Diaphragmatic electromyography monitoring in preterm infants
Kraaijenga, J.V.S.

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CHAPTER 1

General introduction and outline of thesis
GENERAL INTRODUCTION

Preterm infants

Preterm birth, before a gestational age (GA) of 37 weeks, is a common complication of pregnancy worldwide. Globally about 1 in 10 infants (approximately 15 million infants) is born prematurely every year.1 In developed countries, prematurity is the leading cause of perinatal and neonatal morbidity and mortality.1,2 Immaturity of the respiratory system is one of the major morbidities.2 The transition from fetal to neonatal life requires a rapid conversion to a stable respiratory system for successful gas exchange.3

In preterm infants, central and peripheral mechanisms that account for the control of breathing are still adapted to intra-uterine life which complicates breathing.4 The chest wall and soft tissues of the trachea are both highly compliant in preterm infants and predispose to upper and lower airway collapse and obstruction. During inspiration, the diaphragm generates a negative intra-thoracic pressure that may cause instability and retraction of the rib cage due to the highly compliant and instable chest wall. Preterm infants therefore display more asynchronous ribcage and abdominal movement compared to full-term infants and the underdeveloped lungs are vulnerable to injury.4,5 For this reason, preterm infants are at high risk of respiratory failure with a compromised lung function and impaired control of breathing as the most common causes.4,6–8 Due to a compromised lung function, work of breathing (WOB) is often increased and gas exchange impaired.8 Impaired control of breathing leads to irregular breathing which can lead to apnea (a cessation of breathing) or periodic breathing (e.g. a pattern of breathing characterized by respiratory cycles of 10-15 seconds with pauses of 5-10 seconds).

Apnea of Prematurity

Apnea of prematurity (AOP) is most widely defined as a cessation of breathing for more than 20 seconds, or shorter respiratory pauses accompanied by an oxygen saturation (SpO2) < 80% and/or bradycardia < 100 beats per minute.9 AOP can be classified into three groups: (1) central apnea, a cease in airflow due to absence of respiratory effort; (2) obstructive apnea, a cease in airflow caused by (large) airway obstruction and; (3) mixed apnea, a cease in airflow caused by a combination of characteristics of both central and obstructive apnea.7,9

Central and mixed apnea account for most of the apneic episodes.10 The frequency of apnea is inversely proportional to GA, and almost all infants with a GA less than 30 weeks are affected. AOP frequently persist until the infants reach 36 weeks corrected age, but in extremely premature infants this period may extend to 44 weeks postconceptional age.9,11

Apnea with short respiratory pauses will not lead to a decrease in oxygenation and are of little consequence. However, respiratory pauses can be problematic when leading to chronic

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intermittent hypoxemia which occurs often in premature infants. Hypoxic episodes, especially if prolonged, are associated with an increased risk of adverse neurodevelopmental outcome in preterm infants. Furthermore, it is an important cause for prolonged need of respiratory support, longer time to achieve full oral feeds and an increased incidence of retinopathy of prematurity. In order to prevent these effects early and effective treatment for AOP is very important.

Pharmacological treatment

Caffeine
Pharmacological treatment with xanthine therapy has been used for prevention and treatment of central apnea since the 1970s. The methylxanthine caffeine is the first choice of treatment. At the short-term, caffeine leads to a decrease in the frequency of central apnea and to an increase in minute ventilation, both resulting in a decrease in the need for mechanical ventilation. At the long-term, caffeine is associated with a lower incidence of bronchopulmonary dysplasia and improves neurodevelopmental outcome at a corrected age of 18 months.

The caffeine induced increase in minute ventilation and is mainly attributed to an increase in tidal volume (Vt). The way in which caffeine increases Vt is not completely understood. It is thought that caffeine has its primary mechanism of action by blocking inhibitory adenosine A1 receptors thereby inducing excitation of respiratory neural output. An alternative mechanism of action could be that caffeine induces excitation of respiratory neural output by blocking excitatory adenosine A2A receptors at gamma-amino butyric acid (GABA) neurons which result in a decrease in GABA output.

