Neurally adjusted ventilatory assist and proportional assist ventilation both improve patient-ventilator interaction

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Neurally adjusted ventilatory assist and proportional assist ventilation both improve patient-ventilator interaction

Matthieu Schmidt1,2,3,6*, Felix Kindler3, Jérôme Cecchini1,2, Tymothée Poitou4, Elise Morawiec1,2,3, Romain Persichini3, Thomas Similowski1,2,3 and Alexandre Demoule1,2,3,5

Abstract

Introduction: The objective was to compare the impact of three assistance levels of different modes of mechanical ventilation; neurally adjusted ventilatory assist (NAVA), proportional assist ventilation (PAV), and pressure support ventilation (PSV) on major features of patient-ventilator interaction.

Methods: PSV, NAVA, and PAV were set to obtain a tidal volume ($V_T$) of 6 to 8 ml/kg (PSV100, NAVA100, and PAV100) in 16 intubated patients. Assistance was further decreased by 50% (PSV50, NAVA50, and PAV50) and then increased by 50% (PSV150, NAVA150, and PAV150) with all modes. The three modes were randomly applied. Airway flow and pressure, electrical activity of the diaphragm (EAdi), and blood gases were measured. $V_T$, peak EAdi, coefficient of variation of $V_T$ and EAdi, and the prevalence of the main patient-ventilator asynchronies were calculated.

Results: PAV and NAVA prevented the increase of $V_T$ with higher levels of assistance (median 7.4 (interquartile range (IQR) 5.7 to 10.1) ml/kg and 7.4 (IQR, 5.9 to 10.5) ml/kg with PAV150 and NAVA150 versus 10.9 (IQR, 8.9 to 12.0) ml/kg with PSV150, $P < 0.05$). EAdi was higher with PAV than with PSV at level100 and level150. The coefficient of variation of $V_T$ was higher with NAVA and PAV (19 (IQR, 14 to 31)% and 21 (IQR 16 to 29)% with NAVA100 and PAV100 versus 13 (IQR 11 to 18)% with PSV100, $P < 0.05$). The prevalence of ineffective triggering was lower with PAV and NAVA than with PSV ($P < 0.05$), but the prevalence of double triggering was higher with NAVA than with PAV and PSV ($P < 0.05$).

Conclusions: PAV and NAVA both prevent overdistention, improve neuromechanical coupling, restore the variability of the breathing pattern, and decrease patient-ventilator asynchrony in fairly similar ways compared with PSV. Further studies are needed to evaluate the possible clinical benefits of NAVA and PAV on clinical outcomes.

Trial registration: Clinicaltrials.gov NCT02056093. Registered 18 December 2013.

Introduction

Partial ventilatory assistance minimizes adverse effects of controlled mechanical ventilation, such as excessive sedation and ventilator-induced diaphragm dysfunction [1-3]. The most widely used partial ventilatory assistance mode is pressure support ventilation (PSV) [4], in which a constant preset level of pressure assists each inspiration, regardless of the patient’s inspiratory effort. Mismatching between patient demand and level of assistance is therefore possible and can be potentially harmful: underassistance may induce respiratory discomfort [5], and overassistance may cause lung overdistention and volutrauma [6]. Of note, underassistance and overassistance may both generate patient-ventilator asynchrony that is associated with poorer clinical outcomes [7].

Proportional Assisted Ventilation (PAV) and Neurally Adjusted Ventilatory Assist (NAVA) have been designed to overcome this weakness of PSV. These two modes adjust proportionally the amount of assistance delivered. NAVA adjusts ventilator assistance to the electrical activity of the diaphragm (EAdi), recorded with an esophageal catheter [8]. PAV adjusts ventilator assistance to the activity of respiratory muscles estimated by an
algorithm [9]. Previous studies have shown the potential benefits of PAV and NAVA to prevent the risk of overassistance [10-13], to increase the variability of the breathing pattern [14-20], and to improve patient-ventilator interaction and synchrony [11,12,21-26]. PAV and NAVA have been previously compared with PSV but not with each other. This comparison would be clinically relevant, as these two modes have their own specific strengths and weaknesses [9,27].

In the study reported here, we hypothesized that PAV and NAVA improve patient-ventilator interaction in similar ways. The aim of this study was therefore to compare, in patients recovering from acute respiratory failure, the respective impacts of various levels of NAVA, PAV, and PSV on four major features of patient-ventilator interaction: (1) breathing pattern, including prevention of overassistance; (2) respiratory drive; (3) breathing pattern variability, and (4) patient-ventilator synchrony.

Materials and methods
The study was conducted over a period of 3 months in a 10-bed Intensive Care Unit (ICU) in an 1,800-bed university hospital. The protocol was approved by the Comite de Protection des Personnes Ile de France VI. Informed consent was obtained from patients or relatives.

Patients
Patients initially intubated and ventilated in the ICU were eligible for inclusion in the study if (1) they had been ventilated for acute respiratory failure via an endotracheal tube for more than 48 hours, (2) the condition that had required mechanical ventilation had improved (in particular, the ability to trigger the ventilator with an FiO2 of ≤50% and positive end-expiratory pressure (PEEP) ≤5 cmH2O), (3) sedation had been stopped for more than 6 hours, (4) hemodynamic stability was achieved without vasopressor or inotropic medication. Exclusion criteria were known or suspected phrenic nerve dysfunction or other neuromuscular disorders that may involve the diaphragm or impair respiratory drive. Patients with contraindications to EAdi catheter placement (for example, gastroesophageal varices or obstruction, recent gastroesophageal surgery, facial surgery or trauma, or upper gastrointestinal bleeding) were excluded. Patients in whom the decision had been made to withhold life-sustaining treatment were also ineligible for inclusion.

