Titration and Implementation of Neurally Adjusted Ventilatory Assist in Critically Ill Patients*

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Background: Neurally adjusted ventilatory assist (NAVA) delivers assist in proportion to the patient’s respiratory drive as reflected by the diaphragm electrical activity (EAdi). We examined to what extent NAVA can unload inspiratory muscles, and whether unloading is sustainable when implementing a NAVA level identified as adequate (NAVAal) during a titration procedure.

Methods: Fifteen adult, critically ill patients with a PaO2/fraction of inspired oxygen (FIO2) ratio < 300 mm Hg were studied. NAVAal was identified based on the change from a steep increase to a less steep increase in airway pressure (Paw) and tidal volume (VT) in response to systematically increasing the NAVA level from low (NAVAlow) to high (NAVAhigh). NAVAal was implemented for 3 h.

Results: At NAVAal, the median esophageal pressure time product (PTPes) and EAdi values were reduced by 47% of NAVAlow (quartiles, 16 to 69% of NAVAlow) and 18% of NAVAlow (quartiles, 15 to 26% of NAVAlow), respectively. At NAVAhigh, PTPes and EAdi values were reduced by 74% of NAVAlow (quartiles, 56 to 86% of NAVAlow) and 36% of NAVAlow (quartiles, 21 to 51% of NAVAlow; p < 0.005 for all). Parameters during 3 h on NAVAal were not different from parameters during titration at NAVAal, and were as follows: VT, 5.9 mL/kg predicted body weight (PBW) [quartiles, 5.4 to 7.2 mL/kg PBW]; respiratory rate (RR), 29 breaths/min (quartiles, 22 to 33 breaths/min); mean inspiratory Paw, 16 cm H2O (quartiles, 13 to 20 cm H2O); PTPes, 45% of NAVAlow (quartiles, 28 to 57% of NAVAlow); and EAdi, 76% of NAVAlow (quartiles, 63 to 89% of NAVAlow). PaO2/FIO2 ratio, PaCO2, and cardiac performance during NAVAal were unchanged, while Paw and VT were lower, and RR was higher when compared to conventional ventilation before implementing NAVAal.

Conclusions: Systematically increasing the NAVA level reduces respiratory drive, unloads respiratory muscles, and offers a method to determine an assist level that results in sustained unloading, low VT, and stable cardiopulmonary function when implemented for 3 h.

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Key words: diaphragm; electromyography; respiration; respiratory failure; ventilators

Abbreviations: au = arbitrary units; CLdyn = dynamic lung compliance; CoVent = conventional ventilation; EAdi = electrical activity of the diaphragm; FIO2 = fraction of inspired oxygen; NAVA = neurally adjusted ventilatory assist; NAVAal = adequate neurally adjusted ventilatory assist level; NAVAhigh = highest neurally adjusted ventilatory assist level; NAVAlow = lowest neurally adjusted ventilatory assist level; PAV = proportional assist ventilation; Paw = inspiratory airway pressure; PBW = predicted body weight; PEEP = positive end-expiratory pressure; Pes = esophageal pressure; Ptp = transpulmonary pressure; PTPes = esophageal pressure time product; RRneural = neural respiratory rate; RRvent = ventilator respiratory rate; SAS = sedation agitation scale; Ti neural = neural inspiratory time; VE = minute ventilation; VT = tidal volume

In critically ill patients, the application of mechanical ventilation should ensure sufficient ventilation, avoid excessive exertion or disuse of the respiratory muscles, and avoid ventilator-induced lung injury. Given the high variability in disease processes and states, the application of predefined, uniform values for ventilator parameters, such as tidal volume (VT) or airway pressure (Paw), is unlikely to provide...
optimal assist at all times. How to tailor ventilator settings to each individual patient is difficult due to the lack of tools for monitoring patients’ respiratory demand and responses to mechanical ventilation.

