Normative values for electrical activity of the diaphragm in full term neonates during awake and sleep stages

Jacqueline Elizabeth Wilmoth

The University of Toledo

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Jacqueline Elizabeth Wilmoth
University of Toledo
2010
Dedication

I would like to personally thank all the people in my life who supported me throughout this journey.
Acknowledgements

**Major Advisor**
Dr. Howard Stein

**Co-investigator**
Jill Burton, PA-SIII
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Introduction

Background and significance of the project

Throughout the body there are chemical and neural receptors that recognize change in pH, PCO2, and PO2 and regulate these inputs to the respiratory control centers in the brain. The respiratory center then sends impulses along the phrenic nerve to the diaphragm and other respiratory muscles to contract creating an area of negative pressure which elicits a breath (Johnson & Kazemi, 2009). Respiration is a regulated process matched to the metabolic demands of the body; as metabolism increases, respiration must increase (Nigg, MacIntosh, & Mester, 2000). Minute ventilation is the measure of the amount of air moved through the lungs in one minute; the product of tidal volume times respiratory rate. Tidal volume is the normal volume of air displaced during inspiration and expiration (Hasan, 2010). In a neonate, the tidal volume is smaller than average adults; therefore to compensate and provide adequate oxygenation to meet the metabolic demands of the body, their respiratory rate must increase. An average respiratory rate for a neonate is 30 - 60 breaths per minute compared to an average of 12 – 20 breaths per minute in an adult (Naglar & Wang, 2009).

Healthy neonates sleep up to 20 hours a day (Price & Gwin, 2008). The stages of wakefulness include awake and sleep. The rhythms of breathing are different for each stage of wakefulness. In the awake stage, the respiratory rate is quick and under voluntary control. The sleep stage in neonates is characterized by slower, more regular respiration rates as compared to the awake stage (Montgomery-Downs & Thoman, 1998).

In the past, respiration patterns have been measured using chest plethysmography, balloon catheters, and motility monitoring systems. When studying the pattern of respirations, researchers have collected data on respiratory rate, lung volume, PCO2, and PO2. A recent
measure of respiration is electrical activity of the diaphragm (Edi). Edi is a measure of the diaphragmatic electromyography (EMG) found using electrodes within a nasogastric tube. The Edi minimum represents the tonic electrical activity present in the diaphragm muscle at rest between breaths and is responsible for maintaining functional residual capacity. Edi peak is a measurement of the amplitude of the electrical impulse needed to elicit a contraction in the diaphragm and is responsible for inspiratory effort.

The Edi signal has been proposed as a parameter to evaluate respiratory function. Recent application of the Edi signal has been used in neurally adjusted ventilatory assist (NAVA) in which Edi is used to monitor and control the timing and magnitude of pressure delivered by mechanical ventilation (Beck, et al., 2009). The use of NAVA has improved patient ventilator synchrony and has been shown to effectively unload the work of respiratory muscles at all lung volumes (Bengtsson & Edberg, 2009; Sinderby, et al., 2007) In past studies, Edi has been presented as arbitrary units (au) or as a percentage change. Normative values of electrical activity of the diaphragm in full-term neonates are not known (Beck, et al., 2009). The purpose of the study was to establish normative Edi values in full term neonates during awake stage and sleep stage.
Definitions

**Electrical activity of the diaphragm (Edi):** the electrical impedance generated by the diaphragm muscle.

**Edi Peak:** the highest amplitude of Edi required to elicit contraction of the diaphragm muscle and maintain inspiratory effort

**Edi Min:** baseline electrical activity of the diaphragm at rest between breaths which maintains functional residual capacity. Also known as Tonic Edi.

**Full term neonate:** in this study, neonates delivered between 37 and 42 weeks with no active respiratory problems at the time of the study.

**Awake stage:** when the neonate appeared awake with open eyes and gross body movement

**Sleep stage:** stage of sleep when the neonate appeared relaxed with regular respiration, no eye movements, and no gross body movements.

**NAVA:** Neurally Adjusted Ventilatory Assist allows a patient to synchronize spontaneous respiratory effort with mechanical ventilation
Literature review

Electrical Activity of the Diaphragm

The neural impulse for respiration is generated in the central nervous system and drives the respiratory muscles. Researchers are interested in values such as respiratory rate, total lung capacity, airway resistance, functional residual capacity, and residual volume. To measure these values, different devices have been used on many different populations.

