Transcutaneous electromyography of the diaphragm

Monitoring breathing and the effect of respiratory support in preterm infants

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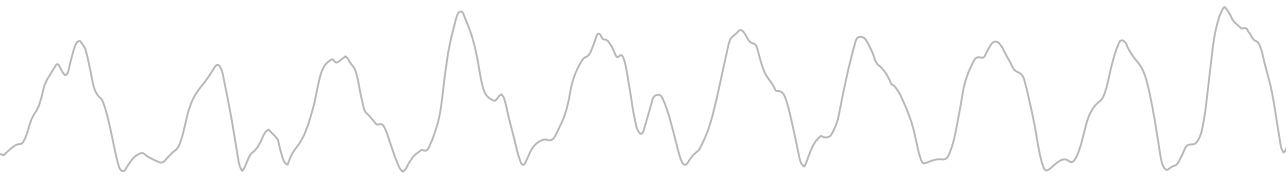
Chapter 9

General discussion and conclusion



In this thesis, the possible use of transcutaneous electromyography of the diaphragm (dEMG) in clinical care of preterm infants suffering from common respiratory diagnoses was investigated. The results and implications of the presented research will be discussed in this chapter in the context of four clinical applications for transcutaneous dEMG: 1) monitoring of breathing patterns, 2) monitoring the effect of pharmacological treatments for common respiratory diagnoses on diaphragmatic activity, 3) monitoring the effect of non-invasive respiratory support on diaphragmatic activity and 4) breath detection for future synchronization of ventilation.

Monitoring breathing patterns

Periodic breathing and apnea of prematurity (AOP) are common in preterm infants, especially in those born before 30 weeks of gestation.[1–3] Different types of apnea exist: central, obstructive and mixed apnea. Each type of apnea requires a specific treatment such as pharmacological stimulation of the respiratory center in the brain stem and respiratory support.[3,4] To be able to titrate treatment to the main type of apnea an infant is suffering from, accurate respiratory monitoring is essential and apnea should be classified correctly. However, the standard monitoring technique currently used in neonatal intensive care, chest impedance, has limited abilities to monitor breathing patterns and to classify apnea.[5,6]

Transcutaneous dEMG provides information on spontaneous breathing based on electrical activity of the diaphragm, the main respiratory muscle, and can be used to describe breathing patterns in preterm infants.[2,7] Therefore, it is hypothesized that this technique could improve apnea classification compared to chest impedance.

In the study on apnea classification described in **chapter 2**, it is shown that classification of obstructive apnea and, to a lesser extent, central apnea, but not mixed apnea, was more accurate based on transcutaneous dEMG tracings of spontaneous breathing preterm infants compared to classification based on chest impedance tracings. It is of interest to see that classification of obstructive apnea improved most and that classification of mixed apnea did not improve. These findings may have several explanations. Based on the results of our study, the detection of obstructive apnea using chest impedance tracings seems to be most difficult relative to the other types of apnea, and therefore the greatest improvement could be reached in the classification of this subgroup. Furthermore, transcutaneous dEMG tracings display an increase in diaphragmatic activity during obstructive apnea which could be easily distinguished from normal breathing and this increased activity is not measured with chest impedance. Central apnea are often classified correctly in chest impedance tracings and therefore less improvement could be made in classification of this type of apnea based on transcutaneous dEMG tracings. In both tracings no breathing activity is visible

during central apnea which is easily recognized. Classification of mixed apnea did not improve, probably due to the combined characteristics of both obstructive and central apnea in this type of apnea which makes classification of mixed apnea difficult in both chest impedance and transcutaneous dEMG tracings.

The improvement in apnea classification found in this study indicates that monitoring spontaneous breathing with transcutaneous dEMG might lead to better guidance of treatment for individual infants suffering from AOP. Despite the fact that no other breathing patterns than apnea were investigated in **chapter 2**, it seems to be reasonable that monitoring other breathing patterns, for example periodic breathing, in preterm infants can be improved in daily clinical care by using transcutaneous dEMG as well. Furthermore, transcutaneous dEMG might be used to quantify the effect of respiratory treatments in terms of apnea reduction.

