Transcutaneous electromyography of the diaphragm

Monitoring breathing and the effect of respiratory support in preterm infants

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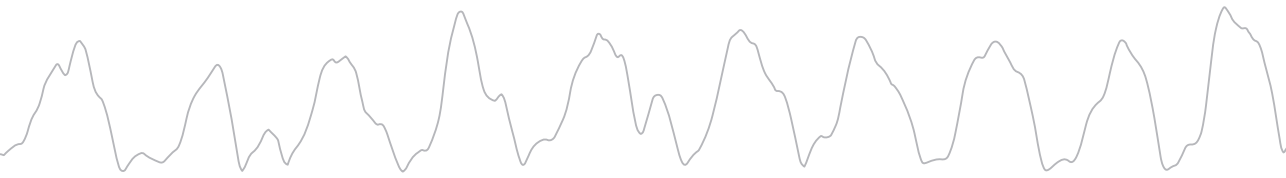
Chapter 1

General introduction and outline of the thesis



Prematurity

Preterm infants are born with a gestational age (GA) less than 37 weeks. Preterm birth can be classified as extremely preterm (< 28 weeks of gestation), very preterm (28 to 32 weeks of gestation) and moderate to late preterm (32 to 37 weeks of gestation).[1] Prematurity is a global health problem with preterm birth rates ranging from 5 to 18% of all births[2,3] and its complications are the leading cause of mortality for children under 5 years of age worldwide.[4] In 2016, 6.9% of the infants born in the Netherlands were born preterm[5], and all very and extremely preterm infants need intensive care treatment.

Due to the immaturity of all organ systems, several complications can occur in infants born preterm. Common short-term morbidities are respiratory failure, sepsis, necrotizing enterocolitis, intraventricular hemorrhage and bronchopulmonary dysplasia. The long term outcome of preterm infants is variable and ranges from no disabilities later in life to severe neurodevelopmental impairment.[6]

This thesis will focus on the respiratory condition of preterm infants. First, an introduction will be given on the consequences of preterm birth for the respiratory system. Second, common respiratory diagnoses in preterm infants are discussed, followed by treatment options. Next, the function and monitoring of the diaphragm, the main respiratory muscle, will be described and transcutaneous electromyography of the diaphragm will be introduced.

Development and physiology of the respiratory system

The respiratory system consists of the lungs, the airways, the chest wall, the respiratory muscles, chemical and mechanical receptors, and the respiratory control center in the brain stem. The main function of the respiratory system is gas exchange, i.e. the uptake of oxygen from the inspired air and the excretion of carbon dioxide from the blood stream into the expired air, also referred to as oxygenation and ventilation. In preterm infants, all components of the respiratory system are immature and therefore respiratory physiology is different compared to older infants, children and adults.

Lung development can be divided into five subsequent, partly overlapping, stages starting after three weeks of gestation: 1) the embryonic stage (3 to 7 weeks of gestation), 2) the pseudoglandular stage (5 to 17 weeks of gestation), 3) the canalicular stage (16 to 26 weeks of gestation), 4) the saccular stage (24 to 38 weeks of gestation) and 5) the alveolar stage (36 weeks of gestation to 8 years of age).[7] After preterm birth, the lungs are still in the canalicular and saccular stage of development. During the canalicular stage the terminal bronchioles develop, epithelial cells start to differentiate in type I pneumocytes that are needed for gas exchange and membranes are formed between the pneumocytes and the pulmonary capillaries. At the end of this stage of

development, gas exchange is possible although the surface area is small and almost no type II pneumocytes, needed for surfactant production, exist. In the saccular stage, alveoli start to develop. Expansion of the surface area and thinning of the membranes makes gas exchange more efficient. Furthermore, type II pneumocytes start to mature and to produce surfactant, a surface active substance which reduces the surface tension of the sphere shaped precursors of alveoli.[7]

After birth, the lungs must take over the gas exchange function which in utero is regulated by the placenta. However, after preterm birth, with lungs still in the canalicular or saccular stage of development, gas exchange is impaired due to a small surface area and the relative thick air-blood barrier, limiting the diffusion capacity. Furthermore, lung mechanics are unfavorable. The compliance of the lungs, defined as the change in volume per change in pressure, is low and the elastic recoil is high due to low surfactant levels. As a result the lungs tend to go to a low end-expiratory volume state. Normally, the elastic recoil of the lungs is counteracted by the relatively stiff chest wall, however this effect is limited in preterm infants due to the high compliance of the chest wall. Together this results in a resting state of the respiratory system at low functional residual capacity. Airway resistance is relatively high in preterm infants due to the small diameter of the airways, relative high tissue density and the presence of lung fluids and excretions. This increases the risk of airway collapse, obstruction and atelectasis.[7–9]

Low compliance of the lungs and the high airway resistance result in a high work of breathing in preterm infants. This work of breathing needs to be delivered by the respiratory muscles. The main respiratory muscle is the diaphragm, a dome shaped muscle separating the thoracic and abdominal cavity. It consists of two muscular parts and a central tendon and it starts to develop at the end of the third week of gestation. The development starts at the level of what will become the third to fifth cervical vertebra and the precursors of the diaphragm move downwards during the development of the fetus to the final position of the diaphragm at the height of the first lumbar vertebra.[10] The innervation of the diaphragm is by the phrenic nerve which arises from the third to sixth cervical spinal nerves, and the blood supply is via an anastomotic network of the internal mammary, intercostal and inferior phrenic arteries.[10,11] In preterm infants, the diaphragm is immature with a low muscle mass consisting of mainly type 2 muscle fibers, i.e. fast twitching, quickly fatiguing, muscle fibers using glycogen stores. Additionally, the diaphragm has a more horizontal position in preterm infants compared to older infants, children and adults which might reduce the force that can be generated.[7–9,12]

