Neurally adjusted ventilatory assist after surgical treatment of intracerebral hemorrhage: a randomized crossover study

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Abstract
Objective: We assessed the neuromechanical efficiency (NME), neuroventilatory efficiency (NVE), and diaphragmatic function effects between pressure support ventilation (PSV) and neuromatically adjusted ventilatory assist (NAVA).

Methods: Fifteen patients who had undergone surgical treatment of intracerebral hemorrhage were enrolled in this randomized crossover study. The patients were assigned to PSV for the first 24 hours and then to NAVA for the following 24 hours or vice versa. The monitored ventilatory parameters under the two ventilation models were compared. NME, NVE, and diaphragmatic function were compared between the two ventilation models.

Results: One patient’s illness worsened during the study. The study was stopped for this patient, and intact data were obtained from the other 14 patients and analyzed. The monitored tidal volume was significantly higher with PSV than NAVA (487 [443–615] vs. 440 [400–480] mL, respectively). NME, NVE, diaphragmatic function, and the partial pressures of arterial carbon dioxide and oxygen were not significantly different between the two ventilation models.

Conclusion: The tidal volume was lower with NAVA than PSV; however, the patients’ selected respiratory pattern during NAVA did not change the NME, NVE, or diaphragmatic function.

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What do we already know about neutrally adjusted ventilatory assist?

Neurally adjusted ventilatory assist (NAVA) can improve patient comfort and increase respiratory variability. NAVA also confers a lower risk of overassistance than pressure support ventilation.

What are the new findings in this article?

In this randomized crossover study of 15 patients who had undergone surgical treatment of intracerebral hemorrhage, NAVA maintained suitable partial pressures of arterial carbon dioxide and oxygen with a lower tidal volume compared with pressure support ventilation. NAVA was safe for use after surgical treatment of intracerebral hemorrhage with a suitable electrical activity of the diaphragm signal. Additionally, the patients’ selected respiratory pattern did not change the diaphragmatic function during NAVA.

Introduction

Neurally adjusted ventilatory assist (NAVA) can detect a patient’s electrical activity of the diaphragm (EAdi), which reflects the patient’s neural drive and may be obtained through a nasogastric tube with electrodes that measure the electromyographic signals of the diaphragm. The strength of pressure support during NAVA mainly depends on the patient’s EAdi and user-set “NAVA level.” A physiological study showed that NAVA improves oxygenation and comfort by increasing respiratory parameter variability, showing great superiority mainly in critically ill patients after abdominal surgery. However, although NAVA maintains a minute volume similar to that of pressure support ventilation (PSV), it provides a smaller tidal volume and poses a lower risk of overassistance.

One study showed that neuromechanical efficiency (NME) and neuroventilatory efficiency (NVE) were improved by NAVA but not by PSV after prolonged controlled ventilation. NME is reflected by the inspiratory pressure generation normalized to inspiratory effort, calculated by the airway pressure during inspiratory occlusion of the respiratory circuit divided by EAdi. NVE is reflected by the ability to generate the tidal volume normalized to the neural drive, calculated by dividing the tidal volume by EAdi.

Mechanical ventilation itself can cause diaphragmatic dysfunction, and this is usually called ventilator-induced diaphragmatic dysfunction (VIDD). NAVA can result in respiratory pattern changes, such as a smaller tidal volume during NAVA, and whether such a patient’s selected respiratory pattern changes the diaphragmatic function is unclear. Diaphragmatic movement assessed by bedside ultrasonography has been used to evaluate diaphragmatic function.
NAVA can improve comfort and increase respiratory variability after abdominal surgery in selected patients, and NAVA confers a lower risk of overassistance than PSV. To the best of our knowledge, no physiological clinical tests have been established to evaluate whether NAVA is satisfactory after surgical treatment of intracerebral hemorrhage.

The present randomized crossover study was designed to investigate the effects of NAVA on NME, NVE, and diaphragmatic function after surgical treatment of intracerebral hemorrhage.

**Methods**

This single-center, randomized crossover study was conducted from May 2019 to December 2019 in the Department of Neurosurgery intensive care unit of our hospital. This study was conducted in accordance with the CONSORT recommendations because of its clinical and randomized design. The experimental protocol was approved by the Ethics Committee of Yijishan Hospital’s Institutional Review Board. Before inclusion, written informed consent was obtained from each participant or their next-of-kin. The trial was registered before patient enrollment at www.chictr.org.cn (the primary registries of the WHO Registry Network, clinical trial registration no. ChiCTR1900022861, Principal investigator: Tao Yu, date of registration: 28 April 2016).