Monitoring the effect of pharmacological treatments

Preterm infants suffering from respiratory diagnoses as respiratory distress syndrome (RDS) and AOP, are often treated with pharmacological therapies. The working mechanism of frequently used pharmacological treatments in these preterm infants are often not (completely) understood.[8–10] More insight in the effect of pharmacological therapies on the main effector of breathing, the diaphragm, might improve the clinical use of these drugs.

Transcutaneous dEMG provides information on neural breathing effort and it has been shown to detect changes in diaphragmatic activity after the start of a pharmacological treatment.[11–13] Therefore, we hypothesized that transcutaneous dEMG could be used to get insight in the effect of commonly used pharmacological treatments such as exogenous surfactant administration for preterm infants suffering from RDS (**chapter 3**) and doxapram treatment for preterm infants with severe AOP (**chapter 4**).

Minimally invasive surfactant therapy (MIST) is nowadays used to administer exogenous surfactant to spontaneous breathing preterm infants, avoiding invasive mechanical ventilation.[14] It has been shown that MIST leads to a rapid improvement in lung volume and oxygenation.[15] In **chapter 3** of this thesis, transcutaneous dEMG measurements during MIST showed a reduction in peak and tonic activity of the diaphragm one hour after the administration of exogenous surfactant in most preterm infants. This reduction in neural breathing effort was accompanied by a significant reduction in need for extra oxygen.

Neural breathing effort is thought to be associated with the compliance of the respiratory system.[11,16] Therefore, MIST seems to lead to an improvement in compliance of the respiratory system, comparable with exogenous surfactant administration via an endotracheal tube.[17,18] However, there was a marked individual variability in

diaphragmatic activity in response to exogenous surfactant in our study. This variability may be caused by individual differences in the response based on, for example, pre-existing disease severity, surfactant deposition during the administration and surfactant inactivation after it is administrated. Furthermore, in line with previous studies, it probably takes more than one hour to reach a new balance in the respiratory system following exogenous surfactant treatment.[19,20] The attending physician treating preterm infants with MIST and the nurses taking care of these infants after the procedure, need to be aware of the variable and, sometimes, late effects of this therapy on neural breathing effort.

The interpretation of the results of this study is limited by the small number of infants included and the relative short measurement time of one hour. Furthermore, the infants in this study were not sedated during the procedure which might have influenced our findings. Sedation might lead to a reduction in spontaneous breathing effort before the MIST procedure starts with consequently less reduction in diaphragmatic activity after MIST independent of the changes in respiratory mechanics. On the other hand, the non-sedated state of the included infants might have led to agitation and movement artefacts impairing the signal analysis. In addition, no comparison could be made to surfactant administration via an endotracheal tube in terms of diaphragmatic activity response, which would be of interest to investigate if the individual variability could, partly, be explained by the route of administration.

Next to exogenous surfactant administration, the effect of doxapram on diaphragmatic activity was studied in **chapter 4**. Doxapram is used as adjuvant therapy for preterm infants suffering from AOP unresponsive to caffeine and maximal non-invasive respiratory support. In this study, no change in diaphragmatic activity after the start of doxapram treatment was seen. Therefore, it is concluded that doxapram does not lead to a more forceful contraction of the diaphragm. However, the number of apneic events was reduced after the start of doxapram treatment, and therefore it is considered that this therapy leads to a more sustained respiratory drive.

Preterm infants included in this doxapram study were already treated with caffeine. Previous research has shown that caffeine increases diaphragmatic activity.[12,13] It might be that caffeine treatment leads to maximal stimulation of diaphragmatic activity and possibly the start of doxapram treatment could not add more diaphragmatic activity. Furthermore, it might be that neural breathing effort directly before and after an apneic event was altered by doxapram treatment. Unfortunately, neural breathing effort in these apneic segments could not reliably be analyzed with the available data analysis algorithms.

Monitoring the effect of non-invasive respiratory support

Non-invasive respiratory support is preferred in spontaneous breathing preterm infants to avoid invasive mechanical ventilation, which is associated with adverse long-term outcomes such as bronchopulmonary dysplasia and neurodevelopmental impairment.[21,22] Different modalities of non-invasive respiratory support are available with different intensity of treatment.