Neurally adjusted ventilatory assist (NAVA) delivers pressure in proportion to the electrical activity of the diaphragm (EAdi) throughout inspiration1 and hence responds to the patient’s respiratory drive. A proportionality factor (referred to as the NAVA level) determines the delivered pressure for a given EAdi amplitude (i.e., centimeters of H2O per unit of EAdi). Studies in animals and healthy volunteers have demonstrated that NAVA protects against excessive Paw and Vt by a down-regulation of EAdi at high NAVA levels,2,3 unloads the respiratory muscles, and improves subject-ventilator synchrony.4

The aim of the present study was to evaluate to what extent NAVA can unload inspiratory muscles, and whether unloading without evidence of progress respiratory failure is sustainable when implementing a NAVA level identified as adequate (NAVAal) during a titration procedure. We hypothesized that the down-regulation of EAdi in response to the stepwise increase in the NAVA level prevents excessive increases in Paw and Vt once the level of assist satisfies the patient’s respiratory demand. We assumed that such a patient-controlled limitation of Paw and Vt during a NAVA level titration procedure can be used to identify a NAVA level that results in stable cardiopulmonary function when implemented for 3 consecutive h.

**Materials and Methods**

**Patients**

The protocol was approved by the Research Ethics Board of St. Michael’s Hospital. Patients were recruited from June 2005 to April 2006. Written informed consent was obtained from substitute decision makers.

Invasively ventilated patients (PaO2/fraction of inspired oxygen [FIO2] ratio ≤ 300 at FIO2 ≤ 0.8) who were stable from a cardiopulmonary perspective and who were able to pneumatically trigger the ventilator were eligible for the study, regardless of the assist level used during conventional ventilation (CoVent). Settings for CoVent and positive end-expiratory pressure (PEEP) level were used as prescribed by the clinician. Exclusion criteria and detailed methods are provided in the online supplementary material.

**NAVA Methods**

All patients were ventilated with a commercially available ventilator (Servo300 ventilator; Maquet; Solna, Sweden) modified to perform both CoVent and NAVA. During NAVA the ventilator was controlled by the EAdi that was processed as previously described by Sinderby and colleagues.1,5–8 Briefly, during NAVA the EAdi signal is used to trigger cycle-on and cycle-off of the inspiratory assist. The delivered Paw during inspiration is determined by the EAdi amplitude multiplied by the proportionality factor (NAVA level) every 16 ms.

**Study Protocol**

**NAVA Level Titration:** Schematic figures of the study protocol are provided in the online supplement (Figs E1 and E2). First, in order to increase respiratory drive while not provoking too much distress, the NAVA level was reduced to a minimal level of 0.1 to 1.0 cm H2O/arbitrary units (au), resulting in a minimal assist of 3.2 cm H2O (quartiles, 2.0 to 4.0 cm H2O) above PEEP for a total of 3 min or until the EAdi doubled. This lowest NAVA level will subsequently be referred to as NAVAlow.

When sufficient EAdi was detectable, as defined by a maximum EAdi signal during NAVAlow of about two times the trigger level, a NAVA level titration was performed as follows: the NAVA level was increased every third minute in steps of 1 cm H2O/au while observing the Paw response displayed in a trend graph. The transition from an initial steep increase in Paw (first response) to a less steep increase in Paw (second response) was identified by researchers through royalties. Drs. Beck and Sinderby each own 50% of Neurovent Research Inc. Neurovent Research Inc is a research and development company that builds the equipment and catheters for research studies. Neurovent Research Inc has a consulting agreement with Maquet Critical Care. Dr. Slutsky consults for companies that make ventilators, specifically Maquet Critical Care and Hamilton Medical, and is compensated for these consultations. Drs. Brandre, Leong-Poi, Brunet, and Hutcheson have reported to the ACCP that no compensated for these consultations. Drs. Brunet, Leong-Poi, Slutsky, and Sinderby, University of Toronto, Toronto, ON, Canada; and the Division of Cardiology (Drs. Leong-Poi and Hutchison), St. Michael’s Hospital, Toronto, ON, Canada. Some of the results have been presented in abstract format at the annual meetings of the European Society of Intensive Care Medicine in Barcelona, Spain, September 24 to 27, 2006, and of the American Thoracic Society in San Francisco, CA, May 18 to 23, 2007.

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The work was performed at the Department of Critical Care Medicine, St. Michael’s Hospital, Toronto, ON, Canada. Drs. Beck and Sinderby have made inventions related to the neural control of mechanical ventilation that are patented. The license for these patents belongs to Maquet Critical Care. Future commercial uses of this technology may provide financial benefit to Drs. Beck and Sinderby through royalties. Drs. Beck and Sinderby each own 50% of Neurovent Research Inc. Neurovent Research Inc is a research and development company that builds the equipment and catheters for research studies. Neurovent Research Inc has a consulting agreement with Maquet Critical Care. Dr. Slutsky consults for companies that make ventilators, specifically Maquet Critical Care and Hamilton Medical, and is compensated for these consultations. Drs. Brandre, Leong-Poi, Brunet, and Hutcheson have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article. Manuscript received July 15, 2008; revision accepted October 15, 2008.

