Neurally Adjusted Ventilatory Assist Increases Respiratory Variability and Complexity in Acute Respiratory Failure

Matthieu Schmidt, M.D.,* Alexandre Demoule, M.D., Ph.D.,† Christophe Cracco, M.D.,‡ Alexandre Gharbi, M.Sc.,§ Marie-Noëlle Fiamma, Ph.D.,¶ Christian Straus, M.D., Ph.D.,# Alexandre Duguet, M.D., Ph.D.,** Stewart B. Gottfried, M.D.,†† Thomas Similowski, M.D., Ph.D.**

ABSTRACT

Background: Neurally adjusted ventilatory assist (NAVA) is a partial ventilatory support mode where positive pressure is provided in relation to diaphragmatic electrical activity (EAdi). Central inspiratory activity is normally not monotonous, but it demonstrates short-term variability and complexity. The authors reasoned that NAVA should produce a more "natural" or variable breathing pattern than other modes. This study compared respiratory variability and complexity during pressure support ventilation (PSV) and NAVA.

Methods: Flow and EAdi were recorded during routine PSV (tidal volume ~6–8 ml/kg) and four NAVA levels (1–4 cm H₂O/µVEAdi) in 12 intubated patients. Breath-by-breath variability of flow and EAdi-related variables was quantified by the coefficient of variation (CV) and autocorrelation analysis. Complexity of flow and EAdi was described using noise filtration, largest Lyapunov exponent, Kolmogorov-Sinai entropy, and three-dimensional phase portraits.

Results: Switching from PSV to NAVA increased the CV and decreased the autocorrelation for most flow-related variables in a dose-dependent manner (P < 0.05, partial χ² for the CV of mean inspiratory flow 0.642). The changes were less marked for EAdi. A positive noise limit was consistently found for flow and EAdi. Largest Lyapunov exponent and Kolmogorov-Sinai entropy for flow were greater during NAVA than PSV and increased with NAVA level (P < 0.05, partial χ² 0.334 and 0.312, respectively). Largest Lyapunov exponent and Kolmogorov-Sinai entropy for EAdi were not influenced by ventilator mode.

Conclusions: Compared with PSV, NAVA increases the breathing pattern variability and complexity of flow, whereas the complexity of EAdi is unchanged. Whether this improves clinical outcomes remains to be determined.

What We Already Know about This Topic

❖ Normal ventilation varies considerably from breath to breath, but this is lost with traditional positive pressure ventilation
❖ Neuromuscular activated ventilatory assist (NAVA) uses diaphragmatic electromyography to trigger ventilation in a more natural manner

What This Article Tells Us That Is New

❖ In 12 intensive care patients, NAVA resulted in more complexity of airflow and breathing pattern compared with positive pressure ventilation
❖ NAVA may more closely mimic natural ventilation and thereby improve respiratory support

Contrary to controlled mechanical ventilation, modes of partial ventilatory assistance unload the respiratory muscles while preserving their spontaneous contractile activity.

* Research Fellow, Resident in Intensive Care Medicine. ** Professor, Assistance Publique—Hôpitaux de Paris, Service de Pneumologie et Rénalisation, Groupe Hospitalier Pitié-Salpêtrière, and Université Paris 6—Pierre et Marie Curie. † Assistant Professor, Assistance Publique—Hôpitaux de Paris, Service de Pneumologie et Rénalisation, Groupe Hospitalier Pitié-Salpêtrière, Université Paris 6—Pierre et Marie Curie, and Université Paris 6—Pierre et Marie Curie, Institut National pour la Santé et la Recherche Médicale, UMRS974, Paris, France. § Attending Physician, Assistance Publique—Hôpitaux de Paris, Service de Pneumologie et Réanimation, Groupe Hospitalier Pitié-Salpêtrière. ¶ Biomedical Engineer, École Supérieure de Physique et de Chimie Industrielles de la Ville de Paris, Équipe de Statistiques Appliquées, Paris, France. ¶¶ Associate Professor, Université Paris 6—Pierre et Marie Curie, and Université Paris, Equipe de Statistiques et de Recherche Médicale et Épidémiologique, Service de pneumologie et de réanimation, Groupe Hospitalier Pitié-Salpêtrière. §§ Biomedical Engineer, McGill University Health Centre, Meakins-Christie Laboratories, McGill University, Montreal, Quebec, Canada.

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Address correspondence to Dr. Demoule: Assistance Publique—Hôpitaux de Paris, Service de Pneumologie et Rénalisation, Groupe Hospitalier Pitié-Salpêtrière, 47–83 Boulevard de l’Hôpital, 75015 Paris Cedex 13, France. alexandre.demoule@psl.aphp.fr. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. Anesthesiology's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.
This, in theory, might help to prevent ventilator-induced diaphragm dysfunction, but it also raises the issue of maintaining patient-ventilator synchrony. The latter requires matching the timing of mechanical assistance to neural inspiration and inspiratory flow delivery to ventilatory demand. Failure to achieve patient-ventilator synchrony is associated with worsened sleep architecture, increased duration of mechanical ventilation, and, in extreme cases, the inability to discontinue ventilatory support. In this regard, improving patient-ventilator synchrony has been among the main objectives of recently developed modes of partial ventilatory support.

