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지도 교수 김 한 석

이 논문을 의학석사 학위논문으로 제출함

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Randomized Crossover Study of Neurally Adjusted Ventilatory Assist (NAVA) in Preterm Infants

by

Juyoung Lee

A thesis submitted to the Department of Clinical Medical Sciences in partial fulfillment of the requirements for the Degree of Master of Science in Clinical Medical Sciences at Seoul National University College of Medicine

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Professor _____Chairman

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Abstract

Randomized Crossover Study of Neurally Adjusted Ventilatory Assist (NAVA) in Preterm Infants

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Introduction: Neurally adjusted ventilator assist (NAVA) is a new method of mechanical ventilation, which delivers pressure assistance that is proportional to the electrical activity of the diaphragm.

Methods: To find out whether NAVA can be used to improve the lung-protective ventilator care of preterm infants, a prospective, randomized controlled, crossover clinical trial was performed. Twenty-six mechanically ventilated preterm infants were assigned to crossover ventilation with NAVA and synchronized intermittent mandatory ventilation (SIMV) + pressure support (PS) for 4 hours each in a randomized order. A 1-hour interval for washout was provided between the 2 modes of ventilation. The ventilator

settings were adjusted to maintain similar levels of end-tidal partial pressure of CO_2 ($EtCO_2$). The ventilator parameters, vital signs, and gas exchange effects under the 2 ventilatory modes were compared.

Results: Nineteen infants completed the 9-hour crossover comparison protocol. The peak inspiratory pressure (PIP), work of breathing (WOB) and peak electrical activity of the diaphragm (EAdi) with NAVA were significantly lower than those in SIMV + PS (P = 0.043, 0.002 and 0.004, respectively). Calculated tidal volume to peak EAdi ratio and PIP to peak EAdi ratio were higher with NAVA (P = 0.003 and 0.017, respectively). There were no significant differences in the mean airway pressure, inspiratory oxygen fraction (FiO_2) and blood gas values. None of the measurements of vital signs differed significantly between the two modes.

Conclusions: NAVA lowered PIP and reduced WOB in preterm infants at equivalent FiO_2 and partial pressure of CO_2 of capillary blood in comparison to SIMV + PS.

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Keywords: interactive ventilatory support, intermittent positive-pressure ventilation, neonatal critical care

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List of Abbreviations

NAVA, neurally adjusted ventilatory assist

SIMV, synchronized intermittent mandatory ventilation

PS, pressure support

NICU, neonatal intensive care unit

PEEP, positive end-expiratory pressure

PIP, peak inspiratory pressure

MAP, mean airway pressure

Mv, minute ventilation

TV, expiratory tidal volume

WOB, work of breathing

EAdi, electrical activity of the diaphragm

$EAdi_{peak}$, peak electrical activity of the diaphragm

$EtCO_2$, end-tidal partial pressure of CO_2

FiO_2, inspiratory oxygen fraction

SpO_2, oxygen saturation

BP, blood pressure

HR, heart rate

RR, respiratory rate

SN group, SIMV + PS first and subsequently switched to NAVA

NS group, NAVA first, switched to SIMV + PS next

PTP, pressure-time product

Introduction

The main objectives of mechanical ventilation in preterm infants include the restoration and maintenance of adequate gas exchange, the reduction of work of breathing (WOB), and the optimization of patient-ventilator interactions, while trying to avoid or minimize ventilator-induced lung injury (1, 2). Though noninvasive respiratory support is the best choice whenever possible to protect fragile premature lungs, mechanical ventilation remains an essential element in the critical care of preterm infants with respiratory distress. Many attempts have been made to develop optimal ventilatory strategies that minimize ventilator-related complications in preterm infants (3, 4), but there is still no consensus as to the best ventilation mode for critically ill preterm newborns (5, 6).

Ideally, assisted mechanical ventilation should provide precisely the amount of support that is needed by the patient. Each breath should not only be supported when initiated by the patient, but this support should also be tailored to the current needs of the patient. One step toward better regulation of assisted mechanical ventilation has been the development of the neutrally adjusted ventilatory assist (NAVA) mode.

NAVA is a form of partial respiratory support that is initiated upon the detection of an electrical signal from the diaphragm muscle, and pressure assistance is provided in proportion to and synchronous with the electrical activity of the diaphragm (EAdi) (7). EAdi is recorded by a specially modified naso/orogastric tube that has a sensor that isolates electrical signals of the

diaphragm from other electrical signals in the body (8).The amount of assistance provided for a given EAdi depends on a user-controlled gain factor, called the NAVA level (9). When phrenic nerves are intact, EAdi is the earliest and best signal available to estimate the neural respiratory drive (9, 10). It is feasible to obtain high-quality EAdi signals in preterm infants, and recent studies indicate that the triggering and cycling-off delays in preterm infants are short enough to safely and effectively control a ventilator (11, 12). Several studies have demonstrated patient–ventilator interaction is improved in NAVA compared with other conventional ventilatory modes in children and adults (13-18). Nevertheless, until recently, few articles have focused on neonates and premature infants (11, 19).

The goal of this study was to compare the conventional ventilatory mode, synchronized intermittent mandatory ventilation (SIMV) + pressure support (PS), with NAVA to determine whether NAVA could reduce the inspiratory pressure with respiratory unloading and whether more gentle but safe ventilatory support could be achieved using NAVA in preterm infants.

