Standardized Unloading of Respiratory Muscles during Neurally Adjusted Ventilatory Assist

A Randomized Crossover Pilot Study

Francesca Campoccia Jalde, M.D., Ph.D., Fredrik Jalde, M.Sc., Mats K. E. B. Wallin, M.Sc., M.D., Ph.D., Fernando Suarez-Sipmann, M.D., Ph.D., Peter J. Radell, M.D., Ph.D., David Nelson, M.D., Ph.D., Staffan Eksborg, M.D., Ph.D., Peter V. Sackey, M.D., Ph.D.

ABSTRACT

Background: Currently, there is no standardized method to set the support level in neurally adjusted ventilatory assist (NAVA). The primary aim was to explore the feasibility of titrating NAVA to specific diaphragm unloading targets, based on the neuroventilatory efficiency (NVE) index. The secondary outcome was to investigate the effect of reduced diaphragm unloading on distribution of lung ventilation.

Methods: This is a randomized crossover study between pressure support and NAVA at different diaphragm unloading at a single neurointensive care unit. Ten adult patients who had started weaning from mechanical ventilation completed the study. Two unloading targets were used: 40 and 60%. The NVE index was used to guide the titration of the assist in NAVA. Electrical impedance tomography data, blood-gas samples, and ventilatory parameters were collected.

Results: The median unloading was 43% (interquartile range 32, 60) for 40% unloading target and 60% (interquartile range 47, 69) for 60% unloading target. NAVA with 40% unloading led to more dorsal ventilation (center of ventilation at 55% [51, 56]) compared with pressure support (52% [49, 56]; $P = 0.019$). No differences were found in oxygenation, CO_2, and respiratory parameters. The electrical activity of the diaphragm was higher during NAVA with 40% unloading than in pressure support.

Conclusions: In this pilot study, NAVA could be titrated to different diaphragm unloading levels based on the NVE index. Less unloading was associated with greater diaphragm activity and improved ventilation of the dependent lung regions.
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CONTROLLED mechanical ventilation is commonly used to treat patients in respiratory failure.[1–4] However, the physiologic benefits from promoting or assisting spontaneous breathing have been described, such as lower risk for developing ventilator induced diaphragm dysfunction,[5] improvement of pulmonary function,[6,7] more homogenous distribution of aeration and oxygenation improvement.[8]

Neurally adjusted ventilatory assist (NAVA) is a spontaneous breathing mode controlled by the electrical activity of the diaphragm (EAdi), first described in 1999[9] and used clinically for the last 10 yr.[10,11] NAVA provides ventilatory assist proportional to the EAdi with an adjustable factor called NAVA level.

Editor's Perspective

What We Already Know about This Topic

- Neurally adjusted ventilatory assist matches the mechanical pressure from the ventilator to the patient's respiratory drive sensed from the electrical activity of the diaphragm, but the optimal degree of diaphragm unloading is uncertain

What This Article Tells Us That Is New

- This pilot study of 10 patients titrated neurally adjusted ventilatory assist to different levels of diaphragm unloading; less unloading was associated with greater diaphragm activity and improved ventilation of dependent lung

This article is featured in "This Month in Anesthesiology," page 1A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has a visual abstract available in the online version. The work has been presented in a preliminary draft at the Ph.D. dissertation session on June 10, 2016, in Stockholm, Sweden.

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A few studies have described the titration of the NAVA level,[12–15] but without standardized indices. A standardized method to set the NAVA level may potentially help clinicians at the bedside to optimize ventilator support, avoiding fatigue caused by insufficient support and preventing ventilator-induced diaphragm dysfunction[16] caused by muscle inactivity.[17]

A recent index, the neuroventilatory efficiency (NVE), which describes the capacity of the respiratory muscles to convert the EAdi to ventilatory volume, has been developed to estimate the proportion of respiratory muscle unloading[18,19] and as a potential tool to predict patients' extubation readiness.[20,21] The NVE requires a measurement of volume and EAdi during an unsupported breath. NVE–based unloading could potentially be used to adjust NAVA to a specific degree of unloading.

The primary aim of this study was to assess the feasibility of titrating the NAVA assist to different levels of muscle unloading according to an approach based on NVE. We hypothesized that unloading could be titrated to a specific target. More specifically, our aim was to assess the number of patients that reached the unloading targets within ±10 percentage units and assess the number of NAVA level adjustments in each step to reach the target unloading. Because a previous electrical impedance tomography (EIT) study comparing NAVA and pressure support on acute lung injury patients indicated that moderate levels of assist in NAVA may promote a more homogeneous distribution of ventilation,[22] a secondary aim was to investigate whether reduced unloading would improve the distribution of ventilation, from ventral to dorsal areas, assessed with EIT.

