Original Paper

Neonatology

Neonatology 2018;113:140–145
DOI: 10.1159/000484081

Received: June 23, 2017
Accepted after revision: September 20, 2017
Published online: December 1, 2017

Classifying Apnea of Prematurity by Transcutaneous Electromyography of the Diaphragm

Juliette V. Kraaijenga Gerard J. Hutten Cornelia G. de Waal Frans H. de Jongh Wes Onland Anton H. van Kaam

Department of Neonatology, Emma Children's Hospital, Academic Medical Center, Amsterdam, The Netherlands

Keywords
Obstructive apnea · Central apnea · Monitoring · Chest impedance · Electromyography

Abstract
Background: Treatment of apnea is highly dependent on the type of apnea. Chest impedance (CI) has inaccuracies in monitoring respiration, which compromises accurate apnea classification. Electrical activity of the diaphragm measured by transcutaneous electromyography (EMG) is feasible in preterm infants and might improve the accuracy of apnea classification. ***Objectives:*** To compare the accuracy of apnea classification based on diaphragmatic EMG (dEMG) and CI tracings in preterm infants. ***Methods:*** Fifteen cases of central apnea, 5 of obstructive apnea, and 10 of mixed apnea were selected from recordings containing synchronized continuous tracings of respiratory inductive plethysmography (RIP), airway flow, heart rate (HR), oxygen saturation (SpO_2), and breathing activity measured by dEMG and CI. Twenty-two assessors (neonatologists, pediatricians-in-training, and nurses) classified each apnea twice; once based on dEMG, HR, and SpO_2 tracings, and once based on CI, HR, and SpO_2. The assessors were blinded to the type of respiratory tracing (dEMG or CI) and to the RIP and flow tracings. ***Results:*** In total 1,320 assessments were performed, and in 71.1% the apnea was classified correctly. Subgroup analysis based on respiratory tracing showed that 74.8% of the dEMG tracings were classified correctly compared to 67.3% of the CI tracings ($p < 0.001$). This improved apnea classification based on dEMG was present for central (86.7 vs. 80.3%, $p < 0.02$) and obstructive (56.4 vs. 32.7%, $p < 0.001$) apnea. The improved apnea classification based on dEMG tracing was independent of the type of assessor. ***Conclusion:*** Transcutaneous dEMG improves the accuracy of apnea classification when compared to CI in preterm infants, making this technique a promising candidate for future monitoring systems.

Introduction

Impaired control of breathing resulting in apnea is common in preterm infants with a gestational age (GA) of <30 weeks [1]. Apnea can be classified into 3 groups: (1) central apnea, i.e., a cease in airflow due to absence of respiratory effort; (2) obstructive apnea, i.e., a cease in airflow caused by upper-airway obstruction; and (3) mixed apnea, i.e., a cease in airflow caused by a combination of both the above [1, 2]. Central and mixed apneas

KARGER

E-Mail karger@karger.com
www.karger.com/neo

Juliette V. Kraaijenga
Department of Neonatology (room H3–146)
Emma Children's Hospital, Academic Medical Center
PO Box 22660, NL–1100 DD Amsterdam (The Netherlands)
E-Mail juliettekraaijenga@gmail.com

account for most apneic episodes [3]. The frequency of apnea is inversely proportional to the GA, and in almost all infants apnea is accompanied by hypoxemia and bradycardia [1, 4].

Hypoxemic episodes, especially if prolonged, are associated with an increased risk of adverse neurodevelopmental outcome in preterm infants [5]. Prompt and adequate treatment of apnea is therefore of the utmost importance. However, the optimal treatment of apnea is highly dependent on the type of apnea, so correct classification based on accurate cardiorespiratory monitoring is essential. For instance, central apnea is probably best treated with caffeine, while nasal continuous positive airway pressure (nCPAP) might be a better choice for obstructive apnea, as it splints the upper airway [6, 7].

Chest impedance (CI) is the current standard for bedside cardiorespiratory monitoring of preterm infants. It measures changes in electrical impedance caused by changes in lung aeration and chest wall movement [8]. CI provides continuous monitoring of the heart rate (HR), respiratory rate (RR), and breathing pattern; the last of these is used for the detection and classification of apnea. However, CI has important limitations, such as inaccuracies in monitoring respiration due to cardiac interference and non-breathing-related chest wall movement. This may compromise the accurate detection and classification of apnea [8–11].

