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Pilot Study to Evaluate the Impact of NAVA Compared to SIMV on Cardiac Function in Preterm Neonates

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Abstract:

Background: *Improved patient-ventilator synchrony with Neurally Adjusted Ventilatory Assist (NAVA) may not only benefit the respiratory system but may also impact the cardiovascular system. This study evaluated cardiac function in neonates on NAVA ventilation compared to SIMV.*

Methods: *Randomized, single-center, blinded, crossover pilot trial in premature neonatal subjects (23-36 weeks gestation) on invasive NAVA vs. SIMV. A quantitative assessment of left ventricular (LV) function was performed using echocardiographic imaging during each ventilatory mode.*

Results*: 14 subjects were randomized. During NAVA ventilation improvement was noted for LV output (194.1 ± 59.5 vs. 172.6 ± 45.4 ml/kg/min, p = 0.04), LV volume (69 ± 7.6 vs. 65.4 ± 5.2 %), p = 0.05) and cardiac index (1.9 ± 0.7 vs. 1.7 ± 0.6 L/min/m^2, p=0.04) compared to SIMV.*

Conclusion*: This pilot study demonstrates that neonates have improved cardiac function on NAVA ventilation compared to SIMV. Higher cardiac output during NAVA ventilation may result from better cardio-respiratory synchronization.*

Keywords: Neurally Adjusted Ventilatory Assist (NAVA), SIMV, premature neonates, cardiac output, cardiorespiratory synchrony, echocardiography, ejection fraction

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Introduction

Neurally Adjusted Ventilatory Assist (NAVA) uses the diaphragm's electrical activity (Edi) to allow the ventilated neonate to trigger on and off cycles of ventilatory assistance. Through the Edi signal, the neonate determines the peak inspiratory pressure, tidal volume, and duration of the respiratory support delivered by the ventilator. This signal is detected by embedded sensors within a specialized nasogastric tube (NAVA catheter) positioned at the crural diaphragm level, giving breath-to-breath feedback to the Servo ventilator (Getinge, Germany (1). Edi is not influenced by changes in muscle length, chest wall configuration, and/or lung volume (2-4) and correlates with phrenic nerve activity (5).

Multiple studies in the pediatric and neonatal population show improved oxygenation, work of breathing, and patient-ventilator synchronization on NAVA ventilation compared to synchronized intermittent mandatory ventilation (SIMV) or pressure support ventilation (2-4,6-8). Additionally, these studies demonstrate less trigger delay and a lower asynchrony index in non-invasive NAVA compared with non-invasive ventilation in Pressure Support mode (6) or when comparing invasive NAVA to SIMV in term and preterm patients (7,8).

"Cardiac output values in neonates increase linearly with advancing birth weight and gestational age (9). However, there is less information about the effect of positive pressure ventilation (PPV) on neonatal cardiac function."

Cardiac output values in neonates increase linearly with advancing birth weight and gestational age (9). However, there is less information about the effect of positive pressure ventilation (PPV) on neonatal cardiac function. PPV results in variations in pulse pressure and increases intrathoracic pressure, decreasing cardiac preload (10,11). Liet et al. compared conventional ventilation with NAVA in infants (7.8±4.1 months) who had undergone cardiac surgery and showed that on NAVA, there were lower peak inspiratory pressures, higher systolic arterial pressures, and increased cardiac index (12). The effects of NAVA effect on the cardiovascular system and hemodynamics in premature neonates have been poorly studied.

Point-of-care echocardiography has been used to study cardiac function in neonates (13). The most common technique for ventricular systolic function assessment in neonates is based on ventricular dimension and sizes, as recommended by international guidelines on Point-of-Care Ultrasound (14). Two-dimension images or M-mode have been used to calculate the ventricular volumes (end-systolic or -diastolic) (15).

This study aimed to evaluate cardiac function in neonates on NAVA ventilation compared to SIMV.

Methods

Trial Design: This was a randomized, single-center, blinded (to the cardiologist reading the echo), interventional, crossover pilot study.

Participants and Data Collection: This trial was performed in the neonatal intensive care unit (NICU) at ProMedica Russell J.

Ebeid Children's Hospital, Toledo, Ohio, USA. The study protocol was approved by the local Institutional Review Board (IRB18-035). Prior to enrollment, written consent was obtained from parents. Subject enrolment was performed by the study investigators. Echocardiographic data were obtained by either of two certified pediatric Echo technicians. A board-certified cardiologist read this data. Collected data were de-identified and recorded in a dedicated database.