Besides the diaphragm, the intercostal, the abdominal and accessory respiratory muscles, such as the sternocleidomastoid and scalene muscles, contribute to respiration. Contraction of the intercostal and accessory respiratory muscles during inspiration lifts the thoracic wall upwards creating a larger intrathoracic space. However, the intercostal and accessory respiratory muscles are attached to horizontally placed ribs mainly

existing of cartilage in preterm infants which makes contraction of these muscles less effective. Normally, expiration is a passive process, however under some circumstances contraction of the abdominal muscles can support expiration.[8]

To achieve adequate gas exchange, breathing is regulated based on arterial levels of oxygen (PaO_2), carbon dioxide ($PaCO_2$) and the pH, sensed by the peripheral and central chemoreceptors in the carotid arteries, aorta and the ventrolateral part of the medulla, respectively.[13,14] Furthermore, mechanoreceptors sensing stretching of lung tissue, the airways and the chest wall give feedback to the respiratory center in the brain stem.[15] A good functioning closed feedback loop of the respiratory center in the brain stem, the central and peripheral chemoreceptors, the mechanoreceptors, together with the effectors of respiration, i.e. the respiratory muscles, is needed for adequate control of breathing.

Immaturity of respiratory control affects all levels of the control of breathing loop in preterm infants, which leads to irregular breathing and difficulties to maintain adequate gas exchange. Both the response to $PaCO_2$ and PaO_2 is altered in preterm infants. The sensitivity of the central chemoreceptors is low for $PaCO_2$ and the response to hypoxemia (low PaO_2) in the peripheral chemoreceptors is insufficient. This leads to inadequate responses to changes in arterial gasses, central breathing depression and periodic breathing.[13,15,16]

Altogether, the characteristics of the immature respiratory system contribute to the fact that preterm infants are prone for respiratory failure.

Common respiratory diagnoses in preterm infants

Respiratory failure is a clinical complex of symptoms characterized by the inability to maintain sufficient gas exchange. As described before, the immaturity of the respiratory system in preterm infants might lead to respiratory insufficiency due to a compromised lung function and impaired control of breathing. This immaturity contributes to the existence of common respiratory diagnoses in preterm infants such as respiratory distress syndrome (RDS) and apnea of prematurity (AOP).

Respiratory distress syndrome

Neonatal RDS is a very common diagnosis in the first days of life in preterm infants caused by surfactant deficiency and structural immaturity of the respiratory system leading to a compromised lung function.[17,18]

Clinically, RDS is characterized by an increased work of breathing, tachypnea, expiratory grunting, chest retractions, and cyanosis in room air. These symptoms can be explained by the compromised lung function, i.e. low lung compliance and low functional residual capacity with high surface tension that needs to be overcome to

achieve sufficient air influx into the lungs for adequate gas exchange. Tachypnea is a method to try to maintain adequate minute volume during inefficient breathing with small tidal volumes, and is a mechanism to achieve dynamic hyperinflation leading to a higher end-expiratory lung volume. Expiratory grunting is a strategy to increase end-expiratory lung volume by prolonging the expiration against a partially closed upper airway and might reduce the incidence of atelectasis. The high transpulmonary pressure needed to inflate the lungs leads to retraction of the chest wall during inspiration. The diminished gas exchange capacity of the lungs leads to cyanosis in room air with high oxygen need and a rise in $PaCO_2$.[19]

The incidence of RDS increases with decreasing GA and nearly all extremely preterm infants are affected. Symptoms of RDS usually develop in the first hours of life and are, without treatment, progressive in the following 48 to 72 hours and gradually decline thereafter. The development of treatment options for RDS, mainly exogenous surfactant administration, which will be discussed later, have reduced mortality and morbidity rates in preterm infants dramatically.[20]

Apnea of prematurity

AOP affects almost all preterm infants born with a GA less than 30 weeks.[21] Apnea is most commonly defined as a cessation of breathing for more than 20 seconds or a shorter cessation of breathing accompanied by bradycardia and/or hypoxemia.[21] Three subgroups of apnea exist: central, obstructive and mixed apnea, which each require specific treatment. Central apnea are characterized by a cease in airflow and no breathing effort. During obstructive apnea there is no airflow due to obstruction of the upper airways despite breathing attempts made. Mixed apnea have both a central and obstructive component; it most often starts with a central cessation of breathing followed by breathing movements against an obstructed airway.[15] Mixed apnea are the most common and account for 50 to 70% of all apnea in preterm infants suffering from AOP.[20]

Several factors in the immature respiratory system make preterm infants prone for AOP, for example a low end-expiratory lung volume, a low baseline oxygenation and alterations in the sensitivity of chemoreceptors.[15] Adequate end-expiratory lung volume functions as an oxygen storage during respiratory pauses preventing a direct drop in blood oxygen saturation. However, preterm infants have low end-expiratory lung volume levels and therefore do not have this buffer to prevent direct desaturation. Directly after birth, the peripheral chemoreceptors, mainly responding to changes in PaO_2, need to adapt to the hyperoxic environment and are initially inhibited. Within a week, a new set point to the higher oxygen tension is established. This new set point might be hypersensitive and might lead to rapid changes in breathing on small fluctuations in arterial gasses known as periodic breathing, characterized by short

respiratory pauses followed by compensatory fast breathing episodes.[14,22] Persistent periodic breathing can result in apnea. Central chemoreceptors are mainly triggered by alterations in $PaCO_2$ which lead to changes in pH levels in the cerebrospinal fluid. In preterm infants, the response to an increase in $PaCO_2$ to increase ventilation is reduced and the apnea threshold of $PaCO_2$ is close to the $PaCO_2$ maintained during normal breathing what makes them prone for apneic events.[14–16]

AOP develops mainly after the first week of life, is progressive for about 4 weeks, than stabilizes and declines slowly over a period of weeks thereafter.[23,24] In most preterm infants, AOP resolves around 36 weeks of gestation, however in extremely preterm infants apnea may continue up to 4 weeks after term age.[21]

Prolonged hypoxemia and/or bradycardia due to apnea in infants suffering from AOP, are associated with neonatal morbidity and long term impaired neurological development.[23,25] Therefore, adequate treatment, tailored to the type of apnea, is needed.[26] To achieve this goal detailed monitoring of breathing and correct classification of apnea is essential.