**Patients**

Fifteen patients undergoing surgical treatment of intracerebral hemorrhage were prospectively enrolled from May 2019 to December 2019. Before inclusion, they had been endotracheally intubated or had undergone tracheotomy and been mechanically ventilated by PSV with 5 to 10 cm H$_2$O of positive end-expiratory pressure and 8 to 12 cm H$_2$O of pressure support. The inclusion criteria were the presence of intracerebral hemorrhage or subarachnoid hemorrhage (SAH) and provision of written informed consent from the patient or a family member. The exclusion criteria were pregnancy or lactation, age of <18 years, lack of a clear diagnosis of SAH, the inability to undergo surgery or other interventions because of a critical condition, lack of invasive intracranial pressure monitoring, admission to the hospital >72 hours after onset of SAH, and clinical contraindications for use of NAVA (including any contraindications for EAdi catheter placement or EAdi signal instability).

**Study design**

PSV was used for 5 minutes at the beginning of the study. The doctor adjusted the pressure support level to obtain a suitable minute volume with a tidal volume of 6 to 8 mL/kg predicted body weight and a respiratory rate of 15 to 30 breaths/minute. The support level of NAVA was set to provide a similar minute volume as determined by prior use of PSV for 5 minutes. Each patient was consecutively ventilated for 24 hours with PSV or NAVA using a Servo-i ventilator (Getinge Group, Gothenburg, Sweden) in random order.

With respect to the ventilatory settings, the flow inspiratory trigger was 2 L/minute during PSV. As a back-up during NAVA for all patients, the neural inspiratory trigger was 0.5 μV. The flow inspiratory trigger was 2 L/minute to permit ventilation triggered by flow or EAdi according to the principle of “first arrived, first served.” When the EAdi was unstable or unable to trigger the ventilator, the ventilator automatically converted to PSV mode. When the EAdi was stable or able to trigger the ventilator, the ventilator automatically converted to NAVA mode. The neural
expiratory trigger was 30% of the maximal peak EAdi value during NAVA, the ventilatory setting of the flow expiratory trigger was 30% of the maximal peak flow value, and the inspiratory rise was 5% during PSV. All of these ventilatory settings were kept constant during the study.

The positive end-expiratory pressure was kept constant during the study; the fraction of inspired oxygen of the ventilator was adjusted to obtain an oxygen saturation of >95%. When PSV was used, the clinician could adjust the pressure support assistance level by 2 cm H2O each time, and when NAVA was used, the clinician could adjust the NAVA level by 0.2 cm H2O/microvolts each time, if necessary. For both NAVA and PSV, the clinician attempted to maintain a tidal volume of 6 to 8 mL/kg predicted body weight and a respiratory rate of 15 to 30 breaths/minute.

Measurements and data collection

Blood pressure, three-lead electrocardiography, and oxygen saturation derived from pulse oximetry were monitored routinely. Intracranial pressure was measured with an invasive intracranial pressure monitor (Codman ICP Express; Codman, Johnson & Johnson, Raynham, MA, USA). Arterial blood gas analyses were conducted at baseline and 24 hours of mechanical ventilation in both the NAVA and PSV groups. The Critical Care Pain Observation Tool and the Richmond Agitation–Sedation Scale were used as appropriate to evaluate the pain, comfort, sedation, and agitation levels. The doses of analgesia and sedation were managed by the nurse and recorded and evaluated every 4 hours to achieve suitable analgesia and sedation levels.

EAdi was obtained by use of an EAdi catheter through a nasogastric tube with electrodes placed on its distal end. The correct position of the EAdi catheter was confirmed by pushing the specific function button “EAdi catheter positioning” of the ventilator to check the EAdi signal (Figure 1). EAdi, EAdi-derived monitoring index, NME, and NVE were measured to evaluate the patients’ diaphragmatic contractility. Because data collection only takes a few seconds, this method is safe and repeatable, and it is widely used to evaluate patients’ diaphragm efficiency. According to previous studies,5,7,17 NME was calculated as the ratio of one airway pressure value and one EAdi value during 2 to 3 s of end-expiratory occlusion (i.e., one inspiratory effort).5,7,17 NVE was measured by monitoring five unassisted breaths and calculated as the ratio of the tidal volume divided by EAdi during inspiration5,7,17 (Figure 1).