To date, it remains a clinical challenge to adjust the level of respiratory support to the need of the individual preterm infant. Selecting the initial mode of non-invasive respiratory support and weaning from this support thereafter, is often based on a 'trial and error' approach which does not take individual differences in immaturity into account.[23–25]

It was hypothesized that transcutaneous dEMG provides objective parameters of spontaneous neural breathing effort which may be used to guide the selection and weaning of non-invasive respiratory support in preterm infants. Before guidance of weaning based on transcutaneous dEMG can be investigated, first it needs to be objectified if changes in neural breathing effort can be detected with this technique when weaning from non-invasive respiratory support and to what extent modes of respiratory support differ in terms of diaphragmatic activity needed for sufficient breathing.

In **chapter 5**, transcutaneous dEMG was used to measure neural breathing effort when preterm infants were weaned from nasal continuous positive airway pressure (nCPAP) to less supportive low flow nasal cannula (LFNC). As expected, diaphragmatic activity increased after weaning from nCPAP to LFNC. Therefore, transcutaneous dEMG measurements provide valuable information on the effect of changes in the mode or level of respiratory support on neural breathing effort, which seems to be a reflection of the clinical respiratory condition of these infants. The possible use of transcutaneous dEMG for the guidance of weaning was further endorsed with the finding that the increase in diaphragmatic activity was most prominent in preterm infants failing the weaning attempt. This finding gives a first indication that objective parameters may be obtained by transcutaneous dEMG which can differentiate between preterm infants that are adequately supported and those who are not. This indicates that these objective parameters might have the potential to be used in future to adjust the level of respiratory support to the needs of an individual infant.

In addition to measuring changes in diaphragmatic activity after weaning from respiratory support, dEMG may also be used to compare the level of support given by different modes of non-invasive respiratory support. High flow nasal cannula (HFNC) is a relatively new mode of non-invasive respiratory support which might be as effective as nCPAP in preventing invasive mechanical ventilation.[26–28] However, limited data are

available on the physiological effects of HFNC and, for example, which flow rates are needed to obtain similar respiratory support as nCPAP.[29–31] In **chapter 6**, HFNC was compared to nCPAP in terms of neural breathing effort measured with transcutaneous dEMG. No changes in transcutaneous dEMG parameters as well as clinical parameters were seen when infants are transitioned from nCPAP to HFNC, using a 1 to 1 ratio for pressure and flow. These results suggest that nCPAP and HFNC deliver a comparable level of respiratory support.

In contrast to the results in **chapter 5**, describing weaning from nCPAP to LFNC, diaphragmatic activity did not differ between infants failing HFNC compared to infants successfully transitioned to HFNC. This might be explained by the fact that the time to failure was longer during HFNC (>24 hours) than during LFNC (<3 hours). Maybe, the measurement duration of three hours was not long enough to detect differences in diaphragmatic activity in infants failing on HFNC. Furthermore, the results of our study may be different when using higher initial flow rates during HFNC, as described in clinical trials on this mode of non-invasive respiratory support.[26,27,32]

It needs to be taken into account that both in **chapter 5** and **chapter 6**, stable preterm infants were included whom were deemed ready to wean from nCPAP based on clinical characteristics. The results of both studies may differ in unstable and younger preterm infants, for example directly after birth or after extubation from invasive mechanical ventilation. This might explain why HFNC seems to be comparable to nCPAP in our study in contrast to recent clinical trials showing more HFNC failure compared to nCPAP failure in preterm infants directly after birth.[32–34]

Measuring diaphragmatic activity by transcutaneous dEMG may also be helpful in determining the interaction between nasal intermittent positive pressure ventilation (nIPPV) and spontaneous breathing. During nIPPV, the ventilator provides peak inflation pressures which ideally should be synchronized with spontaneous breathing efforts of the infant. However, this synchronization remains a clinical challenge and therefore non-synchronized nIPPV is mainly used in daily clinical care.[35] Non-synchronized nIPPV leads to patient-ventilator asynchrony both during the inspiration and expiration. The incidence of this asynchrony has not been systematically described in preterm infants. Therefore, patient-ventilator asynchrony in preterm infants treated with non-synchronized nIPPV was quantified based on transcutaneous dEMG measurements of spontaneous breathing in **chapter 7**.

