Physiological measurements of transition & resuscitation at birth

Jeroen van Vonderen

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ISBN: 978-90-9028423-1

Cover design: Rowan van Doorn
Printing: Pasmans Drukkerij B.V., Den Haag

Jeroen J. van Vonderen was recipient of a grant from the Willem-Alexander Kinderfonds

The printing of this thesis was financially supported by:
Advanced Life Diagnostics, Abbvie, Fisher & Paykel Healthcare and Chiesi

Physiological measurements of transition and resuscitation at birth

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op donderdag 11 september 2014
klokke 11.15 uur

door

Jeroen Johannes van Vonderen
geboren te Leiden
in 1987

Promotiecommissie

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CHAPTER 1

Introduction

At 2:00 clock in the night a registrar and neonatal consultant rush to the operating theatre. They were called in by the obstetrician, who wanted to perform a caesarean section on a 26 weeks pregnant mother suffering from severe pre-eclampsia. While preparing the resuscitation table and ventilation, the neonatal consultant discussed with the registrar what was to be expected. He told the registrar which clinical signs and parameters are important to be observed and acted upon. Shortly thereafter the infant was born and the cord was clamped immediately in order to have the infant on the resuscitation table as soon as possible. The infant was placed in a plastic wrap and a hat was put on to prevent heat loss (1). Meanwhile breathing and heart rate were assessed by auscultation and a pulse oximeter probe was attached on the right hand. No breathing was observed and the infant was bradycardic (heart rate < 100 beats per minute (bpm)) on which they decided to give mask ventilation according to the guideline (2). No chest excursion were observed and therefore inspiratory pressures were increased (2). The consultant and registrar were relieved once the heart rate increased, but oxygen saturation remained low at 50% and they increased the inspired oxygen (2). No improvement of the saturation was seen and oxygen was increased further in a stepwise manner until they ended up providing 100% of inspired oxygen. Thereafter mask ventilation was stopped temporarily and the infant was evaluated, who started to show subtle breathing movements but intercostal retractions were visible. These retractions became more apparent which triggered the consultant to call out to the registrar "This baby has stiff lungs and needs more help, we better intubate him now". After one attempt by the registrar, the consultant took over with more success. Once ventilation was given via the endotracheal tube clear chest excursions were visible and after 1 minute oxygen saturation was within normal range which allowed the consultant to decrease inspired oxygen. The infant was placed in the transport incubator taken to the operating room and shown to the mother. All vital signs were fine and the baby was spontaneously moving arms and legs.. The consultant said to the parents "your baby needed help breathing, we placed a tube in his airways to do this and he is now cooperating with the ventilator". The infant was then brought to the NICU where ventilation was continued. Afterwards the neonatal consultant evaluated their resuscitation and concluded that they did a good job. He told the registrar to give the infant surfactant as soon as the chest x-ray was taken. However, half an hour later the registrar called him, the baby was ventilated in air and inspiratory pressures had to be decreased because the baby had a low $PaCO_2$, "do you still want me to give surfactant?" Two hours later the infant was extubated, placed on non-invasive ventilation and did not need extra oxygen.

The neonatologist and the registrar certainly did a good job based on the current knowledge of transition and prevailing guidelines (2;3). These guidelines are predominantly focused on lung aeration at birth and establishment of gas exchange. If the infant does not manage to do this spontaneously the caregiver should primarily provide non-invasive ventilation (2). Proper ventilation is then determined by two parameters that will help the caregiver making decisions: 1) adequate chest movements (is there breathing present or is the ventilation given appropriate?) 2) heart rate (if heart rate increases then breathing or ventilation improved oxygenation of the heart). However, it is very difficult to observe chest movements in a preterm infant (4) and increase in heart rate doesn't necessarily mean the lungs are well aerated. Both parameters do not provide the caregiver the information if breathing or ventilation given is adequate (4;5). In addition, the hemodynamic changes that occur during transition are not considered, while the ventilation given at birth can have large consequences for hemodynamics and ultimately the brain. During the transition at birth the infant undergoes major physiological changes of both the pulmonary and hemodynamic tract which are closely linked (6). Most of our knowledge of transition is based on small observational studies and extrapolated from animal data (7-12). The transition is much more complex than assumed by the caregiver standing ready to give support to the infant. The few parameters which are used for evaluation and effect of respiratory support and therapy do not tell the complete story and therefore inadvertent measures can be taken easily.

It is important to understand the transitional changes as the most vulnerable moment of a preterm infant is at birth. Several studies have shown that injury to lungs and brain can easily occur by our actions taken at birth (13). For this reason there is renewed interest in the transition and delivery room management. Recently it was shown that improving care of preterm infants at birth can lead to a decrease in mortality and morbidity later in life (13). Several measures and interventions that seem to be more adequate than current practice have been suggested (5;14;15). However, much of the approach in the delivery room recommended in the guidelines (2;3) is dogmatic from origin.

This thesis tries to unravel the black box which neonatal transition still is and will bring us closer to understand what physiologically happens at birth and also what happens when we intervene. A better understanding will allow us to improve our current practice and to develop new strategies for appropriate support of preterm infants with transitional problems. The parameters discussed in this thesis were gathered in a non-invasive manner. Most of these parameters are currently used in the NICU to inform us of the condition of infant and evaluate the effects of our treatment.

Although intimately linked, the transitional changes can be roughly divided into pulmonary and circulatory changes (16). The pulmonary changes are clearance of lung liquid, aeration of the lung and creation of functional residual capacity with air (17). For this thesis we used respiratory function monitoring (tidal volumes and pressures), exhaled CO_2, respiratory inductance plethysmography, pulse oximetry and video data to give us more details of the respiratory effort of the infant and the effect of our respiratory support.

The circulatory changes are a fast increase in pulmonary blood flow, changes in right and left ventricular output and a sudden increase of the systemic vascular resistance when the umbilical cord is clamped (6). For this thesis we used echocardiography, pulse oximetry, electrocardiography, perfusion index and non-invasive blood pressure measurements to investigate the hemodynamic changes at birth. As the heart rate is considered the most vital and objective parameter for evaluating an infant's condition and interventions given (2), we also investigated the reliability of measuring this parameter using a pulse oximeter.

Outline of the thesis

The aim of this thesis was to improve our understanding regarding the respiratory and hemodynamic transition at birth in both preterm and term infants. This thesis consists of a review of the current available literature and observational studies using physiological parameters. The thesis has been divided in three parts for Airway, Breathing and Circulation.

The studies are performed in the Leiden University medical Center, Leiden, the Netherlands. However, part of the studies described are products of collaboration with Monash Institute of Medical Research (professor Stuart Hooper) in Melbourne, Australia, the Royal Women's Hospital (professor Peter Davis) in Melbourne, Australia and the pediatric hospital "V. Buzzi" (dr. Gianluca Lista) in Milan, Italy.

In **chapter 2** the available literature on physiological measurements of the respiratory and hemodynamic transition at birth was reviewed. Both old methodologies and new, less cumbersome methodologies were discussed.

Part 1 – Airway

We described the effect, effectivity and consequences of the respiratory support provided during neonatal resuscitation at birth. Hot-wire anemometry was used to measure respiratory function parameters using a flow probe placed between the T-piece of the ventilator and a face mask or nasal tube. The clinical effect was measured using pulse oximetry.

The aim of the observational studies presented in **chapter 3 and 4** was to investigate the effect of our ventilation strategies. In **chapter 3** we described the effect of the initial sustained inflation applied to preterm infants for lung liquid clearance and aeration at the start of ventilation. In **chapter 4** two interfaces for neonatal ventilation (face mask and nasal tube) were compared in a randomized controlled trial.

In the studies presented in **chapter 5 and 6** we investigated the influence of ventilation technique and the anatomy of the respiratory system on volume measurements at birth. In **chapter 5** we investigated the effect of dead space variance during mask ventilation and in **chapter 6** we studied differences in tidal volumes measured during mask ventilation (ventilating the oropharynx and lungs) compared to endotracheal ventilation (bypassing the oropharynx).

Part 2 – Breathing

We present observational studies describing the consequences of breathing during positive pressure ventilation at birth. Respiratory function measurements were performed using a hot-wire anemometer and a variable orifice pneumotach. Gas exchange was measured using a volumetric CO_2 device and changes in functional residual capacity using respiratory inductance plethysmography.

In **chapter 7** we investigated the relation between respiratory patterns and effort in very preterm infants at birth and failure of continuous positive airway pressure later on. The effect of oxygenation on respiratory effort at birth is described in **chapter 8**. In **chapter 9** we present a case report of a newborn born after the mother received opiates and describe an unique observation of the effect of naloxone. In **chapter 10** gas exchange and changes in functional residual capacity were measured in very preterm infants mask ventilated at birth.

Part 3 – Circulation

Physiological changes of the circulatory system were studied in healthy term infants. Cardiac function and ductus arteriosus flow were measured using echocardiography and blood pressure changes were measured non-invasively. Furthermore heart rate was compared using electrocardiography and pulse oximetry during neonatal transition and the perfusion index was assessed in preterm and term infants. Measurements were collected the first 10 minutes after birth.

In **chapter 11** we described the left ventricular function and its relationship to blood pressure, heart rate and oxygen saturation. Changes of the ductus arteriosus flow was investigated in **chapter 12**. In **chapter 13** the effect of crying on ductus arteriosus flow was determined. In **chapter 14 and 15** the perfusion index in both term and preterm infants was measured in the first 10 minutes after birth and in **chapter 16** heart rate measured by pulse oximetry was compared with ECG measurements and echocardiography.

In **chapter 17** the main findings of the thesis are discussed and future perspectives are given. The main findings are summarized in English in **chapter 18** and in Dutch in **chapter 19**.

References

1. Vohra S, Roberts RS, Zhang B, Janes M, Schmidt B. Heat Loss Prevention (HeLP) in the delivery room: A randomized controlled trial of polyethylene occlusive skin wrapping in very preterm infants. J Pediatr 2004;145:750-3.
2. Kattwinkel J, Perlman JM, Aziz K, Colby C, Fairchild K, Gallagher J, *et al*. Part 15: neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122:S909-S919.
3. Perlman JM, Wyllie J, Kattwinkel J, Atkins DL, Chameides L, Goldsmith JP, *et al*. Part 11: Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation 2010;122:S516-S538.
4. Poulton DA, Schmolzer GM, Morley CJ, Davis PG. Assessment of chest rise during mask ventilation of preterm infants in the delivery room. Resuscitation 2011;82:175-9.
5. Hooper SB, Fouras A, Siew ML, Wallace MJ, Kitchen MJ, Te Pas AB, *et al*. Expired CO2 levels indicate degree of lung aeration at birth. PLoS One 2013;8:e70895.
6. van Vonderen JJ, Roest AA, Siew ML, Blom NA, van Lith JM, Walther FJ, *et al*. Noninvasive measurements of hemodynamic transition directly after birth. Pediatr Res 2014;75:448-52.
7. Lind J, Peltonen T, Tornwall L, Wegelius C. Roentgenological lung findings in the newborn infant's 1st breath. Z Kinderheilkd 1963;87:568-78.
8. Boon AW, Milner AD, Hopkin IE. Physiological responses of the newborn infant to resuscitation. Arch Dis Child 1979;54:492-8.
9. Bosma JF, Lind J. Roentgenologic observations of motions of the upper airway associated with establishment of respiration in the newborn infant. Acta Paediatr Suppl 1960;49:18-55.
10. Hull D. Lung expansion and ventilation during resuscitation of asphyxiated newborn infants. J Pediatr 1969;75:47-58.
11. Karlberg P, Cook CD, O'Brien D, Cherry RB, Smith CA. Studies of respiratory physiology in the newborn infant. II. Observations during and after respiratory distress. Acta Paediatr 1954;43:397-411.
12. Palme-Kilander C, Tunell R. Equipment for recording pulmonary gas exchange immediately after birth during spontaneous breathing and assisted ventilation. Med Biol Eng Comput 1993;31:67-71.
13. Schmolzer GM, Te Pas AB, Davis PG, Morley CJ. Reducing lung injury during neonatal resuscitation of preterm infants. J Pediatr 2008;153:741-5.
14. Schmolzer GM, Morley CJ, Wong C, Dawson JA, Kamlin CO, Donath SM, *et al*. Respiratory function monitor guidance of mask ventilation in the delivery room: a feasibility study. J Pediatr 2012;160:377-81.
15. Te Pas AB, Siew M, Wallace MJ, Kitchen MJ, Fouras A, Lewis RA, *et al*. Establishing functional residual capacity at birth: the effect of sustained inflation and positive end-expiratory pressure in a preterm rabbit model. Pediatr Res 2009;65:537-41.
16. van Vonderen JJ, Roest AA, Siew ML, Walther FJ, Hooper SB, Te Pas AB. Measuring physiological changes during the transition to life after birth. Neonatology 2014;105:230-42.
17. Te Pas AB, Davis PG, Hooper SB, Morley CJ. From liquid to air: breathing after birth. J Pediatr 2008;152: 607-11.

CHAPTER 2

Measuring physiological changes during the transition to life after birth

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Neonatology 2014;105:230-42

Abstract

The transition to life after birth is characterized by major physiological changes in respiratory and hemodynamic function, which are predominantly initiated by breathing at birth and clamping of the umbilical cord. Lung aeration leads to the establishment of functional residual capacity, allowing pulmonary gas exchange to commence. This triggers a significant decrease in pulmonary vascular resistance, consequently increasing pulmonary blood flow and venous return. Clamping the umbilical cord also contributes to these hemodynamic changes by altering the cardiac preload and increasing peripheral systemic vascular resistance. The resulting changes in the systemic and pulmonary circulations influence blood flow through both the oval foramen and ductus arteriosus. This eventually leads to closure of these structures and the separation of the pulmonary and systemic circulations.

Most of our knowledge on human neonatal transition is based on human (fetal) data from the 1970s and extrapolation from animal studies. However, there is renewed interest in performing measurements directly at birth. By using less cumbersome techniques, (n.b. and probably more accurate), our previous understanding of the physiologic transition at birth is challenged, as well as the causes and consequences for when this transition fails to progress. This review will provide an overview of physiological measurements of the respiratory and hemodynamic transition at birth. Also it will give a perspective on some of the upcoming technological advances in physiological measurements of neonatal transition in infants that are unable to make the transition without support.

Introduction

The fetal to neonatal transition at birth starts when the newborn takes the first breaths, initiating major physiological respiratory and hemodynamic changes (1). During the initial breaths lung liquid is cleared and air remains in the lung at the end of expiration providing a functional residual capacity (FRC) (2). Aeration of the lungs decreases pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) is increased by clamping of the umbilical cord after birth (3). These events trigger major changes in the newborns' circulatory system (3). Uniform lung aeration, establishing FRC and decreasing PVR is required to commence effective pulmonary gas exchange, which in turn improves the infant's heart rate (HR), cardiac output (CO) and oxygenation.

Although many observations have been made in humans (2), most of the understanding of the fetal to neonatal transition originates from animal studies (4). Investigating this major life event in the delivery room is difficult as the neonatal transition can be very rapid and as a result time pressure is high. In addition, most of the techniques used for physiological measurements performed in the 1960-1980s would currently be considered unethical (X-rays, esophageal balloons, reverse plethysmography, umbilical catheterization, angiocardiography) (1;5). However, less cumbersome and non-invasive techniques are currently used to gather observational data in the delivery room (6;7), challenging our understanding of transition and resuscitative practices (figure 1).

In addition, more sophisticated techniques and approaches are now used in animal models to investigate the transition.

In this review, we will give an overview of the information obtained from current experimental and human physiological studies, which are designed to better understand the pulmonary and hemodynamic transition at birth. Equipped with this new information we will also offer some future insights on how neonatal transition could be facilitated in infants that are unable to make this transition without support.

Figure 1. A) illustrates a respiratory tracing showing pressure (red), flow (green), expiratory volume (blue), capnography (black), HR plethysmography (black) in waveforms. Also it provides HR, oxygen saturation (SaO_2), FiO_2, inspiratory volume (Vti), expiratory volume (Vte) and leak numerically.
B) Shows a respiratory function monitor (Applied Biosignals, Weener, Germany) and set-up as currently used for physiological research of the newborn infant. The flow probe (FP) is connected to the face mask. Also an oxygen analyzer (FiO2) and Pulse oximeter can be added to monitor supplied oxygen as well as oxygen saturation and heart rate.

Pulmonary transition

Breathing at birth

Fetal breathing movements (FBM), needed for lung growth and development, are very similar to breathing activity after birth. Fetal respiratory drive is controlled by similar stimuli (hypoxia and hypercapnia), which arises from the respiratory center and mainly causes activation of the diaphragm via the phrenic nerve (6). However, as fetal breathing movements are restricted to levels of fetal activity, they are discontinuous, occurring <50% of the time. Further, although most FBM generate transpulmonary pressures of <20 cmH_2O, fetuses commonly can make large inspiratory efforts (>30 cmH_2O) (9,10), demonstrating that they are capable of generating transpulmonary pressures needed to aerate the lung after birth (7). The mechanisms controlling the switch to continuous breathing after birth are currently unknown. There is a general belief that activation of chemoreceptors (particularly an increase $PaCO_2$) and physical stimuli (light, temperature and handling) triggers the onset of large inspiratory efforts. Data on this matter is scarce, although animal studies have shown that cooling lambs at birth elicits normal quiet breathing, but no large initial gasps (8). In contrast, painful stimuli elicits gasps in unanaesthetised lambs with an intact umbilical cord, but not sustained respiratory movements (9).

Although hypoxia is considered to be a stimulus for respiratory drive, it remains questionable if this also accounts for the increased respiratory drive at birth (10;11). Hypoxia is known to inhibit breathing movements in the foetus and the hypoxic sensitivity is relatively low shortly after birth (10). After birth, hypoxia increasingly stimulates respiratory drive in the newborn due to a temporal change in O_2 sensitivity, which increases days/weeks after birth (10). Although most preterm infants breathe at birth (12;13), it is not known when the switch from respiratory suppression to stimulation occurs in response to hypoxia. It is possible that hypoxia immediately after birth will produce a weakened or even absent respiratory drive, particularly in preterm infants. Indeed, maturation of the hypoxic sensitivity increase is delayed in preterm lambs (10). In contrast, hyperoxia has been shown to delay onset of breathing in asphyxiated rats, but it is difficult to extrapolate this finding as the rats were more than a week old (14). Also, a delay in the first breath was observed in asphyxiated term infants at birth when 100% oxygen with no titration was given during resuscitation (15). However, the first breath was observed and not measured and it is very difficult to identify the first breath, especially when the infant is ventilated (16).

However, as shown in animals resuscitation with 100% oxygen compared to room-air could also delay the onset of breathing via a mechanism that may involve both hyperoxemic and hypocapnic inhibition of chemoreceptors (14). Antenatally, FBM are inhibited by hypoxia, but hypoxic sensitivity is relatively low shortly after birth and gradually increases days-weeks after birth (10). Hypercapnea is a powerful stimulant for respiratory drive both before and after birth and could induce the large respiratory efforts observed. However, not all infants will be hypercapnic immediately after birth.

Lung liquid clearance and aeration

Experimental studies have predicted that the stress of labor starts fetal lung liquid clearance due to the release of adrenaline, which stimulates pulmonary epithelial cells to activate luminal surface sodium channels. This reverses both the Na^+ flux and the osmotic gradient across the epithelium, causing reabsorption of lung liquid (17). However, the dominant role of sodium channel activation for lung liquid reabsorption after birth has been challenged by recent studies (18). These studies used phase contrast X-ray imaging to image air entry into the lungs during the first breaths in newborn rabbits. They demonstrated that liquid clearance exactly coincides with inspiration and occurs very rapidly (3 ml/kg over the first 5 breaths (at 35 L/kg/h)). They concluded that airway liquid clearance cannot solely be explained by activation of sodium channels, and likely involves transpulmonary pressures generated by the inspiratory effort (18). Cell membrane water channels (Aquaporins (AQPs)) could play an essential role in this process.

During pregnancy different types of AQPs are expressed (19) and at birth expression of pulmonary AQPs changes. Through these channels water can be absorbed into the interstitium in the days after birth (20;21). In preterm infants the expression of AQPs differs compared to term infants possibly increasing incidence of neonatal respiratory distress syndrome and bronchopulmonary dysplasia (20).

Lung liquid clearance by "vaginal squeeze' is an old theory some authors still consider as an important mechanism (22). This theory originates from studies (5;23) performed in 1917 and repeated in 1962 using X-ray imaging showing compression of the fetal chest of term infants passing through the birth canal. In later studies intrathoracic pressures of 70 cmH_2O were measured and oral expulsion of lung liquid was observed during delivery (24-26).

However, the little resistance that the chest offers when following the head in the birth canal makes it unlikely that "vaginal squeeze" *per se* significantly influences liquid clearance (27;28). In contrast, as postural changes during labor can cause lung liquid loss (29), flexion of the fetal trunk, which increases abdominal pressure and elevates the diaphragm, are more likely to cause liquid expulsion (22;23).

Another theory, observed in 1891 in excised lungs, suggested the increase in pulmonary circulation would be responsible for lung aeration ("capillary erection") (30-32). However, this theory has been abandoned since experimental studies (33;34) have shown that pulmonary vasodilation occurs in response to lung aeration, leading to a gradual reduction in pulmonary arterial pressure.

Thoracic recoil after passage through the birth canal is also described to explain lung aeration as suggested in 1901 (35). In 1962 Karlberg *et al*. used reverse plethysmography for lung volume measurements in human infants and reported that elastic recoil of the chest after expulsion from the birth canal caused air entering the lung (1;23;36). The measurements were repeated later, but elastic recoil forcing air into the lung could not be confirmed (25).

Karlberg *et al.* (37) and Milner *et al.* (25) have also measured trans-esophageal pressures using an esophageal balloon catheter. Karlberg *et al.* observed that relatively large sub-atmospheric pressures (20-40 cmH_2O) were necessary before air started entering the lung (37) which was considered to be the "opening pressure" needed to overcome resistance and newly formed surface tension (37). However, Milner *et al*. could not confirm this and stated that the balloon in Karlberg's study was probably misplaced (25). Although "opening pressure" is a misnomer, as the lungs are not collapsed at birth, it is

still used as rationale for initially providing higher ventilation pressures during neonatal resuscitation (32).

More recently, phase contrast X-ray imaging in a newborn rabbit model demonstrated that lung liquid clearance almost exclusively occurs (>95%) during inspiration (4). The transpulmonary pressure gradients generated during inspiration are likely to be primarily responsible for the rapid clearance of airway liquid immediately after birth (4). That is, the inspiratory pressure reduces (i.e. becomes more sub-atmospheric) in both the intrapleural space and the interstitial tissue surrounding alveoli, which forces liquid to move across the alveoli's epithelium into the interstitium. This causes liquid to accumulate in the interstitial space, forming perivascular fluid cuffs (38), resulting in an increase in resting interstitial tissue pressure (4;39;40). End expiratory pressures generated during braking of the expiration (breath holds, crying), surfactant and probably activated epithelial sodium channels are likely to be important in preventing liquid moving back into the alveoli (41). The sum of lung liquid moving into the interstitium and being replaced by air that occupies the airways explains the increase in thorax circumference and shape before and after lung aeration was made visible in radiographs from both humans (42) and newborn rabbits(43). This has been indirectly confirmed by Misserocchi who found a larger pressure in the interstitium at the end of inspiration showing that both FRC and pleural liquid pressure increased simultaneously (44). The movement of liquid from the airways into the surrounding lung tissue has also been visualized in ventilated preterm rabbit pups (4). Eventually, liquid in the interstitium is cleared in approximately 6 hours via the blood and lymph vessels (4;39;40).

Creating and maintaining FRC

From the start of research in respiration during neonatal transition several theories were suggested describing FRC creation and maintenance right after birth, necessary for adequate gas exchange. One theory described that alveoli were splinted open by "air trapping", i.e. more air is inspired than exhaled (45). "Air-trapping" could occur due to braking of expiration, which was described previously as "frog breathing" (46-48). Karlberg *et al*. using chest x-rays and reverse plethysmography, described the first breath, as a deeper and slower breath than subsequent breaths, composed of a large inspiration followed by a braked, slow expiration (49). As a result, large changes in esophageal pressures were found to be related to both changes in inspiratory volume and the subsequent braking of expiration (17;41). During expiratory braking the infant builds up a large intrathoracic pressure by simultaneously closing the glottis and contracting the abdominal muscles. The physiological consequences of this are unclear, although an increase in airway liquid clearance is unlikely because pressure within the interstitial tissue will also increase simultaneously, resulting in little or no change in trans pulmonary pressure (40).

Several breathing patterns have recently been described in infants at birth using a hot wire anemometer attached to a mask (41;48). Patterns that slow expiration (expiratory hold, slow expiration, crying and grunting) and shorten expiratory time (panting) were thought to be important for maintaining FRC in the newborn period (41). Preterm born infants were more commonly found to use breath-holds and cause a complete cessation of expiratory flow whereas term infants most commonly slowed expiration during crying (48). Imaging experiments in spontaneously breathing newborn rabbits have confirmed the role of expiratory braking in preventing liquid moving back into the airways and maintaining FRC (18).

Using reversed plethysmography, Karlberg *et al*. found that in the first minutes after birth, an infant's FRC can reach levels of 20-40 mL (47). Mortola *et al*., using a face mask with a pneumotachograph attached, measured in term infants an average FRC of 42±26 ml (49). However, mask leak could have been a confounding factor. Recent animal studies confirmed that large amounts of FRC are established during the first breaths (3 ml/kg over the first 5 breaths) (18). However, the speed at which FRC is established and maintained is variable (7;18). This is due to the variable effect of the inspiratory efforts, the re-entry of liquid into the airways and the mechanisms such as expiratory holds (18).

Surfactant also plays an important role in creating and maintaining FRC at birth, by reducing the surface tension, lung recoil and the trans pulmonary pressure gradient for lung liquid moving back to the alveolar space (50;51). In addition, surfactant greatly increases the uniformity of lung aeration, which indicates that surface tension determines whether the air/liquid interface progresses down both airways at each airway branch (51).

Hemodynamic transition

As well as the respiratory system, the cardiovascular system undergoes a major transformation after birth. The major components of these transformations occur within minutes of commencing pulmonary ventilation (figure 2 and 3). However, the cardiovascular transition requires hours to days to complete. The immediate consequence of the neonatal transition is the direct reversal of vascular shunts of the foramen ovale (FO) and ductus arteriosus (DA). Due to the continued patency of the FO and DA, transition is prolonged. After birth the increasing afterload will increase the likelihood of left-to-right shunt through the DA in the first days after birth. However, DA constriction will cause shunting through the DA to decrease (52). Changes in SVR and the decrease in PVR resistance that occur during transition will cause BPs and flows in the pulmonary and systemic circulations to

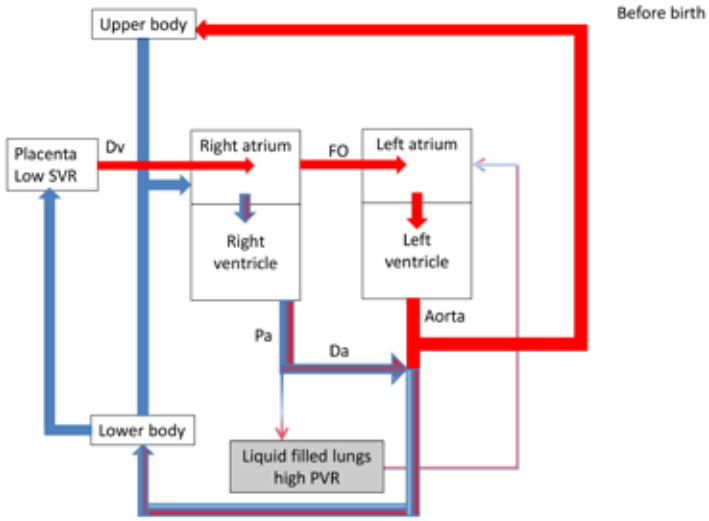

Figure 2. Schematic drawing of the fetal circulation. Red indicates blood with a high oxygen saturation and blue indicates blood with a low oxygen saturation. Before birth blood from the placenta enters the infant through the ductus venosus (Dv) and passes into the right atrium. 2/3rd of the blood shunts through the open foramen oval (FO) and 1/3rd passes through to the right ventricle and into the pulmonary artery (Pa). 90% of the blood shunts through the ductus arteriosus (Da) and only 10% enters the lungs due to the high pulmonary vascular resistance.

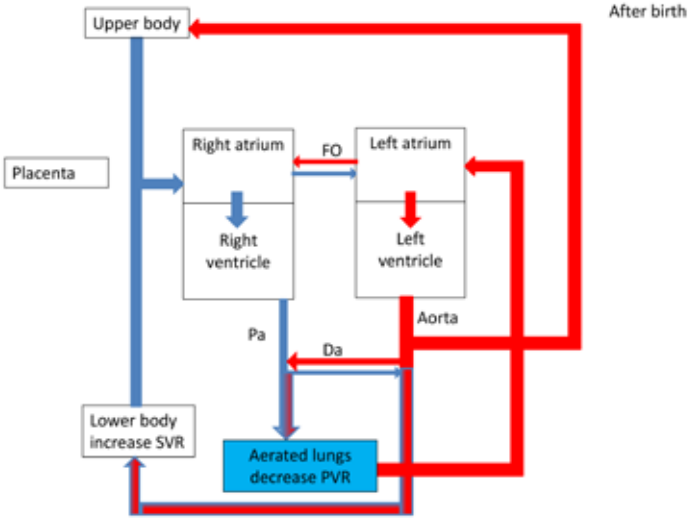

Figure 3. Schematic drawing of the neonatal circulation just after birth. Red indicates blood with a high oxygen saturation and blue indicates blood with a low oxygen saturation. After birth the umbilicus is clamped and there is loss of 30-50% of total venous return. Pulmonary resistance decreases due to aeration of the lungs causing increased pulmonary blood flow through the pulmonary artery (Pa). Blood flow through the ductus arteriosus (Da) and foramen ovale (FO) becomes bidirectional. Up to 50% of the pulmonary blood flow arises from the Da through via a left-to-right shunt.

change. This promotes functional closure of the FO, thus completing transition. The ductus venosus will remain patent up to days after birth (53). However, it will not be of further influence to the cardiovascular system.

In fetal sheep, depending upon the gestational age, approximately 30-50% of combined CO (right- and left ventricle) flows to the placenta (54) and therefore 30-50% of cardiac venous return must come from the placenta. Approximately 50% of umbilical venous blood flow in sheep foetuses (55) and 30% of blood flow in the human foetuses (56) passes through the ductus venosus, by-passing the liver. A large proportion of this oxygenated placental blood passes through the FO and enters the left atrium (57). The remainder of the venous return, which mostly consists of poorly oxygenated blood from the superior and inferior vena cava, enters the right atrium and is directed into the right ventricle. However, as PVR is high in the foetus, most of the right ventricular output (90%) bypasses the lungs and is shunted through the DA into the aorta (54;58). A large portion of this de-oxygenated blood will flow back to the placenta as this organs' vascular resistance is lower than the vascular resistance of the foetus' lower body (34).

The effect of breathing on hemodynamic transition

The decrease in PVR, which is necessary for adequate pulmonary gas exchange after birth, is triggered by the onset of pulmonary ventilation. This emphasises that establishing adequate breathing at birth is important for a proper hemodynamic transition as this has significant influence on the pulmonary blood flow (3;34;54;59). Lind *et al*. visualised the large blood flow through the pulmonary artery in term infants using angiocardiography with Umbradil injected in the umbilical vein directly after birth (60). Up to 50% of the increase in pulmonary blood flow was supplied by a left-to-right shunt through the DA (54), caused by the differential pressures between pulmonary and systemic circulation. As a consequence, particularly the timing in the reversal of blood flow shunting through the DA (from right-to-left to left-to-right) is unclear. The change in shunting direction will create disturbance of the blood flow. This is likely to promote and contribute to anatomical closure of the vascular shunts (DA and FO) separating pulmonary and systemic circulations (54;58).

Effect of umbilical cord clamping on hemodynamic transition

Clamping the umbilical cord at birth has a large impact on the fetal circulation and plays an integral role in the transition. The acute loss of the high flow and low resistance placental vascular bed has two implications 1) SVR instantly increases and 2) venous return to the heart is decreased by 30-50% (54). Both have the potential to compromise the infant's CO.

The timing of cord clamping in relation to lung aeration could influence transition extensively. While before birth the LV preload is mostly dependent on umbilical venous blood flow, after cord clamping the left ventricular output (LVO) becomes largely dependent on pulmonary blood flow and pulmonary venous return. A recent study in preterm lambs hypothesized that breathing before cord clamping would improve cardiovascular stability. It was shown that cord clamping before ventilation reduced HR by 40%, decreased right ventricular output and blood flow in the carotid artery. It was observed that carotid blood flow remained stable and the decrease in HR and right ventricular output associated with cord clamping were greatly reduced when ventilation was commenced before cord clamping (61). It is likely that this cardiovascular stability plays an important part in the benefits of delayed cord clamping such as improved tissue perfusion, lower incidence of necrotising enterocollitis and intraventricular haemorrhage (62).

There is little physiological human data available measuring the quantity and characteristics of fetoplacental transfusion between birth and cord clamping (63-65). Mechanisms have been suggested that could influence fetoplacental transfusion (e.g. uterine contractions and breathing) but still needs to be investigated (61;66).

Measurements for evaluating transition

Heart rate

Currently the only parameter used clinically to evaluate the hemodynamic transition is HR, which is believed to be the primary measure of adequate transition (67). A cut off value of HR of 100 beats per minute was suggested by Virginia Apgar to characterise adequate transition. Although, a HR of <100 beats per minute is commonly observed in healthy term infants in the first minutes after birth, followed by a fast and significant increase (68). The relatively low HR in the first minutes after birth is assumed to be caused by a hypoxia stimulated bradycardia that involves a parasympathetic activated vagal reflex (69). However, the transient bradycardia after birth could also be caused by immediate umbilical cord clamping before the lungs are aerated, which decreases both LVO and right ventricular output.[57] Early cord clamping causes the SVR to increase before PVR is reduced and pulmonary blood flow could increase. As a consequence of the low pulmonary vascular return, together with the sudden decrease in right-to-left shunting through the FO left ventricular preload is low and a baroreflex provoked bradycardia could arise (61).

Oxygen saturation

Despite several experimental and human studies (70-73) showing that fetal oxygen

saturation (SO_2) is low (45-65%) and can be even lower during labor. However directly after birth it was found that there is no significant difference in oxygen uptake between term infants born by caesarean section or infants born vaginally (6.58 mL/min/kg) (74). SO_2 measured peripherally is, however, not necessarily related to central oxygen uptake. Until recently pink color was seen as a sign of a proper transition. It was found that there is a large variation in SO_2 when clinicians stated an infant to be pink (75). SO_2 should preferably be measured preductally using pulse oximetry (76). In 2010 a lower and slowly rising SO_2 was considered acceptable during the transitory phase according to the normograms presented by Dawson *et al* (77). Infants delivered by caesarean section have a significantly lower SO_2 and require a longer time period to reach SO_2 ≥85% (77-79). This could lead to a delayed or compromised transition. Also infants born with a gestational age <37 weeks without medical interventions required a longer time to reach SO_2s (87% vs. 90% at 5 minutes after birth) (77).

Cardiac output and stroke volume

CO is determined by both HR and stroke volume (SV) (CO= HR*SV). It is sometimes still assumed that SV cannot be altered in the neonate because the contractility of the myocardium characteristically functions high on the Frank-Starling curve and is unable to increase further, as well as the fetal myocardium (80). This would imply that a change in end diastolic volume cannot be accompanied by a large change in CO. However, it has been shown in sheep foetuses that SV can be adapted (81). Echocardiography has been used to monitor CO during the neonatal transition (82-84). However, this data was collected in the hours to days after birth when the major changes of neonatal transition already occurred. Recently Noori *et al*. was the first to use echocardiography shortly after birth and observed that as a consequence of rising SV, LVO increased non-significantly from 168 ±42 mL/kg/min at 3-7 min to 186 ±26 mL/kg/min at 9-14 min. after birth. HR decreased and SV increased between the two measurement periods (85). It is possible the increase in LVO was missed in the first minutes as the first measurements were conducted between 3-7 min. However, Noori *et al*. have shown that increasing SV is important for CO during the first minutes after birth (85) as it is later during transition (52).

Blood pressure

Blood pressure (BP) is determined by SVR and CO and although it is not well correlated to systemic blood flow, it is considered an important value for hemodynamic monitoring of critically ill infants (86). However, while HR is considered important for decision making in the delivery room, BP is rarely used for evaluating the neonatal transition or the need for resuscitation at birth.

There is very little data of BP at birth and reference values are lacking. Although the exact time points of measurements are unknown, in 1938 Woodbury *et al*. inserted an umbilical arterial line in term infants directly after birth and observed a mean systolic artery pressure of 80.1 (8.1) mmHg and diastolic 46.3 (8.2) mmHg (87). BP was markedly increased during crying, administration of fluids (87) and increasing gestational age (88). Interestingly small undulations in the BP concomitant with breathing were seen (87). Ashworth *et al.* (using a sphygmanometer on the right arm, preductally) observed lower systolic BPs (±10 mmHg difference) in the hours following birth when the cord was clamped during delivery, compared to when the cord was clamped after birth (89). This could infer that, when the cord is clamped before pulmonary blood flow has increased, there will be less circulating volume. In a more recent study in term infants a mean BP of 42 (11) mmHg at 5 minutes at birth was measured (90). It could be helpful to measure BP preductally during transition to evaluate the hemodynamic transition and assess the CO.

Gas exchange measurements

Palme-Kilander *et al*. and Tunell *et al*. measured carbon dioxide production (V_{CO2}), using a face mask and collection system, directly after birth in both breathing and ventilated infants (91;92). Asphyxiated preterm and term infants needing assisted ventilation at birth, had similar V_{CO2}in the first minutes after birth (91;92). However, breathing infants had higher Vco_2 values than ventilated infants (5-7 vs. 2-4 mL/kg/min) which likely reflects a lower temporal increase in FRC in ventilated infants, indicating that ventilation was not as effective as breathing (74;93). However, a higher energy costs associated with spontaneous breathing cannot be discounted (94).

A similar phenomenon was observed in a recent trial testing the use of end tidal carbondioxide levels ($ETCO_2$) to keep arterial CO_2 ($PaCO_2$) levels within range (95). Although the number of out-of-range $PaCO_2$ values was not reduced, $ETCO_2$ was lower during ventilation than during breathing (95). While studies in the NICU have found that $ETCO_2$ closely correlates with $PaCO_2$ (96-98), it is important not to extrapolate these findings to the situation in the delivery room, when the lung is partially liquid filled. The assumption that $EtCO_2$ will approximate $PaCO_2$ levels relies on the fact that CO_2 exchange in the lung is not diffusion limited. However, a recent study demonstrated that during the early transition period, $EtCO_2$ values are primarily determined by inspiratory lung volumes (99).

Tidal volume

Although extrapolated from studies performed later in life, during ventilation at birth, tidal volumes between 4-8 mL/kg are considered adequate. However, at birth, term infants use significantly larger tidal volumes for their first breaths (11 (5) mL/kg) (1;49).

Table 1. Respiratory parameters for different breathing patterns for infants who did not require respiratory support with a GA of 29 (1.9) weeks and mean birth weight of 1220 (412) g. (41,48)

	Expiratory tidal volume (mL/kg)	Respiratory rate (min^{-1})	Inspiratory time (sec)	Expiratory time (sec)
Preterm infants (<32 weeks; on CPAP)				
Braked expiration	7.2 (3.8)	60 (30)	0.32 (0.14)	1.03 (0.84)
Unbraked expiration	3.7 (2.2)	90 (26)	0.30 (0.09)	0.41 (0.16)
Term infants				
Braked expiration	6.8 (4.2)	50 (23)	0.33 (0.16)	1.33 (1.02)
Unbraked expiration	5.5 (3.4)	91 (31)	0.30 (0.13)	0.43 (0.26)
All infants				
Expiratory hold	5.8 (4.1)	32 (11)	0.36 (0.10)	1.85 (1.14)
Slow expiration	3.5 (2.3)	48 (16)	0.34 (0.15)	1.10 (0.90)
Crying/grunting	7.5 (4.2)	42 (18)	0.38 (0.14)	1.30 (0.75)
Normal expiration/ respiratory rate	4.2 (1.5)	54 (4)	0.40 (0.08)	0.65 (0.11)
Panting	3.1 (1.7)	88 (18)	0.34 (0.07)	0.41 (0.14)

Similarly, Milner *et al*. measured a mean tidal volume of 44.6 mL (range 13.4-90 mL) for the first breath (100). te Pas *et al*. measured tidal volumes in preterm infants breathing on CPAP at birth and during different breathing patterns, found a range of volumes between 3.1 (1.7) mL/kg and 7.5 (4.2) mL/kg was measured (48) (table 1). In infants without support at birth, tidal volumes of more mature preterm infants were comparable to term infants (6.7 (3.9) vs. 6.5 (4.1) ml/kg; ns) (41).

Tissue perfusion

For determination of the tissue perfusion two methods can be used: the perfusion index (PI) and Near Infrared Spectroscopy (NIRS). PI is the ratio of pulsatile blood flow/non-pulsatile static blood flow and deducted from the strength of the photo-plethysmographic signal emitted during pulse oximetry (101). At birth, a consistent PI was observed in healthy term infants and values were higher when compared to infants with sepsis (PI at 1 minute 4.50 (0.83) vs. 1.74 (0.32) and at 5 minutes 4.42 (2.10) vs. 2.18 (1.02)) (102). However, since various factors can influence PI: e.g. changing temperature and local skin vasoconstriction, its value for evaluating transition remains questionable.

NIRS is a technique developed for monitoring perfusion of brain tissue. In term infants at birth regional SO_2 of the brain (rSO_2brain) rapidly adapts to extra-uterine life with 44% at 3 minutes to 76% at 7 minutes, after which it remained stable (90) rSO_2brain was not

affected by manner of birth indicating that blood flow to the brain is possibly determined by auto regulation independently from the mode of delivery (103). Also fractional oxygen extraction ([SO2-rSO2$_{brain}$]/SO2) can be determined using NIRS, which is a measure for the amount of oxygen consumed by the tissue. In the first 5 minutes after birth fractional oxygen extraction rises significantly where after it levels (90). When assuming that cerebral metabolism remains stable, fractional oxygen extraction could also be used as an indirect parameter for cerebral blood flow.

Table 2. Tidal volumes and pressures in infants just after birth during resuscitation measured using a respiratory function monitor.

	Vte of spontaneous breaths (mL/kg)	Vte of prolonged inflation (mL/kg)	Vte of inflations (PPV) (mL/kg)	Breaths between inflations (CPAP) (mL/kg)	Breaths coinciding with inflations (mL/kg)
Preterm infants (<32 weeks)					
Schilleman *et al*. (16)		0.8 (0-5.6)	3.7 (1.4-6.7)	3.3 (2.1-6.6)	4.6 (2.1-7.8)
Schmoelzer *et al*. (108)			8.0 (5.2–11.2)		
Term infants					
Milner *et al*. face mask (100)			4.1 (1.7-6.4)		
Milner *et al*. intubated (100)			7.8 (0.4-11.7)		
Mortola *et al*. (49)	11.7 (5.5)				
Karlberg *et al*. (1)	10.6 (4.4)				
Hull *et al*. asphyxiated intubated (112)					10.8 (1.4)

Physiological measurements during resuscitation

Until recently, accurate physiological recordings were not used to evaluate neonatal resuscitation, but instead, subjective and inaccurate clinical observations were used (67;75;104-107). Several recent studies have now addressed the importance of monitoring neonatal resuscitation by measuring HR, SO_2 and respiratory function in the immediate newborn period (16;108-110).

Observations in the early 70s by Milner et *al*. showed that ventilation during neonatal resuscitation of asphyxiated term infants was often inadequate, only small tidal volu-

mes were administered and substantial FRC was only created when spontaneous breathing started (111). Recently, Schilleman *et al.* also observed much lower tidal volumes during mask ventilation of preterm infants at birth when compared to the volumes inhaled during spontaneous breathing (table 2) (16). Spontaneous breathing occurred more often in between and during inflations than clinicians were aware, which might have contributed to the effect of resuscitation (16). Schmoelzer *et al*. measured higher tidal volumes during ventilation (108), probably as a result of spontaneous breaths in between and during inflations as these were not separately identified and could have been mistaken for inflations during analysis.

Asphyxiated infants often do not breathe at birth. Nevertheless, in intubated asphyxiated infants, tidal volumes of 10.8 (1.4) mL/kg were measured during resuscitation shortly after birth (112). The pressure signals (112) show a pressure drop during inflation. This might implicate an spontaneous inspiration which could explain the high tidal volumes measured.

The observed breaths in asphyxiated infants could be caused by a reflex caused by ventilation (113). Certain reflexes such as the Head's paradoxal reflex could be triggered by alveolar distention during positive pressure ventilation causing spontaneous breaths (114). Furthermore, the reflex was found to be very important for the formation of FRC resulting in volumes of up to 10 mL and negative endotracheal pressures of up to 30 cmH_2O in asphyxiated infants (115). Other reflexes have also been observed, triggering spontaneous expiration after the first manual inflation in newborn infants (112). This could possibly be caused by the Hering-Breuer reflex (116), acting as a mechanism to prevent over-distension of the airways.

Conclusion and future perspectives

It has been shown that is it feasible and not cumbersome to perform non-invasive physiological measurements to evaluate the success or failure of transition and resuscitation if needed. However, more data is needed to develop a full understanding of the physiological mechanisms involved in adaptation to extra-uterine life. This will help us to identify normal or delayed transition. It is of vital importance to improve our resuscitation strategies as the patients that need intervention will keep presenting at lower gestational ages with more complicated (pulmonary and hemodynamic) problems.

Currently it is assumed that proper tidal volumes are in range of 4-8 mL/kg. However, a larger range in tidal volumes was measured in mask ventilated healthy term- and preterm born infants (49;117). Therefore, the safe range of adequate tidal volumes still needs to be determined. The use of a respiratory function monitor could improve our care during the neonatal transition by informing on spontaneous breathing, the amount of tidal volumes of inspired volumes and mask leak (16). Furthermore, the use of a monitor guiding the resuscitation, could also improve the outcome of infants needing resuscitation due to reducing lung injury and as a consequence reducing chronic lung disease and bronchopulmonary dysplasia.

