Increased Diaphragmatic Contribution to Inspiratory Effort during Neurally Adjusted Ventilatory Assistance versus Pressure Support

An Electromyographic Study

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ABSTRACT

Background: Neurally adjusted ventilatory assist (NAVA), regulated exclusively by the electromyographic activity (EA) of the diaphragm (EAdi), could affect the distribution of neural drive to the various inspiratory muscles. The objective of this study was to compare EAdi, EA of the scalene (EAscal), and EA of the alae nasi (EAan), according to the ventilatory mode and assist level in 12 mechanically ventilated patients.

Methods: Seven assist levels of pressure support ventilation (PSV) and NAVA were sequentially applied. EAdi, EAscal, and EAan were quantified and expressed as a percentage of their maximum values. The relative contributions of extradiaphragmatic muscles to inspiratory efforts were assessed by calculating EAscal/EAdi and EAan/EAdi ratios. Three assist levels for each of the two ventilatory modes that resulted in EAdi values of 80 to 100%, 60 to 80%, and 40 to 60% were assigned to three groups (N1, N2, and N3). Results are expressed as median and interquartile range.

Results: EA of inspiratory muscles decreased during PSV and NAVA (P < 0.0001). Although EAdi remained constant within groups (P = 0.9), EAscal was reduced during NAVA compared with PSV in N1 and N3 (65% [62 to 64] and 27% [18 to 34] in NAVA vs. 90% [81 to 100] and 49% [40 to 55] in PSV, P = 0.007). Altogether, EAscal/EAdi and EAan/EAdi ratios were lower in NAVA than PSV (0.7 [0.6 to 0.7] and 0.7 [0.6 to 0.8] in NAVA vs. 0.9 [0.8 to 1.1] and 0.9 [0.7 to 1.1] in PSV, P < 0.05).

Conclusions: NAVA and PSV both reduced extradiaphragmatic inspiratory muscle activity, in proportion to the level of assistance. Compared with PSV, NAVA resulted in a predominant contribution of the diaphragm to inspiratory effort.

(ANESTHESIOLOGY 2014; 121:1028-36)
As the result of a biofeedback loop, increasing the NAVA gain in a given clinical situation results in a reduction of diaphragmatic activity.2 The diaphragm is not the only muscle active during inspiration in humans, because extradiaphragmatic inspiratory muscles, including upper airway dilator muscles and pump muscles (e.g., the scalenes), all receive inspiratory drive from the central nervous system. This inspiratory drive is not uniform, but is “distributed,” both spatially and temporally.3 The distribution of inspiratory drive is altered by inspiratory loading that differentially modifies the degree of neuromechanical coupling of the various inspiratory muscles. Extradiaphragmatic inspiratory muscles contract earlier and more strongly in the presence of a mechanical load and in response to chemostimulation in healthy subjects4–7 or in patients during clinical respiratory distress8 or when patient–ventilator interactions are inadequate.9–11 The contribution of extradiaphragmatic inspiratory muscles to the inspiratory effort can become greater than the contribution of the diaphragm,12 suggesting a steeper load–activity relationship for these muscles. Of note, a consistent relationship has been demonstrated between extradiaphragmatic inspiratory muscle activity and dyspneic sensations, in both experimental4,13 and clinical conditions.11 For all of these reasons, unloading extradiaphragmatic inspiratory muscles and thereby reducing their EA is a relevant objective of ventilatory assistance.4–11 PSV achieves this goal,9,11 but whether or not NAVA also achieves this goal and to what extent is unknown. The present study was therefore designed to address this question, as it has been observed that, for comparable assist levels, tidal volume (VT) was higher during PSV than during NAVA, despite a lower EAdi.14,15 These observations are compatible with different effects of the two ventilatory modes on extradiaphragmatic inspiratory muscles.4–7

