# Nasal Non-Invasive Neurally Adjusted Ventilatory Assistance for VLBW infants with a history of RDS requiring mechanical ventilation:

## The NIV-NAVA study

PI: Gary Kummet, MD
Faculty PIs: Tarah Colaizy, MD, MPH and Jon Klein, MD

**Last IRB review/approval**: 4/18/22
University of Iowa IRB #201208771

**Introduction:**

Neurally adjusted ventilatory assistance (NAVA) is a technology that has grown rapidly and is now being utilized in neonatology intensive care units in the United States and Europe. NAVA aims to improve on patient ventilator synchrony by measuring diaphragmatic activity via an esophageally placed electrical catheter. This mode of ventilation provides individualized breath to breath support independent of air leak (Brown & DiBlasi, 2011; Stewart, Jagelman, & Webster, 2011).

Acute and chronic complications associated with endotracheal injury have been extensively studied and increase with the number of failed attempts at extubation and the duration of intubation (Attar & Donn, 2002; Gomes Cordeiro, Fernandes, & Troster, 2004; Joshi, Mandavia, Stern, & Wiglesworth, 1972; Miller & Carlo, 2008). By applying NAVA technology to these patients complications can be potentially minimized or completely avoided. NAVA has demonstrated that it is effective in decreasing peak inspiratory pressure (PIP) (Bengtsson & Edberg, 2010) and can provide additional ventilatory assistance (Stein & Howard, 2011)possibly facilitating earlier extubation and avoidance of complications associated with endotracheal intubation.

One of the main advantages of NAVA ventilation is the ability to improve patient ventilatory synchrony. Use of the electrical activity of the diaphragm (Edi) to trigger ventilator breaths decreases asynchrony. Edi triggered breath delivery facilitates breath to breath adjustment dependent on the patients' respiratory effort. As the patient increases their effort, the ventilator increases support based on adjustable ventilator settings (Cammarota et al., 2011; Clement, Thurman, Holt, & Heulitt, 2011; Colombo et al., 2008; de la Oliva, Schuffelmann, Gomez-Zamora, Villar, & Kacmarek, 2012; Schmidt et al., 2012).

Many of the benefits of NAVA ventilation have yet to be extensively studied in the preterm infants, with most of the known data coming from invasive applications of this

technology and adult studies (Beck et al., 2009; Cammarota et al., 2011; Schmidt et al., 2012; Stein & Howard, 2011).

This prospective study will look at extubated very low birth weight (VLBW) infants who received surfactant and are stable on their current distending pressures via continuous positive airway pressure (CPAP) or nasal cannula. This is a cross over trial utilizing NAVA to demonstrate that it can improve ventilatory support determined by improved blood gas parameters.

**Preliminary Data:**

We have retrospectively studied NAVA technology using a noninvasive strategy to provide nasal ventilation. All very low birth weight infants (VLBW) (less than 1500 grams) with respiratory distress syndrome treated with surfactant in our NICU from July 2011 to August 2012 and ventilated with noninvasive nasal NAVA were eligible. The change in partial pressure of carbon dioxide (pCO2) of VLBW infants who had increased NAVA support in response to a capillary blood gas were studied. The pre- and post-intervention pCO2 differences were determined for n=24 patients and the differences ranged from a decrease of 16 mmHg to an increase of 5 mmHg with a median value of -3.5 mmHg. This decrease was found to be significant using the Wilcoxon signed-rank test ($p<0.001$).

**Study Design:**

Prospective cross-over of NIV NAVA compared to nasal CPAP or high flow nasal cannula respiratory support in VLBW infants with a history of RDS.

**Study Population / Eligibility**:

- Birth weight was less than 1500 grams with clinical history of respiratory distress syndrome treated with surfactant
- Chronological age greater than or equal to seven days.
- At least 48 hours post-extubation and medically stable as determined by the treating medical team
- On one of the follow modes of mechanical support receiving a distending pressure via nasal pharyngeal tube (NP) or nasal cannula: continuous positive airway pressure (CPAP), intermittent mechanical ventilation (IMV), or neutrally adjusted ventilatory assistance (NAVA).
- Infants may be on high flow nasal cannula if the flow is large enough to provide a positive end expiratory pressure (PEEP) of 6 as defined by PEEP of 6 = 0.68 * weight (kg) + 0.92 (Sreenan, Lemke, Hudson-Mason, & Osiovich, 2001)
- Infants will be required to have a capillary blood gas obtained via heel stick after placement of heel warmer within 24 hours of study entry that demonstrates a pH of less than 7.35 and/or a partial pressure of carbon dioxide (pCO2) greater than 45 mmHg.

**Exclusion criteria**:

- Severe congenital abnormalities
- Grade III or IV interventricular hemorrhage.

**Enrollment:**

Local neonatal intensive care unit census will be screened at a minimum of one time per week to determine if there are neonates who potentially meet the enrollment criteria

defined above. The patients' clinical course will be monitored and when the infant requires minimal ventilatory support the parent(s) of said infants will be approached. The study will be explained and consent will be sought. If consent is granted, the infant's medical course will be monitored and once the infant is extubated and stable for a minimum of 48 hours on one of the approved ventilatory modes the routinely obtained morning capillary blood gas will be monitored until the infant meets study entry criteria.

