally adjusted ventilatory assist.

Recent findings

Compared with pressure support, neurally adjusted ventilatory assist has been shown to improve patient–ventilator interaction and synchrony in patients with the most challenging respiratory system mechanics, such as very low compliance consequent to severe acute respiratory distress syndrome and high resistance and air trapping due to chronic airflow obstruction; enhance redistribution of the ventilation in the dependent lung regions; avert the risk of patient–ventilator asynchrony due to sedation; avoid central apneas; limit the risk of high (injurious) tidal volumes in patients with acute respiratory distress syndrome of varied severity; and improve patient–ventilator interaction and synchrony during noninvasive ventilation, irrespective of the interface utilized.

Summary

Several studies nowadays prove the physiological benefits of neurally adjusted ventilatory assist, as opposed to the conventional modes of partial support. Whether these advantages translate into improvement of clinical outcomes remains to be determined.

Keywords

acute respiratory failure, mechanical ventilation, neurally adjusted ventilatory assist, noninvasive ventilation, patient–ventilator interaction

INTRODUCTION

First described in its general principles 15 years ago [1], neurally adjusted ventilatory assist (NAVA) is a mode of partial ventilatory assistance that has become commercially available in the last few years. With proportional assist ventilation (PAV), NAVA is the only mode of ventilation delivering assistance in proportion to a patient's demand [2]. Although with both PAV and NAVA the assistance remains under the patient's control, PAV utilizes 'conventional' pneumatic signals, such as flow and volume, whereas NAVA has the unique feature to control ventilator functioning through the electrical activity of the diaphragm (EAdi). In NAVA, in fact, the mechanical support is on-triggered and off-triggered by the EAdi, as assessed by transesophageal electromyography, and is proportional to EAdi throughout each inspiration [1]. The EAdi signal is obtained through a dedicated feeding tube, mounting a distal array of multiple electrodes, and processed to provide the highest possible quality of signal [1]. EAdi, expressed in microvolts, is multiplied by a user-controlled gain

factor, the NAVA level (NAVA_L), whose unit is cmH₂O/μV. The airway pressure applied by the ventilator depends on the magnitude of both EAdi and NAVA_L. For a given NAVA_L, the airway pressure varies breath-by-breath in proportion to EAdi, whose profile resembles as mirror image.

Since its introduction in clinical use, a growing number of studies investigating the effects of NAVA have been performed in animal models, healthy individuals, and adult and pediatric patients during both invasive and noninvasive ventilation (NIV) (Fig. 1). Because the studies dealing with pediatric

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KEY POINTS

- Neurally adjusted ventilatory assist (NAVA) is a proportional mode of ventilation in which the ventilator is driven and controlled by the electrical activity of the diaphragm rather than by the conventional pneumatic signals.
- Irrespective of the interface adopted and the cause of acute respiratory failure, NAVA guarantees adequate gas exchange and, compared with pressure support, improves patient–ventilator interaction, averts the risk of overassistance, and minimizes the occurrence of asynchronies.
- At increasing levels of assistance, as opposed to pressure support, NAVA results in minimal changes in breathing pattern and determines tidal volumes that frequently do not exceed 6 ml/kg and in general do not reach 8 ml/kg; also, compared with NAVA, tidal volume is more variable and ventilation more distributed in the dependent lung regions.
- NAVA has been repeatedly shown to offer several physiological advantages compared with the conventional forms of partial assistance. Whether these advantages translate in improvement of clinical outcomes remains to be assessed.

patients represent nowadays a consistent fraction of the overall published articles on NAVA, we prefer not to include them in the present review article, leaving the pediatric population to further dedicated work. Accordingly, the present review addresses the current knowledge on NAVA in adult intensive care unit (ICU) patients, either intubated or receiving NIV, focusing, in particular, on the most recent studies.

NEURALLY ADJUSTED VENTILATORY ASSIST IN INTUBATED PATIENTS

The effects of NAVA have been assessed with respect to several physiological outcomes.