Materials and methods

A prospective, randomized, controlled and crossover comparison of NAVA and SIMV + PS was conducted from March to August of 2011 in the neonatal intensive care unit of Seoul National University Children's Hospital. Approval for this study was obtained by the Seoul National University Hospital Institutional Review Board, and written informed consent was obtained from the parents of neonates prior to their enrollment in this study. This study was conducted in compliance with the current revision of the Declaration of Helsinki and the Good Clinical Practice guidelines, and registered with ClinicalTrials.gov (NCT01389882).

Preterm infants supported by mechanical ventilation via endotracheal tube who had adequate spontaneous breathing were included in the study. The mandatory mechanical ventilation frequency was below 25 breaths/min. Patients were hemodynamically stable without the use of inotropic agents and were neurologically alert without the use of sedatives or anesthetic drugs. Patients with major congenital anomalies, intraventicular hemorrhage (grade III or higher), or phrenic nerve palsy were excluded from the study.

A pilot study was conducted with 4 preterm infants to test whether NAVA could lower the inspiratory pressure relative to that observed during SIMV + PS. The mean $\pm$ SD of the change in peak inspiratory pressure (PIP) was 1.69 $\pm$ 2.43 cmH_2O. Based on the pilot results, the required sample size for the main study was calculated to be 10 infants for each group (α = 0.05 and β = 0.20). Therefore, assuming a 20% dropout rate, we estimated that 26

patients would be required for sufficient power to draw conclusions from the study.

Protocol

All of the patients were ventilated using a ventilator with NAVA option (Servo-i; Maquet Critical Care AB, Solna, Sweden).Before beginning the study, the standard orogastric tube was replaced with a specially modified catheter, with an electrode sensor to detect the EAdi (EAdi Catheter; Maquet Critical Care AB). The catheter can also be used for feeding and for venting the stomach. The proper position of the catheter could be identified by the detection of electrical signals by the catheter.

Each infant was studied over 9 hours (Figure 1). SIMV + PS or NAVA was used for 4 hours, and the alternative method of ventilatory assistance was subsequently used for the remaining 5 hours. To rule out carryover effects, a 1-hour washout period was observed after changing the ventilatory modes. The results were only recorded during the 8-hour study period, omitting the 1-hour washout period. The order in which the ventilatory modes were applied was determined by a block randomization method after patient enrollment on the website of the Medical Research Collaborating Center of Seoul National University Hospital. Patients were randomly assigned 1:1 to the 2 groups.

During NAVA, the EAdi was used to control the ventilator. The trigger level was set at 0.5 uV above the minimal resting EAdi. During SIMV + PS using the Servo-i, the airway flow was measured with an ultrasonic expiratory flow transducer, and the airway flow was used to trigger the ventilator. Whereas

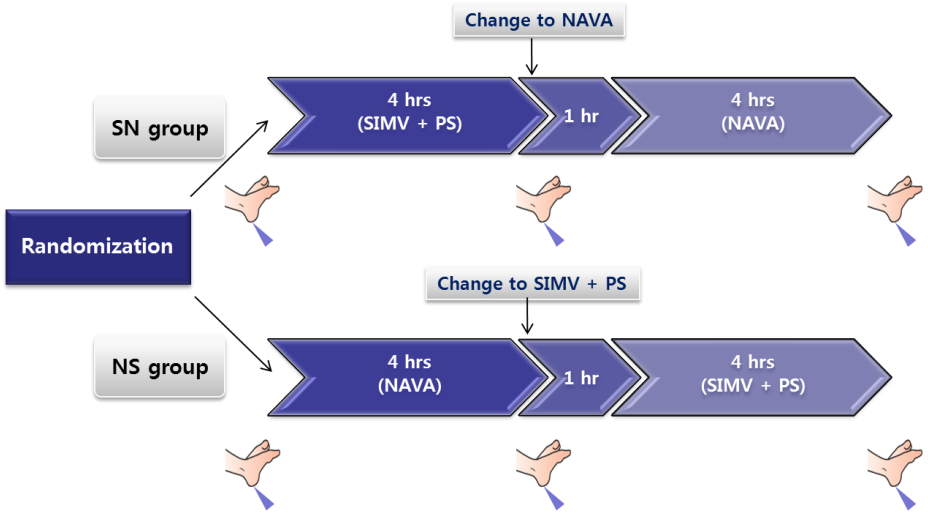

Figure 1. Study protocol.

the transition from mechanical inspiration to expiration was time-cycled in SIMV, the trigger to end inspiration in NAVA was automatic and expiration began when the EAdi signal decreased to 70% of its maximal value.

The ventilator settings used for the conventional SIMV+ PS mode were set at the discretion of the clinical teams. For each patient, the ventilator settings were adjusted to maintain consistent values of the end-tidal partial pressure ofCO_2 ($EtCO_2$), which was continuously measured by a capnometer (EMMA; Phasein, Danderyd, Sweden) (8) connected to an endotracheal tube for the entire study period. During NAVA mode, the NAVA level was adjusted (increased or decreased) until the minute ventilation volumes were similar to those achieved by the previous ventilatory mode. Backup ventilation (pressure control mode, rate 30/min) was available in case EAdi was absent for more than 10 seconds. Positive end-expiratory pressure (PEEP) was same for both modes.