Experimental studies in animals and adults have shown that treatment by caffeine also improves contractility of the diaphragm, the major respiratory muscle. However, the working mechanism by which caffeine might improve diaphragmatic contractility is unclear. Studies in adults that were conducted in the 80’s have suggested that caffeine augments contractile protein activation by increasing sarcoplasmic reticulum calcium concentration. Caffeine may also affect muscle function by adrenal release of epinephrine thereby improving diaphragmatic contractility. Despite its frequent use in preterm infants with AOP, the effect of caffeine on diaphragmatic activity in preterm infants has never been studied.

Doxapram
Pharmacological treatment with doxapram can be administered additionally to preterm infants when treatment with caffeine fails and AOP persists. Stimulation of the breathing center in the brain and stimulation of peripheral chemoreceptors in the carotic body are some of the multiple working mechanism of doxapram. Doxapram as a respiratory stimulant has shown to increase minute ventilation by increasing RR in adults studies. Limited studies
in preterm infants have shown that doxapram reduces the frequency of AOP compared with placebo. However, doxapram is currently not recommended for routine use in preterm infants because there is insufficient evidence on both efficacy and safety.

**Respiratory support treatment**

**Nasal continuous positive airway pressure (nCPAP)**

nCPAP is the preferred mode of non-invasive respiratory support in preterm infants which are treated for impaired control of breathing or compromised lung function. nCPAP at pressures of 3 to 6 cmH₂O is thought to increase pharyngeal pressure by splinting the upper airway and is effective in reducing the severity and frequency of obstructive and mixed apnea. Most often, nCPAP and caffeine are combined for treatment of AOP.

nCPAP is also effective to restore lung function and reduce WOB. It stabilizes lung volume of preterm infants and is effective in increasing the functional residual capacity (FRC) of the lung and therefore oxygenation, since normal FRC is required to prevent ventilation and perfusion mismatch and hypoxemia. nCPAP maintains a higher end-expiratory lung volume (EELV) leading to a decrease in the depth and duration of oxygen desaturation during apnea. Compared to invasive mechanical ventilation, primary nCPAP started in the delivery room decreases the risk of death and bronchopulmonary dysplasia. Although nCPAP is well tolerated in preterm infants, it can lead to nasal trauma and pneumothorax.

**Nasal intermittent mandatory ventilation (NIMV)**

NIMV provides (non-invasive) positive pressure inflations via a nasal interface (mask or prongs) in addition to PEEP. These inflations can be non-synchronized or synchronized to the spontaneous breathing efforts of the infants. Signals that have been used to synchronize inflations in preterm infants are flow, airway pressure, pneumatic capsules detecting abdominal movement and diaphragmatic electrical activity. NIMV and synchronized NIMV are both commonly used modes of non-invasive respiratory support in preterm infants. Compared to nCPAP, the frequency of apnea is reduced more effectively with NIMV and it also reduces the rate of re-intubation after extubation.

**High flow nasal cannula (HFNC)**

Heated humidified HFNC is increasingly used in the neonatal intensive care unit (NICU) over the last few years. HFNC is as effective as nCPAP in providing respiratory support for preterm infants and shows similar rates of death, need for re-intubation or rates of chronic lung disease. Thereby, HFNC is thought to be as effective as nCPAP for treatment of apnea, including the frequency or duration of apnea. HFNC is easy to apply and causes less nasal trauma than nCPAP in preterm infants.
**Low flow nasal cannula (LFNC)**

LFNC is used to deliver oxygen by flow rates of 1 litre per minute (L/min).\(^{36}\) It consists of two small, thin, tapered tubes (<1 cm in length) that are placed in each nostril without occluding them. LFNC is often used in preterm infants during weaning as a step between nCPAP and being completely without non-invasive respiratory support. LFNC is also frequently used in preterm infants with chronic lung disease.\(^{36,40}\) Apart from oxygen supply, LFNC does not contribute to an improvement of lung function as nCPAP, NIMV or HFNC.\(^{36}\) Although in clinical practice LFNC is also used in the treatment of AOP, there is little evidence to support its efficacy.