Imaging techniques such as MRI could prove promising in improving our understanding of the mechanism of labor and its implications for the physiological changes taking place during birth (118). Gas exchange measurements during transition, using capnography, could assist in defining adequate tidal volumes (96-98) and the total amount of proper gas exchange. However, this technique can be influenced by other variables such as mask leak and the dead space of the mask and sensor. Therefore, the value of capnography still needs to be determined. Capnography can immediately provide data on the effectivity of gas exchange, but does not provide information on total amount of FRC. Measurement of the changes in FRC will be helpful in improving our ventilation strategies. This will however be challenging. FRC could be determined using non-invasive techniques such as respiratory inductance plethysmography which could prove helpful in providing information on relative FRC changes and the work of breathing (119;120). However, FRC measurements gathered with respiratory inductance plethysmography should be collected simultaneously with leak free volume measurements in order to calculate the absolute changes in FRC. Furthermore, this will provide insight in the effectivity of mask ventilation and effect of (changing) interventions. BP- and PI measurements could help us to evaluate the hemodynamic transition. However, more data is needed to define reference values and temporal changes after birth. Both parameters are advisory on the physiological changes during transition in terms of circulation and perfusion and could be used to intervene if the transition is not taking place as it should. Echocardiography and NIRS have been shown to be valuable research tools for investigating transition. Especially NIRS is useful to monitor the effect of transition on the most important organ of the human body (the brain) and may help to predict prognosis of the neurological outcome. In conclusion, these non-invasive physiological measurements will help us to translate concepts derived from current experimental studies to human infants and increase our knowledge of human physiology.

References

1. Karlberg P, Cherry RB, Escardo FE, Koch G. Respiratory Studies in Newborn Infants II. Pulmonary Ventilation and Mechanics of Breathing in First Minutes of Life, Including Onset of Respiration. Acta Paediatrica Scandinavica 1962;51:121-136.
2. Te Pas AB, Davis PG, Hooper SB, Morley CJ. From liquid to air: breathing after birth. J Pediatr 2008;152:607-11.
3. Heymann MA. Control of the pulmonary circulation in the fetus and during the transitional period to air breathing. Eur J Obstet Gynecol Reprod Biol 1999;84:127-32.
4. Hooper SB, Kitchen MJ, Siew ML, Lewis RA, Fouras A, Te Pas AB, *et al*. Imaging lung aeration and lung liquid clearance at birth using phase contrast X-ray imaging. Clin Exp Pharmacol Physiol 2009;36:117-25.
5. Warnekros K. Schwangerschaft und Geburt im Rontgenbilde. Wiesbaden: JF Bergman 1917;719-741.
6. Hooper SB, Harding R. Fetal lung liquid: a major determinant of the growth and functional development of the fetal lung. Clin Exp Pharmacol Physiol 1995;22:235-47.
7. Vyas H, Field D, Milner AD, Hopkin IE. Determinants of the first inspiratory volume and functional residual capacity at birth. Pediatr Pulmonol 1986;2:189-93.
8. Dawes G.S. Oxygen supply and consumption on late fetal life and the onset of breathing at birth. In: Fenn W.O, Rahn H, editors. Handbook of physiology: Sec 2. Respiration.Washington DC: American Phyiological Society; 1965. p. 1313-28.
9. Harned HS, Jr., Wolkoff AS, Pickrell J, MacKinney LG. Hemodynamic observations during birth of the lamb. Studies of the unanesthetized full-term animal. Am J Dis Child 1961;102:180-9.
10. Davey MG, Moss TJ, McCrabb GJ, Harding R. Prematurity alters hypoxic and hypercapnic ventilatory responses in developing lambs. Respir Physiol 1996;105:57-67.
11. Rigatto H, De LT, V, Gates DB. Effects of O2 on the ventilatory response to CO2 in preterm infants. J Appl Physiol 1975;39:896-9.
12. O'Donnell CP, Kamlin CO, Davis PG, Morley CJ. Crying and breathing by extremely preterm infants immediately after birth. J Pediatr 2010;156:846-7.
13. Schilleman K, Siew ML, Lopriore E, Morley CJ, Walther FJ, Te Pas AB. Auditing resuscitation of preterm infants at birth by recording video and physiological parameters. Resuscitation 2012;83:1135-9.
14. Bookatz GB, Mayer CA, Wilson CG, Vento M, Gelfand SL, Haxhiu MA, *et al*. Effect of supplemental oxygen on reinitiation of breathing after neonatal resuscitation in rat pups. Pediatr Res 2007;61:698-702.
15. Saugstad OD, Rootwelt T, Aalen O. Resuscitation of asphyxiated newborn infants with room air or oxygen: an international controlled trial: the Resair 2 study. Pediatrics 1998;102:e1.
16. Schilleman K, van der Pot CJ, Hooper SB, Lopriore E, Walther FJ, Te Pas AB. Evaluating Manual Inflations and Breathing during Mask Ventilation in Preterm Infants at Birth. J Pediatr 2013;162:457-63.
17. Barker PM, Olver RE. Invited review: Clearance of lung liquid during the perinatal period. J Appl Physiol 2002;93:1542-8.
18. Siew ML, Wallace MJ, Kitchen MJ, Lewis RA, Fouras A, Te Pas AB, *et al*. Inspiration regulates the rate and temporal pattern of lung liquid clearance and lung aeration at birth. J Appl Physiol 2009;106:1888-95.
19. Escobar J, Gormaz M, Arduini A, Gosens K, Martinez A, Perales A, *et al*. Expression of aquaporins early in human pregnancy. Early Hum Dev 2012;88:589-94.
20. Modi N. Clinical implications of postnatal alterations in body water distribution. Semin Neonatol 2003;8:301-6.
21. Zelenina M, Zelenin S, Aperia A. Water channels (aquaporins) and their role for postnatal adaptation. Pediatr Res 2005;57:47R-53R.
22. Riley CA, Boozer K, King TL. Antenatal corticosteroids at the beginning of the 21st century. J Midwifery Womens Health 2011;56:591-7.
23. Borell U, Fernstrom I. The shape of the foetal chest during its passage through the birth canal. A radiographic study. Acta Obstet Gynecol Scand 1962;41:213-22.

24. Karlberg P. The first breaths of life. In: Gluck L, editor. Modern Perinatal Medicine. Year Book ed. Chicago: Medical Publixhers Inc.1974;391-408.
25. Saunders RA, Milner AD. Pulmonary pressure/volume relationships during the last phase of delivery and the first postnatal breaths in human subjects. J Pediatr 1978;93:667-73.
26. Stoeckel W. Lehrbuch der Geburtshilfe. ed. 4 Jena: Gustav Fisher 1920;226.
27. Bland RD. Loss of liquid from the lung lumen in labor: more than a simple "squeeze". Am J Physiol Lung Cell Mol Physiol 2001;280:L602-L605.
28. Martius H, Bickenbach W. Leherbuch der Geburtshilfe. ed. 3 Stuttgart: George Thieme Verlag 1956;79.
29. Lines A, Hooper SB, Harding R. Lung liquid production rates and volumes do not decrease before labor in healthy fetal sheep. J Appl Physiol 1997;82:927-32.
30. Avery ME, Frank NR, Gribetz I. The inflationary force produced by pulmonary vascular distention in excised lungs; the possible relation of this force to that needed to inflate the lungs at birth. J Clin Invest 1959;38:456-62.
31. Jaykka S. Capillary erection and lung expansion; an experimental study of the effect of liquid pressure applied to the capillary network of excised fetal lungs. Acta Paediatr Suppl 1957;46:1-91.
32. von Basch SSK. Klinische und Experimentelle Studien. Berlin: August Hirschwald 1891; 69.
33. Lauer RM, Evans JA, Aoki H, Kittle CF. Factors controlling pulmonary vascular resistance in fetal lambs. J Pediatr 1965;67:568-77.
34. Teitel DF, Iwamoto HS, Rudolph AM. Changes in the pulmonary circulation during birth-related events. Pediatr Res 1990;27:372-8.
35. Olshausen R. Beitrag zur Lehre vom Mechanismus der Geburt. Stuttgart: Ferdinand Enke; 1901;65.
36. Karlberg P, Adams FH, Geubelle F, Wallgren G. Alteration of the infant's thorax during vaginal delivery. Acta Obstet Gynecol Scand 1962;41:223-9.
37. Gruenwald P. Surface tension as a factor in the resistance of neonatal lungs to aeration. Am J Obstet Gynecol 1947;53:996-1007.
38. Bland RD. Dynamics of pulmonary water before and after birth. Acta Paediatr Scand Suppl 1983;305: 12-20.
39. Miserocchi G, Poskurica BH, Del Fabbro M. Pulmonary interstitial pressure in anesthetized paralyzed newborn rabbits. J Appl Physiol 1994;77:2260-8.
40. Siew ML, Te Pas AB, Wallace MJ, Kitchen MJ, Lewis RA, Fouras A, *et al*. Positive end-expiratory pressure enhances development of a functional residual capacity in preterm rabbits ventilated from birth. J Appl Physiol 2009;106:1487-93.
41. Te Pas AB, Wong C, Kamlin COF, Dawson JA, Morley CJ, Davis PG. Breathing Patterns in Preterm and Term Infants Immediately After Birth. Pediatric Research 2009;65:352-6.
42. Lind J, Peltonen T, Tornwall L, Wegelius C. Roentgenological lung findings in the newborn infant's 1st breath. Z Kinderheilkd 1963;87:568-78.
43. Hooper SB, Kitchen MJ, Wallace MJ, Yagi N, Uesugi K, Morgan MJ, *et al*. Imaging lung aeration and lung liquid clearance at birth. FASEB J 2007;21:3329-37.
44. Miserocchi G, Agostoni E. Pleural liquid and surface pressures at various lung volumes. Respir Physiol 1980;39:315-26.
45. Thibeault DW, Wong MM, Auld PA. Thoracic gas volume changes in premature infants. Pediatrics 1967;40:403-11.
46. Bosma JF, Lind J. Roentgenologic observations of motions of the upper airway associated with establishment of respiration in the newborn infant. Acta Paediatr Suppl 1960;49:18-55.
47. Karlberg P, Koch G. Respiratory studies in newborn infants. III. Development of mechanics of breathing during the first week of life. A longitudinal study. Acta Paediatr Suppl 1962;135:121-9.
48. Te Pas AB, Davis PG, Kamlin CO, Dawson J, O'Donnell CP, Morley CJ. Spontaneous breathing patterns of very preterm infants treated with continuous positive airway pressure at birth. Pediatr Res 2008;64: 281-5.

49. Mortola JP, Fisher JT, Smith JB, Fox GS, Weeks S, Willis D. Onset of respiration in infants delivered by cesarean section. J Appl Physiol 1982;52:716-24.
50. Clements JA. Surface tension of lung extracts. Proc Soc Exp Biol Med 1957;95:170-2.
51. Siew ML, Te Pas AB, Wallace MJ, Kitchen MJ, Islam MS, Lewis RA, *et al*. Surfactant increases the uniformity of lung aeration at birth in ventilated preterm rabbits. Pediatr Res 2011;70:50-5.
52. Winberg P, Jansson M, Marions L, Lundell BP. Left ventricular output during postnatal circulatory adaptation in healthy infants born at full term.. Arch Dis Child 1989;64:1374-8.
53. Kondo M, Itoh S, Kunikata T, Kusaka T, Ozaki T, Isobe K, *et al*. Time of closure of ductus venosus in term and preterm neonates. Arch Dis Child Fetal Neonatal Ed 2001;85:F57-F59.
54. Crossley KJ, Allison BJ, Polglase GR, Morley CJ, Davis PG, Hooper SB. Dynamic changes in the direction of blood flow through the ductus arteriosus at birth. J Physiol 2009;587:4695-704.
55. Rudolph AM. Hepatic and ductus venosus blood flows during fetal life. Hepatology 1983;3:254-8.
56. Kiserud T, Rasmussen S, Skulstad S. Blood flow and the degree of shunting through the ductus venosus in the human fetus. Am J Obstet Gynecol 2000;182:147-53.
57. Kiserud T, Eik-Nes SH, Blaas HG, Hellevik LR. Foramen ovale: an ultrasonographic study of its relation to the inferior vena cava, ductus venosus and hepatic veins. Ultrasound Obstet Gynecol 1992;2:389-96.
58. Rudolph AM. The changes in the circulation after birth. Their importance in congenital heart disease. Circulation 1970;41:343-59.
59. Heymann MA. Regulation of the pulmonary circulation in the perinatal period and in children. Intensive Care Med 1989;15:S9-S12.
60. Lind J, Wegelius C. Human fetal circulation: changes in the cardiovascular system at birth and disturbances in the post-natal closure of the foramen ovale and ductus arteriosus. Cold Spring Harb Symp Quant Biol 1954;19:109-25.
61. Bhatt S, Alison B, Wallace EM, Crossley KJ, Gill AW, Kluckow M, *et al*. Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. J Physiol 2013 15;591:2113-26.
62. Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database Syst Rev 2012;8:CD003248.
63. Aladangady N, McHugh S, Aitchison TC, Wardrop CA, Holland BM. Infants' blood volume in a controlled trial of placental transfusion at preterm delivery. Pediatrics 2006;117:93-8.
64. Linderkamp O. Placental transfusion: determinants and effects. Clin Perinatol 1982;9:559-92.
65. Stembera ZK, Hodr J, Janda J. Umbilical blood flow in healthy newborn infants during the first minutes after birth. Am J Obstet Gynecol 1965;91:568-74.
66. Yao AC, Hirvensalo M, Lind J. Placental transfusion-rate and uterine contraction. Lancet 1968;1:380-3.
67. Richmond S, Wyllie J. European Resuscitation Council Guidelines for Resuscitation 2010 Section 7. Resuscitation of babies at birth. Resuscitation 2010;81:1389-99.
68. Dawson JA, Kamlin CO, Wong C, Te Pas AB, Vento M, Cole TJ, *et al*. Changes in heart rate in the first minutes after birth. Arch Dis Child Fetal Neonatal Ed 2010;95:F177-F181.
69. Klingenberg C, Sobotka KS, Ong T, Allison BJ, Schmolzer GM, Moss TJ, *et al*. Effect of sustained inflation duration; resuscitation of near-term asphyxiated lambs. Arch Dis Child Fetal Neonatal Ed 2012.
70. Carbonne B, Langer B, Goffinet F, Audibert F, Tardif D, Le GF, *et al*. Multicenter study on the clinical value of fetal pulse oximetry. II. Compared predictive values of pulse oximetry and fetal blood analysis. The French Study Group on Fetal Pulse Oximetry. Am J Obstet Gynecol 1997;177:593-8.
71. Kubli FW, Hon EH, Khazin AF, Takemura H. Observations on heart rate and pH in the human fetus during labor. Am J Obstet Gynecol 1969;104:1190-206.
72. Kuhnert M, Seelbach-Goebel B, Butterwegge M. Predictive agreement between the fetal arterial oxygen saturation and fetal scalp pH: results of the German multicenter study. Am J Obstet Gynecol 1998;178:330-5.
73. Seelbach-Gobel B, Heupel M, Kuhnert M, Butterwegge M. The prediction of fetal acidosis by means of intrapartum fetal pulse oximetry. Am J Obstet Gynecol 1999;180:73-81.

74. Palme-Kilander C, Tunell R, Chiwei Y. Pulmonary gas exchange immediately after birth in spontaneously breathing infants. Arch Dis Child 1993;68:6-10.
75. O'Donnell CP, Kamlin CO, Davis PG, Carlin JB, Morley CJ. Clinical assessment of infant colour at delivery. Arch Dis Child Fetal Neonatal Ed 2007;92:F465-F467.
76. Dawson JA, Davis PG, O'Donnell CP, Kamlin CO, Morley CJ. Pulse oximetry for monitoring infants in the delivery room: a review. Arch Dis Child Fetal Neonatal Ed 2007;92:F4-F7.
77. Dawson JA, Kamlin CO, Vento M, Wong C, Cole TJ, Donath SM, *et al*. Defining the reference range for oxygen saturation for infants after birth. Pediatrics 2010;125:e1340-e1347.
78. Nuntnarumit P, Rojnueangnit K, Tangnoo A. Oxygen saturation trends in preterm infants during the first 15 min after birth. J Perinatol 2010;30:399-402.
79. Rabi Y, Yee W, Chen SY, Singhal N. Oxygen saturation trends immediately after birth. J Pediatr 2006;148:590-4.
80. Sharma A, Ford S, Calvert J. Adaptation for life: a review of neonatal physiology. Anaesthesia and intensive care medicine 2010;12:85-90.
81. Van Hare GF, Hawkins JA, Schmidt KG, Rudolph AM. The effects of increasing mean arterial pressure on left ventricular output in newborn lambs. Circ Res 1990;67:78-83.
82. Agata Y, Hiraishi S, Oguchi K, Misawa H, Horiguchi Y, Fujino N, *et al*. Changes in left ventricular output from fetal to early neonatal life. J Pediatr 1991;119:441-5.
83. Popat H, Kluckow M. Noninvasive assessment of the early transitional circulation in healthy term infants. Neonatology 2012;101:166-71.
84. Walther FJ, Benders MJ, Leighton JO. Early changes in the neonatal circulatory transition. J Pediatr 1993;123:625-32.
85. Noori S, Wlodaver A, Gottipati V, McCoy M, Schultz D, Escobedo M. Transitional Changes in Cardiac and Cerebral Hemodynamics in Term Neonates at Birth. J Pediatr 2012;60:943-8.
86. Kluckow M, Evans N. Relationship between blood pressure and cardiac output in preterm infants requiring mechanical ventilation. J Pediatr 1996;129:506-12.
87. Woodbury RA, Robinow M, Hamilton WF. Blood pressure studies on infants. Am J Physiol 1938;122:472-479.
88. Salihoglu O, Can E, Beskardes A, Koc BS, Tan I, Can G, *et al*. Delivery room blood pressure percentiles of healthy, singleton, liveborn neonates. Pediatr Int 2012;54:182-9.
89. Ashworth AM, Neligan GA. Changes changes in the systolic blood-pressure of normal babies during the first twenty-four hours of life. Lancet 1959;1:804-7.
90. Urlesberger B, Grossauer K, Pocivalnik M, Avian A, Muller W, Pichler G. Regional oxygen saturation of the brain and peripheral tissue during birth transition of term infants. J Pediatr 2010;157:740-4.
91. Palme-Kilander C, Tunell R. Equipment for recording pulmonary gas exchange immediately after birth during spontaneous breathing and assisted ventilation. Med Biol Eng Comput 1993;31:67-71.
92. Tunell R, Copher D, Persson B. Pulmonary gas exchange and blood gases in the immediate neonatal period. Acta Obstet Gynecol Scand 1969;48:90.
93. Palme-Kilander C, Tunell R. Pulmonary gas exchange during facemask ventilation immediately after birth. Arch Dis Child 1993;68:11-6.
94. Rurak DW, Gruber NC. Increased oxygen consumption associated with breathing activity in fetal lambs. J Appl Physiol 1983;54:701-7.
95. Kong JY, Rich W, Finer NN, Leone TA. Quantitative End-Tidal Carbon Dioxide Monitoring in the Delivery Room: A Randomized Controlled Trial. J Pediatr 2013.
96. Nangia S, Saili A, Dutta AK. End tidal carbon dioxide monitoring--its reliability in neonates. Indian J Pediatr 1997;64:389-94.
97. Rozycki HJ, Sysyn GD, Marshall MK, Malloy R, Wiswell TE. Mainstream end-tidal carbon dioxide monitoring in the neonatal intensive care unit. Pediatrics 1998;101:648-53.
98. Wu CH, Chou HC, Hsieh WS, Chen WK, Huang PY, Tsao PN. Good estimation of arterial carbon dioxide by end-tidal carbon dioxide monitoring in the neonatal intensive care unit. Pediatr Pulmonol 2003;35:292-5.

99. Hooper SB, Fouras A, Siew ML, Wallace MJ, Kitchen MJ, Te Pas AB, *et al*. Expired CO2 levels indicate degree of lung aeration at birth . PlosOne 2013; 8:e70895.
100. Milner AD, Saunders RA. Pressure and volume changes during the first breath of human neonates. Arch Dis Child 1977;52:918-24.
101. De Felice C, Latini G, Vacca P, Kopotic RJ. The pulse oximeter perfusion index as a predictor for high illness severity in neonates. Eur J Pediatr 2002;161:561-2.
102. De Felice C, del VA, Criscuolo M, Lozupone A, Parrini S, Latini G. Early postnatal changes in the perfusion index in term newborns with subclinical chorioamnionitis. Arch Dis Child Fetal Neonatal Ed 2005;90:F411-F414.
103. Urlesberger B, Kratky E, Rehak T, Pocivalnik M, Avian A, Czihak J, *et al*. Regional Oxygen Saturation of the Brain during Birth Transition of Term Infants: Comparison between Elective Cesarean and Vaginal Deliveries. J Pediatr 2011;159:404-8.
104. Brugada M, Schilleman K, Witlox RS, Walther FJ, Vento M, Te Pas AB. Variability in the assessment of 'adequate' chest excursion during simulated neonatal resuscitation. Neonatology 2011;100:99-104.
105. International Liaison Committee on Resuscitation. The International Liaison Committee on Resuscitation (ILCOR) consensus on science with treatment recommendations for pediatric and neonatal patients: neonatal resuscitation. Pediatrics 2006;117:e978-88.
106. Kattwinkel J, Perlman JM, Aziz K, Colby C, Fairchild K, Gallagher J, *et al*. Neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Pediatrics 2010;126:e1400-e1413.
107. Poulton DA, Schmolzer GM, Morley CJ, Davis PG. Assessment of chest rise during mask ventilation of preterm infants in the delivery room. Resuscitation 2011;82:175-9.
108. Schmolzer GM, Kamlin OC, O'Donnell CP, Dawson JA, Morley CJ, Davis PG. Assessment of tidal volume and gas leak during mask ventilation of preterm infants in the delivery room. Arch Dis Child Fetal Neonatal Ed 2010;95:F393-F397.
109. Schmolzer GM, Kamlin CO, Dawson JA, Morley CJ, Davis PG. Tidal volume delivery during surfactant administration in the delivery room. Intensive Care Med 2011;37:1833-9.
110. Schmolzer GM, Morley CJ, Wong C, Dawson JA, Kamlin CO, Donath SM, *et al*. Respiratory function monitor guidance of mask ventilation in the delivery room: a feasibility study. J Pediatr 2012;160:377-81.
111. Milner AD, Vyas H, Hopkin IE. Efficacy of facemask resuscitation at birth. Br Med J (Clin Res Ed) 1984;289:1563-5.
112. Hull D. Lung expansion and ventilation during resuscitation of asphyxiated newborn infants. J Pediatr 1969;75:47-58.
113. Head H. On the Reglation of Respiration: PART I. Experimental. J Physiol 1889;10:1-152.
114. Cross KW. Head's paradoxical reflex. Brain 1961;84:529-34.
115. Boon AW, Milner AD, Hopkin IE. Physiological responses of the newborn infant to resuscitation. Arch Dis Child 1979;54:492-8.
116. Hannam S, Ingram DM, Rabe-Hesketh S, Milner AD. Characterisation of the Hering-Breuer deflation reflex in the human neonate. Respir Physiol 2001;124:51-64.
117. Murthy V, Dattani N, Peacock JL, Fox GF, Campbell ME, Milner AD, *et al*. The first five inflations during resuscitation of prematurely born infants. Arch Dis Child Fetal Neonatal Ed 2012;97:F249-F253.
118. Bamberg C, Rademacher G, Guttler F, Teichgraber U, Cremer M, Buhrer C, *et al*. Human birth observed in real-time open magnetic resonance imaging. Am J Obstet Gynecol 2012;206:505-6.
119. Courtney SE, Pyon KH, Saslow JG, Arnold GK, Pandit PB, Habib RH. Lung recruitment and breathing pattern during variable versus continuous flow nasal continuous positive airway pressure in premature infants: an evaluation of three devices. Pediatrics 2001;107:304-8.
120. Stick SM, Ellis E, LeSouef PN, Sly PD. Validation of respiratory inductance plethysmography ("Respitrace") for the measurement of tidal breathing parameters in newborns. Pediatr Pulmonol 1992;14:187-91.

PART 1

Airway

CHAPTER 3

The direct effect of a sustained inflation in preterm infants at birth

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J Pediatr. 2014 [in press]

Abstract

Background: A sustained inflation (SI) at birth enhances lung aeration, increases functional residual capacity (FRC) and reduces need for mechanical ventilation in preterm infants. However, face mask ventilation of preterm infants is difficult, therefore clinical effect of the SI is unclear.

Methods: In this observational study inflation pressures and tidal volumes were recorded using respiratory function monitoring of preterm infants <32 weeks gestation receiving a SI. Inspiratory- (Vti) and expiratory tidal volumes (Vte) of the SI and cumulative Vti and Vte of breaths (Vti_{br}, Vte_{br}) during the SI were determined. Heart rate (HR) and oxygen saturation (SpO_2) were determined before and after the SI.

Results: 70 infants were included (median (IQR) GA 29 (27-30) weeks). Mean (SD) SI duration was 10.5 (2.9) s using PIP 24.2 (2.3) cmH_2O and PEEP 6.0 (1.8) cmH_2O. In 20/70 infants, no volumes were delivered during the SI due to mask leak. No leak occurred in 50/70 infants of which 36/50 breathed during the SI. In 14/50 infants who did not breathe, Vti and Vte were 0.9 (0.4-2.7) mL/kg and 0.6 (0.1-2.0) mL/kg with FRC gain of 0.0 (-0.5-0.6) mL/kg. In 36/50 infants who breathed during the SI, Vti was 2.9 (0.9-9.2) mL/kg and Vte 3.8 (1.0-5.9) mL/kg, whereas Vti_{br} was 16.4 (6.8-23.3) mL/kg, and Vte_{br} 5.8 (1.2-16.8) mL/kg with FRC gain of 7.1 (1.7-15.9) mL/kg. HR and SpO_2 did not increase immediately after the SI.

Conclusions: A SI of 10 s and 25 cmH_2O in preterm infants at birth was not effective unless infants breathed. Although large mask leak accounted for ~1/3 of failures, as FRC gain was only associated with breathing, we speculate that active glottic adduction may be responsible for most failures.

Introduction

Many preterm infants need positive pressure ventilation (PPV) to aerate their lungs after birth and overcome the high surface tension and frictional forces caused by liquid-filled airways (1). It has been suggested that an initial sustained inflation (SI) can improve lung aeration and functional residual capacity (FRC) during resuscitation of preterm infants at birth (2;3). During a SI, a positive inflation pressure (PIP) is administered for a prolonged period, which allows time for the air/liquid interface to move into the distal airways (4).

Recent studies performed in preterm rabbit pups using simultaneous phase contrast X-ray imaging and plethysmography have shown that an initial SI immediately after birth provided more uniform lung aeration, larger FRC and more consistent tidal volumes than regular PPV (4;5). An experimental study using an SI of 20 s for resuscitation of asphyxiated lambs improved respiratory and hemodynamic function, showing a prompt increase in heart rate (HR) after the SI is applied (6). Although clinical studies reported less need for intubation, mechanical ventilation and BPD when a SI was applied at birth (7-10), the direct clinical effect in preterm infants remains uncertain.

The effect of the initial PPV at birth is largely dependent on effective mask technique, but this can be difficult to achieve (11-15). Most clinicians are not aware of mask leak, airway obstruction and occurrence of inadvertent high peak pressures (12;16;17). We recently measured the effect of mask ventilation in preterm infants at birth using respiratory function monitoring and often observed inadequate low tidal volumes and large mask leak (18). We also reported that spontaneous breathing during PPV frequently occurred (18).

In animal experiments it was shown that a SI improved lung function without adverse circulatory effects and positively affected cerebral oxygenation (19). A recent trial in preterm infants showed beneficial effects of a ventilation strategy where also SI of 10 s was incorporated. (10). We recently reported the respiratory function measurements of 5 initial inflations of 2-3 s (18), but the direct effect of a 10 s SI has not yet been investigated in human infants. When leak occurs during the SI, gas flow remains positive for a prolonged period and a supraphysiological inspired tidal volume (Vti) will be measured. However, as very little volume entered the airways, the expired tidal volume (Vte) is very low. In the absence of mask leak, low inspired volumes also occur when the mask obstructs the mouth and nose, secretions block the oropharynx, the glottis is closed or the PIP is not high enough to overcome the frictional resistance of moving the air-liquid interface distally.

The aim of this observational study was to investigate the direct clinical effect of a SI during initial respiratory support in preterm infants at birth by measuring clinical parameters and lung function.

Methods

The local institutional review boards of the Leiden University Medical Center approved physiological- and video recordings at birth in the delivery room when respiratory support was expected. Recordings are performed as a standard of care in our unit. The data for this observational study were prospectively collected for audit, teaching and research purposes and written parental consent was obtained after birth.

Respiratory support was delivered with a T-piece resuscitator (Neopuff, Fisher & Paykel, Wellington, New Zealand) and a properly sized round face mask (35mm face mask; Fisher & Paykel, Wellington, New Zealand or size 0/0 or 0/1 face mask; Laerdal, Stavanger, Norway). Since 2010 our local resuscitation guidelines deviated from the national guidelines by recommending to start respiratory support (PPV or continuous positive airway pressure) in preterm infants (< 32 weeks gestational age) with an initial SI of 10s using a PIP of 25 cmH_2O and a PEEP of 5 cmH_2O with fractional inspired oxygen of 0.3. Respiratory support was given if the infant was apneic (PPV), had labored breathing (continuous positive airway pressure) and/or the HR was below 100 beats per minute (bpm).

Physiological and video recordings were performed in preterm infants if there was time to set up the equipment. The use of a respiratory function monitor (Acutronic Medical Systems AG, Hirzel, Switzerland), a pulse oximeter (Masimo Radical 7, Masimo Corporation, Irvine CA, USA) and Spectra program (Spectra, Grove Medical Limited, Hampton, UK) for physiological recordings has been described in detail in a previous publication (18). According to the manufacturer the Florian respiratory function monitor is able to measure accurately down to 90 mL/min (1.5 mL/s) (20). However, to determine accuracy of the Florian we performed a bench study using a gas flow analyzer (Biotek Instruments, Winooski, VT, USA) observing the following: 1) gas flow could be measured accurately down to a gas flow of 50 mL/min (0.8 mL/s), 2) below 50 mL/min gas flow was measured, but values became inaccurate, 3) when gas flow was stopped the Florian accurately showed zero flow. It has been shown in previous studies that hot-wire anemometers are capable of accurately measuring even lower gas flows (21;22).

Recordings were reviewed from infants born between 2009 and 2013. Recordings were made of infants who were expected to need respiratory support born < 32 weeks of gestational age, without congenital malformations regardless if prenatal steroids were administered or oligo- or anhydramnios existed. Recordings were analyzed only when a face mask was used for administration of the initial SI.

Vti, Vte and cumulative Vti and Vte of spontaneous breaths (Vti_{br}, Vte_{br}) during the SI were determined. When during a SI breathing occurred Vti and Vte were determined at the plateau level prior to the breath. Leak (%) was calculated using the formula $([V_{ti} - V_{te}]/V_{ti}) \times 100$. When little mask leak occurred tidal volumes and gain in FRC could be calculated. In this case flow goes back to zero soon after commencing the SI when the passive inflation has ended. FRC gain was calculated by subtracting total expiratory volume from inspiratory volume. HR and SpO_2 were determined directly before and after the SI and 30s and 60s after the SI using a pulse oximeter (Masimo Radical 7, Masimo Corporation, Irvine, CA, USA).

The following gas flow and volume wave characteristics were identified during the SI:

A) As described in previous clinical (3;8-10) and experimental studies (4;5;23) the lung function of an effective SI would be characterized by a volume that increases during a prolonged period of PIP. The gas flow will be characterized by a peak positive flow at the start, followed by slower positive gas flow reflecting airway recruitment caused by the liquid-air interface moving distally and creating a FRC. As the flow wave characteristics of face mask leak are similar to FRC recruitment, it is difficult to differentiate effect of the SI on FRC from mask leak. However, when mask leak occurs during a SI with a flow of 8-10 L/min, a continuous leak with high gas flows is observed. Thus, when the measured inspired volume (Vti) was supraphysiological (higher than the total lung capacity of around 60 mL/kg) and the expired tidal volume (Vte) was small, this was deemed to be due to mask leak.

B) The flow returns to zero immediately after the initial positive peak in flow at the start of the SI. This reflects that no mask leak occurred, but also little or no movement of the liquid-air interface recruiting the airways. Appearance of spontaneous breaths can be identified during the SI by the presence or absence of inspiratory and expiratory gas flow patterns during the SI. Infants can continue breathing after the SI or infants can stop breathing after the SI. (figure 1).

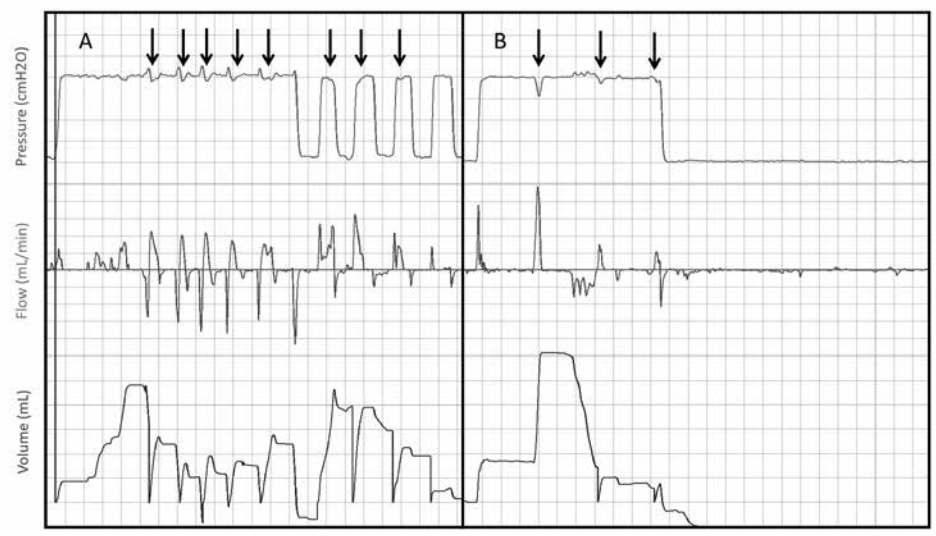

Figure 1. recording of a SI with breathing which continues directly after the SI during PPV, also large leak occurs during these inflations, (A) and a SI with breathing where breathing recommences after a prolonged period of apnea during which the infant is evaluated (B). Breaths are indicated by the arrows. Pressure, flow and volume are indicated.

Statistical Analyses

Data were analyzed with SPSS (IBM, version 20.0, 2012, IL, USA). Results are presented as mean (SD) for normally distributed values or median (IQR) and median (range) for non-normally distributed values. Variables were compared using a paired t-test or ANOVA for normally distributed values and a chi-squared test for binomial distributed data. Statistical significance was defined as $p< 0.05$. Reported p-values are 2-sided.

Results

Recordings of 131 infants were reviewed and 61 infants needed to be excluded from analysis (gestational age (median (range) 28 (24-31) (11 infants did not receive any respiratory support, 15 infants only received continuous positive airway pressure, in 14 infants the SI could not be recorded or not administered and 21 infants received 5 SI s of 2-3s). In total 70 infants were included in the study. Demographics were comparable and are stated in table 1.

Table 1. demographics for the infants included in the study. P-values for the difference between the three groups are given. Numbers are median (range) unless otherwise indicated

	Large leak (n= 20)	No breathing (n= 14)	Breathing (n= 36)	p-value
Sex (% male)	70	57	59	0.85
Birth weight (g) (mean [SD])	1140 (225)	1016 (314)	1061 (313)	0.27
Gestational age (weeks)	28 (27-31)	27 (24-31)	29 (24-31)	0.15
Apgar 1 minute	5 (1-10)	3 (1-7)	5 (1-10)	0.11
Apgar 5 minutes	7 (5-10)	7 (5-10)	7 (2-10)	0.56
Apgar 10 minutes	9 (7-10)	9 (7-10)	8 (3-10)	0.06
Mode of delivery (% cesarean section)	39	50	50	0.14
Complete course of corticosteroids (%)	44	79	73	0.20

Effect of the SI: lung function measurement

In 70 infants SI's were given with a mean (SD) length of 10.5 (2.9) s using a PIP of 24.2 (2.3) cmH_2O and a PEEP of 6.0 (1.8) cmH_2O. The median (IQR) Vte of the initial SI was 2.1 (0.0-5.1) mL/kg. In 10/70 infants a second SI was given with Vte 0.5 (0.0-4.4) mL/kg and in 3/70 infants a third SI was given with Vte 2.7 (0.0-7.7) mL/kg.

The SI's were differentiated according to the defined gas flow and volume characteristics. A) In 20 infants gas flow remained positive during SI. All measured Vti was supraphysiological with median (range) Vti of 133.8 (64.3-672.8) mL/kg and very little Vte (0 (0-7.8) mL/kg), most likely caused by large leak (calculated 100 (1) %) (figure 2A).

B) In 50 infants gas flow went back to zero immediately after the initial peak flow at the beginning of SI. In 14/50 infants no breathing was observed during the SI. Median (IQR) Vti and Vte was 0.9 (0.4-2.7) and 0.6 (0.1-2.0) mL/kg, respectively, resulting in a FRC gain of 0.0 (-0.5-0.6) mL/kg (figure 2B).

In 36/50 infants, breathing was observed during the SI. In these 36 infants, 2 (1-4) breaths were taken during the SI producing a Vti of 2.9 (0.9-9.2) mL/kg and a Vte of 3.8 (1.0-5.9) mL/kg; the Vti_{br} was 16.4 (6.8-23.3) mL/kg and Vte_{br} 5.8 (1.2-16.8) mL/kg with a FRC gain of 7.1 (1.7-15.9) mL/kg. In 29/36 infants breathing continued after the SI (figure 1A) and in 7/36 infants breathing was observed during the SI but these infants did not recommence breathing until 24.8 (12.0) s after the SI (figure 1B).

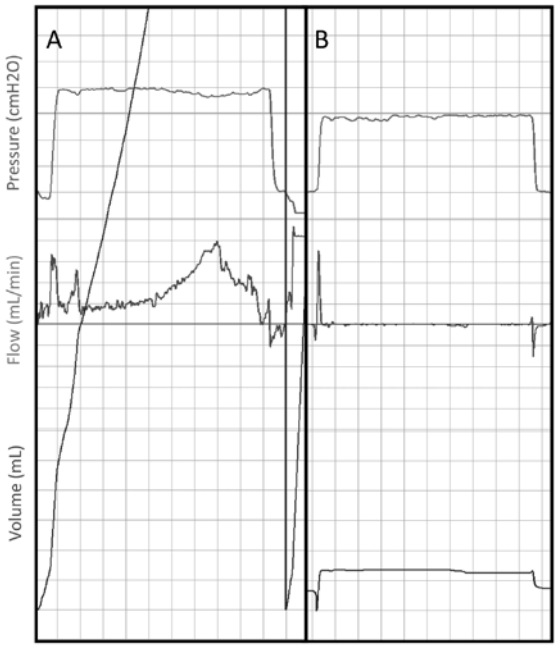

Figure 2. recording of a SI with large leak (A) and SI without leak or breathing (B). Pressure, flow and volume are indicated.

Effect of the SI on HR and SpO_2

The SI did not significantly alter HR in any of the groups of infants before vs. after the SI. In infants with large leak or no breathing during the SI HR was significantly increased from directly after the SI to 60 s after the SI. In infants who were breathing during the SI there was no significant difference (table 2). Similarly, SpO_2 levels before vs. after the SI were not significantly different. Also no significant differences were found up to 60 s after the SI (table 3).

Table 2. Mean (SD) HR (bpm) determined before- and directly after the SI and at 30s and 60s after the SI for infants with large leak during the SI and infants who breathed or did not breathe during the SI.

	Large leak (n= 20)	**No breathing (n= 14)**	**Breathing (n= 36)**
HR before SI	90 (32)	86 (32)	99 (34)
HR after SI	87 (28)	82 (28)	99 (34)
p-value (before-after SI)	0.60	0.54	0.38
HR 30s	104 (45)	71 (25)	109 (38)
HR60s	114 (27)	103 (31)	107 (37)
p-value (after SI-60s)	0.03	0.03	0.93

Table 3. Mean (SD) SpO_2 (%) determined before- and directly after the SI and at 30s and 60s after the SI for infants with large leak during the SI and infants who breathed or did not breathe during the SI.

	Large leak (n= 20)	**No breathing (n= 14)**	**Breathing (n= 36)**
SpO_2 before SI	58 (24)	35 (20)	56 (16)
SpO_2 after SI	57 (24)	30 (16)	56 (24)
p-value (before-after SI)	0.60	0.11	0.58
SpO_2 30s	49 (31)	35 (18)	64 (17)
SpO_2 60s	55 (18)	40 (21)	63 (19)
p-value (after SI-60s)	0.67	0.81	0.56

Discussion

This is the first study reporting airflow and volume measurements when applying a SI via a face mask in preterm infants at birth. We observed that a SI of 10s with a peak pressure of 25 cmH_2O was not effective in creating adequate tidal volumes and FRC. In contrast, spontaneous breathing during the SI resulted in larger tidal volumes, which was probably responsible for the establishment of a large fraction of the reported FRC gain in these infants. In a considerable number of the infants recruited into the study, the effect of SI on FRC gain was impaired by large leak and limited volume was delivered. However, even in infants where no leak was present, the delivered volumes achieved by the SI were very low. The absence of any direct clinical response, i.e. prompt increase in HR or SpO_2, in apneic infants confirms that the SI's applied were inadequate.

In contrast to our findings, previous studies in asphyxiated term infants (3) and in preterm rabbit pups (4;5) reported that SI was effective in creating inspiratory volume and FRC. Applying an initial SI of 5 s in asphyxiated term infants led to mean volumes of 12 (8) mL/kg and a FRC of 6 (3) mL/kg (3). Furthermore, in preterm rabbit pups an initial SI of 5, 10 and 20 s led to inspiratory volumes of 5, 10 and 23 mL/kg respectively, resulting in an immediate FRC of 6, 8 and 13 mL/kg (5). In both studies the SI was applied via an endotracheal tube, bypassing the glottis and minimizing leak. In our study SI's were applied via a face mask and large leak explains why little or no volume was delivered in a large proportion of the patients. However in the absence of significant leak, it is possible that closure of the vocal cords in both breathing (i.e. between breaths) and apneic infants could cause obstruction and this would explain the low volumes delivered during the SI. Indeed, it is well established that the fetal glottis is actively adducted during apnea, which prevents

lung liquid loss during apnea (24). Thus, possibly that the glottis is adducted in apneic infants immediately after birth. In both experimental and human studies it has been demonstrated that in spontaneous breathing preterm rabbit pups and infants expiratory braking maneuvers (expiratory hold) frequently occurred. During this braking the glottis is adducted (25-27). It is also possible that obstruction occurred at pharyngeal level by the relative large tongue (28) or obstruction of the nose and mouth with improper mask technique (25-27;29). However, this would also cause obstruction during inspiration and air entering the lung during inspiration was frequently observed during the SI. In addition, the duration of the SI was shorter compared to other studies. (9;30). It is possible that the pressure was not high enough and/or the duration was not long enough (i.e. pressure time integral; 25 cmH_2O applied with a duration of 10 s) for efficient lung aeration. However, the duration and pressure with which a SI is administered have been chosen as a standard practice after clear benefit shown by a randomized controlled trail (10).

The purpose of applying a SI for lung aeration is to overcome the high resistance of the liquid filled lung by administering PIP for a prolonged period. In this context, an effective SI given via a face mask would be characterized by an early inspiratory increase in gas flow (pressurization oropharynx and trachea). After the initial increase a smaller positive gas flow would be expected to continue throughout a large part of the SI, which reflects the gradual increase in lung air volume due to the air-liquid interface moving distally. Although we observed comparable flow patterns, these were most likely caused by a large leak as supraphysiological volumes entered the lung and very little volume returned at the end of the SI. In infants where no leak occurred, the gas flow returned to zero immediately after the early peak flow.

The results in this study are in line with our previous study where we observed low tidal volumes during mask ventilation, but spontaneous breathing did markedly contribute to the effectiveness of resuscitation (18). The volumes of the spontaneous breaths during the SI were considerably larger than the tidal volumes created by the SI and are larger than what is currently considered as the safe range for ventilation (4-8 mL/kg) (31). However, it has been shown, in term infants, that the first inspired tidal volumes resulting from spontaneous breaths are reportedly larger than the consecutive breaths (32;33). As an increase in FRC was only seen when breaths were observed during the SI, it is possible that an SI augments or induces a breathing reflex. When air does not enter the lung the SI will pressurize the upper airway. Tomori *et al*. have described that increased pressurization causes an inspiratory aspiration reflex, although this is not followed by a normal expiration (34). In some infants breaths only occurred during the SI, which could be caused by a Heads paradoxical reflex (35). However, to induce this reflex, air must enter the lung.

HR increased promptly (within 4 s) after initiating a SI in intubated term asphyxiated lambs (6), but this could not be confirmed in our study. The lack of effect in HR and SpO_2 in apneic infants reflects the likelihood that SI's given were probably ineffective. This is in line with the observation of Fuchs *et al.*, where little effect was seen after the first SI (30). However, the first SI was 20 cmH_2O, but the second SI was given at 25 cmH_2O this showed an effect on HR and SpO_2 (30). It was also observed that HR and SpO_2 remained low in the first minute after administration of the first SI (30). The characteristics of the applied SI were similar to the SI used in our RCT comparing 2 delivery room strategies (10). Our current study makes it unlikely that the application of a SI contributed to the short term benefits found (10). However, experimental animal data (4-6;23) showed several beneficial short-term effects of applying SI at birth and this warrants more clinical studies to determine how to apply the SI more, effectively, including studying the appropriate length and pressure.

Limitations

In this study we used a hot wire anemometer, placed between the mask and T-piece, which is not designed to measure the very low gas flows expected during a SI and we may have underestimated the volumes administered during the SI. However, a bench test showed that the Florian could measure, although inaccurate, flow even below 50 mL/min and zero flow were observed when flow was stopped. Therefore, we are confident that only very small gas flows could have been missed, which would have a negligible effect on lung aeration. Differences in Vte and Vti during the SI caused by mask leak could be misinterpreted as FRC. However, since the SI was given for 10 s it was clearly visible that gas flow went to zero and remained zero, indicating that if a difference in Vti and Vte occurs, it must be a gain or loss in FRC.

This was an observational study of our current practice where a convenience sample was taken and no randomization occurred. We were able to record data in infants if there was time to set up the equipment and the research team was available. Therefore, a bias could have occurred. However there was no selection in the preterm infants recorded, not being able to record infants occurred by chance.

