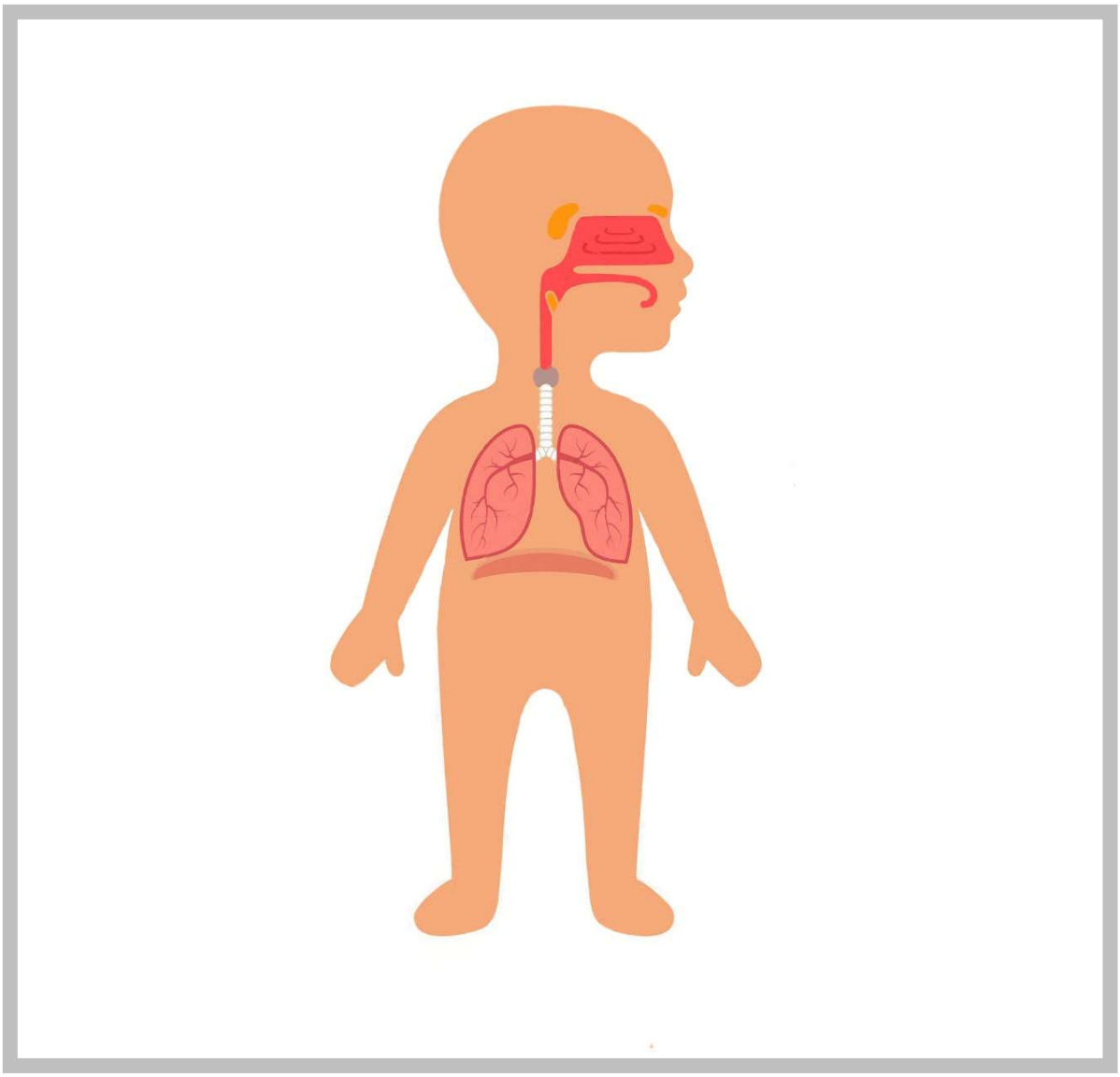
Electrode positioning of transcutaneous electromyography of the diaphragm in preterm infants

Master's Thesis Technical Medicine



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Electrode positioning of transcutaneous electromyography of the diaphragm in preterm infants

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Preface

Door het schrijven van deze scriptie, ben ik aan een einde gekomen van zeven jaar lang studeren. Zeven jaar waarin ik mijzelf heb mogen ontwikkelen als een Technisch Geneeskundige, maar ook als persoon. Een aantal jaren geleden kwam ik voor de keuze te staan om een studie te gaan kiezen, en wat vond ik deze keuze moeilijk. Van jongs af aan was ik er bijna zeker van dat ik graag kinderarts wilde worden, totdat ik erachter kwam dat ik de bètavakken toch wel erg leuk vond en er ook goed in was. In de studie Technische Geneeskunde vond ik de combinatie tussen de “gewone” geneeskunde en de aandacht voor technische vakken, en ik ben nog altijd erg blij met de keuze die ik toentertijd heb gemaakt.

In september 2014 ben ik begonnen aan de master track Medical Sensing and Stimulation. In mijn masterstages heb ik kennis en ervaring mogen opdoen op de kindergeneeskunde, de hoofd-hals chirurgie, de intensive care én zelfs in een bedrijf, namelijk bij Inreda Diabetic BV. Waarom dan mijn keuze voor de NICU, waar ik het afgelopen jaar mijn afstudeerstage heb mogen doen? Ik werd aangetrokken tot deze afdeling door de combinatie van hoog complexe zorg en de patiëntenpopulatie, want mijn interesse voor de kindergeneeskunde ben ik nooit verloren. Ik ben dan ook vol enthousiasme begonnen in het Emma Kinderziekenhuis aan mijn afstudeerstage en heb daar het afgelopen jaar met veel plezier gewerkt om mijzelf nu dan ook echt Technisch Geneeskundige te mogen noemen.

Ik heb mij het afgelopen jaar bezig gehouden met de klinische haalbaarheid van het meten van diafragma activiteit in prematuren met behulp van transcutane EMG elektroden geplaatst op verschillende posities op de borstkast van het kind. Ik mocht mij verdiepen in de anatomie, fysiologie en pathologie van een prematuur en in de technieken die mogelijk zijn wat betreft de cardiorespiratoire monitoring van deze specifieke patiëntenpopulatie. Deze master thesis heeft mijn wetenschappelijke kennis, academische vaardigheden en praktische vaardigheden verbreed en verrijkt. Zoals herkenbaar is voor velen, is deze thesis tot stand gekomen met vallen en opstaan, maar uiteindelijk ligt er dan ook iets waar ik tevreden en trots op ben. Dit alles heb ik nooit voor elkaar kunnen krijgen zonder de hulp en support van verschillende mensen.

Allereerst wil ik al mijn begeleiders bedanken voor de tijd en energie die zij gestoken hebben in mijn begeleiding. Ik wil graag Dr. Jeroen Hutten bedanken voor zijn enthousiasme over diafragma EMG en voor dit onderzoek. Je hebt mij altijd goede feedback gegeven en geholpen waar nodig was. Dr. ir. Frans de Jongh, bedankt voor je kritische blik en je brede kennis. Je nam altijd veel tijd voor discussies, waarin er vaak weer nieuwe vragen naar voren kwamen. Daarnaast wil ik graag Linda en Ruud bedanken, mijn dagelijks begeleiders, voor jullie tijd en kennis om mij vertrouwd te laten raken met het uitvoeren van EMG metingen bij premature neonaten, voor jullie medische en technische support en feedback maar vooral ook voor jullie gezelligheid. Drs. Paul van Katwijk, ik wil je graag bedanken voor de afgelopen twee jaar waarin jij mijn procesbegeleider was en mij hebt geholpen om mijzelf te ontwikkelen als een Technisch Geneeskundige. Ik heb veel over mijzelf geleerd tijdens onze gesprekken, over mijn leerproces, mijn kwaliteiten en valkuilen. Dank je wel voor onze fijne en persoonlijke gesprekken, die ik zeer heb gewaardeerd.

Naast mijn begeleiders wil ik ook graag de overige leden uit mijn afstudeercommissie bedankten. Prof. dr. ir. Bennie ten Haken, hartelijk dank voor het voorzitten van mijn afstuderen. Ik vind het erg fijn dat u beschikbaar en bereid was om de rol van vervangend voorzitter op u te nemen. Ook wil ik graag Lex van Loon bedanken voor je deelname als extern lid in mijn afstudeercommissie.

Uiteraard wil ik ook graag alle patiënten en hun ouders bedanken voor hun deelname aan mijn onderzoek en daarmee hun bijdrage aan mijn master thesis.

Bedankt lieve Roseanne, voor je gezelligheid als kamergenootje! Maar ook voor je luisterend oor als ik even mijn verhaal kwijt moest. Mede dankzij jou heb ik een hele leuke tijd gehad op de NICU in het AMC. Ook wil ik graag mijn lieve vriendinnetjes bedanken voor jullie interesse, support, afleidende theemomentjes en bemoedigende gesprekken tijdens mijn afstuderen. In het bijzonder wil ik mijn TG vriendinnetjes, Karin, Kirsten, Marijn, Seraya en Suzan bedanken voor 7 onvergetelijke studiejaren!

Tot slot, lieve papa en mama en lieve Kai, bedankt voor jullie support tijdens mijn studie en voor het feit dat jullie er altijd voor mij zijn en mij vertelden dat ik het wel kon, als ik er zelf even niet zoveel vertrouwen in had. Zonder jullie was ik nooit zover gekomen!

Robin Bekhuis

Utrecht, juni 2018

Abstract

Introduction

Monitoring the respiration of preterm infants is important in neonatal intensive care. Transcutaneous electromyography of the diaphragm (dEMG) is a feasible non-invasive, bedside cardiorespiratory monitoring tool in preterm infants to monitor respiration based on the electrical activity of the diaphragm. This method has the advantage over the currently used cardiorespiratory monitoring technique, chest impedance, that it is able to provide information on the neural breathing effort. Before transcutaneous EMG of the diaphragm can be implemented in the NICU as clinical monitoring tool, one of the requirements is the positioning of the electrodes on different locations on the chest of the infant whereby signal quality remains comparable. The feasibility to measure the electrical activity of the diaphragm by means of dEMG at different positions of electrode placement in preterm infants needs to be established.

Methods

dEMG was measured at standard electrode position (i.e. two electrodes bilaterally at the costo-abdominal margin in the nipple line and one at the height of the sternum, the so-called ground electrode) and at one of the five non-standard electrode positions (i.e. lateral, medial, superior or inferior to the two standard electrodes or bilaterally on the dorsal surface of the chest at the same height as the two standard electrodes) for 1 hour in stable preterm infants with a gestational age < 37 weeks. Six 30-second stable dEMG recordings simultaneously recorded on the standard electrode position and the non-standard electrode position were selected by visual inspection for each 1-hour recording. The percentage differences in derived dEMG parameters at non-standard electrode positions compared to standard electrode position were analyzed. Analysis of the dEMG parameters included peak activity of the diaphragm ($dEMG_{peak}$), tonic activity of the diaphragm ($dEMG_{tonic}$), the amplitude ($dEMG_{amp}$) and area under the curve (AUC). In addition, respiratory rate (RR_{dEMG}), heart rate (HR_{dEMG}), coefficients of variation and phase differences were calculated for the selected dEMG recordings.

Results

Twenty-three preterm infants (gestational age (mean ± SD) 30.9 ± 2.6 weeks; birth weight (mean ± SD) 1593 ± 582 gram) were included. There were no statistically significant differences for $dEMG_{peak}$, $dEMG_{tonic}$, $dEMG_{amp}$ and AUC at lateral, superior, medial and dorsal electrode positions compared to the standard electrode position. The percentage differences in $dEMG_{peak}$, $dEMG_{tonic}$, $dEMG_{amp}$ and AUC at inferior electrode position compared to the standard electrode position did decrease significantly (median -59.7, IQR -66.3 to -52.7%; median -51.2, IQR -55.6 to -39.0%; median -63.7, IQR -71.5 to -57.5%; -58.0, IQR -63.5 to -49.5%, respectively). No significant differences were found for the calculated RR_{dEMG} and HR_{dEMG} at non-standard electrode positions compared to the standard electrode position.

Conclusion

It is feasible to measure diaphragmatic activity using dEMG at most non-standard electrode positions on the chest of the preterm infant. Diaphragmatic activity at inferior electrode position showed statistically significant differences compared to the standard electrode position. RR and HR can be measured accurately at different positions of electrode placement.

List of abbreviations

AMC	Academic Medical Center Amsterdam
AOP	Apnea of prematurity
CI	Chest impedance
CV	Coefficient of variation
dEMG	Transcutaneous electromyography of the diaphragm
$dEMG_{peak}$	Peak (maximal) electrical activity of dEMG
$dEMG_{tonic}$	Tonic (minimal) electrical activity of dEMG
$dEMG_{amp}$	Amplitude of dEMG; peak dEMG activity minus tonic dEMG activity
EKZ	Emma Children's Hospital (Dutch: Emma Kinderziekenhuis)
FiO_2	Fraction of inspired oxygen
FRC	Functional residual capacity
GA	Gestational age
$[H^+]$	Concentration of hydrogen molecules
HR	Heart rate
IQR	Interquartile range
NICU	Neonatal intensive care unit
pCO_2	Partial pressure of carbon dioxide
pO_2	Partial pressure of oxygen
RMS	Root mean square
RR	Respiratory rate
SD	Standard deviation
SpO_2	Oxygen saturation
µV	Micro-volt
WOB	Work of breathing

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Chapter 1 – Introduction

Preterm infants are born before a gestational age (GA) of 37 weeks.[1] Premature birth is a common complication of pregnancy worldwide. It is estimated that globally more than 1 in 10 infants are born prematurely every year.[2] This corresponds to approximately 15 million infants. Due to the preterm birth, all organ systems are underdeveloped, both structural and functional. Underdevelopment of the respiratory system is one of the major morbidities in preterm infants.[1] The transition from fetal to neonatal life demands infants to rapidly develop a stable respiratory system for adequate gas exchange.[3]
In preterm infants, lung function is compromised due to the immature lung tissue. As a result of this compromised lung function, gas exchange is often impaired and work of breathing (WOB) is increased.[4] In addition, the respiratory center that controls breathing is not yet adapted to extra-uterine life in preterm infants. It leads to irregular breathing which can lead to apnea (a cessation in respiration) or periodic breathing (a breathing pattern characterized by respiratory cycles of 10-15 seconds with pauses of 5-10 seconds).[5,6] This impaired control of breathing can make sufficient breathing and gas exchange problematic.[5]
Due to the compromised lung function and the impaired control of breathing, preterm infants are at high risk of respiratory failure.[7,8] The more preterm the infant, i.e. a GA of less than 28 weeks, the greater the risk for respiratory failure.[9] These infants are born while the respiratory system is still developing and gas exchange begins.[9] For abovementioned reasons, adequate monitoring and specific treatments (e.g. respiratory support) are often required in preterm infants.

Impaired control of breathing is rather physiological, related to the immaturity of the respiratory regulation, than pathological in preterm infants.[6] Under normal circumstances breathing is regulated by the respiratory center in the brainstem, located in the pons and medulla. This center regulates the stimulation of the diaphragm, the principle respiratory muscle of inspiration[10], via the phrenic nerve. The immaturity of the central respiratory drive can result in apnea of prematurity (AOP), defined as a cessation in respiration of ≥20 seconds or a cessation in respiration accompanied by blood oxygen desaturation (SpO_2 <80%) and/or bradycardia (heart rate (HR) <80/min).[6,11,12] Apnea can be classified as central, obstructive or mixed.[13,14] Central apnea is characterized by a cease in airflow due to absence of respiratory effort. During obstructive apnea respiratory efforts are made, but obstruction of the (upper) airways causes a cease in airflow. Mixed apnea is characterized by a cease in airflow caused by a combination of characteristics of both central and obstructive apnea.[3,6,8]

Mixed apnea account for more than half of all apneic episodes in preterm infants, followed by central and obstructive apnea in decreasing frequency.[6,8,11,13] The incidence of apnea is inversely proportional to GA[15], and almost all infants with a GA less than 30 weeks are affected.[11] AOP frequently persists until the infants reach 34 weeks postconceptional age, but in extremely preterm infants this period may even extend beyond the term age.[6,11]

Short respiratory pauses, as occur in periodic breathing, are not deemed harmful when an adequate oxygenation is maintained. However, respiratory pauses can be problematic if associated with prolonged hypoxemic episodes which occur often in preterm infants.[5] Prolonged hypoxemic episodes during apnea accompanied by bradycardia are associated with impaired neurodevelopmental outcome in extremely preterm infants at a corrected age of 18 months.[16,17] Early and effective therapy to minimize these hypoxemic episodes is therefore essential. The optimal treatment is highly dependent on the type of apnea and therefore correct detection and classification based on cardiorespiratory monitoring is important. Initially, apnea can be treated by tactile stimulation and optimization of position, followed by pharmacological treatment and/or (non-) invasive respiratory support. For example, caffeine might be the first treatment of choice for central apnea while nasal continuous positive airway pressure (nCPAP) might be a better choice for obstructive apnea.[18]

1.1 Rationale

Accurate cardiorespiratory monitoring is essential in preterm infants, providing correct detection and classification of the type of apnea. Correct measurement of HR, respiratory rate (RR), breathing pattern and SpO_2 are decisive for detection of periods of bradycardia, cessation in respiration and oxygen desaturation.[5,19] Chest impedance (CI), the current standard cardiorespiratory monitoring of preterm infants, measures changes in electrical impedance caused by changes in lung aeration and chest wall movements by means of three transcutaneous ECG electrodes.[7,20] CI provides continuous monitoring of HR, RR and breathing pattern, in which the latter is used for detection of apnea. However, CI has important limitations such as the limited ability to distinguish obstructive apnea from normal respiration due to movement of air back and forth within the chest wall cavity during airway obstruction.[20] This will result in similar impedance changes to normal respiration. Another limitation of CI is the inability of measuring the respiratory effort, i.e. the energy that is needed to breathe, that is made.[20] Furthermore, CI is affected by cardiac interference, resulting in the difficulty that HR might be interpreted as breathing during central apneic episodes. These limitations constrain the ability of CI to detect and classify AOP which is needed to select the optimal treatment.