**Mechanical ventilation (MV)**

MV is a mode of invasive respiratory support that can assist or completely take over spontaneous breathing, depending on the condition and need of the infant. Although this will result in a complete resolution of AOP, MV has the disadvantage of being a major risk factor for developing secondary lung injury and increasing the risk of bronchopulmonary dysplasia.\(^{25}\) For this reason MV is considered a last resort to treat AOP in preterm infants after pharmacological treatment and non-invasive support modes have failed.\(^{24}\)

Although all modes of respiratory support discussed above may play a role in the treatment of apnea and also in optimizing lung function in preterm infants, it is unclear how the optimal mode and its settings should be selected. There is a lack of objective parameters to guide the process of selection and weaning from different modes of (non-invasive) respiratory support. In the clinical setting, most clinicians use a “trial and error” approach for selecting and weaning respiratory support based on changes in the clinical condition of the infant.\(^{41,42}\) The weaning attempt can be either successful (the infant remains on less respiratory support) or failing (the level of support needs to be increased). It is clear that such a “trial and error” approach can lead to both under- and overtreatment. Therefore, more objective parameters to start and guide weaning of respiratory support in preterm infants are urgently needed.

**Cardiorespiratory monitoring techniques**

Considering the high frequency of AOP and its possible (serious) sequellae, it is evident that accurate cardiorespiratory monitoring is essential in preterm infants. Monitoring should provide reliable detection of AOP but also provide information to allow for accurate classification of apnea. The latter is important for selecting the optimal treatment, which is dependent on the type of apnea.\(^4\)

In spontaneous breathing preterm infants on respiratory support, accurate measurement of respiratory rate (RR), heart rate (HR) and SpO\(_2\) are crucial for detection of apnea or bradycardia.\(^4\) There are several techniques for cardiorespiratory monitoring. In general, monitoring devices have to be accurate and validated and they have to provide continuous...
data on HR, RR and SpO₂. The monitoring device has to be patient and user friendly and suitable for preterm infants (e.g. allow for nursery and Kangaroo mother care and cause no skin lesions). Furthermore, it has to be applicable at the bedside without interfering with other equipment present in the intensive care unit.

In the next paragraph the most common (cardio)respiratory monitoring devices that can be used in the NICU are described.

*Chest Impedance*

Chest impedance (CI) is the most widely used method for cardiorespiratory monitoring in the NICU worldwide. It provides continuous monitoring of HR, RR and breathing pattern. Three surface electrodes are used for electrocardiography (ECG) monitoring and two of these electrodes are placed on either side of the infant’s chest to measure RR (Figure 1). CI measures changes in electrical impedance between the two electrodes during respiration. Impedance monitoring is based on the principle that air has a higher level of impedance than tissue. During inspiration, the length between the two electrodes will increase, as well as the amount of air in the lungs, both resulting in a decrease in conductivity and an increase in the voltage of impedance. The increase or decrease in impedance during tidal breathing is seen as the respiratory pattern on the monitor. CI is a non-invasive way of monitoring, allowing for long-term continuous measurement of respiration. CI can be safely used in preterm infants > 26 weeks, however due to the risk of skin lesions CI is not preferred in extremely preterm infants younger than 26 weeks. Although CI is most widely used, this technique has important limitations. CI can provide inaccurate data due to cardiac interference, movement artefacts and non-breathing related chest wall movements (e.g. even during absence of upper-airway airflow there might be intrapulmonary gas flows), which will result in similar impedance changes to normal respiration. Therefore CI is sometimes unable to distinguish ineffective breathing effort from true breathing and to detect obstructive and mixed apnea correctly.

![Figure 1. Placement of ECG electrodes](image)
Respiratory inductance plethysmography

Respiratory inductance plethysmography (RIP) is a non-invasive monitoring technique that provides information on respiration at the bedside. RIP uses two elastic bands, one placed around the ribcage and one placed around the abdomen (Figure 2). During tidal breathing, ribcage and abdomen bands will expand, leading to an extension of the sinusoidal shaped wire in both bands and a corresponding increase in inductance. Because ribcage and abdomen are measured individually, the RIP device can be used to detect asynchronous, 180 degrees out of phase (paradoxical) movements between the ribcage and abdomen, which is present during obstructive apnea. The sum of both bands can also be calibrated for actual changes in lung volume. In this way RIP can be used for measuring $V_t$ and changes in EELV.