Neurally adjusted ventilatory assist (NAVA) is a mode of partial ventilatory support in which neural inspiratory activity is monitored through the continuous esophageal recording of the diaphragmatic electromyogram. Assistance is cycled on and off according to the time course of this signal and is delivered in proportion to its intensity. As a result, NAVA should intrinsically overcome important forms of patient-ventilator asynchrony, such as ineffective triggering and expiratory asynchrony, but also flow asynchrony.

Depending directly on the central inspiratory activity, NAVA should result in a breathing pattern reflecting the natural variability observed in healthy adults. Indeed, ventilation in normal human subjects is not monotonous but exhibits considerable breath-to-breath variability in discrete breathing pattern variables such as tidal volume (Vt), inspiratory time (Ti), and mean inspiratory flow (Vt/Ti). The ventilatory activity is also nonlinear in nature and exhibits chaos-like mathematical complexity. Ventilatory variability and complexity are influenced by several factors including the load–capacity relationship of the respiratory system, vagal afferent traffic to the brain, and the activity of the central pattern generators. This is also true in critically ill patients during assisted mechanical ventilation and during spontaneous breathing trials in the process of ventilator weaning. In this latter setting, the variability of breathing has a prognosis value.

In addition, recent data suggest that inputting some variability into mechanical ventilation might be beneficial. Noisy ventilation has, thus, been shown to improve oxygenation in animal models of lung injury. This is associated with a positive effect on respiratory mechanics—reduced mean inspiratory peak airway pressure and elastance—and with reduced histologic damage even in comparison with a tidal volume reduction strategy.

Therefore, we reasoned that NAVA, because it directly links mechanical assistance to neural inspiratory activity, should result in greater breathing pattern variability and complexity compared with conventional ventilator modes. We also reasoned that because respiratory loading decreases the variability of breathing, increasing levels of NAVA should increase the breathing pattern variability and complexity.

To test these hypotheses, we studied respiratory variability and complexity in mechanically ventilated patients switched from pressure support ventilation (PSV) to progressively increasing levels of NAVA. In addition, to elucidate how the load–capacity relationship of the respiratory system contributes to the variability and complexity identified in the ventilatory flow signal, we analyzed the diaphragmatic electrical activity (EAdi) signal in the same manner as the ventilatory flow signal and compared their dynamics.

Materials and Methods

The study took place during a 5-month period (May 1, 2008, to September 30, 2008) in a 10-bed intensive care unit within a 2,000-bed university hospital. As an observational protocol, it was approved by the institutional review board of "Société de Pneumologie de Langue Française" (Paris, France). Informed consent was obtained from the patient or family member.

Patients

We analyzed the recordings obtained in patients in whom the treating physician decided to use NAVA during weaning from mechanical ventilation according to the clinical practice policy in place in the intensive care unit. Preconditions for the institution of NAVA included (1) poor clinical tolerance of PSV for at least 2 h when adjusted to provide a Vt of 6–8 ml/kg at a setting not exceeding 25 cm H2O; this was decided by the clinician in charge of the patient—who was not involved in the research—either because of a direct indication by the patient that his or her breathing was a matter of discomfort or according to usual clinical criteria; (2) a Ramsay sedation scale score less than 4 in the absence of sedation for at least the preceding 12 h; (3) FiO2 less than or equal to 50% and positive end-expiratory pressure less than or equal to 10 cm H2O; (4) hemodynamic stability without vasopressor or inotropic medication; (5) estimated remaining duration of mechanical ventilation more than 48 h. The exclusion criteria were mainly related to the clinical contraindications to the use of NAVA. Individuals with known or suspected phrenic nerve dysfunction, other neuromuscular disorders that may adversely alter EAdi signal quality, impaired respiratory drive, contraindications to EAdi catheter placement (e.g., gastroesophageal varices or obstruction, recent gastroesophageal surgery, facial surgery or trauma, or upper gastrointestinal bleeding), or clinical instability for any reason were excluded. Patients in whom the decision to withhold life-sustaining treatment had been made and pregnant women and those younger than 18 yr were also not considered. According to these criteria, 12 patients were evaluated. The clinical characteristics and indications for mechanical ventilation in the 12 patients are summarized in table 1. Male patients were intubated with an 8-mm internal diameter endotracheal or tracheostomy tube. In female patients, a 7.5-mm internal diameter endotracheal tube was used.

