

Characterization of Neural Breathing Pattern in Spontaneously Breathing Preterm Infants

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ABSTRACT: The aim was to characterize the neural breathing pattern in nonintubated preterm infants. The diaphragm electrical activity (EAdi) and heart rate were simultaneously measured repeatedly for 1 h over several days using a modified feeding tube equipped with miniaturized sensors. The EAdi waveform was quantified for phasic and tonic activity, neural timings, and prevalence of recurring patterns, including central apnea. Ten infants with mean age 7 d (range, 3–13 d) were studied. Their birth weight was 1512 g (1158–1800 g) and GA at birth 31 wk (28–36 wk). Neural inspiratory and expiratory times were 278 ms (195–450 ms) and 867 ms (668–1436 ms) and correlated with GA ($p < 0.001$). Tonic EAdi represented 29.5% of phasic EAdi (16–40%) and was related to GA ($r = 0.61$, $p < 0.001$). For the group, 68% of the time was regular phasic breathing (without tonic activity) and 29% of the time with elevated tonic activity. Central apneas >5 s occurred on average 10 times per hour (2–29). Heart rate reductions were correlated to central apnea duration. In conclusion, esophageal recordings of the EAdi waveform demonstrate that neural breathing pattern is variable, with regards to timing, amplitude, and pattern with a distinct amount of tonic diaphragm activity. (*Pediatr Res* 70: 607–613, 2011)

Neonatal respiration has been described as being variable (1) with spontaneous changes in pattern between eupnea, apnea (2), sigh (3), and an irregular breathing pattern that is sometimes referred to as “periodic breathing” (4,5). Measurements to characterize breathing patterns vary between investigators and have yet to be standardized. Most have focused on the final mechanical output at the airway, such as tidal volume or flow (6), or chest wall displacement by respiratory inductance plethysmography (7). Considering the immature development of the respiratory muscles and the

chest wall in preterms and the breath-to-breath variability in respiratory system compliance and resistance (8), these final “mechanical” signals may not reflect the true neural respiratory center output. In addition, standard mechanical measurements may not necessarily be able to discriminate between obstructive and true central apneas.

The neural signals for breathing can be inferred by measurements of the electrical activity of the diaphragm (EAdi) (9–11). A validated and standardized method for measuring EAdi signals has been described (12) in infants (13–15) and involves the use of microsensors placed on a conventional naso/orogastric feeding tube, thereby imposing no additional level of invasiveness on preterms who require tube feeding. Esophageal measurement of the EAdi allows assessment of neural respiratory pattern without requiring airway or abdominal sensors. The EAdi waveform provides information about the “phasic” (tidal) inspiratory effort made to overcome respiratory load. As well, it can quantify the amount of diaphragm activity present during end expiration, the so-called “tonic EAdi” (14). The tonic EAdi is believed to be involved in the maintenance of end-expiratory lung volume (EELV) (16), as studied in intubated infants (14) and rabbits with acute lung injury (17). An absent EAdi signal (*i.e.* a flat EAdi waveform) is an indicator of central apnea. In addition, the ECG can be measured with the same microsensors, allowing changes in heart rate to be monitored simultaneously with the EAdi.

The aim of this study was to characterize the neural breathing patterns in nonintubated preterm infants. Specifically, the aims were to 1) quantify the magnitude and prevalence of phasic and tonic EAdi 2) evaluate the relationship between central apneas and changes in heart rate, and 3) investigate the neural breathing strategies adopted before and after a central

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Drs. Beck and Sinderby have made inventions related to neural control of mechanical ventilation that are patented. The license for these patents belongs to Maquet Critical Care. Future commercial uses of this technology may provide financial benefit to Drs. Beck and Sinderby through royalties. Drs. Beck and Sinderby each own 50% of Neurovent Research Inc (NVR). NVR is a research and development company that builds the equipment and catheters for research studies. NVR has a consulting agreement with Maquet Critical Care. A. Slutsky is a paid consultant to Maquet Critical Care.

Abbreviations: CV, coefficient of variation; **EAdi**, electrical activity of the diaphragm; **EAdi_{phasic}**, using breath by breath analysis, the peak of the inspiratory EAdi waveform; **EAdi_{tonic}**, using breath by breath analysis, the EAdi value at end-exhalation; **EAdi_{max}**, using 5-sec epochs method, the maximum EAdi value; **EAdi_{min}**, using 5-sec epochs method, the minimum EAdi value; **EELV**, end-expiratory lung volume; **EMG**, electromyogram; **Nrr**, using breath-by-breath analysis, neural respiratory rate; **Nte**, using breath-by-breath analysis, neural expiratory time; **Nti**, using breath-by-breath analysis, neural inspiratory time; **Ntt**, Neural total breath time calculated as Nti + Nte

apnea. We anticipated that the tonic EAdi would be elevated in preterm infants, because it may be one mechanism to prevent derecruitment of the lung in the face of alveolar instability and increased chest wall compliance.

