New modes of mechanical ventilation: proportional assist ventilation, neurally adjusted ventilatory assist, and fractal ventilation
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Increased knowledge of the mechanisms that determine respiratory failure has led to the development of new technologies aimed at improving ventilatory treatment. Proportional assist ventilation and neurally adjusted ventilatory assist have been designed with the goal of improving patient–ventilator interaction by matching the ventilator support with the neural output of the respiratory centers. With proportional assist ventilation, the support is continuously readjusted in proportion to the predicted inspiratory effort. Neurally adjusted ventilatory assist is an experimental mode in which the assistance is delivered in proportion to the electrical activity of the diaphragm, assessed by means of an esophageal electrode. Biologically variable (or fractal) ventilation is a new, volume-targeted, controlled ventilation mode aimed at improving oxygenation; it incorporates the breath-to-breath variability that characterizes a natural breathing pattern.

Keywords
mechanical ventilation, patient–ventilator interaction, alveolar recruitment, neuromechanical coupling, breath-to-breath variability


In the last two decades, ventilator manufacturers have proposed several “new” modes of mechanical ventilation, which have been carefully investigated by ICU researchers [1]. Some of these became popular and widely used in clinical practice, whereas others, despite encouraging preliminary results, often did not reach enough popularity to have a clinical role. Surprisingly, quite often these “unsuccessful” modes produced a large number of studies that more often than not exceeded the number of ICU patients actually treated. Nevertheless, because the main reason to admit a patient to the ICU is to provide him or her with ventilatory assistance, the continuous recognition of previously neglected physiologic aspects and advancements in the knowledge of disease mechanisms are still leading to the development of novel technologies aimed at improving the outcome of patients receiving ventilatory treatment in the ICU.

Mechanical ventilation is essentially instituted to buy time, allowing the patient to recover from the underlying disease causing respiratory failure. The main difference between modes is essentially the manner in which positive pressure is applied to the airway, and, therefore, a “new” mode generally introduces a novel approach to support delivery [2]. Controlled modes of mechanical ventilation are often needed in patients with severe acute hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS). In this case, the principal purpose of a new mode is to improve oxygenation without further damaging the lung. When a controlled mode is not necessary, forms of partial ventilatory assistance are preferred, in which the delivery of mechanical support is triggered by the patient’s own spontaneous breathing [3]. Accordingly, with these modes, the main objective is to enhance the coordination between the patient’s own spontaneous breathing and mechanical assistance [3].

Matching mechanical support with patient demand to improve patient–ventilator interaction: proportional assist ventilation and neurally adjusted ventilatory assist
Forms of partial ventilatory assistance have been developed to avoid some of the adverse effects related to controlled mechanical ventilation, such as excessive ventilation [4,5], use of sedatives and muscle relaxants [6], and muscle atrophy resulting from disuse [7]. With these modes, the ventilator interacts with the patient to as-
sume part of the work of breathing. Our understanding of the complexity of the interplay between patient and ventilator has increased remarkably over the past decade. Unfortunately, however, several studies showed that the ability to coordinate patient effort and ventilator operation is often limited, and mechanical ventilation may paradoxically result in an increased energy expenditure of the respiratory muscle [8–11].

On-and-off cycling, the amount, and the intrabreath profile of the positive pressure delivered are the major determinants of patient–ventilator interaction during partial support [3]. With pressure support ventilation (PSV) and assist–control ventilation, positive pressure is delivered by the ventilator as a consequence of the patient’s respiratory effort; however, an increased patient demand does not correspond to an increase in airway pressure. Paradoxically, in volume-preset assist–control ventilation, the increased intensity of muscle effort results in a reduced amount of assistance delivered. A challenging approach to the improvement of patient–ventilator interaction would be to match ventilatory support with the neural output of the respiratory centers [12] so that the patient receives more assistance when demand is high and less assistance when demand is low. Two strategies, proportional assist ventilation (PAV) [13] and a new experimental mode of mechanical ventilation, neurally adjusted ventilatory assist (NAVA) [14], attempt to achieve this goal.