Protocol Termination Criteria

One of the investigators observed at the bedside throughout the entire study period. The protocol was discontinued if any of the following problems developed: requirement of an increase in the inspiratory oxygen fraction (FiO_2) >0.1 to maintain oxygen saturation (SpO_2) >88%, the $EtCO_2$ increased by>20 mmHg, or the respiratory rate (RR) was >80/min and the heart rate (HR) was >200/min.

Assessment and Monitoring

Ventilator settings and ventilatory measurements were recorded automatically every minute using the Data Acquisition Macro v. 1.3 (Maquet Critical Care AB) and were evaluated with a dedicated computer program (Microsoft Excel 2007; Microsoft, Redmond, Washington). The primary outcome for assessment was the PIP. Secondary outcomes included the mean airway pressure, expiratory tidal volume(TV), dynamic compliance, WOB, peak EAdi ($EAdi_{peak}$), FiO_2, and RR. The inspiratory WOB of the patient was determined by the data acquisition program of the Servo-i ventilator running the Campbell diagram software (BicoreCP-100; Viasys Healthcare, Palm Springs, California) (20).

HR, RR, SpO_2, and $EtCO_2$ were monitored continuously. Blood pressure was measured noninvasively every 2 hours, and chest x-rays were taken before and after the study. Before beginning the study and at the end of each 4-hour period of either SIMV + PS or NAVA ventilation, capillary blood gases were sampled and analyzed using an i-STAT Portable Clinical Analyzer 300 (Abbott Point of Care Inc, Princeton, New Jersey). Adverse outcomes were defined as hypotension and air leakage, such as pneumothorax or pulmonary emphysema.

An independent data and safety monitoring board supervised the study investigation and reviewed the data from the first 4 patients and after completion of the study. The board had access to all of the data, and none of their analyses resulted in modifications or termination.

Statistical Analyses

We defined the validation data as per-protocol analyses and analyzed only the data from subjects who completed the study. Statistical analysis was performed using SPSS v. 19.0 (SPSS Inc, Chicago, Illinois). Student *t* tests or Mann-Whitney U tests were used to evaluate the descriptive statistics of all of the baseline characteristics. To evaluate the carryover effect of the first applied ventilator mode on the following mode, Student *t* tests or Wilcoxon rank sum tests were used. After testing for the normal distribution of each ventilator variable, paired *t* tests or Wilcoxon signed-rank tests were used to test for significant differences between the two ventilatory modes.

Results

Of the 26 preterm infants enrolled, 2 patients were excluded prior to the study, and 5 patients discontinued the protocol because they met a criterion for termination during the study. The remaining 19 patients completed the 9-hour crossover comparison study (Figure 2).

One of the 5 patients was terminated after initiation of the protocol because the parents withdrew their consent for the study. For the remaining 4, tachypnea (RR >80/min) developed. Tachypnea developed in 3 of the patients during the SIMV + PS mode on the second postnatal day. Hemodynamically significant patent ductus arteriosus was assumed to be the cause of tachypnea. The other patient developed tachypnea during the NAVA mode, during which the NAVA level was only 0.3 cmH_2O/mV and ventilatory support was not needed. The patient was extubated shortly after termination of the protocol.

There were no significant differences in demographic or baseline capillary blood gas data between the 2 groups (Table 1). During the SIMV + PS mode, the median support pressure above PEEP was 8.5 cmH_2O (range 5-14 cmH_2O), the set inspiratory time ranged from 0.3-0.5 seconds, and the median trigger flow was 4 L/min (range 3-5 L/min).

The NAVA level during NAVA mode ranged from 0.3-1.5 cmH_2O/mV. The average number of apnea episodes during NAVA mode was 1.8/hours (range 0-6.25/h), whereas the average number of apnea episodes during SIMV + PS was 0.25/h (range 0-4.75/h).

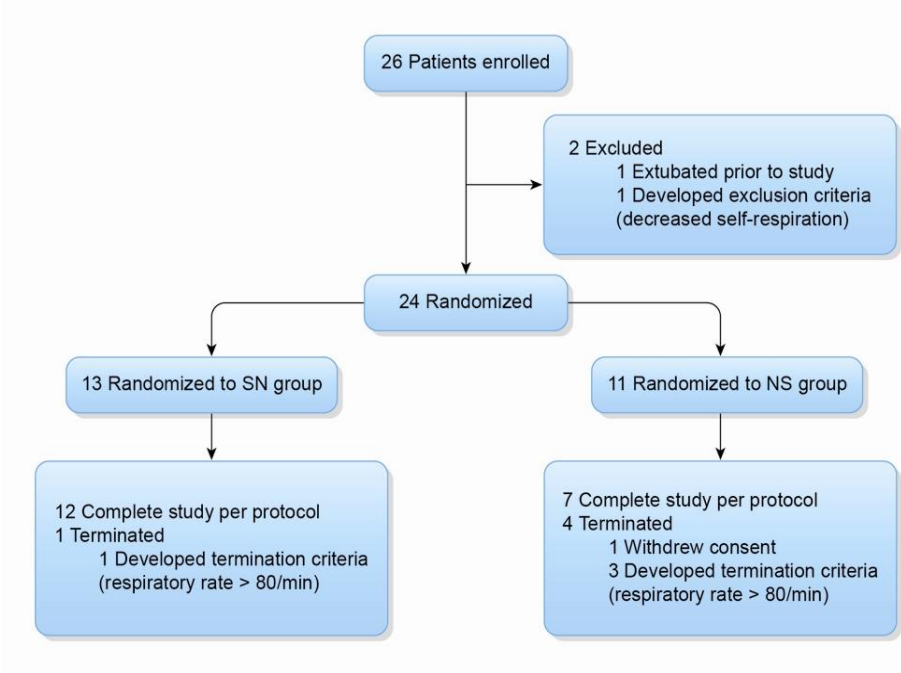

Figure 2. Study participants.