Ventilation equipment
The conventional nasogastric tube was removed and replaced by a 16 Fr EAdi catheter (Maquet Critical Care, Solna, Sweden), and its position was controlled according to the manufacturer’s recommendations [28]. PSV and NAVA were delivered by using a Servo-I ventilator (Maquet Critical Care), and PAV+ was delivered by using a PB840 ventilator (Covidien, Boulder, CO, USA). Male and female patients were ventilated with an 8- and 7.5-mm internal diameter endotracheal tube, respectively.

Study protocol
Inspiratory pressure support level was initially titrated to obtain a tidal volume (VT) of 6 to 8 ml/kg of predicted ideal body weight. Flow-trigger sensitivity was set at the lowest possible level without inducing auto triggering, and cycling-off was set at 30% of peak inspiratory flow (default value). This level of assistance was defined as PSV100. Patients were then switched to NAVA, and the corresponding NAVA level to obtain a similar VT of 6 to 8 ml/kg was determined during a 5-minute period. This NAVA level was termed NAVA100. Patients were finally switched to PAV, and the percentage unloading (%Assist) was set also to obtain a similar VT of 6 to 8 ml/kg. This %Assist corresponded to PAV100. In each of the three modes, the assist level was further decreased by 50%, corresponding to PSV50, NAVA50, and PAV50, and then increased by 50%, corresponding to PSV150, NAVA150, and PAV150. In the Results section, PSV100, NAVA100, and PAV100 define a medium assistance level also termed level100; PSV50, NAVA50, and PAV50 define a low assistance level, also termed level50; and PSV150, NAVA150, and PAV150 define a high assistance level also termed level150. Of note, inspiratory pressure-support level in PSV50 could not be lower than 7 cmH2O. A high upper pressure limit at 45 cmH2O was set in PAV and NAVA.

Positive end-expiratory pressure (PEEP) and inspired oxygen fraction (FiO2) were maintained constant throughout the study period at the values in use before patient enrollment. The endotracheal tube was suctioned before the beginning of each trial. Each patient underwent three 30-minute trials, in each mode, consisting of 20-minute stabilization followed by 10-minute recording stored on a computer for further analysis. The three modes were applied in computer-generated random order. At the end of each trial, arterial blood was sampled for gas analysis (Radiometer ABL 330, Tacussel, Copenhagen, Denmark) via a catheter, and dyspnea was rated by using a visual analogue scale when possible.

Data acquisition
Flow was measured with a heated Fleisch pneumotachograph, dead space 51 ml (Hans Rudolph, Kansas City, MO, USA) and airway pressure was measured by a pressure transducer (DP 15-32, Validyne, Northridge, CA, USA) for all modes. Digital EAdi signal was converted into an analog signal (National Instruments, Austin, TX, USA). During all three modes of ventilation, the EAdi waveform was simultaneously recorded with flow and
airway pressure from the respective ventilator (see Additional file 1). All signals were digitized at a 100-Hz sampling rate (PowerLab/4SP, ADInstruments, Castle Hill, Australia) and recorded on a personal computer for subsequent analysis (Chart software, ADInstruments, Castle Hill, Australia).

Data analysis

Respiratory Parameters and Breathing Pattern

Neural respiratory rate (RR), VT, duration of pneumatic inspiration (Ti), maximum EAdi, (EAdi max), area under the curve of EAdi during inspiratory time (EAdi AUC, integrated from baseline to peak), and the VT-(ml/kg)/EAdi max ratio were calculated offline from the 10-minute airway flow and EAdi recordings. The coefficient of variation (standard deviation divided by the mean) for both flow (CVVT) and EAdi-related variables (CVEAdi max) was calculated. Maximum (P max) and mean inspiratory airway pressure (P mean) were measured and calculated from airway pressure recordings.

Patient-ventilator interaction

Within the three modes and in all conditions, correlations between EAdi max and P max and between EAdi AUC and VT were calculated. The inspiratory trigger delay was measured as the time difference between the beginning of the increase in the EAdi signal and the beginning of the ventilator inspiratory flow. The expiratory trigger delay was measured as the time difference between EAdi max and the end of the insufflation, as defined by a ventilator inspiratory flow equal to zero. Using the EAdi waveform, we quantified the three main types of asynchronies according to previously published definitions [7,25] (see also Additional file 2): (1) ineffective efforts; (2) auto-triggering, and (3) double triggering. Of note, only type II double triggering, defined as one neural inspiration triggering two breath cycles, was considered [25] (see example in Additional file 3). The number of each type of asynchrony was reported as the total number of each event per minute. A global asynchrony index (AI) was computed [7].

Statistical analysis

Statistical analysis was performed with Prism 4.01 software (GraphPad Software, San Diego, CA, USA). Normality testing failed for all results (Kolmogorov-Smirnov). Results are therefore expressed as median (25 to 75 interquartile range). Within each of the three assistance level groups (that is, level 50, level 100, and level 150), Friedman ANOVA for repeated measures was performed to compare breathing pattern, variability, prevalence of the main asynchronies and blood gases measured with PAV, NAVA, and PSV, respectively. Comparison between the three modes was followed, when appropriate, by a pairwise comparison by using the Dunn post hoc test. The relationships among both EAdi max and P max and EAdi AUC and VT were examined by using a linear regression analysis, and the coefficient of correlation (r2) was determined. Differences were considered significant when the probability p of a type I error was less than 5%.