Conclusion

In this observational study we measured that an initial SI of 10 s and 25 cmH_2O in preterm infants at birth was not effective in creating lung volumes unless infants had spontaneous respiratory efforts and no immediate effect in HR and oxygen saturation was observed. Large mask leak did not result in clinically relevant tidal volumes and in the absence of leak only very small tidal volumes were observed. This could be caused by obstruction (possibly due to a closed glottis) or by a pressure-time integral which was too low. It is possible that the SI has an effect by inducing reflexes, eliciting or augmenting inspiratory effort, which aerates the lung. Further studies are warranted to investigate whether larger pressure-time integrals are more effective and if infants who breathe at birth also benefit from an SI.

References

1. Te Pas AB, Davis PG, Hooper SB, Morley CJ. From liquid to air: breathing after birth. J Pediatr 2008;152: 607-11.
2. Boon AW, Milner AD, Hopkin IE. Lung expansion, tidal exchange, and formation of the functional residual capacity during resuscitation of asphyxiated neonates. J Pediatr 1979;95:1031-6.
3. Vyas H, Milner AD, Hopkin IE, Boon AW. Physiologic responses to prolonged and slow-rise inflation in the resuscitation of the asphyxiated newborn infant. J Pediatr 1981;99:635-9.
4. Te Pas AB, Siew M, Wallace MJ, Kitchen MJ, Fouras A, Lewis RA, *et al*. Establishing functional residual capacity at birth: the effect of sustained inflation and positive end-expiratory pressure in a preterm rabbit model. Pediatr Res 2009;65:537-41.
5. Te Pas AB, Siew M, Wallace MJ, Kitchen MJ, Fouras A, Lewis RA, *et al*. Effect of sustained inflation length on establishing functional residual capacity at birth in ventilated premature rabbits. Pediatr Res 2009;66:295-300.
6. Klingenberg C, Sobotka KS, Ong T, Allison BJ, Schmolzer GM, Moss TJ, *et al*. Effect of sustained inflation duration; resuscitation of near-term asphyxiated lambs. Arch Dis Child Fetal Neonatal Ed 2013;98:F222-F227.
7. Lindner W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birth weight infants: spontaneous breathing or intubation? Pediatrics 1999;103:961-7.
8. Lindner W, Hogel J, Pohlandt F. Sustained pressure-controlled inflation or intermittent mandatory ventilation in preterm infants in the delivery room? A randomized, controlled trial on initial respiratory support via nasopharyngeal tube. Acta Paediatr 2005;94:303-9.
9. Lista G, Fontana P, Castoldi F, Cavigioli F, Dani C. Does sustained lung inflation at birth improve outcome of preterm infants at risk for respiratory distress syndrome? Neonatology 2011;99:45-50.
10. Te Pas AB, Walther FJ. A randomized, controlled trial of delivery-room respiratory management in very preterm infants. Pediatrics 2007;120:322-9.
11. Wood FE, Morley CJ, Dawson JA, Kamlin CO, Owen LS, Donath S, *et al*. Improved techniques reduce face mask leak during simulated neonatal resuscitation: study 2. Arch Dis Child Fetal Neonatal Ed 2008;93:F230-F234.

12. Finer NN, Rich W, Wang C, Leone T. Airway obstruction during mask ventilation of very low birth weight infants during neonatal resuscitation. Pediatrics 2009;123:865-9.
13. Klimek J, Morley CJ, Lau R, Davis PG. Does measuring respiratory function improve neonatal ventilation? J Paediatr Child Health 2006;42:140-2.
14. South M, Morley CJ. Monitoring spontaneous respiration in the ventilated neonate. Arch Dis Child 1986;61:291-4.
15. Keszler M. Volume-targeted ventilation. J Perinatol 2005;25 Suppl 2:S19-S22.
16. Wood FE, Morley CJ, Dawson JA, Davis PG. A respiratory function monitor improves mask ventilation. Arch Dis Child Fetal Neonatal Ed 2008;93:F380-F381.
17. Schilleman K, Witlox RS, Lopriore E, Morley CJ, Walther FJ, te Pas AB. Leak and obstruction with mask ventilation during simulated neonatal resuscitation. Arch Dis Child Fetal Neonatal Ed 2010;95:F398-F402.
18. Schilleman K, van der Pot CJ, Hooper SB, Lopriore E, Walther FJ, Te Pas AB. Evaluating manual inflations and breathing during mask ventilation in preterm infants at birth. J Pediatr 2013;162:457-63.
19. Sobotka KS, Hooper SB, Allison BJ, Te Pas AB, Davis PG, Morley CJ, *et al*. An initial sustained inflation improves the respiratory and cardiovascular transition at birth in preterm lambs. Pediatr Res 2011;70: 56-60.
20. Acutronic Medical Systems A. Florian Respiration Monitor, Instructions for use. 2014.
21. Christman PJ, Podzimek J. Hot-wire anemometer behavior in low velocity air flow. J. Phys. E: Sci. Instrum. 1981;14:46-51.
22. Godal A, Belenky DA, Standaert TA, Woodrum DE, Grimsrud L, Hodson WA. Application of the hot-wire anemometer to respiratory measurements in small animal. J Appl Physiol 1976;40:275-7.
23. Harding R, Hooper SB. Regulation of lung expansion and lung growth before birth. J Appl Physiol (1985) 1996;81:209-24.
24. Siew ML, Wallace MJ, Kitchen MJ, Lewis RA, Fouras A, Te Pas AB, *et al*. Inspiration regulates the rate and temporal pattern of lung liquid clearance and lung aeration at birth. J Appl Physiol (1985) 2009;106:1888-95.
25. Te Pas AB, Wong C, Kamlin CO, Dawson JA, Morley CJ, Davis PG. Breathing patterns in preterm and term infants immediately after birth. Pediatr Res 2009;65:352-6.
26. Fuchs H, Schilleman K, Hummler H, Te Pas AB. Techniques and Devices to Improve Noninvasive Ventilation in the Delivery Room. Neoreviews 2012;e353-e363.
27. Fuchs H, Lindner W, Buschko A, Trischberger T, Schmid M, Hummler HD. Cerebral oxygenation in very low birth weight infants supported with sustained lung inflations after birth. Pediatr Res 2011;70: 176-80.
28. Schmolzer GM, Te Pas AB, Davis PG, Morley CJ. Reducing lung injury during neonatal resuscitation of preterm infants. J Pediatr 2008;153:741-5.
29. Karlberg P, Cherry RB, Escardo FE, Koch G. Respiratory Studies in Newborn Infants .2. Pulmonary Ventilation and Mechanics of Breathing in First Minutes of Life, Including Onset of Respiration. Acta Paediatrica Scandinavica 1962;51:121-26.
30. Vyas H, Field D, Milner AD, Hopkin IE. Determinants of the first inspiratory volume and functional residual capacity at birth. Pediatr Pulmonol 1986;2:189-93.
31. Tomori Z, Benacka R, Donic V. Mechanisms and clinicophysiological implications of the sniff- and gasp-like aspiration reflex. Respir Physiol 1998;114:83-98.
32. Head H. On the Reglation of Respiration: PART I. Experimental. J Physiol 1889;10:1-152.

CHAPTER 4

Mask versus nasal tube for stabilization of preterm infants at birth: respiratory function measurements

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Submitted

Abstract

Background: We recently compared the nasal tube (NT) with the face mask (FM) as interface for stabilization of very preterm infants at birth and showed no difference in intubation rate and short term clinical outcome. In a subgroup physiological measurements were performed to measure the effectiveness of both interfaces for delivering positive pressure ventilation (PPV).

Methods: During the trial infants < 30 weeks gestation were allocated to respiratory support with NT of FM. Respiratory function, heart rate and oxygen saturation were measured if time and personnel was available to set up the equipment.

Results: 43 infants were included (18 resuscitated using NT and 25 using FM). The first 5 minutes were analyzed and in the NT group 1566 inflations and in FM group 1896 inflations were given, of which 32% and 34% respectively coincided with breathing. During inflations higher leak was found via NT compared to FM (98 (33-100)% vs. 14 (0-39)% ($p<0.0001$)) and obstruction occurred more often (8.2 vs. 1.1% ($p<0.0001$). Expired tidal volumes were significantly lower during inflations using NT compared to FM (0.0 (0.0-3.1) vs. 9.9 (5.5-12.8) mL/kg ($p<0.0001$), during inflations where breathing coincided (4.4 (2.1-8.4) vs. 9.6 (5.4-15.2) mL/kg; $p<0.0001$) and were similar during breaths (4.7 (2.8-6.9) vs. 4.8 (2.7-7.9) mL/kg; ns). Heart rate was not significantly different between both groups, but oxygen saturation was significantly lower in the NT group at 1 minute after start of respiratory support.

Conclusion: The nasal tube as interface is less effective for delivering positive pressure ventilation in preterm infants at birth.

Introduction

Very preterm infants often need positive pressure ventilation (PPV) to aerate their lungs after birth (1;2). Successful ventilation is dependent on a proper mask technique to minimize the amount of air leakage, airway obstruction, and inadequate tidal volumes (2) volumes (2). However, large and variable leaks are often observed during mask ventilation of infants at birth (3;4), leading to variable tidal volumes delivered which may result in ineffective PPV and lung injury (5).

A nasal tube (NT) can be used as alternative interface to deliver PPV (6). Recently we compared in a randomized controlled trial (RCT) the clinical outcome when using a NT or a FM during PPV of preterm infants at birth (7). We observed no difference in the rate of intubation <24 hours of birth and concluded that a NT is a good alternative for a FM. In order to investigate the direct effect and effectivity of PPV via FM or NT we recorded in a subgroup respiratory function monitoring, pulse oximetry, fraction of inspired oxygen (FiO_2) and video data.

The aim of this study was to compare the effectivity of a NT with FM as an interface for delivering PPV in very preterm infants at birth by measuring the direct effect using physiological parameters.

Methods

The RCT was registered in the Netherlands (Dutch Trial Registry, NTR 2061) and Australia (Australia and New Zealand Clinical Trials Register, ACTRN 12610000230055).The RCT and the collection of physiological data was approved by the local institutional review board of the Leiden University Medical Center (LUMC), Leiden, the Netherlands and the Royal Women's hospital (RWH), Melbourne, Australia. Written parental consent was obtained before birth, or when this was not suitable as soon as possible after birth.

The randomization procedure and application of the FM and NT have been described in a previous publication (7). If the infant had poor respiratory effort and/or a heart rate (HR) <100 beats per minute (bpm), PPV was commenced using the allocated interface. The initial settings of the T-piece ventilator for the RWH was peak inspiratory pressure (PIP) 30 cmH_2O with a positive end-expiratory pressure (PEEP) of 5 cm H_2O , for LUMC this was 20 cmH_2O and 5 cmH_2O. Change of inspiratory pressures was left to the discretion of the caregiver. PPV was provided at a rate of 40 to 60 inflations per minute. Initial fraction

of inspired oxygen (FiO_2) was 0.21 and switched to 1.0 when 1) cardiac massage was needed, 2) PPV was administered for 1 minute and heart rate (HR) was <100 beats per minute (bpm) or 3) SpO_2 <70% at 5 minutes. FiO_2 was then titrated down as quickly as possible (when SpO_2 >90%).

Physiological and video recordings were performed if there was time to set up the equipment. The use of a respiratory function monitor (RFM) (Acutronic Medical Systems AG, Hirzel, Switzerland) and the Spectra program (Spectra, Grove Medical Limited, Hampton, UK) to collect physiological measurements have been described in detail in a previous publication (3) The collection of data was blinded from the caregiver as it could influence outcome of the RCT.

Analysis was performed on a breath-by-breath basis. Vti and Vte of inflations were determined for the first 5 minutes after the start of respiratory support. The following flow profiles were identified: 1) breathing in between inflations, 2) inflations coinciding with breathing and 3) inflations (figure 1) (8). Leak was only calculated during inflations. We manually reviewed every inflation for leak and defined leak as when the inspiratory flow wave would not return to the 0-baseline and the expiratory flow wave is smaller or absent. The percentage of leak was calculated using the formula ($[V_{ti} - V_{te}/V_{ti}] \times 100\%$) and large leak was defined as >60% (3). Also obstruction, no tidal volume visible during inflation, was determined (3) (figure 1). Differences in leak are given for the entire group and for each individual center (RWH and LUMC). Breathing rate was calculated by determining all breaths (on CPAP, in between and during inflations) during the first 5 minutes after the start of respiratory support.

To determine clinical effect the HR and SpO_2 were determined at 1, 2, 3, 4 and 5 minutes after start of respiratory support using a pulse oximeter (Masimo Radical 7, Masimo Corporation, Irvine CA, USA).

Statistical Analyses

Data were analyzed using SPSS (IBM, version 20.0, 2012, IL, USA). Results are presented as mean (SD) for normally distributed values or median (IQR) and median (range) for non-normally distributed values. Data were compared using a Mann-Whitney U test for non-normally distributed parametric values or a Fisher's exact test for binary non-related values. Statistical significance was defined as $p < 0.05$. Reported p-values are 2-sided.

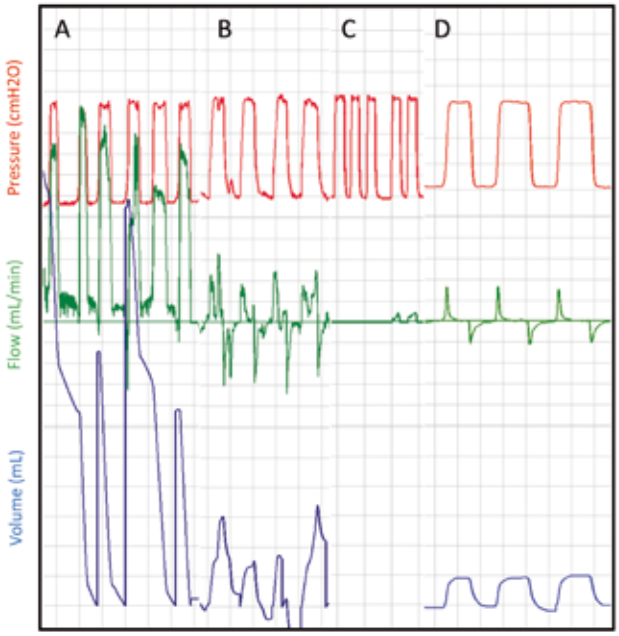

Figure 1. A: Ventilation with 100% leak, **B:** Ventilation with breathing, **C:** Ventilation with obstruction, **D:** Effective ventilation. Pressure is given in red, gas flow in green and volume in blue

Results

During the study period physiological parameters were recorded in 55 infants included in the trial. 12 infants were excluded from analysis because no PPV was given (4) or recordings were of poor quality (8). Thus, 43 infants were included of which 18 received PPV via a NT and 25 via a FM. Demographics are shown in table 1.

Table 1. demographics of infants ventilated using nasal tube or face mask.

interface	Gestational age (weeks)	Birth weight (grams)	Celestone full course (%)	Sex (% male)	Apgar 1 min	Apgar 5 min
NT (n = 18)	28 (25-29)	918 (793-1074)	78	61	3 (1-7)	7 (2-9)
Face mask (n = 25)	27 (24-29)	950 (691-1222)	56	40	5 (1-9)	7 (2-10)

Inflations

During the first 5 minutes infants in the NT group received 61 (45-116) inflations and 68 (28-105) inflations in the FM group (ns). In the NT group a total of 1566 inflations were analyzed, of which 501 (32%) coincided with breathing, in the FM group 1896 inflations were analyzed, of which 644 (34%) coincided with breathing.

A lower median (IQR) PIP was delivered when nasal tube was used (NT vs. FM: PIP 28.0 (24.0-31.2) cmH_2O vs. 29.3 (27.6-30.3) cmH_2O; p<0.0001), but PEEP was similar between the groups (5.3 (4.9-5.6) cmH_2O vs. 5.2 (4.2-6.6) cmH_2O; ns). Pressures given per hospital are shown in table 2.

Leak, and obstruction during inflations

Leak was significantly higher when inflations were given via a NT when compared to a FM (98 (33-100) % vs. 14 (0-39) % (p<0.0001)). The frequency of high leak (>60%) occurred more often when using a NT (67% vs. 21%; p<0.0001). Obstruction occurred more often when using a NT (8.2% vs. 1.1%; p<0.0001). Leak for each hospital is shown in table 2.

Tidal volumes delivered

Tidal volume delivered was significantly lower when inflations were given via a NT (0.0 (0.0-3.1) mL/kg vs. 9.9 (5.5-12.8) mL/kg (p<0.0001) and during inflations coinciding with breaths (4.4 (2.1-8.4) vs. 9.6 (5.4-15.2) mL/kg; p<0.0001). Tidal volume during breathing on CPAP was not significantly different (4.7 (2.8-6.9) vs. 4.8 (2.7-7.9) mL/kg; ns). Tidal volumes during inflations for each hospital are shown in table 2.

Table 2. Airway pressures (PIP and PEEP), leak and expiratory tidal volume (Vte) for nasal tube (NT) and face mask (FM) (** = p<0.0001) during inflations.

	RWH	**LUMC**
PIP NT (cmH_2O)	29.8 (27.9-33.4)	20.9 (18.9-24.0)
PIP FM (cmH_2O)	29.8 (28.4-30.3)	19.3 (18.9-20.1)
PEEP NT (cmH_2O)	5.3 (4.2-5.6)	5.5 (5.0-6.7)
PEEP FM (cmH_2O)	5.2 (4.7-6.6)	3.8 (2.0-7.0)
Leak NT (%)**	100 (67-100)%	0 (0-29)%
Leak FM (%)**	42 (0-100)%	11 (0-91)%
Vte NT (mL/kg) **	0 (0-2.3)	1.4 (0-4.8)
Vte FM (mL/kg) **	10.4 (6.8-12.7)	5.9 (2.2-15.2)

Breathing rate

Breathing rate was not different between NT and FM during PPV (13 (6-19) vs. 11 (3-17) breaths per minute; ns), during CPAP (24 (19-32) vs. 32 (24-42) breaths per minute; ns) and in total during the first 5 minutes (18 (10-25) vs. 19 (11-33) breaths per minute; ns).

Clinical effect

HR was not significantly different between the groups in the first 5 minutes after birth (table 3). In the NT group SpO_2 was lower in the first 2 minutes and higher at 3-5 minutes after start PPV (table 3). FiO_2 was switched earlier to 100% after start PPV in the NT group, but this did not reach significance (130 (113-188) s vs. 155 (103-252) s). However, infants receiving NT ventilation were given PPV later compared to the FM group (49 (40-92) vs. (76 (56-106) s; ns).

Table 3. Heart rate (HR), oxygen saturation (SpO_2) and inspired oxygen (FiO_2) for infants resuscitated using a nasal tube (NT) and face mask (FM) (* = $p<0.05$) Time points are in minutes after start of ventilation.

	1 minute	**2 minutes**	**3 minutes**	**4 minutes**	**5 minutes**
HR NT (bpm)	101 (63-129)	111 (76-136)	148 (128-154)	147 (123-150)	148 (133-157)
HR FM (bpm)	97 (71-144)	109 (94-142)	145 (120-161)	142 (113-153)	151 (127-159)
SpO_2 NT (%)	38 (16-58)*	34 (23-63)	61 (50-77)	80 (59-97)	89 (63-96)
SpO_2 FM (%)	62 (42-83)*	55 (44-88)	57 (46-95)	63 (48-83)	84 (68-95)
FiO_2 NT (%)	0	35	41	53	41
FiO_2 FM (%)	0	18	40	52	44

Discussion

In this study we described the physiological measurements in a subgroup of preterm infants included in a RCT comparing NT with FM as interface for PPV at birth (7). Recording RFM, pulse oximetry, oxygen given and video made us possible to observe the effectiveness and direct effect of PPV given. During PPV more often high leak and obstruction, leading to inadequate tidal volumes were observed. In contrast, when a FM was used tidal volumes were adequate, with only small leak and occasionally obstruction. There was no difference in HR, but SpO2 was lower in the first 2 minutes after PPV and this probably led, although not significant, to an earlier switch to FiO_2 1.0. These findings implicate that a NT as interface is less effective when compared to a FM for giving PPV to preterm infants at birth.

Previous studies (3;4;9) have reported respiratory function measurements during FM ventilation, but this is the first study where this is compared with PPV via NT. The RWH used higher inspiratory pressures than the LUMC and this lead also to higher Vte (4). The volumes delivered with inflations (without breaths occurring) via FM in the RWH were higher than what was recently reported (10.4 vs. 8.3 mL/kg). In the previous study similar pressures were used, but more leak observed previously which probably explains the lower tidal volume (9). When 4-8 mL/kg is considered as the safe range of tidal volume delivered (5), an initial pressure of 30 cmH_2O for PPV would then be too high for preterm infants. Also in LUMC we now report a higher Vte and lower mask leak when compared to our previous report (3). Both centers focused on face mask technique during local neonatal resuscitation trainings and this might have improved the mask technique of the caregivers in the delivery room. In addition, participating in a trial could also lead to better performances in mask ventilation (Hawthorne effect) (10). Occurrence of obstruction, assessed using the same definition as Schilleman *et al*, was rare in both hospitals when the FM was used (3).

We frequently measured high leak (flow remained positive during inflation) in the NT group. Although we observed on all of the video recording that effort was taken to close the contra-lateral nostril and mouth, it is possible that the nostril or mouth were not completely closed or air could still leave the mouth when it was tightly closed (11). Another possibility for the occurrence of high leak is that clinicians could only choose between 2 tube sizes and the tube could have been too small for certain infants. The frequent occurrence of obstruction probably contributed to the very low Vte when using a NT. Obstruction can occur when the NT is not properly placed with the tip against posterior nasopharyngeal wall. Although caregivers at both centers were trained in the use of a NT, it is possible that other centers, where NT has been used as standard of care in preterm infants at birth, will have different results. Indeed, due to a previous trial (12), caregiver in Leiden have been using the NT for a larger period than in the RWH, which could explain that we observed less leak when using a NT in Leiden.

There was a difference in direct clinical effect between the interfaces used. Although HR was similar in the first 5 minutes after start of PPV, we observed a lower SpO_2 in the first 2 minutes after start of PPV in the NT with an earlier switch to FiO_2 1.0. It is likely that the lower tidal volumes given via NT played a major role in this. It has been shown previously that most infants breathe during ventilation (3). The occurrence of spontaneous breathing during PPV might have mitigated the difference in clinical effect. Similar to previous reports (3;4) the spontaneous breaths increased the Vte of inflations. Indeed,

in the NT group Vte was considerably increased when a breath was concurrent with an inflation, which probably contributed to the effect of PPV given.

We were only able to make recordings in a small subgroup of infants included in the trial and it is possible that this would have led to a selection bias. However, which infant was recorded happened by chance as this depended whether there was time to set up equipment and if the researcher was available for the recording. In addition, the differences we observed between both interfaces are highly significant and we do not expect a larger group would have led to different results. Another limitation to the study is the possibility that when using a nasal tube air could leak during expiration, underestimating the volume that reached the lungs. However, we analyzed the flow waves breath by breath and observed very frequently that inspiratory flow waves were not returning to the baseline which indicated a large leak (figure 1).

Conclusion

By recording physiological parameter and video data in a subgroup of preterm infants included in a randomized trial comparing NT with FM as interface for delivering PPV, we made the following observations. When using the nasal tube 1) it took the caregiver longer before PPV could be given, 2) more frequent high leak and obstruction occurred, 3) more often inadequate tidal volumes were delivered, 4) lower SpO_2 in the first minutes during PPV and sooner the switch to FiO_2 1.0 was made. The occurrence of breathing during PPV might have mitigated the difference in clinical effect between the two interfaces and improved Vte delivered during inflations via NT. Based on these findings the use of a NT as an alternative interface for PPV in preterm infants at birth cannot be recommended.

References

1. Stichting Perinatale Registratie Nederland 2010 [cited 2013 Jan 12];Available from: URL: http://www.perinatreg.nl
2. Te Pas AB, Davis PG, Hooper SB, Morley CJ. From liquid to air: breathing after birth. J Pediatr 2008;152:607-11.
3. Schilleman K, van der Pot CJ, Hooper SB, Lopriore E, Walther FJ, Te Pas AB. Evaluating manual inflations and breathing during mask ventilation in preterm infants at birth. J Pediatr 2013;162:457-63.
4. Schmolzer GM, Kamlin OC, O'Donnell CP, Dawson JA, Morley CJ, Davis PG. Assessment of tidal volume and gas leak during mask ventilation of preterm infants in the delivery room. Arch Dis Child Fetal Neonatal Ed 2010;95:F393-F397.
5. Schmolzer GM, Te Pas AB, Davis PG, Morley CJ. Reducing lung injury during neonatal resuscitation of preterm infants. J Pediatr 2008;153:741-5.
6. Kamlin CO, Schilleman K, Dawson JA, Lopriore E, Donath SM, Schmolzer GM, *et al*. Mask versus nasal tube for stabilization of preterm infants at birth: a randomized controlled trial. Pediatrics 2013;132:e381-e388.
7. Kamlin CO, Schilleman K, Dawson JA, Lopriore E, Donath SM, Schmolzer GM, *et al*. Mask versus nasal tube for stabilization of preterm infants at birth: a randomized controlled trial. Pediatrics 2013;132:e381-e388.
8. Te Pas AB, Kamlin CO, Dawson JA, O'Donnell C, Sokol J, Stewart M, *et al*. Ventilation and spontaneous breathing at birth of infants with congenital diaphragmatic hernia. J Pediatr 2009;154:369-73.
9. Kaufman J, Schmolzer GM, Kamlin CO, Davis PG. Mask ventilation of preterm infants in the delivery room. Arch Dis Child Fetal Neonatal Ed 2013;98:F405-F410.
10. McCarney R, Warner J, Iliffe S, van HR, Griffin M, Fisher P. The Hawthorne Effect: a randomised, controlled trial. BMC Med Res Methodol 2007;7:30.
11. De Paoli AG, Lau R, Davis PG, Morley CJ. Pharyngeal pressure in preterm infants receiving nasal continuous positive airway pressure. Arch Dis Child Fetal Neonatal Ed 2005;90:F79-F81.
12. Te Pas AB, Walther FJ. A randomized, controlled trial of delivery-room respiratory management in very preterm infants. Pediatrics 2007;120:322-9.

CHAPTER 5

Influence of the hand squeeze and mask distensibility on tidal volume measurements during neonatal mask ventilation

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Neonatology 2013; 104:216-21

Abstract

Background: During mask ventilation the mask volume can vary as it is pressurized or when it is squeezed. The change in volume of the mask may affect tidal volumes delivered and difference in inspired (Vti) and expired tidal volumes (Vte).

Objectives: To investigate whether hand squeeze and distensibility of the mask during ventilation influences tidal volume measurements.

Methods: For both experiments we ventilated a leak free mask ventilation model using pressures of 25/5 cmH_2O through a t-piece. Vti and Vte were measured. A) 2 consultants performed mask ventilation with 1) consistent hand squeeze, 2) release during inflation and squeeze during expiration, 3) squeeze during inflation, release during expiration, and 4) gentle squeeze. B) 30 caregivers performed mask ventilation.

Results: Experiment A) Vti was different during consistent hold 1) 8.1 (0.4) and loose grip 4) 8.2 (0.3)mL) compared to squeezing during inflation 2) 18.9 (1.9), or expiration 3) 6.4 (3.5)mL). Variance in difference between Vti and Vte occurred only when mask was squeezed during inflation (-47.4 (101.5)%). Experiment B) volumes measured were consistent (intra-individual coefficient of variance (CV) 3-5%, inter-individual CV 9-10%). When comparing gas flow rate of 6 to 10 L/min, volumes increased approximately 8%, differences in Vti and Vte were small with both flow settings (-0.9 (-3.9-1.4)% and -0.6 (-3.3-1.8)% (ns)).

Conclusion: Variation in mask hold during mask ventilation can influence volume measurement, but this hardly occurs when testing caregivers.

Introduction

Adequate non-invasive ventilation using a mask as interface plays an important role in neonatal resuscitation (1-4). It has been suggested that a respiratory function monitor as a feedback device during neonatal resuscitation will be helpful and can inform the clinician about the tidal volumes delivered and whether mask leak occurs (5). Recently we observed that during mask ventilation caregivers exerted variable forces on the head, which might imply that the mask is squeezed on the face in a variable way (6). The hand squeeze and release could affect the volume of the masks of the mask. In addition, during inflation the mask is pressurized fast which could lead to some distention. Depending on how much flow is used (4), this could happen faster and cause more distention. When the inspiratory pressure is decreased the mask will possibly deflate.

We hypothesized that the interaction between 1) the pressurization and pressure release of the mask and 2) squeezing and release of the mask could result in a variable dead space of the mask affecting the tidal volumes administered during resuscitation and measured by a respiratory function monitor. This interaction could also lead to differences in inspired (Vti) and expired tidal volumes (Vte). This difference is used to calculate mask leak (6) and therefore under- or overestimation of mask leak could occur.

The aim of this study was to investigate whether during mask ventilation, using two different gas flow rates, there is a variation in dead space influencing tidal volumes measurement and the difference in Vti and Vte.

Methods

The study was performed in the Leiden University Medical Center (LUMC), Leiden, the Netherlands. This is a tertiary level perinatal center with an average of 400 neonatal intensive care admissions per year. Thirty registrars, fellows and nurses of the Neonatology department of the LUMC were asked to mask-ventilate a modified leak free manikin (Laerdal Resusci Baby, Laerdal, Stavanger, Norway). The manikin, representing a term newborn, had a modified leak free 50 mL test lung (Dräger, Lübeck, Germany) that was positioned so that chest excursions were visible. Non-distensible tubing connected the lung and mouth.

Our aim is to measure the effect of 'hand-squeeze' and release during mask hold, and pressurization or pressure release of the mask, which can decrease and increase dead space of the mask. To eliminate all other variables that could influence our measure-

ments, the mask (Laerdal size 0/1 round mask, Stavanger, Norway) was glued onto the face of the manikin, making the system leak free. Before each participant entered the room we confirmed that there was no leak in the system or between the mask and face. The mask was glued in such a way that volume changes of the mask were still possible. Positive pressure ventilation was applied using a T-piece infant resuscitator (Neopuff, Fisher & Paykel Healthcare, Auckland, New Zealand). The Neopuff was set to a peak inspiratory pressure (PIP) of 25 cmH_2O and a positive end expiratory pressure (PEEP) of 5 cmH_2O at both gas flow rates; gas flow rate was alternately set to 6 and 10 L/min and 21% oxygen was used.

Gas flow was measured using a Florian respiratory function monitor (Acutronic Medical Systems AG, Hirzel, Switzerland) which uses a hot-wire anemometer as a flow sensor with a dead space of ±1 mL. The hot-wire anemometer measures gas flow across the sensor by measuring differences in conductance. These measurements are then automatically integrated over time of the inflation or expiration to provide Vti and Vte. The manufacturer of the anemometer (Acutronic Medical Systems AG, Switzerland) indicates an accuracy of ±8% (manufacturer's data) (7). When measuring mask ventilation in the delivery room, the amount of mask leak would be expressed as the percentual difference in Vti and Vte ((Vti-Vte)/Vti*100%) which we address as difference in Vti and Vte as the system is leak free (8). The flow sensor was placed distally from the Neopuff, between the T-piece and the facemask. The output signals were digitized and recorded at 200 Hz using a customized data acquisition program (Spectra, Grove Medical Limited, Hampton, UK) (9). For experiment A) we tested if hand squeeze and release could cause a variation in tidal volume and difference in Vti and Vte we asked 2 consultants to ventilate the manikin at 8 L/min and 1) apply a consistent hand squeeze using the two point top hold (2), 2) deliberately let the mask expand during inflation and applying a hand squeeze during expiration, 3) deliberately apply a hand squeeze during inflation and let the mask extend during expiration and 4) apply only a gentle hand squeeze (a loose grip). During all episodes we recorded 30 s of ventilation. Both the selected consultants have more than 10 years of experience in mask ventilation. Furthermore, we empirically tested the maximum volume change by filling the glued mask with water up to the tubing attached to the mouth, which was blocked, and varying mask squeeze from maximal to minimal using a Laerdal 0/1 facemask.

For experiment B) 30 participants were asked to ventilate the manikin. These participants were all experienced in mask ventilation and are trained four times a year in mask ventilation using the two-point top hold. They were randomly selected from the medical staff at work on the days of recording. The mask was held in position by one of the inves-

tigators when participants entered the room. The participants were not fully informed about the aim of this study. All participants were told that solely the effect of mask hold was investigated, not mask position and that mask leak could still occur. The screen of the respiratory function monitor and the laptop were not visible for the participants. All participants were asked to ventilate the manikin for 30 seconds on two occasions: using a gas flow rate of 6 L/min and 10 L/min.
Since both experiment A and B were conducted using a manikin no ethical approval was required.

Statistical analysis
Data were analyzed using SPSS for Windows version 17.0.0. The results are presented as mean (SD) or median (range). Mean percentage of difference in Vti and Vte were compared using a paired t-test. To quantify the intra- and inter-individual differences an ANOVA was used. To express variability in measurements between caregivers (inter-individual) and between inflations per caregiver (intra-individual) we used the coefficient of variation (CV), which was calculated as (SD/mean)*100%. A CV <5% was regarded to reflect good agreement and a CV <10% to reflect acceptable agreement. A p-value <0.05 was considered statistically significant. Reported p-values are two-sided.

Results

Experiment A
Measured Vti were significantly different from consistent hold (1) 8.1 (0.4), 4) 8.2 (0.3) mL) when squeezed during inflation or expiration ((2) 18.9 (1.9), 3) 6.4 (3.5) mL; p<0.0001). Variance in difference between Vti and Vte occurred only when mask was squeezed during inflation and released during expiration with -47.4 (101.5)% (table 1). Maximal volume change measured by filling the mask with water was 21 mL (out of a total dead space of 40 mL). Figure 1a illustrates a measurement during a consistent hold and figure 1b during mask squeeze during inflation and release during expiration.

Table 1. Ventilation of the manikin by 2 consultants applying different mask holds. A) consistent hold, B) allowing mask distention during inflation and squeeze during expiration, C) squeeze during inflation and distention during expiration and D) loose grip. * = P <0.01

	Consistent hold	Squeeze expiration	Squeeze inflation	Loose grip
Vti (mL)	8.1 (0.4)	18.9 (1.9)	6.4 (3.5)*	8.2 (0.3)
Vte (mL)	8.3 (0.5)	19.0 (1.5)	6.3 (1.9)*	8.4 (0.2)
Leak (%)	-2.7 (7.4)	-1.1 (8.4)	-47.4 (101.5)	-1.6 (3.2)

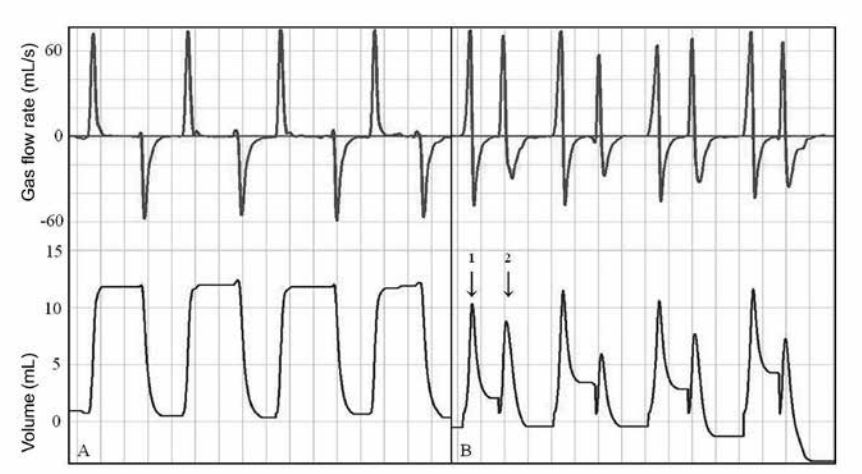

Figure 1. Recordings of 2 ventilation cycles in experiment A (gas flow and volume are given). **A** = consistent hand squeeze, **B** = squeeze during inflation and release during expiration. 1= inspiratory flow interruption by squeeze and inflation, 2= expiratory flow interruption by release.

Experiment B

Participants

In total 1177 inflations were analysed. These were 551 inflations (±37 inflations per minute) at a gas flow rate of 6 L/min and 626 inflations (±42 breaths per minute) at a gas flow rate of 10 L/min. We obtained recordings from 30 participants (10 consultants, 5 registrars and 15 neonatal intensive care unit nurses). All participants were trained and experienced in mask ventilation.

Tidal volume

Increasing gas flow rate from 6 to 10 L/min led to a small but significant increase in Vti from 8.1 (0.8)mL to 8.8 (0.8)mL ($p<0.01$) and Vte from 8.2 (0.8) mL to 8.9 (0.8)mL ($p<0.01$) (figure 2).

The intra-individual CV was 4 (1-7)% for Vti and 5 (1-12)% for Vte at a gas flow rate of 6 L/min. At a gas flow rate of 10 L/min the CV was 3 (1-6)% for Vti and 4 (1-10)% for Vte (figure 3). At both gas flow rates the intra-individual CV showed good agreement.

The inter-individual CV was 9%, which reflects acceptable agreement for both Vti and Vte at a gas flow rate of 6 L/min. At a gas flow rate of 10 L/min inter-individual CV for Vti was 9% and for Vte 10%, which in all cases indicates acceptable agreement (figure 4).

Difference in Vti and Vte

Median difference in Vti and Vte during mask ventilation using a flow of 6 L/min and 10 L/min was respectively -0.9 (-3.9-1.4)% and (-0.6 (-3.3-1.8)% (ns).

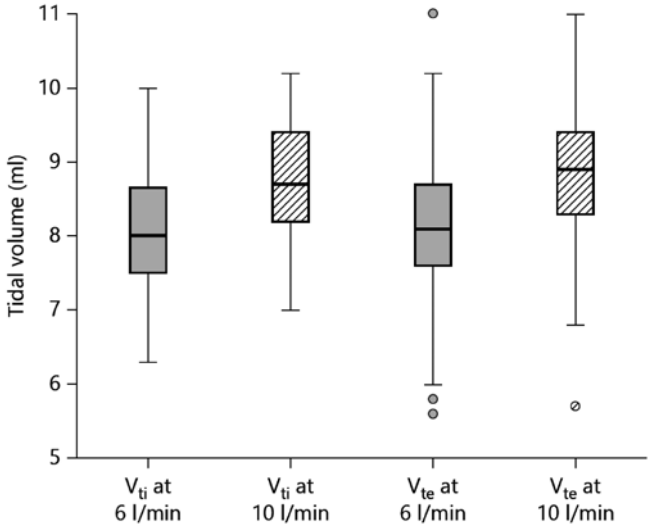

Figure 2. Changes in tidal volumes during positive pressure ventilation at a flow of 6 L/min (grey bars) and at a flow of 10 L/min (hatched bars). The box plots show median values (solid black bar), inter quartile range (margins of box), and range of data.

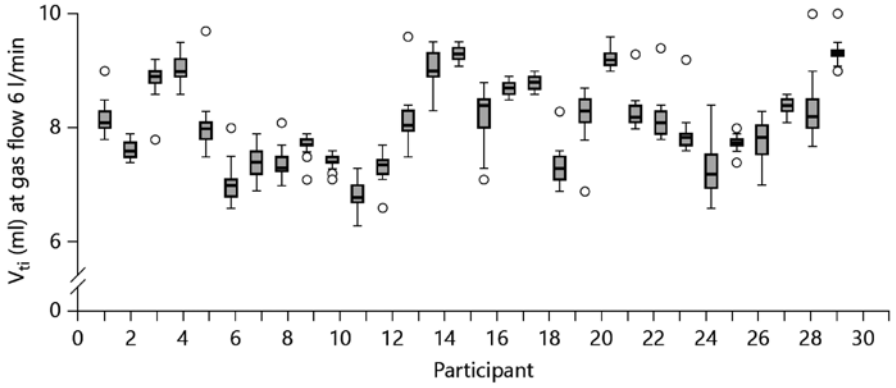

Figure 3. Changes in inspiratory tidal volumes during inflations at a gas flow rate of 6 L/min per participant. The box plots show median values (solid black bar), inter quartile range (margins of box), and range of data.

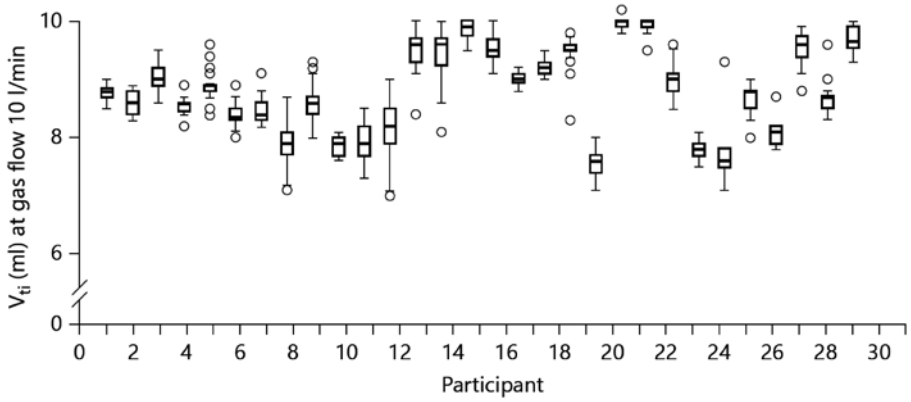

Figure 4. Changes in inspiratory tidal volumes during inflations at a gas flow rate of 10 L/min per participant. The box plots show median values (solid black bar), inter quartile range (margins of box), and range of data.

Discussion

In this study we have evaluated the effect of different applications of squeeze and release by two practitioners on tidal volumes and the difference in Vti and Vte. Also, we have tested the occurrence of variations in tidal volumes and difference in Vte-Vti during ventilation by 30 participants at two different gas flow rates. The maximal volume change between a collapsed and a distended mask is 21 mL.

We observed a difference in measured tidal volumes when hand squeeze and release occurs during ventilation when compared to a consistent hold. Also, when hand squeeze occurred during inflation and was released during expiration we observed a large variation in Vti-Vte difference. If this occurs during mask ventilation, tidal volume to the lung and the amount of mask leak could be over or underestimated. However, when testing caregivers, the measured tidal volumes were quite consistent. Also, the differences between Vti and Vte were minimal. There was some increase in tidal volumes when flow was increased, but the clinical significance of this is questionable. Apparently when caregivers, unaware of the purpose of this study, ventilate the manikin as they normally would, there was little variation in tidal volumes and difference in tidal volumes which might implicate that there was minimal variation in mask squeeze and gaseous distention of the mask.

When, in experiment A, hand squeeze occurred during expiration and was released during inflation the increased dead space of the mask explains the larger tidal volumes

as this is now added to the total measured volume. However, when hand squeeze occurred during inflation and release during expiration, smaller tidal volumes were measured. The squeeze and release caused a flow into the opposite direction and did not only change the flow rate but also interrupted inflation and expiration, which led to measurement of two inflation-expiration cycles instead of one (figure 1b). This also led to unequal in-and expiratory flow waves leading to large Vti-Vte differences. In addition, it is possible that the change in gas flow rate put the flow measurement into different regions of the measurement sensitivity curve, thereby giving different measurements. We speculate that spontaneous breathing interfering with mask ventilation can have similar effects on flow measurements. Indeed, McCallion *et al*. described that during expiratory breaking of infants (causing changes in gas flow) tidal volumes measurements became inaccurate (7;10).

In experiment B the effect of gaseous distention and hand squeeze of the face mask during the administration of PPV caused small variation in tidal volumes delivered providing a CV with good agreement. The observed variations are within the measurement error of the respiratory function monitor and are probably clinically not relevant.

te Pas *et al*. reported that leak decreased using a lower gas flow rate (5 L/min) during PPV when compared to a higher gas flow rate (10 L/min) (11). It was speculated that the higher pressurization, leading to larger gas distension of the mask and thus more bouncing, would explain higher incidence of leak by breaking the seal (11). However, our current findings do not support this relationship. We observed a small increase in measured tidal volumes and the Vti-Vte difference remained very small (within the 8% accuracy level of the hot wire flow meter). When we tested participants in experiment B, we did find a significant difference in Vti and Vte, between participants or inflations given by the same participant. This difference is however not clinically important. Also, comparing a low versus a higher gas flow rate, potentially causing more distention and bouncing of the mask, did not significantly influence the difference in Vti and Vte and tidal volumes significantly. Apparently there is little variation in tidal volumes and the observed difference is within the 8% accuracy level of the respiratory function monitor. It is possible that the consistent "hand squeeze" reduces the effect of pressurization and release.

O'Donnell *et al*. tested the accuracy of the hot wire anemometer during mask ventilation and observed that during inflations with small leak (<51%) a larger change in tidal volume at the face mask was observed compared to the tidal volume that entered the test lung (8). It was concluded that a part of the administered volume distended the mask and therefore did not enter the lungs. The difference in tidal volumes measured at

the mask and in the test lung however decreased as leak increased. However, we could not confirm this in our study. We eliminated leak in our study and we observed that intra- and inter individual variance of the tidal volumes was small reflecting good and acceptable agreement. Therefore, it is likely that in the study of O'Donnell *et al*. (8) the volume differences were caused by the occurrence of leak in both in- and expiration and not by distention.

To test our hypothesis, we needed to eliminate other factors influencing measurements and are therefore bound to a manikin model. The manikin has its limitations (3) and there is no guarantee that we will find the same results in a clinical setting. Mask hold of caregivers, during a stressful resuscitation in the delivery room, could be different than when they ventilate a manikin. Also, although participants were told that leak was possible, less effort could have been provided to reduce mask leak given that the mask was fixated on position due to the visibility of the pressure gauge on the Neopuff. However, participants were taught that a decrease in pressure occur only when there is a large mask leak, as a recent study has shown performed in our unit (10).

Conclusion

We demonstrated in a leak free mask ventilation model that variation in hand squeeze and mask distensibility could influence volume measurements and difference between Vti and Vte. However, when testing caregivers very little variation occurs and not relevant to take into account when measuring tidal volume during mask ventilation.

Acknowledgements

The authors thank the staff of the Neonatal unit, Leiden University Medical Center, Leiden, for their participation and Dr. E.W. van Zwet for his advice on statistics.