Proportional assist ventilation

During partial support, the pressure applied to the respiratory system (PRS) is contributed by the pressure produced by the respiratory muscles (PMUS) and the ventilator (PAW), the latter of which represents the amount of assistance delivered.

$$\text{PRS} = \text{PMUS} + \text{PAW}$$

The load imposed on the respiratory muscles during assisted ventilation can be described by the equation of motion as follows:

$$\text{PMUS} = R \times \dot{V} + E \times V_T + \text{PEEPi} - \text{PAW}$$

where $\dot{V}$ is flow, $V_T$ indicates volume displacement, $R$ is respiratory system resistance, $E$ is respiratory system elastance, and PEEPi is the end-expiratory elastic recoil pressure, which the respiratory muscles must overcome at the onset of inspiration to trigger the ventilator. During PAV, the ventilator instantaneously delivers positive pressure throughout inspiration in proportion to patient-generated flow (flow assist, units cm H$_2$O/L/s) and volume (volume assist, units cm H$_2$O/L). The pressure applied by the ventilator (PAW) therefore is

$$\text{PAW} = FA \times \dot{V} + VA \times V_T$$

Consequently, with PAV, an augmented ventilatory output resulting from an increased effort would correspond to increased support applied by the ventilator: the more the patient requests, the more the ventilator delivers. Unlike other assistance techniques, flow, volume, and airway pressure are not preset. PAV has been shown to be effective in unloading the respiratory muscles [15–18] without imposing a fixed breathing pattern [19] and in enhancing patient comfort [20] and patient–ventilator interaction [21]. Two recent, randomized clinical trials have demonstrated improved patient comfort during noninvasive ventilation with PAV compared with PSV [22•,23••].

Despite these positive results, PAV still seems to be more of an intellectually satisfying research tool than a ventilatory treatment in the clinical setting. Why? A number of theoretical (Fig. 1A) and practical [24] limitations hinder the use of PAV. It has been repeatedly suggested that proper adjustments of PAV settings require knowledge of the mechanical characteristics of the respiratory system [3,15,25]. This information is not easy to obtain in patients receiving partial support. To overcome this problem, some investigators have proposed noninvasive measuring techniques to continuously assess resistance and elastance and modify flow assist and volume assist settings accordingly [26,27•,28•]; however, these techniques are not yet available for clinical use and need to be further and more extensively validated. Furthermore, the PAV algorithm, based on the equation of motion, assumes resistance and elastance to be linear within the tidal breathing range, an assumption that may not always be valid in ICU patients. Moreover, variations in end-expiratory lung volume between breaths affect the transformation of respiratory muscle activation into mechanical output (PMUS); this transformation is referred to as neuromechanical coupling [29]. Other factors altering muscle contractility [30], such as fatigue, electrolyte [31] and acid–base [32] disorders, and shock [33], may also determine neuromechanical uncoupling. In practice, in the presence of weakness of the respiratory muscles and neuromechanical uncoupling, a given activation corresponds to a decreased PMUS.

A good patient–ventilator interaction implies that the onset and end of the patient’s neural inspiration are properly detected, and that the mechanical assistance is delivered in synchrony with the patient’s effort [34]. The manner in which the ventilator support is triggered during PAV is not different from that of other “conventional” modes of partial support because it operates with the same methodology based on airway pressure, flow, or both. The ability to trigger the ventilator is impaired by
the presence of PEEPi, which constitutes a threshold load that the patient has to overcome before the preset negative airway pressure and/or inspiratory flow are generated [35,36]. The effects of PEEPi may be offset by applying extrinsic positive end-expiratory pressure (PEEP), which reduces the patient’s effort and the trigger delay [17]. Nevertheless, determining PEEPi is an invasive and complex measurement in patients with an active inspiration [37,38], and, therefore, it is not usually performed in the clinical setting. When the externally applied PEEP exceeds PEEPi, the additional work resulting from this threshold load can be decreased to a large extent or even entirely abolished; however, this approach is a source of further hyperinflation, which worsens diaphragm weakness [39], hemodynamics [40,41], and gas exchange [41]. Conversely, a PEEP lower than PEEPi produces only limited improvements [42].