Results

The study pertains to a convenience sample of 16 patients (10 males). Their main characteristics and the precipitating factor of acute respiratory failure are summarized in Table 1. Respective assistance levels used for each mode are reported in Table 2. Of note, three patients had chronic obstructive pulmonary disease (COPD) (patients 5, 7, and 16).

Breathing pattern and electrical activity of the diaphragm

Group median values for representative breathing pattern variables are provided in Figure 1 and Figure 2 (see also Additional file 4). Inspiratory pressures for each patient under all conditions are displayed in Additional file 4. Median airway pressure was similar among level 100 and level 150 groups. Within all assistance levels (level 50, level 100, level 150), P max was higher with NAVA than with PAV and PSV (P = 0.001; Figure 1, Table 3). At level 50 and level 100, VT was similar among modes. However, at a high assistance level, VT was significantly higher with PSV 150 than with NAVA 150 and PAV 150 (P < 0.05). Tidal volume was similar with NAVA and PAV regardless of the assistance level. Inspiratory time and RR remained similar within all modes and at each level of assistance. Of note, at level 100, and level 150, EAdi max and EAdi AUC were higher in PAV than in PSV (Figure 2; Table 3). Whereas the VT/EAdi max ratio was similar among groups at level 50, it was higher with PSV than with PAV at level 100 and level 150 (P < 0.0001). In addition, the VT/EAdi max ratio was higher with PSV (P < 0.0001) but did not differ between PAV and NAVA regardless of the assistance level.

Breath-by-breath variability

Group median values for coefficient of variation VTmax and EAdi max are provided in Figure 3 (see also Additional file 5). The coefficient of variation of VT was higher with PAV and NAVA than with PSV at level 100 and level 150 (P < 0.05), whereas the coefficient of variation of VT was similar between NAVA and PAV at each level of assistance. Conversely, the coefficient of variation of EAdi max did not change according to ventilator mode and level of assistance, except at level 150, where it was lower with PAV 150 than with PSV 150.

Patient-ventilator interaction

Table 4 and Additional file 6 show the inspiratory and expiratory trigger delays, the correlation between both
and the prevalence of patient-ventilator asynchrony in each condition. Inspiratory trigger delay was significantly lower in NAVA than in PAV and PSV at level 100 and level 150, respectively. Similarly, expiratory trigger delay was lower during NAVA 100 and NAVA 150 than during PSV 100 and PSV 150, respectively (Table 4). The correlation between EAdi AUC and VT, was higher during NAVA and PAV than during PSV (Table 4). The correlation between EAdi max and Pmax was higher during NAVA than during PAV and PSV (Table 4). At each level of assistance, almost no ineffective efforts were reported with PAV and NAVA, whereas the ineffective efforts were detected with PSV at a higher level (P < 0.05). Inversely, although very few double-triggering events were observed with PSV and PAV, the prevalence of double triggering was significantly higher with NAVA (P <0.05, Table 4). Type II double triggering was due to ventilator cycled off when the EAdi dropped to 70% of its peak, followed by a rebound in inspiratory flow, cause of the retriggering, when cycled off to PEEP (see Additional file 3).

Table 1 Patient characteristics at enrollment

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>BMI (kg.m⁻²)</th>
<th>SAPS 2</th>
<th>Admission diagnosis</th>
<th>MV duration before inclusion (days)</th>
<th>FiO₂</th>
<th>PEEP (cmH₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>32.0</td>
<td>61</td>
<td>Pneumonia</td>
<td>8</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
<td>29.9</td>
<td>63</td>
<td>ARDS</td>
<td>2</td>
<td>0.4</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>91</td>
<td>16.0</td>
<td>55</td>
<td>ARDS</td>
<td>6</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>37.6</td>
<td>56</td>
<td>Pneumonia</td>
<td>12</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>77</td>
<td>27.8</td>
<td>47</td>
<td>Acute respiratory failure due to decompensation of COPD</td>
<td>7</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>27.5</td>
<td>35</td>
<td>Pneumonia</td>
<td>8</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>25.0</td>
<td>26</td>
<td>Acute respiratory failure due to decompensation of COPD</td>
<td>7</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>81</td>
<td>33.2</td>
<td>49</td>
<td>Pneumonia</td>
<td>4</td>
<td>0.4</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>74</td>
<td>18.4</td>
<td>63</td>
<td>Pneumonia</td>
<td>6</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>64</td>
<td>23.5</td>
<td>97</td>
<td>Pneumonia</td>
<td>11</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>11</td>
<td>67</td>
<td>23.0</td>
<td>51</td>
<td>ARDS</td>
<td>12</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>62</td>
<td>22.8</td>
<td>84</td>
<td>ARDS</td>
<td>7</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>13</td>
<td>62</td>
<td>25.0</td>
<td>49</td>
<td>Pneumonia</td>
<td>2</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>14</td>
<td>66</td>
<td>29.4</td>
<td>67</td>
<td>Acute respiratory failure due to decompensation of COPD</td>
<td>21</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>15</td>
<td>65</td>
<td>26.0</td>
<td>72</td>
<td>Pneumonia</td>
<td>12</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>16</td>
<td>67</td>
<td>31.6</td>
<td>46</td>
<td>Pneumonia</td>
<td>2</td>
<td>0.4</td>
<td>5</td>
</tr>
</tbody>
</table>

Median (IQR) 67 (63–75) 27 (23–30) 55 (48–64) 7.0 (5.5-11.0) 0.5 (0.5-0.5) 4 (4–5)

M, male; F, female; BMI, body mass index; SAPS II, Simplified Acute Physiology Score II; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; IQR, interquartile range; ARDS, acute respiratory distress syndrome, COPD, chronic obstructive pulmonary disease.