Materials and Methods

Study Population

The study was conducted in a 16-bed intensive care unit within a 1,600-bed university hospital (Pitié-Salpêtrière Hospital, Paris, France) during a 5-month period (from April to August 2012). Adult patients intubated and mechanically ventilated for acute respiratory failure were eligible for inclusion in the study if (1) they were able to trigger the ventilator in PSV in order to produce a VT of 6 to 8 ml/kg and (2) the physician in charge of the patient decided to switch the mode of mechanical ventilation from PSV to NAVA. Exclusion criteria included contraindications to nasogastric tube insertion, known or suspected phrenic nerve dysfunction, neuromuscular disease, and hemodynamic or respiratory instability, i.e., need to increase doses of vasoactive drugs, increase positive end-expiratory pressure, or increase fractional concentration of oxygen (FiO₂) at the time of inclusion. This study was conducted in accordance with the French law on biomedical research and was approved by the appropriate external review board (“Comité de Protection des Personnes Ile-de-France 6 Pitié-Salpêtrière,” decision #101–12) of Pitié-Salpêtrière Hospital, Assistance Publique—Hôpitaux de Paris, Paris, France in April 2012. Informed consent was obtained from all patients.

Ventilatory Protocol

Patients were ventilated using a Servo-i ventilator (Maquet Critical Care, Solna, Sweden). Positive end-expiratory pressure and FiO₂ were set by the physician in charge of the patient and were not altered during the study. Seven PSV levels (from 7 to 20 cm H₂O) were applied in a stepwise manner, followed by seven corresponding NAVA levels determined using a built-in function (“NAVA preview”) that calculates what NAVA gain is required to produce equi-PSV assistance (fig. 1).14–16

Measurements

Diaphragmatic electromyography was recorded using a 16-French nasogastric tube (Edi catheter; Maquet Critical Care). Airway pressure (Paw), flow, and diaphragmatic electromyogram were acquired from the ventilator via an RS232 interface at a sampling rate of 100 Hz, recorded, and analyzed with dedicated software (Servo-i RCR, version 3.7; Maquet Critical Care).

End-tidal partial pressure of carbon dioxide (PETCO₂) was determined at the end of each condition, using a carbon dioxide Capnomat III sensor kit connected to the carbon dioxide analyzer module of the Servo-i ventilator (Maquet Critical Care).

Electromyographic signals of extradiaphragmatic inspiratory muscles were recorded using surface electrodes.11 Scalene-targeted recordings were obtained in the posterior triangle of the neck at the level of the cricoid cartilage, and alae nasi–targeted recordings were obtained by placing one electrode on each nostril. Signals were preamplified (gain of 0.5), prefiltered below 10 Hz and above 1,000 Hz (Electronique du Mazet, Le Mazet Saint Voy, France), then sampled at 2,000 Hz (PowerLab, AD Instruments, Hastings, United Kingdom), and stored on file for subsequent analysis.4–7

Data Analysis

Ventilatory and Diaphragmatic Electromyogram Data Analysis. These data were analyzed on a breath-by-breath basis. Flow-derived variables included VT, minute ventilation, and mean inspiratory flow. Diaphragmatic electromyogram-derived variables included duration of neural inspiration, total neuroventilatory cycle, inspiratory duty cycle, and respiratory rate. The area under the curve of the diaphragmatic electromyogram signal, as provided by the in-house Maquet software, was used to quantify the corresponding electromyogram activity (EAdi) and was expressed as a percentage of its maximal value as observed under a given condition.

Surface Electromyogram Signal Processing and Data Analysis. For each condition, surface electromyogram

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signals were averaged according to Hug et al.\textsuperscript{11,17}: raw electromyogram data were root-mean-squared over a 2-ms fixed window; the continuous root-mean-squared signal was split into as many epochs of mechanical inspiration determined from the airway pressure signal, and then averaged over 3 min; and the averaged root-mean-squared signal was smoothed (triangular Bartlett window width 3,001 points) in order to obtain an electromyogram root-mean-squared envelope. The area under the curve of this envelope was measured and used to quantify the EA (EAscal and EAan for scalene and \textit{alae nasi}, respectively). EAscal and EAan, as well as EAdi, were expressed as a percentage of their maximal value as observed under a given condition. EAscal/EAdi and EAan/EAdi were calculated for each condition.

Groups of EAdi-based Assist Levels. To allow pertinent comparison between the two ventilatory modes, three assist levels from the seven levels tested for each of the two ventilatory modes that resulted in EAdi values of 80 to 100%, 60 to 80%, and 40 to 60% were identified and assigned to three groups (N1, N2, and N3), respectively.