However, there was no significant oxygen desaturation in the patients attributable to apnea because backup ventilation took effect whenever apnea was detected.

No significant carryover effects were observed (ie, the first applied ventilatory mode did not affect the results of the following mode (Table 2).

In the primary study outcome, PIP was significantly lower during NAVA than during SIMV + PS at equivalent FiO_2 and partial pressures of CO_2 (Table 3). In terms of the secondary outcome variables, there were significant reductions in the patient WOB and $EAdi_{peak}$ with NAVA. There were no differences in PEEP, mean airway pressure, minute ventilation, TV, FiO_2, and RR. The dynamic compliance was slightly higher during NAVA, but the difference was not statistically significant. The $TV/EAdi_{peak}$ and $PIP/EAdi_{peak}$ ratios were calculated to evaluate the efficacy of ventilatory support for reducing the respiratory load (21). With NAVA, both the $TV/EAdi_{peak}$ and the $PIP/EAdi_{peak}$ were significantly higher (P = 0.003 and P = 0.017). Gas exchange results, analyzed at the end of each 4-hour period of either SIMV + PS or NAVA ventilation, did not differ.

Vital signs, including blood pressure, HR, RR, SpO_2, and $EtCO_2$ were maintained at similar levels throughout the study (Figure 3). No acute adverse events occurred in any of the infants during the study, and there were no patients who showed feeding problems during the study.

Table 1. Patient demographics and baseline characteristics

	Total (n = 19)	SN group (n = 12)	NS group (n = 7)	*P* value
Birth data				
Birth weight, median (range), g	990 (370-2510)	970 (370-2510)	1040 (710 - 2480)	0.735*
Birth height, mean ± SD (range), cm	36.6 ± 6.0 (25.5-46.5)	36.7 ± 5.9 (26.5–46.5)	36.4 ± 6.6 (25.5–44.0)	0.898 †
Gestational age, mean ± SD (range), wk	$29^{+1} \pm 3^{+3}$ (24^{+5}-36^{+4})	$29^{+1} \pm 4^{+0}$ (25^{+0}–36^{+4})	$29^{+2} \pm 2^{+4}$ (24^{+5}–33^{+0})	0.931 †
Study day data				
Weight, median (range), g	1210 (670-2580)	1195 (670-2530)	1320 (750-2580)	0.966*
Postmenstrual age, mean ± SD (range), wk	$31^{+2} \pm 2^{+4}$ (27^{+2}-36^{+6})	$31^{+3} \pm 2^{+6}$ (27^{+2}–36^{+6})	$31^{+2} \pm 2^{+1}$ (28^{+2}–34^{+5})	0.963 †
Postnatal age, median (range), day	7 (2-70)	10 (2-37)	6 (4-70)	0.932*
Baseline capillary blood gas data				
pH, mean ± SD (range)	7.32 ± 0.05 (7.25–7.44)	7.31 ± 0.04 (7.25–7.39)	7.34 ± 0.06 (7.26–7.44)	0.149 †
pCO_2, mean ± SD (range), mmHg	47.6 ± 8.2 (35.9–61.5)	48.9 ± 9.3 (35.9–61.5)	45.3 ± 5.9 (38.4–55.6)	0.373 †
pO_2, mean ± SD (range), mmHg	37.2 ± 7.2 (26.0–51.0)	37.7 ± 7.3 (27.0–51.0)	36.3 ± 7.3 (26.0–48.0)	0.697 †
Base excess, mean ± SD (range), mmol/L	-1.5 ± 3.7 (-7.0–5.0)	-1.8 ± 3.5 (-6.0–4.0)	-1.0 ± 4.3 (-7.0–5.0)	0.649 †
HCO_3, mean ± SD (range), mmol/L	24.5 ± 3.4 (19.9–30.2)	24.4 ± 3.5 (20.0–30.2)	24.7 ± 3.6 (19.9–29.1)	0.861 †
Total CO_2, mean ± SD (range), mmol/L	25.8 ± 3.7 (21.0–32.0)	25.8 ± 3.8 (21.0–32.0)	25.8 ± 3.8 (21.0–31.0)	0.990 †

*, Mann-Whitney U test; †, Student *t* test

Table 2. Carryover effect between SIMV + PS and NAVA

	***P* value**
PEEP, cmH_2O	0.667*
PIP, cmH_2O	0.227*
MAP, cmH_2O	0.150*
Mv, L/min/kg	0.359*
TV, mL/kg	0.283*
Dydamic compliance, mL/cmH_2O	0.432†
WOB, mJ/L	0.650†
$EAdi_{peak}$, uV	0.579*
FiO_2, %	0.773†
RR, /min	0.239*