Table 2 Assistance levels in each experimental condition

<table>
<thead>
<tr>
<th>Mode, assistance setting</th>
<th>Level₅₀</th>
<th>Level₁₀₀</th>
<th>Level₁₅₀</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSV, inspiratory pressure (cmH₂O)</td>
<td>7.0 (7.0-7.2)</td>
<td>14.0 (11.5-15.2)</td>
<td>21.0 (17.2-21.7)</td>
<td>The inspiratory pressure support level, set by the clinician, is kept constant regardless of the mechanical properties of the lung/thorax and patient effort.</td>
</tr>
<tr>
<td>NAVA, NAVA level (cmH₂O/µV)</td>
<td>0.6 (0.4-0.9)</td>
<td>1.3 (0.8-1.8)</td>
<td>1.9 (1.2-2.7)</td>
<td>The NAVA level is a proportional gain factor expressed in cmH₂O/µV of EAdi. It represents the magnitude (in cmH₂O) of positive airway pressure applied per µV EAdi during the course of each inspiration.</td>
</tr>
<tr>
<td>PAV, proportion of assistance (%)</td>
<td>27 (25-35)</td>
<td>55 (50–70)</td>
<td>82 (75–95)</td>
<td>The proportion of assistance is the percentage of work provided by the ventilator. The rest of the work is provided by the patient.</td>
</tr>
</tbody>
</table>

EAdi, electrical activity of the diaphragm; PSV, pressure support ventilation; NAVA, neurally adjusted ventilatory assist; PAV, proportional assist ventilation. Data are provided as median (interquartile range).
No autotriggering was observed in any condition. Overall, the asynchrony index was significantly lower with PAV_{50} and PAV_{100} than with NAVA_{50} and NAVA_{100}, respectively (P < 0.05). Of note, only two patients exhibited an AI >10% in PSV_{150}, mostly due to a high number of ineffective efforts (patients 7 and 14). Dyspnea was able to be evaluated in only two patients because of insufficient cooperation (data not shown).

Gas exchange
Neither the mode (PSV, NAVA, PAV) nor the level of assistance (level_{50},_{100},_{150}) influenced PaO_{2}, PaCO_{2}, or pH, which remained not significantly different between all conditions, except for PaCO_{2} that was higher and pH that was lower with PAV_{100} than with NAVA_{100} (see Additional file 7 for detailed blood gas values).

Discussion
The main findings of our study are as follows: (1) PAV and NAVA both prevented overassistance-induced hyperinflation, in contrast with PSV; (2) PAV and NAVA restored a comparable level of breathing-pattern variability that was greater than the variability observed with PSV; (3) Regardless of the level of assistance, PAV and NAVA induced less patient-ventilator asynchrony than PSV, with the exception of double triggering, which was more frequent with NAVA. The similarities observed between NAVA and PSV in terms of breathing pattern, variability, and asynchrony are consistent with the conceptual similarities of these two modes.

Breathing pattern and central respiratory neural output
Increasing PSV assist levels were associated with increasing V_{T} values, in keeping with previous data [29,30]. In contrast, V_{T} remained stable with NAVA and PAV, despite increasing assist levels [12,31], suggesting that these modes protect against overdistention. With PSV, the end of the patient’s inspiratory effort does not determine cycling-off of the ventilator. A patient may therefore trigger a PSV breath with a small inspiratory effort, then relax, and be passively insufflated. If this breath is given at an excessive assist level, the insufflation may continue while the patient has already stopped inspiriting. In contrast, with PSV, NAVA and PAV deliver an insufflation that stops when either the output of the inspiratory centers to the diaphragm ends, in the case of NAVA (12), or when the inspiratory muscle activity ends, in the case of PAV.

In addition, because overdistention contributes to downregulate the activity of respiratory control centers (29), tidal volume is maintained constant with PAV and NAVA but not with PSV. The robustness of this protective biofeedback provided by proportional modes, as opposed to PSV, is illustrated in the present study by the marked alteration of the coupling between V_{T} and EAdi_{max} (that is, higher V_{T} / EAdi ratio) observed with PSV at high levels of assistance (see Figure 2), which was not observed with the two proportional modes.

Breath-by-breath variability
Fluctuations in the resting breathing pattern of healthy humans have been known for a long time [32]. Breathing pattern variability seems to originate from the activity of central pattern generators [33]. It is further influenced by the load–capacity relationship of the respiratory system: the higher the loading, the lower the variability [19,34,35].

In the present study, the variability of V_{T} with NAVA and PAV was greater than with PSV at each assistance level.
level. In contrast, the variability of EAdi was similar between the three modes, except at high assistance level. These data indicate that the increase in breath-to-breath variability observed during NAVA and PAV is actually due to “unmasking” of the underlying variability in central respiratory neural output and is a direct result of improvement of neuromechanical coupling. To our knowledge, these data, previously described in NAVA [19], have never been described with PAV. They suggest that PAV and NAVA both improve neuromechanical coupling in similar ways.