Protocol

Once the decision was made to initiate NAVA, the conventional nasogastric tube was removed and replaced with a...
Table 1. Patient Characteristics at Enrollment

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender (M/F)</th>
<th>Age (yr)</th>
<th>BMI (kg/m²)</th>
<th>SAPS II</th>
<th>Admission Pathology</th>
<th>MV (d)</th>
<th>PSV (cm H₂O)</th>
<th>Vₜ, PSV (ml/kg)</th>
<th>Fio₂ (cm H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>57</td>
<td>41</td>
<td>33</td>
<td>Septic shock, ALI</td>
<td>9</td>
<td>23</td>
<td>6.8</td>
<td>0.40</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>38</td>
<td>22</td>
<td>33</td>
<td>Septic shock, ALI</td>
<td>2</td>
<td>12</td>
<td>10.1</td>
<td>0.40</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>83</td>
<td>55</td>
<td>58</td>
<td>CHF</td>
<td>3</td>
<td>14</td>
<td>5.5</td>
<td>0.40</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>57</td>
<td>24</td>
<td>38</td>
<td>Septic shock, ALI</td>
<td>12</td>
<td>14</td>
<td>6.0</td>
<td>0.40</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>62</td>
<td>25</td>
<td>104</td>
<td>Severe malaria, ALI</td>
<td>7</td>
<td>18</td>
<td>8.7</td>
<td>0.35</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>68</td>
<td>25</td>
<td>87</td>
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<td>7.4</td>
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<tr>
<td>7</td>
<td>M</td>
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<td>28</td>
<td>64</td>
<td>Drug intoxication</td>
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<td>15</td>
<td>6.1</td>
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</tr>
<tr>
<td>8</td>
<td>M</td>
<td>78</td>
<td>39</td>
<td>66</td>
<td>Pneumonia, ALI</td>
<td>4</td>
<td>16</td>
<td>7.4</td>
<td>0.50</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>66</td>
<td>23</td>
<td>60</td>
<td>Pneumonia, ALI</td>
<td>3</td>
<td>12</td>
<td>7.1</td>
<td>0.40</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>68</td>
<td>26</td>
<td>35</td>
<td>Pneumonia, ALI</td>
<td>9</td>
<td>12</td>
<td>7.9</td>
<td>0.50</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>62</td>
<td>29</td>
<td>75</td>
<td>CHF</td>
<td>1</td>
<td>15</td>
<td>8.4</td>
<td>0.40</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>45</td>
<td>23</td>
<td>43</td>
<td>Septic shock, ALI</td>
<td>2</td>
<td>10</td>
<td>6.0</td>
<td>0.30</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>60.6</td>
<td>30.0</td>
<td>58.0</td>
<td></td>
<td>5.1</td>
<td>13.9</td>
<td>7.3</td>
<td>0.40</td>
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<tr>
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<td></td>
<td>3.9</td>
<td>2.8</td>
<td>6.6</td>
<td></td>
<td>1.0</td>
<td>1.2</td>
<td>0.4</td>
<td>0.02</td>
</tr>
</tbody>
</table>

ALI = acute lung injury; BMI = body mass index; CHF = congestive heart failure; Fio₂ = inspired oxygen fraction; MV = mechanical ventilation; PEEP = positive end-expiratory pressure; PSV = inspiratory pressure support level above PEEP; SAPS II = Simplified Acute Physiology Score II; Vₜ, PSV = tidal volume during pressure support (ventilation expressed in milliliters per kilogram predicted body weight); SEM = standard error of the mean.

16-Fr EAdi catheter (Maquet Critical Care, Solna, Sweden). After a period of stabilization on PSV once the EAdi catheter was properly positioned, an initial 10-min recording was performed. The ventilator mode was then switched to NAVA (Servo-i, Maquet Critical Care) with a gain factor of 1 to 4 (NAVA₁, NAVA₂, NAVA₃, and NAVA₄). NAVA level is a proportional gain factor expressed in centimeters of water over microvolt of EAdi. It represents the magnitude (in centimeters of water) of positive airway pressure applied per microvolt of EAdi during the course of each inspiration.

At each NAVA level, 10 min of stabilization were allowed before 10-min recordings were obtained. Fio₂ and positive end-expiratory pressure were kept constant. The pneumatic and EAdi triggers had each been adjusted previously by the treating physicians to be as sensitive as possible without autotriggering.

**Data Acquisition**

In each condition, airway pressure, flow, and EAdi were acquired at 100 Hz from the ventilator via a RS232 interface connected to a computer using commercially available software (Servo-i RCR, Version 2, Maquet Critical Care). Observer graded scores of general comfort in ventilated patients using a previously validated scale (adaptation to the intensive care environment score)²⁶ were obtained by the same study investigator at the end of each condition. Samples for arterial blood gas analysis were drawn at this time as well.