Ideally, the neural output of the respiratory center in the brain stem should be measured to detect and, more importantly, to classify apnea. However, direct measurement of this output is cumbersome and invasive. As a derivative of the respiratory center activity, the electrical activity of the diaphragm, which is thought to estimate the neural output as it is directly related to the phrenic nerve activity, can be measured in newborn infants.[21,22] Kraaijenga et al. showed that transcutaneous electromyography of the diaphragm (dEMG) is a feasible bedside cardiorespiratory monitoring tool in preterm infants, providing an accurate measure of both HR, RR, breathing pattern and the respiratory effort.[7] Furthermore, dEMG might improve the accuracy of central and obstructive apnea classification compared to CI.[18] Therefore, this technique might be a promising non-invasive candidate for continuous cardiorespiratory monitoring.

The currently used ECG electrodes can be repositioned without affecting the monitoring of HR by CI. However, repositioning of the electrodes does influence the monitoring of RR and breathing pattern. Repositioning of the electrodes in preterm infants is inevitable and necessary because leaving the electrodes on the same position for several days can damage the vulnerable skin of a preterm infant.

It is therefore of the utmost importance that the electrodes, used during dEMG based continuous cardiorespiratory monitoring, can be repositioned without loss of dEMG signal quality. However, as a consequence of the repositioning, a change in the measured dEMG parameters that are used to assess information about HR, RR, breathing pattern and respiratory effort could occur. To date, little is known about this effect of changing the electrodes' positions on the quality of the dEMG signal in preterm infants.
Feasibility of different positions needs to be confirmed first before this technique could be implemented in the neonatal intensive care unit (NICU) as clinical monitoring tool. Therefore, this study will focus on the feasibility of using different dEMG electrode positions in preterm infants for cardiorespiratory monitoring.

The main research question in this study is:

> *Is it feasible to measure the electrical activity of the diaphragm by means of transcutaneous electromyography at different positions of electrode placement in preterm infants?*

Sub-questions deduced to answer the main research question are:

> *Can equivalent single parameters be obtained from the electrical activity of the diaphragm measured by transcutaneous electromyography at different positions of electrode placement in preterm infants?*
>
> *Can heart rate and respiratory rate be measured accurately at different positions of electrode placement in transcutaneous electromyography of the diaphragm in preterm infants?*
>
> *Which factors influence the measured electrical activity of the diaphragm by means of transcutaneous electromyography at different positions of electrode placement in preterm infants?*

1.2 Outline of thesis

Chapter 2 of this thesis provides a clinical background on the fetal lung development and physiology, the control of breathing and the primary muscle for respiration, the diaphragm. In addition, a technical background on dEMG is provided. In Chapter 3, the method to investigate the feasibility of measuring diaphragmatic activity at different electrode positions is described. Chapter 4 presents the results of this study. Last, the results are discussed and conclusions are drawn in chapter 5 and 6 respectively.

Chapter 2 – Background

Preterm birth interrupts normal lung development in utero, which results in immature lungs leading to a compromised lung function in preterm infants.[5] Prematurity is also accompanied by immaturity of the respiratory center in the brainstem which leads to impaired control of breathing. The concurrent occurrence of immature lung development and the immature respiratory center in the brainstem makes the preterm infant prone for AOP associated with chronic intermittent hypoxia.[5] To understand these processes, lung physiology at the different stages of lung development in preterm infants and control of breathing are explained.

2.1 Fetal lung development and physiology

Normal lung development is characterized by five stages. The first is the embryonic stage (3 – 7 weeks), followed by the pseudoglandular (5 – 17 weeks), canalicular (16 – 26 weeks), saccular (24 – 38 weeks) and alveolar (late fetal life – 8 years) stages.[9] (Figure 1)

Formation of the conducting airways up to the terminal bronchioles occurs during the pseudoglandular stage.[23] The conducting airways only serve to move air by convection to those regions of the lungs that will participate in gas exchange.[24] In extremely preterm infants, the lung is at the canalicular stage of fetal lung development when they are born. During this period, the respiratory bronchioles, alveolar ducts and primitive alveoli start to develop. These represent the first generations of the respiratory airways. The alveolar-capillary barrier starts to develop; the first step in the formation of the gas exchange regions of the lungs.[9] Also, epithelial cells are differentiating into surfactant producing type II pneumocytes.[9] Surfactant is a surface active substance in the lung, consisting of phospholipids and proteins, decreasing the surface tension within the alveoli. At birth, extremely preterm infants have reduced alveolar-capillary surface areas and therefore an increased diffusion barrier for gas exchange.[5] The exchange of oxygen and carbon dioxide with the pulmonary-capillary blood, which is the main function of the lungs, is impaired. During the saccular stage, which is a transitional stage before full maturation of alveoli occurs in the alveolar stage, the gas exchange area increases and type II epithelial cells continue to mature. There is an increase in the synthesis of pulmonary surfactant, which increases lung compliance by decreasing the surface tension within the alveoli. However, overall synthesis levels of surfactant remain low during this period. Regardless of the insufficient levels of surfactant, the stage of lung development at the time of birth predisposes preterm infants to impaired gas exchange. [25]

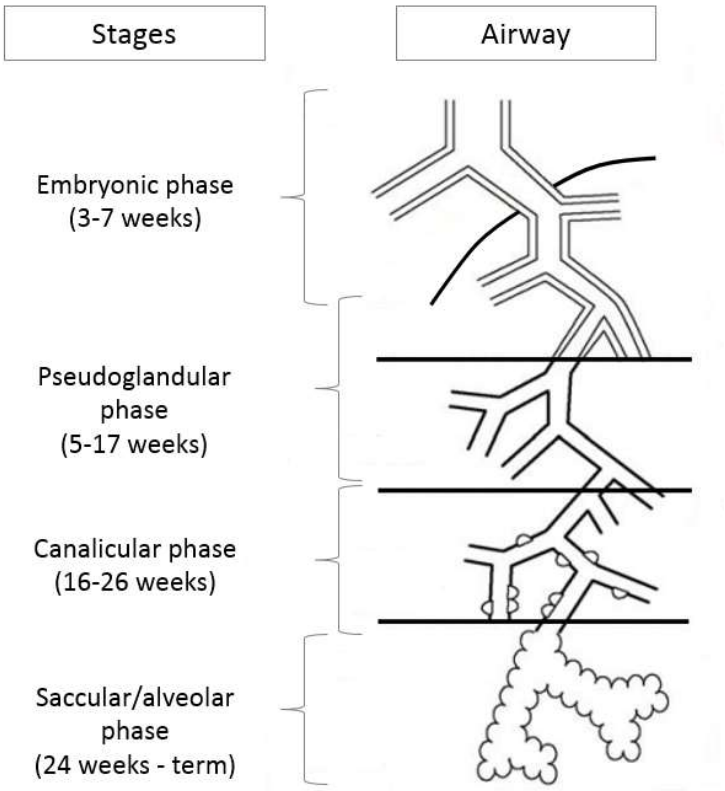


Figure 1: Development of the lung divided into stages.[26]

2.1.1 Lung function and mechanics of the chest wall

The exchange of oxygen and carbon dioxide, which takes place in the alveoli, is the primary function of the respiratory system. To achieve sufficient gas exchange, maintaining adequate lung volume at the end of expiration, also called functional residual capacity (FRC), is necessary. FRC serves as an oxygen buffer that prevents hypoxemic episodes during apnea[5,27,28] and prevents the alveoli to collapse during expiration. However, preterm infants are prone to inadequate FRC. They have a highly compliant chest wall due to its cartilaginous structure, resulting in minimal outward recoil, making the neonatal lung more prone to collapse. Moreover, due to the inadequate levels of surfactant at preterm birth, the infants have a low lung compliance making the alveoli also more prone to collapse. Collapse of the airways during tidal breathing makes the preterm infant susceptible to airway obstruction, leading to inadequate FRC and subsequently impaired gas exchange.[29] To maintain FRC, preterm infants actively elevate their FRC by maintaining inspiratory muscle activation throughout expiration, also called tonic activity.[9]

Besides impaired gas exchange, preterm infants have an increased WOB due to a compromised lung function. The low lung compliance together with the small absolute size of the airways at preterm birth predisposes the infants to this increased WOB. During inspiration, the diaphragm generates a negative intra-thoracic pressure that may cause instability and retraction of the chest wall due to its high compliance. Preterm infants therefore exhibit more paradoxical ribcage and abdominal movement compared to full-term infants, which may contribute to an increased WOB.[20,29]

2.2 Control of breathing

Control of breathing is maintained with a feedback system in which a control system, sensors and effectors play a role. The purpose of control of breathing is to maintain adequate blood levels of partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2) and the concentration of hydrogen molecules [H^+]. Normally, respiration is regulated by the respiratory center which is located in the pons and medulla in the brainstem, and operates as a negative feedback system. The respiratory center consists of three respiratory groups of neurons, two in the medulla and one in the pons. In the medulla are the ventral respiratory group and the dorsal respiratory group located.[30] In the pons are the pneumotaxic and apneustic centers situated, also called the pontine respiratory group.[30] These respiratory groups control breathing by a complex interaction. (Figure 2)

2.2.1 Sensors

Several sensors are involved in the control of breathing. The main sensors involved in control of breathing are the central and peripheral chemoreceptors, found in the brain and in the carotid/aortic bodies respectively. These chemoreceptors are responsible for sensing chemical changes in the blood. pCO_2 is probably the most important drive for respiratory regulation. Although central chemoreceptors are considered the main chemoreceptors that modulate breathing in response to changes in pCO_2 and [H^+], peripheral chemoreceptors in the carotid body also respond to changes in arterial pCO_2.[31] However, the response of the peripheral chemoreceptors can be modulated by the pO_2 as well. In preterm infants, there is an immature respiratory control with a weakened function of the peripheral chemoreceptors. The breathing response to increased pCO_2 in preterm infants is impaired when compared to term neonates or adults.[8] Whereas term neonates and adults increase their ventilation in response to increased pCO_2, preterm infants do this to a lesser extent.[3] Hypoxia enhances the reduced sensitivity to changes in pCO_2, leading to apnea.

2.2.2 Regulator – respiratory center

Neurons that generate the respiratory rhythm are located in the medulla (figure 2). Signals from various sensors are integrated in the medulla, via the carotid nerve (which is a branch of the glossopharyngeal nerve (N. IX)) and via the vagal nerve (N.X).
As mentioned, two respiratory groups are located in the medulla. The dorsal respiratory group primarily contains inspiratory neurons and activates the diaphragm and the external intercostal muscles. The ventral respiratory group contains both inspiratory and expiratory neurons, regulating the switch between inspiration and expiration. It is thought that the so-called pre-Bötzinger complex, which lays in the intermediate ventral respiratory group, is the primary respiratory pattern generator of inspiratory rhythm.[10,30] It is hypothesized that the complex exists of pacemaker neurons.[10,30,32]

Although the medulla generates the normal respiratory rhythm, the pontine respiratory group in the pons can affect respiratory output. The apneustic center has an excitatory effect on the parts of the medulla involved in inspiration (dorsal respiratory group), promoting inspiration. The pneumotaxic center, located in the rostral pons, promotes coordinated respirations. It limits the inspiration such that passive expiration can occur. This center is therefore considered as the antagonist of the apneustic center.[10,30]

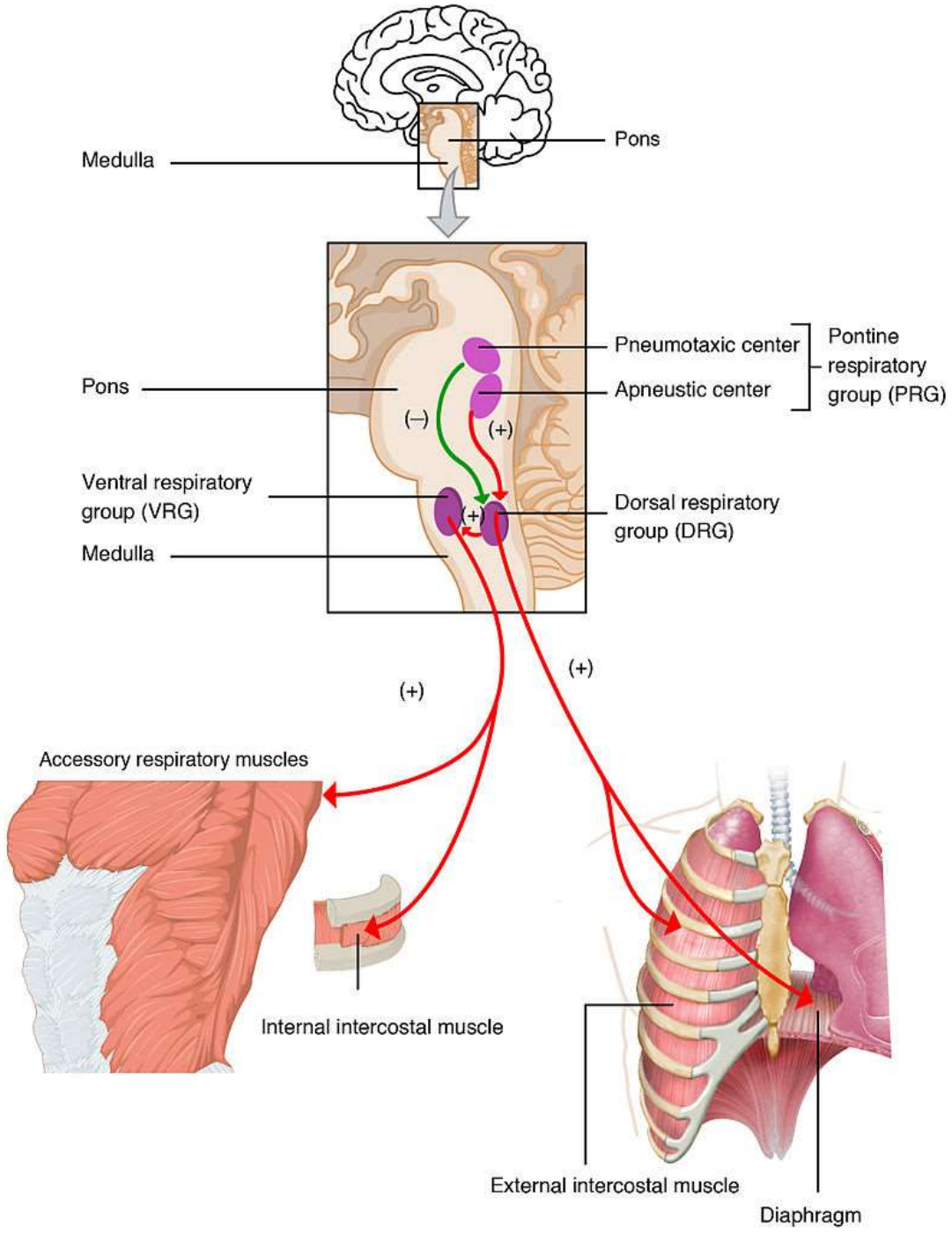


Figure 2: The respiratory center in the brainstem, with the respiratory groups and their influence.[33]

2.2.3 Effectors – respiratory muscles

The respiratory muscles are the effectors of control of breathing. Respiratory muscles can be divided into inspiratory and expiratory muscles. The primary muscle used for inspiration is the diaphragm. (Figure 3) The diaphragm is a dome-shaped muscle inserted to the lower ribs and divided in a left and right hemidiaphragm that can act individually.[10,34] The diaphragm is a skeletal muscle which is innervated by the left and right phrenic nerves which originates from the cervical spinal cord (C3-5)[10,34] and it separates the thoracic cavity from the abdominal cavity. The diaphragm consists of a costal and crural part, connected by the non-contractile central tendon, which forms the crest of the dome-shaped muscle. The muscle fibers of the costal part take origin from the central tendon and are attached to the internal surfaces of the lower six costal cartilages and their adjoining ribs. The muscle fibers of the crural part insert into the upper three lumbar vertebrae.[35] Although the costal and crural part are anatomically different, they are activated simultaneously during inspiration.

