

Electrical activity of the diaphragm: Normative values in term neonates by feeding state

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Table of Contents

Introduction.....	1
Definitions.....	3
Literature Review.....	4
Methods.....	9
Results.....	11
Discussion.....	12
Conclusion	14
References.....	15
Tables	18
Figures.....	20
Apendix: Informed Consent Form.....	22
Abstract.....	26

List of Tables and Figures

Table 1: Population data

Table 2: Population data by feeding state

Figure 1: Mean Edi peak and Edi min by feeding state

Figure 2: Mean respiratory rate and heart rate by feeding state

Introduction

Electrical activity of the diaphragm (Edi) is an esophageal measure of diaphragmatic electromyography (EMG) obtained using a nasogastric tube 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 (American Thoracic Society/European Respiratory, 2002; Breatnach, Conlon, Stack, Healy, & O'Hare). Measurement of the Edi via these action potentials, which are propagated from neural respiratory centers along the phrenic nerve to the diaphragm, assesses the neural control of respiration (Beck, et al., 2009; Breatnach, et al.; Luo, Moxham, & Polkey, 2008; Sinderby, et al., 2001). Edi can be used to measure the tonic activity of the diaphragm (Edi min—baseline electrical activity of the diaphragm muscle at rest between breaths) and the amplitude of electrical activity associated respiratory effort (Edi peak), as well as the frequency and duration of breaths required to meet the individual's respiratory needs. The rate at which the Edi approaches peak from baseline indicates the neural respiratory drive—how quickly the volume and pressure within the lungs must change in order to produce adequate air exchange to meet the present need (Binazzi, Lanini, & Scano, 2004). Changes in an individual's Edi over time can be used as an indicator of diaphragm fatigue (Luo, et al., 2008). Edi measures also 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. A recent application of esophageal measures of Edi is in neurally-adjusted ventilatory assist (NAVA), a ventilation system that is driven by Edi signals rather than the pressure-flow triggers of conventional ventilator systems (Sinderby, Spahija, & Beck, 2005).

In addition to current clinical applications of Edi, Pang et al. (1995) suggested the use of Edi to assess respiratory development and change in neonates, particularly those born

prematurely or with respiratory dysfunction at birth. Comparison of Edi values to those observed in healthy neonates may enhance assessment of respiratory impairment at birth. Respiratory development and progression may be followed with serial Edi measures to identify when, or if, these neonates reach Edi levels of term neonates. In order to make these comparisons, normative values and ranges must first be established.

The purpose of this study was to measure the Edi in term neonates to establish normative values in this population and to determine how these values vary in pre-prandial, feeding, and post-prandial states.

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 Min: baseline electrical activity of the diaphragm, the degree of activation at rest between breaths. Also known as tonic Edi.

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

Minute Ventilation: the product of respiratory rate and tidal volume.

NAVA: Neurally-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.

Pre-prandial state: the thirty minute period immediately preceding feeding.

Feeding state: the period from initiation to cessation of feeding, either by breast or bottle.

Post-prandial state: the thirty minute period immediately following cessation of feeding.

Term neonate: in this study refers to a neonate delivered at 37-42 weeks gestational age, breathing room air without ventilator assist, and nipping all feeds via breast or bottle for the duration of the study.

Literature Review

Electrical Activity of the Diaphragm

Several measures of diaphragmatic electrical activity exist, each with its own disadvantages as well as specific applications. Although intramuscular electromyography (EMG) provides the most precise sampling of the diaphragm muscle electrical impulses, the measurements sample a very small area of the muscle and do not provide good measures of gross diaphragm electrical activity. This technique is useful for evaluating pathology of the muscle itself, but only surface and esophageal measures assess global diaphragm activity to an extent that gives insight into respiration (American Thoracic Society/European Respiratory, 2002). Surface EMG uses electrodes placed on the chest wall and allows global measurement of the diaphragm's electrical activity. These recordings are affected by changes in muscle length during contraction and can be difficult to obtain if the chest wall has a high composition of adipose tissue. Esophageal recordings of the electrical activity of the diaphragm (Edi) do not have the same utilization limitations as surface EMG; they are less susceptible to changes in muscle length, lung volume, and chest wall adipose tissue (American Thoracic Society/European Respiratory, 2002; Beck, Tucci, Emeriaud, Lacroix, & Sinderby, 2004; Breatnach, et al.; Luo, et al., 2008). Compared to surface measures, Edi obtained with an esophageal catheter has less electrical noise or "cross talk" from other respiratory muscles (Emeriaud, Beck, Tucci, Lacroix, & Sinderby, 2006; Luo, et al., 2008) and recordings are less affected by subject movement (Pang, et al., 1995), but this measure contains more artifact of cardiac electrical activity than surface or intramuscular measures (American Thoracic Society/European Respiratory, 2002; Binazzi, et al., 2004). This necessitates careful and standardized methods of electrode placement and subtraction of the ECG signal in order to obtain clear readings of Edi. One concern raised in