Intervention: After a stabilization period of one hour, the first echocardiographic measurements were obtained. The subject was then switched to the other mode of ventilation, and after a stabilization period of one hour, the second echocardiographic measurements were obtained. The subject was then returned to the initial ventilatory mode (Fig 1). PEEP was kept consistent between the two modes.

Figure 1: Study flow chart

Ventilator data were downloaded from the Servo-I (Getinge, Germany) ventilators. Echocardiographic studies were performed using the Philips EPIQ 7 machine with a neonatal phased-array microprobe (12 MHz). Standard 2-D views were taken from apical 5-chamber, apical 4-chamber, apical 2-chamber, parasternal long and short axis. Simpson's volume measurements were made from an apical two-chamber view. Tissue Doppler was measured from a standard four-chamber view. Velocity Time Integral (VTI) was taken from a standard 5-chamber view. Left ventricular ejection fraction (E.F.) was calculated based on fractional shortening from M-mode in the parasternal short axis. Cross-sectional area (CSA) was calculated at the level of the aortic valve annulus at end-systole in the parasternal long-axis view. Velocity time integral (VTI) was measured from the aortic valve velocity, and heart rate (H.R.) was measured during the study. Stroke volume was calculated by VTI x CSA. CSA measurements obtained from the ECHO machine were matched to the results of manual calculation by using the formula: CSA = π x Aortic Diameter^2 / 4 (16). E.F., based on Simpsons 4-chamber and 2-chamber views, were obtained by appropriate software on the ultrasound machine. Left ventricular (LV) output was calculated as follows: LV output (ml/kg/min) = [VTI x CSA (at AV annulus) x heart rate (HR, bpm)] / body weight (in kg) (16,17). Cardiac index (CI) was calculated from LV output and body surface area.

Outcomes: The primary outcome was to evaluate LV output, CI, and E.F. Secondary outcomes evaluated were LV dimensions, SpO_2/FiO_2 ratio, and H.R.

Sample Size and Inclusion Criteria: No previous studies existed to determine sample size, so this was a pilot study with a convenience sample size. Inclusion criteria were preterm neonates 23 -36 weeks of gestation on invasive mechanical ventilation for Respiratory Distress Syndrome. Exclusion criteria were severe cardio-vascular instability, congenital heart defects, and sepsis.

Randomization and Implementation: A coin toss determined the initial ventilation mode (NAVA vs. SIMV). The investigators were responsible for allowing at least one hour of stabilization time between echocardiograms as well as the proper data collection and storage.

Blinding: This pilot study was designed as an assessor-blinded with the cardiologist reading the echocardiography blinded to the ventilation modes and parameters. Both echo-technicians were instructed to avoid discussions with the reading cardiologist, respiratory therapists, or nurses regarding the enrolled subjects or ventilator settings. Attending physicians were unblinded but were restricted in discussions with the reading cardiologist regarding the study subjects.

Statistical Methods: Paired t-test (Excel, Microsoft, 2019) was used to compare the variables on NAVA vs. SIMV. $P<0.05$ was considered significant.

Results

Recruitment: Nineteen subjects met eligibility criteria. Four subjects were excluded after consent was obtained (two were extubated before randomization; two were excluded at the parents' request due to clinical deterioration prior to the study). Fifteen subjects were randomized for this study. One subject in the SIMV group was excluded from statistical analysis, secondary to subsequently being diagnosed with sepsis. Two subjects expired weeks after the enrollment, unrelated to the study. Figure 2 depicts randomization and subject distribution.

Baseline Data: Baseline study population details are shown in table 1.

"All subjects were on NAVA before the study enrollment. Of the 14 subjects in the study, eight were randomized to start on NAVA ventilation and switched to SIMV, and six started on SIMV and switched to NAVA."