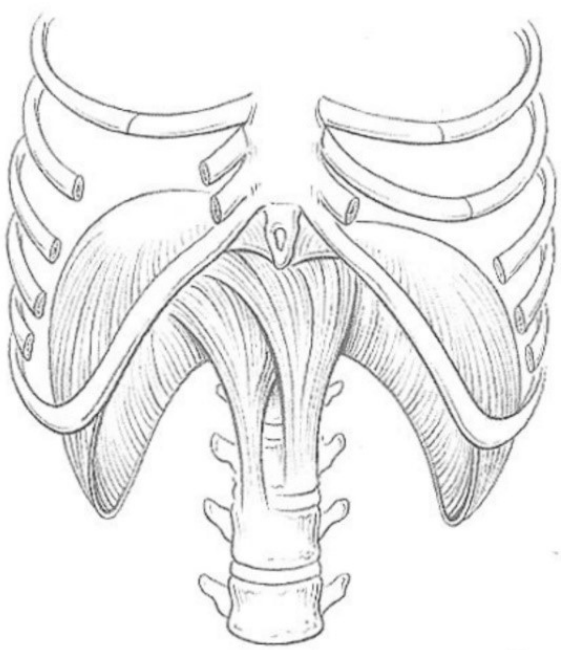


Figure 3: Representation of the diaphragm at full expiratory position.[36]

Respiratory muscles are a special type of skeletal muscles since they are under both involuntarily and voluntarily control.[35] The composition of the muscle fibers in preterm infants is different compared to term neonates or adults. The relative proportion of type I muscle fibers (slow twitch, fatigue resistant) and type II muscle fibers (fast twitch, fatigable) in respiratory muscles changes with development. In preterm infants, 10% of the muscle fibers in the diaphragm are type I muscle fibers whereas term neonates and children older than 2 years have a percent composition of type I muscle fibers in the diaphragm of 25% and 55%, respectively.[37-39] A similar change in muscle fibers is seen for the intercostal muscles.[37] Therefore, it would be reasonable to conclude that preterm infants are more susceptible to respiratory muscle fatigue, which may contribute significantly to respiratory problems in the infant.

During inspiration, the diaphragm contracts which results in flattening and its movement downward towards the abdomen, increasing the intrathoracic volume and creating a negative intrapleural pressure ensuring an increase of air flow into the lungs. Prior to inspiration, the external intercostal muscles stabilize the rib cage of the highly compliant chest wall by pulling the ribs upward and forward.[20] If the needed stability is provided, contraction of the external intercostal muscles can contribute to the intrathoracic volume. The external intercostal muscles are innervated by intercostal nerves (T1-12). The secondary (or accessory) muscles of inspiration include the scalene muscles and the sternocleidomastoid muscles. These muscles are only activated during increased WOB.

Normal expiration is usually a passive process, accomplished by relaxing the muscles of inspiration. The lung tissue recoils due to its elasticity when the diaphragm relaxes and returns to its normal upward and dome-shaped position. Relaxation of the inspiratory muscles results in a decrease in intrathoracic volume and thus an increased pressure in the lungs, causing expiration. Expiration can become an active process during e.g. exercise and voluntary hyperventilation. The abdominal muscles (m. rectus abdominis, external and internal oblique and the m. transverse abdominis) are the most important muscles of expiration. Contraction of these muscles will increase the intra-abdominal pressure, causing the diaphragm to move upward. The internal intercostal muscles assist active expiration by actively pulling down the ribs, leading to a decrease in intrathoracic volume.

As mentioned before, to overcome the high compliance of their chest wall, preterm infants actively elevate their FRC by maintaining inspiratory muscle activation throughout expiration. They prolong their expiration by braking or stopping the expiratory flow.[29] Diaphragmatic control and laryngeal control of the expiratory flow are present at birth in term and preterm infants.[40] These control mechanisms play an important role in maintaining FRC together with the tonic activity and a closed or narrowed glottis during braked expiration.[29,41,42]

2.3 Electromyography of the diaphragm

The bio-electric source of the muscular activity is found in the sarcolemma of muscle fibers.[19,43] Each muscle consists of muscle fibers which are connected to motor neurons. Motor units of the diaphragm consist of a motor neuron and an assembly of skeletal muscle fibers innervated by the axon from that motor neuron. Motor units are the smallest functional units of the muscle involved in contraction. When the motor neuron is stimulated, an action potential is transferred from the motor neuron to the motor endplate. When an action potential contracts the nerve ending, a neurotransmitter (acetylcholine) is released and binds to the post-synaptic receptor, causing a local depolarization at the endplate of the muscle cell membrane. By activating voltage-gate potassium and sodium channels, the depolarization produces an action potential.[35] This leads to a cascade that eventually results in contraction of the motor unit. Contraction of a muscle is the result of simultaneous contractions of several motor units.

Transcutaneous EMG is used to noninvasively measure the electrical activity of muscles during contraction. More specific, electromyography of the diaphragm detects the summation of motor unit action potentials (MUAPs) which are the result of superimposition of the action potentials of the activated muscle fibers that belong to that particular motor unit of the diaphragm.[35] The raw dEMG signal is the result of the electrical activity of many motor units simultaneously and represents an estimate of the global diaphragmatic muscle activity. The electrical activity of the diaphragm measured by dEMG is thought to reflect the neural output of the respiratory center as the electrical activity of the diaphragm is directly related to the activity of the phrenic nerves. Assuming an intact neuromuscular conduction, changes in the amplitude of the dEMG signal indicate changes in neural respiratory drive.[44] Kraaijenga et al. already showed that measuring the electrical activity of the diaphragm using transcutaneous EMG might be a promising non-invasive measurement tool for continuous and prolonged cardiorespiratory monitoring as this technique improves the accuracy of central and obstructive apnea classification compared to the currently used CI.[18]

To analyze the measured dEMG signal, absolute values of the dEMG signal or the frequency spectrum can be used. Analysis using the root-mean-square (RMS) focuses on the absolute electrical activity of the diaphragm. The RMS is a smoothed envelope of the raw signal, especially useful in noisy signals that can be positive and negative, such as the raw dEMG signal. The RMS is defined as the square root of the mean square, in which the mean is calculated over a certain time window. The longer the time window, the more the signal is smoothed and less sensitive for small changes. The RMS is easy to use and is widely accepted as a quantitative measure for EMG analysis.

In this study, diaphragmatic EMG measurements are performed with transcutaneous electrodes. In order to obtain electrical activity of the diaphragm, electrodes are normally placed according to a method described by Prechtl et al.: two electrodes are placed bilaterally at the costo-abdominal margin in the nipple line, and the ground electrode is placed at the height of the sternum.[45] This electrode placement is presented by the two white electrodes labelled with 1 and 2, and the black electrode in figure 4. In this manner, dEMG measures the electrical activity of the costal part of the diaphragm during contraction.[46]

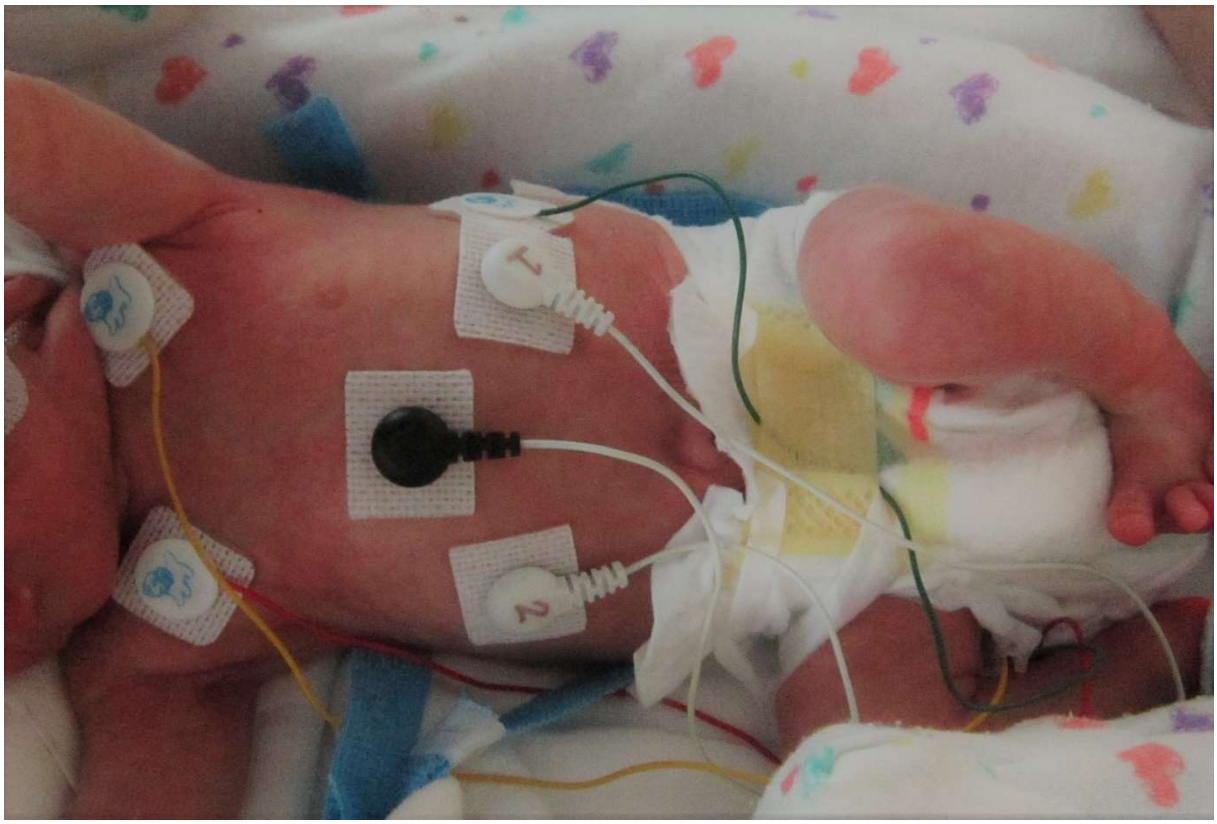


Figure 4: Placement of transcutaneous dEMG electrodes in a preterm infant. Two electrodes are placed bilaterally at the costo-abdominal margin in the nipple line (white electrodes labelled with 1 and 2), and the black ground electrode is placed at the height of the sternum. The electrodes with yellow, red and green wires are CI electrodes and are placed on the infant's chest. The photograph is published with permission of the parents.

It is inevitable and necessary to reposition the electrodes in preterm infants regarding their vulnerable skin. However, repositioning may affect the information about HR, RR, breathing pattern and respiratory effort based on the measured diaphragmatic activity. Therefore, the aim of this study is to analyze if it is feasible to measure equivalent diaphragmatic activity at different dEMG electrode positions in preterm infants in comparison with the standard electrode position.

Chapter 3 – Methods

3.1 Study population

In this single center prospective observational study, dEMG measurements were performed with transcutaneous electrodes placed at different positions on the chest of clinically stable preterm infants. The study was conducted on the Neonatal Intensive Care Unit (NICU) of the Emma Children's Hospital, Academic Medical Center (AMC) Amsterdam. In line with previous studies performed in our department with a similar design, we chose to include a convenience sample of 30 preterm infants.[7,47] The study protocol was approved by the Institutional Review Board and both parents provided written informed consent. (Appendix A1) To be eligible to participate in this study, preterm infants admitted to the NICU had to meet the following inclusion criteria:

- Born at 26 to 37 weeks GA;
- Receiving non-invasive respiratory support with a maximum fraction of inspired oxygen (FiO_2) of 30% or no respiratory support;
- Average of less than two episodes of apnea per hour.

Infants were excluded from participation in this study if they meet any of the following criteria:

- Major (abdominal) congenital anomalies;
- Clinical instability requiring frequent interventions by the nursing staff that may interfere with the measurements;
- The attending physician considered the infant to be too vulnerable to participate in the study;
- Parents were unable to understand and read the Dutch language.

3.2 Study procedures

The preterm infants were prospectively recruited on a consecutive basis on the NICU. In order to give an overview of the included preterm infants in this study, we collected the following patient characteristics: GA, birth weight, postnatal age and weight at the day the measurement was conducted and data on the mode and settings of non-invasive respiratory support during the measurement.

In all preterm infants, transcutaneous EMG signals of the diaphragm were recorded at the bedside using a portable 16-channel digital physiological amplifier (Dipha-16, Demcon, Enschede, the Netherlands). To continuously measure the electrical activity of the diaphragm, five skin electrodes (disposable Kendall H59P Electrodes, Covidien, Mansfield, Massachusetts USA) connected to the header of the Dipha-16 device, were placed on the chest of the infant; two electrodes were placed bilaterally at the costo-abdominal margin in the nipple line and one at the height of the sternum, the so-called ground electrode. These three electrodes represent the standard transcutaneous electrode positioning and have been used in previous research at the NICU (figure 4).

To study the feasibility of measuring equivalent diaphragmatic activity at different electrode positions, the remaining two electrodes were placed bilaterally on one of the five different, non-standard positions, as illustrated in figure 5:

- Lateral (1 cm) from the two standard electrodes in the horizontal plane;
- Medial (1 cm) from the two standard electrodes in the horizontal plane;
- Superior (1 cm) to the two standard electrodes;
- Inferior (1 cm) to the two standard electrodes;
- Bilaterally on the dorsal surface of the body at the same height as the two standard electrodes.

Preterm infants were randomly allocated to one of the five abovementioned non-standard electrode positions using sealed envelopes. Figure 6 represents an example of standard versus superior electrode placement during a measurement.

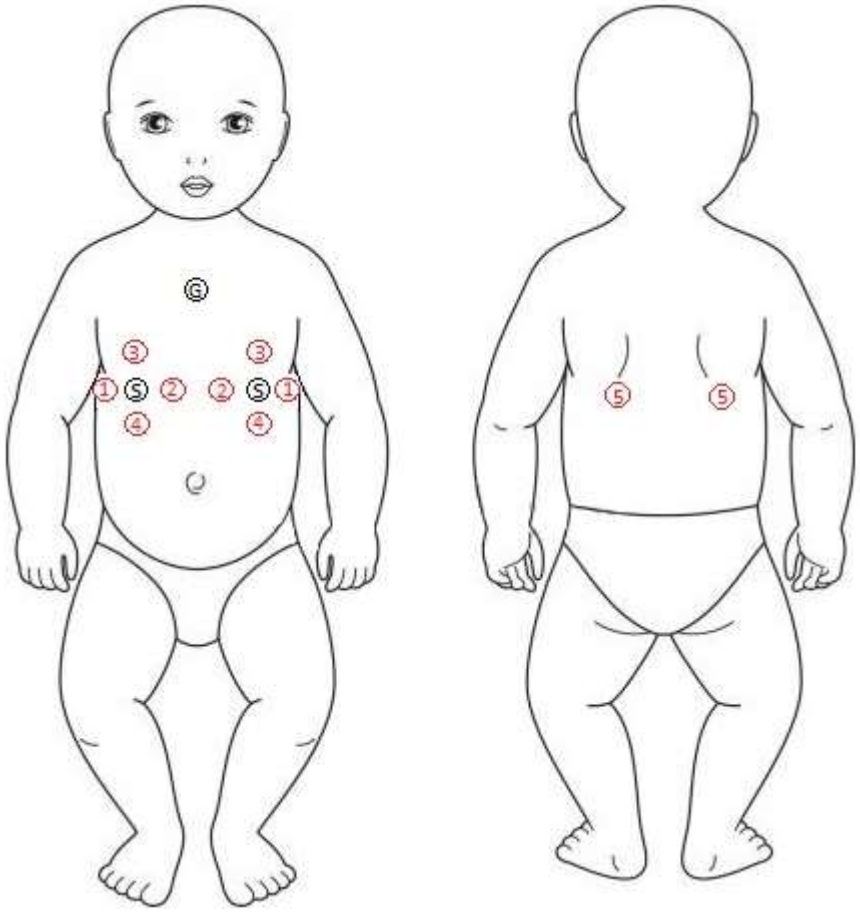


Figure 5: dEMG electrode positions in preterm infants. The black circles with the letter "S" represent the standard transcutaneous electrode positioning. The black circle with the letter "G" represents the placement of the ground electrode. (1) lateral, (2) medial, (3) superior, and (4) inferior to the two standard electrodes and (5) bilaterally on the dorsal surface of the body at the same height as the two standard electrodes.