According to previous studies5,7,17 only one airway pressure and one EAdi value were recorded for each 2 to 3 s of end-expiratory occlusion. If the airway blocking time is too long, it may lead to discomfort and a stress response and thus affect the accuracy of the data collection. The measurement was repeated 1 minute later for a total of three times. NME was calculated from the average value of three end-expiratory occlusions.

Diaphragmatic movement was assessed in the supine position using a 3.5-MHz ultrasonography probe in two-dimensional mode at the right-side anterior axillary line or at the left-side midaxillary line though the intercostal spaces. Using the liver or spleen as the diaphragm acoustic window, the ultrasonography probe was aimed cephalad and dorsally such that the ultrasound beam was perpendicular to the middle and back third of the diaphragm (Figure 1(b)). M-mode ultrasound tracing was used to display the diaphragmatic movement, and the diaphragm appeared as a thick, linear, hyperechoic band. The ultrasound beam line was pointed to the top of the diaphragm dome with an angle of <30° from the long axis to observe maximum
Diaphragmatic movement. Diaphragmatic movement was measured as the vertical height in the M-mode ultrasound tracing image from the baseline position to the maximum height achieved during breathing. The inspiratory peak above the baseline of the diaphragmatic excursion indicates the diaphragmatic movement (Figure 1). The values of diaphragmatic movement were measured by one of the authors (W.K.), and the average of six single measurements of left-sided and right-sided diaphragmatic movement.

**Figure 1.** Study methods. (a) Confirmation of the catheter position. (b) Measurement of diaphragmatic movement using a 3.5-MHz ultrasonography probe in two-dimensional mode. (c, d) Representative case involving PSV and NAVA. (e) Measurement of NVE, calculated as tidal volume / peak electrical activity of the diaphragm. (f) Measurement of NME, calculated as (positive end-expiratory pressure - minimal airway pressure) / peak electrical activity of the diaphragm.

PSV, pressure support ventilation; NAVA, neutrally adjusted ventilator assist; NVE, neuroventilatory efficiency; NME, neuromechanical efficiency.
right-sided diaphragmatic movement was recorded and analyzed. It took approximately 5 minutes to measure diaphragmatic movement for each patient.

**Outcome measurements**

The primary endpoints were the monitored respiratory mechanics parameters, including the tidal volume, minute ventilation, respiratory rate, peak inspiratory pressure, and mean inspiratory pressure obtained at baseline and after 24 hours of mechanical ventilation under both PSV and NAVA. The secondary endpoints were NME and NVE evaluated by measurement of the EAdi signal with NAVA, diaphragmatic function as evaluated by ultrasound-measured diaphragmatic movement, and blood gas exchange as evaluated by the partial pressure of arterial oxygen (PaO₂), partial pressure of arterial carbon dioxide (PaCO₂), and PaO₂/fraction of inspired oxygen (FiO₂) ratio.

**Statistical analysis**

The SPSS 16 statistics software package (SPSS, Inc., Chicago, IL, USA) was used to analyze the data. Normally distributed data are expressed as mean ± standard deviation or as median [interquartile range], as appropriate. If the data were normally distributed, they were analyzed by the paired Student’s t test; otherwise, the Wilcoxon test was used. The difference was statistically significant at a P value of <0.05.

**Results**

In total, 377 patients were screened from May 2019 to December 2019. Of these, three patients were excluded because of an unstable EAdi signal, an EAdi signal that could not be obtained, or an EAdi signal that was too weak to trigger the ventilator. Fifteen patients were randomized to undergo PSV or NAVA for the first 24 hours, and then they underwent NAVA or PSV for the following 24 hours. However, the illness of 1 of these 15 patients worsened during the study. The study was stopped for this patient, and intact data were obtained from the remaining 14 patients and analyzed (Figure 2). The causes of intracerebral hemorrhage in the 14 patients who were included in the present study were a communicating aneurysm (n = 9), basal ganglia hemorrhage (n = 2), hemorrhage of the right thalamus (n = 1), hemorrhage in the right parietal occipital lobe (n = 1), and hemorrhage in the left temporal lobe (n = 1). Seven patients underwent oral endotracheal intubation, and seven patients underwent placement of a tracheotomy tube.

The baseline characteristics of all 14 patients are shown in Table 1. Two patients died within 28 days after hospital admission. One patient abandoned treatment and was automatically discharged from the hospital. The baseline mechanical ventilation settings and monitored respiratory mechanics parameters in the PSV and NAVA groups are shown in Table 2. No significant differences were observed between the PSV and NAVA groups.