Patient-ventilator interaction

As previously observed, NAVA and PAV improved patient-ventilator synchrony as compared with PSV [12,21,22,24,25,31]. Although inspiratory trigger delays in all modes were consistently greater than previously reported [11,36,37], lower inspiratory and expiratory trigger delays seemed to be more frequently noted in NAVA. Wide variability of the delays (see Additional file 6) and their greater values can be ascribed to different ventilators used, varying levels of assist provided, experimental settings themselves, and the different etiologies of respiratory failure. It is noteworthy that, in the present study, PAV and NAVA provided a similar benefit on ineffective triggering. It suggests that PAV and NAVA improve the relationship between EAdi and tidal volume in a similar way, which in turn prevents chest hyperinflation, a major risk factor for ineffective triggering [7].

Two types of double triggering have been described in NAVA [25]. Type I double triggering is the result of a bi-phasic EAdi signal, but its significance is unknown, which is why, strictly speaking, it cannot be considered to be patient–ventilator asynchrony. With type II double triggering, however, one neural inspiration triggers two breaths, which was due to ventilator cycle off when the EAdi dropped to 70% of its peak, followed by a rebound in inspiratory flow, cause of the re-/triggering, when cycled off to PEEP. Pneumatic trigger set to pressure instead of flow might limit the rebound in inspiratory flow. We therefore considered only type II double triggering in the present study and observed that this asynchrony was significantly more frequent with NAVA than with PSV and PAV. The relevance of this asynchrony and how to decrease its prevalence in NAVA need further investigations [25].

The correlation between $V_T$ and $EAdi_{AUC}$ was much weaker in PSV than in NAVA or PAV, whereas no
significant difference was found between NAVA and PAV, which demonstrates that these two modes provide an assistance that is proportional to the central respiratory drive. This is consistent with the recent report from Akoumianaki et al. [38], showing that the correlation between the inspiratory integral of transdiaphragmatic pressure and \( V_T \) was weaker with NAVA than with PAV [38]. Interestingly, the correlation between \( E_{A_{\text{Di}}} \) max and \( P_{\text{max}} \) was higher in NAVA than in PAV, which may have two distinct explanations. First, during NAVA, \( E_{A_{\text{Di}}} \) and airway pressure are by definition strictly proportional and a strong correlation between \( E_{A_{\text{Di}}} \) max and \( P_{\text{max}} \) is intrinsic to NAVA. Second, as opposed to NAVA

### Table 3 Impact of ventilator mode and level of assistance on the main descriptors of breathing pattern and electrical activity of the diaphragm (EAdi)

<table>
<thead>
<tr>
<th>Mode</th>
<th>Level</th>
<th>( P_{\text{mean}} ) (cmH(_2)O)</th>
<th>( P_{\text{peak}} ) (cmH(_2)O)</th>
<th>Respiratory rate (n.min(^{-1}))</th>
<th>Tidal volume (mL.kg(^{-1}) IBW)</th>
<th>Minute ventilation (mL.min(^{-1}))</th>
<th>Inspiratory time (sec)</th>
<th>( E_{A_{\text{Di}}} ) max</th>
<th>( V_T/E_{A_{\text{Di}}} ) max</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSV</td>
<td>50</td>
<td>6.8 (6.1-8.7)</td>
<td>6.6 (5.5-9.9)</td>
<td>6.0 (4.8-8.4)</td>
<td>10.8 (8.9-15.8)</td>
<td>10.6 (8.2-14.1)</td>
<td>10.5 (7.8-13.9)</td>
<td>9.1 (5.9-10.5)*</td>
<td>0.67 (0.27-1.51)</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>9.8 (8.4-13.6)</td>
<td>7.5 (5.8-8.9)</td>
<td>6.0 (4.8-8.4)</td>
<td>12.5 (9.8-17.3)</td>
<td>10.6 (8.2-14.1)</td>
<td>10.1 (7.8-13.9)</td>
<td>7.4 (5.9-10.5)*</td>
<td>0.72 (0.67-0.82)</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>11.4 (9.2-13.4)</td>
<td>8.7 (5.9-10.3)</td>
<td>6.2 (5.4-7.8)</td>
<td>12.5 (9.8-17.3)</td>
<td>10.1 (7.8-13.9)</td>
<td>11.1 (8.6-14.5)</td>
<td>7.4 (5.7-10.1)*</td>
<td>0.85 (0.69-1.18)</td>
</tr>
<tr>
<td>NAVA</td>
<td>50</td>
<td>13.9 (12.4-15.7)</td>
<td>19.2 (16.1-22.4)*</td>
<td>16.2 (13.1-17.9)*</td>
<td>10.9 (8.0-13.8)</td>
<td>10.9 (8.5-13.2)</td>
<td>28.4 (22.6-29.7)</td>
<td>25.9 (23.4-32.3)*</td>
<td>4.7 (2.9-15.1)</td>
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<tr>
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<td>100</td>
<td>20.8 (17.8-22.5)</td>
<td>25.4 (19.9-31.4)*</td>
<td>20.5 (18.5-24.1)*</td>
<td>28.4 (22.6-29.7)</td>
<td>25.9 (23.4-32.3)</td>
<td>29.1 (23.4-41.3)*</td>
<td>25.9 (23.4-32.3)*</td>
<td>10.9 (8.9-12.0)</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>28.4 (22.6-29.7)</td>
<td>29.1 (23.4-41.3)*</td>
<td>25.9 (23.4-32.3)*</td>
<td>28.4 (22.6-29.7)</td>
<td>25.9 (23.4-41.3)*</td>
<td>29.1 (23.4-41.3)*</td>
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<td>10.9 (8.9-12.0)</td>
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<tr>
<td>PAV</td>
<td>50</td>
<td>11.4 (9.2-13.4)</td>
<td>10.9 (8.0-13.8)</td>
<td>10.9 (8.5-13.2)</td>
<td>11.4 (9.2-13.4)</td>
<td>10.9 (8.5-13.2)</td>
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<td>100</td>
<td>20.8 (17.8-22.5)</td>
<td>25.4 (19.9-31.4)*</td>
<td>20.5 (18.5-24.1)*</td>
<td>28.4 (22.6-29.7)</td>
<td>25.9 (23.4-32.3)*</td>
<td>29.1 (23.4-41.3)*</td>
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<td>28.4 (22.6-29.7)</td>
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<tr>
<td></td>
<td>150</td>
<td>28.4 (22.6-29.7)</td>
<td>29.1 (23.4-41.3)*</td>
<td>25.9 (23.4-32.3)*</td>
<td>28.4 (22.6-29.7)</td>
<td>25.9 (23.4-32.3)*</td>
<td>29.1 (23.4-41.3)*</td>
<td>25.9 (23.4-32.3)*</td>
<td>28.4 (22.6-29.7)</td>
</tr>
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</table>