Patient-ventilator asynchrony was present in more than two-thirds of ventilator inflations compared to spontaneous breathing efforts during both the inspiratory phase and expiratory phase of breathing in preterm infants treated with non-synchronized nIPPV. In addition to asynchronous inflations, extra mechanical inflations and unsupported breaths were common as well. The high patient-ventilator asynchrony

found might be explained by the set ventilator frequency with respect to the irregular breathing pattern of the preterm infant. It can be speculated that a set ventilator frequency and inspiratory time that is adjusted to the mean spontaneous respiratory rate of the infant might reduce asynchrony. This needs to be taken into account by the attending physician responsible for the respiratory treatment of preterm infants.

Although the clinical consequences of patient-ventilator asynchrony in preterm infants have not been investigated, asynchronous ventilator inflations are thought to be inefficient and might lead to prolonged dependence of respiratory support as reported in adult intensive care patients.[36] It can be imagined, for example, that initiation of a mechanical inflation at the time an infant is exhaling may lead to high peak inflation pressures which injures the lungs. At the same time, the diaphragm cannot relax which, based on the physiology of muscle contraction, may lead to a less effective contraction during the next breath. On the other hand, it can be speculated that extra mechanical inflations are supportive during apneic events and contribute to the prevention of hypoxic events as reported before.[37–39] However, this can only be the case if the glottis of the infant remains open.

The results of this study underline the need for techniques to synchronize nIPPV with spontaneous breathing efforts. Several techniques to do so have been investigated in the past decades, but all have disadvantages.[40] The most promising technique for synchronization of both inspiration and expiration proportional to an infant's spontaneous breathing effort is neurally adjusted ventilatory assist (NAVA) using transesophageal dEMG.[41,42] However, this technique is invasive, expensive and for this application only available on systems of one specific ventilator distributor. Transcutaneous dEMG is thought to have the same possibilities as NAVA for synchronization of ventilator inflations with spontaneous breathing using a non-invasive and cheaper interface.

Breath detection for future synchronization of ventilation

A first step toward synchronization of non-invasive ventilation is both correct and fast breath detection during spontaneous breathing, which was tested for transcutaneous dEMG in **chapter 8**. The performance of transcutaneous dEMG was compared with the Graseby capsule, a commercially available device using a pneumatic sensor placed on the abdominal wall to synchronize non-invasive ventilation.[43]

The results of the study presented in **chapter 8**, show that a commercially available breath detection algorithm based on the Graseby capsule signal only detects two-thirds of breaths. Development of new algorithms improved breath detection in both the transcutaneous dEMG signal and the Graseby capsule signal. These findings indicate that the algorithm used plays a key role in accurate breath detection. However, it needs to be taken into account that breath detection algorithms can be too sensitive

detecting more breaths than present, for example due to biphasic signal peaks. This overdetection might lead to double ventilator inflations during one spontaneous breath and might affect lung volume and respiratory muscle function. Ongoing development of breath detection algorithms is necessary before transcutaneous dEMG could be used for synchronization of ventilator inflations with spontaneous breathing to be able to reduce patient-ventilator asynchrony.

A promising finding was the faster detection of breaths in the transcutaneous dEMG signal compared to the Graseby capsule signal. Fast breath detection is important to be able to support most of the spontaneous inspiratory activity with a ventilator inflation, especially in preterm infants with high respiratory rates and short inspiratory times. Faster breath detection in the transcutaneous dEMG signal compared to the Graseby capsule signal can be explained based on the physiology of breathing in which contraction of the diaphragm occurs prior to abdominal expansion. However, this physiological time gain will partly be lost due to filtering of the transcutaneous dEMG signal causing a time delay which needs to be reduced as much as possible before implementing this technique in clinical care.

Limitations

Next to the results and implications of the research presented in this thesis, study limitations as well as technical limitations of transcutaneous dEMG, need to be addressed.