**Feasibility of NAVA after surgical treatment of intracerebral hemorrhage**

During the 24-hour period of NAVA, six patients were switched from NAVA to PSV (automatic switch for safety). NAVA was automatically converted to PSV 8 [3–11] times with a total duration of 6 [2–11] minutes, and the time spent in PSV was <0.7% of the total time spent in NAVA. The time period in which the switch occurred was often at night, which resulted in a decreased dose of analgesia and sedation or temporary cessation of the analgesia and sedation agent administered via pump by the nurse or attending physician. PSV automatically switched to NAVA within a few minutes (the EAdi signal has priority to
Assessed for eligibility (n = 377)

Patients who were eligible (n = 103)

Patients who were excluded (n = 88)

The inability to perform surgery or other interventions in a critical condition (n = 9)

Patients admitted to the hospital who had been diagnosed with SAH exceeding 72 h (n = 8)

Patients without invasive intracranial pressure monitoring (n = 63)

Patients with the clinical contraindication for use of NAVA included any contraindications for an EAdi catheter placement (n = 5)

EAdi signal instability (n = 3)

Underwent randomization (n = 15)

Assigned to PSV for the first 24 h, then NAVA for the following 24 h (n = 8)

Assigned to NAVA for the first 24 h, then PSV for the following 24 h (n = 7)

The patient’s illness was getting worse; the study was stopped (n = 1)

The study intervention was discontinued (n = 0)

Analyzed (n = 7)

Analyzed (n = 7)

Figure 2. CONSORT flowchart.
PSV, pressure support ventilation; NAVA, neutrally adjusted ventilator assist; SAH, subarachnoid hemorrhage.
| Patient number | Sex   | Age, years | Height, cm | Weight, kg | Acute Physiology and Chronic Health Evaluation II score | Glasgow Coma Scale score | Hunt–Hess score | Major diagnosis                                                                 | Time between inclusion and admission, days | Total duration of mechanical ventilation, days | 28-day mortality |
|----------------|-------|------------|------------|------------|-----------------------------------------------------|--------------------------|-----------------|---------------------------------------------------------------------------------|---------------------------------------------|-------------------------------------------------|------------------|
| 1              | Male  | 78         | 172        | 60         | 17                                                  | 11                       | —               | Intracerebral hemorrhage at left basal ganglia                                 | 9                                           | 35                                                             | Survived         |
| 2              | Male  | 47         | 178        | 80         | 26                                                  | 10                       | 3               | Left anterior communicating aneurysm                                           | 1                                           | 8                                                              | Died             |
| 3              | Female| 71         | 160        | 55         | 18                                                  | 10                       | 3               | Left anterior communicating aneurysm                                           | 1                                           | 4                                                              | Survived         |
| 4              | Female| 67         | 158        | 60         | 21                                                  | 5                        | 5               | Left posterior communicating aneurysm                                          | 2                                           | 13                                                             | Survived         |
| 5              | Female| 43         | 160        | 60         | 17                                                  | 5                        | —               | Hemorrhage of right thalamus with rupture into the ventricle                  | 1                                           | 10                                                             | Survived         |
| 6              | Male  | 49         | 175        | 85         | 25                                                  | 5                        | —               | Intracerebral hemorrhage at left basal ganglia with rupture into the ventricle | 14                                          | 22                                                             | Survived         |
| 7              | Female| 52         | 163        | 62         | 14                                                  | 4                        | 4               | Left anterior communicating aneurysm                                           | 1                                           | 12                                                             | Survived         |
| 8              | Male  | 33         | 178        | 82         | 15                                                  | 10                       | 3               | Left anterior communicating aneurysm                                           | 6                                           | 12                                                             | Survived         |
| 9              | Male  | 74         | 171        | 70         | 14                                                  | 11                       | 3               | Left anterior communicating aneurysm                                           | 1                                           | 5                                                              | Survived         |
| 10             | Male  | 29         | 176        | 83         | 15                                                  | 7                        | —               | Hemorrhage in right parietal occipital lobe with rupture into the ventricle   | 1                                           | 12                                                             | Survived         |
| 11             | Male  | 57         | 173        | 78         | 24                                                  | 4T                       | —               | Intracerebral hemorrhage in left temporal lobe; moyamoya disease              | 2                                           | 8                                                              | Survived         |
| 12             | Male  | 70         | 176        | 90         | 34                                                  | 9                        | 3               | Left anterior communicating aneurysm                                           | 15                                          | 20                                                             | Abandoned treatment and automatically discharged |