RIP has several advantages over CI monitoring, including the ability to detect obstructive apnea, and being free of cardiac artifacts. However, RIP measurement requires additional monitoring equipment and two extra bands are attached to the infant, which is a problem during nursing procedures. Thereby, it does not provide information on HR and due to warmth and humidity in the incubator the bands will stretch which leads to drift of the signals. Therefore, it will be unlikely that RIP measurements will be implemented for routine monitoring of apnea in the NICU.

Figure 2. RIP measurement for research purpose (blue ribcage and abdominal bands) combined with transcutaneous diaphragmatic EMG measurement.
Flow sensors
The gold standard to measure air flow is the pneumotachograph, also called a pneumotachometer. This device is often used in the clinical setting and uses a resistive element inserted between two cylinders to measure air flow. When airflow passes the resistive element, this will cause a drop in pressure. A differential pressure transducer is attached to the pneumotachograph and measures the fall in pressure via ports on each side of the resistive element that is calibrated to read in units of flow. Tidal volume can be obtained by integration of the flow signal. In this way the pneumotachograph provides information on airflow and volume. The pneumotachograph can be incorporated in, or attached to a nasal or oral mask that is sealed around the infant’s nose and/or mouth in spontaneously breathing infants. Applying gentle pressure to the face is used to obtain a tight seal of the mask. This method is not designed for long-term measurements since it must be held in place to prevent air leak, which commonly occurs in spontaneously breathing infants for example due to movements of the infant.

Another expiratory flow device that can be used to measure respiration is the thermistor or thermocouple. These are temperature-sensing devices measuring the increase in temperature when warmed air crosses the sensor during expiration. During inspiration, the atmosphere air cools the sensor back to room temperature.

Although these devices are placed on the infant’s face as well, they are mostly tolerated well and can therefore be used for long time periods. Unfortunately, the waveforms of the thermistor or thermocouple seems to have a poor correlation with quantitative measurements of flow via plethysmograph or pneumotachograph readings. Therefore, these devices are only used as a qualitative device to provide information on the presence or absence of airflow (e.g. during apnea). Thereby, when combined with sensors detecting chest wall motion, these devices can be used to distinguish obstructive apnea from normal respiration.

Graseby capsule
The Graseby Capsule (GC) is a small pneumatic device that is able to measure respiration in neonates. The GC is taped onto the infant’s abdominal wall in the subxiphoid area with adhesive tape. The GC estimates abdominal pressure and can be used as a triggering device for a standard infant ventilator. On inspiration, the abdomen will expand which causes an increase abdominal volume and pressure and the GC detects this pressure increase. Unfortunately, the GC is not a very reliable method since approximately only 75% of the infant’s breaths are detected by the GC. This does not make the GC an optimal device for monitoring RR. In addition, the GC does not provide information on HR.
Electrical impedance tomography

Electrical impedance tomography (EIT) continuously measures changes in lung volume in adults, children and (preterm) infants.\textsuperscript{54,55} EIT measures regional changes in tissue impedance in a cross-sectional slice of the thorax by using 16 small ECG electrodes on the thorax circumference just above nipple line of the infant’s chest.\textsuperscript{55} These changes are highly correlated to changes in aeration (e.g. actual intrathoracic air and changes in ventilation).\textsuperscript{54,55} It can also provide information on the change in EELV, tidal volume and their regional distributions.\textsuperscript{55} EIT is a non-invasive and relatively novel bedside monitoring technique. However, 16 surface electrodes have to be placed around the circumference of the infant’s chest, which is a cumbersome process especially in preterm infants. Furthermore, no information on HR is provided and for these reasons EIT is still used for research purposes only.\textsuperscript{55}

Electromyography of the diaphragm

The diaphragm

The diaphragm is the principal respiratory muscle of inspiration.\textsuperscript{56} The diaphragm consists of a thin, dome-shaped sheet of muscles divided in a left and right hemidiaphragm inserted to the lower ribs that can act individually.\textsuperscript{56,57} The diaphragm is a striated skeletal muscle, which is innervated by the left and right phrenic nerves originating from cervical segments 3, 4 and 5.\textsuperscript{56,57} The diaphragm can be distinguished in a costal and a crural part, connected by the non-contractile central tendon, which may be considered as electrically neutral. The muscle fibers of the costal part of the diaphragm run from the central tendon to the xiphoid and the inner aspect of the lower 6 ribs and costal cartilages. The muscle fibers of the crural part run from the central tendon to the upper 3 lumbar vertebrae.\textsuperscript{58} The diaphragm is represented in Figure 3.

