Neurally Adjusted Ventilatory Assist (NAVA) versus Conventional Biphasic Positive End Expiratory Pressure (BiPAP) Non-Invasive Respiratory Support in Infants Following Congenital Heart Surgery

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Research Protocol

1. **Study Team**

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2. **Project Title**

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3. **Introduction**

Background/Significance

Mechanical ventilation is often necessary in the care of critically ill pediatric patients, but is not without risk. Traditional and newly emerging modalities of respiratory support operate under the same goals: optimize gas exchange without causing lung damage or discomfort to the patient. However, it has been estimated that around 40% of mechanically-ventilated pediatric patients experience complications related to their respiratory support (1, 2). Complications can include but are not limited to atelectasis, post-extubation stridor, pneumothorax, tissue damage, ventilator-associated pneumonia, tracheal edema, or chronic lung disease.

Over the years, an increased understanding of how a child's physiology interacts with a ventilation system has led to improved technologies. Whereas traditional ventilation modalities such as endotracheal intubation is invasive and can lead to tracheal damage with prolonged use (3), non-invasive ventilation (NIV) modalities avoid the risks associated with tracheal intubation. In addition, NIV can be used at an earlier stage compared to tracheal intubation, and facilitates gradual weaning when used intermittently (4). Two modalities that are widely used in intensive care units are continuous positive air pressure (CPAP) and bilevel positive air pressure (BiPAP). Both of these modalities operate using positive airway pressure to keep the trachea open. CPAP machines are set to deliver a continuous stream of air, while BiPAP machines offer a different level of pressure for inhalation versus exhalation. Collectively, use of these modalities and their benefits are well-documented, including improved gas exchange, decreased respiratory and heart rate, and decreased inspiratory work of breathing (5-8). Building on these strengths, neurally adjusted ventilator assist (NAVA) is emerging as an alternative form of the bi-level NIV with application in multiple settings.

With NAVA support, delivery of positive pressure is based on the electrical activity of the diaphragm (Edi) via a nasogastric (NG) catheter that is placed on the phrenic nerve, which runs along the esophagus. This concordance between the Edi and NAVA lends itself to synchrony between the patient and ventilator, as well as respiratory support that is proportional to the neural effort of the patient (9). Synchronous ventilation support results in decreased neural drive and

improved comfort in intubated patients (10, 11). Prior research has examined the use of NAVA in different patient settings, most notably the PICU and NICU as summarized in **Table 1**. These studies suggest NAVA may contribute to decreased sedation needs (12), improved synchrony (10, 13, 14), improved breath-to-breath mechanical variability (10), increased patient comfort (10), and reduction of wasted breathing efforts (13). In these populations, evidence supports the safety and feasibility of NAVA (12, 15).

Reference	Setting	Design	Intervention	Results
Kallio et al 2014	PICU	Randomized controlled trial	Conventional ventilation (CV) or NAVA	*Ventilation duration*: 3.3hrs NAVA and 6.6hrs CV (P=0.17); *Sedation amount*: 0.80units/hr NAVA and 2.23units/hr CV (P=0.03, excluding postoperative patients)
Ducharme-Crevier et al 2015	PICU	Non-randomized, Crossover	Conventional NIV (CNIV) [30mins], NAVA [60mins], CNIV [30mins]	*Asynchrony index*: 8% NAVA and 27/32% CNIV (P=.05); *Wasted efforts*: 0% NAVA and 12/6% CNIV (P<.01)
De la Olivia et al 2012	PICU	Non-randomized, Crossover	Conventional PS ventilation [10mins], optimized PS [10mins], NAVA [10mins], optimized PS [10mins]	*Asynchrony index*: 2.0% NAVA and 8.5/7.5% optimized PS (P=0.017/0.008); *COMFORT score*: 15 NAVA and 18/17.5 optimized PS (P=0.0125/0.039)
Lee et al 2015	NICU	Randomized, Crossover	Conventional PS ventilation [5mins], NAVA [5mins]	*Trigger delay:* 35.2ms NAVA and 294ms PS (p<0.001); *Inspiratory time in excess:* 32.3% NAVA and 294.6% PS (p=0.001)

Table 1. Selected prior NAVA studies in the PICU or NICU

While many studies have examined NAVA in the PICU and NICU, there is a paucity of research in the cardiovascular intensive care unit (CVICU) setting. PICU and NICU patients often are critically ill with diseased or malfunctioning lungs, but relatively healthy hearts. Conversely, CVICU patients have abnormal hearts with relatively healthy lungs. Given the implications for improved cardiopulmonary interactions (16), NAVA could be beneficial in the CVICU. The use of NAVA in the pediatric CVICU has been described in one article, which compared the use of cPAP versus NAVA in infants < 5 kg following postoperative extubation. The 2015 randomized cross-over trial found that the synchronization rate using NAVA was 99.3% for all respiratory cycles, and EAdi measurements suggest that NAVA decreased the work required to breathe more quickly than nasal cPAP (17). This study focused on proximal measurements of NAVA effectiveness, but more research is needed to understand how NAVA affects the clinical course of CVICU patients. To the investigator's knowledge, no studies to date have examined clinical outcomes in pediatric patients postoperatively in the CVICU. Understanding clinical outcomes following NAVA use could further inform use of the relatively new technology in this clinically complex patient population.