Treatment of common respiratory diagnoses in preterm infants

Treatment of common respiratory diagnoses in preterm infants can be divided in two categories: 1) pharmacological treatment, and 2) respiratory support. The most commonly used therapies will be described.

Pharmacological treatment

Exogenous surfactant

After the discovery of surfactant and the deficiency of this substance in the lungs of preterm infants suffering from RDS in 1959[17], it took about 20 years to develop exogenous surfactant that could be administered into the lungs of these infants.[27] The administration of exogenous surfactant has improved the survival rates of preterm infants suffering from RDS dramatically and is nowadays the cornerstone of the treatment of this syndrome.[28]

Endotracheal administration of exogenous surfactant is effective to reduce clinical symptoms of RDS, to improve oxygenation and to improve lung function.[29] Physiological studies have shown a rapid increase in end-expiratory lung volume in preterm infants treated with endotracheal surfactant.[29,30] Furthermore, the compliance of the respiratory system increases after surfactant administration.[31,32]

Historically, exogenous surfactant is administered to mechanically ventilated preterm infants via an endotracheal tube. However, harmful effects of invasive mechanical ventilation on the lungs and brain, which increase the risk to develop bronchopulmonary dysplasia and long term neurodevelopmental impairment, are established.[33] Therefore,

non-invasive respiratory support has become the primary treatment in spontaneously breathing preterm infants after birth. This requires new techniques to administer exogenous surfactant without invasive mechanical ventilation, for example via the INSURE (INtubation, SURfactant administration and direct Extubation) method, a laryngeal mask, by nebulization or via a small catheter positioned in the trachea.[34]

Minimally invasive surfactant therapy (MIST), also called less invasive surfactant administration (LISA), was first described in 2007[35] and is nowadays often used in neonatal intensive care. A small catheter is positioned in the trachea under direct vision by using a laryngoscope in spontaneously breathing preterm infants with symptoms of RDS supported by nasal continuous positive airway pressure (nCPAP).[35] In the past decade, several studies have compared this minimally invasive strategy to administer surfactant with traditional endotracheal administration.[36–39] Recent systematic reviews and meta-analyses show that MIST is effective in treating RDS, reduces the need for invasive mechanical ventilation and improves the outcome of preterm infants.[40–42] However, the physiological effects of MIST on lung function and breathing effort are poorly studied. To date, a study in preterm lambs and a study in preterm infants treated with MIST have shown an increase in end-expiratory lung volume and a rapid improvement in oxygenation after treatment.[43,44] The effect of MIST on breathing effort still needs to be established.

Caffeine

Central apnea can best be treated with pharmacological therapies. The first line pharmacological treatment of AOP are methylxanthines, of which caffeine is most frequently used.[16,21] Caffeine is a stimulant of the respiratory center in the brain stem leading to a more stable breathing pattern.[16,45] Furthermore, treatment with caffeine decreases the incidence of bronchopulmonary dysplasia, improves neurodevelopmental outcome of preterm infants at 18 months of age and is associated with less motor impairment, better neurobehavioral outcomes and better respiratory function at 11 years of age.[46–50]

Caffeine treatment is indicated in all preterm infants born at less than 30 weeks GA and in older preterm infants with apneic events. Dosing starts with a loading dose and is followed by a daily maintenance dose which can be administered intravenously or orally.[51] The optimal dose of caffeine is not yet established, however it seems that higher doses may be more effective and that the dose needs to be adjusted to the increasing postnatal age to maintain stable caffeine concentrations.[52,53]

The exact working mechanism of caffeine is not completely understood but lies within the domain of adenosine and gamma-aminobutyric acid receptors in the brain. Stimulation of these receptors results in breathing depression, therefore the inhibitory effect of caffeine on these receptors is thought to be its main contribution to the

stabilization of the breathing pattern which leads to less apneic events and prevents hypoxemia.[15,21] In addition, recent studies have shown a direct stimulating effect of caffeine on electrical activity of the diaphragm.[54,55]

Doxapram

Doxapram is an analeptic drug considered for preterm infants with AOP unresponsive to caffeine therapy and maximal non-invasive respiratory support.[56] Observational studies show a decrease in the number of apnea and less need for invasive mechanical ventilation after doxapram treatment.[57–59] However, due to the adverse effects, such as hypertension and gastro-intestinal disturbances, and concerns about the effect on long-term neurodevelopmental outcome, doxapram is considered to be a rescue therapy.[60–62] Dosing of doxapram is via continuous intravenous infusion because it is very rapidly metabolized and dosing regimens in preterm infants range from 0.1 to 2.5 mg/kg/hour.[63,64]

The main effect of doxapram is stimulation of the central nervous system. It is thought to improve the sensitivity of central chemoreceptors and to increase the activity of the respiratory center in the brain stem mediated by potassium channels. To a lesser extent, doxapram may also have a stimulating effect on peripheral chemoreceptors located in the carotid artery and the aorta.[65] The effect of doxapram seems to be dose dependent and physiological studies found an improvement in minute ventilation and tidal volume only when using doses of more than 1 mg/kg/hour.[63,66] However, increasing the dose may also increase the risk of adverse effects. This balance between benefit and harm when increasing the dose needs to be weighed for each individual infant.

A direct effect of doxapram on respiratory muscle function was described in an animal study about 30 years ago.[67] Only high doses of doxapram, exceeding the 2,5 mg/kg/hour dose that is maximally validated in preterm infants, were found to have an effect on the neuromuscular transmission and therefore muscle excitation. In preterm infants, it is unknown if doxapram affects respiratory muscle function.

Respiratory support

Respiratory support is indicated in almost all preterm infants born at a GA less than 32 weeks due to the immaturity of the respiratory system. It is used to stabilize the respiratory system and to improve the respiratory mechanics. Respiratory support can be subdivided in invasive mechanical ventilation and non-invasive respiratory support.

