Electrical Activity of the Diaphragm in a Small Cohort of Term Neonates

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BACKGROUND: Electrical activity of the diaphragm (E_{di}) has been proposed as a parameter to evaluate respiratory function. Normative values of electrical activity of the diaphragm in full-term neonates are not known. This is a small case series to establish preliminary values of E_{di} in term neonates and to determine how these values vary while awake and asleep and during feeding states. METHODS: Three term neonates in room air and nippling feeds at the time of the study were observed for 4 hours. E_{di} was measured by electrodes within a nasogastric tube positioned at the level of the diaphragm. Respiratory rate and heart rate were also recorded. Time while awake and asleep were noted. Feeding states included feeding, 30 min pre-prandial, and 30 min post-prandial. Statistics were analysis of variance and *t* tests, with $P < .05$. RESULTS: Mean E_{di} peak was 11 ± 5 μV. Mean E_{di} minimum was 3 ± 2 μV. E_{di} peak and minimum were higher while awake. E_{di} peak was lower post-prandial. Respiratory rate was higher post-prandial. CONCLUSIONS: These are the first preliminary values for E_{di} in neonates. Higher E_{di} peak while awake may reflect larger tidal volume to meet increased metabolic requirements when awake and active. Post-prandial lower E_{di} peak and higher respiratory rate may indicate compensation for decreased tidal volume from increased intra-abdominal pressure. These data may be useful in identifying respiratory pathology in neonates and monitoring progression toward respiratory health. *Key words: diaphragm excitation; respiration; feeding states; sleep states; electromyographic activity; Neurally Adjusted Ventilatory Assist; NAVA.* [Respir Care 2012;57(9):1483–1487.

Introduction

Electrical activity of the diaphragm (E_{di}) is an esophageal measure of diaphragmatic electromyography obtained using a nasogastric tube with electrodes at the level of the diaphragm. E_{di} measures the total of action potentials of all motor units in the central (crural) portion of the diaphragm.[1,2] Measurement of the E_{di} via these action potentials, which are propagated from neural respiratory centers along the phrenic nerve to the diaphragm, assesses the neural control of respiration.[2-5] E_{di} can be used to measure the tonic activity of the diaphragm (E_{di} min, the minimum or baseline electrical activity of the diaphragm muscle between breaths that prevents derecruitment) and the amplitude of electrical activity associated with inspiratory effort (E_{di} peak), as well as the frequency and duration of breaths required to meet the individual's respiratory needs. E_{di} 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. A recent application of esophageal measures of E_{di} is in Neurally Adjusted Ventilatory Assist (NAVA), a ventilation system that is driven by E_{di} signals rather than the pressure-flow triggers of conventional ventilator systems.[6] Because E_{di} 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.[2-4,6-8] To date, the literature con-

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tains E_{di} data for those with respiratory dysfunction only, most obtained in subjects receiving mechanical ventilation. There are no normal values for E_{di} signals in ventilated neonates, because the respiratory drive, or E_{di} signal, can be manipulated depending on the amount of ventilatory support provided. This lack of E_{di} data in healthy term neonates limits the utility of existing data, as there is no reference E_{di} values for comparison. This may limit the ability of the practitioner to optimize the use of NAVA ventilation (a ventilation mode that uses the E_{di} signal for triggering and volume determination) in critically ill neonates.

Respiration is a physiologic process that is closely regulated by chemoreceptors throughout the body, and, as such, respiration is continuously adjusting to meet metabolic needs. Neonates sleep up to 20 hours a day, and this is divided into active and quiet sleep, based upon changes in gross activity level and respiratory rate and patterns.[9,10] Neonatal respiration is also intricately controlled during feeding; an appropriate suck-swallow-breathe pattern must be established to properly coordinate breathing and feeding. During the continuous-suck phase of feeding, neonates experience a decrease in respiratory rate, tidal volume, and minute ventilation, attributed to decreased CO_2 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.[11-13] It is unclear how E_{di} relates to the observed changes in respiration throughout sleep stages and during feeding, and what insight into neonatal respiration this measure may give. The purpose of this study was to do a small case series measuring E_{di} values in term neonates to establish preliminary values in this population and to determine how these values vary while awake and asleep and in pre-prandial, feeding, and post-prandial states.

Methods

Subjects

This was a prospective observational case series of neonates born at 37–42 weeks gestation. Inclusion criteria required that neonates were in room air and fed by breast or bottle during the study. The study protocol was approved by the institutional review board of The Toledo Children's Hospital.