Materials and Methods

The study was approved by the Regional Ethics Committee at Karolinska Institutet, Solna, Sweden (dnr 2015/521-31/4) on April 22, 2015, and registered at ClinicalTrials.gov (identifier NCT02711722). The patients were screened for enrollment at the neurointensive care unit of Karolinska University Hospital (Solna, Sweden) from May 2015 to September 2016. No statistical power calculation was conducted before the study for the primary endpoint, because this was an exploratory feasibility study. The sample size was based on previous studies investigating ventilation distribution with EIT in critically ill patients[22] and neuromechanical efficiency (NME) index.[23] In total, 13 patients were enrolled, and 10 completed the study protocol. As per ethical approval, written informed consent was obtained from a next of kin. Patients intubated and ventilated for more than 48 h who had started weaning from mechanical ventilation were eligible. Patients with unstable intracranial pressure, severe respiratory, hemodynamic, or bleeding problems were excluded, as well as patients with significant hyperventilation during supported ventilation ($Paco_2$ < 35 mmHg). Because injury to the respiratory centers, spinal cord, or peripheral nerves may impair respiratory function, the first step after inclusion was to verify the patient's integrity of the neural feedback loop in NAVA,[9,24–26] to ensure patients responded by lowering diaphragm activation during higher muscle unloading (see Supplemental Digital Content, http://links.lww.com/ALN/B757, for a description of the screening test).

The study had a crossover design, in which pressure support at the start and the end and three NAVA unloading levels were compared. Patients were their own controls. The order of interventions (NAVA steps) was randomized in each patient by performing the interventions in the order they were drawn blindly from an envelope.

All patients were ventilated with a SERVO-i ventilator (version 7, Maquet Critical Care, Sweden). Positive end-expiratory pressure (PEEP) was kept unchanged throughout the study, whereas FIO_2 was increased by 10% if oxygen saturation dropped less than 95%.

Sedation and nutrition regimes were set according to the attending physician's discretion and kept unchanged during the trial. At study entry, the feeding tube was replaced by a NAVA catheter (Maquet Critical Care) through which nutrition could be continued. The catheter position was verified according to the manufacturer's instructions (SERVO-i user manual).

Two portable computers were connected to parallel RS232 serial ports in the SERVO-i. One computer recorded ventilatory parameters with the Servo Tracker software (version 4.2, Maquet Critical Care). The other computer used a dedicated software (SERVO trend tool, Maquet Critical Care) with automatic detection of the maneuvers (zero assist and end-expiratory hold) to determine NVE, NME, and NVE unloading. All curves from SERVO-i were sampled at 100 Hz. An arterial line was in place to monitor blood pressure and obtain samples for blood-gas analysis, as per clinical routine in our neurointensive care unit.

Study Protocol

The patients underwent five 30-min periods of ventilation to reach a steady state regarding ventilation distribution and gas exchange in each phase. The duration of the titration period (25 min) was established as the feasibility test period but also to minimize the risk of carry over effects with regard to the blood-gas analysis. Baseline ventilation set by the attending physician (PS_{cli1}) was followed by NAVA in three different levels: NAVA matching PS_{cli1} ($NAVA_{cli}$), NAVA with 40% unloading ($NAVA_{40\%}$), and NAVA with 60% unloading ($NAVA_{60\%}$), in randomized order. The patients then returned to pressure support (PS_{cli2}) with the same assist as PS_{cli1} (fig.1). Based on NVE during PS_{cli1}, the assist level was matched in $NAVA_{cli}$ to PS_{cli1} in terms of muscle unloading. At $NAVA_{40\%}$ and $NAVA_{60\%}$, patients had 40 and 60% unloading, respectively, based on NVE measurements (see fig. 1A in the Supplemental Digital Content, http://links.lww.com/ALN/B757, showing an example of the ventilator curves and muscle unloading from one patient during the study).

During the last 5 min in each step (measurement phase; fig.1), no change in NAVA level was allowed, EIT data were recorded, and an arterial blood sample was obtained for gas analysis.