Invasive mechanical ventilation

Invasive mechanical ventilation is the most advanced mode of respiratory support characterized by endotracheal intubation and it does not require spontaneous

breathing. Two main modalities of invasive mechanical ventilation are used: conventional mechanical ventilation and high frequency ventilation.[68] Invasive mechanical ventilation is associated with ventilator induced lung injury, ultimately leading to bronchopulmonary dysplasia and impaired neurodevelopmental outcome.[33,69] Therefore, preferably non-invasive respiratory support is used in daily clinical care of preterm infants and invasive mechanical ventilation is used as rescue therapy in the sickest infants.

Non-invasive respiratory support

Different modalities of non-invasive respiratory support exist, ranging from nasal intermittent positive pressure ventilation (nIPPV) to low flow nasal cannula (LFNC). Each mode has its own working mechanisms, advantages and disadvantages. A distinction can be made between primary and secondary non-invasive respiratory support. The primary mode of non-invasive respiratory support is selected at birth and secondary is the mode of non-invasive respiratory support selected when infants are extubated from invasive mechanical ventilation.

Nasal continuous positive airway pressure

nCPAP is the most commonly used mode of non-invasive respiratory support in preterm infants. It provides continuous positive pressure, ranging from 3 to 10 cmH_2O in daily clinical care, to the airways during the entire breathing cycle.[70] It can be applied via a nasal mask and short or long nasal prongs. The pressure provided has several working mechanisms improving the function of the respiratory system. First, it splints the upper airways and therewith prevents obstruction, which stabilizes breathing. Second, the continuous positive pressure during expiration prevents collapse of the lower airways, mainly consisting of sacculi in preterm infants, thereby improving lung compliance and end-expiratory lung volume. nCPAP also seems to affect the central respiratory drive by alteration of the Hering-Breuer reflex by increasing the inspiratory load that can be generated before the reflex starts to act. This can be explained by a constant stimulation of the mechanoreceptors of the larynx which are coupled to the respiratory center in the brain stem via a direct feedback loop, and by suppression of the intercostal phrenic inhibitory reflex stabilizing the chest wall.[71,72]

Several studies have compared nCPAP as primary mode of respiratory support after birth to invasive mechanical ventilation.[73–76] Meta-analyses of these studies show a reduction in mortality and bronchopulmonary dysplasia in preterm infants treated with nCPAP.[33,77] In addition, nCPAP is proven to be an effective therapy for RDS and AOP.[21,70,78] Therefore, nCPAP is nowadays the primary choice of respiratory support in preterm infants for both preventing invasive mechanical ventilation and treatment of common respiratory diagnoses.

Nasal intermittent positive pressure ventilation

nIPPV is the most advanced mode of non-invasive respiratory support used in daily clinical care of preterm infants. It provides peak inflation pressures on top of a continuous positive airway pressure, mimicking invasive mechanical ventilation. Similar to nCPAP, the interface consists of a nasal mask or short or long nasal prongs. An advantage of nIPPV compared to other modes of non-invasive respiratory support is that it might maintain alveolar ventilation during apnea.[79]

The most consistent effect of nIPPV on the respiratory function found in physiological studies is a reduction in work of breathing.[80–84] In addition, nIPPV might improve end-expiratory lung volume due to the higher mean airway pressure delivered and the expected recruitment of gas exchange units by the application of intermittent peak inflation pressures.[85] However, no change in tidal volume and minute ventilation was found in most physiological studies.[80,81,84] Furthermore, it has been suggested that nIPPV improves gas exchange, although studies have not been consistent on this finding.[82,83,86]

Clinically, nIPPV is an effective method to reduce the need for invasive mechanical ventilation when nCPAP fails, both as primary mode of respiratory support at birth and secondary after extubation.[87–91] A direct effect on the incidence of apnea is seen in two clinical studies.[86,89] However, it remains inconclusive what the effect of nIPPV is on important outcomes such as mortality or bronchopulmonary dysplasia.[87,92,93]

The potential of nIPPV to reduce invasive mechanical ventilation is increased further when the delivery of the peak inflation pressure is synchronized with the spontaneous breathing effort of the infant.[94] However, synchronization of nIPPV with spontaneous breathing is difficult in clinical practice. Several strategies have been evaluated in the past decade to synchronize nIPPV which all have major disadvantages.[79,95] The Graseby capsule is a pneumatic sensor which is placed on the abdominal wall detecting pressure differences due to abdominal expansion during breathing. This technique has been incorporated in a ventilator system. However, its accuracy is not optimal with correct synchronization in only 56 to 88% of spontaneous breaths.[83,96,97] Furthermore, triggering based on the Graseby capsule is relatively slow and it requires experienced staff for correct placement and use.[79,97] A sensitive and fast technique to synchronize is based on flow, in the absence of air leak at the airway opening.[91,92] As this condition, i.e. the absence of air leak, is not often met during non-invasive respiratory support, the use of flow-based triggering is limited during nIPPV. Furthermore, using flow as a method to trigger nIPPV can result in auto-triggering due to condensation in the system.[79,95] Neurally adjusted ventilatory assist (NAVA), mainly used for invasive mechanical ventilation, is getting more and more attention in the neonatal population to provide synchronization of non-invasive respiratory support based on the electrical activity of the diaphragm measured with electromyography (EMG) electrodes mounted on an esophageal catheter.[98,99] It measures neural breathing effort and aims to support breathing proportional to the

infant's effort. However, this technique is invasive, the catheters used are expensive and special software is needed for its use. Therefore, the search for an easy to use, reliable method to synchronize nIPPV with spontaneous breathing in preterm infants without major disadvantages is still ongoing.