METHODS

The protocol was approved by the Research and Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Canada, and written informed consent was obtained from a parent or guardian according to the guidelines of Sunnybrook Health Sciences Centre.

Infants. Infants were eligible if they were born premature (<36 wk) with a birth weight between 1000 and 2000 g. Infants were eligible as long as they were <28 d post natal age and >1000 g at the time of inclusion. Exclusion criteria: pneumothorax, neuromuscular or bleeding disorders, cardiovascular instability, congenital anomaly of the cardiorespiratory system, muscle relaxants or narcotics, phrenic nerve damage/diaphragm paralysis, or esophageal perforation.

Measurements. EAdi was obtained using an array of nine miniaturized electrodes (spaced 6 mm apart) mounted on a conventional (5.5 F) feeding tube (Neurovent Research, Inc., Toronto, Canada) and positioned so that the array would be in the lower esophagus at the level of the diaphragm. EAdi signals were acquired by computer and displayed as a waveform throughout the study (Fig. 1). Oxygen saturation was intermittently noted from the displayed monitor.

Experimental protocol. The day after obtaining consent, the study catheter was inserted *via* the nose or mouth and passed into the esophagus with the tip advancing into the stomach. The insertion route (oral or nasal) was decided by

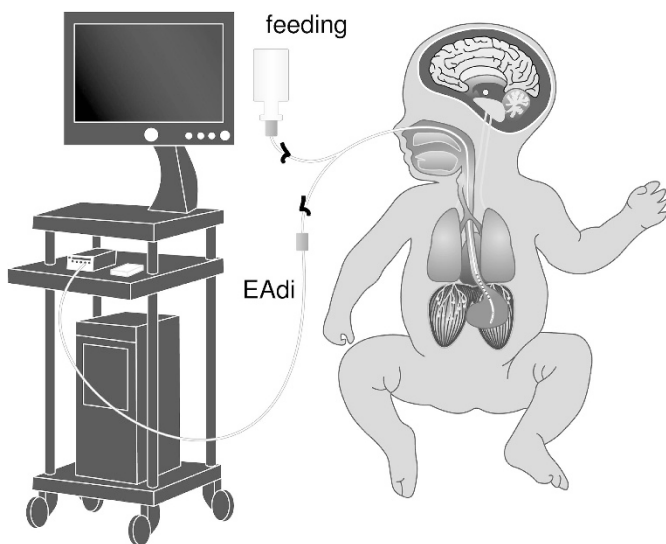


Figure 1. Experimental set-up: a modified nasal or orogastric feeding tube for feeding and measuring EAdi was inserted and connected to a computer for data acquisition.

the clinical team (Table 1). The array was positioned at the level of the crural diaphragm (gastroesophageal junction) with the help of on-line feedback from the EAdi and ECG waveforms (18). The catheter was fixed with tape, and the position of the catheter was noted. The EAdi was recorded for 60 min (Day 1 AM). Repeat 60-min measurements were made at 12, 24, 48, and 72 h after the initial placement of the catheter. In between, the catheter remained *in situ* and was used as an ordinary feeding tube.

Signal processing. EAdi signals were processed according to the American Thoracic Society recommendations (12) and displayed as a waveform (Fig. 2) (19–21).

Analysis. Analysis was performed off-line.

Breath-by-breath analysis (on 1 h of data). Breath by breath analysis was performed on 1 h of data from each infant. Three time cursors were placed for each breath on the displayed EAdi waveform (14,15): 1) onset of neural inspiratory signal, 2) peak of EAdi, and 3) onset of next neural inspiratory signal (Fig. 2).

The time period from onset to peak of EAdi was used to calculate the neural inspiratory time (Nti). The peak of the inspiratory EAdi waveform using this method was called the phasic EAdi (EAdi_{phasic}). The period from peak EAdi to the onset of the next breath was identified as the neural expiration time (Nte). The EAdi value at the end of neural exhalation was called the tonic EAdi (EAdi_{tonic}). Neural total breath time (Ntt) was calculated as Nti + Nte. Neural respiratory rate (Nrr) was calculated as 60/Ntt.