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Original Research
**PEEP Reduction Trial:** While applying NAVAal, PEEP was reduced in steps of 3 cm H2O every third minute to a minimal level of 3 cm H2O.

**Implementation of NAVAal:** After 15 to 20 min receiving CoVent, NAVAal was applied for 3 consecutive h while using the prescribed level of PEEP.

**Follow-up:** The EAdi was recorded daily for 10 min for up to 7 days during CoVent.

**Measurements**

EAdi was measured with an array of electrodes mounted on a nasogastric tube that also contained a balloon to measure esophageal pressure (Pes). Flow was obtained from the ventilator, and Paw was measured at the Y-piece. The signals for EAdi, flow, Paw, and Pes were monitored continuously online and recorded intermittently. Arterial BP and blood gas levels were obtained from a radial artery line. Echocardiography was performed (Sonos 5500; Philips Ultrasound; Bothell, WA) during CoVent and during the third hour receiving NAVAal.

**Data Analysis**

Mean inspiratory deflections of EAdi, Pes, and Paw, neural inspiratory time (Tneural), and ventilator inspiratory time were analyzed off-line breath-by-breath. Vt was derived by integrating inspiratory flow. Dynamic lung compliance (CLdyn), mean dynamic transpulmonary pressure (Ptp) during inspiration, esophageal pressure time product (PTPes), ventilator pressure time product, neural respiratory rate (RRneural), ventilator respiratory rate (RRvent), minute ventilation (Ve), and coefficients of variation were calculated. Average values of all breaths during 5-min periods are reported.

**Statistical Analysis**

The data were not normally distributed (Kolmogorov-Smirnov test). Statistical analysis was performed using a statistical software package (SigmaStat, version 3.11; Systat Software Inc; San Jose, CA). The Wilcoxon signed rank test was used to compare groups with paired data. The Friedman test was used for repeated measurements. Correlation was assessed by linear regression. The level of significance was p < 0.05.

**Results**

Results are presented as the median (quartiles). A convenience sample of 15 patients was enrolled into the study. For patient characteristics, see Table 1. In 14 patients, the maximum EAdi reached between 2.1 and 5.5 times the trigger level during NAVAlow, and between 1.9 and 4.0 times the trigger level during the application of NAVAal. In patient 11, the maximum EAdi at NAVAlow was below the trigger level, and this patient was excluded from the NAVA portion of the study.

**NAVA Level Titration**

Changes observed for Vt, Paw, EAdi, and PTPes during titration of the NAVA level are shown in Figure 1 (and Fig E2 in the online supplementary material) for a single patient and in Figure 2 for the group.