References

1. Te Pas AB, Walther FJ. Ventilation of very preterm infants in the delivery room. 2006;2:187-197.
2. Te Pas AB, Davis PG, Hooper SB, Morley CJ. From liquid to air: breathing after birth. J Pediatr 2008;152: 607-11.
3. Schilleman K, Witlox RS, Lopriore E, Morley CJ, Walther FJ, Te Pas AB. Leak and obstruction with mask ventilation during simulated neonatal resuscitation. Arch Dis Child Fetal Neonatal Ed 2010;95:F398-F402.
4. Schilleman K, Schmolzer GM, Kamlin OC, Morley CJ, Te Pas AB, Davis PG. Changing gas flow during neonatal resuscitation: a manikin study. Resuscitation 2011;82:920-4.
5. Schmolzer GM, Morley CJ, Wong C, Dawson JA, Kamlin CO, Donath SM, *et al*. Respiratory function monitor guidance of mask ventilation in the delivery room: a feasibility study. J Pediatr 2012;160:377-81.
6. van Vonderen JJ, Kleijn TA, Schilleman K, Walther FJ, Hooper SB, Te Pas AB. Compressive force applied to a manikin's head during mask ventilation. Arch Dis Child Fetal Neonatal Ed 2011.
7. Manual, Florian Respiration Monitor. Acutronics Medical Systems AG, Hirzl, Switzerland.
8. O'Donnell CP, Kamlin CO, Davis PG, Morley CJ. Neonatal resuscitation 1: a model to measure inspired and expired tidal volumes and assess leakage at the face mask. Arch Dis Child Fetal Neonatal Ed 2005;90:F388-F391.
9. Main E, Castle R, Stocks J, James I, Hatch D. The influence of endotracheal tube leak on the assessment of respiratory function in ventilated children. Intensive Care Med 2001;27:1788-97.
10. McCallion N, Lau R, Dargaville PA, Morley CJ. Volume guarantee ventilation, interrupted expiration, and expiratory braking. Arch Dis Child 2005;90:865-70.
11. Te Pas AB, Schilleman K, Klein M, Witlox RS, Morley CJ, Walther FJ. Low versus high gas flow rate for respiratory support of infants at birth: a manikin study. Neonatology 2011;99:266-71.

CHAPTER 6

Monitoring tidal volumes in preterm infants at birth: mask versus endotracheal ventilation

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Submitted

Abstract

Objective: Upper airway distention during mask ventilation could reduce gas volumes entering the lung compared to ventilation via an endotracheal tube. Therefore, respiratory tract volumes were measured in lambs and tidal volumes were compared in preterm infants before and after intubation.

Design: In 7 preterm lambs, volumes of the airways (oropharynx, trachea, lungs) were assessed. In 10 preterm infants delta pressures, tidal volumes and leak were measured during ventilation 2 minutes before (mask ventilation) and 2 minutes after intubation (endotracheal ventilation). Inflations coinciding with breaths were excluded.

Outcome measures: Amount of upper airway distention in lambs and differences in inspiratory and expiratory tidal volume before and after intubation.

Results: In lambs, the combined trachea and oropharynx contributed to 14 (12-21) % (median (IQR)) whereas the oropharynx contributed to 9 (7-10) % of the total tidal volume measured at the mouth. In preterm infants, inspiratory (11.1 (7.9-22.6) vs. 5.8 (3.9-9.6) mL/kg ($p=0.01$)) and expiratory (8.3 (6.8-15.4) vs. 4.9 (3.9-9.6) mL/kg ($p=0.02$)) tidal volumes were significantly larger during mask ventilation compared to endotracheal ventilation. Leak was 18.7 (3.3-28.7) % before vs. 0 (0-2.3) % after intubation ($p<0.0001$). Delta pressure was 23.7 (20.8-25.6) cmH_2O before vs. 24.8 (20.8-26.0) cmH_2O after intubation (ns). During mask ventilation expiratory tidal volume increased from 10.0 (5.4-15.6) to 11.3 (7.6-17.0) mL/kg ($p=0.01$), but remained unchanged during endotracheal ventilation.

Conclusion: During neonatal mask ventilation, distention of the upper respiratory tract contributes to the tidal volumes measured and should be taken into account when targeting tidal volumes during mask ventilation.

Introduction

Many preterm infants receive positive pressure ventilation at birth administered via a face mask (1) While this ventilation is commonly evaluated based on chest excursions, this is considered a poor proxy for the tidal volumes administered (2). As inappropriate tidal volumes given at birth increase the risk of lung and brain injury (3), respiratory function monitoring is now recommended to minimize the likelihood of injurious ventilation (4).

Although a tidal volume range of 4-8 mL/kg is currently recommended for neonatal ventilation at birth (5), there is little evidence indicating what tidal volumes are safe in preterm infants. The recommended range is based on spontaneous breathing preterm infants on continuous positive airway pressure (6) and intubated infants in the neonatal intensive care unit receiving volume guaranteed ventilation (7;8).. However, in contrast to spontaneous breathing and endotracheal ventilation, before gas can flow into the lung during mask ventilation, the oropharynx and part of the trachea must be pressurized. As these structures have a finite compliance, pressurization of the upper respiratory tract may cause significant distension resulting in an increase in volume. As a result, it is possible that the proportion of the tidal volume entering and ventilating the gas exchange regions of the lung could be reduced, which should be taken into account when targeting tidal volumes during mask ventilation.

We hypothesized that during face mask ventilation, pressurization of the oropharynx and trachea forms a significant proportion of the tidal volume measured at the mouth opening in deceased newborn lambs. Upon confirming this hypothesis, we then investigated whether this may also occur in infants. To test this, we examined whether equivalent inflation pressures resulted in larger tidal volumes during face mask ventilation compared to ventilation via an endotracheal tube. This was achieved by measuring tidal volumes immediately before and after intubation of preterm infants at birth.

Methods

Lamb study

Seven preterm lambs (Border-Leicester × Merino) born by caesarian section after 123-124 days (term is ~147 days) and ventilated for 2 hours. All lambs were ventilated for at least 2 hours using a tidal volume of 4-8 mL/kg before they were killed by an overdose of pentobarbitone sodium (130 mg/kg IV).

The lambs' esophagus was occluded at the cricoid cartilage. Leak free occlusion was tested before experiments were commenced. Lambs were ventilated using a Neopuff T-piece resuscitator (Neopuff, Fisher & Paykel Healthcare, Auckland, New-Zealand) via a close fitting face mask (DLC Australia Pty Ltd, Victoria, Australia). Tidal volumes were measured using a Florian respiratory function monitor (Acutronic Medical Systems, AG, Switzerland) placed in the respiratory circuit between the face mask and the T-piece of the Neopuff. Gas flow signals were recorded using PowerLab data acquisition system (Powerlab/8SP, AD Industries, Castle Hill, Australia). Inflations were administered with constant peak inflation pressures (PIP) of 35 cmH_2O and positive end expiratory pressures (PEEP) of 5 cmH_2O. The following measurements were performed: 1) the tidal volume was measured during ventilation of the total lung after occlusion of the esophagus, 2) the upper respiratory tract (oropharynx and trachea) were ventilated after occlusion of the trachea above the carina and 3) the oropharynx was ventilated after occlusion of the airway tract at the glottis.

All experimental procedures on animals were approved by the Monash University Animal Welfare Committee.

Human infant study

Infants < 32 weeks of gestation were included when 1) positive pressure ventilation was given via a face mask and 2) they were intubated in the delivery room. All infants were ventilated according to local guidelines (PIP 25 cmH_2O and PEEP 5 cmH_2O and at a rate of 40-60 inflations per minute) using a T-piece ventilator (Neopuff, Fisher and Paykel, Wellington, New Zealand). Pressure and volume were recorded using a Florian respiratory monitor (Acutronic Medical Systems, AG, Switzerland) as described previously (9). The flow sensor was placed distally between the T-piece of the Neopuff and an appropriate size face mask (Laerdal 0/0 or 0/1, Laerdal, Stavanger, Norway) or at the end of an appropriate size endotracheal tube (Oral/Nasal tracheal cuffless tube 2.5 or 3.0, Mallinckrodt, Covidien, Tullamore, Ireland). Infants were nasally intubated and depth of insertion was performed according to the estimated birth weight, using the "7-8-9 rule" (10), with the position of the tube being confirmed by chest x-ray upon arrival at the NICU.

In neonates the gas flow signal was recorded at 200 Hz and integrated to provide inspired and expired tidal volumes using Spectra software (Spectra, Grove Medical Limited, Hampton, UK). Leak was calculated as the difference between inspired- (Vti) and expired tidal volume (Vte) (leak = [((Vti-Vte)/Vti)*100]. PEEP and PIP were measured to calculate delta pressures (PIP-PEEP). Inflations during ventilation were analyzed from 2 minutes before (mask ventilation) and until 2 minutes after intubation (endotracheal

ventilation). Tidal volumes were analyzed on a breath-by-breath basis. Spontaneous breaths and inflations where breaths coincided were identified according to previous described patterns (6) and excluded from this analysis. To assess loss of functional residual capacity after intubation Vte of the first 10 inflations was compared with Vte of the last 10 inflations of face mask and endotracheal ventilation during the 2 minute period.

Oxygen saturations (SpO_2) were measured using a Masimo Radical 7 pulse oximeter (Masimo, Irvine, CA, USA) with a LCNS Neo-3 sensor (Masimo) placed around the ulnar aspect of the infant's right wrist. Average Fraction of inspired oxygen (FiO_2) and SpO_2 were compared from 2 minutes before intubation until 2 minutes after intubation. FiO_2 was measured using a Teledyne oxygen analyzer (Teledyne technologies, Thousand oaks, CA, USA).

The local institutional review boards of the Leiden University Medical Center (Commissie Medische Ethiek, Leids Universitair Medisch Centrum) approved physiological recordings at birth in the delivery room when respiratory support was necessary for research purposes. Written parental consent was obtained before birth, or if not appropriate as soon as possible after birth.

Statistical analysis

Data were analysed using SPSS (IBM, version 20.0.0, Chicago, Illinois). Results are presented as mean (standard deviation (SD)), median (range) or median (IQR) where appropriate. Vti and Vte were averaged for each infant and lamb to give each subject similar weight. Data were compared using a Mann-Whitney U test for non-normally distributed paired data and a related samples Friedman 2-way analysis of variance for paired samples.

Results

Seven lambs were included (median (IQR) weight 3570 (3480-4040) grams). Tidal volume of the total respiratory system was 19.1 (11.8-25.9) mL/kg. The tidal volume of the combined trachea and oropharynx was 4.1 (2.0-4.9) mL/kg, which is 14 (12-21) % of the tidal volume measured during ventilation of the entire respiratory system. The tidal volume of the oropharynx only was 2.3 (1.3-2.7) mL/kg, which is 9 (7-10) % of the tidal volume measured during ventilation of the entire respiratory system. No leak occurred during this ventilation period.

Recordings of 206 infants were reviewed for intubations. 17 infants were intubated in the delivery room. Of these, 7 infants needed to be excluded: 3 infants were ventilated via

a nasal tube and in 4 infants breathing frequently occurred and coincided with almost all inflations. Thus, 10 newborn infants were included (50% males, median (range) GA 26 (24-31) weeks, mean (SD) birth weight 902 (355) grams). The average duration taken to intubate the infants was 63 (28) s. Tube positions were checked in all 10 infants upon arrival at the neonatal intensive care unit, location was considered correct and all were located in the trachea above the carina.

Inflations

In total 1586 inflations were analyzed (843 before intubation and 743 after intubation). PIP was 28.8 (25.5-32.7) cmH_2O before vs. 29.8 (25.0-30.8) cmH_2O after intubation (ns) and PEEP was 6.0 (4.5-7.1) before vs. 5.9 (4.4-8.1) after intubation (ns). Delta pressure (PIP - PEEP) was 23.7 (20.8-25.6) before vs. 24.8 (20.8-26.0) cmH_2O after intubation (ns). Median (IQR) leak was 18.7 (3.3-28.7) % before vs. 0 (0-2.3) %) after intubation ($p<0.0001$).

Tidal volumes

Both the Vti and Vte measured during mask ventilation were significantly higher compared to endotracheal tube ventilation (Vti; 11.1 (7.9-22.6) vs. 5.8 (3.9-9.6) mL/kg ($p<0.01$)) and Vte; 8.3 (6.8-15.4) vs. 4.9 (3.9-9.6) mL/kg ($p =0.02$)) (figure 1). During endotracheal ventilation Vti and Vte were respectively 60 (44-81) % and 54 (29-87) % of the volumes measured during face mask ventilation.

There was a small, but significant, increase in Vte measured during the first 10 inflations compared to the last 10 inflations (10.0 (5.4-15.6) mL/kg vs. 11.3 (7.6-17.0) mL/kg ($p<0.05$) of the two minute mask ventilation period. However, during endotracheal ventilation, the measured Vte did not change ((5.6 (3.7-13.5) mL/kg vs. 5.5 (3.5-11.5) mL/kg) (ns).

Oxygen saturation and fraction of inspired oxygen

Average SpO_2 was not significantly different in the 2 minutes before vs. the 2 minutes after intubation (69 (21) vs. 72 (23) % (ns)). Also, FiO_2 was not significantly different in the 2 minutes before vs. the 2 minutes after intubation (100 (93-100)% vs. 100 (95-100)% (ns)).

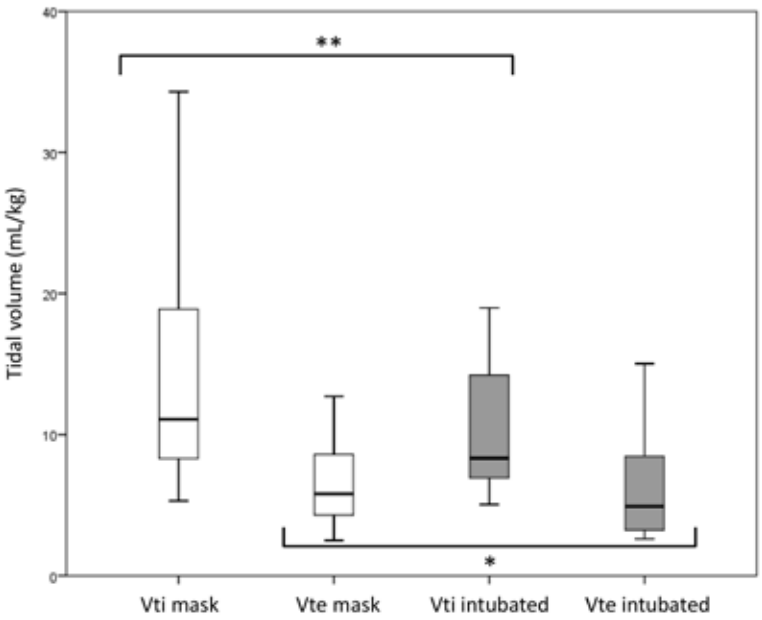

Figure 1. inspiratory (Vti) and expiratory (Vte) tidal volumes measured 2 minutes before (white) and 2 minutes after intubation (grey). The box plots show median values (solid black bar), interquartile range (margins of box), and range of data. * p=0.02, ** p<0.01.

Discussion

The tidal volumes measured in spontaneous breathing infants and ventilated intubated infants have been used to recommend the volume ranges that should be used during mask ventilation of preterm infants at birth. To our knowledge, differences in the delivered tidal volumes during mask and endotracheal ventilation have not previously been investigated. We observed that, during positive pressure ventilation, the measured tidal volumes were significantly higher during mask compared to endotracheal ventilation, despite the delta pressure remaining very similar. In ventilated newborn lambs we demonstrated that pressurization of the oropharynx and trachea can account for part of the measured tidal volumes differences between face mask endotracheal tube ventilation. Thus, it is likely that distention of the upper respiratory tract partly explains the observed differences in tidal volumes. We speculate that inadequate gas exchange could occur during mask ventilation when this extra volume is not taken into account.

During face mask ventilation, the entire respiratory system pressurizes, such that by end inflation pressures should be equal at all points in the respiratory tree, including the upper airway above the glottis. In newborn infants, particularly preterm infants, the trachea, pharynx and larynx contain little cartilage and are therefore more compliant compared to the adult upper respiratory tract (11) As such pressurization of the upper respiratory tract will cause distention and potentially increase the risk of damage and inflammation (12;13) Also as the oral cavity is compliant, application of an inflating pressure should cause distention of the upper respiratory tract as it pressurizes. Part of the higher expiratory volume we observed during mask ventilation is probably due to deflation of the upper respiratory tract as it depressurizes during expiration.

In lambs compared to infants a relatively smaller amount of volume was measured during ventilation of the upper respiratory tract (14% vs. 65%)). This could be explained by differences in anatomy and upper airway compliances between preterm lambs and infants, which determine differences in upper airway distention. Also, it is possible that during mask ventilation of infants, a large amount of air enters the esophagus and stomach. To avoid this problem, in the lambs we obstructed the esophagus, but this prevented us from calculating the relative contribution of flow in the trachea and esophagus to the measured tidal volumes. However, as it is commonly observed that the abdomen becomes distended during incorrect ventilation, it is unlikely that air entering the stomach is returned during expiration and contributes to Vte.

Other phenomena, besides distention of upper airways and trachea, could have influenced the measured differences in volumes during mask and endotracheal ventilation. During the intubation procedure a loss in functional residual capacity could have occurred leading to a decrease in compliance. If this did occur, we then would have expected an increase in tidal volumes in the 2 minutes of ventilation after intubation, but these remained similar. In addition, there were no significant differences in SpO_2 and FiO_2 levels before, during and after intubation, making a loss in functional residual capacity unlikely. Leak could have influenced the volumes measured, but we observed larger leak during mask than endotracheal ventilation and thus this does not explain the smaller volumes during endotracheal ventilation. Finally, distention of the mask during inflations could have influenced tidal volume measurement (14), but it was reported that the contribution of mask distention to tidal volumes is limited (15)

The current recommended range of tidal volumes (4-8 mL/kg) (5) is based on measurements performed in spontaneous breathing infants shortly after birth (6) and intubated preterm infants. However during inspiration a sub-atmospheric pressure in the lungs

and surrounding tissues is created and the transpulmonary pressure gradient causes air to enter the lung. The upper airway and trachea are not pressurized and less volume is needed to aerate the distal airways. (16). During endotracheal ventilation smaller amounts of tidal volumes are measured (3.8 (2.8-4.7) mL/kg) (8) and recommended (4-5 mL/kg) (7). However, during endotracheal ventilation the oropharynx and trachea are largely bypassed and the majority of the measured volume is volume directed into the lungs.

We speculate that, to achieve adequate ventilation, larger tidal volumes are needed during ventilation procedures that pressurize the upper airway to nullify the effect of upper airway distention. It is possible that when the current recommended tidal volumes are used during face mask ventilation, ventilation is mainly restricted to the upper airway and trachea which limits penetration of air into the distal airways. Indeed, this could explain why the SpO_2 remained low and a high FiO_2 was needed during mask ventilation in these infants, despite them receiving apparently large tidal volumes. Further studies are needed before a range of larger tidal volumes can be recommended, especially when considering the fact that distention of the trachea could cause injury in preterm infants (12;13)

The limited number of intubations in the delivery room recorded (8% of all recordings) made it difficult to perform a large study. Currently, a multicenter trial is in progress, examining whether a monitoring will increase the proportion of tidal volumes within a predefined "safe range" of 4-8 mL/kg during ventilation of very preterm infants (< 29 weeks of gestation) in the delivery room (NTR 4104). This trial could provide more data concerning the differences in tidal volumes given during face mask and endotracheal ventilation.

Conclusion

Vte was significantly larger during face mask compared to endotracheal ventilation. This is likely to be caused by distention of the upper respiratory tract during face mask ventilation as shown in a preterm lamb model. Our study suggests that the distention of the upper respiratory tract could be taken into account when targeting tidal volumes during mask ventilation. The observed range in tidal volume in spontaneous breathing preterm infants on continuous positive airway pressure should probably not be extrapolated to infants needing mask ventilation, but further studies are warranted to find the appropriate target range.

References

1. te Pas AB, Davis PG, Hooper SB, Morley CJ. From liquid to air: breathing after birth. J Pediatr 2008;152: 607-11.
2. O'Donnell CP, Davis PG, Lau R, Dargaville PA, Doyle LW, Morley CJ. Neonatal resuscitation 2: an evaluation of manual ventilation devices and face masks. Arch Dis Child Fetal Neonatal Ed 2005;90:F392-F396.
3. Keszler M. Volume-targeted ventilation. J Perinatol 2005;25 Suppl 2:S19-S22.
4. Schmolzer GM, Kamlin OC, Dawson JA, te Pas AB, Morley CJ, Davis PG. Respiratory monitoring of neonatal resuscitation. Arch Dis Child Fetal Neonatal Ed 2010;95:F295-F303.
5. Schmolzer GM, te Pas AB, Davis PG, Morley CJ. Reducing lung injury during neonatal resuscitation of preterm infants. J Pediatr 2008;153:741-5.
6. te Pas AB, Davis PG, Kamlin CO, Dawson J, O'Donnell CP, Morley CJ. Spontaneous breathing patterns of very preterm infants treated with continuous positive airway pressure at birth. Pediatr Res 2008;64:281-5.
7. Keszler M, Abubakar K. Volume guarantee: stability of tidal volume and incidence of hypocarbia. Pediatr Pulmonol 2004;38:240-5.
8. McCallion N, Lau R, Morley CJ, Dargaville PA. Neonatal volume guarantee ventilation: effects of spontaneous breathing, triggered and untriggered inflations. Arch Dis Child Fetal Neonatal Ed 2008;93:F36-F39.
9. Schilleman K, van der Pot CJ, Hooper SB, Lopriore E, Walther FJ, te Pas AB. Evaluating manual inflations and breathing during mask ventilation in preterm infants at birth. J Pediatr 2013;162:457-63.
10. Peterson J, Johnson N, Deakins K, Wilson-Costello D, Jelovsek JE, Chatburn R. Accuracy of the 7-8-9 Rule for endotracheal tube placement in the neonate. J Perinatol 2006;26:333-6.
11. Barash PG, ullen BF, toelting RK, Cahalan M, Stock MC. Clinical Anesthesia. 6 ed. Wolters Kluwer Health; 2009.
12. Lim LH, Wagner EM. Airway distension promotes leukocyte recruitment in rat tracheal circulation. Am J Respir Crit Care Med 2003;168:1068-74.
13. Wagner EM, Jenkins J. Effects of airway distension on leukocyte recruitment in the mouse tracheal microvasculature. J Appl Physiol (1985) 2007;102:1528-34.
14. O'Donnell CP, Kamlin CO, Davis PG, Morley CJ. Neonatal resuscitation 1: a model to measure inspired and expired tidal volumes and assess leakage at the face mask. Arch Dis Child Fetal Neonatal Ed 2005;90:F388-F391.
15. van Vonderen JJ, Kamar R, Schilleman K, Walther FJ, Hooper SB, te Pas AB. Influence of the hand squeeze and mask distensibility on tidal volume measurements during neonatal mask ventilation. Neonatology 2013;104:216-21.
16. Hooper SB, Siew ML, Kitchen MJ, te Pas AB. Establishing functional residual capacity in the non-breathing infant. Semin Fetal Neonatal Med 2013;18:336-43.

PART 2

Breathing

CHAPTER 7

Preterm infants failing on CPAP show respiratory fatigue at birth

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Submitted

Abstract

Background: Continuous positive airway pressure (CPAP) is used to stabilise preterm infants at birth, but many develop respiratory distress and later require increased support. We investigated whether breathing pattern and effort at birth is different for infants who fail CPAP <48 hours after birth.

Methods: Respiratory function recordings of 32 preterm infants were reviewed (15 failed CPAP). Frequency and duration of expiratory holds (EHs) and tidal volumes (VT), peak inspiratory flows, CPAP-level and FiO_2-levels were analysed.

Results: EH incidence increased <6 minutes after birth and remained stable thereafter. EH peak inspiratory flows and VT were similar between CPAP-fail and CPAP-success infants. At 9-12 mins, CPAP-fail infants more frequently used smaller VTs, 0-9ml/kg and required higher peak inspiratory flows. However, CPAP-success infants often used large VTs (>9 ml/kg) with higher peak inspiratory flows than CPAP-fail infants (71.8±15.8 vs. 15.5±5.2 ml/kg.s, $p<0.05$). CPAP-fail infants required higher FiO_2 (0.31±0.03 vs. 0.21±0.01), higher CPAP pressures (6.62±0.3 vs. 5.67±0.26 cmH_2O) and more positive pressure-delivered breaths (45±12 vs 19±9%) ($p<0.05$)

Conclusion: At 9-12 minutes after birth, CPAP-fail infants more commonly used lower VTs and required higher peak inspiratory flow rates while receiving greater respiratory support. VT were less variable and larger VT were infrequently used reflecting early signs of fatigue.

Introduction

Continuous positive airway pressure (CPAP) is progressively replacing intubation and mechanical ventilation as the first choice of respiratory support for premature infants at birth. However, a considerable number of infants who are initially stabilised with CPAP, develop worsening respiratory failure and eventually require intubation for mechanical ventilation and the administration of surfactant (1-6). Early identification of preterm infants who fail CPAP might optimise the timing of surfactant treatment to early administration (within 2 hours) (7) and improve outcomes.

Many measurements have been investigated for their ability to predict CPAP failure in infants such as FiO_2, PaO_2, A-aDO_2, a/A ratio, PaO_2/FiO_2 and the stable micro bubble test as soon as possible after birth (8-13). To date, the respiratory pattern and effort at birth have not been investigated although they are a major determinant of lung gas volumes (14) and may correlate with respiratory distress severity and predict CPAP failure (15). As the preterm infant's chest wall is highly compliant and transiently expands immediately after birth (16), it has limited capacity to oppose lung recoil (17). As such, these infants must utilise their breathing pattern to develop and maintain functional residual capacity (FRC) immediately after birth.

Expiratory holds (EHs), which are breaths characterised by a period of zero flow during expiration and prolong expiratory times (18-20), help to maintain FRC (14,18,21). Studies in newborn rabbits, lambs and infants suggest that the use of EHs is influenced by changes in lung gas volumes and airway pressure (14,19,22,23). Although it is uncertain whether EHs can indicate absolute lung gas volumes, we have previously shown a strong relationship between the incidence of EHs and FRC in newborn rabbits (14).

Large tidal volumes (VTs) at birth promote lung liquid clearance by generating transpulmonary pressures that move liquid from the airspace into the peri-alveolar interstitial tissue (14,16). There is a positive relationship between VT and FRC with large VTs resulting in larger immediate FRC accumulation (24). A similar relationship is observed regarding inspiratory effort and FRC development (24). Clearly, VT and inspiratory flow can influence end-expiratory lung gas volumes.

As preterm infants are commonly surfactant deficient and have a highly compliant chest, they commonly have lower than normal resting lung gas volumes (25,26). It is possible that infants with the lowest lung gas volumes represent those most likely to develop respiratory distress syndrome (RDS) and thus require more respiratory support than CPAP

initiated at birth. Indeed, up to 80% of infants who fail CPAP demonstrate moderate-severe RDS (1,27). As such, preterm infants who fail to establish a good breathing pattern and effort immediately after birth are more likely to be unable to maintain their FRC and eventually require increased respiratory support. We hypothesised that the breathing pattern and effort at birth can predict which infants will fail CPAP within 48 hours after birth.

Methods

This retrospective study was performed at the Leiden University Medical Centre (LUMC) and included respiratory function recordings made between years 2009 and 2011 of infants born <32 weeks of gestation who were supported with CPAP at birth. Recording respiratory function in the delivery room is considered standard of care at LUMC and is performed if time permits to set up the equipment. Recordings are used for teaching, audit and research. The aim of this study was to determine if the breathing pattern and effort at birth could predict which infants could be stabilised with CPAP in the delivery room but later require intubation. Therefore, infants that were intubated in the delivery room were excluded from the analysis.

Resuscitation was performed by neonatologists, neonatal fellows or pediatric registrars who used a T-piece infant resuscitator (Neopuff; Fisher & Paykel Healthcare, Auckland, New Zealand) in combination with a Laerdal silicone round mask of an appropriate size (Laerdal, Stavanger, Norway). Positive pressure ventilation was performed according to Dutch guidelines starting with 5 initial sustained inflations, each lasting 2-3 seconds, a peak inspiratory pressure (PIP) of 20 cmH_2O, a positive end expiratory pressure (PEEP) of 5 cmH_2O and a gas flow rate of 8 L/min using air (28). Positive pressure ventilation was continued if spontaneous breathing was absent or if the infant's heart rate and oxygen saturation were below satisfactory levels. Otherwise, infants were supported with 5-6 cmH_2O of CPAP.

Respiratory interventions were recorded using a webcam and a Florian respiratory function monitor (Acutronic Medical Systems AG, Hirzl, Switzerland), with a hot wire anemometer as a flow sensor between the T-piece and facemask (dead space <1 ml) to detect gas flow in and out of the mask. The flow signal was integrated to measure tidal volumes (VTs) (29). The flow sensor was calibrated before each recording. Pressure was measured from the distal section of the T-piece tubing. Oxygen saturation and heart rate were measured with a Masimo SET pulse oximeter (Masimo Radical, Masimo Corporation, Irvine,

California). FiO_2 was measured using an oxylog (Teledyne technologies, thousand oaks, California). Signals of gas flow, VT, ventilatory pressure, FiO_2, oxygen saturation, heart rate and breathing were digitised and recorded at 200 Hz using Spectra software (Grove Medical, Hampton, UK).

The resuscitators were not blinded to the respiratory monitor, but we recently reported that they rarely used the monitor for feedback (28). The researcher performing the recording was not part of the resuscitation team and did not inform the resuscitators of the saturation, heart rate and respiratory function of the infant displayed by the monitor.

Respiratory function recordings were analysed in 3-minute periods to determine the frequency of EHs, the volume-time integral of EHs (i.e. area under the volume recording of each EH), EH hold duration and EH hold volume. All spontaneous breaths, EHs and other breaths, were analysed for VT and peak inspiratory flow. The volume-time integral of each EH takes into account the remaining lung gas volume and the size and duration of the EH, thus providing an overall measurement of gas exchange potential. Peak inspiratory flow rate was used as a surrogate measure of respiratory strength. CPAP pressure and FiO_2 before the infant was transferred to the neonatal intensive care unit (NICU) was also noted. To blind investigators, if the infant was intubated, the eventual time of intubation was added to the database after the analysis was finished. The threshold for CPAP failure was intubation within 48 hours of age because intubation within this time was most likely due to respiratory distress rather than apnoea's of prematurity or the presence of infection.

Indications for endotracheal intubation in the first 48 hours after birth included at least one of the following; (1) inability to maintain SpO_2 in the target range (85 – 95%) with a maximum CPAP pressure of 8 cmH_2O and $FiO_2 > 0.4$, (2) more than one apnea per hour for 6 hours despite caffeine treatment or any apnea requiring PPV or (3) a respiratory acidosis (pH < 7.25 and pCO_2 >60 mmHg and rising) on two separate blood gases.

Results are presented as mean ± standard error of the mean or otherwise stated. Data were tested for normality and equal variance and data transformations were performed if necessary using SigmaPlot (SigmaPlot 12, Systat Software Inc. Chicago, Illinois). A Student-Newman-Keuls post hoc test was performed to identify statistical differences. A p-value of <0.05 was used for statistical significance. When Student's t-tests were used to compare groups, data that were not normally distributed were analysed using a Mann-Whitney Rank Sum test.

Results

72 respiratory recordings were eligible for analysis. In total 40/72 recordings needed to be excluded for the following reasons: 14 respiratory recordings were of poor quality (excessive movement artefact, significant leak from the facemask or problems with the digitisation of data), 9 infants lacked enough spontaneous breaths to be analysed (<10 spontaneous breaths in the entire recording), for 7 infants the corresponding patient data could not be located, 7 infants were intubated in the delivery room and 3 infants died during the initial resuscitation period. Therefore, a total of 32 respiratory recordings were analysed; 15 recordings of CPAP-failed infants and 17 recordings of CPAP-success infants. The patient characteristics of these groups are presented in Table 1. It was not expected that the same number of recordings were analysed at each time point in the analysis because periods of IPPV were excluded and the duration of assisted ventilation in the delivery room differed between patients. Table 2 presents the number of patients included in each time point.

Table 1. Patient details

	CPAP-fail	**CPAP-success**
Total patients	15	17
Gestational age (weeks)	28.6 ± 0.7	30.1 ± 0.4*
Weight (g)	1090 ± 140	1270 ± 80*
Gender – Male – Female	 6 9	 12 5
Mode of delivery – Caesarean section – Vaginal	 9 6	 8 9
Received antenatal steroids	9	6
Time of intubation (hours)	10.62 ± 2.38	0

Table 2. The number of patient recordings analysed in each time period

Time period (min)	**0-3**	**3-6**	**6-9**	**9-12**
CPAP-fail (n=15)	4	12	13	10
CPAP-success (n=17)	8	16	17	7

Infants who failed CPAP required more inflations at birth (45 ± 12% of all flow waves) compared to infants who were successfully supported by CPAP (19 ± 9% of all flow waves; $p<0.05$). Infants who failed CPAP within 48 hours were intubated, on average, at 6.62 ± 0.31 hours after birth. In the CPAP-fail group, 1999 spontaneous breaths were analysed. In the CPAP-success group, 2004 spontaneous breaths were analysed.

In all infants, the incidence of EHs increased from <5% at 0-3 minutes to ~20% at 3-6 minutes after birth ($p<0.05$) and remained stable at 6-9 minutes and at 9-12 minutes (figure 1A). There were no significant differences between CPAP-fail and CPAP-success groups at any time point ($p>0.05$). The volume-time integral of breaths exhibiting an EH was similar between CPAP-fail and CPAP-success groups at each of the selected time points after birth ($p>0.05$, figure 1B).

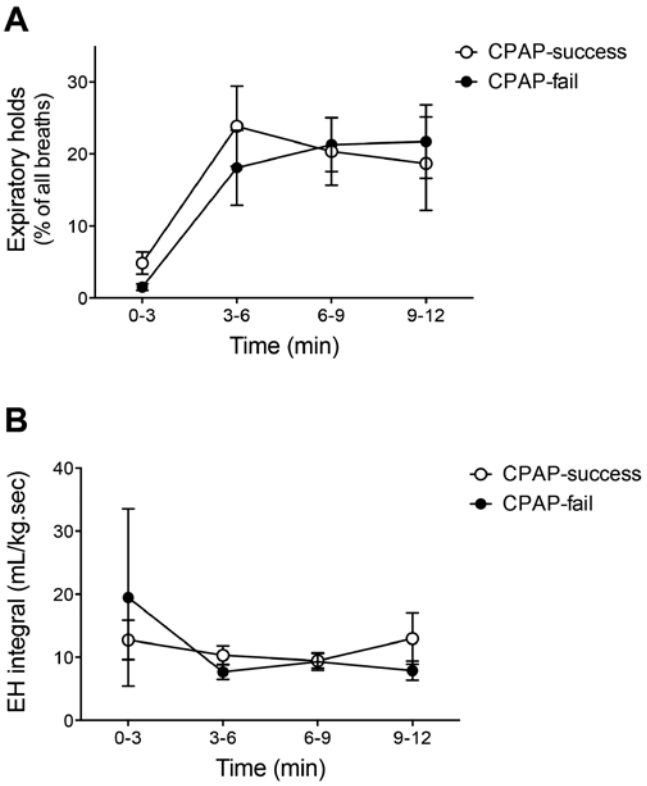

Figure 1. Frequency of EHs and EH integrals in the first 12 minutes. The frequency of EHs **(A)** and EH integral **(B)** in preterm newborns in the first 12 minutes after birth. Open circles are CPAP-success newborns. Closed circles are CPAP-fail newborns.

The duration of the period of zero flow occurring during the EH was not different between CPAP-fail and CPAP-success groups (p>0.05; figure 2A). The average volume of gas in the lungs during the hold was also not statistically different (p>0.05), although the CPAP-success group tended to maintain a greater volume of gas in the lungs than the CPAP-fail group (figure 2B).

The VT of all spontaneous breaths was not different between CPAP-fail and CPAP-success groups at any time point (p>0.05, figure 3A). However, at 9-12 minutes after birth, the CPAP-fail infants had relatively consistent VTs (median [IQR]) (6.3 [4.4-6.9]) whereas VTs within the CPAP-success group demonstrated greater variability (7.5 [5.3-16.4]). The coefficient of variation of VTs at 9-12 minutes in the CPAP-fail group was 0.32, whereas it

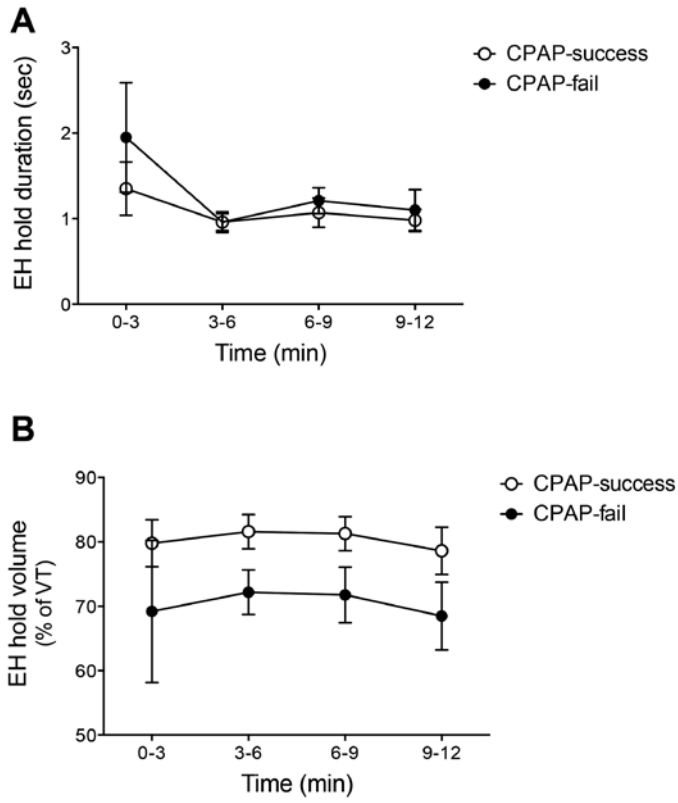

Figure 2. Duration and percentage of gas volume in the lungs during EHs. The duration **(A)** and percentage of gas volume in the lungs **(B)** during the period of zero flow of EHs in preterm newborn in the first 12 minutes after births. Open circles are CPAP-success newborns. Closed circles are CPAP-fail newborns.

was 0.66 in the CPAP-success group. Similar to VT, peak inspiratory flow averaged across all spontaneous breaths was not different between CPAP-fail and CPAP-success groups at most time points ($p>0.05$). However, at 9-12 minutes CPAP-fail infants demonstrated significantly lower peak inspiratory gas flows than CPAP-success infants ($p<0.05$; figure 3B). The peak inspiratory flows at 9-12 minutes were less variable in the CPAP-fail group (29.5 [21.0-35.4] mL/kg/sec) than in the CPAP-success group (33.0 [16.5-54.9] mL/kg/sec). The coefficient of variation was 0.35 in the CPAP-fail group and 0.82 in the CPAP-success group.

Breaths occurring between 9-12 minutes were analysed in individual infants to determine the usage of different sized VTs and peak inspiratory flows in CPAP-fail and CPAP-success infants at this time. CPAP-fail and CPAP-success infants most commonly utilised VTs

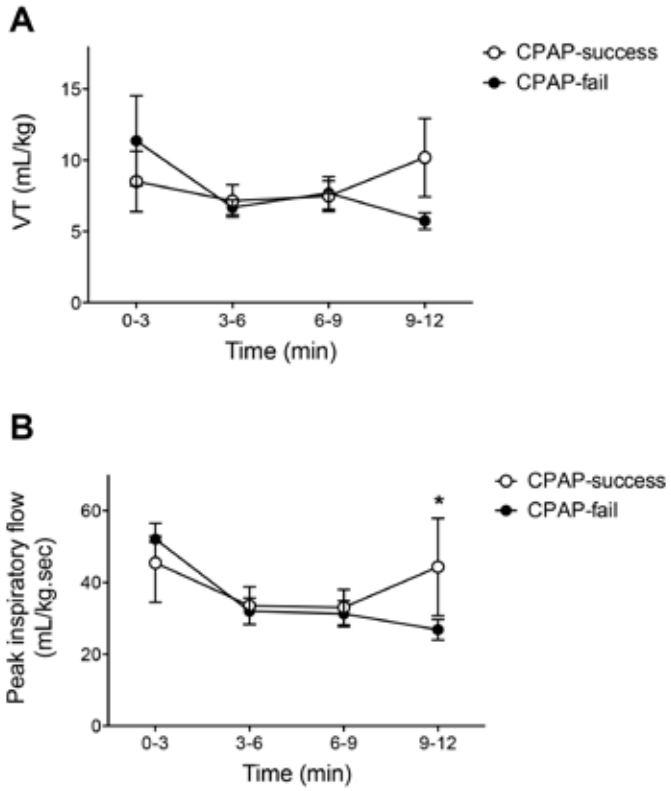

Figure 3. Vts and peak inspiratory flow in the first 12 minutes. The VTs **(A)** and peak inspiratory flow **(B)** of all breaths generated by preterm newborns in the first 12 minutes after birth. Open circles are CPAP success newborns. Closed circles are CPAP fail newborns.

between 3-6 mL/kg at 9-12 minutes after birth (figure 4A; $p<0.05$). Although not significant, CPAP-success infants appeared to utilise almost 2 times as many VTs of >9 mL/kg than CPAP-fail infants. However, CPAP-success infants achieved large inspiratory flows >40 ml/kg.s ~4 times more frequently than CPAP-fail infants (15.5 ± 5.2% vs. 71.8 ± 15.8%, $p<0.05$) (figure 4B). In CPAP-success infants 70% of the very large VTs (>9 mL/kg) were generated by using large inspiratory flows >50 mL/kg.s. In contrast, CPAP-fail infants less commonly used VTs >9 mL/kg and utilised a wide range of inspiratory flows to achieve these volumes.

At 9-12 minutes after birth breaths were separated into VT ranges and the distribution of peak inspiratory flows determined (figure 5). Low VTs (0-3 mL/kg) were mostly achieved

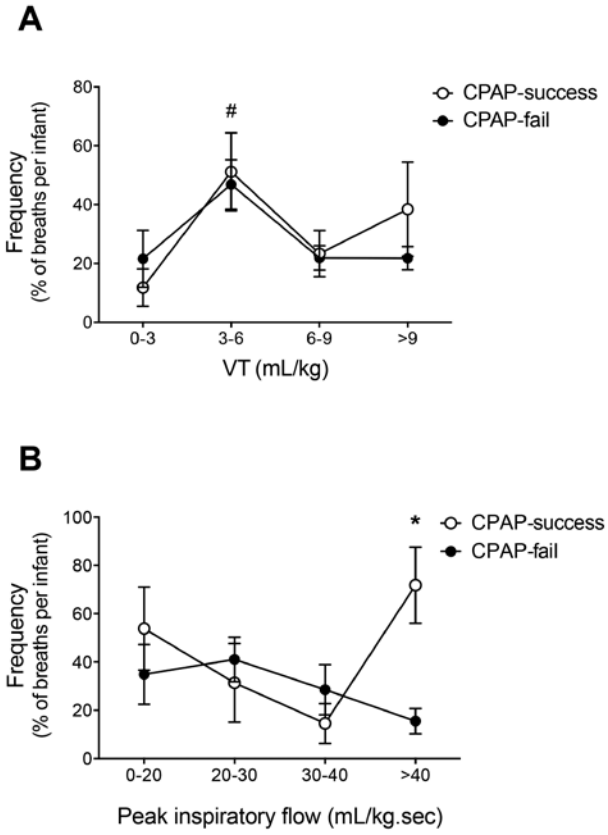

Figure 4. Frequency of Vts and peak inspiratory flows of all breaths in the first 12 minutes. The frequency of different VTs **(A)** and peak inspiratory flows **(B)** of all breaths generated by preterm newborns in the first 12 minutes after birth. Open circles are CPAP-success newborns. Closed circles are CPAP-fail newborns. # indicates that the VT range is significantly greater than any other VT range in both CPAP-success and CPAP-fail infants. * indicates that the frequency of the CPAP-success group is significantly different to the CPAP-fail group at the corresponding peak inspiratory flow.

with slow peak inspiratory flows <15 mL/kg.s in both CPAP-success and CPAP-fail infants. However, VTs of between 3-6 ml/kg, which was the most commonly utilised VT at 9-12 minutes, were achieved with lower flow rates in CPAP-success infants than CPAP-fail infants (figure 6). Larger VTs (6-9 mL/kg) were commonly achieved with inspiratory flows of 15-25 mL/kg.s in the CPAP-success group whereas the same VTs required much higher inspiratory flows of 20-35 mL/kg.s in the CPAP-fail group.

SpO_2 increased similarly in CPAP-fail and CPAP-success infants (figure 6). To achieve these saturations, CPAP-fail infants required greater FiO_2 (0.31 ± 0.03 vs. 0.21 ± 0.01; $p<0.05$) and CPAP levels (6.62 ± 0.3 cmH_2O vs. 5.67 ± 0.26 cmH_2O, $p<0.05$) than CPAP-success infants.

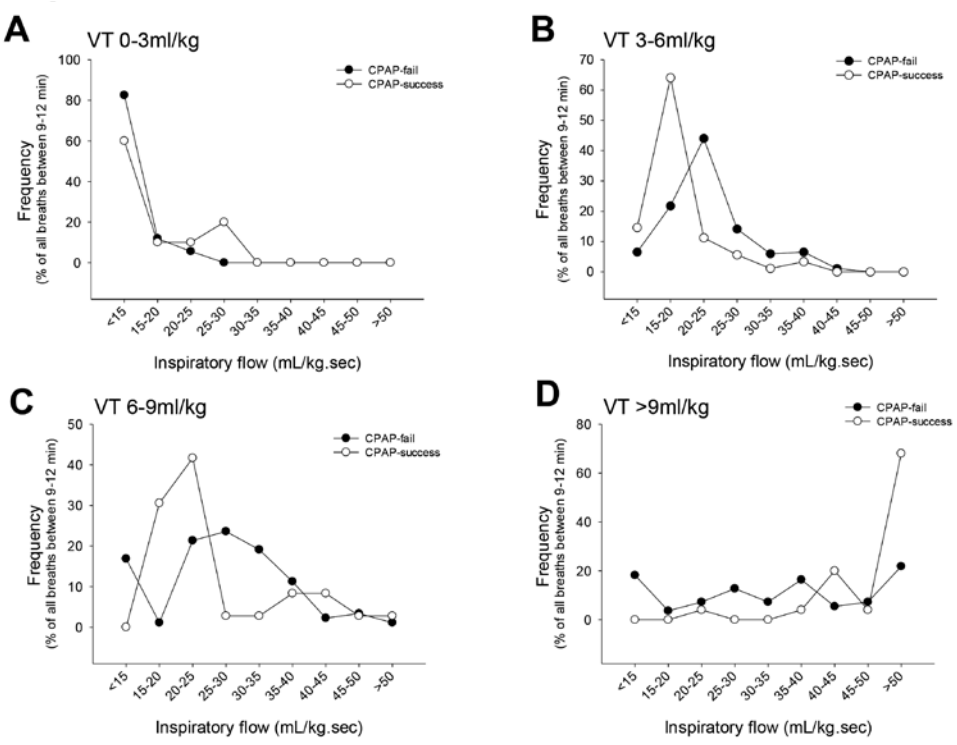

Figure 5. Frequency and peak inspiratory flows of different VT ranges. An analysis of breaths generated between 9-12 minutes after birth separated into different VT ranges; VT 0-3m L/kg **(A),** 3-6 mL/kg **(B)**, 6-9 mL/kg **(C)** and >9 mL/kg **(D)**. Each graph shows the frequency of different peak inspiratory flows of all breaths within the specific VT range. Open circles are CPAP-success newborns. Closed circles are CPAP-fail newborns.