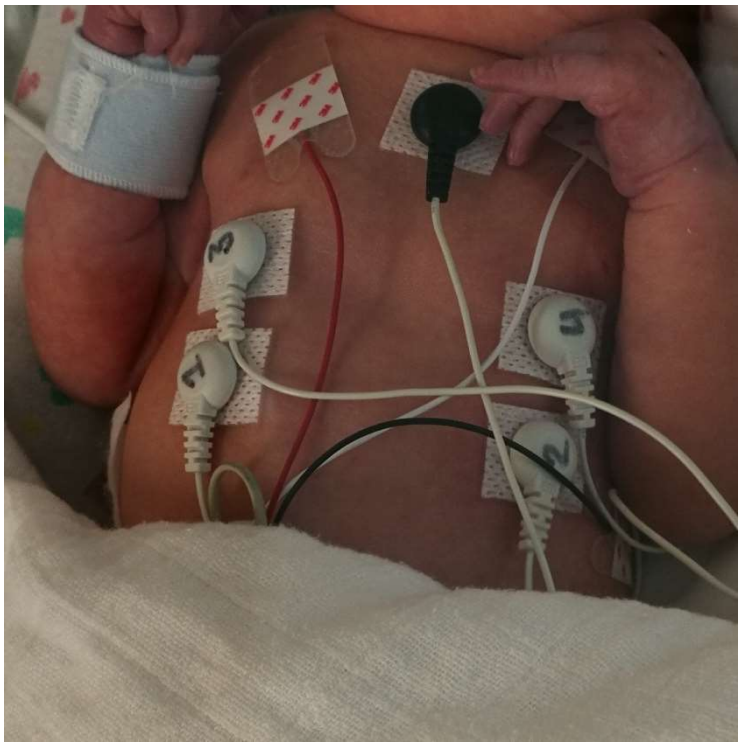


Figure 6: Placement of transcutaneous dEMG electrodes in a preterm infant during a measurement. Two electrodes are placed bilaterally at the costo-abdominal margin in the nipple line (white electrodes labelled with 1 and 2), and the black ground electrode is placed at the height of the sternum. During this specific measurement, two electrodes were placed superior to the standard placed electrodes (white electrodes labelled with 3 and 4). The red electrodes are CI electrodes and are placed on the infant's chest. The photograph is published with permission of the parents.

Diaphragmatic activity and cardiorespiratory parameters were simultaneously recorded by dEMG and CI for one hour. The measurement was performed after nursing procedures and always in consultation with the nurse. During the measurement nursing procedures, except feeding, were postponed to minimize patient disturbance. However, necessary clinical interventions were not delayed because of the measurement.

3.3 Data analysis

3.3.1 dEMG pre-processing

The measured dEMG signals were, without analogue filtering, digitized with a sample frequency of 500 Hz and wirelessly transported to the front-end of the Dipha-16 device, which was connected to a bedside personal computer. In order to analyze the dEMG signals, preprocessing of the raw digital dEMG signals was performed using a custom made application in Polybench (Applied Biosignals, Weener, Germany). Polybench is a software application toolbox capable for data measurement and online processing. The preprocessing involved 1) digital transformation of the raw, monopolar electrophysiological signals into bipolar dEMG signals, 2) followed by filtering with a first order high-pass filter and 3) removal of the electrical activity of the heart according to the gating technique described in 1983 by O'Brien et al.[48] Since dEMG measures electrical muscle activity, it will also measure the electrical activity of the heart. This so called crosstalk is defined as electrical interference from a distant muscle, which is measured at the location of the muscle of interest. The technique described by O'Brien et al. involved removal of the electrical ventricle activity of the heart (QRS) complexes from the dEMG signal after which the remaining gates were filled with the running average in a moving time window.[48] The resulting gated diaphragmatic muscle activity was averaged using the RMS which resulted in a digital respiratory wave form, reflecting the breathing activity of the infant. Using a bipolar configuration, all aspects that two signals of separate electrodes have in common, are removed. In this way, common measured noise is removed and only the true differences between two electrodes with respect to the ground electrode remain. A first order high-pass filter was used to remove low frequency disturbances caused by both artefacts and noise in the environment of the patient or caused by the patient itself. The resulting RMS dEMG signal was used for further analysis.

3.3.2 dEMG post-processing

All recorded and pre-processed dEMG data was analyzed offline by using Matlab (Matlab 2016a, The Mathworks, Inc., Natick, Massachusetts, USA). The recorded dEMG data were imported into a custom made graphical user interface (GUI), shown in figure 7. Each 1-hour recording was subdivided in six windows of ten minutes. From each window, a 30-second stable period simultaneously recorded on the standard electrode position and the non-standard electrode position was selected by visual inspection. A stable period was defined as a period without movement or technical artefacts in the dEMG signal and a signal in which breaths could be discriminated from noise. Figure 8 gives an example of recorded artefact free dEMG data at standard and superior electrode position. Of each patient 180 seconds were analyzed and used to study the feasibility of measuring equivalent diaphragmatic activity at five non-standard electrode positions compared to the standard electrode position.

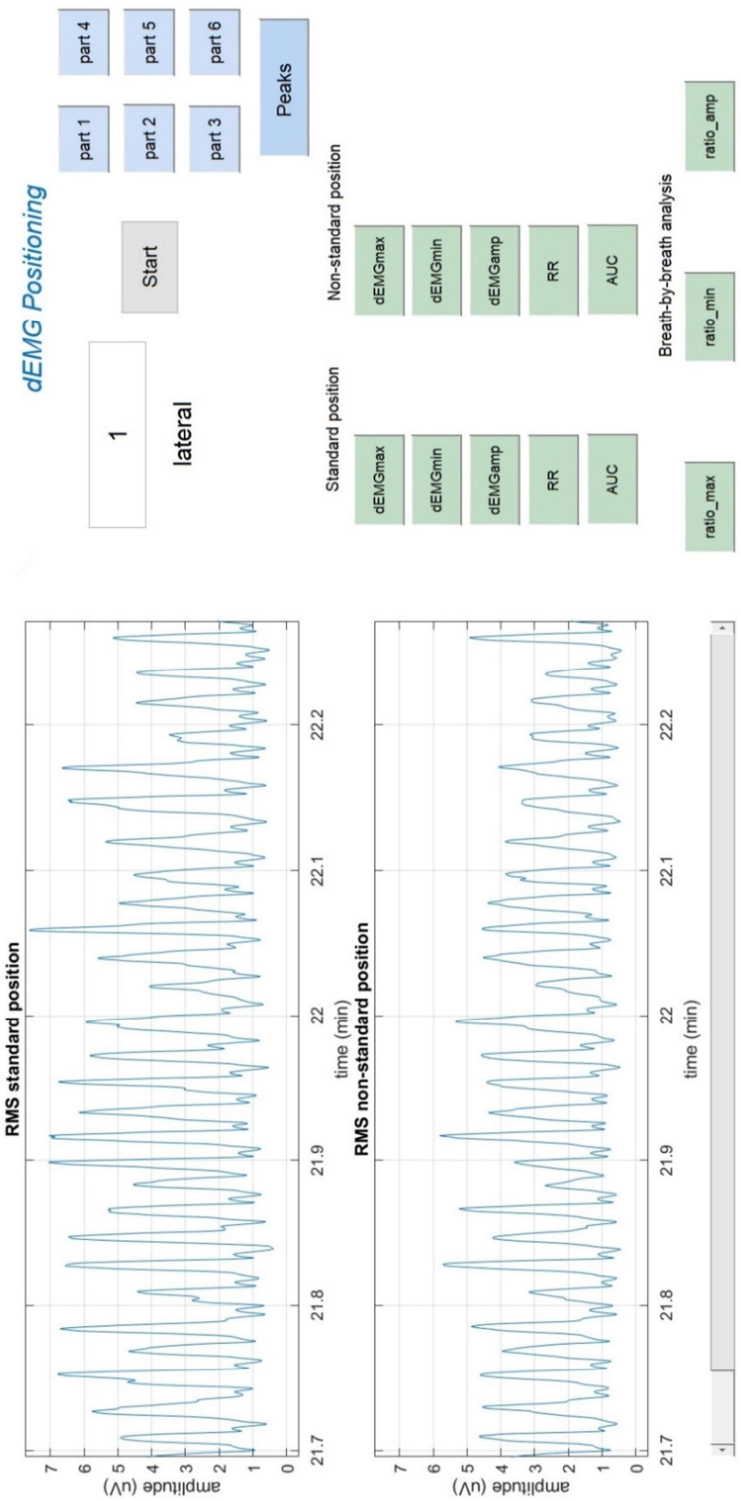


Figure 7: Graphical User Interface. dEMG measurements of preterm infants can be selected on the right side. After pushing the *'Start'* button, the dEMG data measured on standard and non-standard electrode position are plotted on the left side. Six epochs of 30 seconds could be selected using the buttons *'part 1' till 'part 6'*. By pushing the *'Peaks'* button, maximum values and minimum values for each single breath are detected in the selected recordings. By pushing the buttons on the bottom right, dEMG parameters will be calculated.

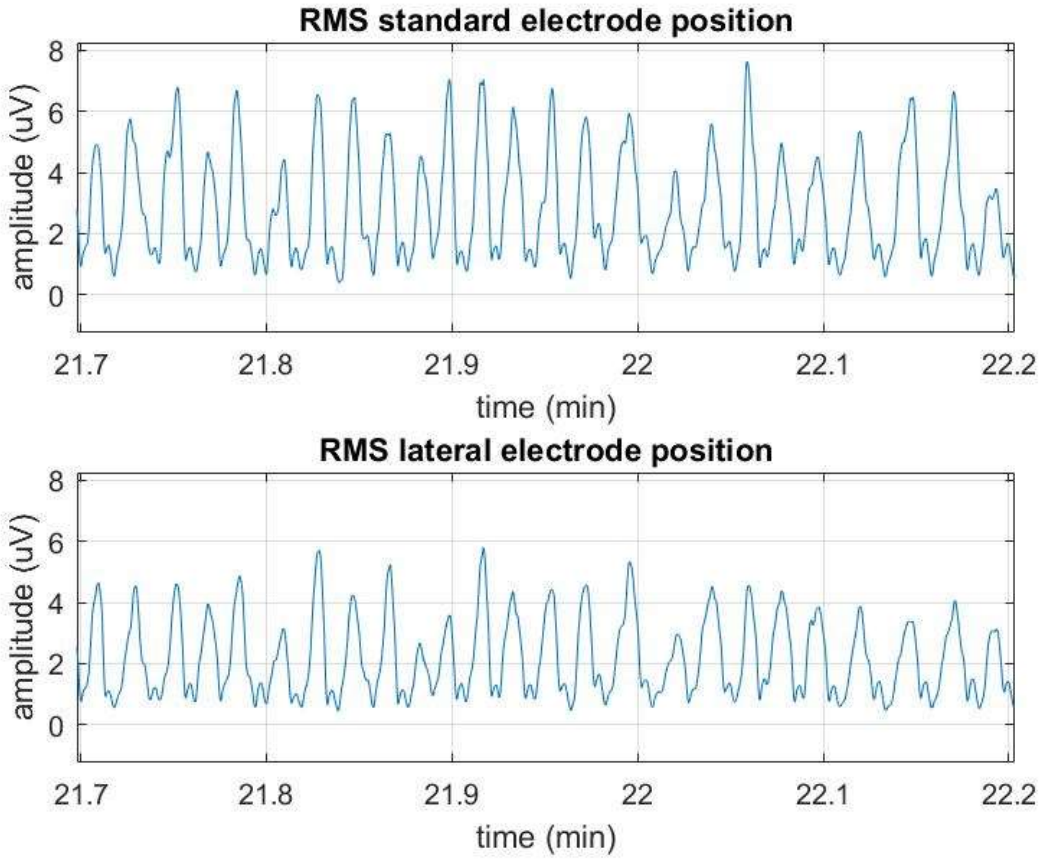


Figure 8: An example of a 30-second stable, artefact free period in the dEMG signal simultaneously measured at standard electrode position and at non-standard, lateral electrode position. (RMS: root mean square, processed dEMG signal; µV: micro-volt)

3.3.3 dEMG parameters

From the averaged dEMG signal at the standard electrode position and non-standard electrode positions, the following dEMG parameters, as listed in Table 1, were derived.

Table 1: Description of the used dEMG parameters in this study.

dEMG parameter	Parameter description	Unit
$dEMG_{peak}$	Maximum of the RMS dEMG signal measured from zero, also called the peak activity of the diaphragm	μV
$dEMG_{tonic}$	Minimum of the RMS dEMG signal measured from zero, also called the tonic activity of the diaphragm	μV
$dEMG_{amp}$	Amplitude of the RMS dEMG signal ($dEMG_{peak} - dEMG_{tonic}$)	μV
AUC_{30sec}	Area under the curve of the RMS dEMG signal	$\mu V \cdot s$
RR_{dEMG}	Respiratory rate detected in the RMS dEMG signal	min^{-1}
HR_{dEMG}	Heart rate detected in the raw dEMG signal	min^{-1}
CV $dEMG_{peak}$	Coefficient of variation of the peak activity of the diaphragm	%
CV $dEMG_{tonic}$	Coefficient of variation of the tonic activity of the diaphragm	%
CV $dEMG_{amp}$	Coefficient of variation of the amplitude	%
$\Delta\varphi$	Phase difference between the RMS dEMG signal at standard position compared to non-standard position.	milliseconds

For each individual breath in the selected recordings, the following dEMG parameters were assessed: peak activity of the diaphragm, tonic activity of the diaphragm and the amplitude. The highest electrical activity, also called the peak activity, was defined as the peak of the RMS curve for each single breath in the selected artefact free recorded dEMG data of each patient. Peak activities were calculated using the *findpeaks* function in Matlab. This function returns a vector with the peaks of the input signal vector, in this case the RMS signal. Peaks that are very close to each other were ignored by using a minimal peak distance. This distance depended on the respiratory rate of the preterm infant and was therefore adjusted for each infant. In addition, we stated that all peaks should have a minimal peak height based on the mean value of the RMS signal. The lowest electrical activity, also called the tonic activity, was defined as the minimum of the RMS curve for each single breath in the same selected dEMG data of each patient. A minimum of the RMS curve was defined as the lowest point prior to a peak and was found by looking back in time from the observed peak to the moment when the RMS curve no longer decreases. A minimal amount of samples between the observed peak and the lowest point prior to that peak was defined based on the respiratory rate of each preterm infant. Using this condition, the incorrect detection of a minimum due to a small increase in the signal was prevented. However, this condition did not cover all incorrect detections of minima due to the irregular breathing of preterm infants, influencing the respiratory rate on which the condition was based. Therefore, we stated that the wrongly detected minima should be ignored and that the detection algorithm should look further back in time until the lowest point prior to the observed peak was found. All conditions for the detection of peaks and minima used by the custom made detection algorithm in Matlab were patient specific. The amplitude was determined by calculating the difference between the highest (peak) and lowest (tonic) electrical activity within each breathing cycle in the selected artefact free recorded dEMG data of each patient. The average amplitude ($dEMG_{amp}$), expressed in micro voltage (μV), was calculated as the average amplitude of all single breaths in the six selected artefact free dEMG epochs of 30 seconds in each patient. Similarly, we calculated the average peak activity ($dEMG_{peak}$) and the average tonic activity ($dEMG_{tonic}$), also expressed in μV.

The diaphragmatic activity at non-standard electrode positions compared to standard electrode position was also evaluated by determining the area under the curve (AUC), expressed in μV·s, of each selected dEMG epoch of 30 seconds in all patients. The AUC was calculated using trapezoidal numerical integration, the function *trapz* in Matlab. This function computed the approximate integral of the selected 30 seconds dEMG recording via the trapezoidal method with unit spacing, representing the AUC of the dEMG epoch of 30 seconds. The average AUC was calculated as the average of the determined AUCs of the six selected dEMG epochs in each patient.

The abovementioned dEMG parameters were determined at standard and non-standard electrode positions. Within each subgroup to which patients were randomly allocated, i.e. the non-standard electrode positions compared to standard electrode position, the calculated dEMG parameters in the selected data were compared between the non-standard and standard electrode position over all patients within that subgroup. To compare the absolute dEMG parameters within each subgroup, standardization is necessary. In literature, various standardization procedures have been described. However, most of these methods focus on healthy individuals or cooperative patients and require a specific task performed by the subjects. As the preterm infants in this study are not cooperative, individual dEMG parameters at non-standard electrode position were expressed as the percentage difference compared with standard electrode position.

Next, the respiratory rate (RR_{dEMG}) was extracted from the artefact free dEMG data at standard and non-standard electrode positions and given in breaths per minute. The RR_{dEMG} was calculated based on the number of peaks that occurred per 30-second period. For each patient, the RR_{dEMG} was averaged over the total period of 180 seconds at non-standard and standard electrode position.

In addition, the heart rate (HR_{dEMG}) was extracted from the raw dEMG data at standard and non-standard electrode positions and given in beats per minute. The HR_{dEMG} was calculated based on the number of QRS complexes that occurred per 30-second period. The *findpeaks* function in Matlab was used to detect the QRS complexes. Conditions regarding this function consisted of a minimal peak distance of 50 samples and a minimal peak height of 250 µV. For each patient, the HR_{dEMG} was averaged over the total period of 180 seconds at non-standard and standard electrode position.