<table>
<thead>
<tr>
<th>Patient/</th>
<th>Gender/</th>
<th>APACHE II Score</th>
<th>SAS</th>
<th>PBW, kg</th>
<th>Time Spent Receiving Invasive Mechanical Ventilation, d</th>
<th>Main Diagnosis</th>
<th>CoVent Mode/</th>
<th>Assist Level in cm H2O</th>
<th>PEEPs Level, cm H2O</th>
<th>CLdyn, mL/cm H2O</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/78</td>
<td>22</td>
<td>3</td>
<td>66</td>
<td>13</td>
<td>Chest trauma with hemothorax</td>
<td>44</td>
<td>PSV/12</td>
<td>14</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>2/F/78</td>
<td>NA</td>
<td>4</td>
<td>55</td>
<td>3</td>
<td>Aspiration of gastric content. Atrial fibrillation</td>
<td>33</td>
<td>PSV/10</td>
<td>5</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>3/F/54</td>
<td>19</td>
<td>4</td>
<td>53</td>
<td>17</td>
<td>Pheochromocytoma, ARDS, pulmonary edema</td>
<td>31</td>
<td>PCV/14</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/M/55</td>
<td>NA</td>
<td>1</td>
<td>68</td>
<td>24</td>
<td>ACS with right heart failure. Patient died.</td>
<td>35</td>
<td>PTV/14</td>
<td>8</td>
<td>39</td>
<td></td>
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<tr>
<td>5/F/54</td>
<td>32</td>
<td>3</td>
<td>55</td>
<td>34</td>
<td>Small bowel perforation with septic shock</td>
<td>46</td>
<td>PTV/10</td>
<td>5</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>6/M/68</td>
<td>28</td>
<td>3</td>
<td>73</td>
<td>12</td>
<td>AAA repair</td>
<td>46</td>
<td>PTV/8</td>
<td>8</td>
<td>78</td>
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</tr>
<tr>
<td>7/F/23</td>
<td>31</td>
<td>3</td>
<td>60</td>
<td>11</td>
<td>Severe asthma, retroperitoneal hematoma</td>
<td>33</td>
<td>PTV/12</td>
<td>5</td>
<td>72</td>
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<tr>
<td>8/M/38</td>
<td>19</td>
<td>2</td>
<td>61</td>
<td>7</td>
<td>Peritonitis after kidney transplant</td>
<td>50</td>
<td>PTV/5</td>
<td>5</td>
<td>92</td>
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</tr>
<tr>
<td>9/M/70</td>
<td>16</td>
<td>3</td>
<td>68</td>
<td>8</td>
<td>AAA repair</td>
<td>57</td>
<td>PTV/12</td>
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<tr>
<td>10/M/78</td>
<td>17</td>
<td>3</td>
<td>63</td>
<td>5</td>
<td>Abdominal wall repair, severe COPD</td>
<td>42</td>
<td>PTV/10</td>
<td>8</td>
<td>24</td>
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<tr>
<td>11/F/75</td>
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<td>3</td>
<td>45</td>
<td>9</td>
<td>Cholecystitis with severe sepsis</td>
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<td>PTV/10</td>
<td>10</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>12/M/59</td>
<td>31</td>
<td>3</td>
<td>73</td>
<td>7</td>
<td>Pulmonary embolism, AAA repair</td>
<td>41</td>
<td>PTV/12</td>
<td>12</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>13/F/46</td>
<td>25</td>
<td>2</td>
<td>52</td>
<td>10</td>
<td>Pneumococci, recovering from ARDS</td>
<td>39</td>
<td>PTV/22</td>
<td>8</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>14/M/58</td>
<td>37</td>
<td>2</td>
<td>75</td>
<td>25</td>
<td>Pulmonary vasculitis, recovering from ARDS</td>
<td>49</td>
<td>PTV/12</td>
<td>10</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>15/M/49</td>
<td>17</td>
<td>1</td>
<td>73</td>
<td>27</td>
<td>Pneumococci, recovering from ARDS</td>
<td>33</td>
<td>PTV/20</td>
<td>20</td>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>

*The patients were mechanically ventilated for 10 days (quartiles, 7 to 19 days) prior to the study. F = female; M = male; APACHE = acute physiology and chronic health evaluation score; PSV = pressure support ventilation; PCV = pressure control ventilation; NA = not available; ACS = acute coronary syndrome; AAA = abdominal aortic aneurysm.
The NAVA level was increased in nine steps (range, 5 to 12 steps) over a 29-min period (quartiles, 21 to 33 min) starting from a NAVAlow at 0.5 cm H2O/au (quartiles, 0.1 to 1.0 cm H2O/au) to the highest NAVA level (NAVAhigh) of 10 cm H2O/au (quartiles, 7 to 12 cm H2O/au; p < 0.001). NAVAl was identified at 4.5 cm H2O/au (quartiles, 4.0 to 7.0 cm H2O/au). At NAVAhigh, PTPes and EAdi were reduced by 74% of NAVAlow (quartiles, 56 to 86% of NAVAlow) and 36% of NAVAlow (quartiles, 21 to 51% of NAVAlow; p < 0.001 for both comparisons), respectively. NAVAhigh was more than twice the NAVAl (p < 0.001).