Due to the challenges faced with synchronization, non-synchronized nIPPV is mainly used in daily clinical care. This leads to patient-ventilator asynchrony, i.e. the start and end of the ventilator inflations are asynchronous with the infant's own breathing attempts. This phenomenon is associated with adverse outcomes in adult and pediatric intensive care patients and might lead to a difficult weaning process, prolonged invasive mechanical ventilation, dynamic hyperinflation, ventilator induced lung injury, diaphragm dysfunction and, ultimately, mortality.[100–103] However, the extent of patient-ventilator asynchrony in preterm infants treated with non-synchronized nIPPV as well as the consequences of this asynchrony in this specific population are not known.

High flow nasal cannula

High flow nasal cannula (HFNC) provides heated and humidified gas through nasal cannula with a flow rate of 3 to 8 liter per minute. The working mechanism of this non-invasive respiratory support mode is not completely understood. The flow provided might lead to a certain distending pressure delivered to the lungs comparable to nCPAP. However, no direct information about the delivered pressure is available and physiological studies show a wide variability of pressures obtained at standard flow rates, depending on system and infant characteristics.[71,104] Besides providing a positive distending pressure, other potential working mechanisms of HFNC have been suggested: it may improve ventilation by wash out of the dead space of the nasopharynx, it may decrease work of breathing and stabilize breathing patterns by stimulation of mechanoreceptors in the pharynx and larynx, and it may reduce metabolic rates by heating and humidifying the gas breathed.[104,105]

HFNC is nowadays used as an alternative for nCPAP in daily clinical care. The main advantage of HFNC over nCPAP is the reduction of stress and nasal trauma.[106–108] Several studies compared HFNC with nCPAP as primary mode of respiratory support after birth and after extubation.[109,110] Studies on the use of HFNC compared to nCPAP after extubation consistently show HFNC to be non-inferior to nCPAP in terms of failure rates and need for invasive mechanical ventilation.[111–113] However, recently a trial comparing HFNC to nCPAP as primary mode of respiratory support after birth has been stopped early due to higher failure rates in the group of infants treated with HFNC.[114]

Information on the effect of HFNC on respiratory function is inconsistent. Some studies display a linear association between flow delivered and pressure built up in the pharynx or esophagus, used as surrogate for pulmonary pressure.[115,116] However, other studies did not find such an association.[117,118] One study, using invasive measurements

with esophageal catheters, has been conducted to establish work of breathing on HFNC and nCPAP, which seems to be comparable.[119] It is important to obtain more information about breathing effort on HFNC compared to nCPAP, preferably in a non-invasive way. Therefore, patient-friendly techniques to measure the effect of respiratory support on spontaneous breathing effort in preterm infants need to be developed.

Low flow nasal cannula

LFNC is the least advanced mode of non-invasive respiratory support characterized by oxygen supply via nasal cannula with a flow rate of 2 liter per minute or less.[120] In clinical care, this method is used to wean from nCPAP and HFNC and to deliver supplemental oxygen, for example in preterm infants with bronchopulmonary dysplasia.[121,122] Some physiological studies have shown that even flow rates of less than 2 liter per minute might provide a positive end-expiratory pressure.[123,124] However, this pressure is widely variable and should not be the reason to select this mode of respiratory support. Furthermore, the use of LFNC to treat AOP in clinical practice is not evidence-based.

Weaning from respiratory support

The need for respiratory support in preterm infants evolves with growth and maturation of the infant and is dynamic over time, depending on the immaturity of the infant at birth and the complications of prematurity faced thereafter. In general, the need for respiratory support reduces over time, although short escalations may be necessary due to complications such as sepsis or necrotizing enterocolitis. Ideally, weaning of respiratory support should be based on the individual need of each infant, however it is difficult to determine this need. Therefore, weaning is mainly based on a 'trial and error' approach and the experience of the attending physician.[125]

Several strategies to wean non-invasive respiratory support are used in clinical care. Weaning from nCPAP can be divided in four main categories: 1) weaning nCPAP directly to room air; 2) gradually weaning of the pressure delivered with nCPAP to a certain minimum; 3) increasing the time off nCPAP over several days; and 4) weaning to HFNC or LFNC.[126,127] It is unclear if one weaning strategy is superior to other strategies.[128–131]

Most criteria to predict if an infant is ready to wean are based on clinical parameters, for example, GA, birth weight and oxygen requirement.[126,127] However these parameters do not take individual differences in maturation into account. Therefore, there is an urgent need for objective parameters to determine the individual need for respiratory support and to guide weaning.

Monitoring respiration in preterm infants

Information on spontaneous breathing of preterm infants is of utmost importance to be able to effectively treat respiratory conditions potentially leading to respiratory failure. The standard technique to monitor respiration in the neonatal intensive care unit (NICU) is chest impedance. This technique measures electrical impedance differences between two electrodes placed on the chest of the infant caused by displacement of air in the lungs and movement of the chest wall during breathing.[132,133] It is used to measure the respiratory rate and to some extent breathing patterns, however its accuracy to classify apnea is questioned and it does not provide information on breathing effort.[132–134]

Monitoring the function of the diaphragm might provide information that can overcome the shortcomings of chest impedance in preterm infants with imminent respiratory failure. In the next section, the function of the diaphragm and the effects of prematurity on the diaphragm are introduced, followed by a description of techniques that can be used to monitor diaphragmatic function, including transcutaneous electromyography of the diaphragm (dEMG), the main topic of this thesis.