Respiratory drive and effort

EAdi is the best (i.e., closest to respiratory centers) signal available for clinical assessment of the respiratory drive, and provides an estimate of the pressure generated by the principal inspiratory muscle [3]. As depicted in Fig. 2, during partial ventilatory assistance, EAdi is influenced by multiple factors, including the amount of assistance and sedation [4,5¹¹]. With NAVA and PAV, the mechanical support delivered by the ventilator is directly (NAVA) or indirectly (PAV) driven and regulated by the effort exerted by the respiratory muscles [2]; this does not

occur with the other assisted modes, in which the mechanical support is not affected by the patient's drive and effort.

When the assistance delivered is insufficiently low, regardless of the mode, the respiratory muscles are not efficiently unloaded and the drive remains high. When the assistance is high, the overall effect on drive and effort varies with the different forms of partial assistance. As indicated in Fig. 2, with NAVA and PAV increasing, ventilator assistance decreases drive, effort, and ventilatory output, which reduce in turn the ventilator support, thereby resetting the equilibrium between effort and assistance at a different point. With the other forms of partial assistance, conversely, an excessive support decreases the drive and makes respiratory muscle effort small, often just sufficient to trigger the ventilator and sometime even insufficient at that purpose [6,7]. In patients with acute respiratory failure (ARF) of different causes, NAVA has been demonstrated to efficiently unload the diaphragm [4,8,9,10¹¹]; differently from pressure support, however, the reduction of EAdi obtained with NAVA is contained and never excessive, and the risk of overassistance is therefore averted [4,8,11]. Stepwise increase of NAVA_L produces a progressive decrease in EAdi that was shown to be approximately 50% at the highest NAVA_L in a mixed population of patients with ARF [12].

EAdi, however, is not affected only by the amount of ventilator support. The output of the respiratory centers is also influenced, with respect to both drive and timing, by sedative administration, through either direct (respiratory centers) or indirect (cortical and limbic) effects (Fig. 2). As a consequence of the direct and tight relation between neural drive and delivered support, NAVA could, in principle, be more detrimentally affected by sedatives than pressure support, assist/control, and the other conventional forms of partial assistance. In a recent study [5¹¹], three levels of sedation (none, light, and deep), obtained by varying rates of propofol infusion, were evaluated and compared in ICU patients with ARF undergoing NAVA and pressure support administered at comparable levels of assistance. With both modes increasing, propofol infusion progressively decreased EAdi (drive) with no effect on the neural duty cycle (timing). Although gas exchange was not significantly different between the two modes, at deep sedation EAdi was lower in pressure support than in NAVA, which led to ineffective triggering in some patients with the former mode, but not with the latter [5¹¹]. Unpublished data presented in abstract form suggest different effects on drive and timing by varying doses of other sedatives.

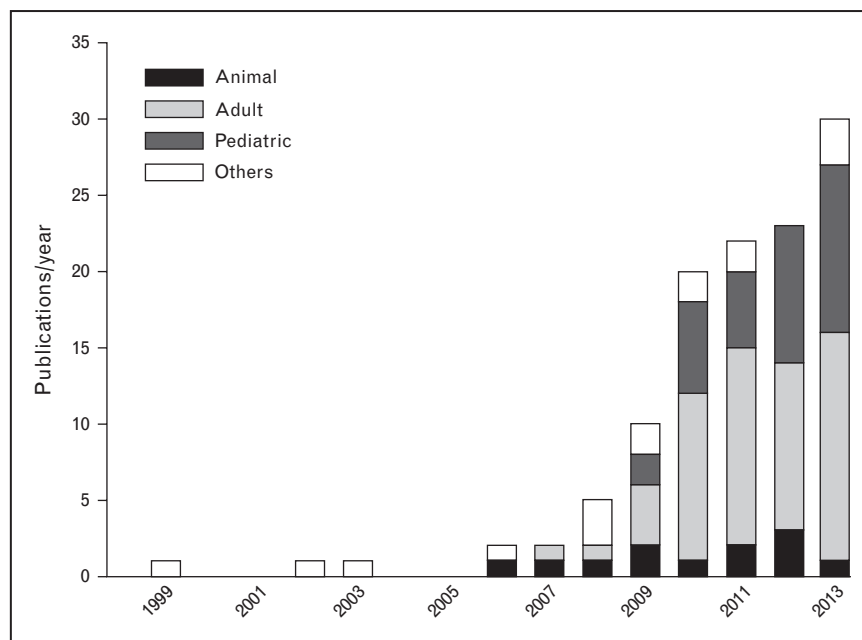


FIGURE 1. Publications on neurally adjusted ventilatory assist (NAVA) from 1999 to 2013. The studies related to NAVA yearly published from 1999 (first description of the technique) to 2013 are shown as a whole and divided according to the type of study: animal (black), adult (light gray) and pediatric patients (dark gray), and others (white), including reviews, editorials, and investigations on healthy individuals. After the introduction of NAVA in clinical use in 2008, the studies related to this mode progressively increased every year, either overall or considering the studies performed on adult and pediatric patients.