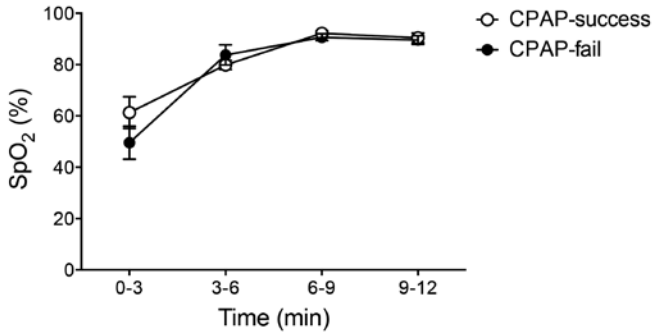

Figure 6. Oxygen saturation changes in the first 12 minutes. Oxygen saturation changes in the first 12 minutes after birth in preterm newborns. Open circles are CPAP-success newborns. Closed circles are CPAP-fail newborns.

Discussion

Several randomised controlled trials have demonstrated that preterm infants can be stabilised with CPAP at birth (2-6). However, a significant proportion of these infants, as many as 50% (2,6), developed respiratory failure and failed CPAP. Our study investigated if the breathing pattern at birth could identify infants that fail CPAP within 48 hours after birth. EH frequency, size and duration over time and average VT and average peak inspiratory flow of all breaths did not predict CPAP failure. However, a sub-analysis of breaths occurring between 9-12 minutes demonstrated that the CPAP-fail infants needed higher inspiratory flows to reach the volumes but used very few breaths of large peak inspiratory flows when compared to CPAP-success infants. This reflects more difficulty in breathing and early signs of fatigue in the CPAP-fail infants. Indeed, infants who failed CPAP required greater respiratory support, such as higher FiO_2 levels, higher CPAP pressures and more positive pressure-delivered breaths, before transport to the NICU.

Low VTs and inspiratory flows have been associated with a greater risk of extubation failure in mechanically ventilated children 3-5 years old (30). Although our results demonstrated a tendency for CPAP-fail infants to have lower VT at 9-12 minutes, this was not statistically different because of the large variation in VTs of the CPAP-success group. However, peak inspiratory flows were significantly lower in CPAP-fail versus CPAP-success infants and both the VTs and peak inspiratory flows were less variable. Mechanically ventilated preterm infants, studied at ~5 days postnatal age, were most likely to fail extubation if they demonstrated less variation in their mean inspiratory flow rate during a 3

minute spontaneous breathing trial before extubation (31). This is similarly observed in adults (32). The coefficient of variation of the VT and peak inspiratory flow at 9-12 minutes suggests that infants who failed CPAP utilised a narrower range of VT and flows than CPAP-success infants.

Large variability reflects the infant's ability to adapt to a changing lung gas volume to maintain adequate lung aeration. A limited range of breaths (VTs and inspiratory flows) may indicate increased difficulty in maintaining lung aeration. These infants are likely at greater risk of later respiratory failure. Indeed, CPAP-fail infants required greater respiratory support such as increased FiO_2, greater CPAP pressures and more manually delivered breaths, to obtain similar oxygen saturations to CPAP-success infants. A need for greater respiratory support by infants that fail CPAP has been previously reported (8,10,11).

Maintaining lung aeration is particularly difficult for newborn infants because insufficient mineralisation of the ribs leads to a highly compliant chest wall (33) that tends to collapse inwards under the lungs natural recoil and particularly during inspiration. This effect is more pronounced in preterm infants (34) who have higher chest wall compliances than term infants (17). Employing faster inspiratory flows to generate larger potential VTs in anticipation that a proportion of the VT will not be achieved could compensate for the loss of potential VT, resulting from chest wall distortion. By increasing their efforts for each breath, CPAP-fail infants can achieve adequate VTs and delay the onset of respiratory distress until hours after birth. Our study demonstrated that CPAP-fail infants required larger inspiratory flow rates to achieve VTs of 3-9 mL/kg than CPAP-success infants. These findings suggest that infants most likely to fail CPAP may be those with the most compliant chest walls. In fact, high Silverman scores, which indicate significant chest wall retractions during breathing, have been associated with CPAP failure (11).

In contrast to the observations made at VTs between 0-9 ml/kg, larger VTs >9 ml/kg were more often achieved by CPAP-success infants using higher peak inspiratory flows than CPAP-fail infants (Figure 6D). This observation may identify the strongest infants who have the strength to generate the fastest inspiratory flows to achieve these larger volumes. In addition, CPAP-success infants may have stiffer chest walls, which may help them generate rapid peak inspiratory flows and more easily achieve large recruitment breaths. Although not statistically significant, larger VTs >9 ml/kg, on average, appeared to make up a larger percent of the breathing pattern in CPAP-success infants than fail infants (Figure 5). CPAP-fail infants, possibly with more compliant chest walls, utilised a wider range of inspiratory flow rates to achieve the large VTs of >9 mL/kg (figure 6). The use of slower rates of inflation to achieve large VTs likely reflects a mechanical problem

and a greater difficulty in simply moving air into the lungs. This suggestion is supported by the finding that these infants required higher flow rates to achieve moderate sized VTs. Further, it raise the possibility that energy failure may be a major contributor to eventual CPAP failure in these infants. That is, the energy requirement to maintain spontaneous breathing on CPAP eventually becomes too great.

High chest wall compliance combined with a low lung compliance increases the risk of inward chest wall distortion (35). Low lung compliance at birth is contributed to by numerous factors such as lung structural immaturity, the absence of surfactant and low lung gas volume due to partially liquid-filled lungs (36-38). The contribution of lung tissue mechanics in CPAP failure is inconclusive; studies have found that infants who received antenatal steroids were less likely to fail CPAP (8, 11) whereas others report no significant relationship between antenatal steroids and CPAP failure (1, 9, 10). Stable microbubble tests or lamella body counts, which indirectly assesses the function of pulmonary surfactant, have shown to be a potential predictor of moderate to severe RDS (12,13). Considering that 70% of newborns that fail CPAP have RDS and 53% demonstrate a severe form on chest X-rays (1), surfactant deficiency may play a role in CPAP failure by promoting low lung compliance. Alternatively, inadequate lung liquid clearance at birth decreases lung compliance. As lung liquid clearance is promoted by increased transpulmonary hydrostatic pressures gradients (14,16), successful lung recruitment at birth, possibly with the use of sustained inflations, could reduce the risk of CPAP-failure (9) by increasing lung compliance and achieving a lower chest wall to lung compliance ratio.

Previous research suggested that EHs are related to lung gas volume; newborn rabbits commonly utilised EHs after >50% of FRC had been accumulated (14), 1-2 week old lambs increased vagal afferent feedback and inhibited EHs when FRC was increased (23) and increasing CPAP in 1-21 day old infants increased FRC and reduced the frequency of EHs (22). In our study the use of EH increased after birth, similar to that observed in rabbit pups (14), however it did not differ between CPAP-fail and CPAP-success infants. EHs likely do not reflect absolute lung gas volumes but rather relative changes in end-expiratory lung gas volumes. Although lung gas volumes were not measured in our study, CPAP-fail infants were likely to have had lower lung gas volumes than CPAP-success infants and indeed CPAP-fail infants required greater respiratory support. Increases and decreases in lung gas volume are not uncommon immediately after birth (14,39). Therefore, each time end-expiratory lung gas volumes decrease, irrespective of original or subsequent lung gas volumes, vagal afferent feedback triggers the use of EHs to restore FRC (40). Therefore, it would be difficult to differentiate between CPAP-success and CPAP-fail infants based on EH usage alone.

One of the major limitations to this study is the short duration of the respiratory recordings analysed. This was limited to the time that the infant is on the resuscitation table; in our study this ranged between 5 to 12 minutes. Within this short recording period, infant's initiated spontaneous breathing and received IPPV at different times. The quality of the respiratory traces were affected by face mask leak and physical movement from the infant caused by positioning the infant into polyethylene wrap or placing the pulse oximeter probe on the infant's wrist. These events further reduced the amount of analysable recording and may have prevented statistical differences from being detected between groups. If recordings were extended or performed later when the infant was quietly breathing and not interfered with by caregivers, clearer differences may have been detected. Indeed, in our study, infants were intubated at an average of 6 hours after birth. Infants intubated in the delivery room (~10%) were excluded, which would have removed the sickest infants from our analysis. However, we believed that this exclusion was necessary because our aim was to determine which infants could be stabilised with CPAP in the delivery room but require more intensive respiratory support later on.

Conclusion

The ability to predict infants who will fail CPAP soon after birth is a valuable tool that would help caregivers initiate treatments and preventative strategies early. This would prevent the infant from being intubated and mechanical ventilated throughout their recovery. Our study suggests that infants most likely to later fail CPAP are those who have weaker respiratory efforts at 9-12 minutes after birth. These infants more infrequently utilised high peak inspiratory flows, required increased peak inspiratory flows to generate moderately sized VTs and were unable to generate rapid peak inspiratory flows to perform recruitment manoeuvres (VTs >9 ml/kg). The difficulty the CPAP-fail infants face to maintain lung aeration immediately after birth is reflected in their greater need for respiratory support at birth before being transferred to the NICU. Further research is required to determine if it is feasible to determine the relationship between VT and inspiratory flow soon after birth or if determining the threshold of different forms of respiratory support will more easily identify infants most likely to fail CPAP.

References

1. Ammari A, Suri M, Milisavljevic V, *et al*. Variables associated with the early failure of nasal CPAP in very low birth weight infants. J Pediatr 2005;147:341-7.
2. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 2008;358:700-8.
3. Finer NN, Carlo WA, Walsh MC, *et al*. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med 2010; 362:1970-9.
4. Sandri F, Plavka R, Ancora G, *et al*. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. Pediatrics 2010;125:e1402-9.
5. Dunn MS, Kaempf J, de Klerk A, *et al*. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. Pediatrics 2011;128:e1069-76.
6. Lopez ES, Rodriguez EM, Navarro CR, Sanchez-Luna M. Initial respiratory management in preterm infants and bronchopulmonary dysplasia. Clinics (Sao Paulo) 2011; 66:823-7.
7. Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database Syst Rev 2000:CD001456.
8. Dimitriou G, Fouzas S, Giannakopoulos I, Papadopoulos VG, Decavalas G, Mantagos S. Prediction of respiratory failure in late-preterm infants with respiratory distress at birth. Eur J Pediatr 2011;170:45-50.
9. Fuchs H, Lindner W, Leiprecht A, Mendler MR, Hummler HD. Predictors of early nasal CPAP failure and effects of various intubation criteria on the rate of mechanical ventilation in preterm infants of <29 weeks gestational age. Arch Dis Child Fetal Neonatal Ed 2011;96:F343-7.
10. De Jaegere AP, van der Lee JH, Cante C, van Kaam AH. Early prediction of nasal continuous positive airway pressure failure in preterm infants less than 30 weeks gestation. Acta Paediatr 2012;101:374-9.
11. Pillai MS, Sankar MJ, Mani K, Agarwal R, Paul VK, Deorari AK. Clinical prediction score for nasal CPAP failure in pre-term VLBW neonates with early onset respiratory distress. J Trop Pediatr 2011;57:274-9.
12. Daniel IWBD, Fiori HH, Piva JP, Munhoz TP, Nectoux AV, Fiori RM. Lamellar Body Count and Stable Microbubble Test on Gastric Aspirates from Preterm Infants for the Diagnosis of Respiratory Distress Syndrome. Neonatology 2010;98:150-5.
13. Fiori HH, Fritscher CC, Fiori RM. Selective surfactant prophylaxis in preterm infants born at < or =31 weeks' gestation using the stable microbubble test in gastric aspirates. J Perinat Med 2006;34:66-70.
14. Siew ML, Wallace MJ, Kitchen MJ, *et al*. Inspiration regulates the rate and temporal pattern of lung liquid clearance and lung aeration at birth. J Appl Physiol 2009;106:1888-95.
15. Hutchison AA, Wozniak JA. Endotracheal measurement of thyroarytenoid activity in newborn lambs. Biol Neonat 2000;78:139-44.
16. Hooper SB, Kitchen MJ, Wallace MJ, *et al*. Imaging lung aeration and lung liquid clearance at birth. FASEB J 2007;21:3329-37.
17. Gerhardt T, Bancalari E. Chestwall compliance in full-term and premature infants. Acta Paediatr 1980;69:359-64.
18. Fisher JT, Mortola JP, Smith JB, Fox GS, Weeks S. Respiration in Newborns - Development of the Control of Breathing. American Review of Respiratory Disease 1982;125:650-7.
19. te Pas AB, Wong C, Kamlin COF, Dawson JA, Morley CJ, Davis PG. Breathing Patterns in Preterm and Term Infants Immediately After Birth. Pediatr Res 2009;65:352-6.
20. te Pas AB, Davis PG, Kamlin CO, Dawson J, O'Donnell CP, Morley CJ. Spontaneous breathing patterns of very preterm infants treated with continuous positive airway pressure at birth. Pediatr Res 2008;64:281-5.
21. Kosch PC, Stark AR. Dynamic Maintenance of End-Expiratory Lung-Volume in Full-Term Infants. J Appl Physiol 1984;57:1126-33.

22. Elgellab A, Riou Y, Abbazine A, *et al*. Effects of nasal continuous positive airway pressure (NCPAP) on breathing pattern in spontaneously breathing premature newborn infants. Intensive Care Med 2001;27:1782-7.
23. Harding R. State-related and developmental changes in laryngeal function. Sleep 1980;3:307-22.
24. Vyas H, Field D, Milner AD, Hopkin IE. Determinants of the first Inspiratory Volume and Functional Residual Capacity at Birth. Pediatr Pulmonol 1986;2:189-93.
25. Mortola JP, Milicemili J, Noworaj A, Smith B, Fox G, Weeks S. Muscle Pressure and Flow During Expiration in Infants. American Review of Respiratory Disease 1984;129:49-53.
26. Frappell PB, MacFarlane PM. Development of mechanics and pulmonary reflexes. Respiratory Physiology & Neurobiology 2005;149:143-54.
27. Dargaville PA, Aiyappan A, De Paoli AG, *et al*. Continuous Positive Airway Pressure Failure in Preterm Infants: Incidence, Predictors and Consequences. Neonatology 2013;104:8-14.
28. Schilleman K, Siew ML, Lopriore E, Morley CJ, Walther FJ, Te Pas AB. Auditing resuscitation of preterm infants at birth by recording video and physiological parameters. Resuscitation 2012;83:1135-9.
29. Schmolzer GM, Kamlin OCOF, Dawson JA, Te Pas AB, Morley CJ, Davis PG. Respiratory monitoring of neonatal resuscitation. Arch Dis Child Fetal Neonatal Ed 2010;95:F295-F303.
30. Khan N, Brown A, Venkataraman ST. Predictors of extubation success and failure in mechanically ventilated infants and children. Crit Care Med 1996;24:1568-79.
31. Kaczmarek J, Kamlin COF, Morley CJ, Davis PG, Sant'Anna GM. Variability of respiratory parameters and extubation readiness in ventilated neonates. Arch Dis Child Fetal Neonatal Ed 2013;98:F70-3.
32. Bien MY, Lin YS, Shih CH, *et al*. Comparisons of predictive performance of breathing pattern variability measured during T-piece, automatic tube compensation, and pressure support ventilation for weaning intensive care unit patients from mechanical ventilation. Crit Care Med 2011;39:2253-62.
33. Gaultier C. Respiratory muscle function in infants. Eur Respir J 1995;8:150-3.
34. Warren RH, Horan SM, Robertson PK. Chest wall motion in preterm infants using respiratory inductive plethysmography. Eur Resp J 1997;10:2295-2300.
35. Heldt GP, McIlroy MB. Distortion of chest wall and work of diaphragm in preterm infants. J Appl Physiol 1987;62:164-9.
36. Siew ML, te Pas AB, Wallace MJ, *et al*. Surfactant increases the uniformity of lung aeration at birth in ventilated preterm rabbits. Pediatr Res 2011;70:50-55.
37. Kelly E, Bryan H, Possmayer F, Frndova H, Bryan C. Compliance of the respiratory system in newborn infants pre- and postsurfactant replacement therapy. Pediatr Pulmonol 1993;15:225-30.
38. Nilsson R, Grossmann G, Robertson B. Artificial ventilation of premature newborn rabbits: effects of positive end-expiratory pressure on lung mechanics and lung morphology. Acta Paediatr 1980;69:597-602.
39. Mortola JP, Gisher JT, Smith JB, Fox GS, Weeks S, Willis D. Onset of respiration in infants delivered by cesarean section. J Appl Physiol 1982;52:716-24.
40. Wong KA, Bano A, Rigaux A, *et al*. Pulmonary vagal innervation is required to establish adequate alveolar ventilation in the newborn lamb. J Appl Physiol 1998;85:849-59.

CHAPTER 8

The administration of 100% oxygen and respiratory drive in very preterm infants at birth

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PLoS One 2013; 18:e76898

Abstract

Aim: To retrospectively investigate the changes of SpO_2 and respiratory drive in preterm infants at birth after administration of 100% oxygen.

Methods: Respiratory parameters, FiO_2 and oximetry of infants <32 weeks gestation before and after receiving FiO_2 1.0 were reviewed during continuous positive airway pressure (CPAP) or positive pressure ventilation (PPV).

Results: Results are given as median (IQR) or percentages where appropriate. Suitable recordings were made in 50 infants (GA 27 (26-29) weeks), 17 received CPAP and 33 PPV. SpO_2 increased rapidly in the first minute after FiO_2 1.0 and remained stable. The duration of FiO_2 1.0 tended to be shorter in the CPAP group than in the PPV group (CPAP vs. PPV: 65 (33-105) vs. 100 (40-280) s; p=0.05), SpO_2 >95% occurred more often in PPV group (53% vs. 69%) and lasted longer (70 (40-95) vs. 120 (50-202) s). In CPAP group, minute volume increased from 134 (76-265) mL/kg/min 1 minute before to 240 (157-370) mL/kg/min (p<0.01) 1 minute after start FiO_2 1.0 and remained stable at 2 minutes (252 (135-376) mL/kg/min; ns). The rate of rise to maximum tidal volume increased (from 13.8 (8.0-22.4) mL/kg/s to 18.2 (11.0-27.5) mL/kg/s; p<0.0001) to 18.8 (11.8-27.8) mL/kg/s; ns). In the PPV group respiratory rate increased from 0 (0-4) to 9 (0-20) at 1 minute (p<0.001) to 23 (0-34) breaths per minute at 2 minutes (p<0.01).

Conclusion: In preterm infants at birth, a rapid increase in oxygenation, resulting from a transient increase to 100% oxygen might improve respiratory drive, but increases the risk for hyperoxia.

Introduction

Hyperoxemia may lead to hyperoxia causing oxidative stress and tissue injury which should be avoided in infants at birth (1;2). Meta-analyses indicate that resuscitation of term infants at birth with air significantly reduced mortality compared with those resuscitated with fraction of inspired oxygen (FiO_2) of 1.0 (1-6). International resuscitation guidelines now recommend term infants should start in air (2;7;8). Less clinical data are available for preterm infants, but guidelines now recommend to use oxygen judiciously during stabilisation of preterm infants at birth (2;7-9).

Since oxygen saturation (SpO_2) percentiles were introduced (10) lower SpO_2-targets in the first minutes after birth are accepted. However, hypoxia inhibits breathing movements in the fetus (11). Although O_2 sensitivity of infants changes in days-weeks after birth (12) and most preterm infants breathe at birth, (13;14) it is not known when the hypoxia-mediated switch from respiratory suppression to stimulation occurs. Possibly hypoxia immediately after birth will produce a weakened or absent respiratory drive as shown in preterm lambs (12). In contrast, it has been shown in asphyxiated term infants (15) and animals (16) that applying 100% oxygen with no titration delayed the time of the first breath.

From 2008 until 2010, the local guidelines of the Royal Women's Hospital (Melbourne, Australia) and the Leiden University Medical Center (Leiden, the Netherlands) recommended starting in air and switching to FiO_2 1.0 if needed and then titrating down in preterm infants at birth. An SpO_2 ≤70% at 5 minutes was used to increase FiO_2 (10). The immediate switch to 100% was a pragmatic choice, but immediate FiO_2 reduction was advocated once the infant was stabilized.

Our aim was to investigate the change in SpO_2 and respiratory drive in preterm infants right after birth in the delivery room after switching from air to FiO_2 1.0.

Methods

The local institutional review boards (IRBs) of the Leiden University Medical Center (Commissie Medische Ethiek, Leids Universitair Medisch Centrum) and Royal Women's Hospital (the Human Research Ethics Committee, Royal Woman's Hospital) approved physiological- and video recordings at birth in the delivery room when respiratory support was necessary for research purposes. Written parental consent to use the recordings for

research was obtained after birth. A retrospective study was performed in both hospitals with data collected between 2008 and 2010. During the period of data collection local guidelines recommended that support was started with air and switched to FiO_2 1.0 when: 1) cardiac massage was needed, 2) positive pressure ventilation (PPV) was administered for 1 minute and heart rate (HR) was <100 beats per minute (bpm) or 3) SpO_2 <70% at 5 minutes. FiO_2 was then titrated down as quickly as possible (when SpO_2 >90%). Recordings were only made when the research team was available.

Respiratory support was delivered with a T-piece resuscitator (Neopuff, Fisher & Paykel, Wellington, New Zealand) and face mask. Local resuscitation guidelines recommended to start PPV (20-25/5 cmH_2O) in preterm infants during apnea or HR <100 bpm. In breathing infants and HR >100 bpm, continuous positive airway pressure (CPAP) (5-6 cmH_2O) is given. Changing pressures was left to the discretion of the caregiver.

The use of a respiratory monitor (Acutronic Medical Systems AG, Hirzel, Switzerland), a Masimo SET pulse oximeter (Masimo Radical, Masimo Corporation, Irvine CA, USA), an Oxylog (Teledyne, Poway CA, USA) and Spectra program (Spectra, Grove Medical Limited, Hampton, UK) for physiological recordings has been described in detail in previous publications (13)

All recordings of infants born at <32 weeks gestation between 2008 and 2010 were reviewed. Using video and respiratory function monitoring other interventions were identified performed during the analyzed period. Infants receiving FiO_2 1.0 were identified and divided into two groups. This was based on the type of respiratory support they received around the time point FiO_2 1.0 was started: group 1) infants were breathing on continuous CPAP and group 2) received PPV.

In all infants we recorded when FiO_2 was increased to 1.0, for what reason(s) (e.g. low HR, low SpO_2), duration and the downward titration rate of FiO_2 1.0. Furthermore we noted the increase in SpO_2 duration of SpO_2 >95%. We used SpO_2 >95% as an indication for increased risk for hyperoxia.

In group 1 (CPAP-group) the effect of FiO_2 1.0 on respiratory drive was investigated. To measure the change in respiratory effort, we analyzed the respiratory rate (RR), expired tidal volume (Vte), minute volume (MV) and the rate of rise to maximum tidal volume (mL/kg/second) during inspiration from 1 minute before until two minutes after starting FiO_2 1.0 (which served as a control period). To measure the maximum rate of tidal volume increase we used spontaneous breaths without mask leak (Vti = Vte).

In group 2 (PPV-group) the tidal volumes and rate of rise will be influenced by the PPV given and we only analyzed RR of the spontaneous breaths from 1 minute before until two minutes after starting FiO_2 1.0. Breaths in between and coinciding with inflations were identified according to previous described methods (15). In apneic infants, starting time of breathing was noted.

As changing of FiO_2 can influence flow and volume measurements (17-19), the respiratory monitor was tested in vitro by delivering a constant tidal volume using a glass syringe and different gas conditions. The results were used to give the following corrections: at FiO_2 1.0, both inspired and expired tidal volumes were corrected by -6% when using cold dry gas and by -10% when heated gas was used.

Data are presented as mean (± SD) or median (IQR) where appropriate. Differences were analyzed with a paired samples t-test for parametric data or a Wilcoxon signed rank test for non-parametric data where appropriate using (SPSS for Windows, version 17.0.0, Chicago, IL, USA). A two-sided p-value <0.05 was considered statistically significant.

Results

Data from 80 recorded infants were reviewed, 30 were excluded (no respiratory support (n=10), no supplemental oxygen (n=7), low quality recordings (n=12) and 1 infant was born dead). Thus, 50 infants with GA 27 (26-29) weeks were analyzed (table 1); during the study window (1 minute before-2 minutes after start of oxygen) 17 breathed on CPAP (CPAP-group) and 33 received PPV (PPV-group).

Table 1. Baseline characteristics for preterm infants breathing on CPAP and infants receiving PPV when a FiO_2 of 1.0 was started

Characteristics	**breathing on CPAP N= 17**	**PVV N= 33**	**p-value**
Gestational age, weeks, mean (SD)	28.9 (1.5)	27.1 (2.1)	<0.01
Birth weight, g, mean (SD)	1073 (227)	993 (311)	<0.0001
Male Sex (%)	10 (60)	16 (49)	ns
Caesarean (%)	8 (47)	18 (54)	ns
Apgar at 1 min, median (IQR	6 (5-7)	4 (2-6)	<0.05
Apgar at 5 min, median (IQR)	8 (8-8)	7 (6-8)	<0.05

The infants in the CPAP-group did not receive PPV during or after the study window. In both groups ventilation pressures were not increased during the study window. (pressures given: CPAP-group CPAP level 5.3 (4.6-5.9) cmH_2O, PPV-group; PIP 21.6 (20.3-24.9) cmH_2O and PEEP 4.2 (3.5-4.7) cmH_2O) and no readjustments of mask position were observed. After the study window 1 infant of the CPAP-group was intubated, but reason was unclear. In the PPV-group, 5 infants were intubated after the study window for apnea and low SpO_2 despite FiO_2 1.0. Cardiac massage was not provided to any infant.

Supplemental Oxygen

In the CPAP-group FiO_2 1.0 was started 300 (225-315) s after birth and was given for 65 (33-105) s. FiO_2 was weaned in 20 (5-60) s to 21 (21-21) %. In all infants oxygen was started for low SpO_2 and HR was >100 bpm. In the PPV-group FiO_2 1.0 was started 180 (120-270) s after birth and was given for 100 (40-280) s. FiO_2 was weaned in 25 (10-47) s to 21 (21-30)%.

Oxygen saturation

In all patients the fastest increase in SpO_2 occurred in the first minute after starting oxygen (figure 1) (CPAP-group: from 62 (16)% to 87 (12)% at 1 minute after and to 93 (5)% at 2 minutes after starting oxygen, PPV-group: from 45 (19)% to 80 (24)% ($p<0.001$) after 1 minute and to 87 (19)% after 2 minutes (figure 1).

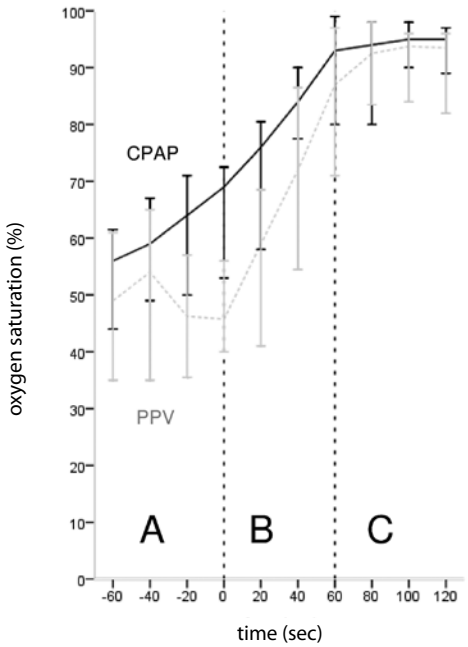

Figure 1. Oxygen saturation (%) of infants on CPAP and infants needing PPV in the minute before and 2 minutes after start of FiO_2 1.0. Black= CPAP-group, light grey= PPV-group, A= minute before start FiO_2 1.0, B= first minute after start FiO_2 1.0, C= second minute after start FiO_2 1.0.

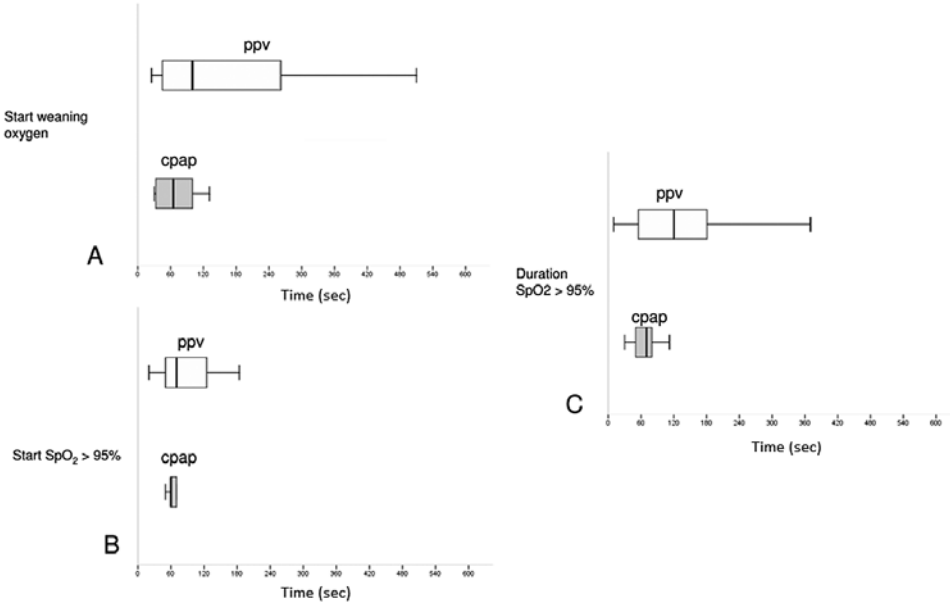

Figure 2. Box plots showing median (IQR) starting time of weaning FiO_2 1.0 (A), starting time of SpO2 >95% (B) in seconds after FiO_2 1.0 is started and duration of SpO2 >95% (C) in infants on CPAP and infants needing PPV. Grey= CPAP-group, white= PPV-group.

SpO_2 >95 % occurred in 9/17 (53%) infants of in group 1 and in 23/33 (69%) infants of group 2. The starting point and duration of SpO_2 >95% are depicted in figure 2.

Changes on respiratory drive when breathing on CPAP

In the CPAP-group, increasing FiO_2 to 1.0 increased RR from 30 (18-41) 1 min before to 35 (24-45) breaths per minute (ns) 1 minute after to 39 (31-44) breaths per minute ($p<0.05$) in the 2nd minute.

Vte and MV increased significantly in 1st minute after increasing FiO_2 to 1.0 and remained stable in the 2nd minute (Vte: from 4.9 (2.3-8.8) mL/kg to 6.7 (3.6-10.4) mL/kg ($p<0.001$) to 6.5 (3.7-10.2) mL/kg (ns); MV: from 134 (76-265) mL/kg/min to 240 (157-370) mL/kg/min ($p <0.01$) to 252 (135-376) mL/kg/min (ns)).

The rate of rise to maximum tidal volume increased from 13.8 (8.0-22.4) mL/kg/s in the minute before to 18.2 (11.0-27.5) mL/kg/s ($p<0.0001$) in the minute after increasing FiO_2 to 1.0 and remained stable at 18.8 (11.8-27.8) mL/kg/s (ns) in the 2nd minute.

Changes on respiratory drive when receiving PPV

PPV was given in 23 apneic infants and in 10 infants for poor respiratory drive. Apneic infants started breathing 80 (50-180)s after FiO_2 1.0 and at that moment SpO_2 was 87% (11) and HR 147 (19) bpm.

RR increased from 0 (0-4) 1 minute before to 9 (0-20) breaths per minute ($p < 0.001$) 1 minute after to 23 (0-34) breaths per minute ($p < 0.01$) in the 2nd minute after switching to FiO_2 1.0.

Discussion

We investigated the influence of switching from air to FiO_2 1.0 on SpO_2 and respiratory drive in preterm infants at birth. Most infants with SpO_2 near the 10th percentile had a good HR but FiO_2 was increased to 1.0 because of low SpO_2. After increasing FiO_2 to 1.0, respiratory drive improved simultaneously with a rapid increase in SpO_2. However, SpO_2 >95% occurred in the majority of infants, especially in the infants who received PPV, which probably reflects the difficulty of simultaneously performing PPV and titrating oxygen. These observations suggest that targeting a higher percentile as currently recommended in international guidelines (7;8) (25th-50th percentile) might improve respiratory drive. A more stepwise increase in FiO_2 and more diligence in reducing FiO_2, for example when SpO_2 >85 %, could reduce the risk of hyperoxia.

We observed that preterm infants started to breathe more vigorously, as indicated by an increased rate and effort, once FiO_2 was increased and SpO_2 improved. Antenatally, hypoxia suppresses fetal breathing movements (11) whereas postnatally, hypoxia stimulates breathing. The sensitivity increases during days-weeks after birth (12). However, the mechanisms driving the large inspiratory efforts and controlling the switch to continuous breathing after birth are unknown, although increasing arterial PO_2 may be involved (20). We speculate that infants in our study, who failed resuscitation with air, respiratory support was insufficient to aerate the lung and supplemental oxygen was required to compensate. We suggest that the resulting increase in oxygenation increased drive from the respiratory center and respiratory effort, which increased lung aeration and FRC. This would explain why FiO_2 1.0 was only required for a short time and could be rapidly weaned allowing most infants to remain stable with little extra oxygen. Although our weaning rate was fast, studies comparing high versus moderate FiO_2 levels in preterm infants found similar levels of FiO_2 at 10 minutes (9,21-23).

Experimental studies have shown that pulmonary vascular resistance at birth is related to ventilation onset and oxygen had little impact (24-26). Also, Sobotka *et al*. found that increasing FiO_2 to 1.0 in hypoxic lambs just after birth improved blood oxygenation, but had no effect on lung compliance and pulmonary blood flow (25). This supports the hypothesis that increased oxygenation after FiO_2 1.0 is achieved by increasing the partial pressure gradient for oxygen diffusion compensating the ventilation perfusion mismatch due to low FRC (25).

The reported Vte increased in infants on CPAP could be explained by improved lung compliance. However, volume increase occurred right after increasing FiO_2 and remained stable in the minute thereafter. Also, RR increase cannot be explained by improving compliance. Alternatively, increased pressures could have elevated Vte, but these remained unchanged. Increasing FiO_2 increases gas density which can influence measurements (17-19). However, after correction, tidal volumes remained significantly larger after FiO_2 1.0 and when considering the rate of rise is also increased it is more likely to be the infant's own effort.

Although studies showed it is feasible to support preterm infants at birth with a FiO_2 of <1.0, most infants starting with low FiO_2 levels needed an increased FiO_2 (0.45-0.6) to reach target SpO_2 levels (21;22). However, the different approaches make it difficult to compare these studies with our observational data reported in this study. We often observed SpO_2 below target. Therefore, starting in air may not be the right approach. Although it is unclear how detrimental a short period of FiO_2 1.0 is at birth (1-2 minutes), more vigilance in preventing SpO_2 levels >95% is needed (2).

In line with our recent report (13), we observed that oxygen use was not always according to the guidelines. Oxygen was given earlier or later than recommended. In the PPV-group a SpO_2 >95% occurred more often and lasted longer, increasing the chances of hyperoxia. These observations may indicate the algorithm was difficult to follow. This will become even more difficult if separate SpO_2 targets for each minute after birth are defined and may lead to a change in focus away from adequate ventilation. Adding an extra person to the resuscitation team could be helpful.

Limitations

The retrospective nature of the study and the relative small sample size precludes any hard conclusion regarding respiratory drive and oxygenation. Recording respiratory parameters at birth is challenging, similar studies do not include large number of infants

(17,28-31). The infants included in this study is a sample of the preterm infants born in the hospitals and a selection bias could have occurred. However, the sample was randomly chosen as recordings were performed if the research team was available. The observed variation in starting time of FiO_2 1.0 complicates comparing with the respiratory drive of infants receiving air. Also, the observational nature of this study prevented us to have a control group of infants needing no support. However, we were interested in the effect of FiO_2 1.0 and measurements before starting oxygen served as a control period.

Conclusions

We observed that during respiratory support of preterm infants switching from air to FiO_2 1.0 increased the risk for hyperoxia. No hard conclusions can be drawn, but our observations might suggest that respiratory drive increased after supplemental oxygen was given and oxygenation improved. The role of SpO_2 levels in stimulating respiratory drive at birth merits further investigation.

References

1. Higgins RD, Bancalari E, Willinger M, Raju TN. Executive summary of the workshop on oxygen in neonatal therapies: controversies and opportunities for research. Pediatrics 2007;119: 790-6.
2. Vento M, Saugstad OD. Oxygen supplementation in the delivery room: updated information. J Pediatr 2011;158: 5-7.
3. Hellstrom-Westas L, Forsblad K, Sjors G, Saugstad OD, Björklund LJ, *et al*. Earlier Apgar score increase in severely depressed term infants cared for in Swedish level III units with 40% oxygen versus 100% oxygen resuscitation strategies: a population-based register study. Pediatrics 2006;118:1798-1804.
4. Rabi Y, Rabi D, Yee W. Room air resuscitation of the depressed newborn: a systematic review and meta-analysis. Resuscitation 2007;72:353-363.
5. Saugstad OD, Ramji S, Soll RF, Vento M. Resuscitation of newborn infants with 21% or 100% oxygen: an updated systematic review and meta-analysis. Neonatology 2008;94:176-182.
6. Tan A, Schulze A, O'Donnell CP, Davis PG. Air versus oxygen for resuscitation of infants at birth. 2005;Cochrane Database Syst Rev:CD002273.
7. Perlman JM, Wyllie J, Kattwinkel J, Atkins DL, Chameides L, *et al*. Part 11: Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. 2010;Circulation 122:516-538.
8. Wyllie J, Perlman JM, Kattwinkel J, Atkins DL, Chameides L, *et al*. Part 11: Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation 2010;81:260-287.
9. Vento M, Moro M, Escrig R, Arruza L, Villar G, *et al*. Preterm resuscitation with low oxygen causes less oxidative stress, inflammation, and chronic lung disease. Pediatrics 2009;124:439-449.
10. Dawson JA, Kamlin CO, Vento M, Wong C, Cole TJ, *et al*. Defining the reference range for oxygen saturation for infants after birth. Pediatrics 2010;125:1340-1347.

11. Gluckman PD, Johnston BM. Lesions in the upper lateral pons abolish the hypoxic depression of breathing in unanaesthetized fetal lambs in utero. J Physiol 1987;382:373-383.
12. Davey MG, Moss TJ, McCrabb GJ, Harding R. Prematurity alters hypoxic and hypercapnic ventilatory responses in developing lambs. Respir Physiol 1996;105:57-67.
13. Schilleman K, Siew ML, Lopriore E, , Morley CJ, Walther FJ, *et al*. Auditing resuscitation of preterm infants at birth by recording video and physiological parameters. Resuscitation 2012;83:1135-1139.
14. O'Donnell CP, Kamlin CO, Davis PG, Morley CJ. Crying and breathing by extremely preterm infants immediately after birth. J Pediatr 2010;156:846-47.
15. Saugstad, OD, Rootwelt T, Aalen O. Resuscitation of asphyxiated newborn infants with room air or oxygen: an international controlled trial: the Resair 2 study. Pediatrics 1998;102:e1.
16. Bookatz GB, Mayer CA, Wilson CG, Vento M, Gelfand SL, *et al*. Effect of supplemental oxygen on reinitiation of breathing after neonatal resuscitation in rat pups. Pediatr Res 2007;61:98-702.
17. Fischer HS, Roehr CC, Proquitte H, Wauer RR, Schmalisch G. Assessment of volume and leak measurements during CPAP using a neonatal lung model. Physiol Meas 2008;29:95-107.
18. Foitzik B, Schmalisch G, Wauer RR. Effect of physical properties of respiratory gas on pneumotachographic measurement of ventilation in newborn infants. Biomed Tech (Berl) 1994;39:85-92.
19. Roske K, Foitzik B, Wauer RR, Schmalisch G. Accuracy of volume measurements in mechanically ventilated newborns: a comparative study of commercial devices. J Clin Monit Comput 1998;14:413-420.
20. Givan DC. Physiology of breathing and related pathological processes in infants. Semin Pediatr Neurol 2003;10:271-280.
21. Escrig R, Arruza L, Izquierdo I, Villar G, Sáenz P, *et al*. Achievement of targeted saturation values in extremely low gestational age neonates resuscitated with low or high oxygen concentrations: a prospective, randomized trial. Pediatrics 2008;121:875-81.
22. Rabi Y, Singhal N, Nettel-Aguirre A. (2011) Room-air versus oxygen administration for resuscitation of preterm infants: the ROAR study. Pediatrics 2011;128:e374-e381.
23. Wang CL, Anderson C, Leone TA, Rich W, Govindaswami B, *et al*. Resuscitation of preterm neonates by using room air or 100% oxygen. Pediatrics 2008;121:1083-9.
24. Lakshminrusimha S, Steinhorn RH, Wedgwood S, Savorgnan F, Nair J, *et al*. Pulmonary hemodynamics and vascular reactivity in asphyxiated term lambs resuscitated with 21 and 100% oxygen. J Appl Physiol 2011;111:1441-1447.
25. Sobotka KS, Hooper SB, Allison BJ, Te Pas AB, Davis PG, *et al*. An initial sustained inflation improves the respiratory and cardiovascular transition at birth in preterm lambs. Pediatr Res 2011;70:56-60.
26. Teitel DF, Iwamoto HS, Rudolph AM. Changes in the pulmonary circulation during birth-related events. Pediatr Res 1990;27:372-378.
27. Te Pas AB, Kamlin CO, Dawson JA, O'Donnell C, Sokol J, *et al*. Ventilation and spontaneous breathing at birth of infants with congenital diaphragmatic hernia. J Pediatr 2009;154:369-373.
28. Schmolzer GM, Dawson JA, Kamlin CO, O'Donnell CP, Morley CJ, *et al*. Airway obstruction and gas leak during mask ventilation of preterm infants in the delivery room. Arch Dis Child Fetal Neonatal Ed 2011;96:254-257.
29. Te Pas AB, Davis PG, Kamlin CO, , Dawson J, O'Donnell CP, *et al*. Spontaneous breathing patterns of very preterm infants treated with continuous positive airway pressure at birth. Pediatr Res 2008;64:281-285.
30. Finer NN, Rich W, Wang C, Leone T. Airway obstruction during mask ventilation of very low birth weight infants during neonatal resuscitation. Pediatrics 2009;123:865-869.
31. Te Pas AB, Wong C, Kamlin CO, Dawson JA, Morley CJ, *et al*. Breathing patterns in preterm and term infants immediately after birth. Pediatr Res 2009;65:352-356.

CHAPTER 9

Effects of naloxone on the breathing pattern of a newborn exposed to maternal opiates

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Acta Paediatr. 2012;101:e309-12

Abstract

Aim: To give new insights into how an infant responded to naloxone, given after acquiring a maternal opiate by recording the breathing pattern directly after birth.

Method: A respiratory recording is presented of an infant during resuscitation in the delivery room after receiving naloxone for respiratory depression, resulting from maternal remifentanyl use.

Results: The infant was born apneic and bradycardic. Normal resuscitation maneuvers had no effect on the respiratory drive. Directly after administration of naloxone, a tachypneic breathing pattern with sporadic expiratory braking maneuvers was observed.

Conclusion: The immediate tachypnea is most likely a direct effect of the naloxone causing an immediate "rebound response" after the release of the opiate induced inhibition of the respiratory drive.

Introduction

Naloxone is the N-ally1 derivative of oxymorphone and acts by competitively binding opiate receptors. Although other opiate antagonists have partial agonistic activity comparable to opiates, naloxone has little or no agonist activity on opiate receptors (1;2). Naloxone administration to neonates exposed to maternal opioids during labor has been common practice for neonatologists in the last 30 years. However the efficacy of this treatment has not been clearly demonstrated. In a systematic review, it was concluded that naloxone administration to newborns exposed to maternal opiates increased alveolar ventilation compared to control newborns (3). However, the significance of this finding is unclear because the newborns reviewed in these studies did not appear to have respiratory depression requiring ventilatory support (3). International guidelines state that focus needs to remain on effective ventilation and airway support for the persistently apneic newborn (4). We describe the breathing pattern of an apneic infant at birth, exposed to maternal acquired opiates, after the administration of naloxone.

Patient and methods

Recording physiological parameters, including respiratory function monitoring, and video recording is considered standard care in our neonatal unit of Leiden University Medical Center, the Netherlands. The recordings are used for audit, teaching and research and are obtained using a Masimo SET pulse oximeter (Masimo, Irvine, California, USA), a Florian respiratory monitor (Acutronic Medical Systems, AG, Switzerland) and a digital video recorder. Informed consent of the parents was received after delivery.

The mother, G1P0, was admitted at 35 weeks and 2 days of gestation with HELLP syndrome. One day after admission she experienced severe abdominal pain. Ultrasound examination revealed a large liver hematoma. The obstetricians decided to deliver the baby by emergency caesarean section. To prevent liver rupture and massive bleeding the mother had to be kept hemodynamically stable. Therefore general anesthesia with remifentanyl was given. Remifentanyl was administered by continuous intravenous infusion, starting with a dosage of 3.3 µg/min 23 minutes before delivery. 10 minutes before delivery the dose was increased to 20 µg/min.

The infant (birth weight 2415 grams) was born apneic, hypotonic and bradycardic (heart rate 60 bpm). The infant was resuscitated using a T-piece infant resuscitator (Neopuff; Fisher & Paykel Healthcare; Auckland; New-Zealand) according to local guidelines with

a rate of 40-60 inflations per minute using a peak inspiratory pressure (PIP) of 30 cmH_2O and a PEEP of 5 cmH_2O, gas flow was set to 8 L/min and fraction of inspired oxygen (FiO_2) was 21%.

At onset, mask ventilation was insufficient due to a large mask leak and as a result, the heart rate did not increase. After correction of mask position and increasing the PIP to 35 cmH_2O, adequate tidal volumes (mean Vte: 6.2 mL/kg, minute volume: 250 mL/kg) were achieved and the heart rate increased to around 120 bpm (112-124).