The diaphragm and its function

Function of the diaphragm

The diaphragm is the main respiratory muscle of the human body and the main effector in the control of breathing cascade. The respiratory center in the brain stem regulates the neural signal send via the phrenic nerve to the diaphragm, which is based on the input of the peripheral and central chemoreceptors and the mechanoreceptors.[14]

Contraction and shortening of the diaphragm leads to a downward displacement of the muscle and expansion of the intrathoracic cavity generating a negative intrathoracic pressure. The created negative intrathoracic pressure induces an air influx into the lungs, i.e. the inspiration starts. The diaphragm can generate its maximal force when the contraction starts in its resting position, depending on the length and the position of the muscle fibers and the firing state of the motoneurons in the motor units.[9,12,135,136]

Effects of prematurity on diaphragm function

In preterm infants, the composition of the diaphragm, in all its aspects, is different compared to older infants, children and adults. First, the motor units, a group of muscle fibers which is activated by a single phrenic nerve motoneuron, are not completely developed. The development of motor units consist of maturation of the motoneurons, organization of the muscle fibers in relation to the motoneurons and the formation of synapses to form the neuromuscular junction.[135] In utero, motoneuron and motor unit development are reflected in fetal breathing movements. Maturation of these

complexes is needed to be able to establish sustained spontaneous breathing and its immaturity might contribute to diaphragm fatigue in preterm infants.[135]

Second, the diaphragm consists of a mixture of type 1 and type 2 muscle fibers. Type 1 muscle fibers are slow twitching, oxygen dependent, fatigue resistant fibers, whereas type 2 muscle fibers are quickly fatiguing.[137] Compared to adults, preterm infants have less type I and more type 2 muscle fibers what may also cause diaphragm fatigue and may contribute to the increased risk of respiratory failure in preterm infants.[12]

Third, the diaphragm insertion is on the lower ribs, which still mainly consist of cartilage in preterm infants, and the zone of apposition is small. Due to the reduced curvature of the thorax and the small zone of apposition, the diaphragm is placed more horizontal in preterm infants compared to older infants, children and adults. This more horizontal position reduces the contraction force the diaphragm can generate which may be further reduced by the provision of too high levels of positive pressure by respiratory support pressing the diaphragm downwards.[7–9,12,138] Furthermore, the respiratory rate and the contraction velocity of the muscle fibers influence the force the diaphragm can generate. Higher respiratory rates and faster contraction results in a fall in the force generated due to less time for the muscle fibers to come to their resting state. Due to the immaturity of the diaphragm on the one hand and the high respiratory forces needed to overcome the low compliance of the lungs on the other hand, the diaphragm is prone for fatigue in preterm infants.[137,139,140]

On top of their immaturity, preterm infants are prone for critical illness, for example sepsis and necrotizing enterocolitis. In adults, critical illness is associated with diaphragm weakness and muscle fatigue and this most probably influences diaphragm function in preterm infants as well. Systemic inflammation can reduce the blood flow to the diaphragm, leading to anaerobic muscle contraction and lactate acidosis. In addition, direct actions of inflammatory cytokines on muscle fibers could lead to contractile protein dysfunction in the diaphragm.[141]

Invasive mechanical ventilation is needed for preterm infants in whom non-invasive respiratory support is insufficient to maintain adequate gas exchange. However, invasive mechanical ventilation is known to impair diaphragm function by bypassing spontaneous muscle activity leading to muscle atrophy.[142] Furthermore, excessive and prolonged invasive mechanical ventilation and patient-ventilator asynchrony, could further damage the diaphragm caused by inflammatory responses and edema.[143]

Based on the combination of the effects of prematurity itself on diaphragm function and the effects of critical illness, preterm infants seem to be prone for diaphragm dysfunction.[8,12]

Monitoring diaphragm function

Monitoring diaphragm function gives insight in breathing effort and might provide information on the effect of prematurity, critical illness, common respiratory diagnoses and their treatments on the activity of the diaphragm in preterm infants. The function of the diaphragm can be monitored with three techniques: transdiaphragmatic pressure measurements, ultrasound and EMG.

Transdiaphragmatic pressure

Due to the caudal movement of the contracting diaphragm during inspiration, a negative intrathoracic pressure (i.e. the intrathoracic volume expands) and positive intra-abdominal pressure (i.e. the intra-abdominal volume diminishes) is created. Measuring both intrathoracic and intra-abdominal pressure can provide information on diaphragm strength. To measure this transdiaphragmatic pressure, calculated as gastric pressure minus esophageal pressure, two pressure sensors are needed: one placed in the stomach and one placed in the esophagus.[144] The gastric pressure is a surrogate measure of intra-abdominal pressure and the esophageal pressure approximates intrathoracic pressure.[8,145] Different types of catheters containing a pressure sensing mechanism can be used: water filled catheters, balloon catheters or catheters equipped with a pressure transducer on the tip.[144,146,147]

Diaphragm strength measured with transdiaphragmatic pressure together with tidal volume measurements can be used to calculate diaphragmatic work of breathing.[144,147] Furthermore, transdiaphragmatic pressure can be used to calculate the tension time index of the diaphragm as *(mean transdiaphragmatic pressure in one inspiration/maximal transdiaphragmatic pressure when breathing against an occluded airway)*(inspiratory time/total time of one breathing cycle)*.[148] This index is a reflection of the strength of the diaphragm and its load.

To date, this method to monitor diaphragm function is only used in research settings. In clinical studies, the tension time index is suggested to be an indicator for clinical performance of the diaphragm, for example to predict extubation failure in mechanically ventilated infants.[146,148] However, it is an expensive and invasive technique requiring experienced and qualified staff to apply the equipment. Furthermore, the pressure sensing catheters can displace during the measurement leading to variations in the measured data which can make interpretation difficult. Transdiaphragmatic pressure measurements are used for short term registrations and the measured pressures can be interpreted only after post-processing of the data, therefore it is not applicable as a bedside tool to monitor diaphragm function. However, it might be useful as a diagnostic tool in specific clinical situations.