Breathing pattern and lung volumes

NAVA being driven by the patient's drive, concerns exist on the possibility of excessively high tidal volumes (V_T), not suited for protective ventilation strategies [13]. In an animal model of acute respiratory distress syndrome (ARDS), incrementing $NAVA_L$ reduced $EAdi$ with minimal changes in respiratory rate and V_T , which remained on average less than 4 ml/kg [14]. These results were subsequently confirmed in the same animal model: $EAdi$ was also reduced when increasing pressure support, but V_T significantly rose at increasing pressure support levels [15]. After injuring the lungs of 27 rabbits, Brander *et al.* [16] compared, at the same positive end-expiratory pressure (PEEP), NAVA and the low- V_T strategy (6 ml/kg) with injurious ventilation (15 ml/kg and no PEEP). Lung injury and nonpulmonary organ dysfunction were significantly lower in both groups, as opposed to injurious ventilation. In the NAVA group, V_T was 3.1 ± 0.9 ml/kg; compared with the conventional low V_T strategy, respiratory rate, arterial oxygen (PaO_2), and carbon dioxide ($PaCO_2$) partial pressures were higher, whereas lung wet-to-dry ratio and bronchoalveolar fluid and systemic biomarkers were similar between the two groups.

Differences in breathing pattern between NAVA and pressure support have been repeatedly shown in mechanically ventilated ICU patients

[4,8,11,17^{**},18,19^{*},20]. Colombo *et al.* [4] first demonstrated, in intubated patients with ARF of different causes, the breathing pattern to be differently affected when varying the amount of assistance with the two modes. Increasing the amount of assistance by 50% determined different rises in V_T , from 6.2 to 9.1 ml/kg in pressure support, whereas from 6.4 to 7.1 ml/kg in NAVA. Moreover, both spontaneous and mechanical respiratory rate and duty cycles decreased during pressure support, but not in NAVA. The ability of NAVA to maintain a reduced (protective) V_T was subsequently confirmed in patients with ARDS in the acute phase [21,22^{**}], in the most severe patients undergoing extracorporeal membrane oxygenation [17^{**},23], and during recovery [8]. The same was found in other patient populations such as postoperative [20] and chronic obstructive pulmonary disease [11]. Recently, in a mixed population of patients with ARF, Patroniti *et al.* [10^{*}] increased $NAVA_L$ (from 0.5 up to 5 $cmH_2O/\mu V$) and found that, on average, V_T did not exceed 6 ml/kg. In 30% of patients, nonetheless, at the highest $NAVA_L$, periodical delivery of elevated (>8 ml/kg) V_T was observed; in three patients, V_T exceeded 10 ml/kg.

In 10 patients with mild to moderate ARDS, Blankman *et al.* [22^{**}] evaluated the aeration of the dependent and nondependent lung regions by