Every 30 seconds the infant's condition was evaluated, but spontaneous breathing was not observed (figure 1). The heart rate remained stable, but peripheral oxygen saturation did not increase and remained at 65% despite adequate ventilation (mean Vte 9 mL/kg, minute volume 370 mL/kg) and FiO_2 was increased from 21 to 100% (according to local guideline). One minute after increasing FiO_2 (3.5 minutes after commencing resuscitation), the oxygen saturation increased to 85%. However this had no effect on respiratory drive.

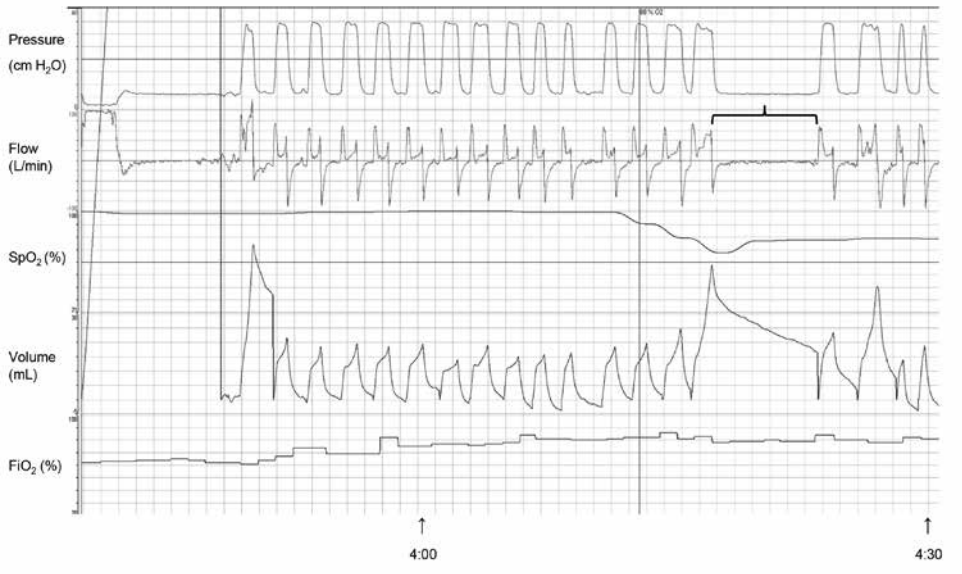

Figure 1. Part of a recording showing 2 periods of respiratory support by giving inflations using the T-piece resuscitator. Airway pressure (cmH_2O), flow (mL/s), FiO_2 and SpO_2 (%) and volume (mL) are given.
Between these periods of inflations performed no spontaneous breathing is seen, indicated by the accolade. In this period only a small change can be seen in volume. But this was caused by movement of the mask by the resuscitator. FiO_2 was titrated down from 100 to 80%.

According to Dutch (5) and local guidelines we have administrated naloxone at 6 minutes after birth because no spontaneous breathing was observed. Naloxone was administered intravenously via the umbilical vein (0.1 mg/kg), using an intravenous canula (Venflon, Bioflow, Ecouen, France). Dutch guidelines make no distinction between intravenous or intramuscular administration (5). Within seconds of naloxone administration, the infant immediately started breathing regularly at an average rate of 100 breaths per minute and heart rate increased to 140 bpm (figure 2). Vte of the spontaneous breaths gradually increased from 4.4 to 6.5 mL/kg over an 80 second period. During this period

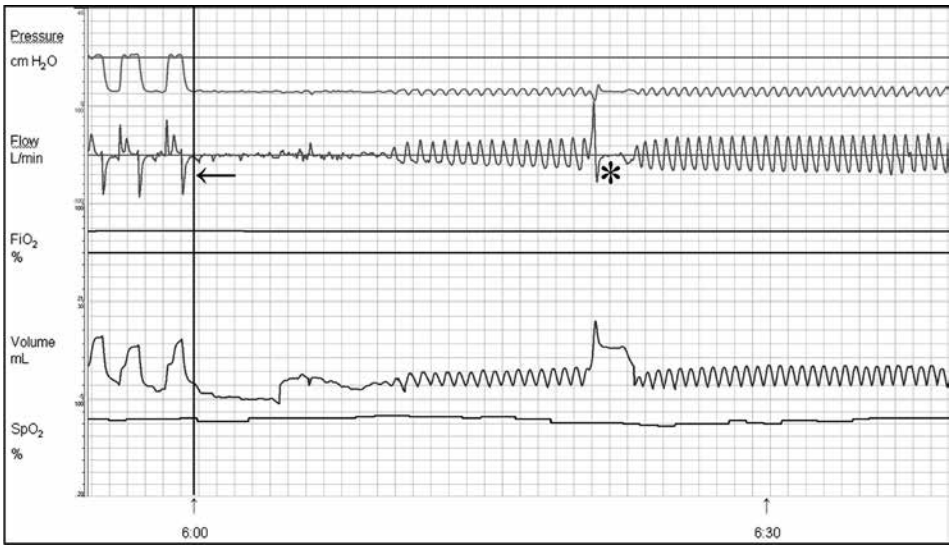

Figure 2. Part of a recording showing the inflations when naloxone was administered. Airway pressure (cmH_2O), flow (mL/s), FiO_2 and SpO_2 (%) and volume (mL) are given.
After naloxone administration at 6 minutes after birth (indicated by the vertical arrow) a spontaneous breathing pattern arose, showing tachypnoea (100 breaths per minute). The first EBM is marked with the *. EBM's are characterized by a short deep inspiration and a prolonged expiration phase. Inflations were stopped just before naloxone adminsitration to observe spontaneous breathing. FiO_2 was 80% during this part of the recording.

of high frequency breathing, the infant did not cry and only three EBM were observed. The transcutaneous oxygen saturation increased to 91% and the FiO_2 was weaned to room air (3 minutes after commencing with FiO_2 100%). After 1.5 minutes of spontaneous breathing, EBM's were more frequent and tidal volumes increased to 8.1 mL/kg. Apgar scores at 1, 5 and 10 minutes where 1, 6, 9 respectively.

At 11 minutes after birth the infant was transported to the NICU with nCPAP, which was stopped after 1 hour. At admission to the NICU (t= 20 minutes after birth) a blood gas was performed; values were pH 7.27, $paCO_2$ 7.6 kPa, paO_2 4.5 kPa, BE -2.4, HCO_3^- 25.6 mmol/L. At that time, the infant's respiratory rate had decreased to 44 breaths per minute. The infant was discharged in good health after 12 days admission to the medium care unit because of prematurity.

Discussion

This is the first observation of the direct effect of naloxone on the respiratory drive and breathing pattern of an apneic infant at birth exposed to maternal opiates. Despite FiO_2 of 1.0 the infant's oxygen saturation remained 85 %. However, in response to naloxone administration, we observed an immediate tachypneic breathing pattern resulting in a rapid recovery in oxygen saturation and FiO_2 was quickly titrated to air. Therefore, it is likely that the increase in respiratory drive was responsible for this recovery.

Tachypnoea has been described in preterm infants directly after birth, but not in term infants. This "panting pattern" is characterized by a respiratory rate greater than 60 breaths/min) that results from a shortening of the expiratory time (I:E time to approximately 1:1) and small tidal volumes are noted. (6). Expiration is immediately followed by an inspiration with no post-expiratory pause. (6). This breathing pattern is thought to assist in creating and maintaining FRC (6;7). in both humans and animals (8). The need for increasing the inspired oxygen level in this infant suggests that an inadequate FRC was created during initial mask ventilation. Once the infant started breathing spontaneously, inspired oxygen levels could be rapidly reduced, as presumably the infant created sufficient FRC during the tachypneic pattern (9). This was consistent with our finding that at the start of breathing only few EBMs were observed, these became more frequent later. An EBM is usually preceded by a short deep inspiration and is characterized by a prolonged expiratory phase (figure 2) (7;8). Siew *et al*. have shown that EBM's occur more frequently once FRC has been established.

The tachypneic breathing could be explained as a rebound response caused by a sudden release of opiate-induced suppression on the infant's respiratory centre at a time when the sensory inputs are providing an increasing stimulus to breath. Indeed, elevated $PaCO_2$ levels are a powerful stimulus for the body to increase respiratory frequency and enlarge the volume of inspired air. (10) Although assisted ventilation was considered adequate, based on the measured tidal volumes, the infant may still have been hypercapnic. Measuring end tidal CO_2 levels could be a valuable addition to evaluate the effec-

tiveness of resuscitation (11). Thus, it is possible that before naloxone treatment, a mild hypercapnea would have provided an increased stimulus to breathe, but as the respiratory centre was suppressed, the infant remained apneic. As with most feedback control systems, a lack of output response (in this case ventilation) usually leads to a greater stimulatory input, which would be further enhanced by an increasing hypercapnea with time. Consequently, the sudden release of the respiratory centre from an opiate-induced suppression (due to naloxone treatment) would have exposed the respiratory centre to a heightened stimulatory drive. This would lead to a transient rebound tachypnoea that would persist until the stimulatory input was sufficiently reduced.

In conclusion the breathing pattern of an apneic infant directly after administration of naloxone is described. This breathing pattern with few EBM illustrates that naloxone can have a direct effect on the mechanisms that control the respiratory drive of infants with respiratory depression due to narcotics. Until now there is little data about the effect of naloxone. Naloxone is rarely used and this would make conducting a large RCT difficult. However, observing the effect of naloxone by respiratory function monitoring and pharmacological studies would give us more insight into effects and actions of naloxone.

References

1. Bradberry JC, Raebel MA. Continuous infusion of naloxone in the treatment of narcotic overdose. Drug Intell Clin Pharm 1981;15:945-50.
2. Evans JM, Hogg MI, Lunn JN, Rosen M. A comparative study of the narcotic against activity of naloxone and levallorphan. Anaesthesia 1974;29:721-7.
3. McGuire W, Fowlie PW. Naloxone for narcotic exposed newborn infants: systematic review. Arch Dis Child Fetal Neonatal Ed 2003;88:F308-F311.
4. Kattwinkel J, Perlman JM, Aziz K, Colby C, Fairchild K, Gallagher J, *et al*. Neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Pediatrics 2010;126:e1400-e1413.
5. NVK werkgroep "Herziening Nederlandse Richtlijn Reanimatie van Pasgeborenen". Richtlijn Reanimatie van pasgeborenen. Jul 2008. Available form: URL: www.nvk.nl/kwaliteit/richtlijnenenindicatoren/richtlijnen/
6. te Pas AB, Wong C, Kamlin CO, Dawson JA, Morley CJ, Davis PG. Breathing patterns in preterm and term infants immediately after birth. Pediatr Res 2009;65:352-6.
7. Te Pas AB, Davis PG, Kamlin CO, Dawson J, O'Donnell CP, Morley CJ. Spontaneous breathing patterns of very preterm infants treated with continuous positive airway pressure at birth. Pediatr Res 2008;64:281-5.
8. Mortola JP, Magnante D, Saetta M. Expiratory pattern of newborn mammals. J Appl Physiol 1985;58: 528-33.
9. Siew ML, Wallace MJ, Kitchen MJ, Lewis RA, Fouras A, te Pas AB, *et al*. Inspiration regulates the rate and temporal pattern of lung liquid clearance and lung aeration at birth. J Appl Physiol 2009;106:1888-95.
10. Nattie E. CO2, brainstem chemoreceptors and breathing. Prog Neurobiol 1999;59:299-331.
11. Molloy EJ, Deakins K. Are carbon dioxide detectors useful in neonates? Arch Dis Child Fetal Neonatal Ed 2006;91:F295-F298.

CHAPTER 10

Functional Residual Capacity and expired CO_2 levels during stabilization of preterm infants at birth

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Submitted

Abstract

Background: Preterm newborns often need respiratory support at birth for lung liquid clearance and aeration. Previous studies provided tidal volume range during breathing and positive pressure ventilation (PPV) at birth, but little is known how efficient these are in lung recruitment and establishing gas exchange. Aim was to measure tidal volume, functional residual capacity (FRC) changes and gas exchange during respiratory support at birth.

Methods: The following measurements were performed: 1) expired tidal volumes (Vte (mL/kg)) using respiratory function monitoring, 2) changes in FRC (AU/kg) per breath using Respiratory Inductance Plethysmography (bands placed around rib cage (RC) and abdomen (AB)), 3) expired CO_2 (ECO_2) using a volumetric CO_2 monitor. For respiratory support a T-piece resuscitator and mask were used with PIP 25 cmH_2O and PEEP 5 cmH_2O. Data was analyzed during sustained inflation (SI), PPV and breathing on CPAP.

Results: 15 infants were included. Vte for inflations, inflations with breathing and breathing were significantly different (4.4 (2.5-8.6) vs. 8.8 (5.7-11.4) vs. 5.7 (3.3-9.8); $p<0.0001$)). Breathing led to the highest ECO_2, while during PPV ECO_2 was higher when breathing coincided (32 (23-38) vs. 20 (13-25) vs. 2 (3-11) mm Hg; $p<0.0001$). Little change in FRC occurred during the SI, PPV and breathing measured at the RC. In contrast, there was FRC gain at the AB during the SI, PPV, but most with breathing.

Conclusion: While Vte during breathing was lower compared to PPV, breathing was most effective in gas exchange and FRC gain than PPV.

Introduction

Most preterm infants have difficulty clearing lung liquid and aerating their lungs at birth due to the highly compliant chest wall, weak respiratory muscles and an insufficient amount of surfactant (1-3). Lung liquid clearance and aeration is an essential prerequisite to establish adequate gas exchange during transition to postnatal life (4). Lung aeration is the primary trigger for a decrease in pulmonary vascular resistance and increase in pulmonary blood flow (5). Positive Pressure Ventilation (PPV) is recommended when an infant has difficulty breathing, remains apnoeic or has a heart rate <100 beats per minute (bpm) at first evaluation (6).

To monitor the effect of PPV international resuscitation guidelines recommend to monitor heart rate (HR), if HR increases then ventilation must be adequate enough (6). In addition, respiratory function monitoring has been recommended to measure flow and calculate the tidal volumes of inflations given (7). However, these parameters provide little information how efficient ventilation is and if so what volume reaches the distal airway for gas exchange. It has recently been shown in animals that measurement of expired CO_2 (ECO_2) at birth can indicate the degree of lung aeration and whether gas exchange is efficient (8). Also, a study in preterm infants suggests that the measurement of CO_2 can be used to guide PPV during neonatal resuscitation (9). However, preterm infants often breathe during PPV at birth and no differentiation has been made between the inflations given and inflations coinciding with breathing (8;9). Previous studies provided tidal volumes during positive pressure ventilation (PPV) and breathing (10-12), but little is known how efficient these are in providing lung recruitment and gas exchange compared to spontaneous breathing.

After lung liquid clearance and aeration, establishing and maintaining end- expiratory volume (functional residual capacity (FRC)) is very important for adequate gas exchange and to prevent ventilation perfusion mismatch at birth (4). Although experimental studies have shown that ventilation strategies such as an initial sustained inflation (SI) and positive end expiratory pressure (PEEP) can be beneficial for FRC, measurements of FRC in preterm infants at birth are difficult to perform. Respiratory Inductance Plethysmography (RIP) is frequently used in the Neonatal Intensive Care Unit to measure FRC changes (13), but so far this has not been used in the delivery room.

For this observational study we measured tidal volume, functional residual capacity (FRC) changes using Respiratory Inductance Plethysmography (RIP) and gas exchange during respiratory support in preterm infants at birth. Our aim was to measure the effect of the SI, PPV and breathing on FRC and gas exchange directly after birth.

Methods

The local institutional review boards of the Leiden University Medical Center and the V. Buzzi Children's Hospital approved physiological recordings at birth. Written informed consent was acquired antenatally.

Respiratory support was delivered with a T-piece resuscitator (Neopuff, Fisher & Paykel, Wellington, New Zealand) and a properly sized round face mask (35 mm face mask; Fisher & Paykel, Wellington, New Zealand or size 0/0 face mask; Laerdal, Stavanger, Norway). Respiratory support was given if the infant was apneic (PPV), had labored breathing (continuous positive airway pressure) and/or the HR was below 100 bpm. Respiratory support was started by giving an initial SI of 10 s in the LUMC and of 15 s in the V. Buzzi hospital using a peak inspiratory pressure (PIP) of 25 cmH_2O and a positive end-expiratory pressure (PEEP) of 5 cmH_2O with fractional inspired oxygen of 0.3 and continuing with PPV or continuous positive airway pressure. Changing inspiratory pressure was left to the discretion of the caregiver.

Respiratory function measurements (pressures, gas flow and tidal volumes and ECO_2) were conducted using a respiratory function monitor MRT-A Respiratory function monitor (Applied Biosignals, Weener, Germany) fitted with a Bicore II (CareFusion, Yorba Linda, CA, USA) and using Polybench software (Applied Biosignals, Weener, Germany). Tidal volumes and pressure were measured using a variable orifice plethysmography sensor (Avea VarFlex Flow Transducer (Carefusion, Yorba Linda, CA, USA)) with a dead space of 0.8 mL. ECO_2 was measured using a Capnostat volumetric capnography device and disposable neonatal sensors (both Carefusion, Yorba Linda, CA, USA) with a dead space of 1 mL. The sensors were telescoped to minimize dead space and placed between the face mask and the T-piece. The combined dead space of the sensors was measured to be 1.5 mL

RIP was measured using two single use 10 inch Respibands Plus (Carefusion, Yorba Linda, CA, USA) placed around the thorax at the nipple line and at the abdomen just above the umbilicus. Umbilical cord clips were used to align the bands closely to the chest and abdomen circumference.

RIP bands were placed by the researcher before the infant was placed in a plastic wrap. Data collection started directly after placing the infant on the resuscitation table and it was continued until the infant was stable. Data was collected at 200 Hz and analyzed using Pulmochart software (Advanced Life Diagnostics, Weener, Germany). For compar-

ison we analyzed the SI, the first 30 s of PPV (inflations and inflations coinciding with breathing) and the first 30 s of spontaneous breathing.

Inspiratory (Vti) and expiratory tidal volumes (Vte) were determined. Distinction was made between breaths, inflations and inflation coinciding with breathing (10). For inflations leak (%) was calculated using the formula ([Vti – Vte]/Vti) × 100%. Also for capnography signals we determined if during PPV and breathing there was obstruction causing stasis of CO_2 in the sensor and during breathing if there was rebreathing of CO_2. Stasis and rebreathing was defined as all volumes below 1.5 mL (dead space of the sensor) and when CO2 did not go to zero after expiration. These inflations and breaths were excluded from analysis.

Statistical analysis

Data were analyzed with SPSS (IBM, version 20.0, 2012, IL, USA). Results are presented as mean (SD) for normally distributed values or median (IQR) and median (range) for non-normally distributed values. Variables were compared using a Wilkinson signed rank test for paired non-normally distributed values or a Kruskall-Wallis Test for comparison between >2 non-normally distributed values. Correlation was calculated using a Pearson product moment correlation. Value of <0.2, 0.2-0.7 and >0.7 were considered to reflect low, moderate and high correlation. Statistical significance was defined as $p<0.05$. Reported p-values are 2-sided.

Results

Measurements were performed in 18 infants, of which 3 recordings were of poor quality and excluded. Thus, 15 infants (median (IQR) gestational age 28 (27-31) weeks, birth weight 1080 (994-1300) grams) were included into the analysis. All infants received an initial SI and in 5/15 infants a second SI was given. 13/15 infants received PPV thereafter and 2 breathed on CPAP. In total 20 SI, 487 PPV inflations, of which 188 coincided with breathing, and 554 spontaneous breaths were analyzed. Rebreathing occurred in 8% (39/487) of inflations and in 19% (105/554) of breaths (figure 1).

The first SI had a mean (SD) duration of 12.8 (4.5) s with a PIP of 23.9 (1.5) cmH_2O. The second SI had a duration of 13.2 (6.0) s with a PIP of 24.3 (0.9) cmH_2O. PPV not coinciding with breathing was given with a PIP of 24.2 (2.1) cmH_2O and a PEEP of 4.3 (1.1) cmH_2O. During breathing a PEEP of 4.5 (1.2) cmH_2O was given.

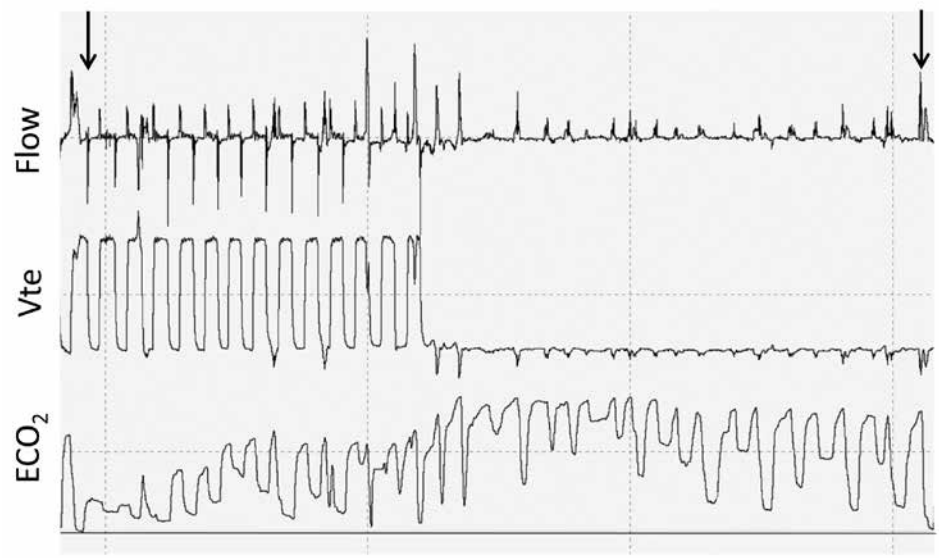

Figure 1. Recording which shows rebreathing occurring during PPV and continuing during breathing on CPAP. Start and en of rebreathing is indicated by the arrows. The horizontal black line indicates 0 mmHg.

Tidal volumes and CO_2

During the first SI, 11/15 infants breathed with an average of 4 (3) breaths per SI and 4/15 infants were apneic. Vte of breaths was 4.8 (1.4-10.8) mL/kg and ECO_2 was 10 (1-18) mm Hg. Vte and ECO_2 were larger when infants were breathing during SI than in apneic infants (Vte of 5.9 (2.4-8.2) vs. Vte of 5.2 (0.2-6.0) mL/kg; $p<0.05$, ECO_2 16 (10-30) mm Hg vs. ECO_2 of 5 (2-15) mm Hg; $p<0.01$)).

During the second SI, 4/5 infants breathed with an average of 2 (1) breaths per SI. Vte of breaths was 5.0 (1.2-11.1) mL/kg and ECO_2 was 22 (7-26) mm Hg. Vte and ECO_2 were larger when infants were breathing during SI than in apneic infant (Vte 5.2 (0.2-6.0) mL/kg, ECO_2 16 (4-25)) vs. Vte 4.6 mL/kg, ECO_2 4 mmHg) ns).

During PPV not coinciding with breathing mask leak was 15 (0-39) %. Vti, Vte and ECO_2 were significantly larger during inflations coinciding with breathing when compared to inflations only (Vti (10.4 (6.6-13.1) vs. 7.2 (4.3-10.9) mL/kg; $p<0.0001$, Vte 8.8 (5.7-11.4) vs. 4.4 (2.5-8.6) mL/kg; $p<0.0001$, ECO_2 20 (13-25) vs. 2 (3-11) mm Hg ($p<0.0001$). Spontaneous breaths had smaller volumes when compared to inflations (Vte of 5.7 (3.3-9.8) mL/kg ($p<0.0001$)), but ECO_2 was significantly larger with 32 (23-38) mm Hg ($p<0.0001$).

ECO_2 increased when Vte increased during PPV inflations coinciding with breathing, but there was only a moderate correlation (0.35; p=0.01) (table 1, figure 2). Also, during the SI, Vte and ECO_2 were only moderately correlated with each other (table 1, figure 3 and 4).

FRC changes

A small but significant (p<0.01) gain in FRC occurred between each breath or inflation when measured at the RC (table 2). There was large and significant FRC gain when measured at the AB (p<0.0001) during the inflations, but especially during breathing (table 2). Furthermore during breathing FRC changes were more variable when compared to the SI and PPV.

Table 1. Correlation of expiratory tidal volume (Vte) and exhaled CO2 (ECO_2) (* p <0.01) during all three modes of ventilatory support.

		Correlation Vte/ECO_2
SI (breathing)		0.49*
PPV	Inflations only	0.29*
	Inflations coinciding with breathing	0.35*
Breathing		0.24*

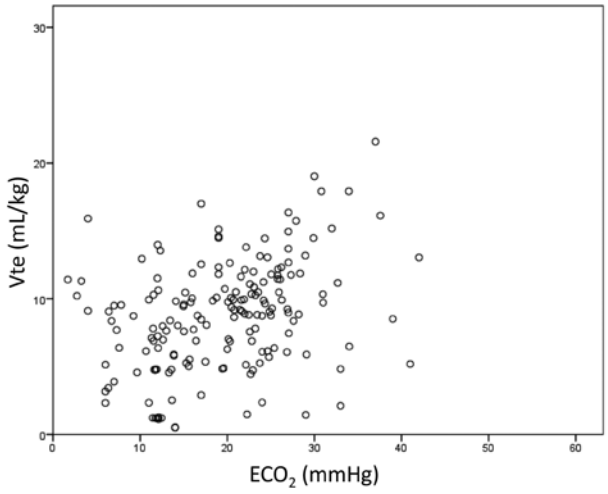

Figure 2. Scatterplot of Vte and ECO_2 of PPV inflations coinciding with breathing.

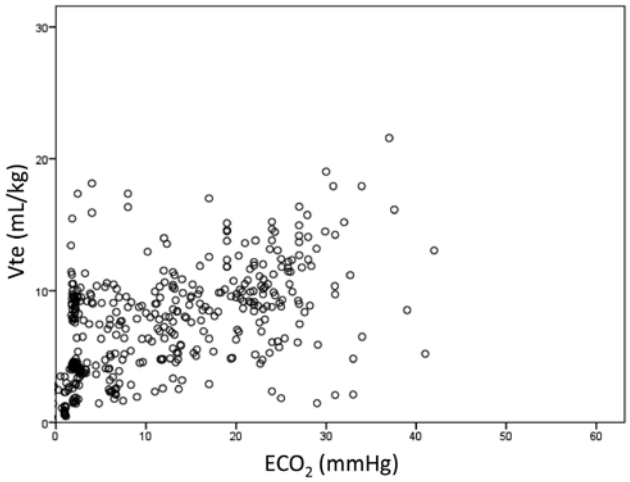

Figure 3. Scatterplot of Vte and ECO_2 of PPV inflations not coinciding with breathing.

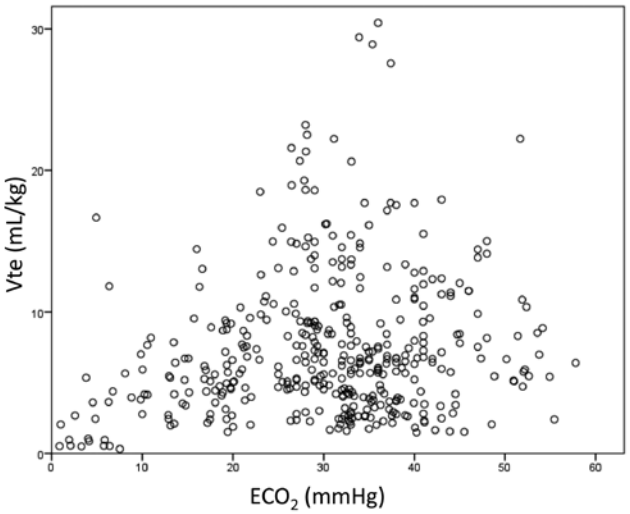

Figure 4. Scatterplot of Vte and ECO2 of spontaneous breaths on CPAP.

Table 2. Median (IQR) FRC changes per breath for all three modes of ventilatory support (AU/kg)

		RC change per breath/ inflation (AU/kg)	AB change per breath/ inflation (AU/kg)
SI		6 (-73-114)	47 (1-146)
PPV	Inflations only	6 (-15-41)	46 (19-100)
	Inflations coinciding with breathing	4 (-41-45)	24 (-9-102)
Breathing		–7 (–57-38)	97 (23-221)
p-value		<0.01	<0.0001

Discussion

In this study we observed that while during the resuscitation of preterm infants the tidal volumes delivered during PPV were considered adequate, effective gas exchange and gain in FRC occurred only when breathing occurred, coinciding with inflations or not. Although the volumes measured during breathing on CPAP were smaller, gas exchange and establishing FRC was more adequate than during inflations. These findings confirm that in preterm infants at birth breathing during and after PPV is more efficient than the inflations given and plays an important part in the success of ventilation given at birth (10). For evaluating the efficiency of PPV and breathing at birth, not only tidal volumes, but also ECO_2 should be taken into account.

In tidal volume measurements a distinction must be made between manual ventilation and spontaneous breathing. During manual ventilation not only the lungs are pressurized, but also the upper respiratory tract. This could cause a difference in the measured tidal volumes and the volumes actually delivered to the lung. For this reason it is possible higher tidal volumes are needed for efficient ventilation than currently recommended (4-8 mL/kg) (7). In addition, it is likely that the subatmospheric pressure generated during spontaneous inspiration is more efficient than the positive pressure applied via the airways (14), promoting faster and more uniform liquid clearance from the airways and lung tissue and a quick increase in FRC (15). Furthermore during spontaneous breathing the infant uses breathing patterns of which expiratory braking manoeuvres are the most important to preserve lung volume (12). Expiratory braking manoeuvres probably cause a more variable FRC gain during breathing compared to inflations and are more effective in creating and maintaining a positive airway pressure in the distal airways than the PEEP applied during mask ventilation.

We observed a smaller increase in FRC at the RC compared to the AB. As the thorax is less compliant compared to the AB it is possible that during pulmonary aeration the distending lung will move downwards and force the AB outwards. Therefore, that the largest gain in FRC, observed during spontaneous breathing with lower tidal volumes, will be measured at the AB. This is in line with a recent study using a preterm rabbit pup model showing that the largest increase in FRC is in the medial and basal lobes of the lung (15). Although we did not observe AB distention clinically, it is possible that we did not measure FRC gain but rather the accumulation of air in the stomach and intestines. During inflation, air could more easily go to the stomach than to the lungs due to the high resistance in the airways caused by the presence of lung liquid and/or an adducted glottis. However, this is unlikely as the largest FRC gain was measured during sponta-

neous breathing during which most of the air enters the lungs as the glottis is relaxed and the airways are mostly cleared.

In our study we observed only a moderate, but significant, correlation between ECO_2 and Vte during breathing and PPV via a mask. A previous study showed good correlation between Vte and ECO_2 in animal models and in a part of the preterm infants (8). As the animals and a part of the human infants in this study were intubated this could cause more adequate gas exchange and thereby better correlation between Vte and ECO_2 as ventilation is directed straight to the lungs. In the infants that showed good correlation was determined individually and because we did not report correlation for infants separately this could explain the difference found. There are several factors that could influence the CO_2 measurements during mask ventilation. 1) Leak is frequent during mask ventilation (10;11;16) and although it was moderate in this study it could still decrease the CO_2 concentration in the sensor and ECO_2 is therefore underestimated. 2) A larger volume could be measured by pressurization (and thus distention) of the upper respiratory tract, while in fact there limited ventilation of the lung due to a closed glottis or inadequate inspiratory pressures, causing discrepancy in volume vs. ECO_2. 3) Despite that we corrected for the dead space of the sensor it is still possible that dead-space ventilation of the mask, oropharynx and trachea cause insufficient renewal of the expired volume measured causing overestimation of the ECO_2. We should be aware that these factors can also occur during face mask ventilation without CO_2 monitoring rebreathing. These factors make interpreting CO_2 data as direct feedback in the delivery room complicated.

Collecting the data in an adequate manner, especially using the RIP bands, was very difficult and it was only possible to include a small group of infants. However the differences in ECO_2 between different modes of respiratory support are highly significant. As the recording started immediately after birth the RIP bands could not be zeroed and we were not able to determine an overall change in FRC. However, we could report the change in FRC per individual breath.

Conclusion

During resuscitation of preterm infants at birth breathing significantly higher ECO_2 and more gain in FRC was observed during breaths when compared to PPV, indicating that breathing was more efficient in establishing gas exchange and FRC. There are several factors influencing CO_2 measurements during mask ventilation and caution should be taken when using this as feedback during resuscitation.

References

1. Gerhardt T, Bancalari E. Chestwall compliance in full-term and premature infants. Acta Paediatr Scand 1980;69:359-64.
2. Keens TG, Bryan AC, Levison H, Ianuzzo CD. Developmental pattern of muscle fiber types in human ventilatory muscles. J Appl Physiol Respir Environ Exerc Physiol 1978;44:909-13.
3. Pringle KC. Human fetal lung development and related animal models. Clin Obstet Gynecol 1986;29: 502-13.
4. Hooper S, Harding R. Role of aeration in the physiological adaptation of the lung to air-breathing at birth. Curr Respir Med Rev 2005;185-95.
5. Crossley KJ, Allison BJ, Polglase GR, Morley CJ, Davis PG, Hooper SB. Dynamic changes in the direction of blood flow through the ductus arteriosus at birth. J Physiol 2009;587:4695-704.
6. Kattwinkel J, Perlman JM, Aziz K, Colby C, Fairchild K, Gallagher J, *et al*. Part 15: neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122:S909-S919.
7. Schmolzer GM, Te Pas AB, Davis PG, Morley CJ. Reducing lung injury during neonatal resuscitation of preterm infants. J Pediatr 2008;153:741-5.
8. Hooper SB, Fouras A, Siew ML, Wallace MJ, Kitchen MJ, Te Pas AB, *et al*. Expired CO2 levels indicate degree of lung aeration at birth. PLoS One 2013;8:e70895.
9. van OS, Cheung PY, Pichler G, Aziz K, O'Reilly M, Schmolzer GM. Exhaled carbon dioxide can be used to guide respiratory support in the delivery room. Acta Paediatr 2014.
10. Schilleman K, van der Pot CJ, Hooper SB, Lopriore E, Walther FJ, Te Pas AB. Evaluating Manual Inflations and Breathing during Mask Ventilation in Preterm Infants at Birth. J Pediatr 2013;162:457-63.
11. Schmolzer GM, Kamlin OC, O'Donnell CP, Dawson JA, Morley CJ, Davis PG. Assessment of tidal volume and gas leak during mask ventilation of preterm infants in the delivery room. Arch Dis Child Fetal Neonatal Ed 2010;95:F393-F397.
12. Te Pas AB, Davis PG, Kamlin CO, Dawson J, O'Donnell CP, Morley CJ. Spontaneous breathing patterns of very preterm infants treated with continuous positive airway pressure at birth. Pediatr Res 2008;64: 281-5.
13. Brooks LJ, DiFiore JM, Martin RJ. Assessment of tidal volume over time in preterm infants using respiratory inductance plethysmography, The CHIME Study Group. Collaborative Home Infant Monitoring Evaluation. Pediatr Pulmonol 1997;23:429-33.
14. Boon AW, Milner AD, Hopkin IE. Lung expansion, tidal exchange, and formation of the functional residual capacity during resuscitation of asphyxiated neonates. J Pediatr 1979;95:1031-6.
15. Siew ML, Wallace MJ, Kitchen MJ, Lewis RA, Fouras A, Te Pas AB, *et al*. Inspiration regulates the rate and temporal pattern of lung liquid clearance and lung aeration at birth. J Appl Physiol 2009;106:1888-95.
16. Kaufman J, Schmolzer GM, Kamlin CO, Davis PG. Mask ventilation of preterm infants in the delivery room. Arch Dis Child Fetal Neonatal Ed 2013;98:F405-F410.
17. Rozycki HJ, Sysyn GD, Marshall MK, Malloy R, Wiswell TE. Mainstream end-tidal carbon dioxide monitoring in the neonatal intensive care unit. Pediatrics 1998;101:648-53.

PART 3

Circulation

CHAPTER 11

Non-invasive measurements of hemodynamic transition directly after birth

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Pediatr Res. 2014;75:448-52

Abstract

Background*:* Cardiac output depends on stroke volume and heart rate (HR). Only HR is used to monitor hemodynamic transition.

Methods: In 24 term newborns born via cesarean section, HR and preductal blood pressure (BP) were measured. Also, using echocardiography, left ventricular dimensions (LVD) and (Doppler derived) output (LVO) were examined at 2, 5 and 10 minutes after birth.

Results: Mean (SD) HR and BP did not change with time (HR: 157 (21) bpm at 2 minutes, 154 (17) bpm at 5 minutes and 155 (14) bpm at 10 minutes; mean BP: 51.2 (15.4) mmHg at 2 minutes, 50.5 (11.7) mmHg at 5 minutes and 49.6 (9.5) mmHg at 10 minutes). Left ventricular end diastolic diameter increased from 2-5 minutes (14.3 (1.3) vs. 16.3 (1.7) mm; $p < 0.001$) and stabilized at 10 minutes (16.7(1.4) mm). LVO increased between 2-5 minutes (151 (47) vs. 203 (55) mL/kg/min ($p < 0.001$)) and stabilized at 10 minutes (201 (45) mL/kg/min). LVO increase was associated with left ventricular stroke volume ($r = 0.94$; $p < 0.001$), not with HR ($r = 0.37$; ns).

Conclusion: LVD and LVO significantly increased the first 5 minutes after birth and stabilized at 10 minutes, whereas BP remained stable. LVO and LVD increase are presumably due to increasing left ventricular preload resulting from pulmonary blood flow and ductal shunting increase.

Introduction

The transition to extra uterine life at birth represents a major physiological challenge which begins with lung aeration and the onset of air-breathing (1). The initiation of breathing and the resulting pulmonary and hemodynamic changes support the successful transition from fetal to postnatal life. The hemodynamic component of the transition includes a rise in heart rate (HR) (2), a decrease in pulmonary vascular resistance (PVR) and an increase in pulmonary blood flow (PBF) in the very first minutes which are initiated by lung aeration and an increase in systemic vascular resistance (SVR) caused by cord clamping (1).

Although pulmonary transition has been the focus of recent experimental (3;4) and clinical studies (5), the subsequent hemodynamic changes and factors regulating this phenomenon, are not completely understood (5). The hemodynamic transition is essential for adequate gas exchange and oxygenation of vital organs and is supported by an increase in PBF which replaces the umbilical circulation in providing preload to the left ventricle (6). However, data obtained from newborn infants are sparse and most knowledge is based on animal studies (5;7;8). Although these animal studies provide important information that informs our general understanding, it is critical to demonstrate that the findings from anaesthetized and ventilated animals are consistent with observations in spontaneously breathing infants. Although cardiac output (CO) depends on HR and stroke volume, HR is the only objective parameter described and currently used to evaluate the hemodynamic condition of an infant at birth (9). Limited data are available on changes in left ventricular dimensions and output within the first 10 minutes after birth. Noori *et al*. described these measurements after birth. However the time point and range of the first measurement was 3-7 minutes, and this study was not designed to assess hemodynamic changes during the first 10 minutes after birth (10). Although blood pressure (BP) values are used later in life, they are not routinely measured in the delivery room and little data is available on BP changes in infants directly after birth.

Therefore, the aim of this study was to assess hemodynamic changes directly after birth with repeated measurements in the first 10 minutes of life with special focus on changes in left ventricular dimensions and output by using Doppler imaging.

Methods

The Leiden University Medical Center is a tertiary perinatal center. For our study we included healthy term infants (≥37 weeks of gestation) delivered by elective cesarean section. The study was approved by the Institutional Review Board of the Leiden University Medical Center. Parents were approached during pre-operation visit or by telephone at least one day before the cesarean section took place.

Because the cesarean sections were scheduled we were able to prepare our equipment in due time. Only infants with an uncomplicated transition at birth (e.g. no respiratory support necessary) were included. None of the woman were in labor during the time of the elective cesarean section. There the infants were not distressed during birth. All infants with suspected malformations or infants who required any form of respiratory support (application of PEEP, extra oxygen or Positive Pressure Ventilation) during transition were excluded.

A stopwatch was started as soon as the infant was born (i.e. when the shoulders were delivered). In accordance with local guidelines the umbilical cord was clamped 30-60 s after birth and cut by the obstetrician. Therefore most infants would have commenced breathing before cord clamping. Thereafter, the baby was placed under a radiant heater and the neonatal caregiver, who was not involved in the research project, provided standard care (drying, keep warm, evaluation of the infant's condition). Stimulation, positioning and suctioning only took place when needed. All measurements were collected at three time points after birth: as soon as the infant was placed on the resuscitation table and at 5 and 10 minutes after birth. During this period the infant remained on the resuscitation table.

SpO_2 was measured continuously using a Masimo Radical 7 pulse oximeter (Masimo, Irvine, California) with a LCNS Neo-3 sensor (Masimo, Irvine, California) placed around the ulnar aspect of the infant's right wrist. ECG electrodes were fixed as soon as the infant reached the resuscitation table and HR was determined using an ECG that was recorded during and in synchrony with the echocardiographic examination (11).

Non-invasive BP was measured preductally using an IntelliVue MP30 Philips Monitor (Philips, Eindhoven, the Netherlands) with a neonatal cuff size 4 (Philips, Eindhoven, the Netherlands) placed on the right upper arm. During a preliminary study we found that simultaneous measurements of BP and SpO_2 led to a low signal on the Masimo pulse oximeter, even if the maximal sensitivity mode is used. Therefore, BP measurements were

limited to a very short period and SpO_2 values were measured immediately after the cuff was released.

To assess the immediate changes in cardiac function after birth, an echocardiographic examination was performed using a Vivid I Cardiovascular Ultrasound system equipped with a 7.0 MHz transducer (GE Healthcare, Waukesha, Wisconsin). Furthermore ECG leads (Neotrode II, Conmed, Utica, New York) were placed. Echocardiographic measurements were obtained as soon as the infant was placed on the resuscitation table and at 5 and 10 minutes after birth. Standard two-dimensional gray scale images were acquired from the parasternal and apical views, including M-mode assessment of the left ventricle and stored in digital format. Doppler pulsed wave measurements were obtained at the aortic annulus (AoAnn) level in the apical "5-chamber" view to assess the velocity time integral (VTI) over the aortic valve.

Assessment of left ventricular dimensions included both left ventricular end-diastolic diameter (LVedd) and left ventricular end-systolic diameter (LVesd) and were obtained M-mode measurements. Shortening fraction (SF) was calculated from LVedd and LVesd using the formula ((LVedd - LVesd)/LVedd) (12). Left ventricular output (LVO) was calculated using the formula (((π*AoAnn^2) /4) * VTI * HR)/ birth weight (13). In this formula (((π*AoAnn^2)/4) * VTI) defines the left ventricle stroke volume (LVSV). The echocardiogram, echocardiographic measurements and data analysis were performed by 1 observer (a senior consultant in pediatric cardiology). All infants received a comprehensive echocardiogram after the procedure to rule out any structural anomalies of the heart.

Data were analyzed using SPSS (IBM, version 20.0.0, Chicago, Illinois). Results are presented as mean (standard deviation (SD)), mean (range) or median (IQR) where appropriate. Individual data of the 3 time-points were compared using a paired sample T-test. To account for multiple comparisons between the three time points, we performed the tests using the Bonferroni corrected level of p= 0.05/3= 0.017. The correlations between LVO, LVSV and HR values were calculated using a Pearson's product-moment correlation. A value <0.2 was considered low, a value between 0.2 and 0.7 was considered moderate and a value >0.7 was considered to reflect high correlation. A p-value of <0.05 was regarded as statistically significant. Reported p-values are two-sided.

Results

The parents of 38 infants were approached for participation in this research project, 30 of whom consented. Six infants were excluded for logistical reasons (late arrival of the research team in 3 cases, absence of the echo cardiographer in 1 case and technical difficulty with the echocardiographic measurement in 2 cases. Therefore 24 infants could be included. Reasons for an elective cesarean sections were: previous cesarean section (16/24), fetal position (3/24), maternal pre-existent disease (3/24) (spina bifida, cervix pathology, previous pelvic fracture) and parent's request (2/24). All mothers received local anesthesia, shortly before the procedure. The infants included in this study had a gestational age of (mean (SD)) 38.5 (0.8) and birth weight of 3541 (458) grams and Apgar scores (median (IQR) of 9 (8-9) at 1 minute, 9 (8-10) at 5 minutes and 10 (9-10) at 10 minutes. All infants started crying before they arrived at the resuscitation table. None of the infants needed stimulation, positioning, suctioning or any respiratory support during transition, e.g. application of PEEP, supplemental oxygen or Positive Pressure Ventilation. All measurements were completed in the 24 included patients at (at 120 (35) s, 300 (0) s and 600 (0) s after birth. All infants underwent delayed cord-clamping varying from 30-60 s. None of the infants had any structural cardiac anomalies.

Heart rate, saturation and blood pressure

SpO_2 increased significantly in the first 10 minutes after birth (table 1). HR and BP did not significantly change in the first ten minutes after birth. (table 1).

Left ventricular changes after birth

LVedd significantly increased from 14.3mm±1.3mm at 2 minutes to 16.3mm ±1.7 mm at 5 minutes ($p<0.001$) after birth and remained stable between 5 and 10 minutes (16.7 mm ±1.4 mm ($p=0.15$)). LVesd increased from 9.4mm ±1.9mm at 2 minutes to 10.0 mm ±2.7 mm at 5 minutes and 10.4 mm ±2.0 mm at 10 minutes, but LVesd was only significantly

Table 1. BP, HR and SpO_2 at 2, 5 and 10 minutes after birth.

Parameter (mean (SD))	2 min.	5 min.	10 min.	p 2-5min.	p 5-10min.
BP systole, mmHg	68.3 (18.3)	71.9 (13.2)	70.9 (10.5)	0.48	0.94
BP diastole, mmHg	41.6 (16.0)	38.3 (11.4)	36.4 (12.3)	0.48	0.74
BP mean, mmHg	51.2 (15.4)	50.5 (11.7)	49.6 (9.5)	0.76	0.82
HR, bpm	157 (21)	154 (17)	155 (14)	0.52	0.70
SpO_2, %	70 (18)	81 (14)	92 (6)	0.01	0.001

different between 2 and 10 minutes (p=0.02) (figure 1). SF of the left ventricle increased in the first 5 minutes (from 29 % ±5 % to 33 % ±7 %; p<0.001) after birth and increased further between 5 and 10 minutes, but did this difference did not reach statistical significance (36 %±6 %; p= 0.12) (figure 2).