With respect to cycling off, the algorithm on which PAV is based represents an improvement compared with the previous modes because the end of the mechanical assistance is related to the decay of flow and volume, which are generated by the patient’s inspiratory effort. However, investigators recently have questioned this assumption, suggesting that as a result of a control system delay and in relation to the respiratory time constant and volume assist/flow assist settings, a delay between neural and mechanical inspiration may actually take place [43••]. Younes et al. [44••] recently found that the compensatory response to delays in opening the exhalation valve was weak, and that the prolongation of the mechanical inflation into the neural expiration worsened dynamic hyperinflation and caused ineffective inspiratory efforts.

Finally, the relation between ventilatory output (volume and flow) and mechanical support (volume assist and flow assist) represents a positive feedback that is unstable in nature. When the preset volume assist value exceeds the actual elastance, the elastic recoil of the respiratory system does not overcome the positive airway...
Neurally adjusted ventilatory assist

Neurally adjusted ventilatory assist was developed in an attempt to overcome the limitations of PAV while maintaining all of its potential advantages (Fig. 1B). The electrical activity of the inspiratory muscles can be used as an index of the inspiratory neural drive [45]. Detection and quantification of the electrical activity of the crural diaphragm (EAdi) by means of an esophageal array of bipolar electrodes has been recently validated in humans [46–49]. Crural EAdi has been shown to accurately express global diaphragm activation in healthy subjects [29] and in patients with either chronic [49] or acute respiratory failure [50••]. Compared with skin surface electrodes, esophageal electrodes are not affected by the activity of postural and expiratory muscles (cross-talk) and by the subcutaneous layers. The array of bipolar electrodes can be mounted on a feeding tube, which is routinely introduced in critically ill patients. For accurate measurement purposes, the active region of the diaphragm is determined by cross-correlating the signals obtained along the electrode array [47]. To enhance the signal-to-noise ratio [48], signal segments with residual disturbances, such as cardiac electric activity, are detected and replaced by the previously measured values [49]. The processed signal is then transferred to the ventilator unit to regulate the ventilatory support, which is therefore instantaneously applied in relation to EAdi (Fig. 2) [14]. In this manner, cycling on, cycling off, and the intrabreath assist profile are determined directly by the EAdi, whereas the amount of assistance for a given EAdi depends on a user-controlled gain factor. Because the ventilator is triggered directly by EAdi, with NAVA, the synchrony between neural and mechanical inspiratory time is guaranteed both at the onset and at the end of inspiration, regardless of PEEPi, air leaks, and respiratory mechanics.

As long as the respiratory centers, phrenic nerves, and neuromuscular junctions are intact and the ventilatory drive is not suppressed by drugs, the amount of support provided should instantaneously correspond to the ventilatory demand, irrespective of variations in muscle length or contractility [14]. A recent preliminary study has shown that in healthy individuals performing inspiratory capacity maneuvers, NAVA can almost abolish transdiaphragmatic pressure swings while maintaining synchrony between inspiratory neural effort and ventilatory assist [51]. Indeed, the use of neural control of mechanical ventilation has the capability to dramatically enhance the coordination between mechanical ventilation and respiratory muscle activity, thereby improving patient comfort. Nevertheless, it should be kept in mind that, despite this tremendous potential, currently NAVA is not available for clinical use and serves only as a research tool that has been used primarily in healthy subjects for short-term studies by only a few investigators. The effects of this mode on breathing pattern and gas exchange have yet to be evaluated, and it remains to be determined whether NAVA can maintain adequate levels of support in different kinds of respiratory failure from admission to weaning.

Introducing breath-to-breath variability during controlled mechanical ventilation to improve oxygenation: biologically variable or fractal ventilation

Our increased knowledge of the mechanisms that cause gas exchange impairment in patients with ARDS has led to investigations of the impact of different ventilatory strategies on oxygenation, lung mechanics, and outcome [52,53]. In particular, it has been recognized how the choice of ventilatory treatment may minimize the risk of further lung damage [52,53]. Although controlled modes of mechanical ventilation are often needed to treat patients with severe ARDS, they may be responsible for alveolar collapse, increased shunt fraction, and deterioration in arterial oxygenation, even in healthy subjects during prolonged general anesthesia [54]. It has been hypothesized that the loss of the physiologic variability of the breathing pattern may contribute to the deterioration in respiratory mechanics and gas exchange observed over time with controlled mechanical ventilation [55].