Measuring electrical activity of the diaphragm might be a more direct and accurate method to monitor respiration in newborn infants. We recently showed that transcutaneous electromyography (EMG) of the diaphragm (dEMG) is feasible in preterm infants and provides accurate data on HR and RR, comparable to CI [12]. No study has investigated if dEMG improves apnea classification compared to CI so far.

Therefore, the aim of this study was to compare apnea classifications by CI and dEMG. We hypothesized that dEMG would allow for a more accurate classification than CI.

Methods

For this study, we used data collected in a previously published prospective observational cohort study conducted in the neonatal intensive care unit (NICU) of the Emma Children's Hospital, Academic Medical Center Amsterdam, the Netherlands [13]. This study assessed the effect of caffeine on the electrical activity of the diaphragm in 30 spontaneously breathing preterm infants with a GA of <34 weeks. All infants were supported with nCPAP using an Infant Flow® or Infant Flow® SiPAP™ system (Vyaire, Yorba Linda, CA, USA) or an AVEA™ ventilator (Vyaire). Written informed consent was obtained from both parents, and the study protocol was approved by the Institutional Review Board.

In all patients, the breathing pattern measured by dEMG was recorded at the bedside using a portable 16-channel digital physiological amplifier (Dipha-16, Macawi, Enschede, The Netherlands). Two transcutaneous electrodes were placed at the costo-abdominal margin in the left and right nipple line, and 1 ground electrode at the height of the sternum [12]. The averaged dEMG data were digitized without analog filtering, and sent wirelessly to the front-end of the Dipha-16 system, which was connected to a personal computer. More details on pre- and postprocessing, sampling rate, the filtering algorithm, and other technical aspects of the dEMG measurement have been described previously [14, 15].

In order to classify the apnea as central, obstructive, or mixed, respiratory inductance plethysmography (RIP) was used as the gold standard. Respiration was therefore also recorded with RIP, which measures rib-cage (RC) and abdominal (AB) excursions via 2 elastic bands that contain a Teflon-coated wire connected to a Bicore-II device (Vyaire). An electrical oscillating signal is sent simultaneously through both wires and the frequency modulation due to the expansion and contraction of the RC and AB bands is converted to voltage changes [16, 17]. The sum signal of the RC and AB bands was also calculated (summed RIP).

CI and transcutaneous oxygen saturation (SpO_2) recorded by an Intellivue MP-90 monitor (Philips Healthcare, Eindhoven, The Netherlands) were captured by a personal computer at a sample rate of 500 Hz using custom-made software.

Finally, a disposable AVEA™ Ventilator VarFlex Flow Transducer (Vyaire), with a deadspace of 0.7 mL and accurate flow measurements in the range of 0.024–30 L/min, was placed at the expiratory limb of the nCPAP system, allowing for the measurement of inspiratory and expiratory flow variation during breathing in all patients.

All tracings were recorded in sync (Fig. 1), and analysis was performed off-line using a custom-made software package (Polybench v1.25.2, Applied Biosignals, Weener, Germany).

For the selection of apnea used and scored in the present study, 3 investigators scanned the data of all infants included in the caffeine study. First, using only stable tracings of flow, SpO_2, and HR, we identified all recorded cases of apnea, defined as: a cessation of breathing in the flow signal for >20 s or of shorter duration if accompanied by hypoxemia (SpO_2 <80%) or bradycardia (a drop in HR to <100 beats/min) [1]. Second, using only the RIP recording (the gold standard), the apnea was independently classified by the investigators who used the following criteria: (1) central apnea: both the RC and AB tracings were flat lines; (2) obstructive apnea: RC and AB tracings moved in opposite (paradoxical) directions while the summed RIP signal approached zero; and (3) mixed apnea: both central and obstructive components were visible in the RIP tracings. In case of disagreement, the investigators tried to reach a consensus about the classification.

Forty-nine cases of apnea were identified, based on the flow, SpO_2, and HR tracings. 34 of which were classified as central, 5 as obstructive, and 10 as mixed apnea, according to the RIP tracings. To limit the workload for the assessors classifying the apnea, 15 of the central apnea cases were randomly selected from the total of 34, and these were used for the final analysis.