Ultrasound of the diaphragm

Ultrasound is a well-known radiologic technique to visualize internal organs of the human body. This technique uses sound waves at an inaudible high frequency to image internal organs by the principle of sound echoing. The composition of each individual tissue determines the sound frequency that is echoed back. Based on the differences in sound reflection per tissue, images can be reconstructed.[149]

Ultrasound can be used to directly visualize the diaphragm as an echogenic line between the echoless lungs and echogenic liver on the right side of the thorax. On the left sight, visualization of the diaphragm is more difficult and not standardized. In general, two ultrasound modes are used to monitor the diaphragm. The brightness mode (B-mode) is the standard ultrasound mode providing a two-dimensional image of the diaphragm in which its thickness can be measured in different stages of a breathing cycle.[138] The motion mode (M-mode) is a more advanced mode providing moving images in which the excursion of the diaphragm can be measured. The direction of diaphragm displacement during breathing can be determined based on the movement towards and away from the ultrasound probe.[150–153] In addition, speckle tracking is a relatively new ultrasound technique that can be used to reflect the movement of the muscle fibers during contraction by selecting a cluster of gray value patterns (speckles) in a small part of the muscle that are tracked in different windows during a contraction.[154]

Several parameters of diaphragm function can be measured with ultrasound. First, the thickness of the diaphragm, a measure of muscle mass proportional to body size in healthy term and preterm infants, can be used to calculate diaphragm strength.[138,155] Second, the thickening fraction of the diaphragm can be calculated as the percentage change in diaphragm thickness during inspiration compared to expiration and this is evaluated as measure of diaphragmatic work of breathing and respiratory effort.[156–158] Third, the excursion of the diaphragm reflects diaphragm movement and function and this is altered in case of diaphragm fatigue and paralysis.[150,153] Last, the deformation and deformation velocity of the diaphragm can be measured with speckle tracking which is highly correlated with transdiaphragmatic pressure measurements to determine breathing effort during inspiration.[154] The thickening fraction of the diaphragm might be a measure of diaphragm atrophy and is suggested to be a predictor for weaning failure in children and adults.[156,159] In preterm infants, ultrasound parameters of the diaphragm and the possible role of these parameters in clinical care have not yet been evaluated.

There is a growing interest in ultrasound of the diaphragm in adult, pediatric and neonatal intensive care and its role in diagnostics and clinical decision making is increasingly studied. However, this technique can only be used for short term registrations and is therefore not suitable for continuous monitoring of diaphragm

function and respiration. Furthermore, intra- and interobserver variability has to be taken into account when interpreting the results.

Electromyography of the diaphragm

EMG uses electrodes to measure electrical muscle activity. During muscle contraction, electrical activity arises due to muscle fiber depolarization which creates an action potential which can be detected by electrodes as a voltage change over time. Muscle fibers are organized in motor units leading to a motor unit action potential. The total electrical activity measured with EMG is the summation of all motor unit action potentials and depends on the number of activated motor units, and the shape and the phase of the action potentials.[160,161]

The electrical activity of the diaphragm can be measured with EMG which is a representative for muscle contraction and is a measure of neural breathing effort.[162] EMG of the diaphragm (dEMG) can be obtained in three ways: intramuscular, transesophageal and transcutaneous. Regardless of the method used, the measured signal needs filtering and processing to get a readable recording of diaphragmatic activity: the electrical activity of the heart and movement artefacts should be removed and displacement of the electrodes should be detected and corrected for.

Intramuscular needle placement measures the muscle fibers' activity directly, however this method is not used in preterm infants due to its invasive nature and complication risk.

Transesophageal dEMG can be used in preterm infants.[163] The dEMG electrodes are placed on a catheter or integrated in a feeding tube which is placed in the esophagus with the electrodes positioned at the level of the diaphragm. This technique has been used in preterm infants to describe breathing patterns and treatment effects.[55,164] Incorporated in a ventilator of one specific brand, transesophageal dEMG is used to synchronize both invasive and non-invasive ventilation proportional to the infant's neural breathing effort which has potential positive effects such as a reduction in patient-ventilator asynchrony.[98,165,166]

Transcutaneous or surface dEMG is a third method to measure the electrical activity of the diaphragm in preterm infants, which already has been described in 1977.[167] The use of transcutaneous dEMG in daily clinical care of preterm infants is investigated in this thesis and therefore this technique to monitor diaphragm function is described in more detail in the next section.

Transcutaneous electromyography of the diaphragm

Application of the technique

Transcutaneous dEMG is a non-invasive, easy to apply technique for bedside monitoring of diaphragm function in preterm infants.[168] The following equipment is needed for transcutaneous dEMG: surface electrodes with shielded cables, a physiological amplifier, a personal computer to record the data and a software package to process the measured signal. At least two electrodes are needed, one placed over the diaphragm (the active electrode) and one on an electrical silent spot such as bony tissue (the reference electrode). The signal measured is the voltage difference between the active electrode and the reference electrode over time (unipolar derivation). When using two active electrodes and a reference electrode, a bipolar derivation can be obtained.[169]

The number of electrodes can vary, creating different leads to measure different parts of the diaphragm. To monitor breathing, most often three electrodes are used to measure the activity of the frontal part of the diaphragm, with two skin electrodes placed on the thorax at the height of the diaphragm in the left and right mid-clavicular line and a reference electrode placed on the sternum.[160,168] To distinguish the activity of the frontal, dorsal, left and right diaphragm, which is useful in diagnosing (hemi) diaphragmatic paresis for example, extra electrode pairs can be used.[170]

Data handling

Most often a bipolar dEMG signal, i.e. the voltage change between two active unipolar derivations, is used. The raw dEMG signal needs to be filtered and processed to get a readable respiratory tracing.[169] First, amplification of the signal is needed to increase the signal-to-noise ratio which makes it easier to distinguish the measured signal from the environment induced noise.[160] Second, a digital first-order high-pass filter is used to correct the signal for several influencing factors such as the placement of the electrodes, the distance between the electrodes and muscle properties.[167,171] Next, the cardiac activity has to be removed from the dEMG signal. The two most frequently used techniques to do so are the gating technique and the subtraction technique. The gating technique removes parts of the signal that contain a QRS complex, the reflection of the contraction of the cardiac ventricles. First, a level detector selects the QRS complexes, followed by a pulse stretcher that generates a gated pulse with the width of a QRS complex removing these complexes. In this 'gated' dEMG signal, the gates are filled with a running average in a moving time window and the root mean square is calculated.[160,167,171] The subtraction technique uses a template of the QRS complex that is constructed based on an average of several QRS complexes in the raw dEMG signal. The template is matched with QRS complexes in the raw dEMG signal by means of cross-

correlation. At maximal correlation the template is adjusted in size and offset with the QRS complexes in the dEMG signal and is then subtracted, resulting in a dEMG signal with minimal disturbance of the electrical activity of the heart.[172,173]