Biologically variable (or fractal) ventilation

Biologically variable ventilation (BVV) is a new mode that mimics spontaneous breath-to-breath variability, incorporating natural variable noise into a volume-targeted, controlled mode. The ventilator is programmed to modulate respiratory rate and tidal volume while maintaining a fixed minute ventilation based on a previously generated data file (Fig. 3) [55]. Recruitment is a continuous and progressive phenomenon that depends not only on PEEP but also on the inflation volume [56–60]. The rationale behind BVV is based on the concept that the alveolar recruitment achieved by high volumes exceeds the derecruitment caused by small volumes, with the net result being an improvement in lung compliance and oxygenation without an increase in mean airway pressure [61,62].

Biologically variable ventilation has been compared with conventional controlled ventilation in a series of animal
studies. BVV significantly improved oxygenation in healthy animals during general anesthesia [63], after re-expansion of a collapsed lung [64], and in oleic acid models of ARDS, with [65] and without [55] PEEP. Boker et al. [66••] also compared the low tidal volume ARDS Network [53] protocol with BVV in a porcine model of ARDS and found a decreased concentration of proinflammatory cytokines in the tracheal aspirate in the animals receiving BVV, which corresponded to improved oxygenation and decreased shunt fraction. Because BVV variability results in periodic deep inflations, and the mere application of periodic sighs has also been shown to provide beneficial effects [56,67••], Mutch et al. [64] compared these two strategies and found BVV to be more effective than periodic sighs of the same magnitude and frequency as the higher BVV tidal volumes.

Notwithstanding the impressive amount of results accumulated, it is important to note that no human study has been conducted yet. The dissimilarities between different animal species suggest that the effects observed in animals should be carefully extrapolated to humans. Indeed, Nam et al. [68] failed to reproduce positive results in a canine model of oleic acid–induced ARDS. Moreover, it is not clear whether conditions of different severity or sustained by diverse origins would respond to this ventilatory approach in a similar manner. For instance, according to the model proposed by Suki et al.
[62], the positive effects of BVV should be strictly related
to a nonlinear pressure–volume curve. Finally, in theory,
the benefits of introducing random noise into mechanical
ventilation should be correlated with a specific range of
variability [61,62]. This prediction has been recently
confirmed by Arold et al. [69••], who found different
responses depending on the amount of incorporated vari-
ability, with the most valuable results being obtained
when the tidal volume was varied by 40% and 60% of its
mean value.

The results obtained in animal models of ARDS strongly
support the validity of the mathematical model that as-
sumes a positive effect of adding random breath-to-
breath variability to mechanical ventilation. Whether
these results may be extrapolated to patients with ARDS
and their eventual impact on clinical outcome variables
need to be demonstrated before BVV can be considered
a valuable additional ventilatory strategy in the ICU.

Conclusions
Proportional assist ventilation and NAVA are forms of
partial ventilatory support designed to amplify the pa-
tient’s own respiratory effort, without imposing a fixed
breathing pattern. BVV is a mode of controlled mechan-
cal ventilation that mimics breath-to-breath variability.
Compared with the conventional modes, although in-
tended for different aims, PAV, NAVA, and BVV all
move toward a more physiologic approach to mechanical
ventilation.

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References and recommended reading
Papers of particular interest, published within the annual period of review,
have been highlighted as:
• Of special interest
** Of outstanding interest
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Twelve patients with chronic obstructive pulmonary disease with acute respiratory failure were randomized to receive mechanical ventilation with proportional assist ventilation (PAV) or pressure support ventilation (PSV). PAV was associated with significantly improved hemodynamic variables and lower ICU mortality compared to PSV. The authors concluded that PAV may be a more effective mode of mechanical ventilation for patients with chronic obstructive pulmonary disease as it may improve respiratory muscle function and reduce the work of breathing.

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In this animal study, BVV improved oxygenation and decreased the concentration of cytokines in the tracheal aspirate compared with volume-targeted, controlled mechanical ventilation delivered according to the ARDS Network protocol.


This study shows that the positive effects of fractal ventilation depend on the amount of incorporated variability, with the best results being obtained at 40% and 60% of the mean tidal volume values.