Normative values of electrical activity of the diaphragm in developing preterm infants

Keith A. Davis II

The University of Toledo
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Acknowledgments

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Introduction

Electrical activity of the diaphragm (Edi) is a measurement of the action potentials from the phrenic nerve that supplies the motor function to the diaphragm. Edi is measured via esophageal electrodes that are attached to a nasogastric tube. At the time of placement, the electrodes are situated at the level of the crural diaphragm so that an electromyography recording can be taken (American Thoracic Society/European Respiratory, 2002).

The Edi is used for a new type of patient controlled ventilation system known as Neurally Adjusted Ventilatory Assist (NAVA). With NAVA, the patient’s Edi controls the initiation, volume and termination of the ventilation; all while staying in synchrony with the individual’s respiratory drive (Beck et al., 2009). This allows for each assisted breath to be altered on a breath-to-breath basis (Biban, Serra, Polese, Soffiati, & Santuz, 2010).

To date, very little Edi data is available in neonates. This makes it challenging to determine how to ventilate neonates on NAVA. A study by Stein, Burton, & Wilmoth (2010) looked at the normative Edi values of healthy term infants. In this small study they found a mean Edi peak of $11\pm5$ mcV and a mean Edi min of $3\pm2$ mcV (Stein, Burton, & Wilmoth, 2010). At this time, there are no normative Edi values for preterm infants.
Definitions

**Electrical Activity of the diaphragm (Edi):** Measurement of neural impulses (action potentials) propagated to the diaphragm to elicit a breath.

**Electromyography (EMG):** Study of the electrical activity of a muscle.

**Esophageal EMG:** Measurement of electrical activity of the crural diaphragm by electrodes within a nasogastric tube centered at the level of the diaphragm (esophageal hiatus).

**Edi Minimum:** baseline electrical activity of the diaphragm, the degree of activation at rest between breaths.

**Edi Peak:** highest amplitude of Edi, an indicator of inspiratory respiratory effort associated with production of a breath.

**NAVA:** Neuurally-adjusted ventilatory assist. A ventilation system in which respiration is driven by Edi signals rather than the pressure-flow triggers of conventional ventilator systems.

**Periodic breathing:** irregular periods of interspersed rapid and slow breathing.

**Apnea:** cessation of breathing, the absence of respiratory effort for 20 seconds or longer.

**Preterm neonate:** in this study refers to a neonate delivered at 24-36 weeks gestational age.


**Literature Review**

Electromyography (EMG) may be used to evaluate the intensity and configuration of the electrical activation of respiratory muscles. If used in combination with tests of mechanical function (i.e. ultrasound), the effectiveness of the muscles’ contractile function can also be determined. EMG measurements can be obtained by using different techniques, each with their own advantages and disadvantages. Surface electrodes can be used to test all of the major respiratory muscles. Following proper skin preparation, electrodes are secured to the skin overlying the muscle(s) to be studied. Despite the advantages of being noninvasive and their capability to sample multiple motor units, various disadvantages of surface electrode recordings make it an unreliable measurement. The disadvantages include: inconsistent placement of electrodes due to no standards for positioning, artifact from adjacent muscle activity and variations in individuals’ anatomy (subcutaneous fat and deformities) (American Thoracic Society/European Respiratory, 2002).

Intramuscular electrode measures are a lot more precise and accurate as a result of minimal artifact from surrounding muscles. It is ideal for the analysis of single motor units, especially for the evaluation of denervation or myopathy. However, intramuscular electrodes tend to be less useful than the other forms of recordings for quantifying global respiratory muscle activity because they are uncomfortable for the subject, difficult to place and involve the risk of infection and pneumothoracies (American Thoracic Society/European Respiratory, 2002).