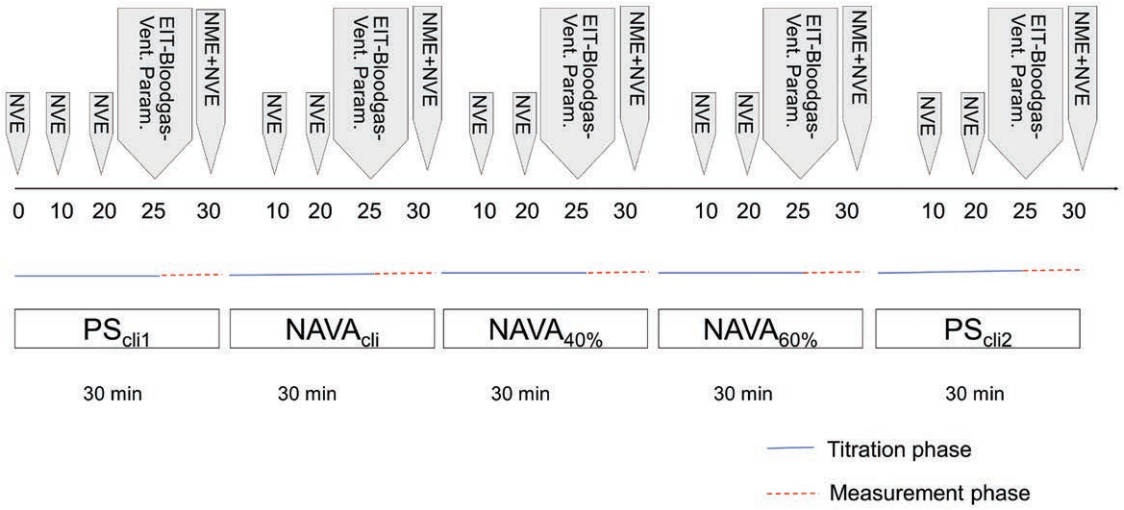

Fig. 1. Chart of the study. The timeline is expressed in minutes. Each study step lasts 30 min; the first 25 min are the titration phase during which the assist level is titrated to reach the unloading target based on the neuroventilatory efficiency (NVE). Every 10 min, a NVE index is determined. The last 5 min are the measurement phase, during which electrical impedance tomography data, ventilatory parameters, and blood-gas samples are obtained and analyzed. At the end of each study step, a neuromechanical efficiency (NME) index is obtained. EIT, electrical impedance tomography; $NAVA_{cli}$, neurally adjusted ventilatory assist matched to the unloading in PS_{cli1}; $NAVA_{40\%}$, neurally adjusted ventilatory assist at 40% unloading; $NAVA_{60\%}$, neurally adjusted ventilatory assist at 60% unloading; PS_{cli1}, pressure support; PS_{cli2}, same as PS_{cli1}; Vent. Param., ventilatory parameters.

NVE. The NVE (tidal volume divided by EAdi, ml/μV)[20] describes the capacity of the respiratory muscles to convert the EAdi to ventilating volume without ventilator assistance. The ventilator assistance is zeroed for one breath, and the inspiratory tidal volume and corresponding peak EAdi are measured (one example of the ventilator curves during the NVE maneuver is shown in fig. 2 in the Supplemental Digital Content, http://links.lww.com/ALN/B757). The maneuver was not repeated in consecutive breaths to avoid the respiratory drive increasing in response to withheld support.

Unloading Based on NVE (UNL_{NVE}). The percentage of unloading provided by the ventilator corresponds to equation 1,

$$UNL_{NVE} = \left(\frac{Tidal\ Volume_{vent}}{Tidal\ Volume_{tot}}\right)*100 = \left(\frac{Tidal\ Volume_{tot} - Tidal\ Volume_{pat}}{Tidal\ Volume_{tot}}\right)*100 = \left(1 - \frac{NVE*\ peak\ EAdi}{Tidal\ Volume_{tot}}\right)*100 \quad (1)$$

where $Tidal\ Volume_{pat}$ indicates volume generated by the patient's own respiratory contribution, $Tidal\ Volume_{vent}$ indicates ventilator assisting volume, and $Tidal\ Volume_{tot}$ indicates the sum of both.

Setting NAVA. Initially the NAVA assist was preliminarily set with the SERVO-i function that superimposes the airway pressure in pressure support with the estimated one in NAVA. If $NAVA_{cli}$ was the first randomized step, the NAVA level was set to match the pressures in pressure support and NAVA. If, instead, the randomized first NAVA step had a lower/higher unloading target than PS_{cli1}, a respectively lower/higher NAVA level was adopted. This preliminary setting was then adjusted to reach the target unloading (one example showing how the titration based on muscle unloading was performed is reported in fig. 1A in the Supplemental Digital Content, http://links.lww.com/ALN/B757). Equation 1 was used to calculate UNL_{NVE} breath by breath. UNL_{NVE} was presented bedside in the SERVO trend tool with a 10-breath moving average and used to target the NAVA assist to reach the unloading, respectively, for $NAVA_{40\%}$, $NAVA_{60\%}$, and $NAVA_{cli}$. The unloading target for $NAVA_{cli}$ was based on UNL_{NVE} obtained during PS_{cli1}. NVE was measured at time 0 in PS_{cli1} and thereafter at 10, 20, and 30 min in each step. A change in NVE would affect the UNL_{NVE}, implying a potential need for a change in NAVA level to match the target unloading (titration phase; fig.1).

NME. The NME (the change in airway pressure divided by the change in EAdi, cm H_2O/μV) indicates the relationship between pressure developed by the inspiratory muscles and the corresponding EAdi and estimates patients' breathing effort during inspiration.[27] NME is obtained during an inspiratory effort against closed valves.[20,24,28] NME was based on the median value of the ratio between airway pressure (P_{aw}) and EAdi,[27] sampled at 100 Hz (see fig. 3 in the Supplemental Digital Content, http://links.lww.com/ALN/B757, showing one example of the ventilator curves during a NME maneuver) and obtained during the measurement phase (fig.1).

In the present study, NME was used to calculate the unloading based on the ventilator-*versus*-patient contribution in terms of pressure rather than volume. The NME has not previously been used to calculate muscle unloading.

Unloading Based on NME (UNL_{NME}). The muscle unloading by the ventilator in terms of pressure corresponds to the following equation,

$$UNL_{NME} = \frac{P_{aw}}{P_{tot}} = \left(\frac{P_{aw}}{P_{aw} + P_{musc}} \right) * 100 \quad (2)$$

where P_{aw} indicates pressure delivered by the ventilator, P_{tot} indicates total lung-distending pressure, and P_{musc} indicates pressure developed by the respiratory muscles.[29] P_{musc} can be calculated as the EAdi multiplied by the NME.[23] Then equation 2 becomes:

$$UNL_{NME} = \left(\frac{P_{aw}}{P_{aw} + NME * peak\ EAdi} \right) * 100 \quad (3)$$

The SERVO trend tool used equation 3 to calculate UNL_{NME} for each study step.