*, Student *t* test; †, Wilcoxon rank sum test

Table 3. Ventilator parameters and blood gases during each ventilatory period for SIMV + PS and NAVA

	SIMV + PS (n = 19)	NAVA (n = 19)	*P* value
Monitored ventilator parameters			
PEEP, mean ± SD, cmH_2O	5.82 ± 0.69	5.91 ± 0.64	0.204*
PIP, mean ± SD, cmH_2O	13.45 ± 3.44	12.45 ± 2.66	0.043*
MAP, mean ± SD, cmH_2O	7.99 ± 1.33	8.02 ± 1.23	0.245*
Mv, mean ± SD, L/min/kg	0.53 ± 0.15	0.51 ± 0.11	0.257*
TV/kg, mean ± SD, mL/kg	8.73 ± 2.08	8.54 ± 2.24	0.601*
Dynamic compliance, mean ± SD, mL/cmH_2O	1.70 ± 0.47	1.84 ± 0.36	0.085*
WOB, median (range), mJ/L	11.13 (3.92-60.79)	8.38 (1.60-30.21)	0.002†
$EAdi_{peak}$, mean ± SD, uV	13.39 ± 5.68	11.43 ± 5.52	0.004*
FiO_2, median (range), %	23.33 (21.08-41.18)	23.47 (20.75-39.07)	0.314†
RR, mean ± SD, /min	53.83	52.68	0.233*
$TV/EAdi_{peak}$, mean ± SD, mL/uV	1.02 ± 0.60	1.26 ± 0.66	0.003*
$TV/EAdi_{peak}$/kg, mean ± SD, mL/uV/kg	0.77 ± 0.39	0.99 ± 0.66	0.016*
$PIP/EAdi_{peak}$, mean ± SD, cmH_2O/uV	1.18 ± 0.56	1.40 ± 0.74	0.017*
Capillary blood gas analysis			
pH, mean ± SD	7.33 ± 0.05	7.33 ± 0.05	0.515*
pCO_2, mean ± SD, mmHg	46.75 ± 7.43	46.64 ± 7.87	0.949*
pO_2, mean ± SD, mmHg	38.89 ± 8.82	37.84 ± 8.51	0.709*
Base excess, mean ± SD, mmol/L	-1.58 ± 4.25	-1.05 ± 3.79	0.235*
HCO_3, mean ± SD, mmol/L	24.46 ± 3.95	24.74 ± 3.57	0.600*
Total CO_2, mean ± SD, mmol/L	25.79 ± 4.12	26.11 ± 3.71	0.591*

*, Paired *t* test; †, Wilcoxon signed-rank test

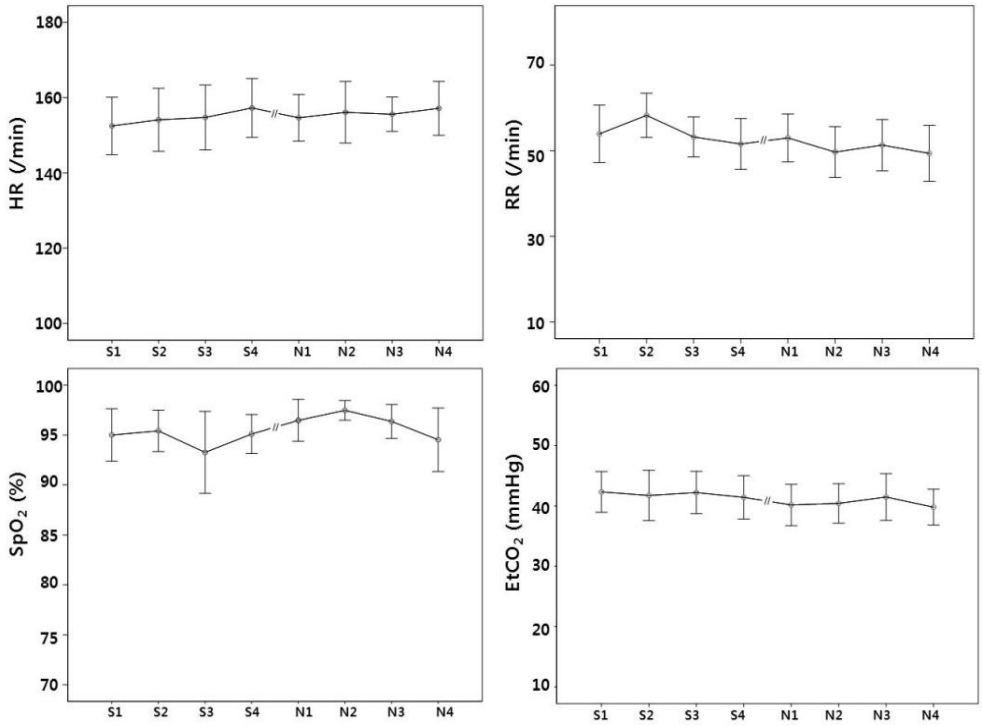

Figure 3. Hemodynamic parameters during the study period.