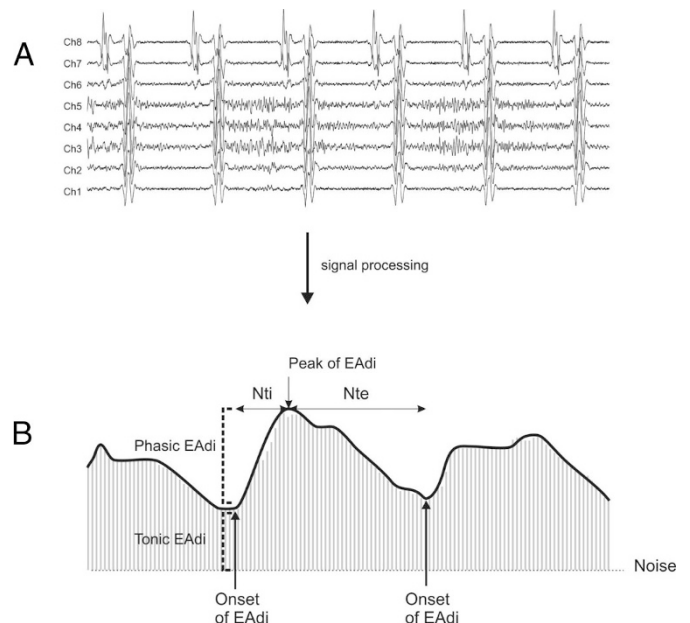


Figure 2. Breath-by-breath analysis method: (A) raw signals from all eight electrode pairs and (B) processed EAdi waveform. Cursors were manually placed at the onset, peak, and subsequent onset of the processed EAdi waveform for calculation of neural timings, and signal strength.

Table 1. Patient characteristics

Subject	Sex	Diagnosis	GA at birth (wk)	Birth weight (g)	Age at study (d)	Weight d 1 (g)	Caffeine d 1? (Y/N)	Total hours studied	Catheter (oral/nasal)
1	M	Hypoglycemia	36	1800	3	1778	N	4	Nasal
2	M	RDS, Apnea of prematurity	31	1684	11	1500	Y	5	Nasal
3	M	RDS mild, Prematurity	31	1634	11	1450	Y	5	Nasal
4	M	RDS	28	1486	11	1386	Y	5	Nasal
5	M	RDS	30	1158	5	1092	Y	5	Nasal
6	M	RDS	30	1736	6	1684	Y	5	Oral
7	M	RDS	33	1760	7	1602	N	5	Oral
8	M	RDS	31	1300	13	1334	N	3	Nasal
9	F	Apnea of prematurity	30	1365	5	1165	Y	4	Nasal
10	F	Apnea of prematurity	30	1205	6	1005	Y	5	Nasal
Mean			31	1513	8	1400		4.6	
SD			2	242	3	255		0.7	

The EAdi time product (a surrogate measurement of diaphragmatic energy expenditure) was calculated as follows: $((EAdi_{\text{phasic}} \times Nti) + (EAdi_{\text{tonic}} \times Nte)) \times Nrr$.

Breaths for which Nte exceeded 5 s were considered to be central apneas (15) and hence were not included in this analysis. For each condition, an average of each variable was calculated.

Five-second epochs (analyzed for all hours of data). The repeated 1-h periods of data were divided into 5-s epochs. The lowest ($EAdi_{\text{min}_5}$) and highest ($EAdi_{\text{max}_5}$) were identified for every epoch (Fig. 3).

Central apnea (all hours of data). Central apneas were defined as periods where the EAdi was a flat tracing for more than 5 s. Each file was visually displayed, and time cursors were placed at the beginning and at the end of each apnea. Apneas were classified by their duration (5–10 s, 10–15 s, and >15 s). For each central apnea, heart rate was calculated ($60/(\text{time interval between two ECG peaks})$), just before the apnea and at the end of the apnea.

The noise level of the signal was obtained during all periods of central apnea that were >5 s and the lowest levels during each 1 h period were considered to be the noise level for that recording period. The lowest noise level was subtracted from all measurements of EAdi magnitudes ($EAdi_{\text{phasic}}$, $EAdi_{\text{tonic}}$, $EAdi_{\text{max}_5}$, and $EAdi_{\text{min}_5}$).

Classification and prevalence of EAdi patterns (all hours of data). Repeating patterns in the EAdi signal could be observed during acquisition of the data at the bedside (Fig. 4). To classify these patterns in off-line analysis, seven types of patterns were predefined. Customized software was developed to facilitate classification based on a visual display of 30-s epochs of the EAdi waveform, with guidelines about the baseline noise level and timings. The investigator performing the analysis scrolled through the 30-s epoch screens and tagged the different breathing patterns according to type 1–type 7, as defined below:

Type 1: central apnea (defined as the signal remaining at the noise level for >5 s).

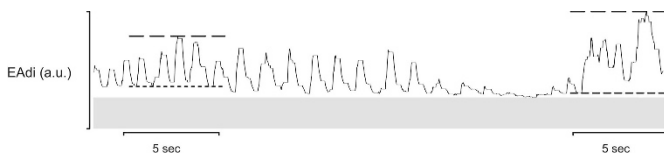


Figure 3. Five-second epoch analysis method: data were divided into 5-s epochs, and a minimum EAdi, short dashed lines ($EAdi_{\text{min}_5}$), and maximum EAdi, long dashed lines ($EAdi_{\text{max}_5}$), were identified. The noise level is indicated by the gray horizontal bar.