**Data Analysis**

**Breath-by-Breath Variability.** Flow-derived breathing pattern parameters were determined on a breath-by-breath basis for each of the five conditions as described under Protocol in Materials and Methods. These included tidal volume (Vₜ), neural respiratory rate, minute ventilation, duration of inspiration (Ti), expiration, total respiratory cycle (Tt), inspiratory duty cycle (Ti/Tt), and mean inspiratory flow (Vₜ/Ti). For EAdi, peak (EAdi_peak), rate of rise (peak value divided by time to peak of EAdi) (EAdi_peak/EAdi_rise), and integrated EAdi activity relative to the end-expiratory baseline value (JEAdi) were also computed on a breath-by-breath basis. The coefficient of variation (CV; SD divided by the mean) and autocorrelation descriptors (number of significantly correlated breaths or lag; autocorrelation coefficient between the first and second breaths or r-lag⁻¹) for both flow and EAdi related variables were then calculated using a software routine developed for Matlab (Mathworks, Natick, MA). Peak (P_peak) and mean inspiratory airway pressure (P_mean) were also obtained and included positive end-expiratory pressure.

**Ventilatory Complexity: Noise Titration.** After subsampling the signal at 5 Hz, the noise titration procedure²⁷ was performed as described previously.¹¹,¹²,¹⁷,²⁸ (see detailed description in Supplemental Digital Content 1, http://links.lww.com/ALN/A571). In brief, this technique first ascertains the presence of nonlinearity in the signal through a statistical process, and then it quantifies the amount of added white noise needed to mask this nonlinearity. A noise limit above 0 means nonlinearity and a certain degree of chaos-compatible complexity.²⁷ It allows the safe use and interpretation of traditional nonlinear descriptors that are all sensitive to noise (see next paragraph).

**Ventilatory Complexity: Sensitivity to Initial Conditions and System Unpredictability.** Various characteristics of a complex dynamical system are useful for their description. These include their sensitivity to initial conditions, or, in other words, how perturbations occurring in the past affect the future behavior of the system. Characteristically, small differences in the starting state of the system can lead to enormous differences in its final state as the result of an exponential growth of error. This happens even though the
considered system is deterministic, namely that it is driven by a mechanism that does not involve random elements. We quantified the sensitivity to initial conditions for flow and EAdi using the largest Lyapunov exponent (LLE) \(29\) (Dataplore v 2.0.9, Datan, Teltow, Germany), which increases as the system is more sensitive to initial conditions. Another characteristic of a complex system is how unpredictable it is. This can be estimated by calculating the Kolmogorov-Sinai Entropy (KSE), \(30\) as the sum of the positive Lyapunov exponents. \(12\) A low value of KSE indicates predictability and regularity, whereas a high value denotes unpredictable and random variations. \(30\)

Three-dimensional phase portraits of the flow and Edi signals were also determined. The phase space of a dynamical system is the multidimensional space in which all the possible states of the system are represented. The phase portrait of a periodical system is a simple closed loop, whereas the phase portrait of a chaotic system is a complicated set of nonrepeating patterns.

### Statistical Analysis

Results are expressed as mean values ± SEM. Statistical analysis was performed with Prism 4.0a software (GraphPad Software, San Diego, CA). Distribution being normal (Shapiro-Wilk test), comparisons between the five conditions were performed with one-way analysis of variance for repeated measures, followed, when indicated, by pairwise comparisons using Tukey post hoc test. Correlations between continuous variables were examined with Pearson correlation when the distribution was normal (Shapiro-Wilk test) and with Spearman correlation when the distribution was not normal, depending on the distribution. Differences were considered significant when \(P < 0.05\). Effect size was estimated through the calculation of the partial \(\eta^2\) using PASW Statistics 18 (Chicago, IL).

### Results

Figure 1 shows an example (patient 12) of the pressure, flow, and EAdi signals during the five conditions. Group mean values for representative breathing pattern variables are provided in figure 2 (see Supplemental Digital Content 1, table 1, http://links.lww.com/ALN/A571). Switching from PSV to NAVA\(_1\) did not seem to significantly modify the pattern of breathing (fig. 2). Increasing the level of NAVA assistance had no significant effect on breathing frequency and the inspiratory duty cycle (Ti/Tt), but it did produce significant increases in Vt \((P < 0.05, \text{partial } \eta^2 = 0.394)\) and Vt/Ti \((P < 0.05, \text{partial } \eta^2 = 0.429)\) when NAVA\(_3\) and NAVA\(_4\) were reached (fig. 2). Minute ventilation paralleled the changes in Vt (see Supplemental Digital Content 1, table 1, http://links.lww.com/ALN/A571). Ti was significantly shorter under NAVA\(_4\) in comparison with PSV (see Supplemental Digital Content 1, table 1, http://links.lww.com/ALN/A571).