Another way of analyzing the electrical activity of respiratory muscles is via esophageal electrodes. Esophageal electrodes are metal electrodes that are attached to a catheter, which can be inserted through the nose or mouth and situated with the electrode rings at the level of the crural diaphragm. The most reliable method to decrease electrode positioning artifacts during active maneuvers is to optimize the diaphragm-electrode positioning. In order to do this, a
catheter with eight electrode rings attached 1 cm apart from each other is utilized to obtain the best possible EMG recordings. All eight electrode readings are continuously collected and the computer selects the pair closest to the crural diaphragm throughout the respiratory cycle. Advantages of esophageal electrodes include having less artifact from surrounding muscles and being unaffected by variations in individuals’ adipose tissue. Although esophageal electrodes tend to the best method of obtaining an EMG of the diaphragm, there is some discomfort associated with the placement of the nasogastric tube as well as a possibility of error in the results if a diaphragmatic hernia is present (American Thoracic Society/European Respiratory, 2002).

The diaphragm is the major respiratory muscle that accounts for nearly three fourths of all respirations in healthy individuals (Luo, Moxham, & Polkey, 2008). Since the phrenic nerve is the only motor nerve of the diaphragm, and the esophageal EMG measures the electrical activity of the diaphragm (Edi), it is considered proportional to the respiratory center’s total nervous output (Lourenco et al., 1966). The patient’s Edi signal can be converted to a proportional breath in the ventilator thus allowing the patient to control the initiation, volume and termination of each breath on an ongoing basis.

A couple of important values that are looked at when Edi is measured are the Edi minimum and peak. Edi peak represents the highest amount of electrical activity that is seen with inspiratory effort. The speed, at which Edi reaches its peak from baseline, denotes how rapidly the volume and pressure of the lungs must change, so that the individual’s gas exchange requirements can be met at that moment (Binazzi et al., 2004). Edi minimum represents the baseline electrical activity of the diaphragm between inspirations. This “tonic” activity of the
diaphragm is believed to assist in the regulation of end expiratory lung volume and prevent lung derecruitment (Emeriaud, Beck, Tucci, Lacroix, & Sinderby, 2006).

Development of Respiration

The central respiratory neurons are located in the brainstem. Between 10 and 20 weeks gestation, nerve cells migrate to this region. At this point, a feedback loop begins to control fetal “breathing” movements. The central chemoreceptors mediate the response to CO2 and blood pH levels. As a result, these “breathing” movements increase at times when CO2 levels are elevated, metabolic rate is high, and energy supplies are boosted (Givan, 2003).

At birth, the commencement of the first breath is a multifactorial process, which in large, is thought to be a result of the hypoxia that occurs during birth. External stimuli (light, touch, sound etc.) also appear to aid in the process. An initial large negative pressure, produced from the diaphragm, is necessary to initiate respirations. Postnatal maturation of the central neuronal network continues to proceed rostrally from the brainstem. The developmental level of this central network is inversely correlated with the existence and frequency of apnea in preterm infants, with the disorganization/immaturity of the respiratory center being the source of apnea. In preterm and neonates, respirations during rapid eye movement (REM) sleep are controlled by the reticular functions that are located in the brain stem, free from metabolic feedback. Conversely, during non-REM sleep, respirations are under chemical control (Givan, 2003).

In response to feedback, the respiratory center sends out an afferent signal to the respiratory muscles. The consequence of this continuous feedback loop is a “constantly adjusting oscillatory pattern of breathing” (Stokowski, 2005). In premature neonates, respirations are irregular, and periodic breathing and apnea are very common due to anatomical
and physiological immaturity (Polin & Fox, 1992). Periodic breathing is a pattern that involves pauses in respiration, less than 20 seconds long, mixed with bouts of normal breathing. Apnea is the cessation of breathing for any period greater than twenty seconds (Stokowski, 2005). While periodic breathing is typically considered to be a relatively benign occurrence, apnea is a lot more serious due to the possibility of it resulting in a drastic decrease in heart rate, decreased cardiac output and decreased delivery of oxygen to the body and especially the brain (Polin & Fox, 1992). Besides having an immature respiratory drive, the fact that the premature infant has a decreased surface area, lung volume, number of alveoli, and alveolar diameter also accounts for the abnormal respirations (Donn & Sinha, 2006). These patterns of breathing are very similar to those of a developing fetus (Stokowski, 2005).