the literature is that Edi measures from the crural portion of the diaphragm may not represent activity of the entire diaphragm (American Thoracic Society/European Respiratory, 2002); however, several studies have found that the crural electrical activity is closely correlated to that of the costal diaphragm, and thus Edi does provide an accurate gross measure of diaphragm activity (Binazzi, et al., 2004; Luo, et al., 2008).

Edi has been used as a measure of neural respiratory control to evaluate patient-ventilator interaction (Beck, et al., 2004; Mellott, Grap, Munro, Sessler, & Wetzel, 2009). With use of Edi, Beck et al. (2004) found that on average 53.4% (\pm 26.2%) of a breath's total duration, as supplied by conventional mechanical ventilation, was asynchronous to neural output. In attempts to address the shortcomings of conventional ventilation, Edi has also been applied widely in the clinical setting in the use of the new NAVA ventilation system. Because Edi is closely linked to the neural respiratory center, its use as a trigger for ventilation may allow a better match to physiologic respiratory needs with less ventilatory asynchrony and lung injury, as well as more successful weaning from ventilatory assist when appropriate (Beck, et al., 2009; Bengtsson & Edberg, 2009; Breatnach, et al.; Luo, et al., 2008; Mellott, et al., 2009; Sinderby, et al., 2005). Moerer et al. (2008) reported that neural input for ventilatory control (NAVA) was associated with only 5% patient-ventilator asynchrony, compared to 30% asynchrony with pneumatic-triggered ventilators. Breatnach et al. (2010) found that when both neural (Edi) and pneumatic signals were available for control of mechanical ventilation in subjects two days to four years old, neural triggers elicited onset and offset in 65% (\pm 21%) and 85% (\pm 8%) of breaths, respectively. This indicates that Edi offers a reduced time delay between the initiation of a breath in the neural respiratory center and its actuation. Also, because Edi monitoring controls NAVA on a breath-by-breath basis, the rate and size of each breath is adjusted to meet the exact

need at that moment (Beck, et al., 2004; Bengtsson & Edberg, 2009; Breatnach, et al.; Sinderby, et al., 2005).

To date, the literature contains Edi data for those with respiratory dysfunction only, most obtained in subjects receiving mechanical ventilation. Edi values in adult males with chronic obstructive pulmonary disease were collected during increasingly strenuous exercise conditions and compared with Edi during maximum inspiration at rest (Sinderby, et al., 2001). Beck et al. (2001) evaluated Edi at varying levels of pressure support ventilation in adults with acute respiratory failure. In this study it was observed that greater levels of respiratory dysfunction were associated with higher Edi peaks. Several studies of Edi in neonates have been conducted, including the study of Emeriaud et al. (2006), in which mechanically ventilated neonates born between 29-40 weeks gestation demonstrated tonic activity of the diaphragm at 12-15% of the activation level associated with inspiration. The authors suggest that mechanical ventilation itself may contribute to the development of resting diaphragm tone and that neonates who are breathing independently may have less diaphragmatic activity at rest than was observed in this study. In a study of premature neonates, Edi levels were recorded during alternating four hour periods of NAVA and pressure control ventilation, with lower Edi peaks observed while on NAVA (Alosh et al., Abstract submitted PAS 2010). Data in healthy subjects is lacking in all age groups which limits the utility of existing data as there is no reference for comparison. Previous studies of Edi presented Edi data in arbitrary units (au) or percent change from maximum. One can speculate about the patterns and levels of Edi that are identified in patients with respiratory dysfunction, but it is not known how these patterns and levels vary, if at all, from those which exist in a state of respiratory health. No normative values have been proposed in any patient population at this time.

Neonatal Respiration and Feeding

Following normal fetal development, multiple protective mechanisms exist in both the digestive and respiratory systems to minimize respiratory complications during feeding. The activation of muscles involved in swallowing has an inhibitory effect on neurons that control respiratory muscles. The presence of food in the upper airway activates chemoreceptors to provide further inhibition of respiration until swallowing has been completed. In addition, while periods of decreased respiratory drive are characterized by relative relaxation of the lower esophageal sphincter, hypoxic conditions and periods of increased respiratory drive are associated with increased sphincter tone. Proper function of these mechanisms decreases a neonate's risk of aspirating food or gastric contents, an important aspect of the coordination of feeding and respiration (Miller & Kiatchosakun, 2004).