Similarly, the indices of EAdi activity were not significantly different between PSV and NAVA\(_1\) (fig. 3). Increasing the NAVA level resulted in a progressive decrease of EAdi\(_{\text{peak}}\), EAdi\(_{\text{peak}}/\text{EAdi}_{\text{trp}}\) and \(\text{fEAdi}\). EAdi\(_{\text{peak}}\) and EAdi\(_{\text{peak}}/\text{EAdi}_{\text{trp}}\) were significantly lower in NAVA\(_4\) than in both PSV and NAVA\(_1\) \((P < 0.05, \text{partial } \eta^2 = 0.399 \text{ and } 0.367, \text{respectively})\), whereas \(\text{fEAdi}\) was significantly lower in NAVA\(_4\) than in NAVA\(_1\) \((P < 0.05)\) (fig. 3) (see Supplemental Digital Content 1, table 1, http://links.lww.com/ALN/A571).
The switch from PSV to NAVA_1 and further increases in NAVA level had no impact on PaO_2/FiO_2 (table 2). However, PaCO_2 was slightly lower and arterial pH somewhat higher during NAVA_4 compared with NAVA_1 ($P < 0.05$) (see Supplemental Digital Content 1, table 1, http://links.lww.com/ALN/A571).

Switching from PSV to NAVA_1 did not result in a significant change in $P_{\text{peak}}$ or $P_{\text{mean}}$ (fig. 4). $P_{\text{peak}}$ particularly but also $P_{\text{mean}}$ rose as the NAVA gain was increased. For NAVA_3 and NAVA_4, $P_{\text{peak}}$ was higher than during PSV and NAVA_1 ($P < 0.05$). $P_{\text{mean}}$ was higher for NAVA_4 than NAVA_1 (fig. 4) (see Supplemental Digital Content 1, table 1, http://links.lww.com/ALN/A571).

No significant change in the adaptation to the intensive care environment score was detected (see Supplemental Digital Content 1, table 1, http://links.lww.com/ALN/A571).

**Breath-by-Breath Variability**

A significant increase in the CV of $V_t/T_i$ ($P < 0.05$, partial $\eta^2 = 0.642$) was immediately apparent during NAVA_4 when compared with PSV (fig. 5). Increasing the level of NAVA produced an increase in the breath-by-breath variability of most of the breathing pattern variables (fig. 5) (see Supplemental Digital Content 1, table 2, http://links.lww.com/ALN/A571). For these variables, the CV was significantly higher in NAVA_4 than in both PSV and NAVA_1. The autocorrelation analysis showed similar trends, but the changes were significant only for $V_t/T_i$ and, to a lesser extent, for respiratory rate. Indeed, the lag of $V_t/T_i$ was lower in NAVA_4 than in both PSV and NAVA_1 ($P < 0.055$, partial $\eta^2 = 0.356$). The autocorrelation coefficient of $V_t/T_i$ and of respiratory rate was lower in NAVA_4 than in NAVA_1 ($P < 0.05$).

Fig. 2. Effects of ventilator mode and level of assistance on representative breathing pattern variables. Compared with pressure support ventilation (PSV), the most noticeable difference is the increase in mean inspiratory flow ($V_t/T_i$) as the neurally adjusted ventilatory assist (NAVA) gain is raised stepwise from 1 to 4 cm H_2O/cm H_2O/µV diaphragm electrical activity (NAVA_1,2,3,4). There is no significant change in respiratory rate ($RR$) or inspiratory duty cycle ($T_i/T_t$). Tidal volume ($V_t$) differs significantly at the highest NAVA gain (NAVA_4). Data are means ± SEM; *$P < 0.05$.

Fig. 3. Effects of ventilator mode and level of assistance on diaphragmatic electrical activity ($E_{\text{Adi}}$). Peak ($E_{\text{Adi\_peak}}$), rate of rise ($E_{\text{Adi\_peak}}/E_{\text{Adi\_tp}}$), and integrated $E_{\text{Adi}}$ per breath ($\int E_{\text{Adi}}$) are similar during pressure support ventilation (PSV) and the lowest level of neurally adjusted ventilatory assist (NAVA). $E_{\text{Adi}}$ indices decrease progressively as NAVA gain increases from 1 to 4 cm H_2O/µV $E_{\text{Adi}}$ (NAVA_1,2,3,4). Data are means ± SEM; *$P < 0.05$.  

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Table 2. Arterial Blood Gas Analysis during Pressure Support Ventilation and at Various Levels of NAVA

<table>
<thead>
<tr>
<th>Arterial Blood Gases</th>
<th>PSV</th>
<th>NAVA₂</th>
<th>NAVA₃</th>
<th>NAVA₄</th>
</tr>
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<tbody>
<tr>
<td>pH</td>
<td>7.38 ± 0.02</td>
<td>7.37 ± 0.03</td>
<td>7.39 ± 0.02</td>
<td>7.40 ± 0.02†</td>
</tr>
<tr>
<td>PaO₂/FIO₂</td>
<td>202 ± 18</td>
<td>203 ± 18</td>
<td>212 ± 20</td>
<td>198 ± 12</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>40.9</td>
<td>40.2</td>
<td>40.5</td>
<td>40.4</td>
</tr>
<tr>
<td>pCO₂</td>
<td>2.9</td>
<td>2.6</td>
<td>2.9</td>
<td>2.7</td>
</tr>
<tr>
<td>pH</td>
<td>7.38 ± 0.02</td>
<td>7.37 ± 0.03</td>
<td>7.39 ± 0.02</td>
<td>7.40 ± 0.02†</td>
</tr>
<tr>
<td>PaO₂/FIO₂</td>
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</tr>
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<td>PaCO₂ (mmHg)</td>
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<td>40.4</td>
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<tr>
<td>pH</td>
<td>7.38 ± 0.02</td>
<td>7.37 ± 0.03</td>
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<tr>
<td>PaCO₂ (mmHg)</td>
<td>40.9</td>
<td>40.2</td>
<td>40.5</td>
<td>40.4</td>
</tr>
</tbody>
</table>