LVSV increased significantly from 1.mL/kg ±0.3 mL/kg at 2 minutes to 1.3 mL/kg ±0.4mL/kg at 5 minutes (p<0.001) and remained stable at 10 minutes after birth with 1.3 mL/kg ±0.3 mL/kg (p =0.99). LVO increased significantly from 151 mL/kg/min ±47 mL/kg/min at 2 minutes to 203 mL/kg/min ±5 mL/kg/min at 5 minutes (p <0.001) and remained stable at 10 minutes after birth at 201 mL/kg/min ±45mL/kg/min (0.76) (figure 3,4). The increase in LVSV was highly correlated with the increase in LVO between 2 and 5 minutes (0.94 (p<0.001)), 5 and 10 minutes (0.92 (p <0.001)) and 2 and 10 minutes (0.90 (p<0.001)). There was a moderate to weak correlation between the increase in HR and LVO, which did not reach significance at all time points (2 and 5 minutes (0.37 (p=0.09)), 5 and 10 minutes (0.20 (p=0.07)) and 2 and 10 minutes (0.40 (p =0.37)) .

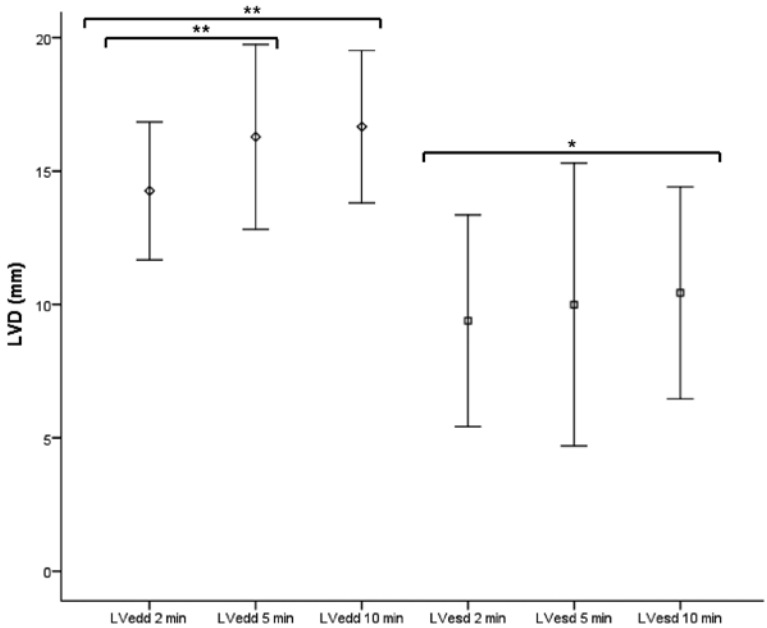

Figure 1. Change of left ventricular end diastolic diameter (white) and change of the left ventricular end systolic diameter (grey) during 2-, 5- and 10 minute time points after birth. Box plots show mean values and standard deviation of data. ** p<0.001, * p<0.01

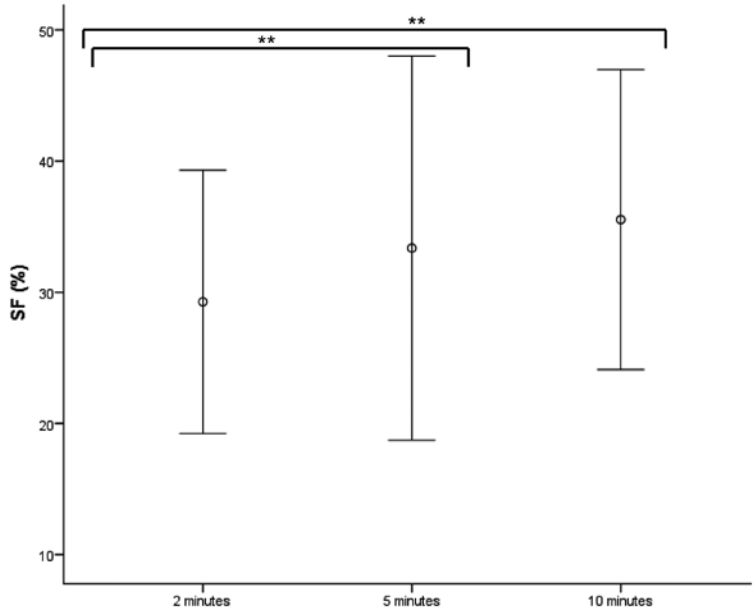

Figure 2. Shortening fraction of the left ventricle during 2-, 5- and 10 minute time points after birth. The box plots show mean values) and standard deviation of data. ** p<0.001

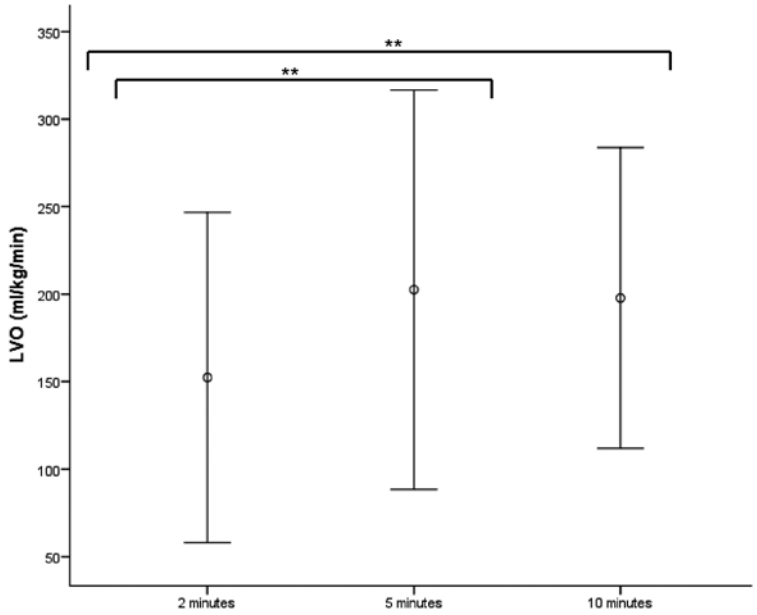

Figure 3. Changes in left ventricular output in mL/kg/min during 2-, 5- and 10 minute time points after birth. The box plots show mean values and standard deviation of data. ** p<0.001

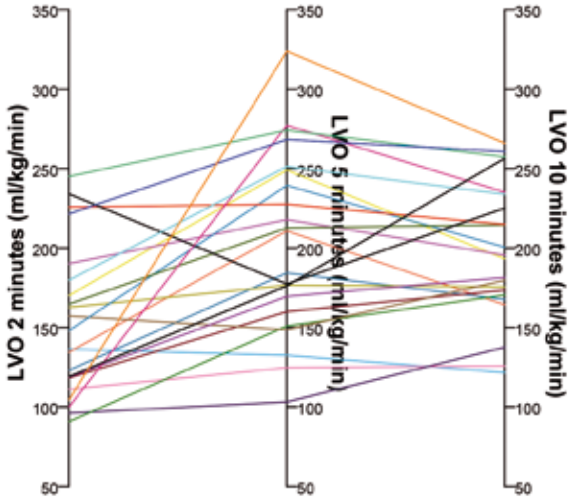

Figure 4. Individual changes of left ventricular output (mL/kg/min) for all patients during 2-, 5- and 10 minute time points after birth.

Discussion

Non-invasive cardiac measurements directly after birth demonstrated a rapid increase in LVO within the first minutes after birth, with no change in BP and no further increase to 10 minutes after birth. LVO was strongly correlated with the increase in LVSV between 2, 5 and 10 minute time points. HR only showed a weak correlation with the increase in LVO. As the increase in LVedd was larger than that of LVesd, causing an increase in SF, we speculate that increased preload mainly induces the increase in LVSV.

Despite the rapid increase in LVO the preductal BP remained unchanged in the first 10 minutes and was comparable to known values measured over the first day after birth (14). BP is the product of CO and vascular resistance and is mediated by cardiovascular reflexes, capillary fluid shifts, stress and relaxation and hormonal control (such as adrenalin) (15). It is possible that the decrease in PVR and increase in SVR following lung aeration and umbilical cord clamping, mitigated the increase in CO resulting in no change in BP. Alternatively, the sudden increase in ductal left-to-right shunting caused by the decrease in PVR and increase in SVR may provide an alternate low resistance pathway for LVO (6). Indeed, experimental and human data showed that the increase in left-to-right shunting through the ductus arteriosus contributes to ~50% of PBF immediately after

birth and ensures that pulmonary venous return and left ventricular preload are increased (6;10;16). Presumably this explains the increase in LVO we observed immediately after birth.

After cord clamping, the increase in left ventricular preload and the resulting increase in LVO are dependent upon the increase in PBF. In newborn lambs left ventricular preload was compromised when the cord was clamped in the absence of lung aeration and increase in PBF (6). Lung aeration and increase in PBF before clamping the cord will minimize the compromise to LVO, because PBF can replace the umbilical venous return as the source of preload. As umbilical cord clamping was delayed by 30-60 s in this study it is highly likely that all infants had commenced breathing, aerated their lungs and initiated an increase in PBF before their umbilical cords were clamped. This may explain why we observed only a 25 % increase in LVO whereas as previous animal experiments have reported a 50 % reduction after cord clamping preceding ventilation, followed by a 50% increase when ventilation was started (6).

In the human fetus LVO was estimated to be 179 mL/kg/min, not dependent on gestational age (13). These values are comparable to measurements of LVO in sheep fetuses (17). We observed that LVO increases to 203 mL/kg/min in the first 10 minutes after birth, which is similar to values reported in other studies at 15 minutes (235 mL/kg/min) (18). and 20 minutes (190 mL/kg) (10) after birth. The increase in LVO we and others have observed in humans is less than the increase in LVO reported in lambs which doubled after birth compared fetal values possibly due to a higher metabolic demand at this time (17). The higher values of CO observed in animals may also be explained by the difference in species.

Compared with values of LVSV measured in the fetus 24 hours before birth (1.21 mL/kg) LVSV, measured in our study, is increased (2.25 mL/kg) immediately after birth (19) but decreases in the hours thereafter (18;19).. Similar changes have been observed in animal studies (6;17). Our results extend these observations by demonstrating that directly after birth a rapid increase in LVO occurs, mainly due to an increase in LVSV. Although it is widely believed that HR is the primary determinant of CO in the newborn due to an inability to increase stroke volume (20), our findings clearly indicate that LVO is not only determined by HR but also by changes in LVSV. As HR did not change significantly in our study this had only moderate influence on the change in LVO.

The changes in LVO and LVSV during neonatal transition, begin when the cord is clamped and the infant start to breathe (8,20). Rising PBF, caused by increased left-to-right

ductal shunting and decreased PVR (6), most likely explains the increase of LVedd, which is responsible for the increase in SF at 5 min after birth as LVesd was not altered. Besides the increase in left atrial preload, the increase in LVedd might also be influenced by the reduction in pericardial pressure and increase in cardiac compliance after the onset of breathing and increase in preload (21). The change in preload can explain the increase in stroke volume by the Frank-Starling mechanism. Similarly, as LVesd is influenced by afterload, it is not surprising that this was only slightly altered in our study as systemic arterial pressure was not increased.

Limitations

It is possible that our measurements were influenced by a delayed cord clamping. Although delayed cord clamping has beneficial effects on outcome for both preterm and term newborn infants, the exact timing necessary for the most benefit has not been established (22). Delayed cord clamping has shown to be beneficial for vascular filling, superior vena cava blood flow, right ventricle output and right ventricular stroke volumes at 48 hours (23). The delay of cord clamping could diminish the effect of the significant loss of venous return that accompanies cord clamping (6), causing the reported changes in LVO to be less compared to changes in LVO in infants after immediate clamping.

Ductal flow and the increase in left-to-right shunt after birth are important in the increase in PBF and pulmonary venous return. However, due to time restrictions and our focus on changes in LV dimensions and output, we did not assess changes in ductal flow and right ventricular output at the various time points after birth.

The echocardiographic measurements could have changed the activity level of the infant. However, we did not observe differences in HR and BP throughout the measurement period. HR was similar to median values observed in healthy term infants (2). Echocardiographic measurements were not analyzed blinded as the timer is shown in the recordings and all loops for measurements are chronically numbered. This could have led to bias. However, we did not anticipate such large differences found between the 2- and 5 minute time point. We report values for a relatively small group. However the observed changes are highly significant using echocardiographic techniques. Furthermore Tsai-Goodman *et al*. and Hudson *et al*. have shown that echocardiographic measurements of the aortic annulus in neonates were highly reproducible (24;25). Also the determination of LVO, by Doppler derives measurements has been shown to be a reliable technique to asses changes in LVO within subjects (25;26). Preferably the measu-

rements would have to be performed during normal transition after vaginal births and not in non-distressed infants born after elective cesarean section. Also the caesarean section could have influenced the transition. We were not allowed to perform the study in vaginal deliveries as this would have large impact on the standard care. However, most infants underwent cord clamping at 30-60 s after birth which allows time for the newborn infant to breathe. Results, therefore, may be comparable to vaginally born infants where delayed cord clamping is utilized.

Conclusion

The unique data reported in this study provides new insights in the immediate cardiac adaptation directly after birth. We showed that a normal transition causes a significant rise in LVedd and LVO most likely due to an increase in preload due decrease in pulmonary vascular resistance. Throughout the period of early transition BP is maintained at the same level.

Our findings in spontaneously breathing infants at birth will add to the current knowledge of what actually happens during transition. A better understanding of the normal physiological adaptation is essential when attempting to understand problems associated with circulation in the immediate newborn period and to develop strategies to support transition.

Acknowledgements

We express our gratitude to the research nurses C. Kolster-Bijdevaate and M. S. Verhart for their help with the inclusion of our patients.

References

1. Te Pas AB, Davis PG, Hooper SB, Morley CJ. From liquid to air: breathing after birth. J Pediatr 2008;152: 607-11.
2. Dawson JA, Kamlin CO, Wong C, Te Pas AB, Vento M, Cole TJ, *et al*. Changes in heart rate in the first minutes after birth. Arch Dis Child Fetal Neonatal Ed 2010;95:F177-F181.
3. Hooper SB, Kitchen MJ, Siew ML, Lewis RA, Fouras A, Te Pas AB, *et al*. Imaging lung aeration and lung liquid clearance at birth using phase contrast X-ray imaging. Clin Exp Pharmacol Physiol 2009;36:117-25.
4. Sobotka KS, Hooper SB, Allison BJ, Te Pas AB, Davis PG, Morley CJ, *et al*. An initial sustained inflation improves the respiratory and cardiovascular transition at birth in preterm lambs. Pediatr Res 2011;70: 56-60.
5. Gao Y, Raj JU. Regulation of the pulmonary circulation in the fetus and newborn. Physiol Rev 2010;90:1291-335.
6. Crossley KJ, Allison BJ, Polglase GR, Morley CJ, Davis PG, Hooper SB. Dynamic changes in the direction of blood flow through the ductus arteriosus at birth. J Physiol 2009;587:4695-704.
7. Heymann MA. Control of the pulmonary circulation in the fetus and during the transitional period to air breathing. Eur J Obstet Gynecol Reprod Biol 1999;84:127-32.
8. Teitel DF, Iwamoto HS, Rudolph AM. Effects of birth-related events on central blood flow patterns. Pediatr Res 1987;22:557-66.
9. Kattwinkel J, Perlman JM, Aziz K, Colby C, Fairchild K, Gallagher J, *et al*. Neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Pediatrics 2010;126:e1400-e1413.
10. Noori S, Wlodaver A, Gottipati V, McCoy M, Schultz D, Escobedo M. Transitional changes in cardiac and cerebral hemodynamics in term neonates at birth. J Pediatr 2012;160:943-8.
11. Kamlin CO, Dawson JA, O'Donnell CP, Morley CJ, Donath SM, Sekhon J, *et al*. Accuracy of pulse oximetry measurement of heart rate of newborn infants in the delivery room. J Pediatr 2008;152:756-60.
12. Rein AJ, Sanders SP, Colan SD, Parness IA, Epstein M. Left ventricular mechanics in the normal newborn. Circulation 1987;76:1029-36.
13. Mielke G, Benda N. Cardiac output and central distribution of blood flow in the human fetus. Circulation 2001;103:1662-8.
14. Kent AL, Kecskes Z, Shadbolt B, Falk MC. Normative blood pressure data in the early neonatal period. Pediatr Nephrol 2007;22:1335-41.
15. Jones JE, Jose PA. Neonatal blood pressure regulation. Semin Perinatol 2004;28:141-8.
16. Disturbances in the postnatal closure of the various blood vessels and channels and their relation to asphyxia: Hearings Before the SubComm. on Blackwell Scientific Publications of the House Comm. on Oxdord, Lind J, (1953).
17. Stopfkuchen H. Changes of the cardiovascular system during the perinatal period. Eur J Pediatr 1987;146:545-9.
18. Winberg P, Jansson M, Marions L, Lundell BP. Left ventricular output during postnatal circulatory adaptation in healthy infants born at full term. Arch Dis Child 1989;64:1374-8.
19. Agata Y, Hiraishi S, Oguchi K, Misawa H, Horiguchi Y, Fujino N, *et al*. Changes in left ventricular output from fetal to early neonatal life. J Pediatr 1991;119:441-5.
20. Sharma A, Ford S, Calvert J. Adaptation for life: a review of neonatal physiology. Anaesthesia and intensive care medicine 2010;12:85-90.
21. Grant DA, Kondo CS, Maloney JE, Walker AM, Tyberg JV. Changes in pericardial pressure during the perinatal period. Circulation 1992;86:1615-21.

22. Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database Syst Rev 2012;8:CD003248.
23. Sommers R, Stonestreet BS, Oh W, Laptook A, Yanowitz TD, Raker C, *et al*. Hemodynamic effects of delayed cord clamping in premature infants. Pediatrics 2012;129:e667-e672.
24. Hudson I, Houston A, Aitchison T, Holland B, Turner T. Reproducibility of measurements of cardiac output in newborn infants by Doppler ultrasound. Arch Dis Child 1990;65:15-9.
25. Tsai-Goodman B, Martin RP, Marlow N, Skinner JR. The repeatability of echocardiographic determination of right ventricular output in the newborn. Cardiol Young 2001;11:188-94.
26. Murase M, Ishida A, Momota T. Serial pulsed Doppler assessment of early left ventricular output in critically ill very low-birth-weight infants. Pediatr Cardiol 2002;23:442-8.

CHAPTER 12

Non-invasive measurements of ductus arteriosus flow directly after birth

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Arch Dis Child Fetal Neonatal Ed. 2014: [Epub ahead of print]

Abstract

Objective: to assess ductus arteriosus (DA) blood flow directly after birth in healthy term infants after elective caesarean section.

Design: In healthy term newborns, echocardiography was performed at 2, 5 and 10 minutes after birth to monitor cardiac output and DA blood flow. Heart rate (HR) was assessed using ECG.

Setting: The delivery rooms of the Leiden University Medical Center.

Patients: 24 healthy term infants born after a cesarean section were included in this study.

Results: Mean (SD) HR did not change (158 (18) beats per minute (bpm), 5 minutes (159 (23) bpm) and 10 minutes (156 (19) bpm). DA diameter decreased from 5.2 (1.3) mm at 2 minutes to 4.6 (1.3) mm at 5 minutes ($p=0.01$) to (3.9 (1.2) mm) ($p=0.01$) at 10 minutes. Right-to-left DA shunting was unaltered (median (IQR) 95 (64-154) mL/kg/min to 90 (56-168) mL/kg/min and 80 (64-120) mL/kg/min respectively (ns)), whereas left-to-right shunting increased significantly between 2 and 5 minutes (41 (31-70) mL/kg/min vs. 67 (37-102) mL/kg/min, ($p=0.01$)) and increased significantly between 2 and 10 minutes (93 (67-125)) mL/kg/min ($p<0.001$). Right-to-left/left-to-right shunting ratio decreased significantly from 2.1 (1.4-3.1) at 2 minutes to 1.4 (1.0-1.8) at 5 minutes ($p<0.0001$) and to 0.9 (0.6-1.1) at 10 minutes ($p<0.0001$).

Conclusions: DA shunting changes swiftly from predominantly right-to-left shunting to predominantly left-to-right shunting at 10 minutes after birth, reflecting differential changes in pulmonary and systemic vascular resistance.

Introduction

Directly after birth, major changes in the respiratory and cardiovascular systems are required for postnatal survival (1;2). This includes ductus arteriosus (DA) closure, a major vascular shunt between the pulmonary and systemic circulation. This closure is preceded by changes in the amount and direction of blood flow through the DA. DA Blood flow is determined by the pressure difference between the pulmonary artery and aorta (3-5). Before birth, high pulmonary vascular resistance (PVR) ensures that blood flows from the right ventricle through the DA and into the systemic circulation (right-to-left (RtoL) shunting) throughout the cardiac cycle. Although blood flows into the lungs briefly during systole, during late systole and throughout diastole blood reflects off the highly resistant pulmonary vasculature and exits the pulmonary circulation across the DA (3-6). This retrograde pulmonary arterial flow causes high diastolic flow through DA in the fetus, as flow in the main pulmonary trunk is zero throughout much of diastole (5). Approximately 90% of right ventricular output (RVO) in the fetus by-passes the lungs and flows across the DA (3).

After birth, lung aeration initiates a sudden decrease in PVR, causing the majority of RVO to enter the pulmonary circulation resulting in a large increase in pulmonary blood flow (PBF) (3;7;8). In contrast to PVR, systemic vascular resistance (SVR) increases due to cord clamping (9). With the increase in SVR and decrease in PVR, the pressure gradient across the DA reverses and blood begins to flow from the systemic into the pulmonary circulation (left-to-right (LtoR) shunting) (3;6;10;11). In lambs, increase in LtoR shunt is responsible for up to 50% of PBF shortly after birth, depending on gestational age (3). However, LtoR flow across the DA is not continuous throughout the cardiac cycle, as RtoL flow occurs briefly during systole and becomes LtoR throughout most of diastole (3).

Although in ventilated lambs DA blood flow directly after birth has been described and several studies evaluated ductal flow in neonates during the first hours to days after birth (12-17), little is known about the immediate changes in DA flow in spontaneously breathing infants at birth. Therefore, we aimed to assess DA flow by repeated measurements using Doppler imaging in the first 10 minutes of life after an elective caesarean section.

Methods

Healthy term infants (≥37 weeks of gestation) delivered by elective caesarean section were included from October 2012 until December 2013. Infants were included after completing enrollment for a previous study that focused on changes in left ventricular dimensions and function directly after birth (18). Parents were approached during pre-operation visit or by telephone at least one day before the caesarean section took place. Consent was obtained both verbally en in writing for all patients before the procedure.

For logistical reasons, only infants born after elective caesarean sections were included, as equipment could be prepared in time. Only infants with an uncomplicated transition at birth (e.g., no respiratory support necessary) and without congenital malformations were included. A stopwatch was started as soon as the infant was born (i.e., when the shoulders were delivered). In accordance with local guidelines, the umbilical cord was clamped 30-60s after birth and cut by the obstetrician. Therefore, most infants commenced breathing before cord clamping. Thereafter, the baby was placed under a radiant heater and the neonatal caregiver provided standard care (drying, keeping warm, evaluation of the infant's condition). Stimulation, positioning and suctioning only took place when needed. All measurements were collected at three time points after birth: as soon as the infant was placed on the resuscitation table and at 5 and 10 minutes after birth. During this period the infant remained on the resuscitation table.

Heart rate (HR) was determined using ECG electrodes (Neotrode II, Conmed, Utica, New York, USA) during the echocardiographic examination. Electrodes were placed as soon as the infant reached the resuscitation table. Oxygen saturation (SpO_2) was measured continuously using a Masimo Radical 7 pulse oximeter (Masimo, Irvine, California) with a LCNS Neo-3 sensor (Masimo, Irvine, California) placed preductally.

To assess immediate changes in cardiac output and DA flow after birth, an echocardiographic examination was performed using a Vivid I Cardiovascular Ultrasound system equipped with a 7.0 MHz transducer (GE Healthcare, Waukesha, Wisconsin, USA). Standard two-dimensional (2D) grey-scale images were acquired from the suprasternal, parasternal and apical views and stored in digital format (20). To assess the velocity time integral (VTI), Doppler pulsed wave measurements were obtained in the apical "five-chamber" parasternal long axis view at the level of the aortic annulus for left ventricular output (LVO) and in the parasternal short axis view at the level of the pulmonary annulus for RVO. Aortic diameter was measured at the level of the aortic annulus in the parasternal long axis, pulmonary diameter was measured at the level of the pulmonary

annulus in the parasternal short axis and diameter of the aortic and pulmonary annulus were measured at each time point (20). The DA was visualized in its long axis from the pulmonary artery and the descending aorta in the suprasternal view. DA diameter (DaDiam) and VTI were assessed using 2D echocardiography and Doppler continuous wave measurements (figure 1). DaDiam was assessed at its smallest part at the pulmonary junction and measured at each time point. Using the continuous wave Doppler measurements the peak velocity of the RtoL and LtoR shunt was assessed. VTI evaluation of DA flow included analysis of three consecutive flow profiles, providing a mean VTI at each time point for each patient (figure 1).

LVO, RVO and DA shunt volume were calculated using the formula $(((\pi \times Ann^2)/4) \times VTI \times HR)/birth\ weight$ (19). To assess relative differences between RtoL versus LtoR shunting, DA flow ratio was calculated based on VTI measurements (RtoL flow VTI/LtoR flow VTI) for each time point. Also, duration of LtoR and RtoL shunting over the DA was measured and the flow time ratio was calculated.

The study was approved by the Institutional Review Board of the Leiden University Medical Center.

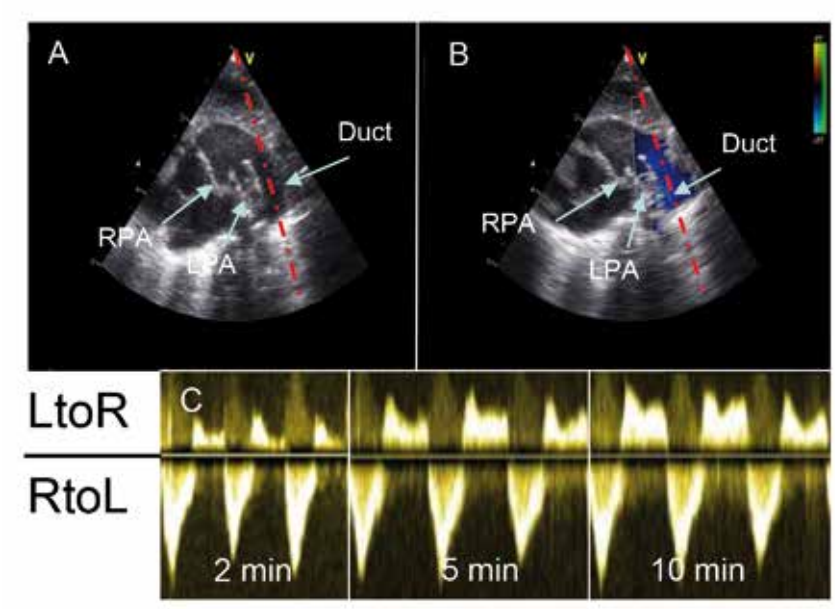

Figure 1. Examples of DA blood flow collected using continuous wave Doppler imaging (A and B) showing the left pulmonary artery LPA, right pulmonary artery (RPA) and ductus arteriosus (DA) marked with arrows. (C) DA shunt at 2 minutes, 5 minutes and 10 minutes after birth.

Statistics

Data were analysed using SPSS (IBM, version 20.0.0, Chicago, Illinois, USA). Results are presented as mean (SD), median (range) or median (IQR) where appropriate. Individual data of the three time-points were compared using a paired sample t-test for normally distributed data or a Mann-Witney U test for non-normally distributed data. To account for multiple comparisons between the time points, tests were performed using the Bonferroni corrected level (p= 0.05/3= 0.017). A two-sided p-value of <0.05 was regarded as statistically significant.

Results

In 26 newborn infant's measurements were performed. In two infants, measurements were stopped as respiratory support was necessary and these infants were excluded from analysis. In total, 24 infants were included in this study (median (range) gestational age 39 (37-39) weeks, mean (SD) birth weight 3561 (713) grams). Data were collected at 121 (42) s, 5- and 10 minutes after birth.

HR was not significantly different between 2 minutes (158 (18) beats per minute (bpm), 5 minutes (159 (23) bpm) and 10 minutes (156 (19) bpm). DA diameter decreased from 5.2 (1.3) mm at 2 minutes to 4.6 (1.3) mm at 5 minutes (p=0.01) and decreased further to 3.9 (1.2) mm) (p=0.01) at 10 minutes. Diameter of the aortic- and pulmonary annulus did not change between time points. SpO_2 increased significantly from 72 (10) % at 2 minutes to 82 (9) at 5 minutes (p=0.001) and increased further to 95 (6) at 10 minutes (p=0.0001).

Right- and left ventricular output

No significant difference in RVO was observed within the first 10 minutes after birth (RVO was 311 (107) at 2 minutes vs. 301 (80) mL/kg/min at 5 minutes (ns) and 343 (125) mL/kg/min at 10 minutes (ns)). LVO increased significantly from 165 (50) mL/kg/min to 191 (57) mL/kg (p=0.01) between 2 and 5 minutes after birth and then increased further to 212 (67) mL/kg/min (p=0.01). Also, LVO significantly increased from 2 to 10 minutes after birth (p<0.0001).

DA shunting

RtoL DA shunting flow was not significantly different at 2, 5 and 10 minutes after birth (median (IQR) 95 (64-154) mL/kg/min to 90 (56-168) mL/kg/min and 80 (64-120) mL/kg/min respectively) although it tended to decrease with time. LtoR shunting increased significantly from 41 (31-70) mL/kg/min to 67 (37-102) mL/kg/min, (p=0.01) between 2

and 5 minutes and then significantly increased to 93 (67-125) mL/kg/min (p<0.001 vs. 2 minutes) at 10 minutes (figure 2).

Peak velocity was not significantly different between 2, 5 and 10 minutes for RtoL shunt (0.95 (0.84-1.16), 0.96 (0.89-1.26) and 1.06 (0.95-1.20) m/s at respectively). However, peak velocity of LtoR shunting was significantly different between 2 and 5 minutes (0.45 (0.37-0.57) vs. 0.51 (0.41-0.70) m/s (p<0.05) and between 5 and 10 minutes (0.51 (0.41-0.70) vs. 0.71 (0.62-0.95) m/s (p<0.01).

Net difference in DA shunting ((LtoR flow)-(RtoL flow)) increased significantly from -53 (-81- to -17) mL/kg/min at 2 minutes (i.e., predominantly RtoL) to -21 (-45- to -1) mL/kg/min at 5 minutes (p=0.001) and increased further to 8 (-9- 33) mL/kg/min (p<0.0001). As a result flow through the DA at 10 minutes was predominantly LtoR. DA flow ratio decreased significantly from 2.1 (1.4-3.1) at 2 minutes to 1.4 (1.0-1.8) at 5 minutes (p<0.0001) and to 0.9 (0.6-1.1) at 10 minutes (p<0.0001) (figure 2, 3). Within a single cardiac cycle, duration of RtoL shunting was similar at 2 and 5 minutes (159 (25) ms vs. 162 (25) ms), but was

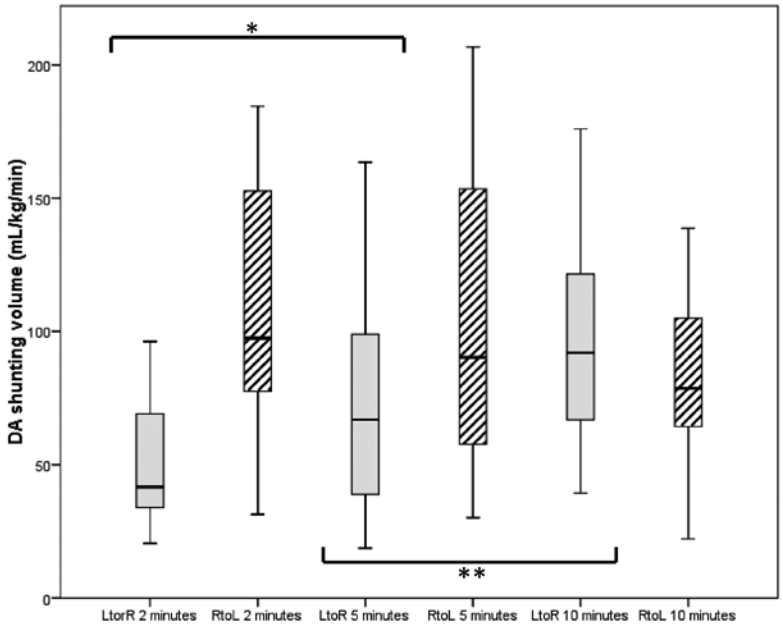

Figure 2. Change of DA LtoR shunting volume (mL/kg/min) (grey) and change of DA RtoL shunting volume (mL/kg/min) (shaded) at 2-, 5- and 10 minute time points after birth. Box plots show median values (solid black bar), IQR (margins of box) and range of data. * p<0.01, ** p<0.001,

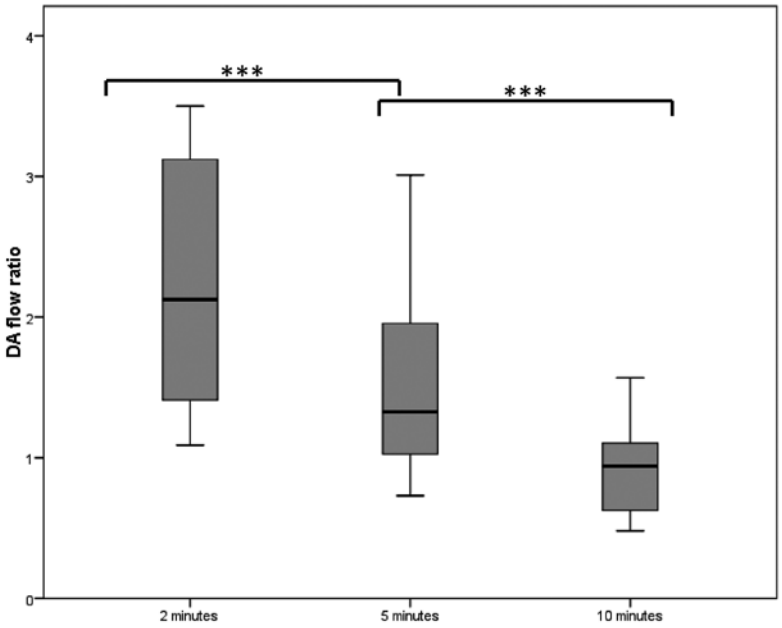

Figure 3. Change of DA flow ratio during 2-, 5- and 10 minute time points after birth. Box plots show median values (solid black bar), inter quartile range (margins of box) and range of data. *** p<0.0001

significantly decreased to 152 (23) ms (p=0.02) at 10 minutes. LtoR shunting duration significantly increased from 167 (71) to 219 (63) ms (p<0.0001) between 2 and 5 minutes and increased further to 236 (40) ms (ns) at 10 minutes. DA flow time ratio significantly decreased from 0.92 (0.71-1.45) to 0.74 (0.59-0.93) (p<0.0001) between 2 and 5 minutes and then significantly decreased to 0.66 (0.53-0.72) at 10 minutes (p<0.0001).

Discussion

This is the first study that presents data on temporal changes in DA blood flow in the first 10 minutes after birth in human infants. Doppler measurements of DA shunting demonstrated a large increase in LtoR shunting despite decrease in DA diameter. Furthermore, the ratio of RtoL vs. LtoR DA flow decreased in a temporal manner after birth, reflecting an overall change from predominantly RtoL- to predominantly LtoR shunting in the first minutes after birth. Observed changes in DA flow directly after birth are the expected combined consequences of the decrease in PVR due to lung aeration and increase in SVR due to cord clamping. Decrease in PVR will only occur during pulmonary aeration

and as a result the ratio of RtoL vs. LtoR DA flow could be regarded as an indicator for the cardiopulmonary transition after birth.

Immediately after birth, lung aeration stimulates a large decrease in PVR, which results in a large increase in PBF that, in addition to umbilical cord clamping, is largely responsible for the hemodynamic transition at birth (3;5;9;20-22). Decrease in PVR and increase in SVR reverses the pressure gradient between the pulmonary and systemic circulation (6;23), which promotes LtoR DA shunting (19). The increase in LtoR shunting most likely causes an increase in LVO, by contributing to PBF and pulmonary venous return leading to increased left ventricular preload (19). The observation that RVO remains relatively unchanged, despite cord clamping, is consistent with findings in lambs when ventilation onset commences before cord clamping (9). Indeed, most infants commenced breathing before cord clamping in this study and therefore the loss in placental venous return is rapidly compensated for. While the mechanisms are unknown, a reversal in blood flow shunting through the foramen ovale (to become predominantly LtoR) after birth is the most likely explanation although increased systemic venous return is also possible (24).

In anaesthetized and ventilated animals, DA blood flow was measured directly after birth (3;9;22;23;25). In lambs it was shown that ventilation resulted in predominantly LtoR DA shunt. Increased oxygenation and cord occlusion, which increases SVR, caused RtoL DA shunting to decrease to negligible levels (23). While net DA flow gradually becomes LtoR within 10 minutes of birth, the direction of blood flow throughout the cardiac cycle remains very dynamic (3). That is, the flow is RtoL during mid-systole because the pressure wave exiting the right ventricle reaches the pulmonary artery-DA junction before the pressure wave exiting the left ventricle reaches the DA-aorta junction (3). As a result, following the onset of systole, the pressure gradient across the DA is RtoL until the pressure wave from the left ventricle reaches the aortic end of the DA, at which point the pressure gradient reverses causing blood to flow LtoR (3). Our findings show that this also occurs in humans and begins rapidly after birth as significant LtoR flow was present within 2 minutes of birth. The gradual increase in LtoR DA flow between 2, 5 and 10 minutes after birth likely reflects both a temporal decrease in PVR and a similar time-related increase in LVO.

In several clinical studies DA shunting was examined during the neonatal transitional period shortly after birth (12-17). Few have systematically reviewed DA shunting shortly after birth. Noori *et al*. performed a prospective observational study and found that at 3-7 minutes after vaginal delivery, DA shunting is mostly bidirectional and DA flow time ratio was 0.8 (0.9) and net DA flow was 1 (46) mL/kg/min (13). Our study extends these

findings and reports that the duration of LtoR shunting increases significantly from 2 to 10 minutes after birth, resulting in a significant decrease in DA flow time ratio.

Pulmonary aeration and subsequent decrease in PVR have a profound hemodynamic effect and clearly influence DA shunting (3). Currently parameters of lung aeration and changes in PVR during transition are lacking. DA flow ratio which takes into account the duration, direction and amount of DA flow, could be useful as it relates pressure changes of the systemic circulation to changes in de pulmonary circulation. When lung aeration and pulmonary transition are disturbed and pulmonary pressure does not decrease it is likely that DA flow ratio is influenced. Therefore we speculate that assessment of DA flow ratio could be used for evaluation of the transition.

Limitations

These observations only include term newborns that were scheduled for elective cesarean section and experienced delayed cord clamping. Care should be taken to extrapolate our findings to vaginal deliveries (and preterm born infants), although similar to a study in vaginal births DA LtoR shunting duration increased over time compared with RtoL shunting (13). Our measurements could be influenced by delayed cord clamping (9) as the delay of cord clamping could diminish the significant loss of venous return that accompanies cord clamping (3), influencing changes in DA shunt and LVO. Measurement of DA blood flow could vary due to flow turbulence, which lead to incorrect measurements and cause overestimation of blood flow (13). However, in the first minutes after birth the DA is large and flow velocity is low as is demonstrated by the low peak velocities reported (13).

Conclusion

This study provides new data on hemodynamic changes directly after birth. DA shunting and DA flow ratio changes rapidly after birth, most likely as a consequence of pulmonary aeration and subsequent decrease in PVR along with the increase in SVR. DA blood flow ratio is a direct reflection of pulmonary and haemodynamic transition and could be used in future studies to assess the neonatal transition.

Acknowledgements

We thank M. S. Verhart for her help with inclusion.

References

1. Rudolph AM, Iwamoto HS, Teitel DF. Circulatory changes at birth. J Perinat Med 1988;16 1:9-21.
2. Te Pas AB, Davis PG, Hooper SB, Morley CJ. From liquid to air: breathing after birth. J Pediatr 2008;152: 607-11.
3. Crossley KJ, Allison BJ, Polglase GR, Morley CJ, Davis PG, Hooper SB. Dynamic changes in the direction of blood flow through the ductus arteriosus at birth. J Physiol 2009;587:4695-704.
4. Reid DL, Thornburg KL. Pulmonary pressure-flow relationships in the fetal lamb during in utero ventilation. J Appl Physiol (1985) 1990;69:1630-6.
5. Rudolph AM. Fetal and neonatal pulmonary circulation. Annu Rev Physiol 1979;41:383-95.
6. Polglase GR, Wallace MJ, Grant DA, Hooper SB. Influence of fetal breathing movements on pulmonary hemodynamics in fetal sheep. Pediatr Res 2004;56:932-8.
7. Gao Y, Raj JU. Regulation of the pulmonary circulation in the fetus and newborn. Physiol Rev 2010;90:1291-335.
8. Wyllie J. Applied physiology of newborn resuscitation. Current Paediatrics 2005;15:143-50.
9. Bhatt S, Alison BJ, Wallace EM, Crossley KJ, Gill AW, Kluckow M, *et al*. Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. J Physiol 2013;591:2113-26.
10. Clyman RI. Mechanisms regulating the ductus arteriosus. Biol Neonate 2006;89:330-5.
11. Hermes-DeSantis ER, Clyman RI. Patent ductus arteriosus: pathophysiology and management. J Perinatol 2006;26 Suppl 1:S14-S18.
12. Mirro R, Gray P. Aortic and pulmonary blood velocities during the first 3 days of life. Am J Perinatol 1986;3:333-6.
13. Noori S, Wlodaver A, Gottipati V, McCoy M, Schultz D, Escobedo M. Transitional changes in cardiac and cerebral hemodynamics in term neonates at birth. J Pediatr 2012;160:943-8.
14. Silverman NH, Lewis AB, Heymann MA, Rudolph AM. Echocardiographic assessment of ductus arteriosus shunt in premature infants. Circulation 1974;50:821-5.
15. Su BH, Watanabe T, Shimizu M, Yanagisawa M. Echocardiographic assessment of patent ductus arteriosus shunt flow pattern in premature infants. Arch Dis Child Fetal Neonatal Ed 1997;77:F36-F40.
16. Urlesberger B, Brandner A, Pocivalnik M, Koestenberger M, Morris N, Pichler G. A left-to-right shunt via the ductus arteriosus is associated with increased regional cerebral oxygen saturation during neonatal transition. Neonatology 2013;103:259-63.
17. Kozak MF, Yoo SJ, Mertens L, Ho A, Grosse-Wortmann L. Assessment of ductal blood flow in newborns with obstructive left heart lesions by cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2013;15:45.
18. van Vonderen JJ, Roest AA, Siew ML, Blomf NA, van Lith JM, Walther FJ, *et al*. Non-invasive measurements of hemodynamic transition directly after birth. Pediatr Res 2013.
19. Mielke G, Benda N. Cardiac output and central distribution of blood flow in the human fetus. Circulation 2001;103:1662-8.
20. Friedman AH, Fahey JT. The transition from fetal to neonatal circulation: normal responses and implications for infants with heart disease. Semin Perinatol 1993;17:106-21.

21. Heymann MA. Control of the pulmonary circulation in the fetus and during the transitional period to air breathing. Eur J Obstet Gynecol Reprod Biol 1999;84:127-32.
22. Iwamoto HS, Teitel D, Rudolph AM. Effects of birth-related events on blood flow distribution. Pediatr Res 1987;22:634-40.
23. Teitel DF, Iwamoto HS, Rudolph AM. Effects of birth-related events on central blood flow patterns. Pediatr Res 1987;22:557-66.
24. Evans N, Iyer P. Assessment of ductus arteriosus shunt in preterm infants supported by mechanical ventilation: effect of interatrial shunting. J Pediatr 1994;125:778-85.
25. Teitel DF, Iwamoto HS, Rudolph AM. Changes in the pulmonary circulation during birth-related events. Pediatr Res 1990;27:372-8.

CHAPTER 13

The influence of crying on the ductus arteriosus shunting and left ventricular output at birth

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Submitted

Abstract

Background: Shortly after birth flow in the ductus arteriosus (DA) changes from right-to-left to left-to-right and contributes considerably to the increase in pulmonary blood flow. Large transpulmonary pressures generated by crying at birth can influence DA shunting.

Objective: To assess differences in DA shunting during quiet breathing and crying directly after birth. Methods: In term healthy newborns born by caesarean section, echocardiography was performed at 2, 5 and 10 minutes after birth. Velocity time integral of DA flow, DA flow ratio (RtoL/LtoR flow) and LVO were assessed using echocardiography. Shunting was compared within each patient during crying and quiet breathing and between time points.

Results: 23 infants were studied. The velocity time integral of left-to-right shunting was significantly larger during inspiratory phase of crying than during quiet breathing (12.8 (9.2-17.4) cm vs. 5.9 (3.9-7.7) cm at 2 minutes ($p<0.0001$), 14.3 (11.5-22.3) mL/min vs. 6.7 (4.1-11.1) cm at 5 minutes ($p<0.0001$) and 18.6 (14.8-22.5) vs. 6.7 (4.4-10.7) cm at 10 minutes ($p<0.0001$) after birth). The increase in left-to-right shunting during crying was independent from the cardiac cycle as QRS-start of shunt interval time was 138 (82) ms during crying and 156 (35) ms during quiet breathing (ns). DA flow ratio was lower in infants who cried at 0-1 time points vs. those who cried at 2-3 time points (ns). LVO was higher in infants who cried at 2-3 time points vs. those that cried 0-1 time points (ns).

Conclusion: crying at birth significantly influences ductus arteriosus shunting during hemodynamic transition.

Introduction

The respiratory and hemodynamic changes during the fetal to neonatal transition at birth are closely interrelated (1,2). Due to a high pulmonary vascular resistance (PVR), most of the blood in the main pulmonary artery flows right-to-left (RtoL) through the ductus arteriosus (DA) before birth, which continues throughout the cardiac cycle (3). After birth, aeration of the lungs triggers a decrease in PVR which increases pulmonary blood flow (PBF) and reverses the pressure gradient across the DA.(REF Crossley) This leads to a change in the direction of flow across the DA, changing from entirely RtoL to predominantly left-to-right (LtoR) (4,5). The DA shunt will contribute for a large part to the increase in PBF and thus increase in left ventricular output (LVO) (1,5).