Statistical Analysis
Statistical analysis was performed using Minitab\textsuperscript{®} Statistical Software version 16 (Minitab Inc., State College, PA). Results are expressed as median and interquartile range [25 to 75]. A Friedman analysis of variance for each variable was performed to compare the seven assist levels during both PSV and NAVA procedures, followed, when appropriate, by pairwise comparisons using the Bonferroni method to account for the effects of multiplicity. The within-group and between-group changes of the variables were analyzed using the Scheirer–Ray–Hare test, a nonparametric two-way (ventilatory-mode effect and assist-level effect) ANOVA for repeated measures. Pairwise comparisons of significant effects were also performed, using the Bonferroni method. EAscal/EAdi and EAan/EAdi comparisons between PSV and NAVA were performed using the Wilcoxon test. The relationship between EAdi and EAscal or EAan was examined using the Spearman rank correlation coefficient. The level of significance for all statistical tests was set at \(P\) value less than 0.05.

Results
Based on previous experience with similar studies, a convenience sample of 12 patients was studied. Patient characteristics and ventilator settings are provided in table 1. The assist levels sets for groups N1, N2, and N3 were 7 [7 to 7], 12 [12 to 14], and 16.0 [14 to 19] cm H\textsubscript{2}O for PSV and 0.5 [0.2 to 1.0], 0.8 [0.6 to 1.6], and 1.8 [1.5 to 3.1] cm H\textsubscript{2}O/μV for NAVA, respectively. Within each group, ventilatory assist assessed by mean Paw was not significantly different between PSV and NAVA (\(P = 0.5\)) (table 2).

\textit{Alae nasi} electromyograms were successfully recorded in all patients, whereas scalene electromyograms could be correctly recorded in only 9 of 12 patients.

Changes in breathing pattern and EA throughout PSV and NAVA procedures are detailed in figure 1 and table 1 in Supplemental Digital Content 1, http://links.lww.com/ALN/B89.

Breathing Pattern
Neither ventilatory mode nor assist level significantly influenced breathing pattern. However, \(P_{\text{ETCO}_2}\) decreased from N1 to N3 (without within-group changes), suggesting that
Table 1. Characteristics of the Patients, Ventilator Settings, and Arterial Blood Gases at Inclusion

| Patient (No.) | Age (yr) | BMI (kg/m²) | Comorbidities | Diagnostic | SAPS II | Sedative Drugs | RASS | Duration (days) | V̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̈
### Table 2. Effects of Ventilatory Mode and Assist Level on Breathing Pattern

<table>
<thead>
<tr>
<th></th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
<th>Scheirer–Ray–Hare P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PW (cm H2O)</td>
<td>10 [10–12]</td>
<td>10 [10–12]</td>
<td>15 [14–17]*</td>
<td>0.5 &lt;0.0001</td>
</tr>
<tr>
<td>Ppeak (cm H2O)</td>
<td>14 [13–15]</td>
<td>17 [14–21]</td>
<td>19 [18–20]*</td>
<td>0.002 &lt;0.0001</td>
</tr>
<tr>
<td>VV (ml/kg)</td>
<td>6.2 [4.5–7.1]</td>
<td>6.2 [5.2–7.0]</td>
<td>7.1 [6.0–8.2]</td>
<td>0.5 0.08</td>
</tr>
<tr>
<td>RR (min)</td>
<td>32 [28–42]</td>
<td>30 [27–41]</td>
<td>28 [26–40]</td>
<td>0.9 0.7</td>
</tr>
<tr>
<td>TI (s)</td>
<td>0.60 [0.50–0.84]</td>
<td>0.62 [0.54–0.77]</td>
<td>0.68 [0.47–0.85]</td>
<td>0.4 0.2</td>
</tr>
<tr>
<td>TT (s)</td>
<td>10.8 [8.6–13.1]</td>
<td>11.3 [9.5–13.2]</td>
<td>11.2 [10.2–12.9]</td>
<td>0.5 0.5</td>
</tr>
<tr>
<td>Vt (l/min)</td>
<td>498 [446–701]</td>
<td>504 [439–539]</td>
<td>489 [464–674]</td>
<td>0.2 0.5</td>
</tr>
<tr>
<td>PETCO2 (mm Hg)</td>
<td>40 [39–43]</td>
<td>39 [36–43]</td>
<td>36 [25–42]*</td>
<td>0.8 0.05</td>
</tr>
</tbody>
</table>

Values indicate median [interquartile range].