Data provided as mean ± standard error of the mean.
* P < 0.05 versus NAVA₂, † P < 0.05 versus PSV.
FIO₂ = inspired oxygen fraction; NAVA₁,₂,₃,₄ = neurally adjusted ventilatory assist with a gain of 1, 2, 3, and 4 cm H₂O/μV diaphragmatic electrical activity; PaO₂ = partial pressure of alveolar oxygen; PaCO₂ = arterial carbon dioxide tension; PSV = pressure support ventilation.

The CV of EAdi_peak, EAdi_peak/EAdi_τp, and EAdi were not significantly increased when PSV was switched to NAVA₁ (fig. 6). Increasing the NAVA gain had a limited effect on the CV for these three EAdi variables until the highest level of assistance was reached. The CV of EAdi_peak/EAdi_τp was higher in NAVA₄ than in all other conditions (P < 0.05, partial η² = 0.365), whereas the CV of the EAdi_peak was higher in NAVA₁ than in NAVA₂ (P < 0.05, partial η² = 0.191). The lag and the autocorrelation coefficient for EAdi_peak/EAdi_τp and EAdi were not significantly altered by the change in ventilator mode and the subsequent increases in NAVA level (fig. 6) (see Supplemental Digital Content 1, table 3, http://links.lww.com/ALN/A571).

Ventilatory Complexity

A positive noise limit was obtained with the noise titration procedure in all patients for both the flow and EAdi signals during PSV and all levels of NAVA, consistently indicating the presence of a nonlinear chaotic system. In all patients and in all conditions for both flow and EAdi, at least one of the Lyapunov exponents was positive, at least one was negative, and their sum was negative, a pattern in keeping with chaos. The LLE for ventilatory flow was higher for NAVA₂, NAVA₃, and NAVA₄ than PSV (P < 0.05, partial η² = 0.334) (fig. 7). The same pattern was observed for KSE (P < 0.05, partial η² = 0.312) (see Supplemental Digital Content 1, table 4, http://links.lww.com/ALN/A571). In contrast, switching from PSV to NAVA and then increasing NAVA gain had no effect on the LLE and KSE of the EAdi signal (fig. 7).

Figure 8A illustrates the difference between flow and EAdi complexity (fig. 8B) and the differential effects of increasing NAVA on this complexity, using three-dimensional phase portraits (example in patient 2). During PSV, the number of flow trajectories seems limited, describing a well-identifiable geometric pattern that is relatively simple. The phase portrait becomes less “geometrical” in NAVA₁, and the trajectories become more numerous and more tangled as NAVA increases. This phenomenon is much less apparent for the EAdi signal, where the phase portrait under PSV is already rather “complicated” (and more so than the flow phase portrait), and increasing NAVA does not radically change the overall shape. Although low, significant correlations were found between some of the breathing pattern variables and the indices of the complexity of ventilatory flow (see Supplemental Digital Content 1, table 5, http://links.lww.com/ALN/A571). There was no such correlation for the EAdi signal.

Discussion

This study demonstrates that, in acutely ill mechanically ventilated patients, switching the mode of ventilatory assistance from PSV to NAVA and then increasing the support provided by NAVA is associated with increased variability of the pattern of breathing (fig. 5). This is also associated with greater complexity of the ventilatory flow signal (fig. 8), as evidenced by the significant increases in LLE and KSE (fig. 7). In contrast, the breath-to-breath variability and complexity of EAdi that seems more marked than their ventila-
Breath-to-Breath Variability

Fluctuations in the resting breathing pattern of humans have long been known and depend on various factors. Breathing pattern variability decreases during sleep and coma, indirectly indicating the likely influence of ventilatory drive and/or respiratory afferent activity. In awake normal humans, breath-to-breath variability tends to decrease and autocorrelation tends to increase in response to mechanical loading, a situation generally associated with modest changes in the central drive to breathe. During weaning from mechanical ventilation, an inverse relationship between the breath-to-breath variability of VT/Ti and dynamic compliance of the respiratory system has been reported. The load–capacity relationship of the respiratory system, therefore, seems to be a major determinant of breath-to-breath variability: the higher the loading, the lower the variability. This is sup-