Measurements

E_{di} was measured by electrodes embedded within a specialized nasogastric tube (Maquet, Solna, Sweden, 8 French, 50 cm) positioned at the level of the diaphragm. The nasogastric tube was connected to a Servo-i ventilator (Maquet, Solna, Sweden), and the E_{di} signal was recorded for the duration of the study. Data output included E_{di} peak, E_{di} min, and respiratory rate, all of which were stored in 1-min increments in the Servo-i 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 subject was observed for a continuous 4-hour period, resulting in 240 measures for each variable observed. Heart rate and S_{pO_2} were recorded from telemetry monitors every 15 min throughout the study.

QUICK LOOK

Current knowledge

Electrical activity of the diaphragm (E_{di}) is an esophageal measure of diaphragmatic electromyography. E_{di} measurements can be used to assesses the neural control of respiration, to measure the tonic activity of the diaphragm and the amplitude of electrical activity associated with inspiratory effort. Patient-ventilator interaction can also be evaluated.

What this paper contributes to our knowledge

Mean peak E_{di} was 11 ± 5 μV, and minimum E_{di} was 3 ± 2 μV in neonates. E_{di} was higher during wakefulness and lower post-prandial. The utility of E_{di} measurements in patient care remains to be determined.

Study Protocol

The nasogastric tube was placed in the stomach, and proper position was confirmed by on-line analysis on the Servo-i software. The nasogastric tube was adjusted so that in the "catheter positioning screen" the E_{di} signal, superimposed as a blue signal, was noted to occur on the middle 2 (out of 4) retrocardiac ECG tracings.[4,14-16] If the nasogastric tube varied from the correct position, the ventilator alerted the operator by an immediate screen message stating "check E_{di} catheter" position, as well as an alert stating the "E_{di} unreliable." Normal activity was not interrupted for the study; subjects were able to feed on demand and be handled by parents throughout the study period. Sleep and awake and feeding states were recorded by an observer. Feeding states were defined as 30 min pre-prandial feeding, and 30 min post-prandial.

Statistical Analysis

Population means, standard deviations, and ranges were calculated for the duration of the study. *t* tests were per-

Table. Edi Peak, Edi Min, Respiratory Rate, and Heart Rate, Overall and During Various Feeding and Activity States

	Edi Peak (μV)	Edi Min (μV)	Respiratory Rate (breaths/min)	Heart Rate (beats/min)
Total	11 ± 5	3 ± 2	53 ± 16	142 ± 13
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
Awake	16 ± 6†	5 ± 2†	53 ± 11	149 ± 11
Sleep	10 ± 4	3 ± 2	53 ± 17	141 ± 2

Data are presented as mean ± SD
* $P < .05$ compared to post-prandial.
† $P < .05$ compared to sleep.
Edi peak = peak electrical activity of the diaphragm
Edi min = minimum electrical activity of the diaphragm

formed to compare the population means between sleep states. Analysis of variance measures were performed to compare the population means for the feeding states. Statistical significance was defined as $P < .05$.

Results

Three neonates were enrolled in this case series; all happened to be female, gestational age 37–40 weeks, postnatal age at time of study 2–7 days, birth weight 3,000 ± 164 g. Thirty sets of parents were approached for participation in the study. The primary barrier to participation was parental concern regarding the risk of nasogastric tube placement in a term infant who otherwise would not have required a nasogastric tube.

Total study time was 720 min, consisting of 143 min awake and 577 min asleep. We analyzed 266 min of data for feeding state comparisons: 120 min pre-prandial, 43 min during feeds, and 103 min post-prandial. One feed ended 13 min before the end of the study period, causing that post-prandial period to be 17 min short.

E_{di} peak, E_{di} min, respiratory rate, and heart rate data are presented in the Table. E_{di} peak was higher while awake than during sleep. E_{di} peak was lower in the post-prandial state than in the pre-prandial and feeding states. E_{di} min was higher while awake than during sleep, but was not different among feeding states. Respiratory rate and heart rate were within normal limits for the study population. Respiratory rate was higher post-prandial than pre-prandial. All neonates were in room air and had oxygen saturation above 95% throughout the study.