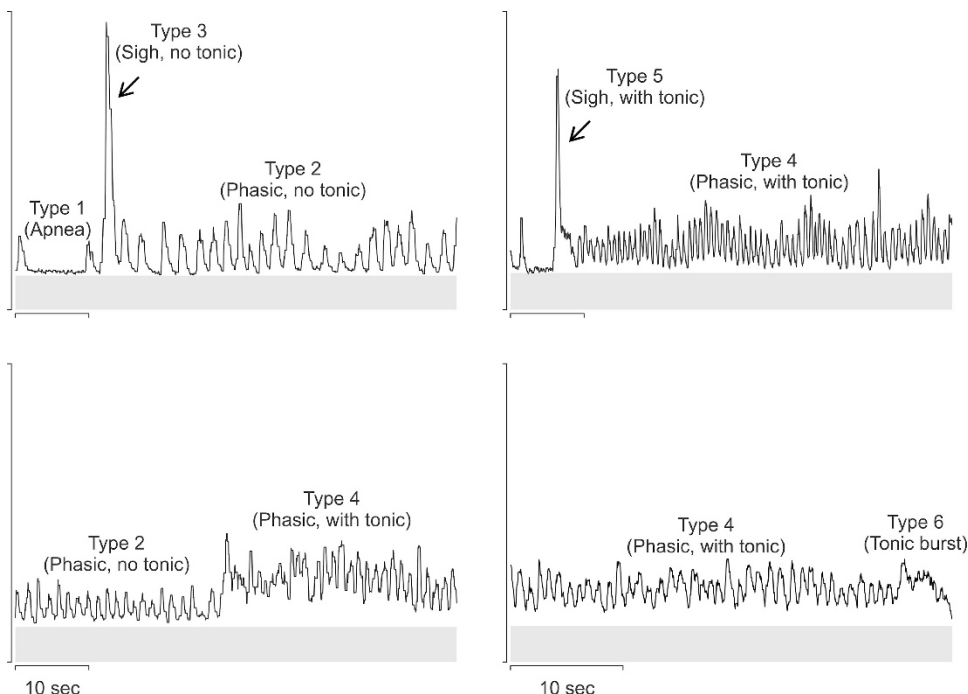


Figure 4. Representative tracings of the different neural breathing patterns on the same day: each panel demonstrates the EAdi waveform obtained in one subject on the same recording day, and demonstrates examples of the different breathing pattern types (1–7, see Methods).

Type 2: regular phasic breathing returning to baseline: phasic breathing with baseline at noise level (*i.e.* without tonic activity) and all breaths with $Nti < 1$ s.

Type 3: “sigh” returning to baseline: any single neural inspiration with $Nti > 1$ s, with subsequent baseline at noise level.

Type 4: regular phasic breathing with tonic activity: phasic breathing with baseline above 20% of noise level (*i.e.* with tonic activity) and breaths <1 s duration (*i.e.* $Nti < 1$ s).

Type 5: “sigh” not returning to baseline. Any single neural inspiration with $Nti > 1$ s with subsequent return to a level of tonic activity (*i.e.* baseline above 20% of noise level).

Type 6: tonic bursts: maintained elevated baseline (>20% of noise level) without any phasic activity.

Type 7: unidentifiable (breathing pattern that does not fall into types 1–6).

After the different time periods were tagged for type of pattern, in each infant, a sum of the time spent in each pattern was calculated and then divided by the total time of recorded data. This yielded a percentage spent within each type of breathing pattern.

Statistical analysis. Statistical analysis was performed with Sigstat 3.2 (Jandel Scientific, San Rafael, CA). Descriptive statistics were used to describe the neural breathing pattern (breath-by-breath analysis on 1-h data). Repeated measures ANOVA was used to calculate differences between days for $EAdi_{\text{max}_5}$, $EAdi_{\text{min}_5}$, and noise obtained with the 5-s epoch technique and for calculating differences in patterns on different days.