Respiratory muscles are under control of autonomic and voluntary respiratory centers in the central nervous system.\textsuperscript{58} On inspiration, the diaphragm contracts and the abdominal contents are forced downward and forward.\textsuperscript{56} At the same time, the external intercostal muscles pull the ribs upward and forward, both causing an increase in the vertical and transverse diameter and volume of the chest cavity.\textsuperscript{58} The accessory muscles of inspiration include the scalene muscles, elevating the first two ribs, and the sternomastoid muscles, raising the sternum.\textsuperscript{56} However, the activity in these muscles is negligible during quiet breathing.

Figure 4. Right lung is shown during inspiration (light dotted) and expiration (heavy dotted). Abbreviations: inspiration (Insp.); expiration (Exp.) [From: Handbook of Physiology, section 3: Respiration, Vol. 1., Fenn W.O. and Rahn H. (Eds)].
In general, in adults and children the expiration is passive during quiet breathing. Since the lung and chest wall are elastic they will return to their equilibrium positions after being actively expanded during inspiration. The expiration becomes active during exercise and voluntary hyperventilation. The abdominal muscles are the most important muscles of expiration. Contraction will increase the intra-abdominal pressure and the diaphragm will move upward. During coughing, vomiting or defecation, these muscles will also firmly contract. The internal intercostal muscles assist active expiration by pulling the ribs downward an inward, leading to a decrease in the volume of the chest cavity.

To overcome the low compliance of their respiratory system leading to a low EELV, preterm infants prolong their expiration by braking or stopping the expiratory flow to achieve a higher lung volume during expiration. During respiration, airflow is controlled by reflex action of diaphragmatic and laryngeal muscle activity. These reflexes play an important role in the control of breathing and retaining lung volume, and are present since birth in term and preterm infants. During braked expiration, the combination of a closed or narrowed glottis and diaphragmatic post-inspiratory activity helps to maintain EELV.

**Electromyography of the diaphragm**

The bio-electric source of the muscular activity is found in the sarcolemma of muscle fibers. An axon and a group of muscle fibers together form a motor unit. The action potentials in motor units can be detected with electromyography (EMG).

The diaphragmatic EMG signal represents an estimate of the global diaphragmatic muscle activity. The electrical activity of the diaphragm measured by EMG is related directly to the activity of the phrenic nerve, which is thought to estimate respiratory center output. When assuming that the neuromuscular conduction is intact, changes in the amplitude of the EMG signal indicate changes in neural respiratory drive. There is a potential value of EMG in detecting impaired control of breathing, diaphragmatic inactivity due to phrenic nerve injury or diaphragmatic muscle fatigue.

The electrical activity of the diaphragm has been shown to be an objective measure of disease state and the efficacy of treatment in dyspneic infants and toddlers with wheezing disorders. Thereby, in asthmatic children, an increase in diaphragmatic electrical activity closely corresponds to a histamine-induced 20% fall in forced expiratory volume in one second. Previous studies on diaphragmatic EMG have suggested that changes in diaphragmatic electrical activity are correlated with WOB. In these WOB studies, the amplitude and peak values of the diaphragmatic electrical activity was significantly higher in infants with, compared to, without small airway obstruction.

Diaphragmatic EMG monitoring techniques can be performed either: (1) invasively using an electrode equipped oesophageal catheter or a special feeding tube or (2) non-invasively using transcutaneous (surface) chest electrodes.
The invasive technique is used mainly for neurally adjusted ventilatory assist (NAVA). This technique uses a naso-orogastric feeding tube with miniaturized sensors inside which are placed at the level of the gastro-oesophageal junction to measure diaphragmatic electrical activity. NAVA is a mode of mechanical ventilation in spontaneously breathing patients monitoring neural respiratory drive. Both the timing and the amount of ventilator assist are controlled by the patient. Recently, Beck et al. has shown that diaphragmatic electrical activity improves patient-ventilator interaction compared to ventilator delivered pressure by using a flow sensor during conventional MV in low birth weight preterm infants. Although the catheter is well tolerated, easy to place, and not prone to signal interference during feedings; it still is an invasive technique and very expensive to use in the NICU.