Discussion

To our knowledge, this is the first case series of E_{di} values in any subjects who were non-ventilated and without respiratory disease at the time of the study. In the existing literature, E_{di} has been reported in arbitrary units and percentage change.[4,5,17,18] These measures were appropriate in prior studies, which evaluated intra-subject variations in E_{di}; however, the data within this study are presented in microvolts (μV), an absolute measure that allows for inter-subject comparison, as calculated by the Servo-i ventilator.

E_{di} peak was higher while the subjects were awake than during sleep, indicating generation of higher electrical amplitude to elicit bigger breaths while awake.[19] The larger tidal volume and increased minute ventilation may reflect the neonate's physiologic response to the increased metabolic requirements while awake and relatively active. E_{di} peak was lower in the post-prandial state than pre-prandial and feeding states. This may also be explained in part by the neonate's activity level and metabolic need 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 E_{di} peak observed.[5,19] In addition, it is possible that the increased abdominal contents and intra-abdominal pressure after the feed decrease the intrathoracic volume to a small degree, permitting only shallower breaths, associated with the lower E_{di} peak.[20] Exhalation is passive after feeding, and the diaphragm can be relatively "relaxed" since the chest wall is supported by the increased abdominal pressure that supports the rib cage and makes the diaphragm more efficient.[20] E_{di} min was lower while asleep than when awake; this indicates lower resting diaphragmatic muscle tone during sleep.

Of importance, we did not see any decrease or deterioration in the E_{di} signal during feeding, suggesting that there is no electrical interference from milk coating the esophagus or catheter. Although these neonates were feeding orally and ventilated patients are gavage fed, the implication of this observation is that the E_{di} signal maintains its reliability during feeding of a ventilated patient. It is unknown at this time if reflux around the catheter interferes with the integrity of the E_{di} signal.

There was no difference in respiratory rate or heart rate between sleep states, contrary to previous studies.[9] Analysis of sleep as only one state may have minimized the inherent heterogeneity between sleep stages and confounded our results. In future studies, electroencephalography may be utilized to differentiate between active sleep and quiet sleep and allow more precise analysis. Respiratory rate was higher in the post-prandial state than in the pre-prandial state. If the post-prandial increase in intra-abdominal pressure does in fact limit the tidal volume after a feed, as suggested above, it follows that respiratory rate would need to increase in order to maintain sufficient minute ventilation. Differences within the feeding cycle that have been observed in breath-by-breath analyses were not evident in this study, in which data were averaged over each minute.[21] Heart rate was unchanged among feedings states. Had heart rate been recorded continuously throughout the study, rather than in 15-min increments, we would anticipate that heart rate would be higher during the feed because of the increased effort associated with active feeding.

The predominant limitation in this case series was the small sample size, primarily related to the difficulty with recruitment. However, there were 4 hours of data, in 1 min increments, for a total of 240 data points per patient and 720 data points overall. This huge data set actually overpowered the data analysis and made small, clinically unimportant variations appear statistically significant. In addition, this was an observational study only, so there was no null hypothesis to prove or disprove. More patients would be needed before these data can be determined to be definitive for this patient population. Using electroencephalography to differentiate awake, active sleep, and quiet sleep may increase the accuracy of sleep stage comparisons and provide clearer delineation of the influence of sleep stage on E_{di} and neural respiratory control. Although it was not the primary measure in this study, continuous heart rate monitoring may improve future analyses.

Conclusions

Despite these limitations, this case series provides useful preliminary E_{di} values that may help guide ventilatory management in sick, intubated infants. The neural respiratory drive, represented by E_{di}, increases in patients with respiratory distress and varies depending on the amount of respiratory distress. On NAVA ventilation the E_{di} signal can be manipulated by the practitioner, depending on the amount of work the patient does versus the amount of work the ventilator does. The amount of ventilatory assist is controlled by a proportionality factor called the NAVA level, which can be adjusted by the practitioner. The higher the assist (high NAVA level), the more unloaded the patient and the lower the patient's respiratory drive (low E_{di}), and vice versa.[6] Therefore, there are no values for E_{di} for intubated patients that are reliable for comparison, as they can be manipulated at will by the practitioner. The goal is to provide enough ventilatory assist (pick the right NAVA level) to allow the patient to do the "normal" amount of work and allow the ventilator to do the remaining work. Providing a NAVA level to achieve "normal" patient E_{di} values (what the E_{di} would be in a healthy normal patient) would suggest that the patient is now adequately unloaded and on optimal ventilatory support. No such data currently exist to help the practitioner. These preliminary data may give the practitioner some guidance as to what E_{di} values to work toward in ventilated term neonates when titrating the NAVA level. In the future it would be beneficial to observe E_{di} 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.