Next, for each apnea ($n = 30$), the HR and SpO_2 tracing recorded by the Intellivue MP90 monitor, combined with the RR tracing

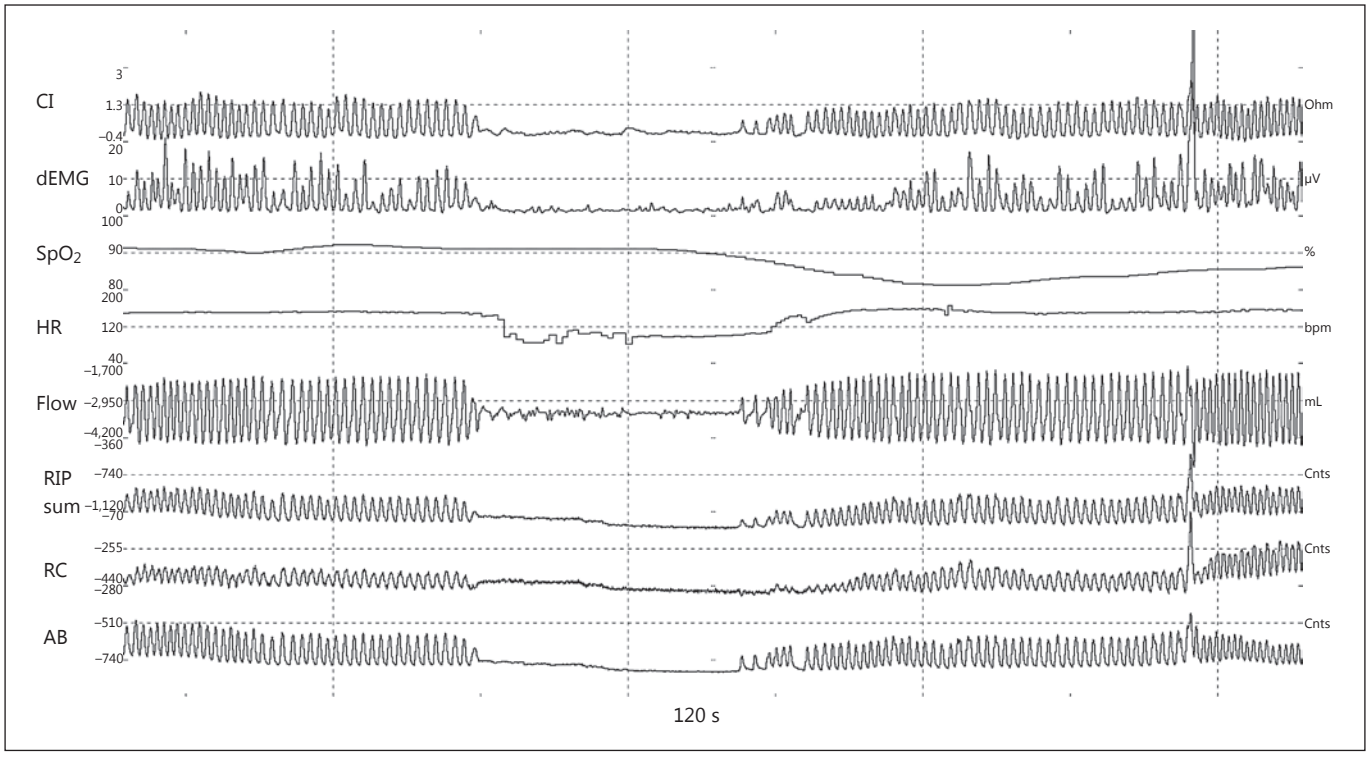

Fig. 1. Example of respiratory tracings of dEMG, CI, and RIP combined with SpO_2, HR, and flow for an apnea classified as central. CI, chest impedance; dEMG, diaphragmatic EMG; SpO_2, oxygen saturation; HR, heart rate; RIP sum, summed rib-cage and abdominal signal of RIP; RC, rib cage signal of RIP; AB, abdominal signal of RIP; µV, microvolt; bpm, beats per minute; mL, millilitre; Cnts, counts.

recorded by either CI (Intellivue MP90 monitor) or dEMG, was captured in 1 image. As a result, each apnea was captured twice, once using the respiratory tracing based on the CI data, and once based on the dEMG recording. The source of the respiratory tracing (CI or dEMG) was only known to the investigators and was not visible on the image, which was then scored by the assessors. The 60 apnea images were then mixed and e-mailed as a PowerPoint presentation to 22 assessors, consisting of clinical neonatologists (n = 9) and pediatricians-in-training (n = 8) working in the NICU as well as a random selection of senior nurses with NICU experience (n = 5). The assessors were asked to classify each apnea as central, obstructive, or mixed, based on the respiratory signal, HR, and SpO_2 tracings. Basing apnea classification on these 3 tracings is standard procedure in our unit and all health care professionals are trained in apnea classification. For this reason, no special instructions on how to classify apnea were provided to the assessors.