Respiratory inductance plethysmography measures respiration from body surface movement. A double layered jacket fitted to the patient is connected to a processing system that records the movements of the chest wall during respiration (Poole, Thompson, Hallinan, & Beardsmore, 2000). The motility monitoring system determines sleep states from movement and respiratory pattern. This method is particularly practical in neonates because the system can be placed in the infant's crib like a blanket (Ariagno, et al., 1997). A pediatric pneumogram evaluates respiratory rate, end tidal CO2 chest impedance, and is useful for determining the source of apnea in neonates - central versus obstructive. Thoracic surface electromyography (sEMG) and thoracic and abdominal strain gauges also measure the electrical activity of the respiratory muscles (Peper & Tibbetts, 1997). A diaphragm EMG measures Edi from an electrode embedded in a nasogastric tube placed in the esophagus. NAVA uses Edi transmitted to a ventilator to synchronize spontaneous respiratory effort with mechanical ventilation.

Studies on Edi have focused on populations with respiratory dysfunction. Studies have evaluated Edi values in adults with acute respiratory failure and Edi values in chronic obstructive pulmonary disease during strenuous exercise conditions compared to maximal inspiration at rest (Beck, et al., 2001; Sinderby, et al., 2001). Premature neonates have been studied to evaluate Edi while on NAVA (Alosh, Stein, Howard, & Stein, 2010). Edi has been measured in intubated
neonates and has shown that the diaphragm remains partially activated during expiration of spontaneous breaths confirming the presence of tonic Edi (Emeriaud, Beck, Tucci, Lacroix, & Sinderby, 2006).

Neonatal Respiration and Sleeping

Healthy neonates are awake for an average of four hours a day (Price & Gwin, 2008). The stages of wakefulness include awake and sleep with the rhythms of breathing differing for each stage. In the awake stage, the respiratory rate is quick and under voluntary control. The sleep stage in neonates is characterized by slower, more regular respiration rates as compared to the awake stage (Montgomery-Downs & Thoman, 1998).

In the neonate, sleep is broken down into two stages; active sleep and quiet sleep. Active sleep is identified by rapid eye movements and restless, jerking muscle movements. Respiration during active sleep is erratic with periodic breathing, periods of rapid respiration followed by slow respiration. Quiet sleep is characterized by the absence of eye or muscle movement and slower, more regular breathing as compared to active sleep. Neonates move through sleep cycles, which repeat many times. A normal sleep cycle length for a neonate is 60 minutes which is then followed by a brief awakening before the start of a new cycle. Most neonates start their sleep cycle in active sleep and spend over 50% of time in active sleep (Bennett, 2005; Gaultier, 1995; Kliegman, Marcante, Jenson, & Behrman, 2005). Studies on respiration rate during sleep wake cycles in healthy full term neonates have shown statistically significant increases in respiration rate during active sleep as compared to quiet sleep (Hathorn, 1974).
Methodology

Research design

The research was prospective, observational studies of neonates in awake and sleep stages.

Population and sampling methods

Neonates born between 37 and 42 weeks not requiring mechanical ventilation or respiratory assistance at the time of the study were recruited. Neonates were selected as a convenience sample from the neonatal intensive care unit at The Toledo Children's Hospital. Mothers were approached shortly after birth to explain the research study and obtain informed consent.

Data collection methods

A specialized nasogastric tube was inserted into the esophagus of the neonate and placement was identified by on-line analysis with SERVO-i ventilator software. Average Edi peak and average Edi minimum was collected and recorded in one minute increments by the SERVO-i ventilator software for a total of four hours. An observer recorded awake and sleep states. Data was downloaded to a flash drive and extracted using Microsoft Excel. Heart rate and respiratory rate were also recorded from the cardiopulmonary monitor every 15 minutes.

Statistical hypotheses

As this was an observational study there was no statistical hypothesis. In analysis of Edi by stage of wakefulness, statistical significance was defined as $\alpha=0.05$.

Statistical analyses

The independent variables in the study were the two stages of wakefulness including awake and sleep. Descriptive variables that were recorded were gestational age, gender, birth
weight, age at time of study, and post-natal course. The dependent variable was the Edi. The average peak and minimum values from all subjects was compiled to establish population normative values including the mean, standard deviation, and range for Edi peak and minimum for both awake and sleep stages.