NAVA has recently been adopted for non-invasive respiratory support in the Children's Hospitals and Clinics of Minnesota CVICU, the cardiovascular care center (CVCC). Close to 10% of CVCC post-operative patients receive a form of bi-level NIV support, either NAVA or BiPAP. The frequency of NIV use in neonates (0 to 28 days of age) can be 30% or higher. We propose a randomized study to compare clinical outcomes following use of NAVA versus BiPAP in CVCC patients following cardiac surgery. Specifically, we will compare duration of NIV, duration of sedation, and hospital length of stay.

Research Question

Is the use of synchronized biphasic support with NAVA associated with shorter duration of non-invasive respiratory support, less sedation requirements, and reduced hospital length of stay compared to conventional BiPAP?

4. Study Design and Methodology

Aim 1: To assess whether the use of neurally adjusted ventilator assist (NAVA) is associated with a shorter duration of non-invasive respiratory support compared to conventional BiPAP.
Aim 2: To assess whether the use of neurally adjusted ventilator assist (NAVA) is associated with less sedation requirements compared to conventional BiPAP.
Aim 3: To assess whether the use of neurally adjusted ventilatory assist is associated with reduced hospital length of stay compared to conventional BiPAP.
Hypothesis: Synchronized biphasic support with NAVA will be associated with shorter duration of non-invasive respiratory support, less sedation requirements, and reduced hospital length of stay.

Overview/Scope

Study Design

This will be a prospective randomized study comparing outcomes of pediatric patients who are treated with NAVA versus BiPAP respiratory support following cardiac surgery. Subjects will include pediatric CVCC patients who undergo cardiac surgery from October 2016 through October 2017 and who are up to 12 months of age. As patients recover from cardiac surgery, they are extubated and may require further respiratory support. If so, they receive CPAP support and then are transitioned to one of two modalities: either NAVA or BiPAP support. Both modalities are routinely used in the Children's CVCC, and the investigators will compare if one modality produces more favorable outcomes than the other. Following CPAP, enrolled subjects will be randomized to receive either NAVA or BiPAP, and their remaining clinical course will follow standard care. Specific measures following initiation of respiratory support will be collected, in addition to characteristics of the operative procedure and patient diagnoses. The study aims to compare duration of respiratory support, sedation requirements, and hospital length of stay between the two modalities.

Time Frame/Duration

This study will be conducted over an 18-month period to allow for subject enrollment, data collection, analysis, and manuscript preparation.

Activity	Month																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
IRB approval																		
Recruitment/enrollment																		
Data collection/ chart abstraction																		
Analysis																		

Manuscript preparation																	

Analysis

Sample Size

We will enroll all consecutive patients who are eligible for inclusion in the 12-month enrollment period and consent to participation, up to 40 patients. An interim analysis will be performed after 20 patients are enrolled to assess means and variance of the primary outcomes, and reassess sample size.

Analytic Approach

Exploratory analysis methods will be used to describe the enrolled patient population, including mean and standard deviation for continuous variables such as length of hospital stay, sedation needs, and intubation as well as frequency and percentage for categorical variables such as STAT score and type of non-invasive PPV.

For the continuous outcomes of interest (duration of non-invasive respiratory support, length of hospital stay and sedation needs), either a two-sample t-test or non-parametric Mann-Whitney U test will be used to compare those patients who received NAVA or BiPAP. For categorical variables, either a chi-square test or Fischer's exact test will be used to compare the two groups. Additional regression analysis will adjust for procedure severity.

Statistical significance will be defined as $p < 0.05$.

5. Subjects

Subjects

We plan to enroll 40 subjects 0 to 12 months of age at time of cardiac surgery over a 1 year period.