Furthermore, the intra-subject variability between the artefact free dEMG signals at standard and non-standard electrode positions within each subgroup was determined by the coefficients of variation (CV) of $dEMG_{peak}$, $dEMG_{tonic}$ and $dEMG_{amp}$. The intra-subject variability at the different electrode positions compared to standard position was used to study the influence of different electrode placement. The CV is a coefficient that is used as a relative measure of dispersion. The CV was calculated as the average of the ratios of the standard deviation (σ) of $dEMG_{peak}$, $dEMG_{tonic}$ and $dEMG_{amp}$ to the mean (µ) of $dEMG_{peak}$, $dEMG_{tonic}$ and $dEMG_{amp}$ multiplied by 100%, in each patient (equation 1).

$$CV_{dEMG_{peak}} = \frac{\sigma_{dEMG_{peak}}}{\mu_{dEMG_{peak}}} \times 100\% \quad (1.1)$$

$$CV_{dEMG_{tonic}} = \frac{\sigma_{dEMG_{tonic}}}{\mu_{dEMG_{tonic}}} \times 100\% \quad (1.2)$$

$$CV_{dEMG_{amp}} = \frac{\sigma_{dEMG_{amp}}}{\mu_{dEMG_{amp}}} \times 100\% \quad (1.3)$$

Last, the phase difference (Δφ) between the artefact free dEMG data at standard and non-standard position for each selected 30-second stable dEMG recording was calculated using the cross-correlation. The *xcorr* function in Matlab was used to calculate this correlation. The cross-correlation reflects the similarity between two signals as a function of the displacement of one signal relative to the other. When using cross-correlation, the two dEMG signals are time-lagged. The cross-correlation is calculated while automatically sliding one signal over the other. The time lag between the two dEMG signals is defined as the time delay between the two signals at the moment of the highest cross-correlation coefficient. If the two dEMG signals are identical, they have a cross-correlation coefficient of 1, with a time-lag of 0. The cross-correlation coefficients and phase differences were averaged over the total period of 180 seconds in each patient.

3.3.4 Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 24.0 (SPSS Inc. Chicago, Illinois) and GraphPad Prism 7 (GraphPad Software, San Diego, California, USA). All data was tested for normality using a Shapiro-Wilk test. All continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), depending on the distribution of the data.
For comparative analyses between the calculated dEMG parameters at standard electrode position and non-standard electrode positions, the Wilcoxon signed-rank test or paired t-test, depending on the distribution of the data, was used. The compared dEMG parameters are: (1) $dEMG_{peak}$, (2) $dEMG_{tonic}$, (3) $dEMG_{amp}$, (4) AUC, (5) RR_{dEMG}, (6) HR_{dEMG}, (7) CV $dEMG_{peak}$, (8) CV $dEMG_{tonic}$ and (9) CV $dEMG_{amp}$. A p-value less than 0.05 indicated a significant difference between the dEMG parameters at non-standard electrode position compared to standard electrode position.

A Spearman's correlation coefficient, ρ_s, and an intraclass correlation coefficient (ICC) were calculated to evaluate the correlation between the derived dEMG parameters at non-standard and standard electrode positions within each subgroup. In case of Spearman's correlation coefficient, a p-value < 0.05 was considered statistically significant. Higher coefficients denote a stronger magnitude of relationship between derived dEMG parameters at non-standard and standard electrode positions. An ICC of 0.41 to 0.60 is defined as a 'moderate' correlation and an ICC of 0.61 to 0.8 is defined as a 'substantial' correlation between the recorded dEMG signals at non-standard and standard electrode positions. An ICC above 0.81 is assumed to be 'almost perfect'.[49]

Chapter 4 – Results

4.1 Patient characteristics

Both parents of thirty-two eligible preterm infants were informed about this study and asked to provide written informed consent. Both parents of twenty-three preterm infants provided written informed consent and therefore these infants were included in this study. One infant was not included due to unsuspected transfer to another hospital and eight parents did not provide written informed consent for the infant to participate in this study. Due to several reasons, e.g. restricted admission rate of patients, we were not able to include the predetermined number of thirty patients within the time frame of this thesis, but inclusion will continue. Of the twenty-three included infants, five measurements were excluded from analysis due to the inability of distinguishing single breaths in these dEMG signals. The remaining 18 preterm infants had a mean GA of 30.9 ± 2.6 weeks and a birth weight of 1593 ± 582 gram and were studied at a mean postnatal age of 32.9 ± 1.4 weeks. Eight of the infants were supported by nCPAP, six infants were supported by high flow nasal cannula, three infants were supported by low flow nasal cannula and one infant did not receive respiratory support. The infants on non-invasive respiratory support had a median FiO_2 of 21% (IQR 21 – 22%).

Electrical activity of the diaphragm was measured at lateral and standard electrode position in five infants, at inferior and standard electrode position in five infants, at superior and standard electrode position in three infants, at medial and standard electrode position in three infants and at dorsal and standard electrode position in two infants. Table 2 shows the patient characteristics per subgroup. No significant differences were found in the patient characteristics per subgroup.

Table 2: Patient characteristics of all preterm infants included in the subgroups

	Lateral (n=5)	Inferior (n=5)	Superior (n=3)	Medial (n=3)	Dorsal (n=2)	P-value
GA (weeks)	29.4 ± 3.8	30.8 ± 2.3	32.3 ± 0.9	32.4 ± 2.1	[30.6 31.1]	0.51
Birth weight (g)	1319 ± 572	1610 ± 513	1770 ± 775	1827 ± 885	[1595 1640]	0.80
PNA (weeks)	33.7 ± 1.0	32.3 ± 1.1	33.6 ± 1.9	33.0 ± 1.9	[31.0 31.9]	0.88
FiO_2 (%)	21 (21 – 28)	21 (21 – 26)	21 (21 – 21)	21 (21 – 21)	[21 21]	0.25

Definitions of abbreviations: n = number of infants, GA = gestational age, PNA = postnatal age, FiO_2 = fraction of inspired oxygen. Characteristics are expressed as mean ± SD, median (IQR) or as a range if n=2, with level of significance $p < 0.05$. Group differences were tested with one-way ANOVA.

4.2 dEMG analysis

The derived dEMG parameters as mentioned in Table 1 were calculated for all abovementioned subgroups at standard and non-standard electrode positions using a custom made GUI. Table 3 shows all standardized calculated dEMG parameters. All derived dEMG parameters at non-standard electrode positions decreased compared to standard electrode position. In the subgroups representing the lateral, superior, medial and dorsal electrode position compared to standard electrode position, derived dEMG parameters did not show statistically significant differences. Δ $dEMG_{peak}$ (%), Δ $dEMG_{tonic}$ (%), Δ $dEMG_{amp}$ (%) and Δ AUC (%) at inferior electrode position compared to standard electrode position were significantly lower ($p < 0.05$). $dEMG_{peak}$ decreased with a median reduction of 59.7% (IQR -66.3 to -52.7%, p=0.04). $dEMG_{tonic}$ decreased with a median reduction of -51.2% (IQR -55.6 to -39.0%, p=0.04). $dEMG_{amp}$ decreased with a median reduction of -63.7% (IQR -71.5 to -57.5%, p=0.04) and AUC decreased with a median reduction of -58.0% (IQR -63.5 to -49.5%, p=0.04). The significant decreases in peak activity, tonic activity, amplitude and AUC at inferior electrode position compared to standard electrode position are also shown by the boxplots in figures 9 through 12.

Table 3: Standardized derived dEMG parameters at five non-standard electrode positions compared to standard electrode position.

	Standard (n=18)	Lateral (n=5)	Inferior (n=5)	Superior (n=3)	Medial (n=3)	Dorsal (n=2)
Δ $dEMG_{peak}$ (%)	0	-14.9 (-26.4 to 42.2)	-59.7 (-66.3 to -52.7)*	-30.7 (-33.0 to -23.3)	-67.3 (-80.3 to -64.3)	[-50.8 -35.0]
Δ $dEMG_{tonic}$ (%)	0	-6.5 (-9.4 to 16.2)	-51.2 (-55.6 to -39.0)*	-9.8 (-11.5 to -2.6)	-36.8 (-60.2 to -20.0)	[-40.4 -33.9]
Δ $dEMG_{amp}$ (%)	0	-16.7 (-30.9 to 51.5)	-63.7 (-71.5 to -57.5)*	-38.3 (-48.1 to -34.2)	-76.4 (-89.4 to -71.2)	[-58.5 -32.9]
Δ AUC_{30sec} (%)	0	-12.0 (-21.5 to 36.5)	-58.0 (-63.5 to -49.5)*	-24.0 (-24.0 to -19.0)	-64.0 (-71.0 to -55.0)	[-47.0 -40.0]

Definitions of abbreviations: n = number of infants, Δ (%) = percentage difference compared to the standard electrode position, $dEMG_{peak}$ = peak (maximal) electrical activity of dEMG, $dEMG_{tonic}$ = tonic (minimal) electrical activity of dEMG, $dEMG_{amp}$ = amplitude of dEMG, AUC_{30sec} = area under the curve of dEMG over 30 seconds.
Data are presented in median (IQR) or as a range if n=2, with level of significance $p < 0.05$ (*) compared to standard electrode position. Statistically significant differences were tested with the Wilcoxon signed-rank test.

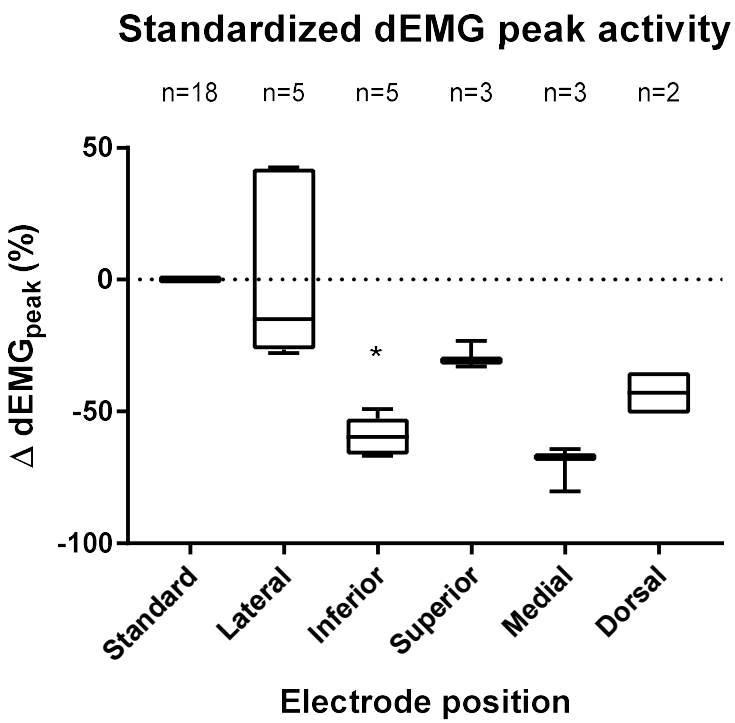


Figure 9: Standardized peak electrical activity at five different electrode positions compared to standard electrode position. Data are presented in median (IQR) or as a floating bar if n=2, with level of significance $p < 0.05$ (*) determined with the Wilcoxon signed-rank test. n = number of infants.

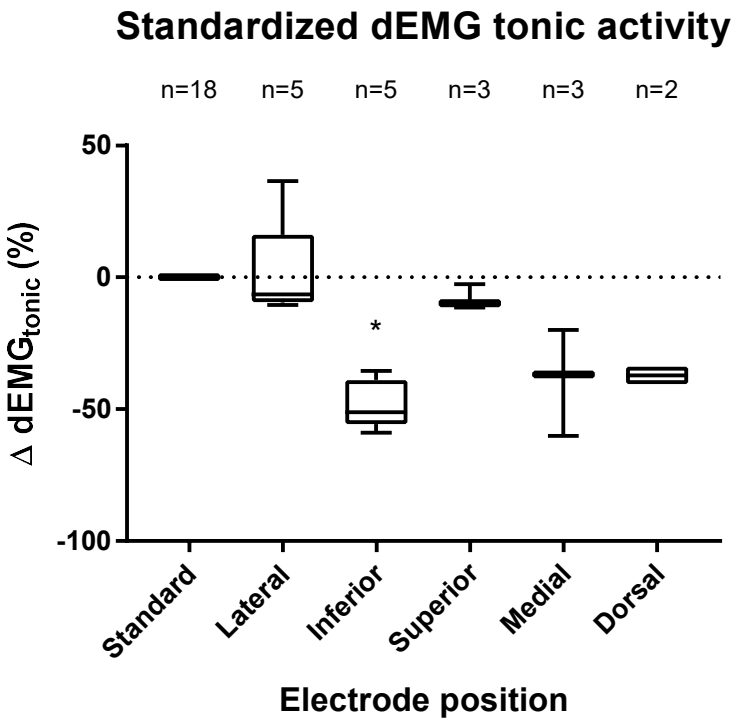


Figure 10: Standardized tonic electrical activity at five different electrode positions compared to standard electrode position. Data are presented in median (IQR) or as a floating bar if n=2, with level of significance $p < 0.05$ (*) determined with the Wilcoxon signed-rank test. n = number of infants.

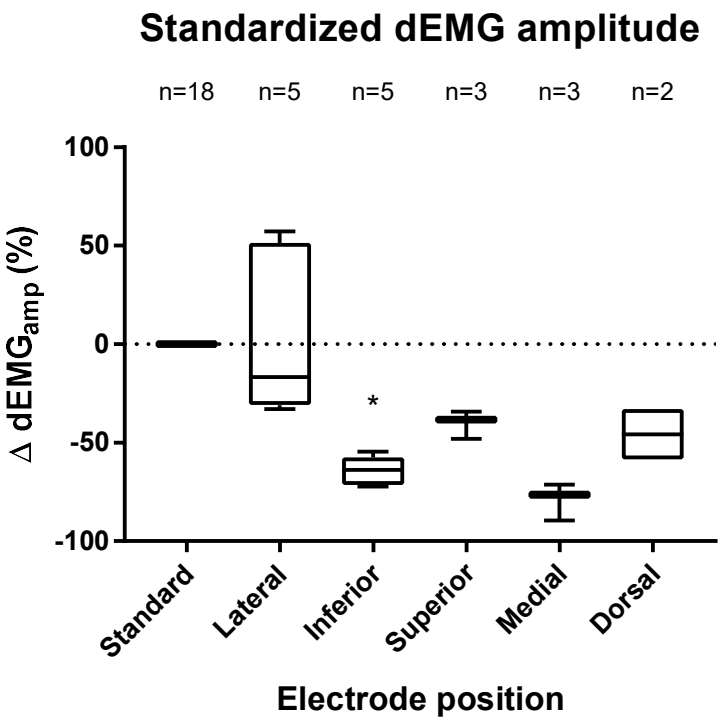


Figure 11: Standardized amplitude of dEMG at five different electrode positions compared to standard electrode position. Data are presented in median (IQR) or as a floating bar if n=2, with level of significance $p < 0.05$ (*) determined with the Wilcoxon signed-rank test. n = number of infants.

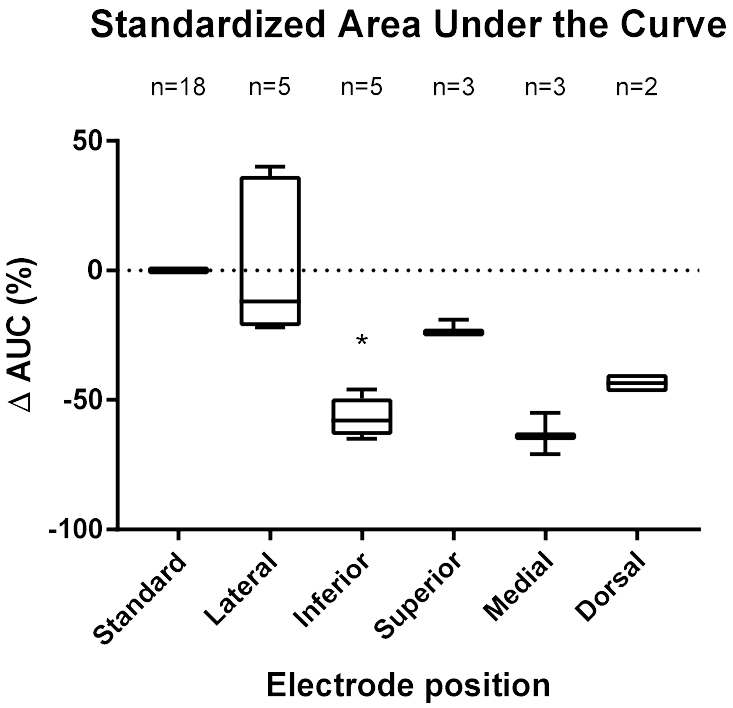


Figure 12: Standardized area under the curve at five different electrode positions compared to standard electrode position. Data are presented in median (IQR) or as a floating bar if n=2, with level of significance $p < 0.05$ (*) determined with the Wilcoxon signed-rank test. n = number of infants.

4.2.1 Correlation

Constructed scatterplots of the relation between the dEMG amplitude measured at standard electrode position and the dEMG amplitude measured at lateral and inferior electrode position revealed highly significant correlations between the dEMG amplitudes measured at those electrode positions (ρ_s = 0.81, p<0.01; ρ_s = 0.80, p<0.01, respectively) (figures 13 and 14). Looking at the ICC, there is a moderate correlation between the dEMG amplitudes measured at lateral versus standard electrode position and at inferior versus standard electrode position (ICC = 0.66; ICC = 0.43, respectively). Correlation coefficients of the dEMG amplitude measured at superior, medial and dorsal electrode position compared to standard electrode position revealed moderate correlations (ρ_s = 0.49; ρ_s = 0.43; ρ_s = 0.40, respectively). Intraclass correlations of the dEMG amplitude measured at these non-standard electrode positions compared to standard electrode position showed moderate agreements (ICC = 0.52; ICC = 0.42; ICC = 0.50, respectively). Scatterplots with their correlation coefficients of these non-standard electrode positions can be found in Appendix A3.