S# = SIMV + PS during a given hour (1-4); N# = NAVA duringa given hour (1-4). The *P*values, as determined by a generalized estimating equation, for HR, RR, SpO_2 and $EtCO_2$ were 0.596(154.6 ±16.6 vs. 155.9 ±13.6/min), 0.852 (54.2 ± 11.8 vs. 50.8 ± 12.4 /min), 0.937 (94.7 ± 5.8 vs. 96.2 ± 4.5 %) and 0.183 (41.9 ± 7.5 vs. 40.5 ± 6.9 cmH_2O), respectively.

Discussion

The present study showed that NAVA lowered the delivered PIP with a decrease in the EAdi and lowered the respiratory work while maintaining an equivalent supply of oxygen and gas exchange relative to SIMV + PS. Although the absolute reduction of inspiratory pressure was small, the difference is probably significant because our study was conducted over a relatively short 4-hour period. Recently, Stein at al. (19) reported a retrospective analysis, which demonstrated NAVA provided better blood gas regulation with lower PIP for 24 hours of observation in very low birth weight preterm infants. In addition to the previous study, our results of reduced $EAdi_{peak}$ with improved values of $TV/EAdi_{peak}$ and $PIP/EAdi_{peak}$ demonstrated the diaphragm unloading effect of NAVA more clearly (21).

The asynchronous delivery of support breath interferes with the natural breathing patterns of the patient, leading to increased WOB. Kallet et al. (22) reported that regardless of the ventilatory mode, the average WOB was markedly elevated (>1 J/L) in adult patients with acute lung injury. These researchers compared 3 pneumatic patient-triggered mechanical ventilatory modes, pressure-control ventilation, pressure regulated volume control, and volume-control ventilation. However, regardless of mode and despite adequate sedation, patients frequently had asynchronous breathing, and the WOB was increased when the ventilator peak inspiratory flow rate and tidal volume were either below or above those that the patient could generate during spontaneous breathing, which means demands of the patients (22). The

improvement in synchrony with NAVA could reduce the inspiratory efforts of the patient. Beck et al. (23) demonstrated marked patient–ventilator asynchrony with an increase of delivered inspiratory pressure in infants during weaning with the SIMV mode. In a more recent work with lung-injured rabbits, the same group demonstrated that only small increases in airway pressure were required to unload the diaphragm when NAVA was used. In contrast, triggered PS ventilation was associated with wasted inspiratory effort and excessive transpulmonary pressures, resulting in a suboptimal diaphragm unloading (24).

In a recent study of infants with bronchiolitis, researchers evaluated the pressure-time product, which estimates the metabolic cost of breathing as a relative indicator of WOB, and demonstrated a decreased pressure-time product with NAVA (25). In our study, we calculated WOB directly using Campbell diagram software (20) and were able to verify the significant reduction during NAVA. Furthermore, we calculated the indices, TV to EAdi ratio and inspiratory pressure to EAdi ratio, which could evaluate the efficacy of ventilatory support for reducing the respiratory load of a patient more accurately even in premature infants who have gas leak from uncuffed endotracheal tubes. These calculations represent the "neuro-ventilatory coupling", which is an index of the ability of the patient to generate inspiratory volume (TV/EAdi) or inspiratory pressure (PIP/EAdi) for a given neural drive (21). A higher value of $TV/EAdi_{peak}$ or $PIP/EAdi_{peak}$ represents the better ability of the patient to generate a volume or pressure attributable to improved diaphragm muscle function and/or reduced respiratory load (26).

The result of improving these indices in this study indicate that ventilatory support of preterm infants by NAVA decreases the respiratory work, facilitates the participation of respiratory muscles in breathing more efficiently, and may protect the premature lung from injury by avoiding excessive volume or pressure delivery. In addition, patients can experience greater comfort by the ventilatory support according to their spontaneous breathing, without sedation and with no need to "fight" the ventilator (Figure 4). These characteristics of NAVA might also enable rapid weaning from mechanical ventilation, which would further reduce ventilator-associated complications, including ventilator induced lung injury. This point is very important for preterm infants who are at risk of developing bronchopulmonary dysplasia and various other morbidities from prolonged mechanical ventilation.

Because NAVA uses the electrical signal from the patient's own respiratory drive to control the ventilator, the application of NAVA to preterm infants could have a risk of apnea, absence of signal from alteration of EAdi catheter, and inadequate EAdi attributable to immature diaphragmatic function. The average frequency of alarm signals from a lack of EAdi signal was 1.8/h (range 0-6.25/h), and there was no significant malposition or dislocation of the EAdi catheter. Aside from 1 patient who was excluded from the study before the randomization because of a decrease in the self-respiration, no infant exhibited significant oxygen desaturation from apnea, and the EAdi signals were detected well with the orally inserted 6 Fr EAdi catheter, even in extremely premature infants. In addition, EAdi was a good way to observe

preterm infants attempting to breathe, which was helpful for evaluating the self-respiration capability and the decision of timing of weaning.

In conclusion, we found that NAVA may not only lower the PIP but also reduce the loading of respiratory muscles in mechanically ventilated preterm infants, suggesting the possible usefulness of NAVA as a lung-protective ventilatory method for neonatal intensive care. However, the subjects of this study were not acutely ill infants. Therefore, the effects of NAVA might be somewhat different in infants with severe lung disease.