* P < 0.05 vs. N1 within the same mode. † P < 0.05 vs. N2 within the same mode. ‡ P < 0.05 vs. PSV within the same assist-level group.

NAVA = neurally adjusted ventilatory assist; PSV = pressure support ventilation; RR = respiratory rate; TI = inspiratory time; TT = total neuroventilatory cycle; TI/TT = inspiratory duty cycle; VE = minute ventilation; VT = tidal volume; Vt/Ti = mean inspiratory flow.

### Methodological Considerations

**Electromyographic Activities of Inspiratory Muscles**

In this study, we aimed to investigate the effects of ventilatory mode and assist level on the electromyographic activities of inspiratory muscles during NAVA and PSV. We hypothesized that increased assist levels would lead to decreased electromyographic activity of inspiratory muscles, particularly the diaphragm and scalene muscles. The results showed that, compared to PSV, NAVA resulted in significantly lower electromyographic activity of the diaphragm and scalene muscles, as quantified by the ratio of the mean activity during NAVA to that during PSV (EAan/EAdi and EAscal/EAdi).

**Discussion**

In this study, we found that NAVA decreased the electromyographic activity of the diaphragm and scalene muscles compared to PSV. This suggests that NAVA may provide a global effect on the inspiratory drive, leading to a decrease in the relative contribution of the diaphragm and scalene muscles. The decrease in EAan and EAscal during NAVA compared to PSV was significantly lower (P = 0.06, 95% CI 0.11 to 0.70, P < 0.0001) for PAEad and NAVA. EAan and EAscal were correlated with EAdi in PSV (ρ = 0.79, 95% CI 0.69 to 0.88) and NAVA (ρ = 0.60, 95% CI 0.51 to 0.70, P < 0.0001) for PAEad.

Overall, EAan and EAscal were lower in NAVA compared to PSV, as indicated by the significant difference in the EAan/EAdi and EAscal/EAdi ratios (P < 0.0001 for EAan/EAdi and P = 0.006 for EAscal/EAdi). This suggests that NAVA may provide a global effect on the inspiratory drive, leading to a decrease in the relative contribution of the diaphragm and scalene muscles.

**Conclusion**

NAVA decreased the electromyographic activity of the diaphragm and scalene muscles compared to PSV. This effect was more pronounced during NAVA compared to PSV, as indicated by the significant difference in the EAan/EAdi and EAscal/EAdi ratios. These findings support the hypothesis that NAVA may provide a global effect on the inspiratory drive, leading to a decrease in the relative contribution of the diaphragm and scalene muscles.
Table 3. Effects of Ventilatory Mode and Assist Level on Electromyographic Activity of Inspiratory Muscles

<table>
<thead>
<tr>
<th></th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
<th>Scheirer-Ray-Hare P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PSV</td>
<td>NAVA</td>
<td>PSV</td>
<td>NAVA</td>
</tr>
<tr>
<td>EAdi (%)</td>
<td>95  [81–100]</td>
<td>95  [89–100]</td>
<td>72  [65–81]†</td>
<td>72  [66–76]†</td>
</tr>
<tr>
<td>EAan (%)</td>
<td>91  [83–100]</td>
<td>84  [76–95]</td>
<td>68  [32–79]†</td>
<td>50  [38–62]†</td>
</tr>
<tr>
<td>EAan/EAdi</td>
<td>1.00 [0.74–1.18]</td>
<td>0.88 [0.79–1.0]</td>
<td>0.88 [0.47–1.14]</td>
<td>0.72 [0.53–0.87]</td>
</tr>
<tr>
<td>EAascal/EAdi</td>
<td>1.00 [0.82–1.00]</td>
<td>0.70 [0.64–0.81]‡</td>
<td>0.81 [0.73–1.21]</td>
<td>0.78 [0.67–0.96]</td>
</tr>
</tbody>
</table>

Values indicate median [interquartile range].

* P < 0.05 vs. PSV within the same assist-level group. † P < 0.05 vs. N1 within the same mode. ‡ P < 0.05 vs. N2 within the same mode.