RESULTS

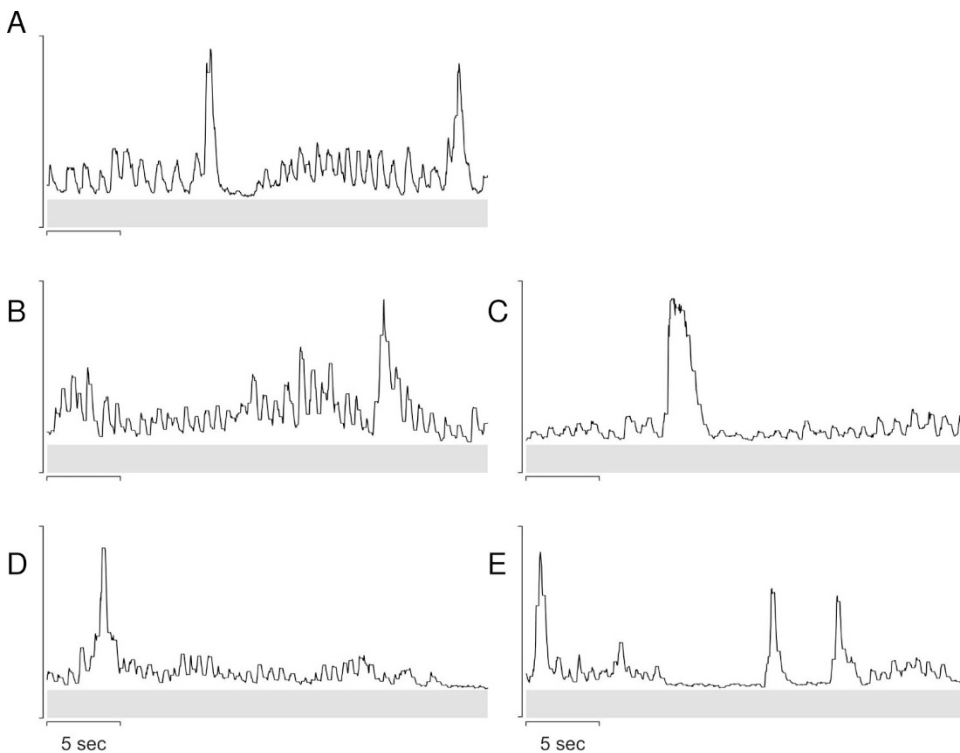
The characteristics of the infants are presented in Table 1. Ten infants (two female) were studied. One infant was on nasal continuous positive airway pressure (CPAP) for the first hour. The other infants were not receiving any respiratory support. A total of 46-h data were analyzed (average 4.6 ± 2.1 h per infant).

Neural timings. Each hour of collected data produced an average of 3169 (range, 2013–3845) breaths for analysis. Nti , Nte , Nrr , and the EAdi-time product are reported for each infant (Table 2). Nti was correlated to Nte ($r = 0.94$, $p < 0.001$). Nrr , Nti , and Nte all correlated significantly with GA (for Nrr : $r = 0.90$, $p < 0.001$; for Nti $r = 0.79$, $p < 0.001$; for Nte $r = 0.92$, $p < 0.001$).

Table 2. Breath-by-breath analysis of the EAdi waveform for 1 h of data

Subject	EAdi _{phasic} (a.u.)	EAdi _{tonic} (a.u.)	Nti (ms)	Nte (ms)	Nti/Ntt	Nrr	EAdi-time product (a.u. × s/min)	Number of breaths analyzed
1	21.3	5	450	1436	0.24	43	737	2013
2	11.7	6.1	278	910	0.24	69	644	3071
3	17.5	10.1	261	772	0.26	73	1291	3354
4	22.8	15.6	260	668	0.28	79	1329	3834
5	29.5	5.8	281	898	0.25	81	754	2900
6	19.5	6.8	240	756	0.25	76	985	3471
7	13.1	7.3	294	1006	0.24	71	826	2418
8	16.3	5.1	194	707	0.22	75	686	3846
9	27.1	11.4	268	759	0.26	82	1376	3410
10	27.9	13.7	250	759	0.25	83	1695	3372
Mean	20.7	8.7	278	867	0.25	73	1032	3169
SD	6.2	3.8	67	225	0.02	12	364	588

a.u., arbitrary units.

**Figure 5.** Representative tracings of the different neural breathing patterns on different days: each panel demonstrates the EAdi waveform obtained in one subject on the different recording days. A, Day 1 AM; B, Day 1 PM; C, Day 2 AM; D, Day 3 AM; E, Day 4 AM.

Strength of EAdi signal. The amount of EAdi_{tonic} represented on average 29.5% of EAdi_{phasic} (range, 16–40%). The magnitude of EAdi_{tonic} was significantly related to GA ($r = 0.61$, $p < 0.001$) but was not related to Nrr ($p = 0.128$). Using the breath-by-breath analysis, the within-subject variability for the magnitude of EAdi_{phasic} and EAdi_{tonic} were high [mean coefficient of variation (CV) for EAdi_{phasic} 125%, CV for EAdi_{tonic} 89%]. The between subject variability was highest for EAdi_{tonic} (CV = 44%) and lowest for Nti/Ntt (CV = 6%).

EAdi_{phasic} calculated breath-by-breath correlated well with EAdimax₅ obtained with the 5-s epoch method ($r = 0.94$, $p < 0.001$). Similarly, EAdi_{tonic} calculated breath-by-breath correlated well with EAdimin₅ ($r = 0.91$, $p < 0.001$). There were no significant differences in EAdimax₅ or EAdimin₅ over days. Within a subject, EAdimax₅ and EAdimin₅ were variable over the 1 h of recording (CV EAdimax₅ = 95%; CV EAdimin₅ = 94%) and between days (mean variability be-