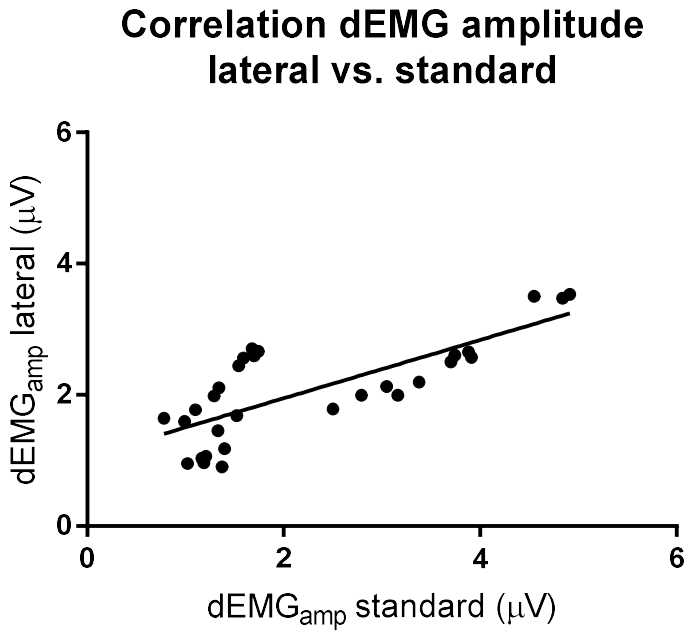


Figure 13: The relation between the dEMG amplitude (μV) measured at standard electrode position and the dEMG amplitude measured at lateral electrode position at six time points for each individual patient. Spearman's correlation coefficient ρ_s = 0.81, intraclass correlation coefficient ICC = 0.66.

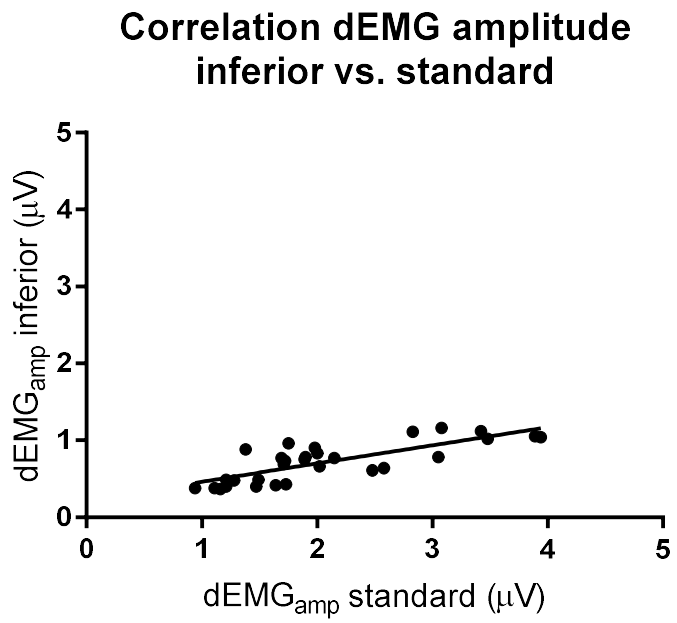


Figure 14: The relation between the dEMG amplitude (μV) measured at standard electrode position and the dEMG amplitude measured at inferior electrode position at six time points for each individual patient. Spearman's correlation coefficient ρ_s = 0.80, intraclass correlation coefficient ICC = 0.43.

4.2.2 Vital parameters

Statistical analysis on RR_{dEMG} and HR_{dEMG}, calculated on non-standard electrode positions compared to standard electrode position, showed no significant differences. This can be seen for the lateral electrode position in Table 4, in which all derived dEMG parameters at lateral electrode position compared to standard electrode position are represented. All derived dEMG parameters for the other non-standard electrode positions can be found in Appendix A2.

The vital parameters calculated from the dEMG signal are highly correlated when measured at non-standard electrode position compared to standard electrode position. Pearson's correlation coefficients ranged from r = 0.94 to r = 1.00 ($p < 0.001$) for RR_{dEMG} measured at non-standard electrode positions compared to standard electrode position. In case of HR_{dEMG}, Pearson's correlation coefficients ranged from r = 0.70 to r = 1.00 ($p < 0.001$, except the p-value for dorsal electrode position, which was p = 0.01). Figure 15 gives a visual impression of the correlation for RR_{dEMG} and HR_{dEMG} measured at lateral electrode position compared to standard electrode position.

Table 4: Derived dEMG parameters at lateral electrode position compared to standard electrode position.

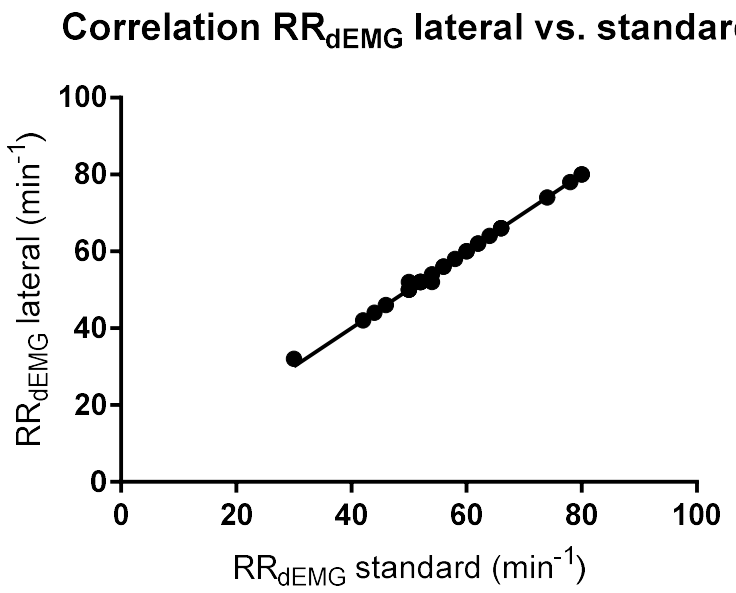
	Standard (n=5)	Lateral (n=5)	P-value
Δ $dEMG_{peak}$ (%)	0	-14.9 (-26.4 – 42.2)	0.50
Δ $dEMG_{tonic}$ (%)	0	-6.5 (-9.4 – 16.2)	0.50
Δ $dEMG_{amp}$ (%)	0	-16.7 (-30.9 – 51.5)	0.50
Δ AUC_{30sec} (%)	0	-12.0 (-21.5 – 36.5)	0.69
RR_{dEMG} (min^{-1})	57 ± 9	57 ± 9	1.00
HR_{dEMG} (min^{-1})	152 ± 9	152 ± 9	1.00
CV $dEMG_{peak}$ (%)	19 (17 – 22)	18 (18 – 20)	0.48
CV $dEMG_{tonic}$ (%)	32 (26 – 39)	29 (26 – 33)	0.22
CV $dEMG_{amp}$ (%)	31 (25 – 32)	27 (26 – 30)	0.41

Definition of abbreviations: n = number of infants, Δ (%) = percentage difference compared to the standard electrode position, $dEMG_{peak}$ = peak (maximal) electrical activity of dEMG, $dEMG_{tonic}$ = tonic (minimal) electrical activity of dEMG, $dEMG_{amp}$ = amplitude of dEMG, AUC_{30sec} = area under the curve of dEMG over 30 seconds, RR_{dEMG} = respiratory rate of dEMG, HR_{dEMG} = heart rate of dEMG, CV = coefficient of variation. Data are expressed as median (IQR) or mean ± SD, with level of significance $p < 0.05$ (*) compared to standard electrode position. Statistically significant differences were tested with the Wilcoxon signed-rank test.

4.2.3 Variability and phase difference

Coefficients of variation calculated for the peak electrical activity, the tonic electrical activity and the amplitude showed no significant differences in variability for the lateral, superior, medial and dorsal electrode position compared to standard electrode position (Table 4 and Appendix A2). In addition, no significant difference in variability for the amplitude measured at inferior electrode position compared to standard electrode position was found (Figure A1, Appendix A2). Statistically significant decreases in variability were found for the coefficients of variation calculated for the peak electrical activity and the tonic electrical activity measured at inferior electrode position compared to standard electrode position (CV $dEMG_{peak}$, median 18% (IQR 17 – 19%), median 20% (IQR 19 – 21%), respectively with $p = 0.03$; CV $dEMG_{tonic}$, median 20% (IQR 19 – 25%), median 30% (IQR 25 – 37%), respectively with $p = 0.04$).

For all non-standard electrode positions compared to standard electrode position, negligible phase differences of a few milliseconds were found (lateral $\Delta\varphi$ = -8.7 ms; inferior $\Delta\varphi$ = 6.3 ms; superior $\Delta\varphi$ = -0.7 ms; medial $\Delta\varphi$ = 4.1 ms; dorsal $\Delta\varphi$ = 35 ms), with an overall mean cross-correlation coefficient > 0.95 indicating almost identical dEMG signals regarding their phase difference.



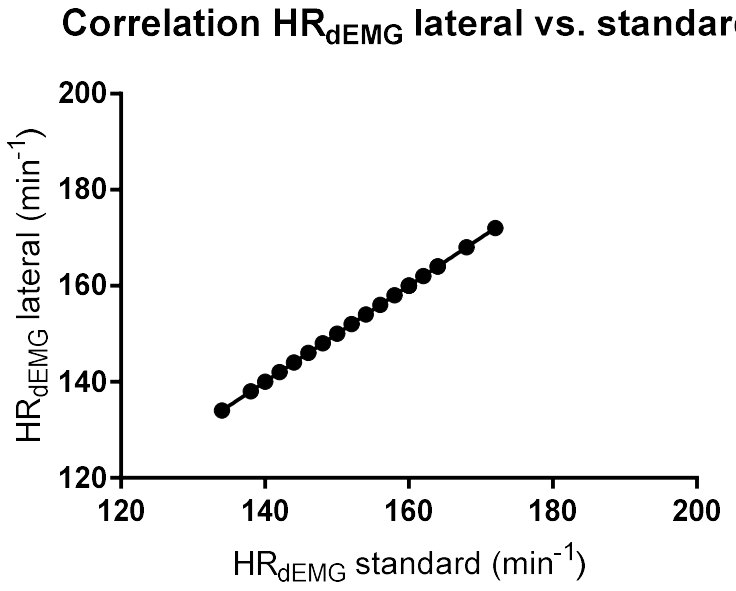


Figure 15: The relation between the RR_{dEMG} and the HR_{dEMG} (min^{-1}) measured at standard electrode position and lateral electrode position at six time points for each individual patient. Pearson's correlation coefficient r = 1.00 and r = 1.00 (perfect line), respectively.

Chapter 5 – Discussion

This thesis described the feasibility of measuring diaphragmatic activity by means of transcutaneous electromyography at different positions of electrode placement on the chest of preterm infants compared to the standard electrode position. We found decreased electrical activity of the diaphragm, expressed as percentage difference in dEMG peak activity, dEMG tonic activity, dEMG amplitude and AUC, measured by dEMG at non-standard electrode positions compared to the standard electrode position. However, the decrease in electrical activity was not statistically significant in the subgroups representing the lateral, superior, medial and dorsal electrode position compared to the standard electrode position. This suggests a comparable diaphragmatic activity measured at those locations on the infants' chest. Only the electrical activity of the diaphragm measured at inferior electrode position decreased significantly from the measurements at the standard electrode position. To our knowledge, this is the first study so far to assess the feasibility of measuring diaphragmatic activity using dEMG at different electrode positions in preterm infants.

The effect of different electrode positions on the quality of the dEMG signal in preterm infants has not been described in literature. However, it has been described in literature that the orientation of the electrodes to the diaphragm, the distance between the measuring electrodes, the amount of subcutaneous tissue between the diaphragm and the electrodes, and the body position of the infant might influence the measured signal.[45,50,51] The optimal position for transcutaneous electrodes of recording diaphragmatic activity in healthy adults was tested by Glerant et al.[52] In addition, they assessed the reproducibility of the EMG signal of the diaphragm. They demonstrated that there are differences between subjects in the best position for transcutaneous electrodes when recording diaphragmatic activity. When the optimal position was identified, a reproducible amplitude of the EMG signal was found. In line with the findings of Glerant et al. we found differences in the best position for transcutaneous electrodes when measuring diaphragmatic activity.

Our findings were based on the measurements of 18 preterm infants. Measurements of five preterm infants were excluded from data analysis, of which three measurements were recorded at superior electrode position, one measurement at medial electrode position and one measurement at dorsal electrode position, all compared to the standard electrode position. It was not possible to distinguish single breaths in these dEMG signals, caused by various reasons. In case of the excluded measurements at superior electrode position the dEMG signal was muted, hampering the distinction between single breaths. By placing the superior electrodes on the infants' chest, it is conceivable that the electrodes are placed superior to the frontal, dome-shaped diaphragm. Therefore, the summation of MUAPs of the diaphragm are detected to a lesser extent at the superior electrode position, resulting in a decrease of the detected electrical activity of the diaphragm. Another explanation for the muted dEMG signal might be the accidental placement of the superior electrodes on a rib, hampering the detection of electrical activity of the diaphragm. It is excluded that the muted dEMG signal is caused by crosstalk of the external intercostal muscles, as these muscles are activated during inspiration and should therefore provide an increase of the dEMG signal.

Looking at the standardized dEMG parameters analyzed at superior electrode position for the included measurements (Table 3), the electrical activity of the diaphragm decreased compared to the standard electrode position. However, this decrease did not differ significantly. Taking into account the differences in detection of electrical activity of the diaphragm at superior electrode position, it might be doubted if placing the electrodes superior to the standard electrode position fulfills the requirement of replacing transcutaneous electrodes providing comparable signal quality.

The measurement at medial electrode position was excluded due to a reduction in the measured diaphragmatic activity, hampering the detection of single breaths. A possible explanation for this reduction is that we did not met the proposed 20-mm interelectrode distance for bipolar transcutaneous EMG electrodes according to the widely referenced report from the Surface EMG for Non-invasive Assessment of Muscles (SENIAM) group.[53] However, it was not possible to fulfill this recommendation due to the limited space on the infants' chest where the dEMG electrodes could be placed. In theory, the adhesive surface of the transcutaneous EMG electrodes can be made smaller providing the possibility of increasing the interelectrode distance. However, the smaller the surface of the electrodes, the greater the tension applied to the surface on the chest of the infant where the electrodes are placed. This can occur when the infant pulls the wires of the electrodes, for example. As a result of the increased tension, more damage can be brought to the infants' vulnerable skin. Therefore, it must be prevented that the adhesive surface of the transcutaneous EMG electrodes will be made too small.

Exclusion of the measurement at dorsal electrode position was based on the existence of excessive movement artefacts due to unrest of the infant during the 1-hour measurement.

As mentioned, statistically significant differences in diaphragmatic activity were found in one subgroup. The standardized dEMG parameters decreased significantly at inferior electrode position compared to the standard electrode position. Normally, when measuring at standard electrode position the electrical activity from the frontal diaphragm is measured.[35] Corresponding to the reasoning for the recording of reduced electrical activity of the diaphragm at superior electrode position, electrodes at inferior position might not be placed at the height of the frontal diaphragm. It is plausible that the summation of MUAPs of the diaphragm are detected to a lesser extent at the inferior electrode position, resulting in a decrease of dEMG peak activity, dEMG tonic activity, dEMG amplitude and AUC. Moreover, the significant decrease in diaphragmatic activity can be caused by crosstalk from the abdominal muscles, the most important muscles of expiration. Unwanted muscle activity of these muscles might be detected by the inferior placed electrodes. It is known that the presence of active muscles near the transcutaneous EMG electrodes can strongly influence the stability of an EMG recording.[53] Campbell et al. also described the problem of contamination of other muscles when diaphragmatic activity is measured by means of transcutaneous electrodes.[54] As the diaphragm is active during inspiration and the abdominal muscles are active during expiration, they can extinguish each other resulting in a reduction in recorded electrical activity of the diaphragm.

Although there are no statistically significant decreases found regarding diaphragmatic activity at lateral, superior, medial and dorsal electrode position compared to the standard electrode position, the decrease might be clinically relevant. For example, important information on the needed diaphragmatic activity in a preterm infant, represented by the peak activity of the diaphragm, might be interpret wrongly. Moreover, changes in the amplitude of the dEMG signal that indicate changes in neural respiratory drive[44] cannot be interpret correctly if the $dEMG_{amp}$ at one of these non-standard electrode positions does not represent a normal value.