The initial increase in Paw and Vt between NAVAlow and NAVAl (first response) was associated with a reduction in PTPes by 47% of NAVAlow (quartiles, 16 to 69% of NAVAlow; p < 0.001), and in EAdi by 18% of NAVAlow (quartiles, 15 to 26% of NAVAlow; p = 0.005), as depicted in Figure 2. Note that the relative reduction for EAdi was smaller than that for PTPes, as previously described.3 Thereafter, further increases in the NAVA level did not significantly change either Paw or Vt (second response), while the reduction of PTPes and EAdi continued from NAVAl to NAVAhigh. The RRneural was 31 breaths/min (quartiles, 20 to 35 breaths/min) at NAVAlow, decreased to 29 breaths/min (quartiles, 20 to 32 breaths/min) at NAVAl (p = 0.05 vs NAVAlow), and was 27 breaths/min (quartiles, 20 to 34 breaths/min) at NAVAhigh (difference not significant vs NAVAl). No change was observed for Tneural during the titration. VE increased from 0.14 L/kg predicted body weight (PBW) per minute (quartiles, 0.11 to 0.18 breaths/min) at NAVAlow to 0.15 L/kg PBW per minute (quartiles, 0.13 to 0.21 L/kg PBW per minute; p < 0.05) at NAVAl and reached 0.16 L/kg PBW per minute (quartiles, 0.14 to 0.22 L/kg PBW per minute) at NAVAhigh (difference not significant vs NAVAl). EAdi and mean negative deflections in Pes during the titration were positively correlated (r = 0.87 [quartiles, 0.67 to 0.94]; p < 0.05).

The relationship among Paw, Pes, and Ptp during the NAVA level titration is depicted in Figure 3. During the first response, Paw and Ptp increased while Pes remained unchanged; whereas, during the second response the relationship between Paw and Pes paralleled the Ptp isopleths such that the lung-distending pressure (and hence Vt) remained unchanged despite a continued increase in the NAVA level.

**PEEP Reduction Trial**

The measured PEEP at the prescribed level was 8.5 cm H2O (quartiles, 5.3 to 11.8 cm H2O) and was reduced to 2.8 cm H2O (quartiles, 2.4 to 3.5 cm H2O; p < 0.001) over 11 min (quartiles, 8 to 13 min) causing the mean expiratory EAdi and RRneural to increase by 3% (quartiles, 1 to 6%; p = 0.005) and by 2.2 breaths/min (quartiles, 0.3 to 3.1 breaths/min;
p < 0.05), respectively. No changes were observed for mean inspiratory EAdi, Vt, and pulse oximetric saturation.

**Implementation of NAVAal for 3 h**

Throughout the 3 h receiving NAVAal, there were no significant changes over time in Vt, Paw, EAdi, Pes, PTPes, Tneural, RRneural, Ve, PACO₂, PAO₂/FIO₂ ratio (FIO₂ remained unchanged during the study in all patients), arterial pH, mean arterial pressure, heart rate, and sedation agitation scale (SAS) score (see Table E1 in the online supplementary material). The average values for Vt, Paw, EAdi, and PTPes during 3 h receiving NAVAal were not different from the values observed at NAVAal during the NAVA level titration (Fig 2).

Comparison of NAVAal at the end of the 3 h of ventilation to CoVent (Table E2) showed slight increases for Ve and RRneural (p < 0.05 for both); large decreases for Paw, Ptp, ventilator pressure time product, and ventilator inspiratory time (p < 0.05 for all); and minute decreases for Vt and Tneural (p < 0.05). The coefficient of variation for Vt during CoVent was 9.1% (quartiles, 6.5 to 12.5%) and was increased to 17.7% (quartiles, 16.1 to 24.8%; p < 0.05) after 3 h receiving NAVAal. No difference was observed for EAdi, Pes, PTPes, PACO₂, PAO₂/FIO₂ ratio, pH, mean arterial pressure, heart rate, and SAS score. Left ventricular stroke volume index showed a clinically negligible, yet significant, decrease during the third hour receiving NAVAal (32.4 mL/m²; quartiles, 27.3 to 44.1 mL/m²) compared to CoVent (33.2 mL/m²; quartile, 25.4 to 38.6 mL/m²; p = 0.041), while cardiac index, left ventricular ejection fraction, and all other parameters assessed by echocardiography remained unchanged when compared to CoVent (difference not significant for all comparisons). The average Vt during 3 h receiving NAVAal was significantly correlated (r = 0.62; p = 0.017) with CLdyn (Fig 4).