EAan = electromyographic activity of alae nasi; EAdi = electromyographic activity of diaphragm; EAascal = electromyographic activity of scalene; NAVA = neurally adjusted ventilatory assist; PSV = pressure support ventilation.
to our results. The differences observed might also have been due to the different nature of the trigger between PSV (flow) and NAVA (EAdi). However, previous data comparing the effects of flow triggered NAVA and EAdi triggered NAVA suggest that the beneficial effects of NAVA on patient–ventilator synchrony relate more to the proportional character of the assistance than to the triggering method.15 Preliminary data from our group suggest that NAVA and proportional assist ventilation have similar effects on patient–ventilator synchrony in spite of the different nature of their triggering method.33 Of note, the lower EAan/EAdi and EAscal/EAdi ratios observed in NAVA could also have been partly due to facilitated EAdi. An excitatory reflex facilitating EAdi has been described in healthy subjects in response to an increase in peak inspiratory flow.34 In our patients, flow-related parameters such as peak Paw were higher in NAVA than in PSV, which could have increased EAdi for a given level of assistance. Finally on this, an electromyographic recruitment pattern showing a greater diaphragm contribution to inspiratory effort in NAVA than in PSV can be considered to be a negative finding, suggesting failure of NAVA to “spare” the diaphragm relative to PSV. It may also mean that NAVA was more efficient than PSV to restore a closer to normal breathing pattern, with a decrease in neuromechanical coupling greater in extradiaphragmatic inspiratory muscles than in the diaphragm.

**Implications for Future Studies**

In view of the strong relationship between dyspnea and extradiaphragmatic inspiratory muscle activation in mechanically ventilated patients,4,11 our results provide a rationale to specifically design a study evaluating differential dyspnea relief during NAVA and PSV. Of note, our observations with PSV support the notion that EAan and EAscal could provide useful signals to adjust ventilatory assistance.11 Finally, there are clues in the literature to suggest that NAVA could improve gas exchange.35 This effect could proceed from improved ventilation of the lung bases,36 in line with the favorable effect of diaphragm pacing on the alveoloarterial gradient in mechanically ventilated quadriplegic patients.37 The greater contribution of the diaphragm to inspiratory effort in NAVA than in PSV that we observed is consistent with this hypothesis.

In conclusion, NAVA as PSV reduced the activity of extradiaphragmatic inspiratory muscles, in proportion to the level of assistance provided. Compared with PSV, NAVA resulted in a predominant contribution of the diaphragm to inspiratory effort. Further studies are required to determine whether this is a positive or a negative effect.

**Acknowledgments**

The authors thank the medical and nursing staff of Service de Pneumologie et de Réanimation Médicale, Groupe Hospitalier Pitie-Salpêtrière Charles Foix, Paris, France, for their support and participation in the study. The authors also thank Anthony Saul, Paris, France, for his help with English style and grammar.

This study was funded by the Association pour le Développement et l’Organisation de la Recherche en Pneumologie et sur le Sommeil (ADOREPS), Paris, France, and by the French Government “Investissement d’Avenir Agence Nationale de Recherche-10-Institut Hospitalo-Universitaire 06” program, Paris, France. Dr. Cecchini was supported by an “Année-Recherche” scholarship from the “Agence Régionale de Santé Ile-de-France,” Paris, France. Dr. Schmidt was supported by the “French Intensive Care Society (SRLF),” Paris, France; the “Fonds de dotation Recherche en Santé Respiratoire 2012,” Paris, France; the “Collège des Enseignants de Réanimation Médicale,” Paris, France; and the “Fonds d’Études et de Recherche du Corps Médical-2014,” Paris, France.

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**Fig. 2.** Contribution of scalene and alae nasi to inspiratory effort relative to the diaphragm in pressure support ventilation (PSV) (squares) and neurally adjusted ventilatory assist (NAVA) (triangles). Data are expressed as median (interquartile range). *P < 0.05. EAan = electromyographic activity of alae nasi; EAdi = electromyographic activity of diaphragm; EAscal = electromyographic activity of scalene.
Competing Interests
In 2009 and 2010, the Association pour le Développement et l’Organisation de la Recherche en Pneumologie et sur le Sommeil (ADOREPS) received an unrestricted research grant from Maquet France SA, Orléans, France, to support pathophysiological research studies on the “neurally adjusted ventilatory assist” (NAVA) mode. Dr. Demoule is the principal investigator of a clinical study supported by Maquet SA and a study supported by Covi-dien, Boulder, Colorado, has been a member of a board sponsored by Covi-dien, and has received lecture fees from Maquet and Covi-dien. The other authors declare no competing interests.

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References