T-tests identified differences between awake stage and sleep stage and p < 0.05 was considered significant.
Results

Thirty mothers were approached to participate in the study. Three female subjects were enrolled. All subjects were 37-40 weeks gestation, less than one week old at time of study, and had an average birth weight of 3000 ± 164 g. Total study time was 720 minutes of which 143 minutes was in awake stage and 577 minutes in sleep stage corresponding with 11 measures of heart rate and respiratory rate during awake stage and 41 measures of heart rate during sleep stage.

Table 1 shows population means for Edi peak, Edi min, respiratory rate, and heart rate. Table 2 summarizes Edi peak and min, respiratory rate, and heart rate by sleep stage.

The average Edi peak while sleeping was 10 ± 4.2 µV and increased 60% while awake to 16 ± 6.1 µV (p < 0.05). The average Edi min while sleeping was 3 ± 1.9 µV and increased 67% while awake to 5 ± 2.4 µV (See Figure 1).

The average respiratory rate was unchanged between awake and sleep stage. The heart rate increased from 141 beats per minute during sleep to 149 beats per minute while awake. Although this did not meet statistical significance, it was trending in that direction (p = 0.07). (see Figure 2).
Discussion

This study aimed to establish normative Edi peak and min for full term neonates during awake and sleep stages.

Of the 720 minutes during the study, 20% of the time was awake stage and 80% was in sleep stage. This is consistent with previously described sleep time in neonates, which stated that neonates spend up to 20 hours per day sleeping (Price & Gwin, 2008).

The average Edi peak while awake was 60% higher than while asleep. This indicates that greater electrical amplitude is used to elicit a breath while awake than while sleeping. This is consistent with an increased respiratory rate while awake than asleep (Berman & Simoes, 1991). The data also showed that the tonic baseline electrical activity of the diaphragm at rest between breaths is greater while awake than while sleeping.

There was no significant difference in the mean respiratory rate between awake stage and sleep stage. Previous studies show higher respiratory rate in awake stage which was not confirmed in this study (Horemuzova, Katz-Salamon, & Milerad, 2000; Naglar & Wang, 2009). This is most likely a statistical anomaly. Our study was only four hours and awake time was limited to less than one hour for each subject. In addition, past research further divided sleep stage into active sleep and quiet sleep which showed variation in respiratory rate (Hathorn, 1974). We were not able to differentiate sleep stage into active sleep and quiet sleep. By accounting for only one sleep stage, differences in respiratory rate may become less apparent. Respiratory rate may have been different if we were able to distinguish active sleep and quiet sleep.
Heart rate while awake was higher than asleep and although it did not meet statistical significance, it trended in that direction ($p = 0.07$). This is in agreement with past data that shows a greater heart rate in awake neonates (Snyder, Hobson, Morrison, & Goldfrank, 1963).

This study is limited by the small sample size. Although many attempts were made to obtain more subjects, the major barrier identified by the parents was the need to place a nasogastric tube in a healthy term neonate. This was compensated by multiple data points.
Conclusion

Normative Edi values were established in term neonates. Edi peak and min were higher during awake stage. Further studies are needed to determine normative values in premature infants and during postnatal development. These normative values can potentially be utilized in the ventilated population to evaluate respiratory function and response to treatment and to study neonates born prematurely and to research their respiratory development and changes in Edi over time.
References


Johnson, D. C., & Kazemi, H. (2009). Control of ventilation. *UpToDate*


<table>
<thead>
<tr>
<th>Population Means</th>
<th>Edi Peak (µV)</th>
<th>Edi Min (µV)</th>
<th>Respiratory Rate (Breaths per minute)</th>
<th>Heart Rate (Beats per minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>11 ± 5.3</td>
<td>3 ± 2.2</td>
<td>52 ± 17.4</td>
<td>142 ± 13.2</td>
</tr>
<tr>
<td>Range</td>
<td>(1.8-37.7)</td>
<td>(0.1-12.2)</td>
<td>(20-84)</td>
<td>(114-179)</td>
</tr>
</tbody>
</table>