Primary Outcome: Titrating NAVA Based on NVE

The feasibility of the NVE-based NAVA titration was assessed in two ways: (1) proportion of patients that reached the unloading targets within ±10 percentage units and (2) number of NAVA level adjustments in each step using the NVE–based unloading.

Secondary Outcome: Effects of Unloading on Distribution of Ventilation Based on EIT

Electrical impedance tomography is a noninvasive technique to assess the regional ventilation distribution bedside.[30] The center of ventilation is localized by quantifying the impedance distribution indicating where ventilation is mostly distributed in the vertical gravitational axis.[31] A value of 50 indicates an equal distribution between ventral and dorsal regions of the lung. Values above 50 indicate more dorsal distribution. The EIT image can also be divided in four equally spaced regions of interest, each measuring 25% of the ventrodorsal distance, named ventral, midventral, middorsal, and dorsal (see fig. 4 in the Supplemental Digital Content, http://links.lww.com/ALN/B757, showing an example of the region of interest distribution from the analysis software). Their relative impedance change during each breath is expressed as a percentage of the total ventilation. The global inhomogeneity index describes the distribution of ventilation in different areas of the lung, providing an estimate of the inhomogeneity of ventilation (see Supplemental Digital Content, http://links.lww.com/ALN/B757, for a more detailed description of the global inhomogeneity index). The differences in impedance changes occurring in the lung from expiration to inspiration is calculated, thus making it possible to follow bedside the dynamic variation occurring in a single patient or to compare different patients.[32]

The EIT monitor (BB2 Swisstom AG, Switzerland) was used in the present study. The EIT belt, provided with 32 active miniaturized electrodes, was positioned around the patient's thoracic cage at the sixth intercostal space. The impedance images were generated as 50 images/s. The explored thorax section included a region of approximately 10 cm above, 5 cm above, and below the belt level.[30]

In the five last minutes of each step, the images were sampled for offline analysis with the Ibex (Swisstom AG) software. The effects of unloading on distribution of ventilation were assessed by using the center of ventilation, the relative distribution in the different regions of interest, and the global inhomogeneity index.

Ventilatory Parameters

Airway pressure, flow, respiratory rate, and EAdi from the last 5 min of each 30-min phase were analyzed.

Criteria for Discontinuation

The criteria to discontinue the trial were the development of respiratory or cardiovascular distress, hypoxemia, and changes in mental status or fever (the criteria are reported in detail in table 1 in the Supplemental Digital Content, http://links.lww.com/ALN/B757).[33]

Statistical Analysis

Statistical analysis was done using IBM SPSS Statistics for Windows (SPSS Inc., version 23.0, USA). We expressed variables as medians and interquartile range (25th and 75th). The data were analyzed with Friedman repeated measures ANOVA. Dunn's test was then used for multiple comparisons of related samples in PS_{cli1}, $NAVA_{40\%}$, $NAVA_{60\%}$, and PS_{cli2}. The level of significance was set at $P \leq 0.05$ (two-tailed tests). The CI for the median was provided for the secondary outcome based on Wilcoxon signed-ranks test.[34]

Results

Three patients did not complete the protocol, one because of an erratic pattern of breathing and two because of very low EAdi. After this exclusion, 10 patients were analyzed (table 2 in the Supplemental Digital Content, http://links.lww.com/ALN/B757, reports the demographic data of the patients).

Primary Outcome: Titrating NAVA Based on NVE

Seven of ten patients in $NAVA_{40\%}$ and eight of ten patients in $NAVA_{60\%}$ reached the unloading target within 10% units (see fig. 5 in the Supplemental Digital Content, http://links.lww.com/ALN/B757, for individual muscle unloading). The observed number of adjustments in NAVA level was 2.5 (1, 5) in $NAVA_{40\%}$ and 3.5 (3, 6) in $NAVA_{60\%}$. The resulting unloading was 43% (32, 60) in $NAVA_{40\%}$, and 60% (47, 69) in $NAVA_{60\%}$ (table 1).

In half of the patients, the unloading was so high during PS_{cli1} that it was impossible to adequately match it with $NAVA_{cli}$. To achieve a stable EAdi, the unloading had to be reduced. For this reason, $NAVA_{cli}$ was excluded from the analysis (table 3 in the Supplemental Digital Content,

http://links.lww.com/ALN/B757, reports the PS_{cli1} levels and the respiratory muscle unloading during PS_{cli1}).

NVE and NME

The resulting NVE based on all maneuvers in all patients was 60 ml/μV (38, 79). The NME was 1.6 cm H_2O/μV (1.4, 1.9). The UNL_{NVE} and UNL_{NME} achieved in each step were similar (table 1).