A

B

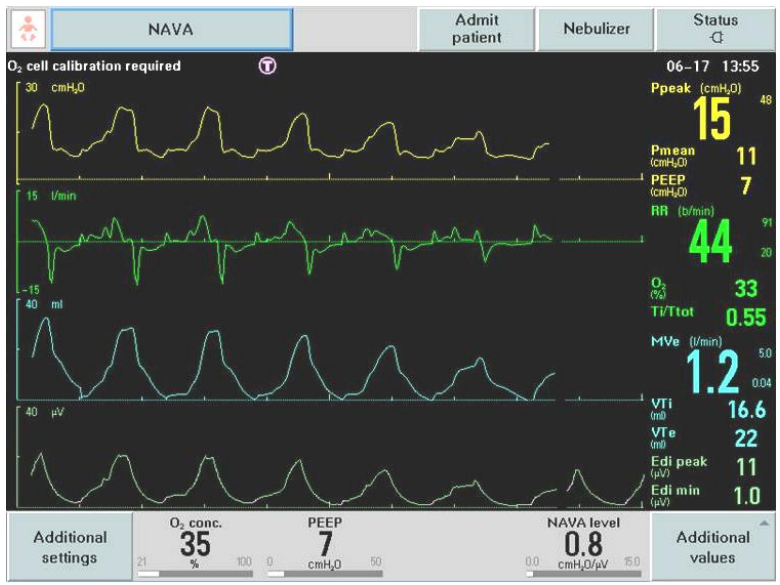

Figure 4. A sample of an EAdi tracing that illustrates the differences between SIMV + PS and NAVA. **A**, Under the SIMV + PS mode, the same PIP was delivered by flow trigger, but each delivered pressure was not synchronized with the EAdi signal. **B**, Under the NAVA mode, respiratory assistance was triggered by the EAdi, each delivered pressure was synchronized with the EAdi, and the level of peak pressure was constantly altered according to the level of EAdi detected. These representative images were captured from the Servo-i ventilator for each mode used during the study.

References

1. Attar MA, Donn SM. Mechanisms of ventilator-induced lung injury inpremature infants. Semin Neonatol. 2002 Oct;7(5):353-60.
2. Sinderby C, Beck J. Proportional assist ventilation and neurally adjusted ventilatory assist—better approaches to patient ventilator synchrony? Clin Chest Med. 2008 Jun;29(2):329-42.
3. Ramanathan R, Sardesai S. Lung protective ventilatory strategies in very low birth weight infants. J Perinatol. 2008 May;28(Suppl 1): S41-6.
4. Allen J, Zwerdling R, Ehrenkranz R, Gaultier C, Geggel R, Greenough A, et al. Statement on the care of the child with chronic lung disease of infancy and childhood. Am J Respir Crit Care Med. 2003 Aug;168(3):356-96.
5. Hummler H, Schulze A. New and alternative modes of mechanical ventilation in neonates. Semin Fetal Neonatal Med. 2009 Feb;14(1):42-8.
6. Richard JC, Lefebvre JC, Tassaux D, Brochard L. Update in mechanical ventilation 2010. Am J Respir Crit Care Med. 2011 Jun;184(1):32-6.
7. Sinderby C, Navalesi P, Beck J, Skrobik Y, Comtois N, Friberg S, et al. Neural control of mechanical ventilation in respiratory failure. Nat Med. 1999 Dec; 5(12):1433-36.
8. Hildebrandt T, Espelund M, Olsen KS. Evaluation of a transportable capnometer for monitoring end-tidal carbon dioxide. Anaesthesia. 2010 Oct;65(10):1017-21.
9. Sinderby C, Beck J, Spahija J, de Marchie M, Lacroix J, Navalesi P, et al.

Inspiratory muscle unloading by neurally adjusted ventilatory assistduring maximal inspiratory efforts in healthy subjects. Chest. 2007 Mar;131(3):711-7.

10. Brander L, Leong-Poi H, Beck J, Brunet F, Hutchison SJ, Slutsky AS, et al. Titration and implementation of neurally adjusted ventilatory assist in critically ill patients. Chest. 2009 Mar;135(3): 695-703.
11. Beck J, Reilly M, Grasselli G, Mirabella L, Slutsky AS, Dunn MS, et al. Patient–ventilator interaction during neurally adjusted ventilatory assist in low birth weight infants. Pediatr Res. 2009 Jun;65(6):663-8.
12. Navalesi P, Colombo D, Della Corte F. Nava ventilation. Minerva Anestesiol. 2010 May;76(5):346-52.
13. Alander M, Peltoniemi O, Pokka T, Kontiokari T. Comparison of pressure-, flow-, and NAVA-triggering in pediatric and neonatal ventilatory care. Pediatr Pulmonol. 2012 Jan;47(1):76-83.
14. Bengtsson JA, Edberg KE. Neurally adjusted ventilatory assist in children: an observational study. Pediatr Crit Care Med. 2010 Mar;11(2):253-7.
15. Breatnach C, Conlon NP, Stack M, Healy M, O' Hare BP. A prospective crossover comparison of neurally adjusted ventilatory assist and pressure-support ventilation in a pediatric and neonatal intensive care unit population. Pediatr Crit Care Med. 2010 Jan;11(1):7-11.
16. Coisel Y, Chanques G, Jung B, Constantin JM, Capdevila X, Matecki S, et al. Neurally adjusted ventilatory assist in critically ill postoperative patients: a crossover randomized study. Anesthesiology. 2010 Oct;113(4):925-35.