\( E_{A_{\text{Di}}} \) max, peak \( E_{A_{\text{Di}}} \); \( E_{A_{\text{Di}}} \) AUC, area under the \( E_{A_{\text{Di}}} \) curve; \( P_{\text{mean}} \); mean inspiratory airway pressure; \( P_{\text{peak}} \), maximum inspiratory airway pressure; PSV, pressure support ventilation; PAV, proportional assist ventilation; NAVA, neurally adjusted ventilatory assist.

Level 100 is a medium assistance level set to obtain a \( V_T \) of 6 to 8 ml/kg ideal body weight. Level 50 is a low assistance level defined as level 100 decreased by 50%. Level 150 is a high assistance level defined as level 100 increased by 50%. Data are provided as median (interquartile range).

* \( P < 0.05 \) with PSV; ** \( P < 0.05 \) with NAVA.

### Figure 3 Impact of ventilator mode and level of assistance on the coefficient of variation of tidal volume (CV\(_{\text{VT}}\)) and maximum electrical activity of the diaphragm (CV\(_{E_{A_{\text{Di}}} \text{max}}\)).

Pressure support ventilation (PSV\(_{100}\)), neurally adjusted ventilatory assist (NAVA\(_{100}\)), and proportional assist ventilation (PAV\(_{100}\)) are medium levels of assistance set to obtain a \( V_T \) between 6 and 8 ml/kg ideal body weight. PSV\(_{50}\), NAVA\(_{50}\), and PAV\(_{50}\) are low levels of assistance defined by decreasing the assistance level by 50% in each condition. Inversely, PSV\(_{150}\), NAVA\(_{150}\), and PAV\(_{150}\) are defined by increasing the assistance level by 50% in each condition. * \( P < 0.05 \) with PSV; ** \( P < 0.05 \) with NAVA; Data are expressed as median and interquartile range.
Table 4 Impact of ventilator mode and level of assistance on patient-ventilator interaction and asynchrony indices