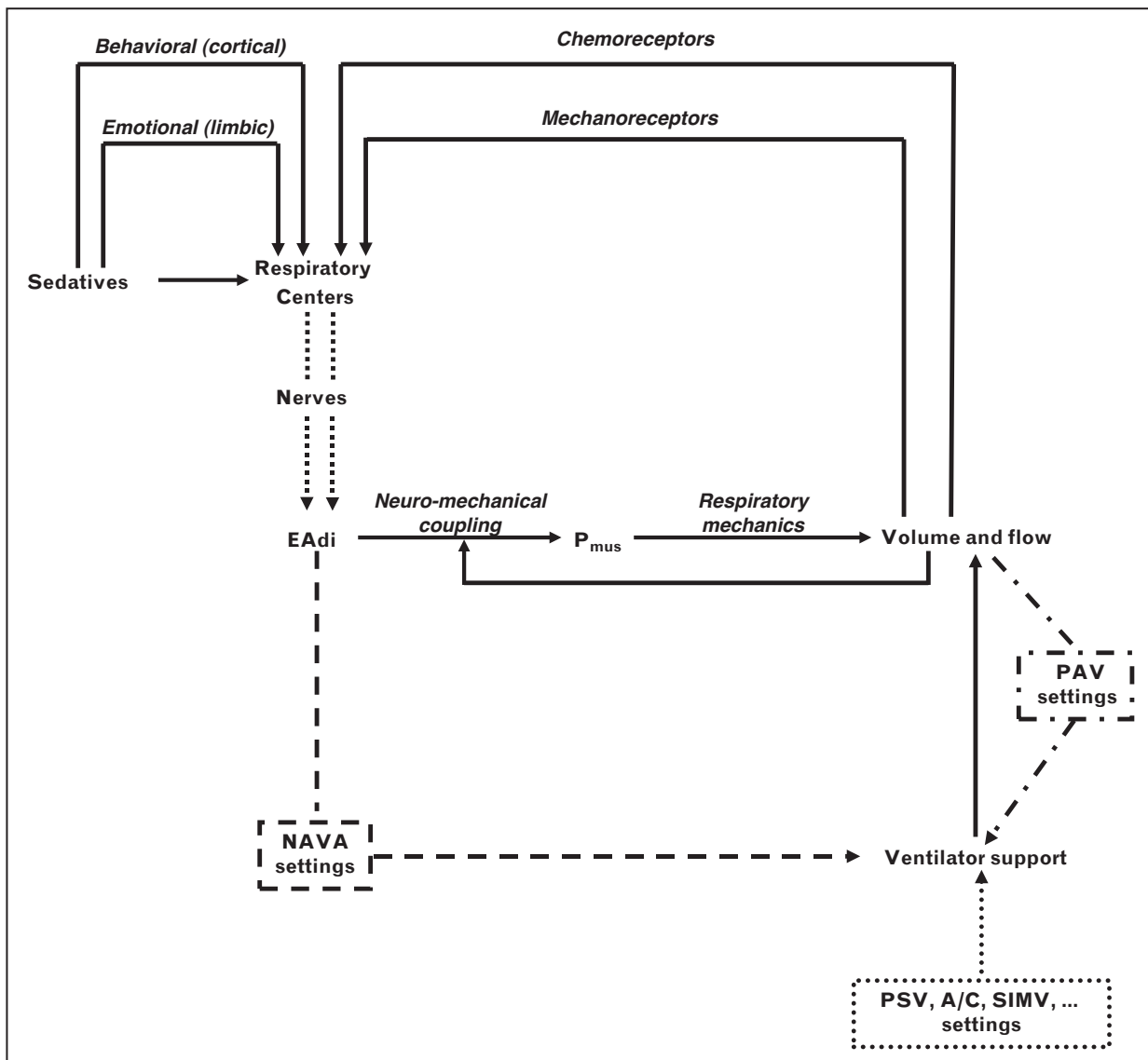


FIGURE 2. Relation between patient's demand and ventilator support with different modes of partial assistance. The figure depicts the composite interplay among respiratory drive, pressure generated by the respiratory muscles (P_{mus}), and ventilatory output (i.e., volume and flow) during partial ventilator assist with different modes of ventilation. The output of the respiratory centers is modulated by stimuli from mechanoreceptors and chemoreceptors, and the cortical or limbic system. Sedatives also affect, directly or indirectly, the output of the respiratory centers. The amount of assistance delivered by the ventilator with the conventional modes (single dotted line), such as pressure support (PSV), assist control (A/C), and synchronized intermittent mandatory ventilation (SIMV), is not influenced by either drive or effort or ventilator output, which exposes this mode to the risk of overassistance. In contrast, with the proportional modes, the delivered support is affected by patient's demand indirectly, by the ventilatory output in proportional assist ventilation (PAV) (dashed-dotted line), or directly, by the neural output of the respiratory centers, as obtained by the electrical activity of the diaphragm (EAdi), in neurally adjusted ventilatory assist (NAVA) (dashed line). With NAVA, moreover, a changed neuromechanical coupling, changes in respiratory mechanics, or air leaks may not disturb the relation between neural output and mechanical support. See text for further explanations. Modified with permission from [2].

means of electrical impedance tomography at varying levels of NAVA and pressure support. Although confirming with an analogous study design the reduced risk of overassistance with NAVA described by Colombo *et al.* [4], this study showed a beneficial

effect on the ventilation of the dependent lung region with NAVA, as opposed to pressure support.

