Diaphragmatic electromyography monitoring in preterm infants
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SUMMARY

This thesis described and discussed the proof of concept of transcutaneous diaphragmatic electromyography (dEMG) monitoring in preterm infants in the neonatal intensive care unit (NICU), including the results of several prospective cohort studies and a case report.

In Chapter 1 we have provided a general introduction and outline of this thesis. Preterm infants are at high risk of respiratory failure due to impaired control of breathing (apnea of prematurity; AOP) and/or a compromised lung function leading to impaired gas exchange and increased work of breathing (WOB). AOP can be classified into central apnea (a cease in airflow due to absence of respiratory effort), obstructive apnea (a cease in airflow caused by upper airway obstruction) or mixed apnea (a cease in airflow caused by a combination of both central and obstructive apnea). Apnea can result in (prolonged) periods of hypoxemia, which have been associated with impaired neurodevelopmental outcome. Apnea is mostly treated with caffeine therapy or non-invasive modes of respiratory support such as nasal continuous positive airway pressure (nCPAP). The optimal treatment depends on the type of apnea. Cardiorespiratory monitoring, continuously measuring heart rate (HR) and respiratory rate (RR), is therefore essential to detect, classify and effectively treat apnea in preterm infants. Chest impedance (CI) is the current standard for cardiorespiratory monitoring but this technique has important limitations leading to a reduced accuracy in detection and classification of apnea, especially obstructive apnea. Other less used or implemented monitoring techniques all have their drawbacks and are therefore not considered adequate alternatives for CI.

Transcutaneous dEMG is a non-invasive technique that directly measures the electrical activity of the diaphragm, the most important respiratory muscle. Studies in adults, children and term neonates have shown that dEMG provides continuous information on HR, RR and breathing pattern. Furthermore, dEMG also quantifies neural breathing effort and this parameter is associated with WOB. This makes dEMG a realistic and promising candidate to replace CI for cardiorespiratory monitoring in preterm infants. It is hypothesized that direct measurement of electrical diaphragmatic activity via dEMG may optimize apnea detection and classification, and provide valuable information on the magnitude of changes in electrical activity, which could theoretically be used to select and wean the mode of respiratory support in preterm infants. However, feasibility of dEMG in preterm infants has not yet been established.

In this thesis we took the next step in exploring the use of the dEMG technique in preterm infants in the NICU and explored if dEMG could overcome the shortcomings of CI.
In Chapter 2 we performed an observational cohort study to determine the feasibility and repeatability of transcutaneous dEMG in preterm infants and compared its most basic functions as a cardiorespiratory monitor, providing continuous data on HR and RR, to CI. Thirty-two preterm infants < 32 weeks GA treated with non-invasive respiratory support were measured during their first week of life. We showed that both HR and RR measured by dEMG and CI were significantly correlated and showed good agreement. This study revealed that monitoring HR and RR with transcutaneous dEMG is feasible and repeatable in preterm infants. The results of this study were considered a first step and warranted further studies on the additional value of dEMG monitoring in preterm infants.

In Chapter 3 we described a case report in which dEMG was used as a diagnostic tool to demonstrate a hemidiaphragmatic paresis in a preterm infant. Until now, diaphragmatic paresis is diagnosed by chest X-ray (CXR) and ultrasound of the diaphragm. Transcutaneous dEMG provides separate and simultaneous information on the right and left electrical activity of the diaphragm and could be an alternative and more direct method of diagnosing (hemi) diaphragmatic paresis in newborn infants. In this study, dEMG was measured in a preterm infant with a GA of 28 weeks, diagnosed with right-sided hemidiaphragmatic paresis confirmed by CXR and ultrasound. The dEMG measurement revealed a strongly reduced electrical activity of the right diaphragm compared to the left side. This case report showed that dEMG monitoring provides additional information on both the electrical activity of the right and left diaphragm, which makes dEMG an ideal candidate for diagnosing hemidiaphragmatic paresis in neonates.

Apnea can be classified into central, obstructive or mixed apnea. Central apnea are mostly treated with caffeine, resulting in a decrease in the frequency of central apnea and an increase in minute ventilation, mainly related to an increase in tidal volume (Vt). Besides inducing excitation of respiratory neural output, it is thought that caffeine also improves contractility of the diaphragm. However, the exact working mechanism of caffeine is unknown. In Chapter 4 we studied the effect of an intravenous loading dose of caffeine on diaphragmatic activity as measured by dEMG and its association on (breathing) variables, including Vt, end-expiratory lung volume (EELV), inspiratory (Ti) and expiratory (Te) time, RR and HR. This study showed that treatment with caffeine resulted in a rapid and sustained increase in diaphragmatic amplitude by 43% and Vt by 30%. Furthermore, the increase in dEMG seemed to be associated to the increase in Vt. Caffeine did not consistently impact the other variables. This study suggests that the increase in diaphragmatic contractility may be one of the underlying mechanisms for the positive effect of caffeine on Vt. These findings also suggest that there is an indication to start caffeine treatment in patients with hypoventilation in addition to true apnea. Of equal importance, this study shows that dEMG is capable of
detecting and quantifying changes in diaphragmatic activity, which are closely related to the diaphragmatic WOB.