Identification of Subjects, Recruitment, and Enrollment

Potential subjects will be identified by monitoring the cardiovascular surgery schedule, and eligibility will be confirmed by the provider. Patients who meet all of the inclusion criteria and none of the exclusion criteria will be approached for consent by study staff. Not all cardiac patients receive NIV support postoperatively, and the decision to provide NIV support is not made by the provider until after the surgery. This will happen either while the patient is intubated, or immediately following extubation. Written informed consent will be sought from parents/guardians. Assent will not be sought in this young patient population. Patients who enroll will be assigned a unique study ID. A log of enrolled subjects will be maintained, and will only be accessible by approved study staff. The target enrollment is 40 patients.

Inclusion Criteria:

- Postoperative cardiac surgery patients admitted to the CVCC
- Recommended for NIV respiratory support following extubation, per provider discretion
- 0-12 months of age

Exclusion Criteria:

- Tracheostomy in place at time of cardiac surgery
- Chronic lung disease
- Pre-operative non-invasive respiratory support

6. Study Procedures

Data Requirements

The data elements will be collected by the research study staff from the subject's electronic medical record. These will include:

- Demographic Data (name, date of birth, age at admission, admission date/time, cardiac diagnosis, comorbidities)
- Operative Data (surgeon, date of procedure, intubation/extubation date/time, date/time returned to CVCC)
- Adverse Event Information (description of event and day post-cardiac surgery that the event(s) took place)
- Medication Data (daily amounts of dexmedetomidine, fentanyl (total fentanyl and boluses of pca fentanyl), midazolam, morphine, lorazepam for up to 14 days postoperatively, date/time patient is on/off the above medications)
- Post-Operative Respiratory Support Data (type of non-invasive respiratory support used, date/time on off CPAP, date/time on/off biPAP/NAVA)
- Pain and Sedation Score Data (daily FLACC/SBS scores for up to 14 days postoperatively)
- Discharge Data (discharge date/time, length of hospital stay, survival at discharge, date/time of death [if applicable], cause of death [if applicable])

Visit Schedule

Eligible patients will be recruited during their admission to the CVCC. Upon enrollment, patients will be randomized to receive either NAVA or BiPAP. What respiratory modality the patient will receive will be determined by drawing a slip of paper from a sealed envelope. Following randomization and provision of respiratory support, patient care will be per standard care. Patient data will be only collected for the reference admission period. There will be no follow-up visits or activities required of the patient for this study following enrollment.

Drug/Device, Handling, Storage (If Applicable)

All devices in this study are currently used and stored in the CVCC. They will continue to be used as per CVCC SOPs.

7. Risks/Benefits

Potential Risks

Subjects will be randomized to respiratory support treatments that are already incorporated into standard care. The potential risks from these treatments are no more than those experienced as part of standard care. There is a risk associated with privacy of personal health information, and there is a risk of breach of confidentiality.

Methods to Minimize Risks

Both NAVA and BiPAP are non-invasive modalities that are safely used in standard care. Providers will follow SOPs for the use of NAVA and BiPAP support to minimize risks. If complications occur, standard care will be provided and patients will be treated accordingly. Electronic data will be stored on secure password-protected computers in limited access files, in a locked office suite. Any paper records will be stored in locked cabinets that only approved study staff have access to. This is a single-site study, and no identifiable patient data will be shared outside of the IRB-approved study staff. Any results from the study will be published in aggregate form, preventing any individual patient's data from being identified.

Potential Benefits

The subjects will not gain added benefit directly from this study, since the treatments provided will be consistent with standard care. This study will contribute to understanding how outcomes may vary with different modalities of respiratory support in this patient population.

Adverse Events

The research staff will document any adverse events that occur in the admission period for enrolled patients following provision of NAVA or BiPAP. Enrolled patients will be monitored in the CVCC, and standard care will be provided. Any unanticipated problems involving risks to the subjects or other (UPIRTSOs) will be reported to the IRB within 10 days.

Stopping Rules and Data Safety Monitoring Plan
The research interventions are both consistent with the standard of care for the study population. No stopping rules are planned.

8. Administrative Procedures
Patient Confidentiality
All study data will be stored on a secure password-protected computer in the locked research office. Patient study files will be stored in a locked cabinet within the research office. Subjects will be given a unique study ID number when entered into the RedCap study database.

Data Management
Data will be collected on paper documents and will be securely stored in a locked cabined within the research office. Only the research study team will have access to these paper documents. Once the data has been collected on the source documents, the data will be entered into a study-specific RedCap database, which is a secure network that is password-protected. All of the study data will be securely stored for up to 3 years or completion of the study and all subsequent publications and presentations of the study results.

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10. Appendix

Appendix 1: The Society of Thoracic Surgeons- European Association for Cardiothoracic Surgery Congenital Heart Surgery Mortality Categories (STAT Mortality Categories)
Appendix 2: Pain and Sedation Scales
Appendix 3: Study Schema
Appendix 4: Data Collection Forms