*Fig. 5. Effects of ventilator mode and level of assistance on the coefficient of variation (CV) and autocorrelation analysis for representative breathing pattern variables. Compared with PSV, values for the CV are somewhat greater during NAVA and rise further as the gain increases from 1 to 4 cm H2O/cmH2O diaphragm electrical activity. Autocorrelation analysis is used here to determine the number of breaths through which a significant correlation or lag is found. Considered an index of “short term memory,” the greater the numerical value of lag, the larger the duration of interbreath correlation. With the exception of mean inspiratory flow, lag seems to be lower during NAVA. Overall, these results are consistent with increased breathing pattern variability during NAVA when compared with PSV. CV = coefficient of variation; CVt VT = CV of tidal volume; CVi VT = CV of the inspiratory duty cycle; CVi VT = CV of mean inspiratory flow; lag = number of breaths among which a significant correlation was found; lag = lag of tidal volume; lag = lag of respiratory rate; lag = lag of tidal volume; lag = lag of the inspiratory duty cycle; lag = lag of mean inspiratory; NAVA = neurally adjusted ventilatory assist with a gain of 1, 2, 3, 4 cm H2O/µV diaphragm electrical activity flow; PSV = pressure support ventilation. Data are means ± SEM; *P < 0.05.
ported by our data. Indeed, we observed that such variability significantly increases with increasing levels of NAVA, namely during progressive unloading of the respiratory system (fig. 5). Respiratory unloading with NAVA also decreased the degree of autocorrelation, but in a much less marked manner (fig. 5). This can probably be taken as an indication that variability and autocorrelation are not measures of the same thing. Of note, the increased breath-to-breath variability that we observed was not accompanied by significant change in Vt, Vt/kg of predicted body weight and Pmean, supporting the idea that NAVA has the intrinsic potential to limit the risk of overassistance through the down-regulation of EAdi that is induced by the increase in assistance. This differs from PSV and is consistent with previous reports from other groups.7,37,38

**Impact of Neuromechanical Coupling on Breathing Pattern Variability**

As mentioned in the introduction, breathing pattern variability seems to depend on several factors that include ventilatory drive and the degree of mechanical loading imposed on the respiratory system. To date, human respiratory variability has been studied only through the analysis of the mechanical output of the ventilatory command (i.e., flow, volume, or thoracoabdominal displacement), including with NAVA where data reporting coefficients of variation of Vt are available.7,37 This does not necessarily provide an accurate picture of the respiratory controllers, however, because the underlying behavior of central respiratory neural output can be substantially altered by the mechanical characteristics of the respiratory system.

The current study overcomes this limitation by using for this analysis, seemingly for the first time, measurements of EAdi that directly reflect central respiratory neural output. These data indicate that the increase in breath-to-breath variability of ventilatory flow observed during NAVA is in fact due to “unmasking” of the underlying variability in central respiratory neural output and a direct result of the improvement in neuromechanical coupling. Indeed, contrary to the variability in breathing pattern variables, the breath-to-breath variability of EAdi was similar during PSV and NAVA and did not increase with the NAVA level (except for NAVA4). In addition, right angles were observed in three-
dimensional phase portraits of flow but not of EAdi (see fig. 8). The absence of right angle trajectories being one of the characteristics of deterministic dynamics reinforces the hypothesis that EAdi might be the most accurate index of intrinsic complexity, whereas flow is influenced by respiratory system mechanics. Therefore, we submit that NAVA-related unloading reveals, in terms of breathing pattern, the underlying variational activity in central respiratory neural output that is itself not particularly sensitive to the mechanical load.

Respiratory Complexity

As in previous studies conducted in this field by our group, we carried out complexity analyses on continuous oscillatory signals (here flow and EAdi), as opposed to a time series of discrete values. To our knowledge, this is one of the few studies to analyze the breathing pattern complexity in mechanically ventilated patients. With this approach, consecutive breaths are described in terms of an ensemble of signal trajectories (fig. 8). If only one trajectory is possible, as in a truly periodic system, complexity is minimal, and all breaths should be identical. This is the case during assist-control mechanical ventilation in passive patients where ventilatory flow is driven solely by the ventilator clock. If, conversely, several trajectories are possible, a given breath can differ from the previous or the following one. The more numerous the trajectories (in other words, the more complex the system), theoretically the more marked the interbreath differences can be (and the less likely autocorrelation). In this view, one expects some similarity between the evolution of breath-to-breath variability (“downstream” point of view) and the evolution of complexity (“upstream” point of view) in response to a given intervention. This is indeed what we observed: both the variability in the breathing pattern and the complexity of ventilatory flow were low during PSV (figs. 7 and 8), became greater with the change to NAVA, and further increased as the NAVA gain increased. Although weak in strength, significant correlations existed between the indices of ventilatory complexity and breathing pattern variability (see Supplemental Digital Content 1, table 5, http://links.lww.com/ALN/A571). Therefore, our data indicate that breath-to-breath variability depends, at least in part, on the underlying complexity of the central ventilatory command.