Signal interpretation

The filtered and processed dEMG signal is ready for interpretation. Automatic peak and trough detection are used to quantify breathing. To qualify breathing, the amplitude of the signal is seen as a surrogate measure for muscle force and is thought to be associated with changes in tidal volume during breathing.[160] Tonic diaphragmatic activity, the lowest activity of the diaphragm during expiration, reflects the muscle tone during expiration indicating to what extent preterm infants use compensating mechanisms to maintain an adequate end-expiratory lung volume.[174,175] Furthermore, analysis of the peak of the signal, area under the curve, inspiratory time, expiratory time, the frequency content and frequency power changes over time can be used to describe breathing patterns.[160,172,173]

Clinical applications

Monitoring diaphragmatic function with transcutaneous dEMG might have several clinical applications, which need to be investigated. First, it could be used to monitor spontaneous breathing. A recent study shows transcutaneous dEMG to be as accurate as the standard chest impedance monitor to determine respiratory rate.[168] Other studies suggest that this technique can be used to obtain information on breathing patterns, which might be of great value in preterm infants suffering from AOP.[160,167]

Second, transcutaneous dEMG is thought to be able to detect changes in neural breathing effort. These changes might be of interest to determine the effect of common treatments for respiratory diagnoses in preterm infants. A recent study showed that diaphragmatic activity measured with transcutaneous dEMG increased after a loading dose of caffeine.[54] Furthermore, it is expected that dEMG would be able to detect changes in neural breathing effort when weaning from respiratory support. This might provide important information on the clinical condition of preterm infants and objective parameters to guide weaning.[144,160,172]

Third, adequate detection of spontaneous breathing with transcutaneous dEMG might be used to determine the interaction of respiratory support given and the spontaneous breathing of the treated preterm infant, for example to detect patient-ventilator asynchrony. Furthermore, transcutaneous dEMG, may have the potential to be used to synchronize invasive as well as non-invasive respiratory support with the infant's spontaneous breathing efforts.

Summary

Respiratory failure is common in preterm infants due to the immaturity of the respiratory system and an altered respiratory physiology. Many preterm infants, especially those born at a GA less than 32 weeks suffer from common respiratory diagnoses such as RDS and AOP. Several pharmacological therapies and respiratory support modes are available to treat these respiratory diagnoses. However, it is difficult to objectify breathing patterns and the effect of treatment on the clinical condition of preterm infants, as well as to determine which therapy is needed by or most effective for an individual infant. Monitoring the function of the diaphragm might give insight in both the quantity and quality of breathing in preterm infants. Transcutaneous dEMG, a non-invasive, easy to apply, bedside monitoring tool measuring the electrical activity of the diaphragm, may be used to provide objective parameters of neural breathing effort to monitor spontaneous breathing and to determine the effect of treatments for common respiratory diagnoses in preterm infants.

Outline of the thesis

The clinical background of preterm birth and its influence on the respiratory system are described in **chapter 1**. Common respiratory diagnoses in preterm infants and treatment options are introduced. The diaphragm, the main respiratory muscle, is discussed as possible source of objective information about the respiratory condition of preterm infants. Transcutaneous dEMG is introduced as a non-invasive, easy to apply, bedside tool to monitor diaphragmatic function and neural breathing effort. This technique may have several clinical applications which need to be studied.

The aim of this thesis is to investigate the possible use of transcutaneous dEMG in clinical care of preterm infants suffering from common respiratory diagnoses. Four different applications of transcutaneous dEMG in spontaneously breathing preterm infants are investigated: 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.

In the first section of this thesis, the use of transcutaneous dEMG to monitor breathing patterns, for example apnea, in preterm infants is investigated. The type of apnea determines the treatment needed, and therefore correct classification of apnea is important. In **chapter 2,** we compare apnea classification based on transcutaneous dEMG with apnea classification based on chest impedance, the standard monitoring technique used in neonatal intensive care.

The effects of pharmacological treatments for common respiratory diagnoses in preterm infants are described in the next section. **Chapter 3** focusses on the effect of exogenous surfactant administration via the MIST procedure on diaphragmatic activity in preterm infants with RDS. AOP unresponsive to caffeine treatment and maximal non-invasive respiratory support could be treated with doxapram. The effect of this analeptic drug on diaphragmatic activity is investigated in **chapter 4**.

In the third section of this thesis, transcutaneous dEMG is used to monitor the effect of non-invasive respiratory support. It remains a clinical challenge to adapt the level of respiratory support to the need of an individual preterm infant. The electrical activity of the diaphragm may be an objective parameter of the respiratory condition of preterm infants and may reflect the need for respiratory support. However, before transcutaneous dEMG can be used to guide the level of respiratory support, its ability to detect changes in diaphragmatic activity after weaning needs to be explored as well as its potential to describe the level of respiratory support provided by different modes. Therefore, weaning from nCPAP to LFNC is investigated in **chapter 5** and in **chapter 6** transcutaneous dEMG is used to compare the level of respiratory support of nCPAP and HFNC. In **chapter 7**, the incidence of patient-ventilator asynchrony in preterm infants

treated with non-synchronized nIPPV was described based on spontaneous breathing measurements with transcutaneous dEMG.

The first step in the use of transcutaneous dEMG to synchronize invasive and non-invasive ventilation with spontaneous breathing, is accurate breath detection. The accuracy and timing of breath detection in the transcutaneous dEMG signal was compared to the Graseby capsule signal in the last section of this thesis, presented in **chapter 8**.

In **chapter 9**, the results of the studies included in this thesis on the possible use of transcutaneous dEMG in clinical care of preterm infants are further discussed, including the clinical implications and limitations of the conducted research. In addition, clinical and technical topics for future research are introduced in **chapter 10**.

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