Edi and NAVA ventilation has been shown to be useful in premature neonates but it has been difficult to interpret Edi values in ventilated preterm neonates when normal values are unknown (Alander, Peltoniemi, Pokka, & Kontiokari, 2011; Beck et al., 2009; Stein, & Howard, 2011). We therefore designed a study to determine normative Edi values in non-ventilated preterm neonates.
Methodology

Population and sampling methods

This was a prospective observational study of preterm neonates born at 25 to 33 weeks of gestation who met the following criteria: extubated; breathing on either high-flow nasal cannula, regular nasal cannula or room air; free of any congenital anomalies; and required a nasogastric tube for their current care. Neonates were enrolled as soon as possible after they met the above criteria. This was a convenience sample of neonates admitted to the NICU at The Toledo Children’s Hospital. Study protocol was approved by the Institutional Review Board of The Toledo Hospital/Toledo Children’s Hospital.

Measurements and quality control

Edi values were obtained by having a NAVA nasogastric tube placed instead of the traditional nasogastric tube. Electrodes within a nasogastric tube were positioned at the level of the crural diaphragm and proper positioning was confirmed by an on-line analysis on SERVO-i software. The nasogastric tube was connected to SERVO-i ventilator software for Edi recording. Data output included peak and minimum Edi and respiratory rate stored in minute increments in the SERVO-i software. The data was then downloaded to a flash drive, and imported into Microsoft Excel for data analysis. Heart rate via telemetry monitors and oxygen saturations were also recorded at fifteen-minute increments throughout the study. Data was collected in 4 hour increments. The NAVA tube was left in place for use as a regular nasogastric tube per standard care parameters. Recordings were done weekly until the infant longer required a nasogastric tube for feedings.
Statistical Analysis

Simple linear regression of the variable as a function of time for each subject was done to determine differences within subjects. Then, the slope for each subject was determined to evaluate if there was a change and, if so, if it was positive or negative. Finally, a two tailed sign test was performed to test the median slope to look for differences between subjects. A p < 0.05 was considered significant.
Results

A total of 17 subjects, 9 males and 8 females were enrolled in the study. Gestational age at birth ranged from 25-33 weeks (28.9 ± 2.7 weeks) and birth weight ranged from 628 to 2520 grams (1219.9 ± 534.4 grams). The subjects were on high flow nasal cannula, nasal cannula or room air.

Overall Edi peak was 10.9± 3.7 (range 3.7 to 18.7) and Edi min was 2.9± 1.1 (range 0.8 to 7.6). There was no difference in both Edi peak and min over gestational age as seen in Figure 1. Figure 2 and 3 shows the Edi peak and min for all the individual subjects over time. There was no difference in Edi peak and min between the different types of non-invasive respiratory support (HFNC, NC, or RA). The mean and range, heart rate, oxygen saturation and respiratory rate were unchanged over gestational age and are shown in Table 1.
Discussion

This study was designed to obtain normative Edi data in non-ventilated preterm neonates and to determine if there are any developmental changes over time.

Edi peak and min in non-ventilated preterm neonates were comparable to those reported in term neonates (Stein, Burton, & Wilmoth, 2010). This suggests that the inspiratory effort and tonic activity of the diaphragm in preterm neonates are as mature as those in term neonates despite having periodic breathing and periods of apnea (Polin & Fox, 1992). Throughout these recordings there was no evidence of any apneic events. We were unable to assess periodic breathing, based on our data collection methods, but we anticipate that all these preterm neonates would show some evidence of periodic breathing as it is a normal finding in this population.