(continued)
trigger ventilator in NAVA). No significant differences were observed between the PSV and NAVA groups in terms of intracranial pressure (12 ± 4 vs. 11 ± 5 mmHg, respectively), systolic blood pressure (131 ± 17 vs. 130 ± 17 mmHg, respectively), diastolic blood pressure (71 ± 10 vs. 70 ± 11 mmHg, respectively), or heart rate (85 ± 15 vs. 88 ± 18 beats/minute, respectively).

**Changes in respiratory pattern**

The monitored respiratory parameters are shown in Table 2. The tidal volume was significantly lower NAVA than PSV (440 [400–480] vs. 487 [443–615] mL, respectively; P < 0.05). No significant differences were observed between the PSV and NAVA groups in terms of the peak inspiratory pressure (15 [13–15] vs. 14 [12–16] cmH2O, respectively), mean inspiratory pressure (7 [6–8] vs. 7 [6–8] cmH2O, respectively), or respiratory rate (20 [16–22] vs. 19 [17–22] breaths/minute, respectively). The minute volume after 24 hours of ventilation was not different between the NAVA and PSV groups (8.1 [7.0–9.7] vs. 9.4 [8.2–11.3] L/min, respectively).

**Blood gas analysis**

The results of the arterial blood sample analysis are shown in Table 3. PaCO2, PaO2, and PaO2/FiO2 at baseline were similar between NAVA and PSV. No significant differences were observed in PaCO2 after 24 hours between the NAVA and PSV groups (33 ± 5 vs. 30 ± 6 mmHg, respectively). The PaO2 (114 ± 25 vs. 109 ± 24 mmHg) and PaO2/FiO2 (309 ± 63 vs. 294 ± 60 mmHg) showed a consistent but slight and nonsignificant increase after 24 hours in the NAVA than PSV group. The pH (7.46 ± 0.03 vs. 7.48 ± 0.07 mmHg) and blood lactate level (1.7 ± 0.8 vs. 1.9 ± 0.9 mmol/L) after 24 hours of ventilation.
Table 2. Baseline mechanical ventilation settings and monitored respiratory mechanics parameters in the PSV and NAVA groups.

| Parameters                              | PSV baseline (n = 14) | PSV 24 hours (n = 14) | P value | NAVA baseline (n = 14) | NAVA 24 hours (n = 14) | P value |
|-----------------------------------------|-----------------------|-----------------------|---------|------------------------|------------------------|---------|
| Intracranial pressure, mmHg             | 13 ± 6                | 12 ± 4                | 0.347   | 10 ± 3                 | 11 ± 5                 | 0.613   |
| Right diaphragmatic movement, cm        | 1.08 ± 0.30           | 1.26 ± 0.23           | 0.141   | 1.27 ± 0.31            | 1.24 ± 0.22            | 0.650   |
| Left diaphragmatic movement, cm         | 1.23 ± 0.30           | 1.24 ± 0.24           | 0.957   | 1.18 ± 0.26            | 1.26 ± 0.25            | 0.551   |
| Mechanical ventilation settings         |                       |                       |         |                        |                        |         |
| PSV support level, cmH2O                | 9 ± 1                 | 9 ± 1                 | 0.333   | NA                     | NA                     | NA      |
| NAVA support level, cmH2O               | NA                    | NA                    | NA      | 2.1 ± 0.6              | 2.2 ± 0.6              | 0.596   |
| FiO2, %                                 | 37 ± 4                | 38 ± 4                | 0.333   | 37 ± 5                 | 36 ± 5                 | 0.164   |
| PEEP, cmH2O                             | 5 ± 0                 | 5 ± 0                 | NA      | 5 ± 0                  | NA                     | NA      |
| Monitored respiratory mechanics parameters|                       |                       |         |                        |                        |         |
| Peak inspiratory pressure, cmH2O        | 15 [13–16]            | 15 [13–15]            | 0.402   | 15 [13–16]             | 14 [12–16]             | 0.470   |
| Mean inspiratory pressure, cmH2O        | 8 [6–8]               | 7 [6–8]               | 0.402   | 8 [6–8]                | 7 [6–8]                | 0.358   |
| Respiratory rate, breaths/minute        | 21 [16–23]            | 20 [16–22]            | 0.539   | 20 [16–21]             | 19 [17–22]             | 0.830   |
| Tidal volume, mL                        | 489 [389–561]         | 487 [443–615]         | 0.454   | 530 [428–612]          | 440 [400–480]          | 0.027   |
| Tidal volume, mL/kg predicted body weight| 7.1 [6.8–8.2]        | 8.4 [7.0–9.2]         | 0.194   | 8.2 [7.1–9.3]          | 6.8 [6.2–7.6]#         | 0.035   |
| Minute ventilation, L/min               | 9.5 [7.9–10.5]        | 9.4 [8.2–11.3]        | 0.874   | 9.5 [7.4–10.8]         | 8.1 [7.0–9.7]#         | 0.150   |
| EAdi, µV                                | 4.5 [2.8–6.1]         | 3.3 [2.1–5.1]         | 0.270   | 3.5 [2.2–5.4]          | 4.2 [2.1–6.0]          | 0.922   |
| NME, cmH2O/µV                           | 62.6 [42.3–124.8]     | 93.2 [57.5–146.6]     | 0.381   | 89.2 [53.2–165.2]      | 50.8 [39.3–170.5]      | 0.24    |
| NVE, mL/µV                              | 1.4 [1.1–3.5]         | 1.9 [1.2–2.5]         | 0.642   | 1.9 [1.2–2.5]          | 1.4 [1.0–2.5]          | 0.572   |