In striking contrast to what was observed with the ventilatory signal, the variability and the complexity of the EAdi signal—those already relatively high during PSV, and comparatively higher than that of the flow signal—remained largely unaffected by the change in ventilator mode to NAVA and the increase in assistance with higher NAVA gain. Therefore, NAVA seems to allow the variability and complexity of the central respiratory activity to translate into their ventilatory flow counterparts. This suggests that the variability and complexity of ventilatory flow are related not only to the load–capacity balance of the respiratory system but also to the neural activity of the respiratory controller. Practically speaking, assessing ventilatory flow variability and complexity could provide a simple means to monitor the respiratory neuromechanical coupling, or load–capacity balance, over time. The variability and complexity analysis performed on the EAdi signal would provide information more...
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Mechanical load or altering the respiratory drive. Nevertheless, increasing breath-to-breath variability by either reducing the mechanical load or altering the respiratory drive. Nevertheless, increase breath-to-breath variability by either reducing the mechanical load or altering the respiratory drive. Nevertheless, increase breath-to-breath variability by either reducing the mechanical load or altering the respiratory drive. Nevertheless, increase breath-to-breath variability by either reducing the mechanical load or altering the respiratory drive.

Study Limitations

Because of the observational design of the study, we examined only a single level of PSV. Therefore, we cannot rule out the hypothesis that progressively increasing PSV would similarly increase breath-to-breath variability by either reducing the mechanical load or altering the respiratory drive. Nevertheless, switching from PSV to NAVA1 increased the CV of Vt and Vt/Ti and decreased the Vt/Ti autocorrelation (fig. 5), while there was no significant change in Vt and breathing frequency (fig. 2). This suggests a specific effect of NAVA on variability, all the more so that the patients may have been somewhat under-assisted during NAVA1 (as reflected by trends in Pmean [fig. 4] and EAdi [fig. 3]). By contrast, NAVA4 could have corresponded to some degree of overassistance, because it was associated with a tendency of variability to reincrease after a sort of a plateau (significant for Vt/Ti, fig. 5).

Also, because the study was observational, there was by definition no randomization of the NAVA levels studied, which is another theoretical limitation of the study. According to the standard clinical practice procedure when attempting to titrate a therapeutic intervention, NAVA was increased in a progressive manner to find the optimal balance between respiratory muscle unloading and overassistance, as reported previously in patients.

Therefore, we cannot rule out the existence of some degree of "sequence" bias. Note that the recordings, however, were not performed immediately after the setting changes, but after 10 min of stabilization.

Finally, in the current study, most patients were studied while they were recovering from an acute lung injury and not during the most acute phase, and so our data apply to moderate acute lung injury.

Of note, the fact that inspiration results from the cooperation between the diaphragm and other respiratory muscles (ribcage muscles, scalenes, and sternomastoids) while NAVA is driven by EAdi alone could contribute to the higher variability observed with NAVA.

Clinical Perspectives

We did not observe a dramatic clinical change after switching from PSV to NAVA in this group of patients, and there was no obvious clinical indication that the stepwise increase in NAVA provided what could have been termed an optimal level of ventilatory support (e.g., no improvement in the adaptation to the intensive care environment score with increasing levels of NAVA). However, the study population is very small, and the experimental protocol was not designed or powered to examine the effects of NAVA on clinical outcomes. Yet, NAVA did increase the respiratory variability and complexity. This is a rationale to design studies examining the impact of NAVA on clinical outcomes known to be associated with greater variability.

NAVA is not the only ventilatory mode that increases the variability of breathing. Noisy ventilation that delivers a Vt with up to 40% CV is a ventilatory mode designed to purposely increase the variability of breathing. Animal studies have shown the benefits of this approach on gas exchange, respiratory mechanics, and lung structure during lung injury. Even though human data are currently not available, these observations lend support to the notion that an increased respiratory variability might be a good thing during mechanical ventilation. Proportional assist mechanical ventilation relies on the dynam-
stract: The proportional assist ventilation (PAV) is a type of assisted ventilation that is designed to improve the efficiency of mechanical ventilation by providing additional ventilation to the patient in a manner that resembles our observations with NAVA. In patients with respiratory disease, PAV is associated with increased breathing pattern variability and its fluctuations. The proportional assist mechanical ventilation-induced mechanical unloading of the respiratory system is associated with increased breathing pattern variability in a manner that resembles our observations with NAVA. In our patients, increasing the level of NAVA support produced an increase in ventilatory flow variability, whereas it did not affect the variability of the diaphragmatic electromyogram that seemed to be high to begin with. In our view, this indicates that NAVA improved the neuromechanical coupling of the respiratory system. Studying the effects of proportional assist mechanical ventilation on the variability of diaphragmatic electromyogram would, thus, provide an interesting way of comparing it to NAVA.

In clinical practice, whether variability is distinctive of patient-ventilator interaction and whether monitoring respiratory variability and/or complexity is an appropriate means to assess this interaction in the clinical setting will have to be studied.

References


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