Secondary Outcome: Effects of Unloading on Distribution of Ventilation

The median center of ventilation at $NAVA_{40\%}$ was 55% (51, 56), and it was greater than in PS_{cli2}, 52% (48, 55; $P = 0.019$); the difference between the center of ventilation in $NAVA_{40\%}$ and PS_{cli2} was 1.91 (median value; 95% CI, 0.330 to 3.747), meaning that the center of ventilation shifted dorsally at $NAVA_{40\%}$ compared with PS_{cli2} (see fig. 6 in the Supplemental Digital Content showing one example of center of ventilation distribution change from pressure support to $NAVA_{40\%}$).

There was no change in the center of ventilation at $NAVA_{40\%}$ compared with $NAVA_{60\%}$, 55% (51, 56) and 53% (51, 56), respectively. The distribution of ventilation across the four regions of interest and their relative contribution are presented in figure 2. The median global inhomogeneity index at $NAVA_{40\%}$ was 0.53 (0.47, 0.61), and it was lower than in PS_{cli2}, 0.59 (0.47, 0.65; $P = 0.014$; fig. 7 in the Supplemental Digital Content, http://links.lww.com/ALN/B757, shows the changes of the global inhomogeneity index in the different study steps); the difference between the global inhomogeneity index in $NAVA_{40\%}$ and PS_{cli2} was 0.040 (median value; 95% CI, 0.009 to 0.060).

Effects of Unloading: Ventilatory Parameters and Blood-gas Analyses

The median P_{aw} in $NAVA_{40\%}$ was lower than in PS_{cli2} ($P = 0.009$; table 2). The median peak EAdi was higher during $NAVA_{40\%}$ than PS_{cli1} ($P = 0.006$). No differences were observed in minute ventilation, respiratory rate, oxygenation and ventilation between the different NAVA, and pressure support steps (table 2 reports median and interquartile range of the ventilatory data, in addition table 4 in the Supplemental Digital Content, http://links.lww.com/ALN/B757, reports the individual ventilatory data). Inspired oxygen fraction was increased in one patient (patient 2, F_{IO_2} from 0.35 to 0.45). There were no missing data, and the data were not examined for outliers.

Table 1. Unloading Based on Neuroventilatory Efficiency and Neuromechanical Efficiency

Ventilation Mode	UNL_{NVE}, %	UNL_{NME}, %	NAVA Level, cm H_2O/μV	No. of NAVA Level Adjustments/ Step
PS_{cli1}	70 (57, 85)	71 (45, 86)		
$NAVA_{40\%}$	43 (32, 60)	41 (33, 62)	0.8 (0.6, 1.2)	2.5 (1, 5)
$NAVA_{60\%}$	60 (47, 69)	65 (56, 68)	2.6 (2.0, 3.7)	3.5 (3, 6)
PS_{cli2}	71 (54, 93)	58 (36, 87)		

This table reports the unloading based on neuroventilatory efficiency (UNL_{NVE}), the unloading based on neuromechanical efficiency (UNL_{NME}), and the number of ventilator assist level adjustments made to keep the unloading constant during each study step. No changes in neutrally adjusted ventilator assist level were necessary during the last 5 min in each study step, corresponding to the recording period of ventilator parameters, electrical impedance tomography, and blood-gas analyses.

NAVA, neurally adjusted ventilatory assist; $NAVA_{40\%}$, NAVA at 40% unloading; $NAVA_{60\%}$, NAVA at 60% unloading; PS_{cli1}, pressure support; PS_{cli2}, same as PS_{cli1}.

Discussion

In this pilot study, we found it feasible to titrate NAVA to unloading targets by the use of a NVE-based unloading assessment. At moderate levels of respiratory muscle unloading ($NAVA_{40\%}$), the diaphragm activity was higher (see table 2 in the main text and fig. 1B in the Supplemental Digital Content, http://links.lww.com/ALN/B757, for an example of ventilator curves and EAdi in one patient), the distribution of ventilation shifted toward the dorsal regions of the lungs (fig. 6 in the Supplemental Digital Content, http://links.lww.com/ALN/B757, showing one example of center of ventilation distribution change from pressure support to $NAVA_{40\%}$) and was slightly more homogenously distributed (fig. 7 in the Supplemental Digital Content, http://links.lww.com/ALN/B757, showing the global inhomogeneity index distribution in the different study steps), and the airway pressure was slightly reduced (table 2). This did not translate into significant improvements in gas exchange.

We observed some intrasubject variability of NVE over time; thus some adjustments of the assist level were needed during the titration phase. The median number of NAVA level adjustments per step was 2.5 and 3.5 (table 1), meaning that around one adjustment was made for each new NVE. We believe this is reasonable considering that our targets were set to specific percentage values. Most of the patients reached the unloading target within a ±10 percentage interval (fig. 5 in the Supplemental Digital Content, http://links.lww.com/ALN/B757, showing the unloading reached in every subject in the different study steps). Because of the limited study period, we cannot predict how often the NAVA level would need to be titrated in the clinical setting. We speculate that in stable conditions and unchanged lung mechanics, there would be little need for frequent NVE measurements. Hourly assessment might, however, be necessary in patients with less stable conditions.