Data are presented as mean ± standard deviation or median [interquartile range] as appropriate. PSV, pressure support ventilation; NAVA, neutrally adjusted ventilator assist; PEEP, positive end-expiratory pressure; FiO2, fraction of inspired oxygen; EAdi, electrical activity of the diaphragm; NME, neuromechanical efficiency; NVE, neuroventilatory efficiency.

*P = 0.031, NAVA 24 hours vs. PSV 24 hours.

#P = 0.039, NAVA 24 hours vs. PSV 24 hours.

^P = 0.062, NAVA 24 hours vs. PSV 24 hours.
were not significantly different between the NAVA and PSV groups.

**NVE, NME, and diaphragmatic function**

Compared with PSV, NAVA showed no change in EAdi (4.2 [2.1–6.0] vs. 3.3 [2.1–5.1] cm), NVE (1.4 [1.0–2.5] vs. 1.9 [1.2–2.5] ml/mV), or NME (50.8 [39.3–170.5] vs. 93.2 [57.5–146.6] cm H₂O/mV) throughout the study period. No significant differences were observed between PSV and NAVA in either right diaphragmatic movement (1.24 ± 0.22 vs. 1.26 ± 0.23 cm) or left diaphragmatic movement (1.26 ± 0.25 vs. 1.24 ± 0.24 cm) after 24 hours of ventilation during the study.

**Discussion**

Our study showed that (1) if a suitable EAdi signal was detected, it was safe and feasible to use NAVA after surgical treatment of intracerebral hemorrhage; (2) similar to PSV, NAVA could maintain a suitable PaCO₂ and PaO₂ during a long period (24 hours) of mechanical ventilation; and (3) although the patients selected a lower tidal volume ventilation during NAVA, the patients’ selected respiratory pattern did not change the NME, NVE, or diaphragmatic function.

**Safety and feasibility of using NAVA**

One study showed that NAVA can improve comfort and increase respiratory variability after abdominal surgery and that it poses a lower risk of overassistance than PSV.⁴ Our results showed a significant difference in the tidal volume between the two groups after 24 hours of ventilation, while there was no significant difference in the respiratory rate or minute ventilation between the two groups after 24 hours of ventilation. This is because compared with patients in the PSV group, some patients in the NAVA group showed rapid increases in the respiratory rate while others showed decreased respiration. Thus, although the tidal volume was significantly different between the two groups, the respiratory rate and minute ventilation were not; however, the results showed a trend toward a significant difference.