Moderate individual variations in diaphragmatic activity, as indicated with the coefficients of variation (CV $dEMG_{peak}$, CV $dEMG_{tonic}$ and CV $dEMG_{amp}$), were found for the measurements at standard electrode position and at non-standard electrode positions in this study. The CV of the peak activity, tonic activity and amplitude at standard electrode position ranged from 18% to 23%, from 25% to 32% and from 28% to 34%, respectively. It is striking that the individual variations found in diaphragmatic activity measured at all non-standard electrode positions (Table 4, Appendix A2) are comparable to these variations. This indicates that, although standardized dEMG parameters can show decreases, whether or not significant, at non-standard electrode positions compared to the standard electrode position, the variation in the recorded signals might be comparable. This finding is of clinical importance, as it suggests that it is possible to measure comparable breathing patterns at different positions of electrode placement on the preterm infants' chest. Correct detection and classification of these breathing patterns is essential in detection of apnea which is common in preterm infants.

The abovementioned finding can be confirmed by looking at the constructed scatterplots of the relation between the dEMG amplitude measured at standard electrode position and the dEMG amplitude measured at a non-standard electrode position. For example, the scatterplot constructed for the subgroup inferior versus standard electrode position, revealed a significant correlation between the dEMG amplitude measured at the two electrode positions (ρ_s = 0.80, $p<0.01$). This indicates that despite the significant differences for diaphragmatic activity found in this subgroup, the dEMG parameters correlate very well. However, looking at the ICC at inferior electrode position compared to the standard electrode position, there is a moderate correlation between the dEMG amplitudes (ICC = 0.43) meaning that there is a greater variance in the measured amplitudes at inferior and standard electrode position. Thus, there is a high correlation, but a moderate agreement between the dEMG amplitude measured at these two electrode positions. This is in line with the statistically significant difference in amplitude mentioned before.

Corresponding to the finding at inferior electrode position, we found a significant correlation between the dEMG amplitudes measured at lateral electrode position and standard electrode position (ρ_s = 0.81, $p<0.01$) and a moderate agreement (ICC = 0.66). However, it is striking that the agreement is higher compared to the agreement found at inferior electrode position. This can be explained by the fact that the differences in diaphragmatic activity found at lateral electrode position compared to the standard electrode position did not decrease significantly.

Based on our findings, electrode placement at lateral position might be the best alternative compared to the standard electrode placement. With a median decrease in $dEMG_{peak}$, $dEMG_{tonic}$, $dEMG_{amp}$ and AUC of 14.9%, 6.5%, 16.7% and 12.0%, respectively, and the mentioned correlations, the clinical usefulness of this electrode position should be considered.

In this study, factors that influenced the measured diaphragmatic activity using dEMG can be mentioned. First of all, we observed that the placement of electrodes distant from the frontal or dorsal diaphragm, as seen in superior and inferior electrode position, influenced the dEMG signal by reducing the measured diaphragmatic activity. In addition, crosstalk might occur when placing the electrodes at those positions. Second, a distance smaller dan 20 mm between two bipolar electrodes might also reduce the measured diaphragmatic activity, as seen in medial electrode position. Last, extensive movement of the infant can result in movement artefacts resulting in unusable dEMG recordings.

Vital parameters

In this study, we also compared the clinical parameters RR and HR based on the EMG of the diaphragm at non-standard electrode positions compared to standard electrode position. Kraaijenga et al. already proved that monitoring RR and HR with transcutaneous EMG of the diaphragm is feasible and repeatable in preterm infants.[7]

This study showed that RR and HR based on the EMG of the diaphragm can be detected very well at different electrode positions on the infants' chest. Nevertheless, in general, we have to be aware of overestimation of respiratory rates due to biphasic breaths. In this study, overestimation of respiratory rates was prevented due to patient specific adjustments to the breath detection algorithm on which the RR based on the dEMG was calculated. However, a breath detection algorithm that does not have to be adjusted for each individual patient is preferred. Therefore, we need to take into account the existence of biphasic breaths, which should be detected as one breath to prevent overestimation of the RR.

Strengths and limitations

Several strengths of this study are worth mentioning. Most importantly, this study is, to our knowledge, the first to prove the feasibility of measuring diaphragmatic activity at different electrode positions on the chest of the infant in which statistical analysis showed comparable measurements of diaphragmatic activity at most non-standard electrode positions compared to the standard electrode position. In addition, this study showed an accurate detection of RR and HR calculated from the dEMG signals at non-standard positions. Another strength is that the measurement protocol in which different electrode positions are used to measure diaphragmatic activity in preterm infants was feasible and easy to implement in this population. Moreover, the measurements were performed using a standardized protocol; the preterm infants were randomly allocated to one of the five positions. The measurements were mostly performed by the same researcher minimizing the variability between measurements.

However, this study has several limitations that need to be addressed. First, all derived dEMG parameters are based on the detection of peaks and troughs in the averaged dEMG signal. In literature, there are no clear descriptions about peak and trough detection methods. Breath detection algorithms consist of several assumptions and criteria to determine inspiration and expiration in respiratory signals. Most of these assumptions for the use of dEMG are based on transesophageal EMG measurements of the diaphragm in mechanically ventilated adult patients and there is no evidence to

apply these assumptions in breath detection algorithms for spontaneously breathing preterm infants.[21,55] In dEMG signals, the start of an inspiration has been defined as the lowest point in the RMS curve before a rise in the signal which is based on a physiological point of view that the rise in the dEMG signal reflects the first contraction of muscle fibers.[21] To detect the lowest point in the RMS curve in this study, we looked back in time from the observed peak to the moment when the RMS curve no longer decreases. Therefore, detection of the peaks must be performed first. Conditions for the detection algorithm differed per individual patient and depended on the respiratory rate of the infant. A disadvantage of detecting the lowest points in the RMS signal by looking back in time, is the created delay if dEMG might be used for synchronization of non-invasive respiratory support with spontaneous breathing in future.

Second, in this study we assigned all patients to a subgroup in which different, non-standard electrode positions were compared to the standard electrode position. This means that we can only investigate possible differences in diaphragmatic activity between one non-standard electrode position compared to the standard electrode position. We could not compare the measured diaphragmatic activity between two non-standard electrode positions, meaning we were not able to compare diaphragmatic activities between patients from different subgroups. Due to the limited space on the chest of the infant, it was not possible to place more than five electrodes on their chest. This limitation restricts this study to the comparison of diaphragmatic activity at one non-standard position relative to the standard electrode position.

Another limitation is the small size of the included preterm infants in each subgroup. For example, differences between derived dEMG parameters for medial and dorsal electrode position compared to the standard electrode position seem statistically significant at first sight, but the sample sizes of these groups are too small to prove statistical significant differences. The small sample sizes of these subgroups are in the first place explained by the randomization and in the second place by the exclusion of measurements based on unusable dEMG recordings. The small numbers in the subgroups prevent firm conclusions on the findings of this study. However, despite the small subgroups, it is possible to say something about the feasibility of measuring comparable diaphragmatic activity at different electrode positions on the chest of the preterm infant.

Last, we only included stable preterm infants receiving non-invasive respiratory support with a maximum FiO_2 of 30% or no respiratory support. Results may differ in less stable infants receiving a more intensive form of non-invasive respiratory support or receiving invasive mechanical ventilation. For example, by intensifying non-invasive respiratory support (i.e. increasing the positive pressure that is given), the diaphragm is pushed downwards resulting in the need of replacement of the standard electrode position. Consequently, electrodes placed at a non-standard position should therefore also be replaced.

Future recommendations

This thesis shows that it is feasible to measure diaphragmatic activity using dEMG at different electrode positions on the chest of the preterm infant. However, to implement continuous monitoring of transcutaneous EMG of the diaphragm in the NICU as a routine clinical monitoring tool, several extensions of the dEMG technique should be investigated.

Future research should primarily focus on the feasibility and reproducibility of measuring comparable diaphragmatic activity at most common electrode placements on the infants' chest. It might be interesting to study other placements besides the positions studied in this thesis. For example, a lateral-medial derivation of the dEMG compared to standard electrode position might be interesting, as lateral-medial might be a common position of placing electrodes on the chest of the infant whereby the frontal diaphragm is still measured. In addition, it might be interesting to study diaphragmatic activity measured oblique-lateral compared to the standard electrode position, taking into account the dome-shaped diaphragm.

Second, a breath detection algorithm regarding peak and trough detection should be optimized in order to improve breath detection and thereby the obtainment of dEMG parameters. Moreover, a breath detection algorithm without the need of adjusting conditions per individual patient needs to be developed. As conditions for breath detection in the algorithm used for this study depended on the RR in preterm infants, it might be a possibility to improve this algorithm by extracting the RR from the currently used cardiorespiratory monitor and to make the breath detection algorithm dependent on the extracted RR. In this way, peaks and troughs will be automatically detected based on the correct RR for each individual patient. In addition, optimization of the breath detection algorithm will prevent overestimation or underestimation of the amount of real breaths in the RMS dEMG signal.

Furthermore, to be able to make firm conclusions on the equivalence of diaphragmatic activity measured at different electrode positions, sample sizes of the subgroups must be increased. After analysis of the dEMG measurements used for this thesis, we completed the inclusion of the predetermined number of thirty patients. Additional analyses needs to be performed on this collected data to study if signal quality remains comparable when the electrodes are placed at different positions on the chest of the infant.

Moreover, normal ranges of absolute values of transcutaneous EMG of the diaphragm are needed. To date, effect of respiratory treatment interventions in terms of diaphragmatic activity measured with dEMG has been displayed as a percentage change compared to a baseline before the intervention.[47,56-58] Based on those data, it is not possible to predict which infants will respond to a certain treatment or which infants will fail weaning, for example. Therefore, normal ranges of absolute values are necessary. Normally, great numbers of measurements are needed in preterm infants of different age, weight and clinical conditions to obtain normal values, followed by big data analysis strategies. However, due to the striking comparable individual variations of diaphragmatic activity measured at standard electrode position, this study could provide direction to the normal values that are needed.

Last, it is of interest to explore the possibility to develop non-adhesive electrodes for dEMG, as the adhesive electrodes cannot be used in infants with a GA < 26 weeks due to the risk of damaging the vulnerable skin. Developing a more practical monitoring device such as a belt with integrated sensors measuring cardiorespiratory parameters in a non-intrusive way would be a possible solution, especially when the monitoring device is wireless. In this way, the non-adhesive electrodes can be placed more easily for a longer time on one position, it improves patient comfort and it might facilitate nursing procedures or kangaroo care between the preterm infants and their parents during monitoring. The contribution of this study to the development of non-adhesive electrodes for dEMG is that the placement of the sensors inside a belt for example, should be placed at the height of the frontal and dorsal diaphragm in the horizontal plane. It is interesting to study the possibility of placing the sensors according to the dome-shaped diaphragm.

Chapter 6 – Conclusion

In conclusion, this study shows that it is feasible to measure diaphragmatic activity using transcutaneous EMG of the diaphragm at different electrode positions on the preterm infants' chest. Statistical analysis showed no significant differences regarding diaphragmatic activity measured at lateral, medial, superior and dorsal electrode position compared to standard electrode position. Statistically significant differences in diaphragmatic activity were found for inferior electrode position compared to standard electrode position. However, the correlation between outcome variables at these two positions was high. Vital parameters, RR and HR, calculated from the dEMG signal, can be measured accurately at different positions of electrode placement on the chest of the preterm infant. Future studies need to confirm these findings in a larger number of infants.

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Appendices

A1. Informed consent form

emma kinderziekenhuis AMC

Positionering van elektrodes bij transcutane elektromyografie van het diafragma bij premature neonaten

Informatie voor ouders

Geachte ouders,

Uw zoon of dochter is te vroeg geboren en ligt nu op de Intensive Care Neonatologie (NICU) van het AMC. Graag willen wij u vragen of uw kind mee mag doen aan een onderzoek naar de activiteit van de ademhalingsspieren. Deelname is geheel vrijwillig. Voordat u een besluit neemt, is het belangrijk om meer te weten over het onderzoek. Lees deze informatie rustig door en vraag de onderzoeker uitleg als u vragen heeft.

Achtergrond en doel van het onderzoek

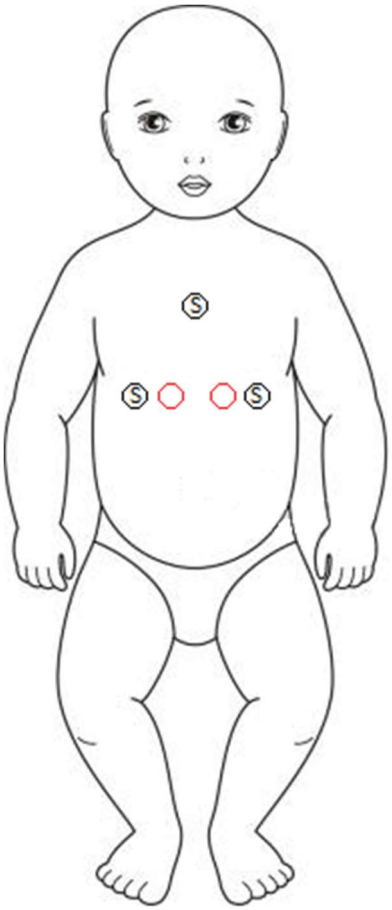
Door de vroeggeboorte van uw kind zijn een groot aantal organen nog onrijp. Hierdoor zult u merken dat uw zoon of dochter zich anders gedraagt dan een voldragen pasgeborene. Door onrijpheid van de hersenen vergeten te vroeg geboren kinderen af en toe goed door te ademen (apneu) en soms leidt dit tot een daling in het zuurstofgehalte in het bloed en een langzamere hartslag (brady). Uw kind ligt aan de monitor, zodat we goed kunnen zien wanneer deze apneus optreden. Niet alle apneus zijn hetzelfde. Soms stopt uw kind met ademen omdat de hersenen geen signaal afgeven om in te ademen (centrale apneu) en soms is er sprake van een tijdelijke blokkade in de (bovenste) luchtwegen waardoor de lucht niet goed in de longen komt (obstructieve apneu), bijvoorbeeld door te veel slijm. Het is voor ons belangrijk om apneus goed te kunnen detecteren en onderscheiden, zodat we de beste behandeling kunnen geven.

Het middenrif is de belangrijkste ademhalingsspier van het lichaam en speelt een belangrijke rol bij de ademhaling van te vroeg geboren kinderen. De standaard monitor die we gebruiken op onze afdeling geeft maar beperkte informatie over de activiteit van het middenrif. Sinds enige jaren bestaat er een nieuwe monitor die extra informatie geeft over de functie van het middenrif. Deze monitor is eerst onderzocht bij zuigelingen en kinderen en dat onderzoek heeft uitgewezen dat de monitor zeer goed functioneert. Daarnaast heeft eerder onderzoek laten zien dat de monitor ook geschikt is om meer informatie te krijgen over de activiteit van het middenrif en over apneus bij te vroeg geboren kinderen. Voor succesvol gebruik van deze

monitor in de dagelijkse praktijk is het belangrijk dat de activiteit van het middenrif op verschillende plekken op het lichaam gemeten kan worden. Door deze afwisseling kunnen de verpleegkundigen de huid van uw kind goed verzorgen, wat irritatie van de huid voorkomt. Wij willen samen met Philips (Philips Electronics Nederland B.V.) graag onderzoeken op onze afdeling of het met de nieuwe monitor mogelijk is om de activiteit van het middenrif op verschillende plekken op het lichaam te meten.

Wat houdt het onderzoek precies in?

Om te beginnen willen wij benadrukken dat uw kind de reguliere behandeling krijgt zoals deze is voorgeschreven door de arts. Ook de standaard monitoring van uw kind en alle normale handelingen veranderen niet door het onderzoek.



Het onderzoek wordt uitgevoerd in samenwerking met Philips. Om informatie te verzamelen over ademhaling en activiteit van het middenrif gebruiken we een extra monitor. Met deze monitor meten we de activiteit van het middenrif. Om te onderzoeken of deze activiteit op verschillende plekken op het lichaam kan worden gemeten, worden er 5 kleine plakkers op de buik of rug van uw kind geplakt: drie plakkers op de plekken aangegeven met de letter S in de tekening en 2 plakkers op bijvoorbeeld de plekken met een rode cirkel. Tevens worden de romp, armen en benen gefilmd om te beoordelen of uw kind beweegt. Deze bewegingen kunnen de meting verstoren en dit is voor ons belangrijk om te weten bij het analyseren van de metingen. De meting duurt in totaal ongeveer 1 uur en zal aansluitend aan een verzorgingsmoment plaatsvinden en alleen wanneer de gezondheidstoestand van uw kind het onderzoek toelaat. Na de meting zullen de plakkers direct worden verwijderd. Natuurlijk laten wij aan u weten wanneer de meting plaatsvindt.

Voor- en nadelen van deelname aan de studie

Er zijn voor uw kind geen voordelen van deelname aan het onderzoek. Dit komt omdat we alleen gegevens registeren en geen aanpassingen doen in de behandeling. Daarnaast zijn er ook geen nadelen voor uw kind; door eerder onderzoek weten wij dat de metingen veilig zijn en niet belastend voor uw kind. De informatie die wij verzamelen met dit onderzoek helpt ons om de behandelingen die we geven aan te vroeg geboren kinderen beter te kunnen monitoren en om deze in de toekomst te kunnen verbeteren.