Statistical Analysis

Statistical analysis was performed using SPSS v23 (SPSS, Chicago, IL, USA). Descriptive data of the study population were expressed as mean ± standard deviation (SD). The number of correctly scored apnea in total, and for the dEMG and CI tracings separately, was expressed as a proportion of the total number of scored apnea images (%). Subgroup analyses were performed for the type of apnea and the different assessors. For between-group analysis (dEMG vs. CI), the McNemar test was used. Next, a multivariate logistic regression analysis was performed, correcting the classification of apnea using (1) the type of apnea, (2) the type of assessor, and (3) the type of measurement technique (CI or dEMG) as covariates. A p value <0.05 was considered statistically significant.

Table 1. Correctly scored apnea in the dEMG and CI groups for classification of apnea

	dEMG	CI	p value
All apnea (n = 1,320)	74.8%	67.3%	<0.001
Central (n = 660)	86.7%	80.3%	<0.02
Obstructive (n = 220)	56.4%	32.7%	<0.001
Mixed (n = 440)	66.4%	65.0%	0.8 (ns)

The p value represents the difference between the dEMG and the CI group (McNemar test). dEMG, all apnea scored based on the dEMG tracing; CI, all apnea scored based on the CI tracing; n, number of images.

Table 2. Correctly scored apnea in the dEMG and CI groups by different assessors

	dEMG (n = 660)	CI (n = 660)	p value
All assessors (n = 22)	74.8%	67.3%	<0.001
Neonatologists (n = 9)	70.7%	65.2%	0.1 (ns)
Pediatricians-in-training (n = 8)	77.1%	68.3%	<0.02
Nurses (n = 5)	78.7%	69.3%	0.055 (ns)

The p value represents the difference between the dEMG and the CI group (McNemar test). dEMG, all apnea scored based on the dEMG tracing; CI, all apnea scored based on the CI tracing; n, number of images (column heads) and assessors (row heads).

Results

The 30 selected apneas originated from the recordings of 12 preterm infants with a mean GA of 29.0 ± 0.8 weeks and a mean birth weight of 1,279 ± 222 g. All the included infants were supported by nCPAP and received caffeine. All flow-based apneas detected were also detected by either CI or dEMG. There was no disagreement between the investigators in classifying the apnea as central, obstructive, or mixed, based on the RIP tracing.

Based on the 60 apnea images which were scored by 22 assessors, a total of 1,320 apnea scores were collected and analyzed. In total, 71.1% of all the images were scored correctly as central, obstructive, or mixed (Table 1). Regarding the apneas based on the respiratory tracings of dEMG, 74.8% were classified correctly versus 67.3% of the apneas based on the respiratory tracings of CI. This difference was statistically significant ($p < 0.001$).

Subgroup analyses based on the type of apnea showed that this improvement in apnea classification in favor of dEMG was most prominent in the obstructive apnea subgroup, and, to a lesser extent, in the central apnea subgroup (Table 1). Furthermore, the highest correct rate in total was reached in the central apnea group (83.5%) and the lowest correct rate in the obstructive apnea group (44.5%).

Subgroup analysis also showed that the improved apnea classification in the dEMG subgroup, compared to the CI subgroup, was a finding consistent across the 3 different groups of assessors, even though it was not statistically significant within each subgroup (Table 2). The differences between the groups of assessors regarding correct classification of apnea were small.

In the multivariate logistic regression analysis, the classification of apnea was still better when based on dEMG than when based on CI ($p = 0.001$). Furthermore, central apneas were scored better than obstructive and mixed apneas ($p < 0.001$). However, there were no differences in the classification of apnea across the 3 groups of assessors after correction for type of apnea and measurement technique ($p = 0.085$).

Discussion

This study shows that classification of apnea using transcutaneous dEMG is feasible in preterm infants. It also suggests that dEMG might improve apnea classification compared to CI, the current monitoring standard.