Coordination of digestive and respiratory actions occurs reflexively at birth but gradually becomes more consciously controlled. Anatomic and neurologic changes and the integration of motor and sensory experiences contribute to feeding and respiratory motor learning, as well as the progressive shift in the locus of control during the postnatal period (Barlow, 2009; Kelly, Huckabee, Jones, & Frampton, 2007; Miller & Kiatchosakun, 2004; Qureshi, Vice, Taciak, Bosma, & Gewolb, 2002).

Coordination of suck and swallow begins toward the end of gestation and is adequate in most neonates by 35-38 weeks gestation; however, timing between suck-swallow and breathing continues to develop during postnatal life (Barlow, 2009). In a longitudinal study of term neonates, Kelly et al. (2007) found that the timing of swallowing relative to respirations continues to change throughout the first year of life, at which point this pattern more closely matches that of adults. During the continuous-suck phase of feeding, neonates experience a

decrease in respiratory rate, tidal volume, and minute ventilation, attributed to decreased CO₂ sensitivity during feeding. In term neonates, these responses are reversed during the alternate intermittent suck-breathe phase of feeding. Prior to 34-35 weeks gestation, however, neonates tend to demonstrate prolonged respiratory pauses during feeding, putting them at a higher risk for developing hypoxia during feeding (Delaney & Arvedson, 2008; Miller & Kiatchoosakun, 2004; Qureshi, et al., 2002). Berman et al. reported a mean respiratory rate during feeding of 50 ± 8 breaths per minute in 253 subjects observed within in the first month of life (1991).

Despite the extent of research that exists on breath-by-breath respiratory patterns in neonates and the suck-swallow-breathe pattern that must be established in order to properly coordinate breathing and feeding, gross changes in respiration during feeding states have been less thoroughly evaluated. It is unclear how Edi relates to the observed changes in respiration during feeding and what insight into neonatal respiration this measure may give.

Methods

Subjects

This was a prospective observational study of neonates born at 37-42 weeks gestation in pre-prandial, feeding, and post-prandial states. Inclusion criteria required that neonates were in room air and fed by breast or bottle during the study. Study protocol was approved by the Institutional Review Board of The Toledo Hospital/Toledo Children's Hospital.

Measurements

Edi was measured by electrodes within a nasogastric tube positioned at the level of the diaphragm. The nasogastric tube was connected to SERVO-i ventilator software and Edi signal was recorded for the duration of the study. Data output included Edi peak, Edi min, and respiratory rate, all of which were stored in one-minute increments in the SERVO-i software, downloaded to a flash drive, and imported into Microsoft Excel for data analysis. Each subject was observed for a continuous four-hour period, resulting in 240 measures for each variable observed. Heart rate was also recorded from telemetry monitors at fifteen-minute increments throughout the study.

Study Protocol

A nasogastric (NG) tube was placed and proper position was confirmed by on-line analysis on SERVO-i software. Normal activity was not interrupted for the study; subjects were able to feed on demand and be handled by parents throughout the study. Data was collected during feeds, 30 minutes preceding feeds, and 30 minutes following feeds.

Statistical Analysis

Population means, standard deviations, and ranges were calculated for the duration of the study. Analysis of variance (ANOVA) measures were performed to compare the population

means for the feeding states. When statistically significant differences were observed among feeding states, t-tests were performed. Statistical significance was defined as $p < 0.05$.

Results

Thirty sets of parents were approached for participation in the study and three gave consent. The primary barrier to participation was parental concern regarding the risk of nasogastric tube placement. Three neonates were enrolled in the study. Gestational age was 37-40 weeks. Postnatal age at time of study was 2-7 days. Birth weight was 3000 ± 164 grams.

Mean and range of Edi peak, Edi min, respiratory rate, and heart rate for the duration of the four-hour study period are presented in Table 1. Of the 720 minutes of data collected, 266 data points were analyzed; 120 minutes pre-prandial, 43 minutes during feeds, and 103 minutes post-prandial. There were less post-prandial data points because one feed ended 13 minutes before the end of the study period. Means of Edi peak and Edi min for each feeding state are presented in Figure 1. Edi peak was lower in the post-prandial state than pre-prandial and feeding states. Mean respiratory rate and heart rate by feeding state are presented in Figure 2. Respiratory rate was higher post-prandial than pre-prandial. Edi min and heart rate were unchanged among feeding states.