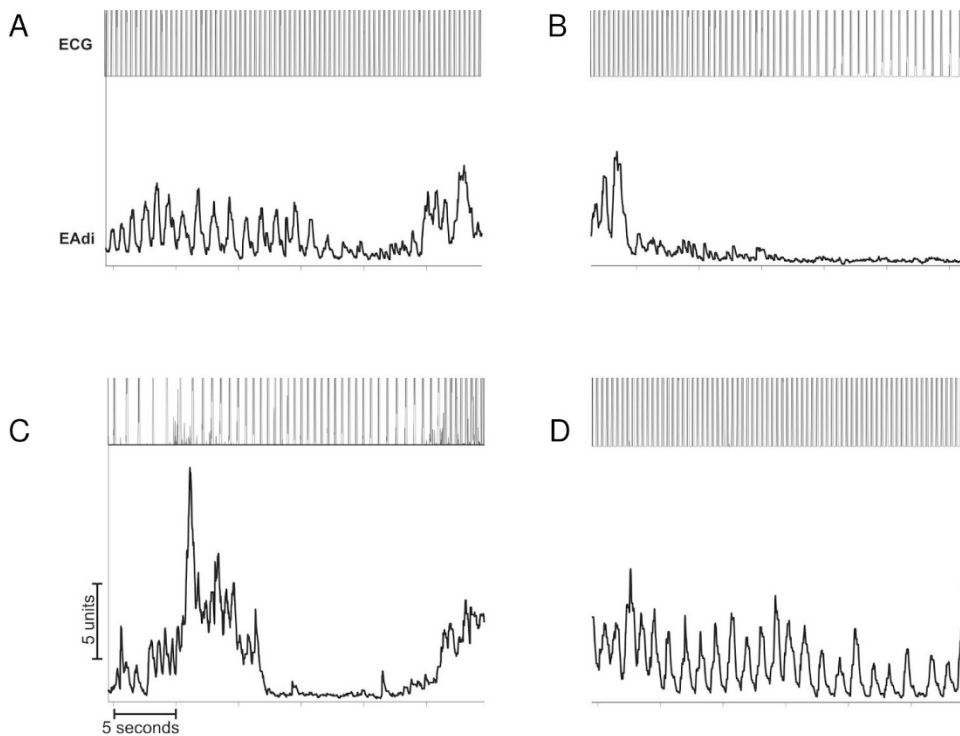
tween days, CV EAdimax₅ = 24%; CV EAdimin₅ = 26%). The between subject variability was 31% for EAdimax₅ and 15% for EAdimin₅.

The EAdi signal was stable over the duration of the study period (4 d). The absolute noise level was constant between study days within a subject (mean variability in noise level day-to-day, CV = 1.6%) and variability was low between subjects (CV = 7.9%). Figure 5 demonstrates in one subject examples of the EAdi signal recorded for 5 h over 4 sequential days.

The prevalence of breathing pattern types (types 1–7) for each infant was analyzed for every hour of recorded data ($n = 46$ h) and is presented in Table 3. For the group average, 68% of the time was spent with a relatively “normal” breathing pattern (regular phasic breathing without tonic activity), and 29% of the time breathing was phasic with elevated tonic activity.

Table 3. Percentage of time spent with each breathing pattern type

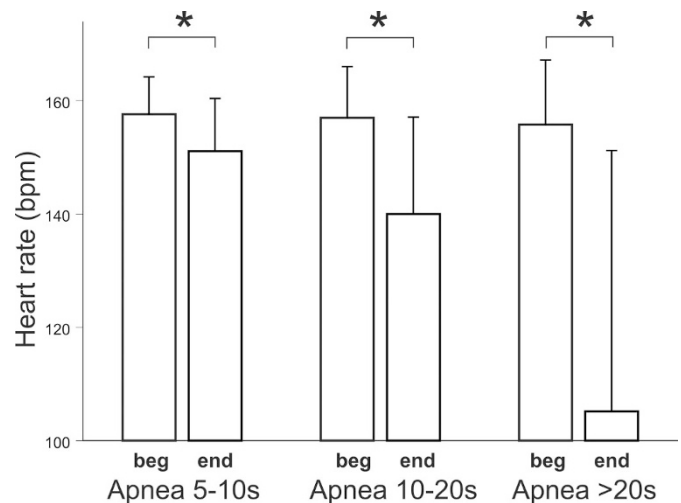
Subject	Type 1 Apnea	Type 2 Phasic no tonic	Type 3 Sigh no tonic	Type 4 Phasic with tonic	Type 5 Sigh with tonic	Type 6 Tonic "bursts"	Type 7 Unidentifiable
1	0.97	83.05	1.38	13.63	0.69	0.18	0.11
2	2.07	68.41	0.64	27.30	1.17	0.23	0.19
3	1.17	68.79	0.63	28.52	0.70	0.08	0.10
4	1.39	65.48	1.08	30.96	0.95	0.07	0.03
5	0.91	79.23	1.81	16.29	1.52	0.12	0.12
6	0.40	70.88	1.22	26.30	0.91	0.11	0.17
7	0.20	77.43	1.09	20.26	0.85	0.07	0.10
8	0.42	71.29	0.41	27.75	0.11	0.03	0.00
9	0.13	44.05	0.68	53.58	1.45	0.02	0.09
10	0.19	54.15	0.67	44.36	0.55	0.08	0.00
Mean	0.79	68.28	0.96	28.90	0.89	0.10	0.09
SD	0.63	11.70	0.43	12.16	0.42	0.06	0.06
Minimum	0.13	44.05	0.41	13.63	0.11	0.02	0.00
Maximum	2.07	83.05	1.81	53.58	1.52	0.23	0.19