There is a growing interest in using the neural activity of the diaphragm for the respiratory management of preterm infants. Most studies have reported on the use of diaphragmatic activity measured by a special transesophageal nasogastric catheter to synchronize invasive and noninvasive respiratory support in preterm infants [18, 19]. Some have suggested that transesophageal dEMG can also be used for assessing breathing pattern and apnea [20], but this has so far not been systematically studied. Our study is the first to compare apnea classification according to dEMG and CI. Furthermore, this is the first study to use the noninvasive and cheaper transcutaneous interface.

We used RIP as the gold standard for apnea classification, as previous studies have shown that this technique has no interference from cardiac artifacts, and is especially suitable for distinguishing between central and obstructive apnea [1, 8, 21]. However, compared to nasal end-tidal CO_2 or nasal/oral thermistors, the ability of RIP to detect apnea has limitations [22]. For this reason, we used a combination of flow, SpO_2, and HR to detect apnea and its consequences, i.e., hypoxemia and bradycardia, from the patients' records.

Consistent with our hypothesis, dEMG monitoring resulted in more accurate classification than CI monitoring in cases of central and obstructive apnea, but not in cases of mixed apnea. It has been suggested that CI has a limited ability to distinguish obstructive apnea from normal respiration [8]. Although air entry will be limited or absent, air can still move back and forth within the chest wall cavity during airway obstruction, resulting in a normal or slightly reduced breathing pattern when measured with CI; however, respiratory muscle activity is significantly increased during obstructive apnea because the infant is breathing against an occluded airway. The concomitant increase in electrical diaphragmatic activity will be picked up by dEMG monitoring. Therefore, the increase in breathing activity during obstructive apnea is expected to be more accurate when using dEMG monitoring than when using CI. This may explain the improved classification of obstructive apnea with dEMG.

During central apnea, there is a cessation of inspiratory effort and flow, which results in absent electrical activity of the diaphragm and no change in lung aeration. Both dEMG and CI tracings should therefore show no activity (flat line). However, previous reports have shown that cardiac activity may interfere with the CI tracing and (falsely) suggest breathing activity [9, 11]. Such cardiac interference is not present in the dEMG tracing due to a special filtering technique, and this may explain the superior classification of central apnea.

A possible explanation why there was no difference between dEMG and CI when classifying mixed apnea is the fact that both central and obstructive components are present in the CI and dEMG tracings. This might make the classification of mixed apnea less dependent on the type of technique (CI or dEMG) for (cardio) respiratory monitoring.

This was the first time that neonatologists, pediatricians-in-training, and neonatal nurses assessed respiratory tracings based on dEMG. It seems that the assessors did not have any difficulty interpreting the dEMG tracings; the results of our study show that the rate of correctly scored apneas based on the dEMG tracings was comparable or better than when based on CI tracings. This finding suggests that dEMG can probably be easily implemented in daily clinical practice. We speculate that classification of apneas will improve even further once assessors are more familiar with interpreting the dEMG tracings.

This study has some limitations that need to be addressed. First, we only assessed a limited number of apneas to keep the workload for each individual assessor within reasonable limits. However, the total number of assessments was 1,320, and we think this is a sufficient number to explore a potential role for dEMG in apnea classification. Second, we only selected apnea from stable RIP, flow, SpO_2, and HR tracings. However, apnea can also occur when tracings are unstable due to, for instance, a patient's movement. It is unclear how dEMG will compare to CI under such circumstances. Finally, we did not measure (absolute) flow directly at the airway opening but at the expiratory limb of the nCPAP system. Although unconventional, the variation in flow did allow us to assess cessation of flow in the respiratory system.

In conclusion, this study shows that electrical activity of the diaphragm measured by transcutaneous dEMG can be used for apnea classification in preterm infants. dEMG improves the classification of central and obstructive but not mixed apnea when compared with the current standard, CI, and this finding was consistent across different assessors. These findings suggest that transcutaneous dEMG is a promising candidate for improved analysis of breathing patterns in monitoring systems in the future.

Acknowledgements

We thank all assessors of our department for scoring the apneas, and also Leo van Eykern and Tom Leenhoven for their technical assistance.

Disclosure Statement

The authors declare no conflicts of interest.