**Study Protocol:**

**Baseline Data Collection:**

Demographic data: Patient gestational age at delivery, admission weight, receipt of surfactant administered, age at extubation, time since extubation, current post menstrual age, previous nitric oxide therapy, current nitric oxide therapy, and current weight. Baseline vitals and ventilation mode: Heart rate, blood pressure, FiO2, oxygen saturations, transcutaneous partial pressure of carbon dioxide (TCO2) and current mode of ventilation will be recorded four times in a one minute period and the values averaged to minimize normal variation. Intervention time will be manipulated to begin no later than one hour after the previous feeding, as to minimize interruption of feedings given the typical every 3 hour feeding schedule used in our NICU.

**Safety**

TCO2 monitor will be attached to the infant by respiratory therapy staff and the device will be calibrated according to protocol (reference TCO2 monitor manual). Carbon dioxide diffusion through the skin will be monitored continuously during the intervention (Bromley, 2008) to assess for periods of hypo or hypercarbia.

**Edi Catheter placement:** Edi catheter size will be selected according to infant's weight and length. It will be inserted according to manufacturer's guidelines and adjustments will be made to optimize positioning (Maquet Critical Care AB). At the time of study initiation and every thirty minutes therafter TCO2, heart rate (HR), respiratory rate (RR), minute ventilation, peak Edi, minimum Edi, and PIP will be recorded four times in a one minute period and the values averaged to minimize normal variation. Current NAVA settings, oxygen saturations, FiO2, and blood pressure (BP) will also be recorded at these times.

Physician member of the research team will be present at bedside during the entire study intervention.

**NAVA settings:**

Infants will be maintained on previous level of PEEP or calculated PEEP, rounding up to whole numbers. Initial NAVA level will be determined by starting with an initial NAVA level of 0.5 microvolts/cm of H20. The NAVA level will then be adjusted either by increasing or decreasing NAVA level settings by 0.1 microvolts/cm of H20 to generate a PIP that is a minimum of 8 cm of H2O greater than the current PEEP. Apnea alarm will be set at 5 seconds, which will initiate the NAVA back up setting if no electrical activity is detected by the Edi catheter. Back up NAVA settings will be set with a PIP of 12 cm of H20 greater than current PEEP, respiratory rate of 60 breaths per minute (RR) and inspiratory time of 0.5 seconds. Fraction of inspired oxygen (FiO2) will be adjusted to keep infant's oxygen saturations within previously established clinical parameters. Infants who are currently receiving respiratory support via NAVA at the time of the study will have their NAVA level increased by 50%, rounding up to the nearest 0.1

microvolts/cm of H20. The other NAVA settings will be adjusted as previously described.

**Study Intervention Procedure and Data Collection:**

At initiation of intervention, and at time 30, 60, 90, and 120 minutes, TCO2, heart rate (HR), respiratory rate (RR), minute ventilation, peak Edi, minimum Edi, and PIP will be recorded four times in a one minute period and the values averaged to minimize normal variation. Current NAVA settings, oxygen saturations, FiO2, and blood pressure (BP) will also be recorded. At 60 minutes of intervention if the TCO2 average has not decreased by 5 mmHg from baseline or has risen, the current NAVA level will be increased by 50%, and the HR, RR, minute ventilation, peak Edi, minimum Edi, and PIP will be recorded as described above. At 90 minutes if the TCO2 average has not decreased by 5 mmHg from baseline or has risen; the NAVA level will be increased by 50% from the current level and data collected as describe at 60 minute intervention. At the completion of the study (120 minutes or pCO2 outside of established limits) the HR, RR, BP, minute ventilation, FiO2, oxygen saturations, peak Edi, minimum Edi, and PIP will be recorded four times in a one minute period and the values average to minimize normal variation. A capillary blood gas will be obtained according to standard unit protocol with a warmed heel.

If at any time during the study the TCO2 level is greater than 80 mmHg the nasal pharyngeal tube will be evaluated for patency and exchanged if needed. If TCO2 levels to do not return to less than 80 mmHg the study will be terminated and management will be deferred to primary medical team. If the TCO2 level is less than 35 mmHg the infant will exit the study early and heart rate, FiO2, oxygen saturations, HR, RR, peak Edi, minimum Edi, and PIP will be recorded four times in a one minute period. The values

will be averaged to minimize normal variation. Blood pressure will also be measured. A capillary blood gas will be obtained according to standard unit protocol with a warmed heel.

**Statistics**

Power calculations were performed using a detectable difference in pre-post pCO2 of 4mmHg based on published findings (Stein & Howard, 2011). Assuming a $\beta=0.2$, a significance level $\alpha=0.05$ and $\sigma=1$, the estimated sample size needed to detect a difference is 35 subjects. To account for possible subject attrition, a total of 40 subjects will be recruited and study data will be collected at the patient's bedside using an electronic data collection form. The pre- and post- intervention capillary pCO2 will be compared using a paired t-test and testing the null hypothesis that there is no difference in pCO2 levels. Further analyses will test if the difference is greater than 5mmHg. In the event that distributional assumptions for the t-test are not satisfied in these data, a nonparametric Wilcoxon signed-rank test will be used to compare the pre- and post-measures. Multiple Linear Regression methods allowing for covariate adjustment will be used to determine if any significant associations exist between patient characteristics and the change in pCO2 levels.

**Planned Tables and Figures**

Table 1 baseline characteristics

Figure 1 PCO2 start vs final

Figure 2 TCO2 vs time

Figure 3 bell shaped curve of delta pCO2

Figure 4 Nasal Pharyngeal NAVA and RAM-cannula bell shaped curve of delta pCO2

Table 2 characteristics of patients who failed NAVA therapy in 2 hours (if needed)

Table 3 characteristics of patients who had significant changes in $pCO_2$ vs those who had no changes (if needed)

Table 4 characteristics of patients who were eligible for the study but declined enrollment

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