**Figure 6.** Representative tracings of EAdi and ECG in one subject: time sequence is Figure 6A to D. Each panel demonstrates the EAdi waveform (bottom in each panel) and the ECG. (A) = 30 s before the apnea, heart rate was 153, and saturation 98%. (B) = slowing in heart rate at the same time as the central apnea. (C) = Heart rate 66, saturation 82%, and the nurse aroused the baby (D). Three minutes later, HR = heart rate 159 and saturation = 99%.

Central apnea and heart rate. Despite representing a small percentage of the hour, the maximum number of type 1 (central apnea >5 s) events occurred on average 10 times per hour (range, 2–29 per hour). Figure 6 demonstrates in one infant the EAdi waveforms (bottom tracings in each panel) with the simultaneous measurement of ECG. The slowing of the heart rate can be observed in Figure 6B during the apneic period. For the group of infants (all hours), there was a significant reduction in heart rate for central apneas 5–10 s in duration, which became stronger for central apneas 10–20 s in duration and for central apneas >20 s duration (Fig. 7).

Sighs. The maximum number of sighs (types 3 and 5 combined) ranged between 12 and 59/h, among infants.

Neural breathing pattern pre- and postapnea. Of all the central apneas identified ($n = 188$), 31.3% were followed by type 3, 4, 5, or 6 (sighs or patterns with tonic EAdi) within 10 s of resolution of the apnea. Eighty-six percent of the central apneas were preceded by type 2 (regular phasic breath-

**Figure 7.** Relationship between central apnea duration and heart rate: group data demonstrating that longer apneas are associated with greater reductions in heart rate. *Statistical significance from beginning to end of apnea.

ing without tonic). Only nine of all the central apneas detected were preceded by a type 3 or 5 (sigh) (4.8%). Infants receiving caffeine ($n = 7$) had more central apneas (>5 s) than those that did not receive caffeine (13 *versus* 6 per hour) but had more type 3 and 5 (sighs) (38 *versus* 24 per hour). The number of central apneas did not correlate with the EAdi-time product.

DISCUSSION

In the present study, we present a new method for simultaneous monitoring of neural respiratory drive and heart rate using a standardized and relatively noninvasive method. The EAdi signal was found to be stable over 4 d of recording. In this group of preterm infants, the EAdi signal was characterized as variable, with regards to timing, amplitude, and pattern with, in many cases, a distinct amount of tonic diaphragm activity. Pattern recognition analysis revealed that more than one-third of the neural breathing pattern is not “regular” phasic breathing. Central apneas >5 s were frequent and were associated with reductions in heart rate that were greater for longer respiratory pauses. Either “sighs” and/or tonic activity followed one-third of these apneic events.

Phasic and tonic EAdi. The output from the respiratory centers is determined through a complex set of functions including responses to inputs from many receptors. The Hering-Breuer (HB) reflexes play a key role in the control of breathing in infants (22–24). The HB reflexes are vagally mediated mechanoreflexes, and respond to inflation beyond a critical volume, and deflation below EELV (25).

In the present study, the amplitude and prevalence of tonic activity of the diaphragm was found to be elevated compared with adults, whose neural breathing pattern can be characterized by regular phasic breathing with a return of the EAdi waveform to baseline between breaths (26). The tonic EAdi is believed by several authors to be one of the mechanisms to prevent lung derecruitment (14,16,27,28). D’Angelo *et al.* (11) showed with rib cage compression that there is an instantaneous augmentation in the postinspiratory activity in all regions of the rabbit diaphragm. Allo *et al.* (17) and Emeriaud (14) demonstrated that removing positive end-expiratory pressure (PEEP) increases tonic EAdi. It is thought that tonic EAdi “brakes” against the passive recoil of the lung and chest wall (16,28).

In the face of alveolar instability and low compliance, it could be hypothesized that those infants with lower GA would demonstrate higher levels of tonic EAdi to maintain EELV. Several other mechanisms may play a role in maintaining EELV, such as increased respiratory rate (14,16,28), which correlated with GA in the present study. The braking of expiratory flow with laryngeal muscles also has a role in preventing derecruitment (28,29), however, this was not evaluated in the present study. We observed up to 59 large neural inspirations per hour; these “sighs” have been identified in preterm infants (30) and are hypothesized to be a mechanism to recruit the lung, especially after an apnea (3). Whether or not the type 3 and type 5 patterns occurred to recruit the lung—or if they were inspiratory efforts during obstructive apneas—could not be determined. We can only speculate that these neural breathing patterns (tonic EAdi and sighs) were

adopted to regulate EELV, because no direct measurements of lung volume were performed.