Our study was motivated by the uncertainty that clinicians face regarding the effect of NAVA level on patient unloading at the bedside. NAVA level, as a gain factor alone, without assessing the proportion of support relative to patients' own effort, is an abstract, poorly defined concept, often difficult to grasp. Should NVE–based titration of the NAVA level expand into clinical practice? To set the assist based on the level of unloading may be more intuitive and offers the possibility of a more quantitative and standardized approach that could contribute to structured, goal-oriented weaning protocols. Measuring the amount of unloading of

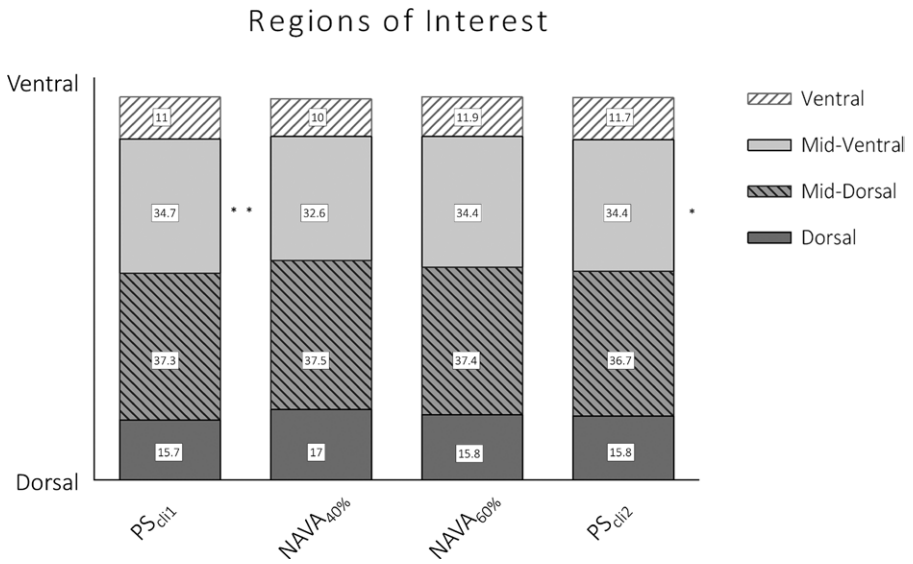

Fig. 2. Lung regions of interest percentage. The figure represents the relative impedance changes in each lung region, from ventral to dorsal, observed during the different study steps. The *P* values are as follows: Friedman repeated measures ANOVA for ventral region $P = 0.218$; Friedman repeated measures ANOVA for midventral region $P = 0.012$; $^{**}P = 0.064$ PS_{cli1} *versus* $NAVA_{40\%}$; $^{*}P = 0.010$ PS_{cli2} *versus* $NAVA_{40\%}$; Friedman repeated measures ANOVA for middorsal region $P = 0.339$; Friedman repeated measures ANOVA for dorsal region $P = 0.062$. $NAVA_{40\%}$, neurally adjusted ventilatory assist at 40% unloading; $NAVA_{60\%}$, neurally adjusted ventilatory assist at 60% unloading; PS_{cli1}. pressure support; PS_{cli2}, same as PS_{cli1}.

Table 2. Ventilatory Parameters

Ventilatory Parameters	PS_{cli1}	$NAVA_{40\%}$	$NAVA_{60\%}$	PS_{cli2}
$P_{aw\|mean}$ (cm H_2O)	12.2 (8.3, 13)	11.4 (8.5, 11.5)	11.6 (10, 12.2)*	12.1 (8.3, 13.2)†
RR (bpm)	15 (11, 17)	16 (13, 18)	16 (11, 19)	15 (10, 18)
Vt (ml)	525 (488, 642)	530 (408, 552)	525 (427, 585)	535 (486, 559)
MV (L/min)	8.4 (5.7, 9.2)	8.2 (5.9, 8.9)	8.3 (5.6, 9.1)	8.4 (5.6, 9.9)
$EAdi_{peak}$ (μV)	2.7 (1.6, 4.7)	5.3 (4.2, 6.9)‡	4.7 (2.8, 5.3)	3.9 (1.7, 7.3)
Pao_2/FIo_2 (mmHg)	330 (285, 367)	300 (292, 337)	315 (277, 345)	307 (277, 352)
$Paco_2$ (mmHg)	40 (38, 44)	41 (38, 44)	41 (37, 43)	40 (38, 43)

Table 2 reports the ventilatory parameters in the different study steps as median and interquartile range. The *P* values are as follows: Friedman repeated measures (RM) ANOVA $P_{aw|mean}$ $P = 0.007$; Friedman RM ANOVA $EAdi_{peak}$ $P = 0.026$; Friedman RM ANOVA Vt $P = 0.279$; Friedman RM ANOVA MV $P = 0.430$; Friedman RM ANOVA PaO_2/FIO_2 $P = 0.484$; Friedman RM ANOVA $PaCO_2$ $P = 0.086$; and Friedman RM ANOVA RR $P = 0.678$.