Discussion

Normative values of Edi do not exist for any population. To our knowledge, ours is the first report of Edi in any subjects who are non-ventilated and without significant respiratory disease at the time of the study. In the existing literature, Edi has been reported in arbitrary units (au) and percentage change. These measures were appropriate in prior studies which evaluated intra-subject variations in Edi with changes in exercise workload, while on different types of ventilators, and with progression of respiratory status. Our data is presented in microvolts (mcV), an absolute measure that will allow for inter-subject comparison.

Relationships in the Edi peak, Edi min, respiratory rate, and heart rate among feeding states were analyzed. Edi peak was lower in the post-prandial state than pre-prandial and feeding states. This may be explained in part by the neonate's activity level during the various feeding states. As a neonate becomes hungry, the neonate awakes from sleep and becomes increasingly active. While feeding, the neonate is awake and actively sucking and swallowing. Both of these states are associated with increased respiratory effort and work of breathing, consistent with the higher Edi peak observed. A neonate generally falls back asleep after completing a feed. It has been shown that the sleep state is characterized by lower Edi peak than the awake state, which was consistent with our findings (Wilmoth, 2010). Prior research indicates that the decreased respiratory rate, tidal volume, and minute ventilation during the continuous-suck phase of feeding is compensated for during the intermittent suck-breathe phase of feeding in term neonates, thus maintaining appropriate oxygenation throughout feeding (Delaney & Arvedson, 2008; Miller & Kiatchoosakun, 2004; Qureshi, et al., 2002). Differences between phases of the feeding cycle that have been observed in breath-by-breath analyses were not evident in this study in which data was averaged over each minute. Respiratory rate was higher in the post-prandial

state than in the pre-prandial state. It is possible that the increased abdominal contents and intra-abdominal pressure after the feed decreased the intrathoracic volume, resulting in shallower breaths associated with the lower Edi peak. In order to maintain sufficient minute ventilation, changes in tidal volume are compensated for by inverse changes in respiratory rate, in this case a postprandial increase in respirations. Edi min did not change among feeding states, indicating that the tonic activity of the diaphragm, the relatively relaxed state between breaths, was not influenced by feeding, changing tidal volume, or respiratory rate.

Conclusions

This normative data may be useful in identifying respiratory pathology in neonates and monitoring progression toward respiratory health. In the future it would be beneficial to observe Edi peak and min in neonates born at a broader range of gestational ages to further identify changes in this signal with gestational and postnatal development.

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	Edi peak (mcV)	Edi min (mcV)	Respiratory Rate (Breaths per minute)	Heart Rate (Beats per minute)
Mean \square SD	11 \square 5	3 \square 2	53 \square 16	142 \square 13
Range	2-38	0-12	20-91	114-179
* p<0.05 compared to post-prandial				

Table 1: Population data

	Edi peak (mcV)	Edi min (mcV)	Respiratory Rate (Breaths per minute)	Heart Rate (Beats per minute)
Pre-prandial	14 ± 7*	4 ± 3	52 ± 15*	147 ± 15
Feeding	13 ± 4*	4 ± 2	55 ± 13	149 ± 10
Post-prandial	11 ± 4	4 ± 2	59 ± 12	143 ± 12
* p<0.05 compared to post-prandial				