The non-invasive technique, transcutaneous diaphragmatic EMG (dEMG), measures the electrical activity of the frontal diaphragm using three surface electrodes placed on the infant’s chest. Two electrodes are bilaterally placed at the costo-abdominal margin in the nipple line, and the ground electrode is placed at height of the sternum. (Figure 5)

Figure 5. Placement of frontal transcutaneous dEMG electrodes in a preterm infant. Two electrodes (white; labelled with 1+2) are bilaterally placed at the costo-abdominal margin in nipple line. The ground electrode (black) is placed at height of the sternum. Also three Cl electrodes (red, yellow and green) are placed on the infant’s chest.
Since dEMG measures electrical muscle activity, it will also measure the electrical activity of the heart. In literature, mainly two techniques have been described to filter out the HR from the signal; the (double)-subtraction technique and the gating technique.\textsuperscript{76} With the subtraction technique, an ECG template is subtracted from the EMG signal of the diaphragm at each occurrence of the ECG waveform. This way of filtering may not work if the heart rate is fluctuating. For the gating technique, the electrical activity of the heart was isolated from the signal by using the gating technique described in 1977 by O’Brien et al.\textsuperscript{71} This technique involves the removal of a section of the ECG signal centered on the QRS-complex, which is used for HR analysis. The remaining gate is filled with a running average and used for RR analysis. This technique has been confirmed in studies of Maarsingh and Hutten.\textsuperscript{75,77} Until now, there is no consensus how to reduce the contamination of the EMG-signal by the ECG-signal and both methods are used.

Studies have shown that transcutaneous dEMG measurement are feasible in adults, children and term infants and can detect changes in diaphragmatic activity.\textsuperscript{75,77,78} Explorative studies on transcutaneous dEMG in preterm infants have been reported over 30 years ago, but until now, this technique has not been validated in preterm infants.\textsuperscript{76,79,80}

Based on the above, dEMG could be considered an interesting and potentially important candidate for cardiorespiratory monitoring in preterm infants. Obtaining information on breathing directly from the main respiratory muscle (diaphragm) might improve monitoring of RR and breathing pattern, including more optimal detection and classification of AOP. In addition, HR can also be extracted from the dEMG signal, making it a realistic alternative for chest impedance. The fact that (neural) breathing activity can also be quantified also opens possibilities to use dEMG to titrate and wean respiratory support in preterm infants.

However, the feasibility of dEMG monitoring but also its use in apnea detection and classification, and quantification of breathing activity still need to be established in preterm infants.
OUTLINE OF THESIS

This thesis starts in Chapter 1 with general aspects of prematurity and its consequences on the respiratory system. Thereby, common types of respiratory failure in preterm infants, the physiology of respiratory muscles and different cardiorespiratory monitoring techniques used in the neonatal intensive care unit are described. The aim of this thesis is to explore if transcutaneous electromyography of the diaphragm (dEMG) can be used as a novel cardiorespiratory monitoring technique for preterm infants. Chapter 2 consists of a prospective cohort study in which the feasibility of dEMG as a cardiorespiratory monitor for preterm infants with a gestational age less than 32 weeks is determined and compared to chest impedance. In Chapter 3, a case report illustrates if transcutaneous dEMG can be used to detect a hemidiaphragmatic paresis in a preterm infant. Chapter 4 describes the effect of a loading dose of caffeine on the electrical activity of the diaphragm, tidal volume and end-expiratory lung volume in preterm infants by measuring dEMG and respiratory inductance plethysmography after caffeine administration. In Chapter 5, the effect of weaning from nasal continuous positive airway pressure to low flow nasal cannula on diaphragmatic activity is described. In Chapter 6, we determined if dEMG is able to classify apnea of prematurity correctly into central, obstructive or mixed when compared to chest impedance. Finally, Chapter 7 and 8 provides a, respectively, English and Dutch summary of this thesis and the most important results are discussed and future perspectives are outlined.
REFERENCES