$^{*}P = 0.002$ $NAVA_{40\%}$ *versus* $NAVA_{60\%}$; †$P = 0.009$ PS_{cli2} *versus* $NAVA_{40\%}$; ‡$P = 0.006$ PS_{cli1} *versus* $NAVA_{40\%}$.

bpm, breaths per minute; $EAdi_{peak}$, peak electrical activity of the diaphragm; MV, minute volume; NAVA, neurally adjusted ventilatory assist; $NAVA_{40\%}$, NAVA at 40% unloading; $NAVA_{60\%}$, NAVA at 60% unloading; $P_{aw|mean}$, mean airway pressure; PS_{cli1}, pressure support; PS_{cli2}, same as PS_{cli1}; RR, respiratory rate; Vt, tidal volume.

the respiratory muscles offers the clinician a simple bedside method to titrate the breathing effort done by the patient and come one step closer to finding the optimal NAVA, avoiding overassistance and muscle atrophy, and/or preventing underassistance and muscle fatigue.

Previously Carteaux *et al.*[35] identified targets of respiratory effort based on peak P_{musc}, corresponding to a range of assistance between 35 and 65% during proportional assist ventilation. We set targets of unloading similarly, to 40 and 60%. We believe that clinicians could initially aim at unloading targets ranging from low (less than 30%), to moderate (30 to 50%), or to high unloading (more than 50%) rather than fixed and narrow percentage targets. A closed-loop feedback system adjusting the NAVA level toward an unloading target could perhaps be a useful adjunct for this purpose.

The unloading target for $NAVA_{cli}$ was intended to match PS_{cli1}. The unloading observed in PS_{cli1} was, however, too high to be matched with NAVA (table 3 in the Supplemental Digital Content, http://links.lww.com/ALN/B757, reporting the PS_{cli1} and the respiratory muscle unloading during PS_{cli1} and fig. 1 [A and B] in the Supplemental Digital Content showing one example from one patient where the target could not be reached in $NAVA_{cli}$). The fact that most patients with PS_{cli1} above 10 cm H_2O had an UNL_{NVE} higher than 75% is of clinical interest. This degree of unloading indicates excessive inspiratory support and indicates a difficulty to titrate pressure support to adequately balance patient's unloading and effort. In contrast, excessive levels of unloading are difficult to reach during NAVA because it is hard to suppress the EAdi, as previously shown.[12]

Regarding our secondary outcome, the regional distribution of ventilation measured by EIT was similar to that found in a previous work,[22] where ventilation was more dorsally distributed at lower pressure support and NAVA. Moderate unloading during $NAVA_{40\%}$ resulted in more dorsally distributed ventilation, as assessed by the dorsal shift in center of ventilation when compared with PS_{cli2} or $NAVA_{60\%}$. Furthermore, the distribution of ventilation became slightly more homogeneous during $NAVA_{40\%}$ compared with PS_{cli2}, as shown by the relatively lower global inhomogeneity index (fig. 7 in the Supplemental Digital Content, http://links.lww.com/ALN/B757, showing the global inhomogeneity index distribution in the different study steps).

Our findings suggest that lower levels of unloading could be related to a beneficial redistribution of ventilation because of a more active diaphragm. The clinical relevance of these modest differences is unclear. The observed airway pressure differences were also rather small from a clinical perspective. It is important to note that, in contrast to previous studies, the included patients had good lung function, with $Pa_{O_2}/F_{I_{O_2}}$ around 330 mmHg, relatively low PEEP, and relatively low EAdi.[36–38] Patients did not develop any pulmonary complications and were ventilated for a median time of 7.5 days (4, 11.5). This may well account for the subtle differences seen in the physiologic variables.

To our knowledge, no previous studies applied NAVA in neurocritical care patients, a challenging patient population to wean, for which the reports on rate of extubation failure are quite inhomogeneous in the literature.[39] Furthermore, the brain injury in itself may affect the breathing pattern and the respiratory drive response to ventilator assist. Because we based the different targets of unloading on the EAdi response, we had to exclude two patients who had very low EAdi (less than 2 μV) despite reducing the NAVA assist. One patient with bleeding in the brainstem was excluded because of a highly irregular breathing pattern and large variation in EAdi, independent of the level of assist. This titration method might not be appropriate when the respiratory drive does not respond to changes in ventilatory load.[16,35,40,41]

This pilot study was primarily an evaluation of a new method to select the level of assistance in NAVA, based on the unloading of the diaphragm. Further studies are needed in lung-injured patients and to investigate the long-term physiologic effects of different levels of unloading.

Limitations of the Study

The study was conducted in a small number of patients. The results would therefore need confirmation in a larger population. With this stated, we consider this pilot evaluation a proof-of-concept study that provides new information for a more standardized and objective means of setting the support in NAVA in the weaning process.

The fact that patients were overassisted during pressure support precluded the comparison with NAVA. We did not measure esophageal pressure, which could be considered a limitation. However, in a previous comparison, UNL_{NVE} correlated well with unloading based on esophageal pressure.[19]

In the SERVO-i ventilator, when zeroing the NAVA level during a NVE maneuver, the ventilator actually delivers a pressure support of 2 cm H_2O above PEEP. Therefore the NVE is not based on a real zero assist maneuver and might systematically underestimate ventilator unloading.[19] We believe, however, that the effect is negligible in the determination of the unloading.