To the best of our knowledge, this is the first study to investigate the safety and feasibility of using NAVA after surgical treatment of intracerebral hemorrhage. To

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**Table 3.** Hemodynamic monitoring and arterial blood gas analysis.

| Parameters        | PSV baseline (n = 14) | PSV 24 hours (n = 14) | P value | NAVA baseline (n = 14) | NAVA 24 hours (n = 14) | P value |
|-------------------|-----------------------|-----------------------|---------|------------------------|------------------------|---------|
| SBP, mmHg         | 136 ± 19              | 131 ± 17              | 0.437   | 126 ± 14               | 130 ± 17               | 0.393   |
| DBP, mmHg         | 72 ± 16               | 71 ± 10               | 0.693   | 69 ± 12                | 70 ± 11                | 0.860   |
| HR, beats/minute  | 89 ± 23               | 85 ± 15               | 0.240   | 88 ± 20                | 88 ± 18                | 0.968   |
| pH                | 7.46 ± 0.05           | 7.48 ± 0.07           | 0.446   | 7.48 ± 0.08            | 7.46 ± 0.03            | 0.487   |
| PaCO₂, mmHg       | 32 ± 5                | 30 ± 6                | 0.147   | 30 ± 6                 | 33 ± 5                 | 0.053   |
| PaO₂, mmHg        | 123 ± 25              | 109 ± 24              | 0.062   | 113 ± 22               | 114 ± 25               | 0.858   |
| HCO₃⁻, mM         | 24 ± 2                | 23 ± 3                | 0.308   | 23 ± 3                 | 24 ± 2                 | 0.035   |
| PaO₂/FiO₂, mmHg   | 340 ± 82              | 294 ± 60              | 0.029   | 286 ± 57               | 309 ± 63               | 0.252   |
| Lactate, mmol/L   | 1.9 ± 0.8             | 1.9 ± 0.9             | 0.417   | 1.7 ± 0.9              | 1.7 ± 0.8              | 0.972   |

Data are presented as mean ± standard deviation.
PSV, pressure support ventilation; NAVA, neutrally adjusted ventilator assist; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; PaCO₂, partial pressure of arterial carbon dioxide; PaO₂, partial pressure of arterial oxygen; FiO₂, fraction of inspired oxygen.
increase the homogeneity of the study population, only patients who had undergone surgical treatment of intracerebral hemorrhage (mainly those with communicating aneurysms) were included. Before randomization, three patients were excluded because of EAdi signal instability. One of these three patients had diagnoses of subarachnoid hemorrhage, right cerebellar hemorrhage, and cerebral hernia. Another of the three patients had diagnoses of hydropcephalus, intraventricular hematocel, left cerebral aneurysm, and subarachnoid hemorrhage. The last of the three patients had diagnoses of moyamoya disease, cerebral hernia, left basal ganglia intracerebral hemorrhage into the ventricle, bilateral ventricular casts, fourth ventricle hematocel, and obstructive hydrocephalus. No EAdi signal was detected in any of these three patients despite the EAdi catheter being placed correctly, or the EAdi signal being too weak to trigger the ventilator. Therefore, this is the first trial to show that the use of NAVA has some limitations in patients with cerebral hemorrhage combined with cerebral hernia or multiple coexisting diseases. These three patients were temporarily ventilated with control model ventilation.

Because the illness of 1 of the 15 patients worsened during this study, the study was stopped for this patient; the other 14 patients completed the study. The present study confirmed that as long as EAdi can be detected and ventilators can be triggered by EAdi, the use of NAVA is safe and feasible in selected patients who have undergone surgical treatment of intracerebral hemorrhage.

Respiratory pattern and gas exchange during NAVA

Consistent with a previous study, we found that the tidal volume was significantly lower during NAVA than during PSV. The ideal pressure support level will not cause discomfort, respiratory distress, or overassisted ventilation. During PSV, the monitored tidal volume is mainly affected by the user-set pressure support level in addition to the patient’s inspiratory effort and the compliance of the whole respiratory system. However, it is difficult to determine a suitable pressure support level during assisted ventilation.

NAVA is superior in terms of avoiding overassistance. If the NAVA level is set too high, the patient can autodownregulate EAdi; thus, the tidal volume decreases, and excessive airway pressure can be avoided. A study involving patients with extracorporeal membrane oxygenation showed that the tidal volume was adjusted to maintain the PaCO2 and PaO2 by closed-loop regulation during NAVA. Another study showed that NAVA is safe in children on extracorporeal membrane oxygenation because it allows the children to drive the mechanical ventilator and regulate the tidal volume according to their needs.

Another study demonstrated that oxygenation improved during NAVA. We found that similar to PSV, NAVA could maintain a suitable PaCO2 and PaO2 during a long period (24 hours) of mechanical ventilation. We observed an increasing trend in PaO2 during NAVA, although it was not statistically significant. We speculate that the reason is at least partly due to NAVA occasionally but temporarily being autoswitched to PSV in some patients.