To restore the compromised lung function and reduce WOB, preterm infants often receive respiratory support with nasal continuous positive airway pressure (nCPAP) and/or low flow nasal cannula (LFNC). There is a lack of objective parameters to guide weaning of non-invasive respiratory support and clinicians often use a “trial and error” approach based on changes in clinical condition. In Chapter 5 we explored if dEMG would be able to detect changes in electrical activity of the diaphragm during weaning from nCPAP to the lesser supportive LFNC and might be a candidate for guiding weaning. We conducted a prospective observational cohort study and included 61 preterm infants accounting for 74 weaning attempts. Weaning led to an immediate increase in the amplitude of the dEMG signal. No relevant differences in other variables (Ti, Te, RR and HR) were found after weaning. Infants failing the weaning attempt (back on nCPAP within 48 hours) tended to have a higher diaphragmatic activity than those successfully weaned. This study shows that dEMG is able to detect and quantify changes in diaphragmatic activity after weaning and that the increase in diaphragmatic activity is most prominent in infants failing the weaning attempt. Therefore, dEMG might be a useful parameter to guide weaning from respiratory support in preterm infants.

Because CI has inaccuracies in monitoring respiration that may compromise accurate detection and classification of apnea, more accurate monitoring of apnea is needed. In Chapter 6 we determined the ability of dEMG to classify apnea correctly in central, obstructive or mixed apnea, when compared to CI. Thirty apnea were classified as central (n=15), obstructive (n=5) and mixed (n=10) based on respiratory inductance plethysmography, airway flow, HR and saturation (SpO2). Twenty-two assessors (neonatologists, pediatricians-in-training and nurses) independently classified each apnea twice; once for the blinded dEMG and once for the blinded CI in combination with HR and SpO2 tracings. This study showed that in total, 71% of the apnea based on dEMG and CI were classified correctly; 75% based on the dEMG tracings compared to 67% based on the CI tracings, p<0.001. A higher significant correct classification rate of central and obstructive apnea was found based on dEMG tracings compared to CI tracings. The improved apnea classification in the dEMG subgroup compared to the CI subgroup was a consistent finding in the three groups of assessors. We concluded that transcutaneous dEMG improves the accuracy of apnea classification compared to current cardiorespiratory monitoring by CI in preterm infants. Based on these results dEMG might be a promising candidate for breath analysis in future monitoring systems.

Finally, in Chapter 7 and 8, in English and Dutch a general summary and conclusion are described and future perspectives are outlined.
CONCLUSION

In conclusion, this thesis provides new and important information on the electrical activity of the diaphragm measured by transcutaneous dEMG in response to clinical procedures and respiratory interventions in preterm infants.

First of all, it shows that dEMG monitoring is feasible and repeatable in preterm infants and that dEMG can be used as a cardiorespiratory monitor providing HR and RR in preterm infants. Second, it shows that dEMG can be used as a diagnostic tool in (regional) pathology of the diaphragm such as (hemi) diaphragmatic paresis. Third, it shows that dEMG is able to detect and quantify changes in diaphragmatic activity following interventions such as caffeine treatment and weaning from non-invasive respiratory support. This makes dEMG a promising candidate to assist the clinician in the process of weaning non-invasive respiratory support in preterm infants. Finally, dEMG may have the potential to overcome the shortcomings of CI in classifying the type of apnea in preterm infants and thus the selection of the most optimal treatment.

FUTURE PERSPECTIVES

This thesis shows clearly that dEMG measurements are feasible in preterm infants and can detect changes in diaphragmatic activity after medical interventions. However, several (practical) extensions of the dEMG technique should be investigated before this technique can be implemented in the NICU as a routine clinical monitoring tool.

Electrical interference and movement artefacts can compromise the signal quality of dEMG. Electrical interference is easy to pick up and limb and body movements can cause amplitude artefacts. Current algorithms try to correct for these artefacts, but need to be optimized further in order to make dEMG monitoring more robust and reliable. Only then can transcutaneous dEMG be used for respiratory monitoring and optimization of (non-invasive) respiratory support. Second, when we performed our dEMG measurements, we simultaneously used two monitoring systems (the dEMG and the CI system). It would be optimal to implement the dEMG measurement device into the current monitoring system to provide information on diaphragmatic activity, as well as the other parameters that are currently available in the NICU. Third, dEMG measurements are performed by three transcutaneous electrodes, which are semi-round of shape. These electrodes need to be flat to reduce pressure points when lying in prone position or when used for longer periods of time. Furthermore, the adhesive electrodes cannot be used in infants with a GA < 26 weeks due to the risk of skin lesions.
Developing a more practical interface such as an electrode jacket or belt without the use of adhesive electrodes would be a possible solution, especially when it can be used wireless. In this way, nursing procedures or kangaroo care between baby and parents can be facilitated.

From a research perspective, there are a number of studies that need to be conducted before dEMG can be used in daily clinical practice. First, our finding that dEMG can detect and quantify changes in electrical activity of the diaphragm needs to be confirmed and extended in future studies with different treatments and interventions, such as doxapram for AOP, minimally invasive surfactant therapy or HFNC. Second, the role of dEMG in guiding weaning or predicting weaning failure needs to be further studied using different modes of respiratory support and larger patient numbers. Third, the possible association between WOB and diaphragmatic activity needs to be confirmed in the preterm population. If these two parameters are related, this will allow for an easy-to-use and patient friendly technique to measure WOB in preterm infants. Based on this parameter clinicians can make more objective decisions in daily respiratory care in preterm infants. Finally, synchronization of non-invasive ventilation with spontaneous breathing in preterm infants has so far been a clinical challenge. The classical parameter for synchronization, airway flow, cannot be used during non-invasive support due to the large leak at the airway opening. It would be very interesting to explore the role of transcutaneous dEMG in detecting breathing effort as it measures the early neural onset of inspiration.