17. Colombo D, Cammarota G, Bergamaschi V, De Lucia M, Corte FD, Navalesi P. Physiologic response to varying levels of pressure support and neurally adjusted ventilatory assist in patients with acute respiratory failure. Intensive Care Med. 2008 Nov;34(11):2010-8.

18. Piquilloud L, Vignaux L, Bialais E, Roeseler J, Sottiaux T, Laterre PF, et al. Neurally adjusted ventilatory assist improves patient-ventilator interaction. Intensive Care Med. 2011 Feb;37(2):263-71.

19. Stein H, Howard D. Neurally adjusted ventilatory assist in neonates weighing <1500 grams: a retrospective analysis. J Pediatr. 2012 May;160(5):786-9.

20. Berman LS, Banner MJ, Blanch PB, Widner LR. A new pediatric respiratory monitor that accurately measures imposed work of breathing: a validation study. J Clin Monit. 1995 Jan;11(1):14-7.

21. Sinderby C, Brander L, Beck J. Bedside monitoring of diaphragm electrical activity during mechanical ventilation. In: Vincent J-L, ed. Intensive care medicine. New York: Springer; 2009. p. 385-93.

22. Kallet RH, Campbell AR, Dicker RA, Katz JA, Mackersie RC. Work of breathing during lung-protective ventilation in patients with acute lung injury and acute respiratory distress syndrome: a comparison between volume and pressure-regulated breathing modes. Respir Care. 2005 Dec;50(12):1623-31.

23. Beck J, Tucci M, Emeriaud G, Lacroix J, Sinderby C. Prolonged neural expiratory time induced by mechanical ventilation in infants. Pediatr Res. 2004 May;55(5):747-54.

24. Beck J, Campoccia F, Allo JC, Brander L, Brunet F, Slutsky AS, et al. Improved synchrony and respiratory unloading by neurally adjusted ventilator assist (NAVA) in lung-injured rabbits. Pediatr Res. 2007 Mar;61(3):289-94.

25. Clement KC, Thurman TL, Holt SJ, Heulitt MJ. Neurally triggered breaths reduce trigger delay and improve ventilator response times in ventilated infants with bronchiolitis. Intensive Care Med. 2011 Nov;37(11):1826-32.

26. Beck J, Spahija J, Sinderby C. Respiratory muscle unloading during mechanical ventilation. In: Vincent J-L, ed. Intensive care medicine. Heidelberg: Springer; 2003. p. 280-7.

초 록

서론: Neurally adjusted ventilator assist(NAVA)는 새로운 개념의 기계 환기요법의 한 형태로, 횡격막의 전기적 활성을 감지하여 그 활성 정도에 비례한 압력을 불어넣어 주는 방식으로 호흡을 보조해준다.

방법: 이 새로운 개념의 보조환기 요법이 미숙아의 폐 손상을 최소화하는 데 효과적인지 알아보고자 총 26명의 미숙아를 대상으로 전향적 무작위 배정 교차시험을 시행하였다. 환자들은 NAVA와 synchronized intermittent mandatory ventilation(SIMV) + pressure support(PS)를 각각 4시간씩 적용하되, 그 순서는 무작위배정에 의해 결정되었고 두 환기요법 적용 사이에 결과를 기록하지 않는 1시간의 간격을 두었으며, 총 9시간의 교차시험 동안 end-tidal partial pressure of CO_2 ($EtCO_2$)를 지속적으로 감시하면서 비슷한 수준을 유지하도록 인공호흡기 setting 설정을 조정하였다. 두 환기요법간의 인공호흡기 변수들과 생체활력 징후, 가스분석 결과를 비교하여 그 차이를 분석하였다.

결과: SIMV + PS에 비해서 NAVA 적용 하에서의 최대 흡기압(peak inspiratory pressure, PIP)과 호흡 일(work of breathing), 최대 횡격막 전기활성도(electrical activity of diaphragm, EAdi) 값이 유의하게 낮았고(P = 0.043, 0.002, 0.004), 환기보조의 효능

(efficacy) 지표인 호흡용적/최대 횡격막 전기활성도(TV/peak EAdi) 및 최대 흡기압/최대 횡격막 전기활성도(PIP/peak EAdi) 값도 NAVA 적용 하에서 유의하게 호전되는 결과를 보였다(P = 0.003, 0.017). 공급된 흡입산소분율(FiO_2), 호기말양압(PEEP), 평균기도압(MAP) 및 가스분석 결과는 두 환기요법에서 차이가 없었으며, 교차시험 내내 환자들의 생체활력 징후도 큰 변화 없이 잘 유지되었다.

결론: 본 연구를 통해 NAVA는 미숙아에서 최대 흡기압과 호흡 일을 감소시키는 유용성이 있다는 것을 알 수 있으며, 기계 환기보조로 인한 폐손상으로 만성폐질환의 발생 위험이 큰 미숙아에서 매우 유용하게 사용될 수 있으리라 기대할 수 있다.

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주요어: 기계 환기 보조, 간헐적 양압 환기, 신생아중환자관리

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