Compared with pressure support, V_T variability was repeatedly found to be higher in NAVA [4,9,10^a], resembling the variability observed in

healthy individuals [24]. Conversely, EAdi variability was similar [9] or even higher [4,20] with pressure support than NAVA. Variability might improve oxygenation while reducing the proinflammatory response [25]. The preserved breathing pattern variability associated with the reduced risk of over-assistance in NAVA has been proposed to explain the absence of central apneas during weaning in nonsedated patients, as opposed to pressure support [26*].

Arterial blood gases

One of the primary reasons to institute mechanical ventilation is to improve arterial blood gases. Considering that NAVA is characterized by high V_T variability [4,9,20], shown in other settings to improve arterial oxygenation [25], and redistribution of the ventilation in the dependent lung regions [22**], an improvement in oxygenation would be somewhat expected. Most of the studies, nonetheless, report no differences in oxygenation between NAVA and pressure support [4,5**,8,9,11,17**,27]. These studies, however, were short term (the time of the experimental trial varying between 10 and 30 min), which may explain why no improvement in oxygenation was observed. The effects of both V_T variability and redistribution of ventilation are related to parenchymal recruitment, which takes time. Indeed, in the only study reporting an improvement in arterial oxygenation with NAVA [20], as compared with pressure support, the two modes were delivered for 24-h periods.

NAVA has been repeatedly shown to be as effective as pressure support in guaranteeing adequate values of P_{aCO_2} and pH [4,8,11,17**,20,27]. Vaschetto *et al.* [5**] found the P_{aCO_2} equally increased with NAVA and pressure support in patients receiving deep sedation by propofol.

Dyspnea

Surprisingly, no study has so far specifically evaluated in intubated patients the effects of NAVA on dyspnea, although Vaghegini *et al.* [28] used the Borg scale to determine comparable levels of pressure support and NAVA in patients with prolonged weaning.

Patient-ventilator synchrony

During partial ventilatory assistance, the ventilator is driven by the patient's spontaneous breathing activity. An optimal interaction between the patient and the ventilator, however, is not guaranteed. In particular, when patient effort and ventilator

support lack concurrence in time, asynchronies occur. Patient-ventilator asynchrony is increasingly recognized as a clinical problem. In fact, patients with a rate of asynchronous breaths exceeding 10% of the overall breath count are characterized by worsened outcome (i.e., longer durations of mechanical ventilation [29-31] and ICU stay [30,31], reduced number of ventilator-free days [31], higher rate of tracheotomy [30], and lower probabilities of survival [29] and home discharge [31]). It remains unclear whether asynchronies are just markers of changed respiratory function in the most severe patients, or rather cause themselves the increased morbidity by prolonging the duration of mechanical ventilation [32]. In the latter case, reducing the rate of asynchrony would determine an improvement of patients' outcomes. Visual inspection of the ventilator waveforms was shown inaccurate in detecting asynchronies, suggesting the use of an additional signal for recognizing their occurrence, such as EAdi or esophageal pressure [7].

Compared with conventional modes of ventilation, NAVA has been repeatedly demonstrated to improve the patient-ventilator synchrony in different clinical conditions [4,5**,8,17**,18,19*]. Incremental ventilator assistance affects the patient's effort during conventional modes, whereas NAVA limits EAdi reduction and the risk of excessively low efforts [4,8,11].

Mechanical properties of the respiratory system may also affect patient-ventilator synchrony. In patients with low respiratory system compliance, pressure support is characterized by a high incidence of premature cycling (i.e., the mechanical breath is shorter than the patient's inspiration) [33]. This was recently confirmed, irrespective of the cycling-off settings, in patients with severe ARDS breathing in pressure support while undergoing extracorporeal membrane oxygenation; in the same patients, NAVA was able to improve patient-ventilator synchrony to suboptimal level [17**]. Some premature cycling, autotriggering, and double triggering prevented an optimal patient-ventilator synchrony [17**]. Ineffective triggering and delayed cycling are common during pressure support in patients with airway obstruction, determining dynamic hyperinflation and auto-PEEP [34]. In pressure support, applying PEEP helps reduce ineffective efforts and varying the cycling-off setting to a higher flow threshold limits delayed cycling. Compared with pressure support, NAVA was shown to eliminate ineffective efforts and drastically decrease on-trigger and off-trigger delays, regardless of the level of assistance [11]. Consistently, in a mixed population including approximately 30% of patients with chronic obstructive pulmonary disease, Piquilloud