Heart rate, respiratory rate and saturations were all within normal range for gestational age. This confirms our enrollment criteria that the subjects studied were in no respiratory distress and clinically stable.

This data provides guidelines on how to approach sick neonates requiring intubation and ventilation. Due to the limited data using NAVA ventilation it has been challenging to understand the role of the Edi signal in guiding ventilatory settings. As NAVA ventilatory support is increased, work of breathing shifts from the patient to the ventilator and the Edi signal decreases (Beck et al., 2009). Knowing normative Edi values in non-ventilated preterm neonates now allows the practitioner to adjust ventilatory support to achieve comparable Edi values to non-ventilated patients.
Conclusion

Normative Edi values in the developing preterm infant are now established. The central neural drive of a 26 week gestational age neonate appears to be as mature as that of a term neonate. This should help the practitioner optimize ventilatory parameters in sick intubated neonates to facilitate earlier extubation and decrease the risk of chronic lung disease.
References


Table 1- Heart rate, respiratory rate and oxygen saturation at each gestational age.

<table>
<thead>
<tr>
<th>Gestational Age (Weeks)</th>
<th>Heart Rate (bpm)</th>
<th>Oxygen Saturation (%)</th>
<th>Respiratory Rate (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 (n = 3 )</td>
<td>160 ± 16</td>
<td>93 ± 4</td>
<td>56 ± 19</td>
</tr>
<tr>
<td>Range</td>
<td>147-177</td>
<td>90-97</td>
<td>38-76</td>
</tr>
<tr>
<td>27 (n = 6 )</td>
<td>167 ± 5</td>
<td>94 ± 5</td>
<td>51 ± 9</td>
</tr>
<tr>
<td>Range</td>
<td>157-173</td>
<td>86-100</td>
<td>36-61</td>
</tr>
<tr>
<td>28 (n = 6)</td>
<td>164 ± 5</td>
<td>93 ± 2</td>
<td>55 ± 11</td>
</tr>
<tr>
<td>Range</td>
<td>156-169</td>
<td>90-96</td>
<td>47-71</td>
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<tr>
<td>29 (n = 8)</td>
<td>163 ± 12</td>
<td>92 ± 5</td>
<td>51 ± 7</td>
</tr>
<tr>
<td>Range</td>
<td>142-175</td>
<td>84-98</td>
<td>41-60</td>
</tr>
<tr>
<td>30 (n = 10)</td>
<td>159 ± 6</td>
<td>95 ± 3</td>
<td>50 ± 10</td>
</tr>
<tr>
<td>Range</td>
<td>149 - 167</td>
<td>89 - 99</td>
<td>38 - 65</td>
</tr>
<tr>
<td>31 (n = 12)</td>
<td>159 ± 8</td>
<td>94 ± 3</td>
<td>53 ± 11</td>
</tr>
<tr>
<td>Range</td>
<td>145 - 170</td>
<td>88 - 98</td>
<td>40 - 71</td>
</tr>
<tr>
<td>32 (n = 14)</td>
<td>157 ± 17</td>
<td>96 ± 3</td>
<td>51 ± 7</td>
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<tr>
<td>Range</td>
<td>116- 174</td>
<td>90 - 99</td>
<td>37 - 60</td>
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<tr>
<td>33 (n = 16)</td>
<td>158 ± 11</td>
<td>96 ± 3</td>
<td>53 ± 8</td>
</tr>
<tr>
<td>Range</td>
<td>136- 173</td>
<td>89 - 99</td>
<td>42 - 74</td>
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<td>34 (n = 11)</td>
<td>157 ± 7</td>
<td>97 ± 3</td>
<td>50 ± 6</td>
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<tr>
<td>Range</td>
<td>143- 167</td>
<td>92-100</td>
<td>38-58</td>
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<td>35 (n = 5)</td>
<td>160 ± 8</td>
<td>95 ± 3</td>
<td>50 ± 5</td>
</tr>
<tr>
<td>Range</td>
<td>151- 171</td>
<td>91-98</td>
<td>45-55</td>
</tr>
<tr>
<td>36 (n = 4)</td>
<td>165 ± 5</td>
<td>93 ± 4</td>
<td>52 ± 9</td>
</tr>
<tr>
<td>Range</td>
<td>160- 170</td>
<td>88-98</td>
<td>44-63</td>
</tr>
</tbody>
</table>
Figure 1- Maturation of Edi peak and min with postnatal development