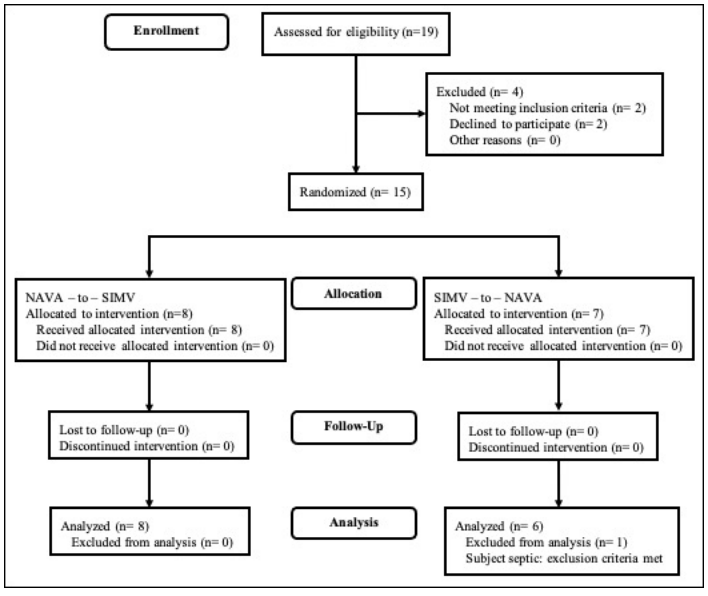

Figure 2: CONSORT participant flow diagram

Outcomes and Estimations: All subjects were on NAVA before the study enrollment. Of the 14 subjects in the study, eight were randomized to start on NAVA ventilation and switched to SIMV, and six started on SIMV and switched to NAVA. Ventilator settings and vital signs at the start of each study on NAVA and SIMV are listed in Table 2. Table 3 depicts the primary and secondary outcomes. Left Ventricular Output, CI, and LV volume were increased in the NAVA group. Cardiac output fell within previously described ranges using pulsed doppler (9).

Subjects	N=14
Gestational age (weeks)	25 (3.2)
Birth weight (grams)	923 (566)
Male (n (%))	9 (64)
Prenatal steroids (n)	12 (85.7)
C-section (n)	11 (78.5)
Apgar score -1 min (median)	5 (2,7)
Apgar score -5 min (median)	7 (6,8)
CRIB-II score	7.1 (3.5)
Postnatal age at the enrolment (days)	8.6 (5.9)
Weight at study (grams)	776 (411)

Table 1: Demographics of the study population. Data are shown as mean (standard deviation), median (interquartile range), or number (%).

	NAVA	SIMV	p
NAVA Level (cmH_2O/mcV)	1.25 (0.7)	n/a	n/a
Apnea time (sec)	1.96 (0.15)	n/a	n/a
PEEP (cmH_2O)	5.9 (1.1)	5.9 (1.1)	1
PIP (cmH_2O)	n/a	14 (1.5)	n/a
Vent Rate (breaths/min)	n/a	40 (7.1)	n/a
FiO_2 (%)	29.2 (6.8)	29.6 (7.3)	0.49
HR (beats/min)	158.9 (12.9)	155.7 (11)	0.39
RR (breaths/min)	46.5 (7.1)	47.8 (7.1)	0.69
SpO_2 (%)	93.3 (3.3)	93.6 (4.7)	0.84
SpO_2/FiO_2 ratio	335 (80)	331 (75)	0.64

Table 2: Ventilatory parameters during each ventilation mode. PIP – peak inspiratory pressure, HR – heart rate, RR respiratory rate. Data are shown as mean (standard deviation). There were no differences between the groups at the start of each study. Statistics were paired t-tests.

"Enhanced ventilator synchrony is achieved when there are shorter trigger delays, avoidance of premature cycle-off, and absence of failures to trigger a breath (4)."

Primary outcomes	NAVA	SIMV	p
LV Output (ml/kg/min),	194.1 (59.5)	172.6 (45.4)	0.04
CI ($L/m^2/min$)	1.9 (0.7)	1.7 (0.6)	0.04
EF (%)	73.9 (7.2)	72.05 (6.95)	0.23
Secondary outcomes			
LVEDV (cm)	1.1 (0.28)	1.13 (0.27)	0.11
LVESV (cm)	0.66 (0.16)	0.7 (0.17)	0.06
LV volume (Simpson 2c)	69.1 (7.6)	65.5 (5.3)	0.05
HR (bpm)	160.1 (15.4)	154.6 (15.3)	0.18

Table 3: Hemodynamic variables during NAVA and SIMV modes. LV Output – left ventricle output (ml/kg/min) and CI- cardiac index ($L/m^2/min$), were calculated. EF- Ejection Fraction (%), LVEDV – left ventricular end-diastolic volume (cm), and LVESV – left ventricular end-systolic volume (cm) were measured by m-mode. LV volume – left ventricular volume (EF%) was measured by 2-D. Data are shown as mean (standard deviation) and were normally distributed. Statistics were paired t-test.

Harm: All recruited subjects tolerated the study well. No immediate or late complications were related to the ventilation mode changes or echocardiograms. Thirteen of fifteen enrolled subjects were discharged from the NICU. Two subjects died later from reasons unrelated to the study.

"This is the first study to demonstrate/evaluate the improved cardiac function of premature neonates being ventilated with NAVA versus SIMV."

Discussion

This is the first study to demonstrate/evaluate the improved cardiac function of premature neonates being ventilated with NAVA versus SIMV.