Table 2: Population data by feeding state

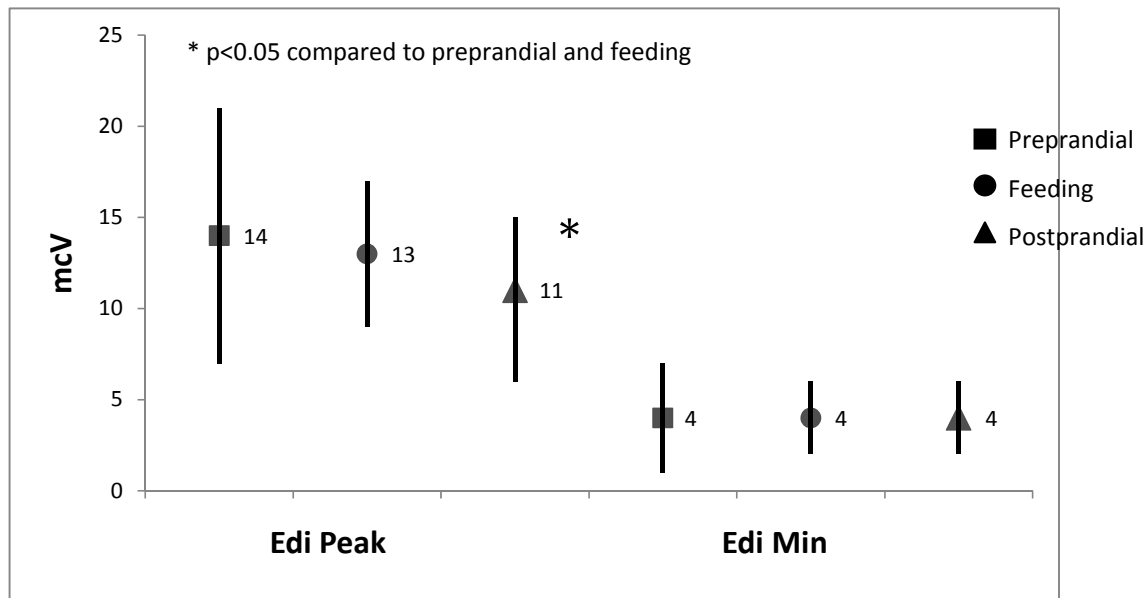


Figure 1: Mean Edi peak and Edi min by feeding state

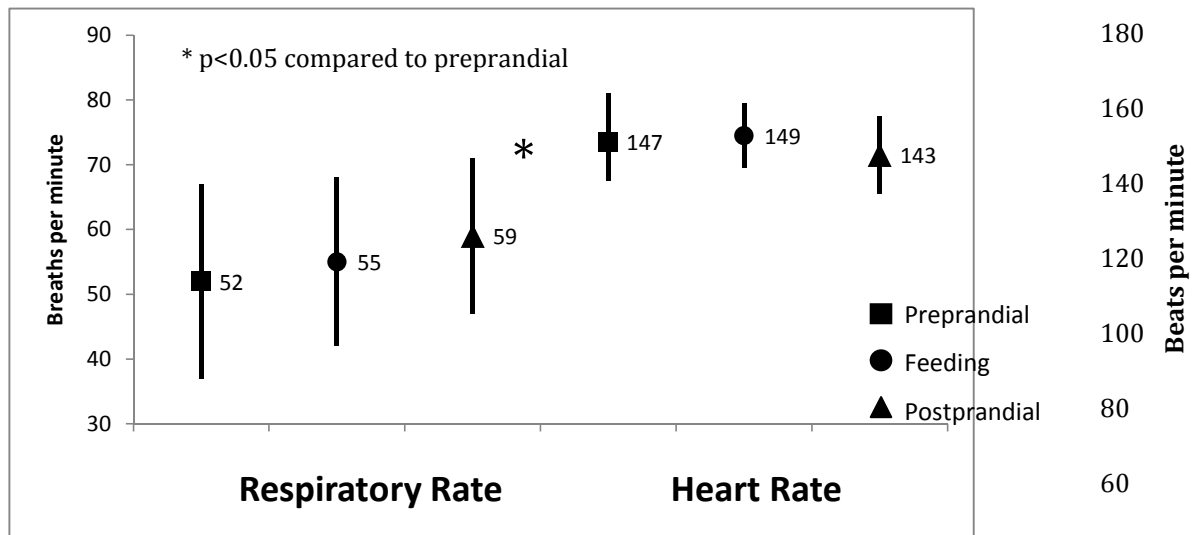


Figure 2: Mean respiratory rate and heart rate by feeding state



INFORMED CONSENT FORM

Title: Normative values of electrical activity of the diaphragm in healthy 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. 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 values of electrical activity of the diaphragm (Edi) in term neonates and to determine how these values vary across feeding states. *Methods:* Edi was measured by electrodes within a nasogastric tube positioned at the level of the diaphragm. Three term neonates without active respiratory problems and on ad lib feeds were each observed for four hours. Edi peak, Edi min, respiratory rate, and heart rate were collected during feeds and 30 minutes preceding and following feeds. Statistics were ANOVA with $p < 0.05$. *Results:* Mean Edi peak was 11 ± 5 mcV. Mean Edi min was 3 ± 2 mcV. Postprandial Edi peak was lower than preprandial and feeding. Respiratory rate was higher postprandial. Edi min and heart rate were unchanged. *Conclusion:* These are the first normative values for Edi in neonates. Postprandial lower Edi peak and higher respiratory rate may indicate compensation for decreased tidal volume from increased intra-abdominal pressure.