References

1 Sale SM: Neonatal apnoea. Best Pract Res Clin Anaesthesiol 2010;24:323–336.
2 Martin RJ, Abu-Shaweesh JM, Baird TM: Apnoea of prematurity. Paediatr Respir Rev 2004;5:S377–S382.
3 Finer NN, Barrington KJ, Hayes BJ, Hugh A: Obstructive, mixed, and central apnea in the neonate: physiologic correlates. J Pediatr 1992;121:943–950.
4 Eichenwald EC: Apnea of prematurity. Pediatrics 2016;137:e20153757.
5 Poets CF, Roberts RS, Schmidt B, Whyte RK, Asztalos EV, Bader D, Bairam A, Moddemann D, Peliowski A, Rabi Y, Solimano A, Nelson H: Association between intermittent hypoxemia or bradycardia and late death or disability in extremely preterm infants. JAMA 2015;314:595–603.

6 Martin RJ, Abu-Shaweesh JM: Control of breathing and neonatal apnea. Biol Neonate 2005;87:288–295.
7 Abu-Shaweesh JM, Martin RJ: Neonatal apnea: what's new? Pediatr Pulmonol 2008;43: 937–44.
8 Di Fiore JM: Neonatal cardiorespiratory monitoring techniques. Semin Neonatol 2004;9:195–203.
9 Lee H, Rusin CG, Lake DE, Clark MT, Guin L, Smoot TJ, Paget-Brown AO, Vergales BD, Kattwinkel J, Moorman JR, Delos JB: A new algorithm for detecting central apnea in neonates. Physiol Meas 2012;33:1–17.
10 Wilkinson JN, Thanawala VU: Thoracic impedance monitoring of respiratory rate during sedation – is it safe? Anaesthesia 2009;64: 455–456.
11 Upton CJ, Milner AD, Stokes GM: Combined impedance and inductance for the detection of apnoea of prematurity. Early Hum Dev 1990;24:55–63.
12 Kraaijenga JV, Hutten GJ, de Jongh FH, van Kaam AH: Transcutaneous electromyography of the diaphragm: a cardio-respiratory monitor for preterm infants. Pediatr Pulmonol 2015;50:889–895.
13 Kraaijenga JV, Hutten GJ, de Jongh FH, van Kaam AH: The effect of caffeine on diaphragmatic activity and tidal volume in preterm infants. J Pediatr 2015;167:70–75.
14 Maarsingh EJ, van Eykern LA, Sprikkelman AB, Hoekstra MO, van Aalderen WM: Respiratory muscle activity measured with a noninvasive EMG technique: technical aspects and reproducibility. J Appl Physiol (1985) 2000;88:1955–1961.
15 O'Brien MJ, van Eykern LA, Prechtl HF: Monitoring respiratory activity in infants: a non-intrusive diaphragm EMG technique; in Rolfe P (ed): Non-Invasive Physiological Measurements, ed 2. London, Academic Press, 1983, pp 131–177.
16 Markhorst DG, Van Gestel JP, Van Genderingen HR, Haitsma JJ, Lachmann B, Van Vught AJ: Respiratory inductive plethysmography accuracy at varying PEEP levels and degrees of acute lung injury. J Med Eng Technol 2006;30:166–175.
17 Valta P, Takala J, Foster R, Weissman C, Kinney JM: Evaluation of respiratory inductive plethysmography in the measurement of breathing pattern and PEEP-induced changes in lung volume. Chest 1992;102:234–238.
18 Stein H, Beck J, Dunn M: Non-invasive ventilation with neurally adjusted ventilatory assist in newborns. Semin Fetal Neonatal Med 2016;21:154–161.
19 Beck J, Reilly M, Grasselli G, Mirabella L, Slutsky AS, Dunn MS, Sinderby C: Patient-ventilator interaction during neurally adjusted ventilatory assist in low birth weight infants. Pediatr Res 2009;65:663–668.
20 Ng E, Schurr P, Reilly M, Dunn M, Beck J: Impact of feeding method on diaphragm electrical activity and central apnea in preterm infants (FEAdi study). Early Hum Dev 2016; 101:33–37.
21 Brouillette RT, Morrow AS, Weese-Mayer DE, Hunt CE: Comparison of respiratory inductive plethysmography and thoracic impedance for apnea monitoring. J Pediatr 1987; 111:377–383.
22 Weese-Mayer DE, Corwin MJ, Peucker MR, Di Fiore JM, Hufford DR, Tinsley LR, Neuman MR, Martin RJ, Brooks LJ, Davidson Ward SL, Lister G, Willinger M; CHIME Study Group: Comparison of apnea identified by respiratory inductance plethysmography with that detected by end-tidal CO_2 or thermistor. Am J Respir Crit Care Med 2000;162: 471–480.