Figure 2- Maturation of Edi peak for individual patients with postnatal development
Figure 3 - Maturation of Edi min for individual patients with postnatal development
Title: Normative Values of Electrical Activity of the Diaphragm in Preterm Infants

Principal Investigator: Howard Stein, MD  
Sub-Investigators: Keith Davis II, PA-SII, Rachel Hall, PA-SII

Why is this study being done?
You are being asked to give permission for your baby to participate in a research study of electrical activity of the diaphragm (Edi) in preterm babies. Edi measures the signal from the breathing center in the brain that goes to the diaphragm (the muscle that helps the lungs push air out). This signal is responsible for determining the size of the breath and the rate of breathing. The purpose of the study is to identify normal Edi in preterm neonates at rest. Data collection will benefit future patients in its application to identification of abnormal breathing function. Approximately 60-96 babies will participate in this study conducted at The Children’s Toledo Hospital. Your baby was selected as a possible participant in this study because he or she was delivered between 24-35 weeks, is not on any form of mechanical breathing support, and has a feeding tube currently in place for routine use.

What will happen if you take part in this study? (Procedures and Duration)
If you decide to participate, your baby will have the regular feeding tube replaced by a specialized NAVA feeding tube. This NAVA feeding tube has electrodes imbedded in the wall to detect the Edi signal. This specialized feeding tube will be connected to a monitor that collects Edi data. Participation will last 3-4 hours and will occur in the baby’s room. During this time your baby will remain in the isolette or crib but you will be able to remain with your baby the entire time. At the end of the study this tube can be used until it is time to replace it as normally done for routine care. This tube will be used weekly, instead of the regular feeding tube, to measure Edi until your baby reaches 35 weeks corrected age or no longer needs a feeding tube.

What side effects or risks could result from being in this study?
Feeding tubes are placed in babies frequently without complications. Possible complications, although extremely rare include esophageal perforation (a hole in the esophagus) or tissue trauma when the feeding tube is placed. This, however, is not an additional risk to your baby since the baby will require a feeding tube to be placed for routine care. Over the past 19 years the complication rate per feeding tube placement in this NICU is 1 in 125 000. The feeding tube will be placed by an experienced doctor or nurse who will continue to be available throughout the
study. We have been using this special nasogastric tube, to measure electrical activity of the diaphragm, for almost 3 years and have placed hundreds of these tubes without any complications. There are no long-term complications of this procedure.

**What are the benefits to participating and will you be paid to participate?**
There is no direct benefit to your baby and you will not be paid for participating in this study. The results of this study will benefit future babies, especially those requiring mechanical ventilation (help breathing) at birth and in the identification of abnormal breathing patterns.

**What other choices do you have if you do not take part in this study?**
You can choose not to participate in this study. Your choice not to participate will not affect your child’s care at The Toledo Children’s Hospital.

**Will your medical information be kept private?**
You and your child’s medical records will be maintained in accordance with federal and state laws. Efforts will be made to keep you and your child’s personal information confidential. The research investigator(s) cannot guarantee absolute confidentiality. Private identifiable information about you may be used or disclosed for the purpose of conducting this research project as described earlier in the consent form. The information that may be used or disclosed includes the following: physician/clinic records and hospital records.