*Table 1:* Population means for Edi peak, Edi min, respiratory rate, and heart rate
<table>
<thead>
<tr>
<th></th>
<th>Edi Peak (µV)</th>
<th>Edi Min (µV)</th>
<th>Respiratory Rate (Breaths per minute)</th>
<th>Heart Rate (Beats per minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake</td>
<td>16 ± 6.1 *</td>
<td>5 ± 2.4 *</td>
<td>50 ± 11.6</td>
<td>149 ± 11</td>
</tr>
<tr>
<td>Range</td>
<td>(3.0 - 37.7)</td>
<td>(0.7 - 12.2)</td>
<td>(20 - 64)</td>
<td>(133 – 161)</td>
</tr>
<tr>
<td>Sleep</td>
<td>10 ± 4.2</td>
<td>3 ± 1.9</td>
<td>53 ± 18.9</td>
<td>141 ± 13</td>
</tr>
<tr>
<td>Range</td>
<td>(1.8 - 27.1)</td>
<td>(0.1 - 10.6)</td>
<td>(21 - 84)</td>
<td>(114 -179)</td>
</tr>
</tbody>
</table>

* p < 0.05 compared to sleep

*Table 2: Means by sleep stage for Edi peak, Edi min, respiratory rate, and heart rate*
Figure 1: Average Edi peak and Edi min for awake and sleep stages with standard deviation

* p < 0.05 compared to sleep
Figure 2. Average respiratory rate and heart rate for awake and sleep stages with standard deviation * p < 0.05
Appendix

INFORMED CONSENT FORM

**Title:** Normative values of electrical activity of the diaphragm in term neonates by feeding state and stages of wakefulness and sleep.

**Principal Investigator:** Howard Stein, MD

**Sub-Investigators:** Jill Burton, PA-SII, Jacqueline Wilmoth, 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 healthy full-term 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 values before, during, and after feeds and when babies are awake and asleep. Data collection will benefit future patients in its application to identification of abnormal breathing function. Ten babies will participate in this study conducted at The Toledo Hospital. Your baby was selected as a possible participant in this study because he or she was delivered after a full-term pregnancy and is healthy.

**What will happen if you take part in this study? (Procedures and Duration)**

If you decide to participate, your baby will be moved to a room in the Neonatal Intensive care Unit. Your baby will then have a feeding tube placed through the nose into the stomach by an experienced doctor or nurse. The specialized feeding tube will be connected to a monitor that collects Edi data. Nothing will be given to your baby via the NG tube. Your baby will also be monitored on a portable electroencephalograph (EEG), which is a non-invasive way to measure how deeply a baby is sleeping. This is done by taping gel monitors onto the babies scalp. Participation will last 4 - 5 hours. During this time your baby will be able to sleep and feed normally and you will be able to remain with your baby the entire time. At the end of the study all tubes and patches will be removed and the baby will go back to regular nursery.

**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 bleeding when the feeding tube is placed. 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 the NAVA nasogastric tube for almost 2 years and have placed about 130 of these nasogastric 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 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 Hospital or Toledo Children’s Hospital. The costs of such treatment will be paid for by The Toledo 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 NG 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

_______________________________________  _________________
Signature of Mother                       Date

_______________________________________
Printed Name of Father

_______________________________________  _________________
Signature of Father                       Date

_______________________________________
Printed Name of Person Obtaining Consent

_______________________________________  _________________
Signature of Person Obtaining Consent     Date

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

Objective: To establish normative electrical activity of the diaphragm (Edi) values in full term neonates during awake and sleep stages. Method: Term neonates not requiring mechanical ventilation or respiratory assistance at the time of the study were recruited. Edi was monitored using SERVO-i ventilator software for four hours. Respiratory rate and heart rate were recorded every 15 minutes. T-tests were performed; p < 0.05 was considered significant. Results: Population Edi peak was $11 \pm 5.3 \mu V$ and Edi min was $3 \pm 2.2 \mu V$. Edi peak while asleep was $10 \pm 4.2 \mu V$ and increased to $16 \pm 6.1 \mu V$ while awake. The average Edi min while asleep was $3 \pm 1.9 \mu V$ and increased to $5 \pm 2.4 \mu V$ while awake. No change in respiratory rate or heart rate. Conclusion: These are the first normative values for neonates. Edi peak and min were higher while awake than asleep.