NAVA-REdi Study Protocol

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| **Neurally Adjusted Ventilatory Assist (NAVA)– Reference values for Electrical Activity of Diaphragm**  **(NAVA-REdi Study)** |

**PICO**

What are the normal reference values for electrical activity of the diaphragm (Edi) in preterm and term neonates with no respiratory distress?

**INTRODUCTION**

What is NAVA?

Neurally Adjusted Ventilatory Assist (NAVA) is a new ventilatory technique in neonates.1 Conventional ventilators use the change in airflow as trigger for mechanical breath (Flow trigger). These mechanical breaths have a set tidal volume or peak inspiratory pressure and inspiratory and expiratory times that may or may not be in synchrony with the patient. NAVA detects electrical excitation in the diaphragm and synchronises the mechanical breath with this electrical activity (neural trigger). Patient determines peak inspiratory time, respiratory rate, inspiratory and expiratory times in synchrony with the ventilator. There is some early evidence to suggest that NAVA provides better physiological and ventilatory parameters than conventional pressure support ventilation in paediatrics patients recovering from Adult Respiratory Distress Syndrome(ARDS)3,4

What is electrical activity of the diaphragm (Edi)?

The trigger for NAVA system is the Electrical activity of the diaphragm (Edi), measured esophageally using a special nasogastric tube (Edi catheter) with electrodes at the level of the diaphragm. Edi measures the total of action potentials of all motor units in the central (crural) portion of the diaphragm. Measurement of the Edi occurs via these action potentials, which are propagated from neural respiratory center along the phrenic nerve to the diaphragm, assesses the neural control of respiration. Edi measures two components: (1) Edi min – Measure of the tonic activity of the diaphragm, i.e. the minimum or baseline electrical activity of the diaphragm muscle between breaths that prevents de-recruitment of lungs during expiration, and (2) Edi peak – measures the amplitude of electrical activity associated with inspiratory effort.

What are the normal Edi values?

Edi measures have been used to evaluate patient-ventilator interactions, assessing the level of synchronization between the individual’s neural respiratory output and the support provided by the ventilator. To date, the literature contains Edi data for those with respiratory dysfunction only, most obtained in subjects receiving mechanical ventilation. There are no normal values for Edi signals in ventilated neonates, because the respiratory drive, or Edi signal, can be manipulated depending on the amount of ventilator support provided. This lack of Edi data in healthy preterm and term neonates limits the utility of existing data, as there is no reference Edi values for comparison. This may limit the ability of the practitioner to optimize the use of NAVA ventilation (a ventilation mode that uses the Edi signal for triggering and volume determination) in critically ill neonates. The only available data of “normal” Edi reference values were from 3 term neonates by Stein et al.4 Stein et al. quantified Edi peak and min values in 3 non-ventilated, spontaneously breathing term neonates. Edi peak was 11±5 and Edi min was 3±2 mV. Edi peak was higher while awake than during sleep and lower in the postprandial state than pre-prandial and feeding states. Edi min was higher while awake than during sleep, but was not different among feeding states. There was no decrease or deterioration in the Edi signal during feeding, suggesting that there is no electrical interference from milk coating the oesophagus or catheter. Although these are the first Edi values reported in healthy neonates, the study is limited by the small sample size.

**AIM**

To determine the reference values for Edi peak and Edi min for preterm and term neonates with no respiratory distress.

**HYPOTHESES**

We hypothesise that Edi peak and Edi min were higher in (1) Higher gestational age group, (2) awake and postprandial states and (3) after caffeine administration.

**OUTCOMES**

**Primary:**

1. Edi peak and Edi min

**Secondary:**

1. Respiratory rate
2. Oxygen saturations

**MATERIALS AND METHODS**

**Study Design**

Prospective observational study

**Participants**

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| **Inclusion criteria** | | **Exclusion criteria** |
| Babies with no respiratory support and gastric feeding tube in situ | Known congenital anomalies | |
| Born 29-42 weeks gestation | Infants with respiratory distress | |
| Informed parental consent  Gastric tube -fed | Major neurologic conditions and brain anomalies Neuromuscular diseases  Apneas  Conditions affecting innervation of diaphragm | |

**Intervention**

Eligible neonates from 29-42 weeks GA will be identified. Senior nurse providing care to the baby may inform the parents of this study and if parents show interest, they will be approached by a senior clinician (consultant or fellow), who is already involved in the patient’s care and parental consent will be obtained. Current practice in our NICU is to replace the oro/nasogastric tube every 72 hours. When the tube is due for a change, appropriate size Edi catheter will replace the oro/nasogastric tube and will be used as the feeding tube. Edi Catheter will be connected to Servo-n ventilator. Edi signal will recorded for 4 hours, which is the total duration of the study. Many of the preterm infants are on regular daily caffeine to prevent apneas. If the infant is on regular caffeine, study measurements will be performed to coincide with 1 hour prior to and 3 hours after caffeine administration. Data output included Edi peak, Edi min, and respiratory rate, all of which were stored in 1-min increments in the Servo-n software, downloaded to a flash drive, and imported into a spreadsheet (Excel, Microsoft, Redmond, Washington) and statistics software (SPSS, SPSS, Chicago, Illinois) for data analysis.

Each infant will be observed for a continuous 4-hour period, including at least 1 hour pre-prandial and 2 hours postprandial. Heart rate and SpO2 will be recorded from vital monitors every 15 min throughout the study.

After the 4-hour study, Edi catheter will be disconnected from the servo-n ventilator and will be used as normal feeding tube. Edi catheter can be used for at least 2 weeks without change. However as per standard procedure with the conventional feeding tube, the Edi catheter will be changed after 3-7 days.

**Safety**

Edi catheter is similar to the conventional gastric tube in diameter but with special electrodes placed at the end to measure Edi. Edi catheter is routinely used by staff in our NICU as a feeding tube in those neonates who are on NAVA ventilator. There are no additional risks other than risks associated with any other conventional feeding tube including malposition, blockage, gastric or intestinal perforation.

**STATISTICAL ANALYSIS**

Demographic and other baseline clinical characteristics will be summarized by frequencies and percentages for categorical variables and mean and standard deviation as well as by quartiles for continuous variables. Where values are missing, the denominator will be reported. Differences between groups will be determined by chi-square or Fishers exact test for categorical data, t test for parametric continuous data and Wilcoxon rank-sum for nonparametric continuous data. Population means, standard deviations, and ranges will be calculated for the duration of the study. Analysis of variance measures will be performed to compare the population means for the feeding states. Statistical significance is defined as P <0.05.

**Sample Size**

Using the estimated mean (+/-SD) Edi peak of 11+/-3 in term neonates, a sample size of 16 in each group will be required to see the mean Edi difference of 30% in preterm infants for alpha 0.05 and power 0.80.

**Subgroup Analysis**

The Edi peak and Edi min means, standard deviations, and ranges will be stratified into pre-specified groups:

* Gestational Age Groups (29-36 weeks; 37-42 weeks)
* Awake, resting, pre-prandial and 1 hour post-prandial states.
* 1 hour Pre and 3-hour post caffeine administration

All data analysis will be done using IBM SPSS Statistics 22.

**SIGNIFICANCE OF STUDY**

To date, the literature contains Edi data mostly from those with respiratory dysfunction only, most obtained in subjects receiving mechanical ventilation. This lack of Edi data in healthy preterm and term neonates limits the utility of existing data, as there is no reference Edi values for comparison. Knowledge on normal reference values gained from this study increases the ability of the practitioner to optimize the use of NAVA ventilation in critically ill neonates.

**REFERENCES**

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