You have the right to access your child’s medical records. You may request that your child’s research medical record be released to your personal physician. Organizations that may inspect and/or copy your research medical records for quality assurance and data analysis include: Food and Drug Administration and ProMedica Health System Institutional Review Board. This information may be further disclosed if the recipient(s) described on this form are not required by law to protect the privacy of the information. Data from this study may be used in medical publications or presentations, but any information identifying you or your child will be removed.

The use and disclosure of your protected health information will conclude at the end of this study. If after you have entered this study and you wish to withdraw from participation, you have the right to change your mind about allowing the investigator to have access to this health information, although the investigator may use information already collected to maintain the completeness of the study. If you decide to revoke permission to use your child’s personal information, you should contact Dr. Howard Stein of Toledo Children’s Hospital at 419-291-8380.

**What are the costs of taking part in this study?**
There is no cost for participation in this study. You will not be charged for any of the study procedures.

**What happens if you are injured because you took part in this study?**
If your baby is injured as a direct result of participating in this study, treatment can be obtained at The Toledo Children’s Hospital. The costs of such treatment will be paid for by The Toledo Children’s Hospital. In the event of injury, contact Howard Stein, M.D. at 419 291-8380.
By signing this form you are not giving up any of your legal rights as a research subject.

**Are any research team members being paid for conducting this study?**
The investigators performing this study are not receiving any direct or indirect compensation to conduct this study. Dr. Stein is a speaker for Maquet, the manufacturer of the specialized nasogastric tube and monitoring device. All other investigators have no financial link to the makers of data monitoring devices used in this study.

**What are your rights if you take part in this study?**
Participation in this study is voluntary. If you decide not to participate in this study, your decision will not affect your future relations with any ProMedica Health System institution, its personnel, and associated hospitals. You have the right not to participate in this study, and refusing to participate will not affect the present or future medical care you receive and will not cause any penalty or loss of benefits to which you are otherwise entitled. If you withdraw from the study early, the research team may continue to collect follow-up information on your health status to be used as part of the study if you agree.

**Who can answer your questions about the study?**
Before you sign this form, please ask any questions on any aspect of this study that is unclear to you. You may take as much time as necessary to think this over. If you have any questions regarding your rights as a research patient, you may contact the Chairperson of the ProMedica Health System Institutional Review Board at 419-291-5362, during office hours Monday through Friday, 8 a.m. to 4:30 p.m.
Signatures:
You are making a decision whether or not to participate in this study. Your signature indicates that you have read and understood the information provided above, have had all your questions answered, and have decided to participate.

__________________________________________
Printed Name of Subject (Your baby)

__________________________________________
Printed Name of Mother

__________________________________________  Date
Signature of Mother

__________________________________________  Date
Printed Name of Father

__________________________________________  Date
Signature of Father

Printed Name of Person Obtaining Consent

__________________________________________  Date
Signature of Person Obtaining Consent

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP

If you have any questions concerning this study or consent form beyond those answered by the investigator, including questions about the research, your rights as a research subject or research-related injuries, please feel free to contact the ProMedica Health System Institutional Review Board at 419-291-5362.
Abstract

Introduction: Electrical activity of the diaphragm (Edi) reflects central respiratory drive. Edi peak measures the neural inspiratory effort and Edi min reflects tonic activity of the diaphragm. There are no normative Edi values for preterm infants.

Objective: To determine normative Edi values in non-ventilated preterm neonates throughout postnatal maturation.

Methods: Prospective observational study of premature neonates off mechanical ventilation. Edi data was collected weekly, using a specialized NG tube with embedded electrodes, for 4 hours until the neonate no longer required a nasogastric tube. Statistics were linear regression with sign test. p < 0.05 was significant.

Results: 17 neonates were enrolled at gestational ages ranging from 25 – 33 weeks. There was no change in Edi peak or min with increasing gestational age.

Conclusion: These are the first normative data available in non-ventilated premature neonates. Edi peak and min do not change over time as the neonate matures.