Improved cardio-respiratory synchrony may occur due to the regulation of the heart's primary pacemaker (atrioventricular node), which is modulated by the same autonomic system that regulates respiratory rhythm. However, this only partially explains cardio-respiratory synchronization. For instance, when the innervation of the heart is interrupted in a patient post-heart transplantation, there are still respiratory modulations, mechanical coupling, and synchronization between cardiovascular and respiratory systems (18). This may be due to chest movement generating intrathoracic pressure variances. This increased preload stretches the sino-atrial node and alters the electrical properties of the myocyte membrane, ultimately influencing the heart rhythm. In addition, the synchrony between these two systems is regulated by the efferent nerves from the cardiorespiratory center of the brainstem, whose afferent nerves collect information about blood pressure, blood gas status, and heart rate via arterial baroreceptors and chemoreceptors (19). As a neonate matures, the coordination between the cardiovascular and respiratory systems increases, causing variability in the heart rate to respiratory synchronization ratio. In the first few weeks, neonates have synchronization ratios of approximately 5:2 (heart rate: respiratory rate). After 20 days of life, it lengthens to 4:1 (varying from 7:2 - 9:2) (20).

Enhanced ventilator synchrony is achieved when there are shorter trigger delays, avoidance of premature cycle-off, and absence of failures to trigger a breath (4). When the synchronization index is higher, intrathoracic pressure is decreased. Lower intrathoracic pressure increases the cardiac preload of both ventricles (Frank-Starling Law), which raises the left ventricle stroke volume. Lower intrathoracic pressure from improved synchrony also increases diastolic dilation of the LV and prolongs diastolic filling time. With the preserved systolic function of the myocardium, the larger volume yields a higher LV output. This hypothesis is supported by the fact that systolic blood pressure is higher during NAVA compared to conventional ventilation modes (12).

"Improved synchronization promotes oxygenation, which relaxes pulmonary vasculature. Lower right ventricular (R.V.) afterload can increase R.V. systolic function and increase LV preload, thus increasing C.O. Better synchronization prevents unnecessary hyperinflation avoiding compressing pulmonary vasculature mechanically, resulting in decreased LV preload and C.O."

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During SIMV, variable pulse and intrathoracic pressure results in inconsistent stroke volume (S.V.), as well as R.V. and LV diastolic volumes that are not necessarily in synchrony with the needs of the neonate. Compared to SIMV, NAVA allows for variable inspiratory pressures, flow, and duration in synchrony with the neonate respiratory drive. As a result, intrathoracic pressure adapts in response to the patient's physiological needs. It may be hypothesized that variable intrathoracic pressure provides variable RV/LV systolic and diastolic functions and results in higher C.O. In addition, variable intrathoracic pressure may produce more intraventricular septal compliance and contractility (ventricular interdependence), which can increase LV end-diastolic volume and subsequently, CO. Lastly, variable intrathoracic pressure results in non-uniform compression of the lateral ventricular wall, which may also improve LV diastolic function and S.V.

Less than 5% of total body oxygen is consumed for metabolic needs of breathing (21). Patient-ventilator asynchrony during SIMV ventilation may increase consumption, leading to unnecessary total body oxygen consumption and oxygen demand. The initial compensatory mechanism is tachycardia with tachypnea. Both responses decrease LV refilling and S.V. via a combination of previously described mechanisms.

Limitations: LV cardiac output was challenging to measure using transthoracic echocardiography. Volumes lower than 1 ml were rounded up by the software program. The decision was therefore made to use VTI for LV output calculation, considering the very small sizes of the study subjects. LV cross-sectional area (CSA) is a stable parameter, easily measurable on echocardiography. Average H.R. was used for calculation of LVOT, as each echocardiography session lasted approximately 10-15 min and the H.R. changed dynamically during this period. Despite these limitations, our measurements were comparable to those reported by Boet et al. (22) and fell within the expected range for preterm neonates.

"This pilot study demonstrates that neonates have improved left ventricular function while ventilated with NAVA compared to SIMV."

Conclusion:

This pilot study demonstrates that neonates have improved left ventricular function while ventilated with NAVA compared to SIMV. Future studies are needed to investigate if these differences extend to other cardiac function parameters and evaluate the role of improved ventilatory synchrony in cardiorespiratory function.

Quick Look:

Current Knowledge

Neurally Adjusted Ventilatory Assist (NAVA) ventilation is known to improve patient-ventilator synchrony. NAVA is being used with increasing frequency in premature neonates. Evidence is lacking on the effect of NAVA ventilation on cardiac function.

What This Paper Contributes To Our Knowledge

In a study comparing cardiac function on NAVA ventilation and SIMV in premature neonates, subjects had improved left ventricular function, increased left ventricular output, cardiac index, and left ventricular volume. NAVA ventilation may provide cardiac benefits when used in premature neonates.