The nasogastric NAVA catheter remained in situ for 5 days (quartiles, 3 to 7 days). During the follow-up period, the average of the maximum EAdi amplitude was 3.2 times the trigger level (quartiles, 2.7 to 3.7 times the trigger level). In the patient who could not be ventilated with NAVA, the maximum EAdi amplitude during follow-up exceeded two times the trigger level on follow-up day 3.
Discussion

The present study demonstrates that systematically increasing the NAVA level in critically ill patients results in 74% unloading of the inspiratory muscles. NAVAal was identifiable based on the transition from an increase in the lung-distending pressure at lower NAVA levels to a limitation of the lung-distending pressure at higher NAVA levels.

Partial unloading of the inspiratory muscles during implementation of NAVAal for 3 h (PTPes was reduced by 55%NAVAlow and EAdi was reduced by 24%NAVAlow) seemed to satisfy the respiratory demand of the patients as evidenced by stable respiratory parameters and cardiopulmonary function.

In agreement with previous work in rabbits with acute lung injury,4,10 the present study demonstrated a two-phased response to increasing the NAVA level (Figs 1–3; Fig E2 in the online supplementary material). At lower NAVA levels, Paw, VT, and Ptp increased (first response) while inspiratory muscles were progressively unloaded (EAdi and PTPes decreased). At higher NAVA levels, the rate of increase in Paw slowed down and VT as well as Ptp plateaued (second response) while unloading of the inspiratory muscles continued (EAdi and PTPes further decreased).

During the first response, the Paw and Pes relationship crossed the Ptp isopleths (ie, the lung-distending pressure, and hence the VT, increased while the inspiratory effort was only minutely de-
increased) [Fig 3]. During the second response, the Paw and Pes relationship paralleled the Ptp isopleths (ie, the lung-distending pressure, and hence the VT, remained unchanged while the inspiratory efforts were substantially decreased). Different from the results of the present work, we demonstrated that VT and Ptp did not change when performing a similar NAVA level titration in healthy volunteers, suggesting that in the absence of respiratory failure (ie, when the subject’s respiratory demand is satisfied even without ventilatory assist) the predominant response to increasing NAVA level is the prevention of further lung distension (ie, the second response).³

Marantz et al¹¹ varied the level of assist with proportional assist ventilation (PAV) from near-maximal levels to the lowest tolerable level and found that unique values for V̇e, VT, and RR were identifiable for each patient. Similar to the present study, increasing the PAV level resulted in a reduction in the patient's effort, such that ventilatory parameters essentially remained unchanged over a wide range of unloading (ie, the second response).³

During the titration procedure, the RRvent decreased minutely from NAVAlow to NAVAAal and remained unchanged thereafter. This is in accordance with previous findings in rabbits,⁴ healthy subjects,³ and mechanically ventilated patients,¹³ but is clearly different from observations made during pressure support ventilation.⁴¹³¹⁴ The difference in the response of RRvent between NAVA and conventional modes has been attributed to late off-cycling with conventional modes, causing the assist mode of the ventilator to persist into neural exhalation, prolonging exhalation, and reducing RRneural by affecting the Hering-Breuer reflex.⁴¹²¹⁵ Also, increasing the frequency of wasted inspiratory efforts with increasing assist levels has been attributed to the slowing of RRvent during conventional assist.⁴¹⁴¹⁶ This suggests that RRvent has little value in determining patient comfort and determining the level of unloading in mechanically ventilated patients.

Based on the above discussion, one could hypothesize that the two-phased response in Paw, Ptp, and VT to the NAVA level titration describes a transition from an initially insufficient level of assist (first response) to an assist level that satisfies the patient’s respiratory demand (second response). During the first response, the patient “welcomes” the delivered pressure and allows Paw, Ptp, and VT to increase, a response that is likely mediated through respiratory muscle afferents.⁶¹⁷ During the second response, the subject’s respiratory demand appears to be satisfied, and maintenance of VT and Ptp by down-regulation of the EAdi becomes prioritized. The second response is most likely in part vagally mediated.¹⁰¹⁸

Although the NAVAlow for the group was more than twice NAVAAal, the increases in mean inspiratory Paw (approximately 1 cm H₂O) and VT (approximately 0.8 mL/kg PBW) were relatively small. If the EAdi had not been down-regulated between NAVAlow and NAVAAal, the Paw delivered at NAVAAal would have been more than double the Paw delivered at NAVAlow. The irregular ventilatory pattern at NAVAAal (Fig 1, B), which has also been observed in animals¹⁰ and probably reflects overassist, is different from the findings of resonant amplitude oscillations and runaway due to the overcompensation of loads with PAV.¹²¹⁹ With NAVA, the assist is delivered synchronous and proportional to the EAdi even at the highest NAVA levels (ie, at maximal unloading), and regardless of irregularities in the breathing pattern. Of note, an irregular breathing pattern can frequently be observed in mechanically ventilated subjects and per se does not necessarily indicate overassist.