Central apneas. Premature infants often demonstrate recurring apneas, which is more frequent in infants of lower GA and birth weight (2,31). In the present study, we did not observe this relationship perhaps because of the lack of distinction made between central and obstructive apneas, both types being associated with absence of airflow. In the present study, central apneas were evaluated and defined as no diaphragm activity >5 s. We are confident that the loss of EAdi signal was not due to malfunctioning of the electrodes because the ECG could still be observed.

One possibility to explain the occurrence of central apnea is that the diaphragm may be overexerted by the continuous and elevated activity of the diaphragm. In this case, central apneas could actually be considered as a strategy for diaphragmatic rest. However, our results of no relationship between the EAdi-time product and the number of central apneas contradict this hypothesis.

It is well known that apnea can lead to oxygen desaturation and bradycardia (32,33). If prolonged, the apnea and bradycardia episodes can have a negative impact on cerebral circulation (34). These episodes are usually detected when the heart rate or saturation decline to a level where they trigger alarms, alerting personnel about the apneic event. The present study may provide a method for detecting milder forms of apnea before the occurrence of detrimental physiological changes.

Techniques for monitoring in the NICU. In intubated and nonintubated preterm infants, monitoring is crucial for early detection of clinical instability and response to therapy. If the goal is to monitor respiratory drive, in the nonintubated preterm infant, breathing pattern can be monitored noninvasively with the use of pneumotachs, which provide information about tidal volume and flow; however, this instrument may in itself affect the breathing pattern (35) because it imposes an added dead space. Recently, Te Pas *et al.* (6) examined flow patterns using a mask and hot wire anemometer in preterm and term infants immediately after birth and needed to apply a bias flow to compensate for the added dead space. Displacement of the chest wall using Respiratory Impedance Plethysmography has also been used for noninvasive measurement of breathing pattern but requires calibration to a measured tidal volume, and loses accuracy during ventilator assistance and over time (7).

Surface electromyography (EMG) of the respiratory muscles has been used in several physiological studies in infants (5,23,24,28,29). Surface EMG recordings are susceptible to changes in muscle-to-electrode distance (12) and cross-talk from other muscles (12), *e.g.* postural muscles. In light of the fact that premature infants are often not receiving sedation and remain active, surface EMG recordings of EAdi may not represent respiratory activity reliably.

In contrast to surface EMG recordings, the signal processing of the esophageal EAdi “tracks” the movement of the diaphragm along the array (19) every 16 ms and eliminates common mode signals such as cross-talk signals from postural muscles. This is because of the “double-subtraction” signal processing technique (19). Disturbances induced by swallow-

ing are detected and filtered. The method used in the present study does not interfere with breathing pattern, and does not require calibration, as would measurements of airway flow. As well, the signal properties were found to be stable over 4 d, as demonstrated by the stable noise level. The EAdi measured in the esophagus is thus a measurement of the crural (hiatal) diaphragm activity. Although it has been recognized that the costal and crural behave as separate muscles (36), the crural diaphragm EMG correlates to phrenic nerve activity (10), and to global diaphragm activity (11,20,21,37).

Critique. The present study was designed to characterize neural breathing pattern in preterm neonates under general and routine clinical conditions by using a new method to capture EAdi. Evaluating the effectiveness of this technique in larger, relatively stable infants was felt to be prudent before testing in smaller neonates and/or those who have significant respiratory disease. Interventions such as feeding, caffeine administration, sleep/behavioral state, and gross body movements—many of which are known to influence apnea and tonic EAdi (36,38)—were not controlled for. This may explain the high intrasubject variability in neural breathing parameters observed.

In the present study, it was only possible to note the oxygen saturation intermittently. Had a simultaneous recording of oxygen saturation been possible, the interplay between central apnea, bradycardia, and desaturation could have been further examined. As well, because of the lack of simultaneous and continuous recordings of oxygen saturation, we could not investigate the possible role between hypoxia and tonic EAdi, a link previously described in animals (39).

Besides measurements of oxygen saturation, it is important to recognize the influence of arterial carbon dioxide (39–41) on diaphragm activity and upper airway muscle activities. In our institution, transcutaneous carbon dioxide measurements and arterial blood gases are not routinely performed in non-intubated infants, and we cannot comment about the role of carbon dioxide in our findings.

This study demonstrates that the neural breathing pattern in preterm infants is more complex than previously believed. Thirty percent of the time is spent breathing with breathing pattern consisting of a continuously active diaphragm. Monitoring the EAdi provides insight into the neural respiratory pattern of premature infants and may be useful in the assessment of therapeutic interventions to treat apnea.

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