References:

1. *Sinderby C, Beck J." Neurally Adjusted Ventilatory Assist." Principles and Practice of Mechanical Ventilation. Third ed: McGraw Hill; 2012.*
2. *Beck J, Reilly M, Grasselli G, et al. Patient-ventilator interaction during neurally adjusted ventilatory assist in low birth weight infants. Pediatr Res. 2009;65(6):663-668.*
3. *Alander M, Peltoniemi O, Pokka T, Kontiokari T. Comparison of Pressure-, Flow-, and NAVA-Triggering in Pediatric and Neonatal Ventilatory Care. Pediatric Pulmonology. 2012;47:76-83.*
4. *Bordessoule A, Emeriaud G, Morneau S, Jouvet P, Beck J. Neurally Adjusted Venitlatory Assist (NAVA) improves patient-ventilator interaction in infants compared to conventional ventilation. Pediatr Res. 2012;72(2):194-202.*
5. *Beck J, Sinderby C, Lindstrom L, Grassino A. Effects of lung volume on diaphragm EMG signal strength during voluntary contractions. J Appl Physiol. 1998;85:1123-1134.*
6. *Lee J, Kim H, Jung Y, et al. Non-invasive neurally adjusted ventilatory assist in preterm infants: a randomised phase II crossover trial. Arch Dis Child Fetal Neonatal Ed. 2015;100(6):F507-513.*
7. *Mally P, Beck J, Sinderby C, Caprio M, Bailey S. Neural Breathing Pattern and Patient-Ventilator Interaction During Neurally Adjusted Ventilatory Assist and Conventional Ven-*

tilation in Newborns. Pediatr Crit Care Med. 2018;19(1):48-55.
8. Longhini F, Ferrero F, De Luca D, et al. Neurally adjusted ventilatory assist in preterm neonates with acute respiratory failure. Neonatology. 2015;107(1):60-67.
9. Walther FJ, Siassi B, Ramadan NA, Ananda AK, Wu PY. Pulsed Doppler determinations of cardiac output in neonates: normal standards for clinical use. Pediatrics. 1985;76(5):829-833.
10. Heskamp L, Lansdorp B, Hopman J, Lemson J, de Boods WP. Ventilator-induced pulse pressure variation in neonates. Physiol Rep. 2016;4(4).
11. Shekerdemian L, Bohn D. Cardiovascular effects of mechanical ventilation. Arch Dis Child. 1999;80(5):475-480.
12. Liet JM, Barriere F, Gaillard-Le Roux B, Bourgoin P, Legrand A, Joram N. Physiological effects of invasive ventilation with neurally adjusted ventilatory assist (NAVA) in a crossover study. BMC Pediatr. 2016;16(1):180.
13. Kluckow M, Seri I, Evans N. Functional echocardiography: an emerging clinical tool for the neonatologist. J Pediatr. 2007;150(2):125-130.
14. Singh Y, Tissot C, Fraga MV, et al. International evidence-based guidelines on Point of Care Ultrasound (POCUS) for critically ill neonates and children issued by the POCUS Working Group of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC). Crit Care. 2020;24(1):65.
15. Lopez L, Colan SD, Frommelt PC, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr. 2010;23(5):465-495; quiz 576-467.
16. McGovern M, Miletin J. Cardiac Output Monitoring in Preterm Infants. Front Pediatr. 2018;6:84.
17. Singh Y. Echocardiographic Evaluation of Hemodynamics in Neonates and Children. Front Pediatr. 2017;5:201.
18. Slovut DP, Wenstrom JC, Moeckel RB, Wilson RF, Osborn JW, Abrams JH. Respiratory sinus dysrhythmia persists in transplanted human hearts following autonomic blockade. Clin Exp Pharmacol Physiol. 1998;25(5):322-330.
19. Koshiya N, Smith JC. Neuronal pacemaker for breathing visualized in vitro. Nature. 1999;400(6742):360-363.
20. Mrowka R, Patzak A, Schubert E, Persson PB. Linear and non-linear properties of heart rate in postnatal maturation. Cardiovasc Res. 1996;31(3):447-454.
21. Loer S, Scheeren T, Tarnow J. How much oxygen does the human lung consume? Anesthesiology. 1997;86(3):532-537.
22. Boet A, Jourdain G, Demontoux S, De Luca D. Stroke volume and cardiac output evaluation by electrical cardiometry: accuracy and reference nomograms in hemodynamically stable preterm neonates. J Perinatol. 2016;36(9):748-752.

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All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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