The optimal speed of performing the NAVA level titration procedure has not been established. We opted for a slow increase in the NAVA level (3 min at each NAVA level) to ensure that patients would adapt to each new level. This approach seems to have been effective, as respiratory parameters during the implementation of NAVAAal for 3 h were not different from those observed during the titration procedure at NAVAlow. Viale et al²⁰ demonstrated that it takes only five to six breaths for the respiratory drive to adjust after a change in PSV, suggesting that the rate of increase in NAVA levels during a titration could probably be faster, and that, therefore, a

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**Figure 4.** The average VT during 3 h receiving NAVAAal was correlated ($r = 0.62; p = 0.017$) with the CDyn as assessed during CoVent. Note that the calculation of CDyn contains the variable VT. Hence, we cannot exclude that random variability in the common variable forced a correlation between VT and CDyn.
NAVA level titration procedure might be also applicable in more severely ill patients.

A reduction in PEEP by about 6 cm H\textsubscript{2}O caused a small but significant increase in mean expiratory EAdi, the so-called tonic EAdi. Although lower in magnitude, this is consistent with the findings by our group of a vagally mediated tonic EAdi in rabbits with acute lung injury\textsuperscript{2} and in intubated pediatric patients\textsuperscript{21} following a reduction of PEEP. The presence of tonic EAdi and the absence of a decrease in pulse oximetric saturation with reduced PEEP in our patients is in support of a reflex preventing the lungs from derecruitment.

During 3 h receiving NAVAal, all respiratory parameters as well as cardiopulmonary function remained stable, and there was no indication of respiratory failure in any patient.\textsuperscript{22,23} The median VT of the group was close to 6 mL/kg PBW, a value chosen somewhat arbitrarily by the ARDSNet investigators\textsuperscript{24} for their lung-protective strategy. However, in contrast to the ARDSNet study,\textsuperscript{24} the variability in VT among our patients was high, ranging from 4.5 to 10.1 mL/kg PBW. The positive correlation between VT and CL\textsubscript{dyn} during NAVAal raises the possibility that choosing the level of assist based on a NAVA level titration may provide an approach to individualizing ventilatory parameters. Our finding that neural feedback promotes lower VT by down-regulating inspiratory effort in patients with the least compliant lungs agrees with current perceptions about protection against ventilator-induced lung injury.\textsuperscript{25–27}

In the present study, the coefficient of variation for VT during NAVA was more than twice the value during CoVent. Previous work\textsuperscript{28,29} has shown a similar increase in VT variability with PAV compared to PSV, suggesting that adjusting the ventilator assist in proportion to the patient’s demand on a breath-by-breath basis enhances the patient’s ability to respond quickly to alterations in both the respiratory demand and the functional properties of the respiratory system.

CONCLUSION

This study demonstrates in patients with hypoxemic respiratory failure that NAVA (1) is well integrated into and modulated by respiratory system feedback, and (2) substantially reduces respiratory drive and unloads respiratory muscles. Systematically increasing the NAVA level offers a method to determine a level of adequate unloading based on a characteristic response of Paw and VT. The implementation of the titrated NAVA level (NAVAal) for 3 h results in sustained unloading with protective VT, while breathing pattern and cardiopulmonary function remain stable, suggesting that NAVA is a feasible mode of ventilation for critically ill patients with hypoxemic respiratory failure. Although the present study provides principal evidence of the physiologic response to increasing the NAVA level, future studies are required to standardize the titration procedure and the identification of NAVAal.

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REFERENCES

6. Sinderby C, Spahija J, Beck J. Changes in respiratory effort sensation over time are linked to the frequency content of diaphragm electrical activity. Am J Respir Crit Care Med 2001; 163:905–910
18 Ma A, Bravo M, Kappagoda CT. Responses of bronchial C-fiber afferents of the rabbit to changes in lung compliance. Respir Physiol Neurobiol 2003; 138:155–163