<table>
<thead>
<tr>
<th></th>
<th>PSV</th>
<th>NAVA</th>
<th>PAV</th>
</tr>
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<tr>
<td>Inspiratory trigger delay (msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>level50</td>
<td>162 (109–241)</td>
<td>157 (138–289)</td>
<td>185 (140–305)</td>
</tr>
<tr>
<td>level100</td>
<td>170 (140–282)</td>
<td>124 (100–238)</td>
<td>224 (176–280)</td>
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<tr>
<td>level150</td>
<td>266 (140–427)</td>
<td>164 (99–278)*</td>
<td>201 (166–317)</td>
</tr>
<tr>
<td>Expiratory trigger delay (msec)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>level50</td>
<td>156 (112–191)</td>
<td>151 (125–175)</td>
<td>152 (107–175)</td>
</tr>
<tr>
<td>level100</td>
<td>212 (176–273)</td>
<td>157 (140–188)*</td>
<td>182 (116–230)</td>
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<tr>
<td>level150</td>
<td>255 (227–541)</td>
<td>146 (131–218)*</td>
<td>225 (169–333)</td>
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<td>Relationship between Pmax and EAdi max (r²)</td>
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<tr>
<td>level50</td>
<td>0.02 (0.01-0.04)</td>
<td>0.55 (0.51-0.65)*</td>
<td>0.02 (0.00-0.04)*</td>
</tr>
<tr>
<td>level100</td>
<td>0.03 (0.01-0.08)</td>
<td>0.85 (0.78-0.90)*</td>
<td>0.04 (0.00-0.07)*</td>
</tr>
<tr>
<td>level150</td>
<td>0.03 (0.01-0.06)</td>
<td>0.64 (0.43-0.86)*</td>
<td>0.03 (0.02-0.08)*</td>
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<tr>
<td>Relationship between V1 and EAdi Luc (r²)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>level50</td>
<td>0.15 (0.14-0.19)</td>
<td>0.48 (0.40-0.57)*</td>
<td>0.39 (0.25-0.45)*</td>
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<tr>
<td>level100</td>
<td>0.13 (0.06-0.22)</td>
<td>0.64 (0.60-0.79)*</td>
<td>0.29 (0.21-0.42)</td>
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<tr>
<td>level150</td>
<td>0.02 (0.01-0.06)</td>
<td>0.72 (0.65-0.88)*</td>
<td>0.28 (0.25-0.41)*</td>
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<tr>
<td>Ineffective efforts (n.min⁻¹)</td>
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<tr>
<td>level50</td>
<td>0.00 (0.00-0.07)</td>
<td>0.00 (0.00-0.09)*</td>
<td>0.00 (0.00-0.03)*</td>
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<tr>
<td>level100</td>
<td>0.03 (0.00-0.26)</td>
<td>0.00 (0.00-0.09)*</td>
<td>0.00 (0.00-0.00)*</td>
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<td>level150</td>
<td>0.27 (0.01-1.23)</td>
<td>0.00 (0.00-0.00)*</td>
<td>0.00 (0.00-0.00)*</td>
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<tr>
<td>Auto-triggering (n.min⁻¹)</td>
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<td></td>
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<tr>
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<td>0.00 (0.00-0.03)</td>
<td>0.00 (0.00-0.00)</td>
<td>0.00 (0.00-0.00)</td>
</tr>
<tr>
<td>level100</td>
<td>0.00 (0.00-0.03)</td>
<td>0.00 (0.00-0.00)</td>
<td>0.00 (0.00-0.00)</td>
</tr>
<tr>
<td>level150</td>
<td>0.00 (0.00-0.00)</td>
<td>0.00 (0.00-0.00)</td>
<td>0.00 (0.00-0.00)</td>
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<tr>
<td>Double triggering (n.min⁻¹)</td>
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<td>level50</td>
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<td>0.42 (0.08-0.59)*</td>
<td>0.00 (0.00-0.03)*</td>
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<tr>
<td>level100</td>
<td>0.00 (0.00-0.18)</td>
<td>0.33 (0.10-0.92)*</td>
<td>0.00 (0.00-0.10)*</td>
</tr>
<tr>
<td>level150</td>
<td>0.00 (0.00-0.21)</td>
<td>0.30 (0.02-0.87)*</td>
<td>0.00 (0.00-0.20)*</td>
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<tr>
<td>Asynchrony index (%)</td>
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<td></td>
<td></td>
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<tr>
<td>level50</td>
<td>0.21 (0.06-0.65)</td>
<td>1.41 (0.34-2.91)*</td>
<td>0.13 (0.00-0.44)*</td>
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<tr>
<td>level100</td>
<td>0.61 (0.04-1.28)</td>
<td>1.73 (0.38-2.69)</td>
<td>0.00 (0.00-0.58)*</td>
</tr>
<tr>
<td>level150</td>
<td>1.65 (0.58-5.77)</td>
<td>1.17 (0.05-3.99)</td>
<td>0.19 (0.00-1.12)</td>
</tr>
</tbody>
</table>

EAdi Luc, area under the diaphragmatic electrical activity curve; PSV, pressure support ventilation; NAVA, neurally adjusted ventilatory assist; PAV, proportional assist ventilation; VT, tidal volume. Level100 is a medium assistance level set to obtain a VT of 6 to 8 ml/kg of ideal body weight. Level50 is a low assistance level defined as level100 decreased by 50%. Level150 is a high assistance level defined as level100 increased by 50%. The number of each type of asynchrony is reported as the total number of each event per minute. Asynchrony index is defined as the total number of asynchrony events × 100/(ventilator respiratory rate + ineffective efforts).

*P < 0.05 with PSV; †P < 0.05 with NAVA; data are expressed as median (interquartile range).

that delivers an assistance proportional to the only diaphragm activity, PAV delivers an assistance that is proportional to the whole inspiratory activity of respiratory muscles. As a consequence, PAV integrates not only diaphragm activity, but also the activity of extradiaphragmatic inspiratory muscles such as scalenes or parasternal intercostal muscles [39].

Limitations of the study

Our study has several limitations. First, as patients at high risk of asynchrony (for example, difficult-to-wean or severe COPD patients) were not specifically selected in this study [7] and because we targeted a VT of 6 to 8 ml/kg in level100 [40], a very low incidence of asynchrony was observed with all modes and conditions. This study may therefore have underestimated the benefits of NAVA and PAV [20,39,41,42], but we deliberately decided to compare these modes in patients in the recovery phase after acute respiratory failure encountered in daily practice rather than in a very selected population, with the risk of showing results that would be transposable only to a niche population.

Second, the trials in our study were probably not sufficiently long to allow an improvement of gas exchange. This might explain why, despite a greater variability of the breathing pattern in PAV and NAVA, no impact on PaO₂ was observed in contrast with previously published results [14].

Third, the choice of a resulting VT of 6 to 8 ml/kg to match the assistance level100 with the three modes may be questionable. Indeed, a poor correlation between VT and PAV %Assist [43] as well as NAVA level [18] has been reported. In addition, the high VT variability may have jeopardized the accuracy of its setting. However, the fact that we observed a comparable Pmax with the three modes at assistance level100 suggests that the patients received a comparable level of assistance.