First, the changes in transcutaneous dEMG parameters measured in the studies are interpreted as a reflection of neural breathing effort. However, it is unclear to what extent neural breathing effort correlates with actual work of breathing.[16] A good correlation between these two parameters would confirm the usefulness of transcutaneous dEMG as non-invasive measurement tool to assess the clinical respiratory condition of preterm infants. Transcutaneous dEMG might than replace laborious and invasive work of breathing measurements and its potential contribution to clinical decision making will become more prominent.

The sample sizes of the studies in this thesis were relatively small, as is often the case in physiological studies. Therefore, the results presented only generate hypotheses by describing the effect of different treatments on diaphragmatic activity. Furthermore, the duration of the measurements to describe the effect of different respiratory treatments on diaphragmatic activity might have been too short to capture all relevant changes in diaphragmatic activity. The results of the studies may be different when measurements would have been longer.

The individual variability in diaphragmatic activity was high, indicating that the activity of the diaphragm is dynamic over time. This may have influenced the

interpretation of the changes in the parameters measured because it could not clearly be distinguished which changes are due to normal variability and which are due to an intervention. By using the percentage change over time in a group of preterm infants, the individual variability should not be of significant influence. However, before transcutaneous dEMG could be used at the bedside, the measured values should be standardized and corrected for infant characteristics.

Furthermore, the effect of respiratory treatments investigated in this thesis might be different in preterm infants with different characteristics. For example, the effect of exogenous surfactant administration might be different in preterm infants on invasive mechanical ventilation or when they are sedated during the MIST procedure. In addition, the response in diaphragmatic activity when weaning from nCPAP to HFNC or LFNC might be different in the first days of life or when preterm infants are in a less stable condition.

In addition to the study limitations, transcutaneous dEMG measurements have several limitations itself. First, the placement of the electrodes influences the signal measured due to the orientation of the electrodes to the diaphragm, the tissue thickness between the diaphragm and the electrodes, and the body position of the preterm infant.[7,44,45] Therefore, it is unclear if replacement of the electrodes leads to changes in the measured signal which would influence the results. This especially needs to be taken into account when transcutaneous dEMG would be used for continuous monitoring in neonatal intensive care where replacement of electrodes is necessary to prevent skin damage.

Several processing steps are needed to produce a readable respiratory waveform out of the raw transcutaneous dEMG signal.[46] It has to be taken into account that the software for signal recording and signal analysis used in this thesis introduces a time delay induced by necessary filtering steps, for example to remove cardiac interferences. Two techniques have been described for cardiac interferences filtering: the gating technique, as used in this thesis, and the subtraction technique.[46,47] It is unknown which technique is most suitable for data processing in preterm infants who have a much higher heart rate and respiratory rate than adults.

Data analyses in all presented studies are done with custom made algorithms. Using different algorithms might not necessarily lead to exactly the same results. This needs to be taken into account when comparing the results presented in this thesis to future studies. Furthermore, analyses are based on certain assumptions. For example the cut-off values that are used to determine the start and end of an inspiration. These cut-off values are mainly based on data of transesophageal dEMG measurements in adult intensive care patients.[48,49] It is unclear to what extent these assumptions are correct for transcutaneous dEMG data in preterm infants.

Conclusion

This thesis shows that transcutaneous dEMG can be used to monitor breathing patterns and to classify apnea. Second, measurements of diaphragmatic activity provide information on the working mechanism of pharmacological treatments for RDS and AOP. Third, the technique can detect changes in neural breathing effort after weaning from non-invasive respiratory support and can be used to compare the level of support of different modes of non-invasive respiratory support. Furthermore, the interaction between spontaneous breathing efforts of preterm infants and ventilator inflations could be described. Fourth, the first step toward synchronization of ventilator inflations with spontaneous breathing measured with transcutaneous dEMG is taken by improved breath detection.

Based on the results presented in this thesis, transcutaneous dEMG is a promising technique to improve and individualize respiratory treatment for preterm infants. Three main clinical applications can be brought forward for transcutaneous dEMG in neonatal intensive care: 1) monitoring of breathing patterns, 2) guiding of respiratory treatment, and 3) synchronization of respiratory support with spontaneous breathing. However, for each clinical application, specific requirements of the technique need to be met and before transcutaneous dEMG can be implemented in clinical care, improvements have to be made in data acquisition, analysis and interpretation.

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