Toestemming

Voor deelname van uw kind aan de studie is uw schriftelijke toestemming nodig. Daarom vragen wij u om het bijgevoegde toestemmingsformulier te ondertekenen. Deelname is geheel vrijwillig en als u besluit uw kind niet deel te laten nemen aan het onderzoek dan hoeft u niets te doen en verandert er niets in de behandeling van uw kind. Ook hoeft u niet aan te geven waarom u geen toestemming geeft.

Nadat u toestemming heeft gegeven, kunt u altijd alsnog besluiten om deze in te trekken. Ook hiervoor geldt dat u geen reden hoeft te geven en dat de behandeling van uw kind niet zal veranderen.

Privacy

Tijdens dit onderzoek zullen medische informatie en persoonsgegevens van uw kind worden verzameld en gebruikt. Deze gegevens worden gecodeerd opgeslagen, de naam van uw kind wordt weggelaten. Alleen de onderzoekers van de NICU van het AMC kunnen de identiteit van uw kind achterhalen. Om te controleren of het onderzoek goed is uitgevoerd, kan het zo zijn dat vertegenwoordigers van het AMC, de opdrachtgever van dit onderzoek, of medewerkers van de Inspectie voor de Gezondheidszorg de informatie willen inzien. De inzage vindt alleen plaats onder verantwoordelijkheid van de behandelend arts en alle gegevens worden geheim gehouden.

Philips zal alleen de gecodeerde data en de filmpjes zonder geluid uit het onderzoek ontvangen en geen andere informatie op basis waarvan de identiteit van uw kind eventueel achterhaald kan worden. De verkregen resultaten zullen eerst en vooral worden gebruikt in het kader van onderzoek. Daarnaast kan het worden gebruikt in de ontwikkeling en commercialisering van producten of apparaten die aansluiten bij het doel van dit onderzoek.

U heeft ten allen tijden het recht om achteraf te besluiten af te zien van het delen van de data met Philips. De data wordt door Philips dan vernietigd. Tevens wordt bij Philips periodiek bekeken of de gedeelde data nog bruikbaar is. Data die niet meer bruikbaar is, zal worden vernietigd.

Als uw kind mee mag doen aan het onderzoek dan betekent dit dat u hier toestemming voor geeft. Na afloop van de studie zal het onderzoeksdossier 15 jaar worden bewaard op een veilige plek binnen het AMC.

Goedkeuring van het onderzoek

Het onderzoek is goedgekeurd door de Medisch Ethische Toetsingscommissie (METC) van het AMC.

Verzekering voor proefpersoenen

Omdat aan het onderzoek geen risico’s zijn verbonden, heeft de METC besloten dat het niet nodig is om voor dit onderzoek een verplichte schadeverzekering af te sluiten.

Wilt u nog meer weten?

Indien u nog vragen heeft over het onderzoek kunt u via telefoonnummer 020-5663971 contact opnemen met de hoofdonderzoeker prof. dr. A.H.L.C. van Kaam (sein 58063) of met dr. G.J. Hutten (sein 64156). Daarnaast kunt u voor onafhankelijk advies en aanvullende vragen terecht bij mevr. A. van Wassenaer, kinderarts-neonatoloog op de afdeling neonatologie van het AMC (020-5664059).

emma kinderziekenhuis AMC

Positionering van elektrodes bij transcutane elektromyografie van het diafragma bij premature neonaten

Toestemmingsverklaring

Ik ben gevraagd om toestemming te geven, zodat mijn kind meedoet aan dit medisch-wetenschappelijk onderzoek:

Naam kind: Geboortedatum: __ / __ / __

Ik heb de informatiebrief voor ouders gelezen. Ik kon aanvullende vragen stellen. Deze vragen zijn naar tevredenheid beantwoord. Ik heb voldoende tijd gehad om te beslissen of mijn kind meedoet.

Ik weet dat meedoen geheel vrijwillig is en weet dat ik op ieder moment kan beslissen dat mijn kind toch niet meedoet. Daarvoor hoef ik geen reden te geven.

Ik ga akkoord met inzage van het onderzoeksdossier door mogelijke vertegenwoordigers van het AMC, de opdrachtgever van dit onderzoek, of medewerkers van de gezondheidsinspectie, zoals vermeld in de informatiebrief. Hierbij kunnen alleen de onderzoekers van de NICU in het AMC de identiteit van mijn kind achterhalen.

Ik stem toe dat de gecodeerde data en filmpjes zonder geluid mogen worden gedeeld met, en gebruikt door, Philips, handelend uit naam van Philips Research, en partners.

Ik geef toestemming om de onderzoeksgegevens van mijn kind 15 jaar na afloop van dit onderzoek in het AMC te bewaren.

Ik vind het goed dat mijn kind meedoet aan dit onderzoek.

Naam ouder/voogd 1:

Handtekening: Datum: __ / __ / __

Naam ouder/voogd 2:

Handtekening: Datum: __ / __ / __

Ik verklaar hierbij dat ik bovengenoemde persoon/personen volledig heb geïnformeerd over het genoemde onderzoek.

Naam onderzoeker:

Handtekening: Datum: __ / __ / __

A2. Outcome variables at different electrode positions

Table A1: Derived dEMG parameters at inferior electrode position compared to standard electrode position.

	Standard (n=5)	Inferior (n=5)	P-value
Δ $dEMG_{peak}$ (%)	0	-59.7 (-66.3 to -52.7)	0.04*
Δ $dEMG_{tonic}$ (%)	0	-51.2 (-55.6 to -39.0)	0.04*
Δ $dEMG_{amp}$ (%)	0	-63.7 (-71.5 to -57.5)	0.04*
Δ AUC_{30sec} (%)	0	-58.0 (-63.5 to -49.5)	0.04*
RR_{dEMG} (min^{-1})	70 ± 12	70 ± 13	0.66
HR_{dEMG} (min^{-1})	148 ± 7	148 ± 7	1.00
CV $dEMG_{peak}$ (%)	20 (19 – 21)	18 (17 – 19)	0.03*
CV $dEMG_{tonic}$ (%)	30 (25 – 37)	20 (19 – 25)	0.04*
CV $dEMG_{amp}$(%)	28 (27 – 34)	29 (28 – 37)	0.07

Definition of abbreviations: n = number of infants, Δ (%) = percentage difference compared to the standard electrode position, $dEMG_{peak}$ = peak (maximal) electrical activity of dEMG, $dEMG_{tonic}$ = tonic (minimal) electrical activity of dEMG, $dEMG_{amp}$ = amplitude of dEMG, AUC_{30sec} = area under the curve of dEMG over 30 seconds, RR_{dEMG} = respiratory rate of dEMG, HR_{dEMG} = heart rate of dEMG, CV = coefficient of variation. Data are expressed as median (IQR) or mean ± SD, with level of significance $p < 0.05$ (*) compared to standard electrode position. Statistically significant differences were tested with the Wilcoxon signed-rank test.

Table A2: Derived dEMG parameters at superior electrode position compared to standard electrode position.

	Standard (n=3)	Superior (n=3)	P-value
Δ $dEMG_{peak}$ (%)	0	-30.7 (-33.0 to -23.3)	0.11
Δ $dEMG_{tonic}$ (%)	0	-9.8 (-11.5 to -2.6)	0.11
Δ $dEMG_{amp}$ (%)	0	-38.3 (-48.1 to -34.2)	0.11
Δ AUC_{30sec} (%)	0	-24.0 (-24.0 to -19.0)	0.11
RR_{dEMG} (min^{-1})	73 ± 10	69 ± 8	0.11
HR_{dEMG} (min^{-1})	152 ± 20	152 ± 20	1.00
CV $dEMG_{peak}$ (%)	18 (17 –18)	14 (14 – 17)	0.11
CV $dEMG_{tonic}$ (%)	26 (22 – 33)	21 (21 – 23)	0.11
CV $dEMG_{amp}$ (%)	29 (27 – 29)	29 (28 – 32)	0.29

Definition of abbreviations: n = number of infants, Δ (%) = percentage difference compared to the standard electrode position, $dEMG_{peak}$ = peak (maximal) electrical activity of dEMG, $dEMG_{tonic}$ = tonic (minimal) electrical activity of dEMG, $dEMG_{amp}$ = amplitude of dEMG, AUC_{30sec} = area under the curve of dEMG over 30 seconds, RR_{dEMG} = respiratory rate of dEMG, HR_{dEMG} = heart rate of dEMG, CV = coefficient of variation. Data are expressed as median (IQR) or mean ± SD, with level of significance $p < 0.05$ (*) compared to standard electrode position. Statistically significant differences were tested with the Wilcoxon signed-rank test.

Table A3: Derived dEMG parameters at medial electrode position compared to standard electrode position.

	Standard (n=3)	Medial (n=3)	P-value
Δ $dEMG_{peak}$ (%)	0	-67.3 (-33.0 to -23.3)	0.11
Δ $dEMG_{tonic}$ (%)	0	-36.8 (-60.2 to -20.0)	0.11
Δ $dEMG_{amp}$ (%)	0	-76.4 (-89.4 to -71.2)	0.11
Δ AUC_{30sec} (%)	0	-64.0 (-71.0 to -55.0)	0.11
RR_{dEMG} (min^{-1})	55 ± 14	54 ± 12	0.66
HR_{dEMG} (min^{-1})	142 ± 13	138 ± 11	0.18
CV $dEMG_{peak}$ (%)	19 (18 – 23)	14 (12 – 18)	0.11
CV $dEMG_{tonic}$ (%)	25 (25 – 33)	13 (12 – 24)	0.11
CV $dEMG_{amp}$ (%)	29 (25 – 31)	30 (28 – 37)	0.29

Definition of abbreviations: n = number of infants, Δ (%) = percentage difference compared to the standard electrode position, $dEMG_{peak}$ = peak (maximal) electrical activity of dEMG, $dEMG_{tonic}$ = tonic (minimal) electrical activity of dEMG, $dEMG_{amp}$ = amplitude of dEMG, AUC_{30sec} = area under the curve of dEMG over 30 seconds, RR_{dEMG} = respiratory rate of dEMG, HR_{dEMG} = heart rate of dEMG, CV = coefficient of variation. Data are expressed as median (IQR) or mean ± SD, with level of significance $p < 0.05$ (*) compared to standard electrode position. Statistically significant differences were tested with the Wilcoxon signed-rank test.

Table A4: Derived dEMG parameters at dorsal electrode position compared to standard electrode position.

	Standard (n=2)	Dorsal (n=2)	P-value
Δ $dEMG_{peak}$ (%)	0	[-50.8 -35.0]	0.18
Δ $dEMG_{tonic}$ (%)	0	[-40.4 -33.9]	0.18
Δ $dEMG_{amp}$ (%)	0	[-58.5 -32.9]	0.18
Δ AUC_{30sec} (%)	0	[-47 -40]	0.18
RR_{dEMG} (min^{-1})	[48 61]	[50 59]	1.00
HR_{dEMG} (min^{-1})	[148 153]	[151 152]	0.66
CV $dEMG_{peak}$ (%)	[22 23]	[22 23]	1.00
CV $dEMG_{tonic}$ (%)	[27 34]	[22 27]	0.18
CV $dEMG_{amp}$ (%)	[32 35]	[32 37]	0.32

Definition of abbreviations: n = number of infants, Δ (%) = percentage difference compared to the standard electrode position, $dEMG_{peak}$ = peak (maximal) electrical activity of dEMG, $dEMG_{tonic}$ = tonic (minimal) electrical activity of dEMG, $dEMG_{amp}$ = amplitude of dEMG, AUC_{30sec} = area under the curve of dEMG over 30 seconds, RR_{dEMG} = respiratory rate of dEMG, HR_{dEMG} = heart rate of dEMG, CV = coefficient of variation. Data are expressed as a range, with level of significance $p < 0.05$ (*) compared to standard electrode position. Statistically significant differences were tested with the Wilcoxon signed-rank test.

A3. Correlations

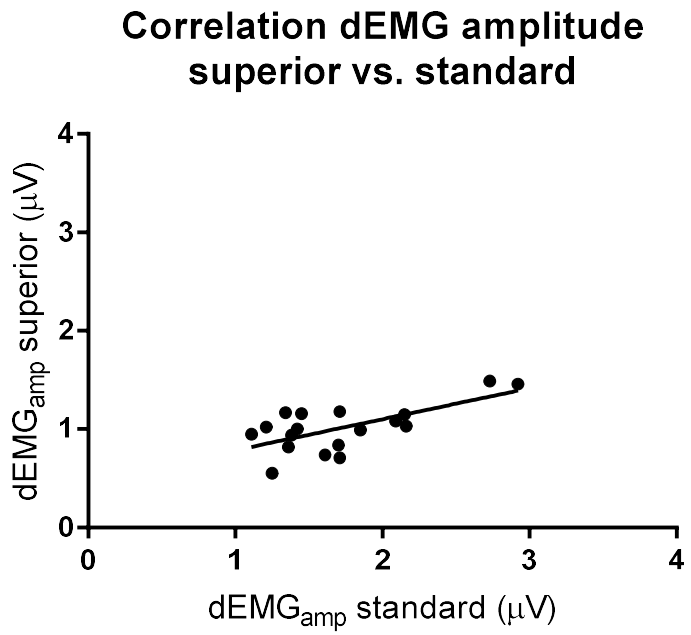


Figure A1: The relation between the dEMG amplitude (μV) measured at standard electrode position and the dEMG amplitude measured at superior electrode position at six time points for each individual patient. Spearman's correlation coefficient ρ_s = 0.49, intraclass correlation coefficient ICC = 0.52.

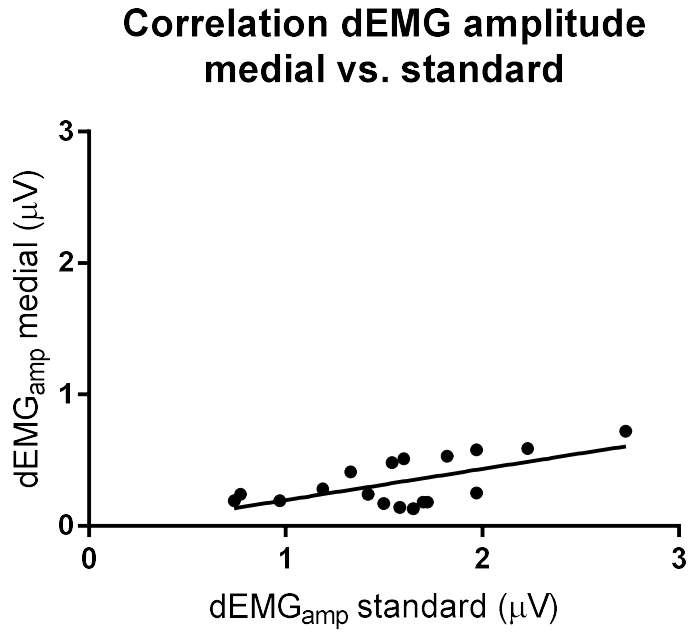


Figure A2: The relation between the dEMG amplitude (μV) measured at standard electrode position and the dEMG amplitude measured at medial electrode position at six time points for each individual patient. Spearman's correlation coefficient ρ_s = 0.43, intraclass correlation coefficient ICC = 0.42.

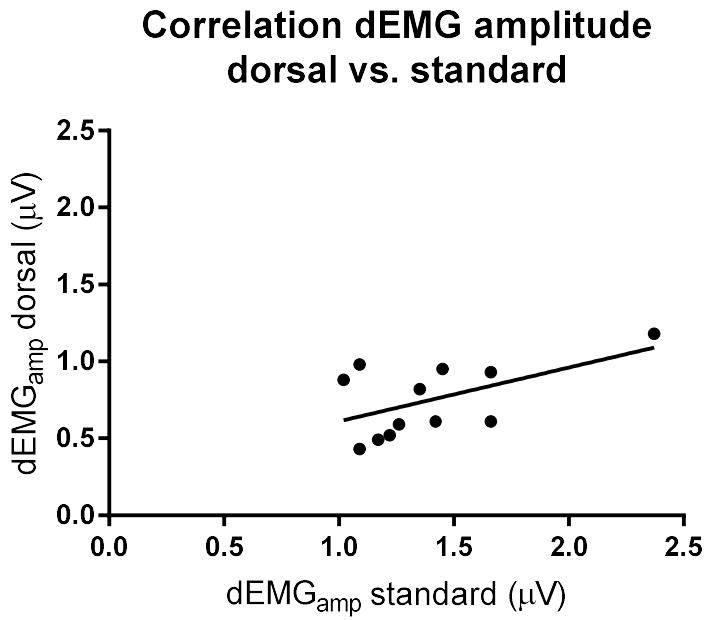


Figure A3: The relation between the dEMG amplitude (μV) measured at standard electrode position and the dEMG amplitude measured at dorsal electrode position at six time points for each individual patient. Spearman's correlation coefficient ρ_s = 0.40, intraclass correlation coefficient ICC = 0.50.