Fourth, because we focused on patients in the recovery phase after acute respiratory failure and because PSV50 could not be lower than 7 cmH₂O, PSV100 settings could sometimes be very close to PSV50.

Fifth, although the expiration starts at 70% of the EAdimax in NAVA, the expiratory trigger delay was calculated as the time difference between EAdimax and the end of insufflation by the ventilator within the three modes. Finally, contrary to the sequence of the ventilatory modes tested, the sequence of the level of assistance was not randomized. Therefore, we cannot rule out a potential time effect.

Clinical implications

Most of our findings are potentially clinically relevant. Lung-protective ventilation has become a major concern in ICU patients, even in those without acute respiratory distress syndrome [44,45]. Preventing alveolar overdistention and subsequent volutrauma caused by lung hyperinflation is now a major therapeutic goal. In this
respect, NAVA and PAV provide an interesting tool to prevent overassistance-induced hyperinflation.

Variability of breathing pattern has become a matter of concern in ICU patients, as a recent study showed that a higher variability of respiratory rate was associated with better prognosis [46]. In addition, a more variable breathing pattern is associated with better pulmonary function in animal models of lung injury [47-51]. Finally, severe patient-ventilator asynchrony is associated with longer duration of mechanical ventilation and a greater need for tracheostomy [7]. Of note, patient-ventilator asynchrony may be either a cause or a consequence of the severity of the respiratory disease requiring mechanical ventilation. Whether optimization of ventilatory settings, by using PAV or NAVA, can shorten the duration of mechanical ventilation by reducing the incidence of asynchrony, has therefore not been demonstrated.

Conclusion
In conclusion, PAV and NAVA both prevent overdetermination and improve neuromechanical coupling and patient-ventilator asynchrony in fairly similar ways compared with PSV. Further studies are needed to evaluate the possible clinical benefits of NAVA and PAV on clinical outcomes, especially in the recovery phase of acute respiratory failure.

Key messages
- The variability of $V_T$ with NAVA and PAV is greater than with PSV at each assistance level.
- PAV and NAVA both restore “natural” variability of breathing.
- The increase in breath-to-breath variability observed during NAVA and PAV is due to “unmasking” of the underlying variability in central respiratory neural output and is a direct result of improvement of neuromechanical coupling.
- NAVA and PAV both improve patient-ventilator synchrony as compared with PSV, especially on ineffective triggering.

Additional files

**Additional file 1:** Waveforms of EAdi, pressure and flow for all three modes (PSV$_{100}$, NAVA$_{100}$, PAV$_{100}$) in the same patient.

**Additional file 2:** Definitions of patient-ventilator interaction indices and the main asynchronies collected.

**Additional file 3:** Example of Type II double triggering under NAVA.

**Additional file 4:** Inspiratory pressure (cmH$_2$O) over PEEP for each patient under the three modes and three assist levels.

**Additional file 5:** Impact of ventilator mode and assistance level on the coefficients of variation of neural respiratory rate, tidal volume, and peak electrical activity of the diaphragm (EAdi$_{max}$).

**Additional file 6:** Distribution of the inspiratory trigger delays per mode.

**Additional file 7:** Impact of ventilator mode and level of assistance on gas exchange.

**Abbreviations**
AI: Asynchrony index; CV: coefficient of variation; CV$_{EAdi_{max}}$: coefficient of variation of EAdi$_{max}$; EAdi$_{max}$: electrical activity of the diaphragm; EAdi$_{max}$: maximum electrical activity of the diaphragm; EAdi$_{int}$: integrated EAdi activity; IQR: interquartile range; NAVA: neurally adjusted ventilatory assist; PAV: proportional assisted ventilation; PEEP: positive end-expiratory pressure; $P_{peak}$: peak airway pressure; PSV: pressure support ventilation; RR: respiratory rate; T1: inspiratory time; VT: tidal volume.

**Competing interests**
The Association pour le Développement et l’Organisation de la Recherche en Pneumologie, a nonprofit structure that supports the research activities of the “Service de Pneumologie et Réanimation Médicale, Groupe Hospitalier Pitie-Salpétrière,” has received an unrestricted research grant from Maquet France SA, Orléans, France (2009), and Coviden, Dublin, Ireland (2013), to support pathophysiological research studies on NAVA and PAV, respectively. A. Demoule is the principal investigator of a study on NAVA, has been a consultant for Coviden, and has given lectures for Coviden and Maquet. The others authors have no conflict of interest.

**Authors’ contributions**
MS conceived the study and contributed to the data collection, analysis, statistics, and writing of the manuscript. FK contributed to the data collection and analysis. JC contributed to data collection and analysis. TP contributed to the data analysis and the revision of the manuscript. EM contributed to the data collection, their analysis, and the revision of the manuscript. RP contributed to the data collection and revised the manuscript. TS drafted the design of the study, and contributed to the writing and the revision of the manuscript. AD conceived the study and contributed to the data collection, analysis, statistics, and writing of the manuscript. All authors read and approved the manuscript.

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Dr. Romain Persichini is an ICU physician.
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Pr. Alexandre Demoule is a Professor of intensive care.

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Written informed consent was obtained from the patients for publication of their individual details and accompanying images in this manuscript. The consent form is held by the authors and is available for review by the Editor-in-Chief.

**Author details**
References