NVE, NME, and diaphragmatic function

We found that the tidal volume was significantly lower during NAVA than during PSV. This result is consistent with the findings of a previous study. To the best of our knowledge, this is the first study to evaluate whether the respiratory pattern during NAVA impairs the efficiency of the central
drive to generate inspiratory pressure and tidal volume. Owing to a relatively linear relationship between EAdi and inspiratory pressure and tidal volume, normalization of the inspiratory pressure and tidal volume to EAdi provides an effective and repeatable method by which to compare the efficiency of the central drive to generate inspiratory pressure and tidal volume.\(^7\) Liu et al.\(^7\) demonstrated that patients who failed to be successfully extubated had a lower efficiency of converting EAdi, representing neuromuscular activity, into tidal volume and inspiratory pressure, thereby indicating a weaker diaphragm. Our study showed that NAVA did not impair the efficiency of the central drive to generate inspiratory pressure and tidal volume.

Because mechanical ventilation can decrease diaphragm contractility, it can cause diaphragmatic dysfunction; this is usually called VIDD.\(^8,9\) One study showed that NAVA could result in respiratory pattern changes, namely a smaller tidal volume during NAVA.\(^4\) Whether such a patient’s selected respiratory pattern jeopardizes diaphragmatic function or is a result of diaphragmatic dysfunction remains unclear. Diaphragmatic movement as assessed by ultrasonography to evaluate diaphragmatic function is repeatable and noninvasive at the bedside and has been used extensively.\(^10,26–28\)

Our study showed that the patient’s selected respiratory pattern did not change the diaphragmatic function during NAVA. VIDD adversely affects patient outcomes, and VIDD can occur even during assisted ventilation.\(^29\) NAVA is an effective method to monitor the central drive and deliver a diaphragm-protective mechanical ventilation pattern. During NAVA, the ventilator is controlled by the patients though the EAdi monitor and proportionally assists the patients’ inspiratory effort. NAVA has the potential to avoid overassistance or underassistance and to enhance diaphragm recovery from disease.

Some patients were ventilated for 6, 9, 14, and 15 days before inclusion in the study, which may have resulted in reduced diaphragmatic muscle mass and function. This is one reason for the large variation in the results and for representation of the data as median [interquartile range]. However, the present study was a self-crossover randomized controlled study; all patients were assigned either to PSV for the first 24 hours followed by NAVA for 24 hours or to NAVA for the first 24 hours followed by PSV for 24 hours. This design method reduced baseline heterogeneity, and our results showed no significant baseline heterogeneity between the PSV and NAVA groups.

**Limitations**

This study has several limitations. First, we did not evaluate the variability of breathing during NAVA because a previous study already confirmed that NAVA is a ventilation model that may increase the variability of breathing.\(^4\) One of the most important advantages of NAVA is reduced patient–ventilator dyssynchrony. This may be particularly important in neurosurgery intensive care units. Some data regarding dyssynchrony in terms of premature cycling, ineffective triggering, and double- or autotriggering in patients were submitted to a Chinese-language journal and thus could not be presented in this manuscript. Second, we only included patients with spontaneous intracerebral hemorrhage (most of whom had aneurysmal intracerebral hemorrhage); no patients with traumatic intracerebral hemorrhage were included. Therefore, our results cannot be extrapolated to patients with traumatic intracerebral hemorrhage. Third, although the sedation and analgesia levels of all patients were evaluated using the Critical
Care Pain Observation Tool and Richmond Agitation–Sedation Scale scores every 4 hours, there was no immediate feedback closed-loop adjustment system for the sedation and analgesia levels and the available sedative drugs. Thus, the effect of sedatives on EAdi remains unknown. Fourth, only the short-term effects of NAVA and PSV on gas exchange, NVE, NME, and diaphragmatic function were investigated. We cannot determine whether NAVA has any effect on mortality or other clinical outcomes. Large-sample clinical studies are still needed to confirm the effect of NAVA on the long-term prognosis of patients with intracerebral hemorrhage.

In conclusion, our results showed that NAVA can maintain a suitable PaCO₂ and PaO₂. NAVA is safe in patients who have undergone surgical treatment of intracerebral hemorrhage with suitable EAdi signals. During NAVA, the patient’s selected respiratory pattern did not change the NME, NVE, or diaphragmatic function. Clinical studies are required to evaluate the effect of NAVA on the long-term prognosis of patients who have undergone surgical treatment of intracerebral hemorrhage.

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Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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