Conclusions

This pilot study suggests that it may be feasible to titrate the NAVA assist to target the respiratory muscle unloading based on the NVE index. Moderate respiratory muscle unloading generated a redistribution of ventilation toward the dorsal regions of the lungs. Further studies are warranted to investigate the effects of reduced NAVA unloading in more lung-injured patients and the potential clinical benefits of different unloading targets.

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Competing Interests

Dr. Campoccia Jalde received a research grant from Maquet Critical Care (Solna, Sweden) at the time of the study. Dr. Mats Wallin and M.Sc. Fredrik Jalde are currently working at Maquet Critical Care.

Reproducible Science

Full protocol available at: francesca.campoccia-jalde@sll.se. Raw data available at: francesca.campoccia-jalde@sll.se.

Correspondence

Address correspondence to Dr. Jalde: Karolinska University Hospital, Karolinska Vägen, 171 76 Stockholm, Sweden. francesca.campoccia-jalde@sll.se. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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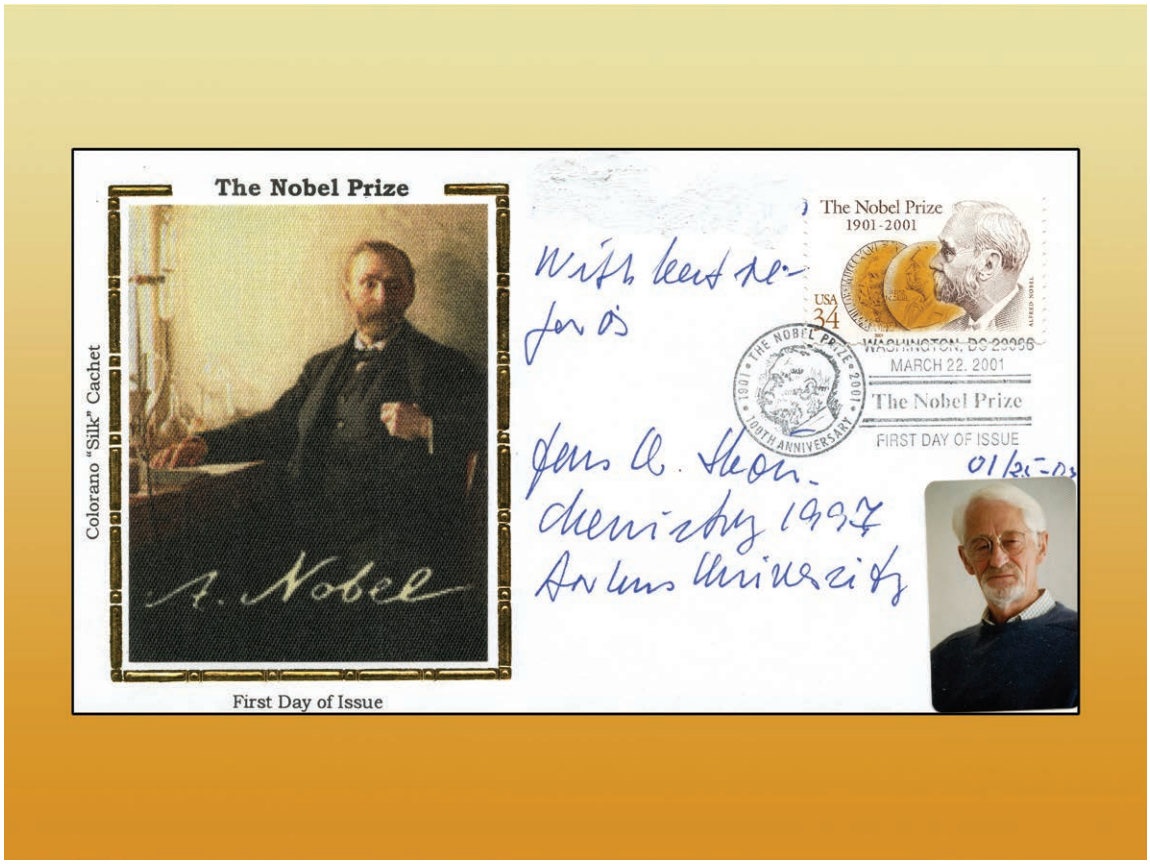
ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Birth Centennial of Nobel Laureate Skou, an Investigator of Local Anesthetics and the Sodium–Potassium Pump



In 1947 a Danish physician–physiologist, Jens Christian Skou (1918 to 2018, *lower right*), began working at the Institute for Medical Physiology at Aarhus University. Although his 1951 doctoral dissertation correlated local anesthetic activity with lipid solubility, Skou eventually investigated the physiology of nerves in shore crabs' legs. In 1957 Skou became the first to discover an ion-transporting enzyme, the sodium–potassium pump. Forty years later, in Stockholm, Sweden, Skou was awarded his half of the 1997 Nobel Prize in Chemistry. This month, October of 2018, marks the birth centennial of Jens Christian Skou, whose "curiosity-based research" led him from local anesthetics to worldwide fame.

George S. Bause, M.D., M.P.H., Honorary Curator and Laureate of the History of Anesthesia, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.