et al. [18] observed neither ineffective efforts nor delayed cycling during NAVA, although a few premature cycling and double triggering were detected. Recently, in a population with clinical suspicion of air trapping, Bellani *et al.* [19[■]] confirmed that NAVA is able to improve triggering performance at different levels of applied PEEP, in comparison with pressure support.

NONINVASIVE NEURALLY ADJUSTED VENTILATORY ASSIST

The use of NIV to avoid ARF deterioration and avert the need for endotracheal intubation and invasive ventilation has markedly increased [35,36]. NIV is delivered most commonly in pressure support mode using automated software for air-leak compensation. Recent work indicates rates of asynchrony as high as 40% during NIV [37].

Beck *et al.* [38] first described noninvasive NAVA in 2008 in an experimental animal model of ARDS; NAVA, delivered through a single nasal prong, efficiently unloaded the respiratory muscles [38]. At increasing level of assistance, in contrast to NIV delivered by conventional modes, NAVA has been shown to avoid glottis closure during inspiration in lambs [39].

Cammarota *et al.* [40[■]] compared NAVA with pressure support in patients with postextubation hypoxemic ARF receiving NIV through a helmet, a well tolerated interface often characterized by high rate of asynchronies [41]. Respiratory rate, EAdi, and blood gases were no different with the two modes. Compared with pressure support, however, NAVA reduced the inspiratory trigger delay, prolonged the time of inspiration during which the diaphragm was active and the ventilator was concurrently delivering assistance, and eliminated the asynchronies [40[■]].

These findings were subsequently confirmed to varying extent during NIV delivered by mask [42[■]–44[■]]. Piquilloud *et al.* [42[■]] compared pressure support and NAVA in delivering NIV via face mask in a series of patients with ARF or at risk of postextubation respiratory failure. They [42[■]] also found EAdi and arterial blood gases no different between the two modes, and the trigger delays and asynchronies significantly improved with NAVA, compared with pressure support.

In patients receiving postextubation prophylactic NIV, Schmidt *et al.* [43[■]] delivered both pressure support and NAVA either with or without automatic air-leak compensation. No differences in breathing pattern and EAdi were found among the four tested combinations; regardless of the algorithm for air-leak compensation, NAVA reduced the delays and

improved synchrony, as opposed to pressure support [43[■]]. Noteworthy, the NIV algorithm significantly reduced the incidence of asynchronous events during pressure support, but not with NAVA [43[■]]. Comfort and dyspnea, as assessed by a Visual Analogue Scale, were no different among conditions [43[■]]. A further study in a population of patients with ARF of varying cause [44[■]] confirmed similar breathing pattern and improved patient–ventilator interaction and synchrony in NAVA, compared with pressure support.

CONCLUSION

NAVA is a novel form of proportional assistance offering several physiological advantages, compared with the conventional modes of partial support, during either invasive ventilation or NIV. In particular, NAVA improves patient–ventilator interaction, averting the risk of overassistance and limiting the occurrence of asynchronies. Whether these physiological improvements translate into clinical benefits remains to be determined by randomized trials assessing clinical outcomes.

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Conflicts of interest

Paolo Navalesi contributed to the development of a new interface for noninvasive ventilation (not mentioned in the present work), whose license for patent belongs to Intersurgical S.p.A., and receives royalties for that invention. His research laboratory has received equipment and grants from Maquet Critical Care and Intersurgical S.p.A. He also received honoraria/speaking fees from Maquet Critical Care, Covidien AG, Breas, Hill-Rom, and Linde AG. Federico Longhini has no conflict of interest to declare.

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- of outstanding interest

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- This study confirms in patients receiving NIV through a facial mask that NAVA improves the patient–ventilator interaction and synchrony and results in similar values of arterial blood gases and diaphragm electrical activity, as compared with pressure support.