REFERENCES

1. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med 2002;166(4):518-624.
2. Breatnach C, Conlon NP, Stack M, Healy M, O'Hare BP. A prospective crossover comparison of neurally adjusted ventilatory assist and pressure-support ventilation in a pediatric and neonatal intensive care unit population. Pediatr Crit Care Med 2010;11(1):7-11.
3. Beck J, Reilly M, Grasselli G, Mirabella L, Slutsky AS, Dunn MS, et al. Patient-ventilator interaction during neurally adjusted ventilatory assist in low birth weight infants. Pediatr Res 2009;65(6):663-668.
4. Luo YM, Moxham J, Polkey MI. Diaphragm electromyography using an oesophageal catheter: current concepts. Clin Sci (Lond) 2008; 115(8):233-244.
5. Sinderby C, Spahija J, Beck J. Changes in respiratory effort sensation over time are linked to the frequency content of diaphragm electrical activity. Am J Respir Crit Care Med 2001;163(4): 905-910.
6. Sinderby C, Spahija J, Beck J. Neurally-adjusted ventilatory assist. In: Slutsky AS, Brochard L, editors. Mechanical ventilation: update in intensive care medicine. Vincent JL, series editor. Berlin: Springer-Verlag; 2004:125-134.
7. Bengtsson JA, Edberg KE. Neurally adjusted ventilatory assist in children: an observational study. Pediatr Crit Care Med 2010;11(2): 253-257.
8. Mellott KG, Grap MJ, Munro CL, Sessler CN, Wetzel PA. Patient-ventilator dyssynchrony: clinical significance and implications for practice. Crit Care Nurse 2009;29(6):41-55.
9. Montgomery-Downs H, Thoman EB. Biological and behavioral correlates of quiet sleep respiration rates in infants. Physiol Behav 1998; 64(5):637-643.
10. Horemuzova E, Katz-Salamon M, Milerad J. Breathing patterns, oxygen and carbon dioxide levels in sleeping healthy infants during the first nine months after birth. Acta Paediatrica 2000;89(11):1284-1289.
11. Delaney AL, Arvedson JC. Development of swallowing and feeding: prenatal through first year of life. Dev Disabil Res Rev 2008;14(2): 105-117.
12. Miller MJ, Kiatchoosakun P. Relationship between respiratory control and feeding in the developing infant. Semin Neonatol 2004;9(3): 221-227.
13. Qureshi MA, Vice FL, Taciak VL, Bosma JF, Gewolb IH. Changes in rhythmic suckle feeding patterns in term infants in the first month of life. Dev Med Child Neurol 2002;44(1):34-39.
14. Beck J, Sinderby C, Lindström L, Grassino A. Influence of bipolar electrode positioning on measurements of humna crural diaphragm EMG. J Appl Physiol 1996;81(3):434-449.

15. Sinderby C, Beck J. Proportional assist ventilation and neurally adjusted ventilatory assist - better approaches to patient ventilator synchrony? Clin Chest Med 2008;29(2):329-342.
16. Barwing J, Ambold M, Linden N, Quintel M, Moerer O. Evaluation of the catheter positioning for neurally adjusted ventilatory assist. Intensive Care Med 2009;35(10):1809-1814.
17. Emeriaud G, Beck J, Tucci M, Lacroix J, Sinderby C. Diaphragm electrical activity during expiration in mechanically ventilated infants. Pediatr Res 2006;59(5):705-710.
18. Sinderby C, Beck J, Spahija J, de Marchie M, Lacroix J, Navalesi P, et al. Inspiratory muscle unloading by neurally adjusted ventilatory assist during maximal inspiratory efforts in healthy subjects. Chest 2007;131(3):711-717.
19. Beck J, Sinderby C, Lindström L, Grassino A. Effects of lung volume on daiphragm EMG signal strength during voluntary contractions. J Appl Physiol 1998;85(3):1123-1134.
20. Heldt GP. The effect of gavage feeding on the mechanics of the lung, chest wall, and diaphragm of preterm infants. Pediatr Res 1988; 24(1):55-58.
21. Cohen M, Brown DR, Myers MM. Cardiorespiratory measures before and after feeding challenge in term infants are related to birth weight. Acta Paediatrica 2009;98(7):1183-1188.