Before birth fetal breathing movements decreases PVR and increase PBF in the liquid-filled fetal lungs, which was thought to result from reduced RtoL shunting through the DA (6). However, the effect of breathing on PVR and DA shunting directly after birth has not been investigated. It has previously been suggested that crying may be an important mechanism for lung liquid clearance during transition, due to the intra-thoracic pressure gradients generated by this activity (7). A cry is preceded by a large inspiration and is characterized by a forced expiration through a partially closed vocal cord. As such, it is comparable to a Valsalva maneuver (7). It has been shown in adults that both large inspirations and Valsalva maneuvers influence venous return and cardiac output (8). There is little data of the effect of crying on hemodynamics during the fetal to newborn transition. Baba *et al* observed an increase pre-post ductal difference in oxygen saturation during crying in infants with meconium aspiration syndrome several hours after birth which may indicate that crying influences ductal shunting for up to several hours after birth (9).

We hypothesized that crying has significant effects on the hemodynamic changes at birth, particularly on shunting through the DA. To investigate this we measured the effect of breathing on DA flow directly after birth by comparing DA blood flow during crying and quiet breathing.

Methods

Healthy term infants (≥37 weeks of gestation) delivered by elective cesarean section between October 2012 and December 2013 were included in this study. The study was approved by the Institutional Review Board of the Leiden University Medical Center. Parental consent was obtained during pre-operation visit or by telephone at least one day before the caesarean section was performed.

For this study only uncompromised infants born after elective caesarian sections, without congenital malformations, were included, as these infants are routinely evaluated on a resuscitation table, while infants after vaginal deliveries are directly placed on the chest of the mother. The non-invasive measurements performed did not influence standard care. Infants were excluded when transition at birth was complicated and respiratory support was needed.

A stopwatch was started as soon as the infant was born (i.e. when the shoulders and head were delivered). In accordance with local guidelines the umbilical cord was clamped 30-60s after birth and cut by the obstetrician. Therefore, most infants commenced breathing before clamping of the umbilical cord. Thereafter, the baby was placed under a radiant heater and the neonatal caregiver, who was not involved in the research project, provided standard care (drying, keeping warm, evaluation of the infant's condition). Stimulation, positioning and suctioning were left at the discretion of the neonatal caregiver. Measurements were collected at three time points after birth: as soon as the infant was placed on the resuscitation table and at 5 and 10 minutes after birth and it was noted if infants were crying during the measurements. During this period the infant remained on the resuscitation table. ECG electrodes (Neotrode II, Conmed, Utica, New York, USA) were placed as soon as the infant reached the resuscitation table and heart rate (HR) was determined using the ECG that was recorded during and in synchrony with the echocardiographic examination.

HR and time duration between the QRS complex were assessed using the ECG trace and start of LtoR shunting was assessed during quiet breathing and crying. To assess variation in this interval the coefficient of variation (CV) was calculated.

To assess differences in blood flow over the DA due to crying, an echocardiographic examination was performed using a Vivid I Cardiovascular Ultrasound system equipped with a 7.0 MHz transducer (GE Healthcare, Waukesha, Wisconsin, USA). DA velocity-time integral (VTI) was assessed using 2D echocardiography and Doppler continuous wave measurements at the DA in the suprasternal view. VTI evaluation of DA flow during crying included analysis of 3 VTI flow profiles during crying and 3 consecutive flow profiles during quiet breathing, providing a mean VTI at each time point. During crying a distinct flow pattern was visualized by Doppler imaging (figure 1). This pattern consist of a noise signal, due to expiration against partially closed vocal cords (figure 1) (7). Directly after the cry the infant was observed to take a large inspiration, which caused a concomitant Doppler signal of LtoR flow through the DA (figure 1). As a consequence of the noise signal during expiration VTI could only be determined during observed inspiration directly

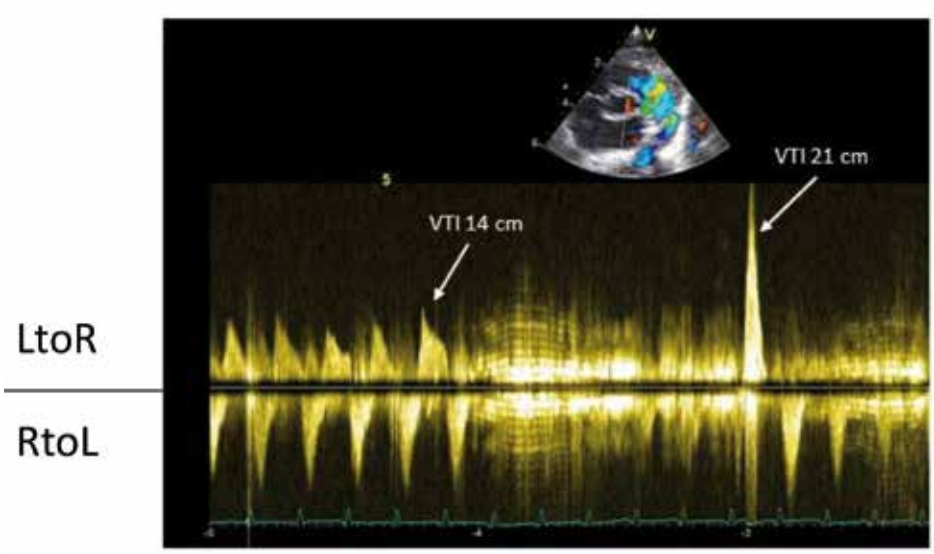

Figure 1. Doppler registration of DA LtoR and RtoL shunting. Noise is caused by crying after which an inspiration of the infant causes a large increase of VTI.

after crying. DA LtoR VTI was only compared during quiet breathing and crying if both signals were of good quality and if they occurred in at most a 30 s interval. Crying could occur before or after quiet breathing. The percentual increase in VTI (VTI of LtoR shunt during crying/ VTI of LtoR shunt during quiet breathing - 100%) was calculated.

Relative differences in DA RtoL versus LtoR flow through the DA were assessed in infants who cried 0-1 and 2-3 times during the measurement time points and DA flow ratios were calculated (RtoL flow/LtoR flow). Crying was audio-visually observed at the time of measurement. LVO was assessed using Doppler pulsed wave measurements obtained at the aortic annulus (AoAnn). The aortic annulus was assessed using 2D echocardiography in the suprasternal view. LVO was assessed during quiet breathing at each time point. LVO was calculated using the formula $(((\pi*Ann^2)/4) * VTI * HR)/birth\ weight)$ (10).

To prevent inter individual variation between observers all echocardiograms and measurements were performed by 1 senior pediatric cardiology consultant. All data were analyzed by one researcher who was not involved in the recordings. All infants received a comprehensive echocardiogram after the procedure to rule out any structural anomalies of the heart.

Statistical analysis

Data were analysed using SPSS (IBM, version 20.0.0, Chicago, Illinois). Results are presented as mean (standard deviation (SD)), mean (range) or median (IQR) where appropriate. Paired continuous data was compared using a paired T-test. Normally distributed data of the 3 time-points were compared using a one way ANOVA. Non-normally distributed paired data was compared using the Wilcoxon signed ranks test. Non-normally distributed values of the three time points were compared using a Kruskall-Wallis test. A p-value of <0.05 was regarded as statistically significant. Reported p-values are two-sided.

Results

Patients

DA blood flow was measured in 23 neonates, of which only 3 were not observed to cry (mean (range) GA 38 (37-39) weeks, mean (SD) birth weight 3420 (403) grams and median (IQR) Apgar scores of 9 (8-9) at 1 minute, 10 (9-10) at 5 minutes and 10 (9-10) at 10 minutes). DA blood flow during crying was evaluated in 20 term and healthy infants DA flow ratio and LVO were measured in all infant at all time points. 13 infants cried during 2-3 time points, 10 infants cried during 0-1 time points (3 infants did not cry at all time points). Crying and quiet breathing was observed in 14 infants at 2 minutes, for 9 infants at 5 minutes and 9 infants at 10 minutes and in these infants DA shunt was determined.

Heart rate and QRS interval

Heart rate was not different during crying or quiet breathing (163 (22) vs. 160 (20) beats per minute). LtoR shunting during crying was independent from the cardiac cycle as the time difference between start QRS and start of LtoR shunt was larger and more variable (138 (82) ms, CV 59%) during crying when compared to quiet breathing (156 (35) ms, CV 22%), which was not significant different.

Differences in VTI LtoR shunt

At 2, 5 and 10 minutes after birth median (IQR) VTI during inspiratory phase of crying was significantly larger than during inspiratory phase of quiet breathing (2 minutes:12.8 (9.2-17.4) cm vs. 5.9 (3.9-7.7) cm; 5 minutes 14.3 (11.5-22.3) cm vs. 6.7 (4.1-11.1) cm; 10 minutes 18.6 (14.8-22.5) cm vs. 6.7 (4.4-10.7) cm; all time points p <0.0001) (figure 2). Over time there was a percentage increase in VTI during crying vs. quiet breathing (77 (50-233) % at 2 minutes, 122 (74-232) % at 5 minutes and 134 (83-281) % at 10 minutes), but this did not reach statistical significance.

DA flow ratio and LVO

DA flow ratio (RtoL / LtoR flow) decreased in time, but was not significantly different between infants who cried at 2-3 time points vs. 0-1 time points 2.1 (1.4-2.4) vs. (2.4 (1.3-2.4)) at 2 minutes (ns), 1.3 (1.0-1.6) vs. (1.4 (1.1-2.2) at 5 minutes (ns) and 0.9 (0.6-1.1) vs. (0.9 (0.6-1.3)) at 10 minutes (ns). (figure 3).

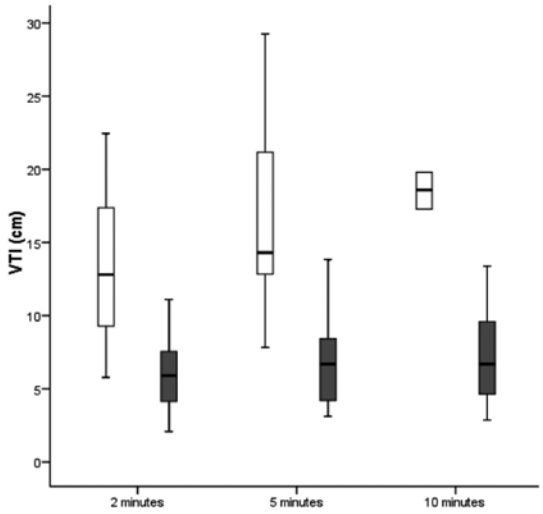

Figure 2. VTI for all infants at 2, 5 and 10 minutes after birth. VTI of LtoR shunt is shown during crying and in grey VTI of LtoR shunt is shown during quiet breathing. The box plots show median values (solid black bar), inter quartile range (margins of box) and range of data.

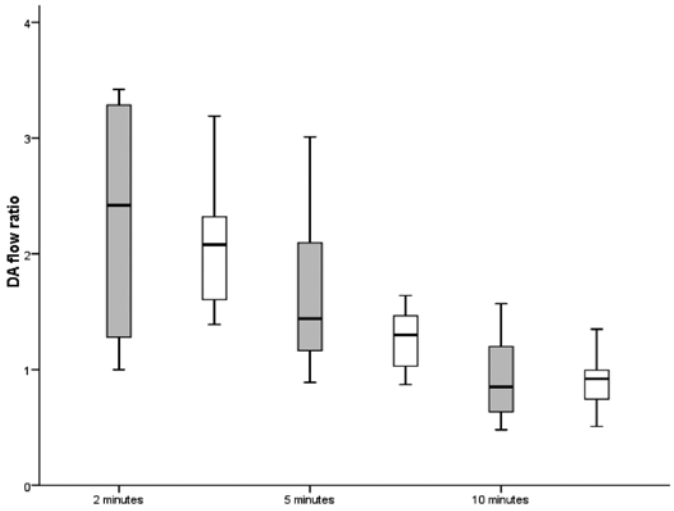

Figure 3. Change of DA flow ratio at 2-, 5- and 10 minute time points after birth for infants who cried at 0-1 time points (grey) and cried at 2-3 time points (white). Box plots show median values (solid black bar), inter quartile range (margins of box) and range of data.

LVO was increased in infants who cried at 2-3 time points vs. infants who cried at 0-1 time points, but this did not reach statistical significance. (at 2 minutes 173 (61) mL/kg/min vs. 157 (35) mL/kg/min (ns), at 5 minutes 196 (64) mL/kg/min vs. 185 (49) mL/kg/min (ns) and at 10 minutes 224 (83) mL/kg/min vs. 201 (46) mL/kg/min (ns)).

Discussion

We observed that during inspiratory phase of crying there is a significant increase LtoR shunting through the DA compared to quiet breathing. Although not significant, VTI increased over time during crying, while this remained stable during quiet breathing. Infants who cry more often at birth showed a trend towards a lower DA flow ratio and higher LVO immediately after birth. This indicates that the large inspirations associated with crying have a significant impact on DA shunting and thus left ventricular preload and output. Our observation is a good example that the respiratory and hemodynamic changes at birth closely interact with each other.

This the first study reporting the effect of crying on the hemodynamic changes directly after birth. Previous studies have demonstrated the hemodynamic effect of crying at later ages when flow through the DA may have ceased or is markedly less dynamic. However, no previous study had reported the effect of the large inspiration that accompanies crying on DA hemodynamics (7). Experimental studies have shown that lung aeration and breathing play a significant role in the decrease in PVR (4,5,11-13). After birth PBF significantly increases and 50% of the blood originates from a LtoR shunt through the DA (4,5). We speculate that the large sub-atmospheric pressures cause a trans-pulmonary pressure difference occur during the first breaths of extra-uterine life. These result into a sudden decrease in PVR, which leads to a larger pressure gradient between the pulmonary and systemic circulation and thereby increase the DA LtoR shunt (4,5). This is reflected by the lower DA flow ratio which signifies a faster neonatal transition in infants who cry.

Due to the noise signal caused by crying were not able to perform accurate flow measurements during this activity. However, it is likely that RtoL shunting increases during the expiratory phase of the cry, because this is associated with large supra-atmospheric transpulmonary pressures. which are known to increase PVR. In addition, it is well described that persistent pulmonary hypertension worsens during the arousal by crying (14). In infants with meconium aspiration and persistent pulmonary hypertension, increases in pre-post ductal oxygen saturation differences are observed during cry-

ing (15). Also, Dinwiddie *et al*. demonstrated in infants of 1-3 days old with respiratory distress syndrome that the cry resembles a Valsalva maneuver with a decrease in systemic blood pressure (16). It has been described that a Valsalva maneuver increases the pulmonary blood pressure (9). Although we studied infants with healthy lungs in transition, it is probable that an increase in RtoL DA shunting occurs during the expiratory phase of crying. Together with the increase in LtoR shunt during inspiration it is possible that this could lead to a net balance in DA blood flow.
Although the net effect stills needs to be established, we observed that LVO is larger at every time point in infants who cried more often. The increase in LtoR DA shunt that accompanies the large inspiratory phase of crying, contributes to an increase in PBF leading to a rise in pulmonary vascular return and LVO (5). The increase in DA blood flow shunting also enhances oxygenation of arterial blood and could be beneficial for the neonatal transition, although it reduces the efficiency of blood flow distribution to the viscera creating a short circuit (5).

A limitation of this observational study is the small sample size. Also, in this study we only included infants born by caesarean section which could give a delay in transition. However, none of the infants included needed any intervention. Although not all infants cried at every time point, all infants breathed soon after birth and oxygen saturation and heart rate were within the normal ranges. Furthermore, we could only observe visually if infants cried. Future research needs to address the direct quantitative effects of crying.

Conclusion

We observed in healthy term infants at birth born via caesarean section that the large inspirations during crying significantly increases LtoR DA shunting directly after birth. Also, crying seems to have a positive influence on the increase in LVO at birth. Further studies are needed to investigate the net effect, but it is possible that crying influences the hemodynamic transition.

Acknowledgements

We express our gratitude to M. S. Verhart and C. Kolster-Bijdevaate for their help with the inclusion of our patients.

References

1. van Vonderen JJ, Roest AA, Siew ML, Blom NA, van Lith JM, Walther FJ, Hooper SB, Te Pas AB. Noninvasive measurements of hemodynamic transition directly after birth. Pediatr Res 2014;75:448-52.
2. van Vonderen JJ, Roest AA, Siew ML, Walther FJ, Hooper SB, Te Pas AB. Measuring physiological changes during the transition to life after birth. Neonatology 2014;105:230-42.
3. Rudolph AM, Iwamoto HS, Teitel DF. Circulatory changes at birth. J Perinat Med 1988;16:9-21.
4. van Vonderen JJ, Te Pas AB, Kolster-Bijdevaate C, van Lith JM, Blom NA, Hooper SB and Roest AA. Non-invasive measurements of ductus arteriosus flow directly after birth. Arch Dis Child Fetal Neonatal Ed. In press 2014.
5. Crossley KJ, Allison BJ, Polglase GR, Morley CJ, Davis PG, Hooper SB. Dynamic changes in the direction of blood flow through the ductus arteriosus at birth. J Physiol 2009;587:4695-704.
6. van Eyck J, van der Mooren K, Wladimiroff JW. Ductus arteriosus flow velocity modulation by fetal breathing movements as a measure of fetal lung development. Am J Obstet Gynecol 1990;163:558-66.
7. Te Pas AB, Wong C, Kamlin CO, Dawson JA, Morley CJ, Davis PG. Breathing patterns in preterm and term infants immediately after birth. Pediatr Res 2009;65:352-6.
8. Wang Z, Yuan LJ, Cao TS, Yang Y, Duan YY, Xing CY. Simultaneous beat-by-beat investigation of the effects of the Valsalva maneuver on left and right ventricular filling and the possible mechanism. PLoS One 2013;8:e53917.
9. Baba A, Ishida T, Okada M, Akazawa Y, Hirabayashi K, Saida K, Sakaguchi K, Koike K. Right-to-left shunting in the ductus arteriosus is induced readily by intense crying and rapid postural change in neonates with meconium-stained amniotic fluid. Pediatr Crit Care Med 2012;13:60-5.
10. Mielke G, Benda N. Cardiac output and central distribution of blood flow in the human fetus. Circulation 2001;103:1662-8.
11. Hooper SB, Harding R. Role of aeration in the physiological adaptation of the lung to air breathing at birth. Curr Respir Med Rev 2005;1:185-95.
12. Iwamoto HS, Teitel DF, Rudolph AM. Effects of lung distension and spontaneous fetal breathing on hemodynamics in sheep. Pediatr Res 1993;33:639-44.
13. Teitel DF, Iwamoto HS, Rudolph AM. Changes in the pulmonary circulation during birth-related events. Pediatr Res 1990;27:372-8.
14. Storme L, Aubry E, Rakza T, Houeijeh A, Debarge V, Tourneux P, Deruelle P, Pennaforte T. Pathophysiology of persistent pulmonary hypertension of the newborn: impact of the perinatal environment. Arch Cardiovasc Dis 2013;106:169-77.
15. Baba A, Ishida T, Okada M, Akazawa Y, Hirabayashi K, Saida K, Sakaguchi K, Koike K. Right-to-left shunting in the ductus arteriosus is induced readily by intense crying and rapid postural change in neonates with meconium-stained amniotic fluid. Pediatr Crit Care Med 2012;13:60-5.
16. Dinwiddie R, Pitcher-Wilmott R, Schwartz JG, Shaffer TH, Fox WW. Cardiopulmonary changes in the crying neonate. Pediatr Res 1979;13:900-3.

CHAPTER 14

The perfusion index of healthy term infants during transition at birth

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Abstract

Background: Pulse oximetry (PO) derived perfusion index (PI) can be used to determine peripheral perfusion, but values during transition at birth have not been described.

Aim: To describe PI values in healthy term infants over time after birth.

Methods: PI of healthy term infants was recorded in the first 10 minutes after birth using a PO sensor placed preductally at the right wrist. Variability of PI was calculated using the coefficient of variation (CV).

Results: Recordings of 89 term infants (71 born vaginally, 18 by cesarean section) were included. No significant trend could be observed in vaginally delivered infants, but a significant increase was observed in infants born by cesarean section. Median PI was significantly higher in vaginally born infants compared to infants born by cesarean section (2.0 (1.3–2.9) vs. 1.8 (1.2–2.6); $p<0.001$).

Conclusions: Healthy term infants during transition at birth have no significant change in perfusion when vaginally born, but a small increase was observed in infants born by a cesarean section.

Introduction

In recent years, pulse oximetry (PO) has been recognized as an easily applicable, non-invasive monitoring tool and is used in the delivery room (DR) to monitor transition at birth (1-3). It is recommended to use PO for objective evaluation of heart rate (HR) and oxygen saturation (SpO_2) at birth (4;5) and to decide if interventions are necessary (6-8). In addition to HR and SpO_2, the infrared signal of a PO can also be used to determine the perfusion index (PI). PI is the ratio of the pulsatile signal (arterial blood flow) indexed against the non-pulsatile signal (static blood flow, skin and other tissues) and is a non-invasive indicator for peripheral perfusion (9). PI values of infants in the first days after birth have been described (10) and a low PI (<1.24) has been reported as an indicator for severe illness in infants (10;11)

During transition, significant respiratory and hemodynamic changes occur, influencing cardiac output and both systemic and peripheral perfusion (12-15). So far only SpO_2 and HR are used for evaluation, but these parameters do not reflect the complete hemodynamic status of the infant at birth (16). PI as a continuous parameter given by the PO could be useful for evaluating hemodynamic changes at birth and identify transitional problems. However, PI values in term infants during transition have been reported (17), but PI was not given with respect to time after birth.

The objective of this study was to evaluate PI of healthy term infants during the first 10 minutes after birth.

Methods

Measurements of PO recordings of healthy term infants born via uncomplicated vaginal delivery or elective cesarean section needing no support were used. The study was approved by the institutional review board of the LUMC and parents were antenatally approached for consent. Recordings of term infants born between February 2012 and March 2013 were reviewed retrospectively. Recordings were included if PI measurements were obtained shortly after birth and time of birth was indicated.

PI, HR and SpO_2 were recorded by placing a PO sensor (M-LNCS NeoPt-500, Masimo SET, Masimo, Irvine, CA, USA) preductally (on the ulnar aspect of the right wrist) (18) and subsequent connection to a PO (Masimo Radical 7, Masimo, Irvine, CA, USA) (19). PI, HR and SpO_2 were recorded at maximum sensitivity every 10 seconds from 2 minutes after birth

until either 10 minutes after birth or earlier when the infant was placed in the transport incubator. The recorded values were collected using Spectra Physiological Recording Program (Grove Medical, London, UK) and stored on a laptop. Twenty seconds of time points (10 seconds before and after each 60 seconds) were averaged for each infant at minute intervals. Data were considered valid for analysis if PI, HR and SpO_2 were simultaneous present at a time point and the pulse wave was confirmed to be artifact free.

Statistical Analysis

Data were analyzed using SPSS 20.0 for Windows (IBM, Chicago, IL, USA). All variables were tested for normality using the Kolmogorov-Smirnov test. Data were presented as mean (SD), median (IQR) or absolute frequencies (percentage) where appropriate. For non-normally distributed data, a Mann-Whitney U test was used to compare PI between term infants born vaginally and by cesarean section and a Wilcoxon signed rank test was used to compare PI between time points within groups. A (two-sided) p-value of < 0.05 was considered as statistically significant.

Results

In 89 infants PO values were recorded and analyzed, of which 71 were born vaginally and 18 by cesarean section (table 1). HR and SpO_2 were within normal ranges as stated in the reference ranges (table 2) (20;21).

According to the criteria, 85% (6,600 data points) of the PI measurements were included. The median PI of the total cohort in the first 10 minutes after birth was 1.9 (1.3–2.9). No trend could be observed in vaginally delivered infants, but a small increase was observed in infants born by cesarean section (table 3). Overall PI was higher after a vaginal delivery when compared to after a cesarean section (2.0 (1.3–2.9) versus 1.8 (1.2–2.6); $p < 0.001$).

Table 1. Demographic and clinical characteristics.

	Vaginal delivery (n = 71)	Cesarean section (n = 18)
Gestation, mean (SD), wk	40 (1)	38 (1)
Birth weight, mean (SD), g	3575 (482)	3355 (454)
Male gender, n (%)	29 (41)	10 (56)
Apgar, median (IQR)		
1 minute	9 (9–9)	9 (8–9)
5 minutes	10 (10–10)	9 (8–10)

Table 2. Heart rate (bpm) and oxygen saturation (%) measurements of healthy term infants in the first 10 minutes after birth.

	Vaginal delivery (n = 71)		Cesarean section (n = 18)	
Time (m)	**HR (bpm)**	**SpO_2 (%)**	**HR (bpm)**	**SpO_2 (%)**
2	142 (77–169)	82 (73–90)	80 (69–159)	74 (70–81)
3	150 (120–165)	85 (76–91)	152 (115–166)	78 (69–87)
4	146 (134–158)	85 (80–91)	159 (149–166)	79 (71–87)
5	141 (133–152)	88 (79–93)	150 (135–162)	82 (75–89)
6	144 (123–156)	89 (83–94)	156 (146–163)	89 (83–92)
7	144 (132–157)	91 (86–95)	153 (144–163)	89 (84–94)
8	143 (130–156)	92 (87–95)	154 (146–162)	89 (84–94)
9	143 (133–154)	93 (88–96)	148 (143–159)	90 (87–95)
10	144 (134–153)	93 (90–97)	158 (145–165)	90 (83–96)

Table 3. Wilcoxon signed-rank test comparing perfusion index of healthy term infants in the first 10 minutes after birth.

	Vaginal delivery (n = 71)			Cesarean section (n = 18)		
Time (m)	**n**	**PI (%)**	***p* value**	**n**	**PI (%)**	***p* value**
2	60	2.01 (1.39–3.28)	< 0.01	11	1.50 (0.83–2.80)	
3	64	2.08 (1.53–2.77)	< 0.05	15	1.40 (1.20–2.00)	0.27
4	66	1.98 (1.35–2.80)	< 0.01	16	1.60 (1.15–2.70)	< 0.001
5	67	1.89 (1.30–3.05)	0.65	15	1.40 (0.91–2.80)	0.26
6	69	2.10 (1.36–3.31)	0.34	18	1.93 (1.39–3.10)	< 0.05
7	69	1.80 (1.23–3.16)	0.10	18	1.70 (1.30–2.30)	< 0.01
8	70	1.97 (1.34–2.79)	0.31	18	2.00 (1.20–2.60)	< 0.05
9	70	1.90 (1.22–2.83)	0.36	18	2.10 (1.20–2.60)	0.97

When the data are plotted with respect to time after birth, PI after vaginal delivery was higher compared to cesarean section in the first 5 minutes, after which values were similar (figure 1).

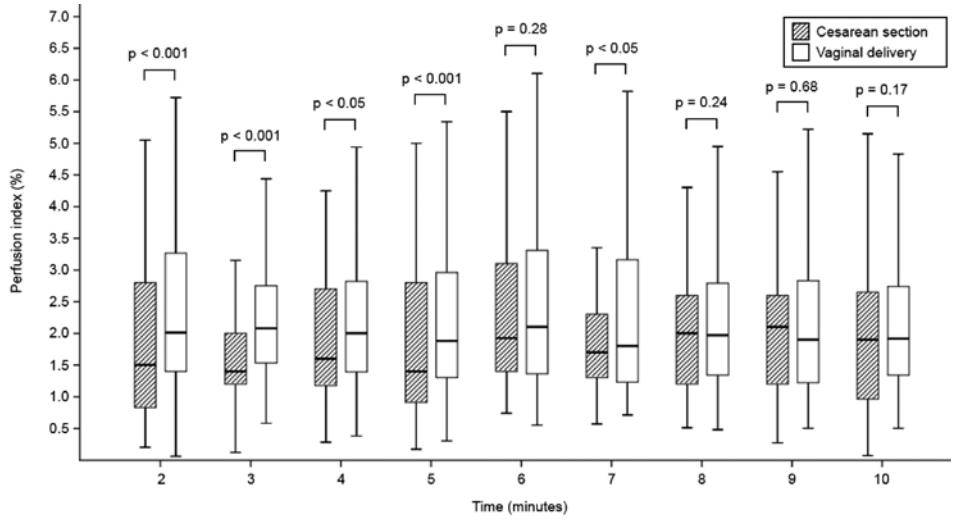

Figure 1. Perfusion index of healthy term infants in the first 10 minutes after birth. The box plots show median values (solid black bar), interquartile range (margins of box), and range of data.

Discussion

In this study we observed very little changes in PI of healthy term infants during transition after birth. The PI of infants born by cesarean section when compared to vaginally born infants was lower in the first minutes, after which they increased to similar levels as vaginally born infants.

Our finding that PI is quite consistent during transition at birth confirms previous findings where de Felice *et al*. reported no difference between a PI value measured at 0–1 minute and 1–5 minutes after birth (17). This indicates that pulsed wave forms measured preductally remain consistent despite the large hemodynamic changes that occur during transition. All infants cried and most likely aerated their lungs in the first breaths after birth before the cord was clamped. It has been shown that breathing before cord clamping leads to a more stable cardiovascular function and systemic circulation, which could have led to consistent PI (22;23). Also after cord clamping, the systemic vascular resistance increases while the lungs are aerated PVR decreased, which causes a left-to-right ductal shunt (24). This could have mitigated changes in peripheral circulation, which is in line with our previous observation that peripheral blood pressure remained

stable during transition (16). More studies on circulation in the extremities would be needed to confirm or refute this.

We measured, preductally, a lower PI than Felice *et al*. measured postductally in healthy term infants (2.1 (1.5) vs 4.4 (2.1)) (17). This difference is difficult to explain, as a decreased perfusion would have been expected postductally when an increase in left-to-right shunt would occur in the ductus arteriosus (25). However, as PI is a scaled numerical value derived from the magnitude of the pulsations it is possible that the ductal steal (increase in left-to-right shunt in ductus arteriosus) would lead to larger pulse waves forms postductally. This is similar to the presence of bounding pulses as a clinical sign for a patent ductus arteriosus.

De Felice *et al*. also reported PI values <1.24 to be an accurate predictor for a high severity illness (17). Although we have not compared the values of the healthy term cohort with sick infants at birth, we cannot confirm this cut-off value <1.24 as approximately 25% of our healthy term infants have a PI <1.24. None of these infants needed support or were admitted later on.

The lower PI of infants born by cesarean section in the first minutes could reflect a delay in hemodynamic adaptation during transition. All were elective cesarean and these infants were born with lung liquid to clear as they were not exposed to uterine contractions and the surge of catecholamines (26). This could have led to a delay in lung aeration, which has then consequences for the hemodynamic adaptation. Indeed, a similar difference in postpartum adaptation between both methods of delivery is seen in terms of HR (20) and SpO_2 changes (21;27).

PI has been reported to vary between individuals due to changes associated with local vasodilatation and vasoconstriction, reflecting changes in the physiologic state at the measurement site (9). Comparable to HR and SpO_2, a trend in PI would give the caregiver more information than a single value. Although we reported values of healthy term infants, comparison with term infants with transitional problems is needed to determine whether PI can be a useful parameter for hemodynamic evaluation of transition and decision making.

In conclusion, we reported PI measurements in healthy term infants with respect to the course of time. during the first 10 minutes after birth. There was no significant change in PI in this period in vaginally born infants, but a small increase was observed in infants born by a cesarean section. Comparative data of infants with transitional problems are needed before PI can be used as an additional parameter for decision making at birth.

References

1. Dawson JA, Davis PG, O'Donnell CPF, Kamlin CO, Morley CJ. Pulse oximetry for monitoring infants in the delivery room: a review. Archives of Disease in Childhood - Fetal and Neonatal Edition 2007;92:F4-F7.
2. Kamlin CO, O'Donnell CPF, Davis PG, Morley CJ. Oxygen saturation in healthy infants immediately after birth. The Journal of Pediatrics 2006;148:585-9.
3. Prasad S, Watcher D, Aitchison R, Aitchison P, Wang E, Kharasch M. Neonatal resuscitation guidelines. Disease-a-Month 2013;59:196-201.
4. Dawson JA, Kamlin CO, Wong C, te Pas AB, O'Donnell CPF, Donath SM, *et al*. Oxygen saturation and heart rate during delivery room resuscitation of infants <30 weeks' gestation with air or 100% oxygen. Archives of Disease in Childhood - Fetal and Neonatal Edition 2009;94:F87-F91.
5. Singh JK, Kamlin CO, Morley CJ, O'Donnell CPF, Donath SM, Davis PG. Accuracy of pulse oximetry in assessing heart rate of infants in the neonatal intensive care unit. Journal of Paediatrics and Child Health 2008;44:273-5.
6. Kopotic RJ, Lindner W. Assessing high-risk infants in the delivery room with pulse oximetry. Anesth Analg 2002;94:S31-S36.
7. Perlman JM, Wyllie J, Kattwinkel J, Atkins DL, Chameides L, Goldsmith JP, *et al*. Part 11: Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation 2010;122:S516-S538.
8. Vento M, Aguar M, Leone TA, Finer NN, Gimeno A, Rich W, *et al*. Using Intensive Care Technology in the Delivery Room: A New Concept for the Resuscitation of Extremely Preterm Neonates. Pediatrics 2008;122:1113-6.
9. Lima AP, Beelen P, Bakker J. Use of a peripheral perfusion index derived from the pulse oximetry signal as a noninvasive indicator of perfusion. Crit Care Med 2002;30:1210-3.
10. Granelli A, Ostman-Smith I. Noninvasive peripheral perfusion index as a possible tool for screening for critical left heart obstruction. Acta Paediatr 2007;96:1455-9.
11. De Felice C, Latini G, Vacca P, Kopotic RJ. The pulse oximeter perfusion index as a predictor for high illness severity in neonates. Eur J Pediatr 2002;161:561-2.
12. Teitel DF, Iwamoto HS, Rudolph AM. Effects of Birth-Related Events on Central Blood Flow Patterns. Pediatr Res 1987;22:557-66.
13. Bhatt S, Alison BJ, Wallace EM, Crossley KJ, Gill AW, Kluckow M, *et al*. Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. The Journal of Physiology 2013;591:2113-26.
14. Richardson BS, Carmichael L, Homan J, Johnston L, Gagnon R. Fetal cerebral, circulatory, and metabolic responses during heart rate decelerations with umbilical cord compression. Am J Obstet Gynecol 1996;175:929-36.
15. Crossley KJ, Allison BJ, Polglase GR, Morley CJ, Davis PG, Hooper SB. Dynamic changes in the direction of blood flow through the ductus arteriosus at birth. The Journal of Physiology 2009;587:4695-704.
16. van Vonderen JJ, Roest AA, Siew ML, Blom NA, van Lith JM, Walther FJ, *et al*. Noninvasive measurements of hemodynamic transition directly after birth. Pediatr Res 2014;75:448-52.
17. De Felice C, Del VA, Criscuolo M, Lozupone A, Parrini S, Latini G. Early postnatal changes in the perfusion index in term newborns with subclinical chorioamnionitis. Arch Dis Child Fetal Neonatal Ed 2005;90:F411-F414.
18. O'Donnell CPF, Kamlin CO, Davis PG, Morley CJ. Obtaining pulse oximetry data in neonates: a randomised crossover study of sensor application techniques. Archives of Disease in Childhood - Fetal and Neonatal Edition 2005;90:F84-F85.
19. O'Donnell CPF, Kamlin CO, Davis PG, Morley CJ. Feasibility of and Delay in Obtaining Pulse Oximetry during Neonatal Resuscitation. The Journal of Pediatrics 2005;147:698-9.

20. Dawson JA, Kamlin CO, Wong C, Te Pas AB, Vento M, Cole TJ, *et al*. Changes in heart rate in the first minutes after birth. Arch Dis Child Fetal Neonatal Ed 2010;95:F177-F181.
21. Dawson JA, Kamlin CO, Vento M, Wong C, Cole TJ, Donath SM, *et al*. Defining the reference range for oxygen saturation for infants after birth. Pediatrics 2010;125:e1340-e1347.
22. Meyer MP, Mildenhall L. Delayed cord clamping and blood flow in the superior vena cava in preterm infants: an observational study. Archives of Disease in Childhood - Fetal and Neonatal Edition 2012;97:F484-F486.
23. Sommers R, Stonestreet BS, Oh W, Laptook A, Yanowitz TD, Raker C, *et al*. Hemodynamic Effects of Delayed Cord Clamping in Premature Infants. Pediatrics 2012;129:e667-e672.
24. Crossley KJ, Allison BJ, Polglase GR, Morley CJ, Davis PG, Hooper SB. Dynamic changes in the direction of blood flow through the ductus arteriosus at birth. J Physiol 2009;587:4695-704.
25. Vidal M, Ferragu F, Durand S, Baleine J, Batista-Novais AR, Cambonie G. Perfusion index and its dynamic changes in preterm neonates with patent ductus arteriosus. Acta Paediatr 2013;102:373-8.
26. Jobe AH, Ikegami M. Lung development and function in preterm infants in the surfactant treatment era. Annu Rev Physiol 2000;62:825-46.
27. Rabi Y, Yee W, Chen SY, Singhal N. Oxygen saturation trends immediately after birth. J Pediatr 2006;148:590-4.

CHAPTER 15

The perfusion index of preterm infants receiving respiratory support at birth

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Submitted

Abstract

Background: The perfusion index (PI) derived from a pulse oximeter (PO) reflects changes in peripheral perfusion. So far no data on the PI of preterm infants in the first minutes after birth are available.

Aim: To compare PI values after birth in preterm infants receiving non-invasive and invasive respiratory support.

Methods: Preductal PI of preterm infants receiving non-invasive support during the first 10 minutes after birth was recorded using PO and compared with PI of infants intubated in the delivery room.

Results: Recordings of 55 preterm infants (38 non-invasive support and 17 intubated) were included. No significant trend of PI could be observed in course of time in both groups. There was a small, but significant difference in PI of infants receiving non-invasive support than the intubated infants (1.6 (1.0–3.0) vs. 1.8 (1.0–2.5); $p < 0.001$).

Conclusions: PI was consistent in preterm infant during transition at birth. PI in preterm infants receiving non-invasive support was lower than intubated infants, but the clinical relevance is uncertain. No trend in PI could be observed with respect to time after birth.

Introduction

Pulse oximetry (PO) has become invaluable for monitoring neonatal transition and to determine the effectiveness of interventions in the delivery room (DR) (1-6). Heart rate (HR) and oxygen saturation (SpO_2) are currently recommended for objective evaluation of the hemodynamic transition (7;8). However, these parameters do not reflect the complete hemodynamic status of an infant at birth (9).

The perfusion index (PI) is a non-invasive indicator of peripheral perfusion obtained from a PO, and is calculated as the ratio of the pulsatile (AC) signal indexed against the non-pulsatile (DC) signal (AC/DC × 100) (10). Low PI values have been associated with poor perfusion and cut-off values have been reported as an indicator for severe illness in newborn infants (11;12). Moreover, PI-values of preterm infant in the first days after birth have been published in several studies, showing a gradual increase over time to reach a steady state after the first days after birth (13;14). However, while peripheral and systemic perfusion are significantly influenced by the major physiological changes that occur during transition (15-18), little data is available on PI values of preterm infants immediately after birth. PI could be a valuable additional parameter for monitoring neonatal transition and evaluating hemodynamic changes at birth.

We recently reported PI-values of healthy term infants at birth, showing stable PI values and no trend in course of time. We do not know if this lack of trend in PI also accounts for preterm infants, especially when transition is not successful. We evaluated PI in preterm infants receiving respiratory support in the first 10 minutes after birth. We compared infants who managed to remain on CPAP in the DR with infants who were intubated, as this would reflect the success or failure of transition.

Methods

For this retrospective study we used recordings of preterm infants born between February 2007 and March 2013. Recording of physiological parameters at birth for audit, teaching and research has been approved by the institutional review board of the LUMC and parents gave written informed consent for use of the recordings after birth. PO recordings of preterm infants who received continuous positive airway pressure (CPAP) or positive pressure ventilation (PPV) administered using a face mask and preterm infants who were intubated at any given time in the DR were retrospectively reviewed. Recordings were included if PI measurements were obtained immediately after birth and time of birth was indicated.

PO recordings were obtained by placing a PO sensor (M-LNCS NeoPt-500, Masimo SET, Masimo, Irvine, CA, USA) on the infant's right hand or wrist (19) as soon as possible after birth. Subsequently, the PO sensor was connected to a PO (Masimo Radical 7, Masimo, Irvine, CA, USA) (20). PI, HR and SpO_2 were recorded at maximum sensitivity every 10 seconds from 2 minutes after birth until either 10 minutes after birth or earlier when the infant was placed in the transport incubator. The recorded values were collected using Spectra Physiological Recording Program (Grove Medical, London, UK) and stored on a laptop. Twenty seconds of time points (10 s before and after each 60 s) were averaged for each infant at minute intervals. Data were considered valid for analysis if PI, HR and SpO_2 were simultaneous present at a time point and the pulse wave was confirmed to be artifact free (21).

Resuscitation was performed according to the local guidelines (22). Intubation in the DR is left to the discretion of the caregiver, but in the local guideline criteria are stated when intubation is deemed necessary if (a) persistent hypoxemia was present after 60 s of effective PPV with a HR of <100 bpm, (b) the infant was breathing with the assistance of CPAP of 8 cmH_2O and FiO_2 >0.4, with a SpO_2 of <85% or (c) HR was <60 bpm and cardiac massage was required.

Statistical Analysis

Data were analyzed using SPSS 20.0 for Windows (IBM, Chicago, IL, USA). All variables were tested for normality using the Kolmogorov-Smirnov test. Data were presented as mean (SD), median (IQR) or absolute frequencies (percentage) where appropriate. Measurements of the two groups in our cohort were compared using a Wilcoxon signed-rank test. A (two-sided) p-value of <0.05 was considered as statistically significant.

Results

A total of 66 preterm infants were recorded, of which 11 infants were excluded because the exact time of birth was not recorded. Thus, recordings of 55 infants were analyzed, of which 38 received non-invasive respiratory support (non-invasive group) and 17 were intubated (intubated group) in the DR (mean time of intubation was 6 (3) minutes. Patient characteristics are shown in table 1. HR and SpO_2 of both groups are shown in table 2.

A total of 92% (4,388 data points) valid PI measurements could be obtained from the PO. Overall median PI was lower in the non-invasive group when compared to the intubated group (1.6 (1.0–3.0) vs. 1.7 (0.9–2.5); p<0.001). In the non-invasive group, PI decreased in

Table 1. Demographic and clinical characteristics

	Non-invasive group (n = 38)	Intubation group (n = 17)
Gestation, mean (SD), wk	27 (2)	27 (2)
Birth weight, mean (SD), g	971 (322)	930 (404)
Male gender, n (%)	11 (29)	7 (41)
Apgar 1 minute, median (IQR)	6 (2–8)	2 (2–6)
Apgar 5 minutes, median (IQR)	6 (6–9)	6 (4–8)

Table 2. Heart rate (bpm) and oxygen saturation (%) measurements of preterm infants in the first 10 minutes after birth.

	Non-invasive group (n = 38)		Intubation group (n = 17)	
Time (m)	HR (bpm)	SpO_2 (%)	HR (bpm)	SpO_2 (%)
2	92 (75–135)	42 (24–56)	86 (69–100)	44 (17–66)
3	129 (101–145)	49 (35–66)	100 (80–162)	55 (26–75)
4	140 (120–155)	65 (45–79)	148 (98–158)	57 (37–76)
5	141 (124–153)	70 (55–85)	145 (125–157)	67 (51–81)
6	143 (132–155)	84 (67–93)	135 (93–154)	65 (43–82)
7	145 (138–156)	90 (80–96)	143 (111–166)	67 (50–93)
8	150 (140–162)	93 (86–96)	161 (136–167)	94 (50–97)
9	151 (137–162)	92 (85–96)	153 (144–166)	81 (61–95)
10	157 (140–166)	94 (85–96)	161 (149–172)	91 (71–95)

the first minutes after birth and subsequently remained stable in course of time (figure 1, table 3). In the intubated group, PI decreased between 4 and 7 minutes (i.e., during the period of time in which most infants were intubated), but remained stable over time (table 3).

When plotted in minutes after birth, PI in the non-invasive group was in general lower compared to the intubated group, although this did not reach statistical significance at most minutes (figure 1).

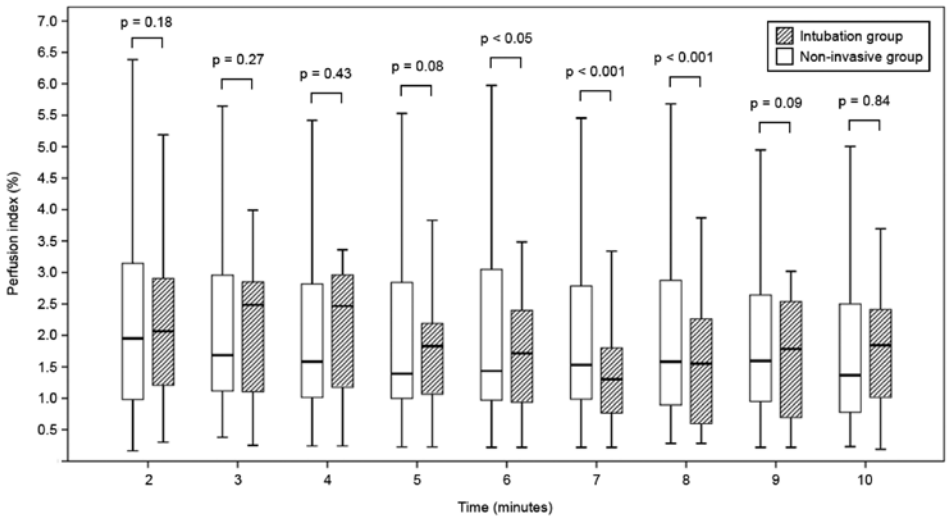

Figure 1. Perfusion index of preterm infants during the first 10 minutes after birth. Box plots equal median, interquartile range, and range.

Table 3. Wilcoxon signed-rank test comparing perfusion index of preterm infants in the first 10 minutes after birth.

	Non-invasive group (n = 38)			**Intubation group (n = 17)**		
Time (m)	**n**	**PI (%)**	***p* value**	**n**	**PI (%)**	***p* value**
2	31	1.95 (0.98–3.16)		15	1.50 (1.21–2.91)	
3	35	1.69 (1.11–2.96)	< 0.01	15	2.49 (1.10–2.85)	0,09
4	37	1.59 (1.02–2.82)	0.05	16	2.47 (1.13–2.97)	0.51
5	37	1.39 (1.00–2.85)	0.57	16	1.83 (0.06–2.19)	< 0.01
6	37	1.44 (0.97–3.07)	0.22	17	1.72 (0.94–2.40)	< 0.01
7	38	1.53 (0.99–2.81)	0.15	16	1.31 (0.77–1.80)	< 0.001
8	34	1.58 (0.89–2.89)	0.14	16	1.56 (0.59–2.26)	< 0.001
9	33	1.60 (0.95–2.67)	0.71	16	1.79 (0.70–2.54)	0.41
10	29	1.37 (0.78–2.51)	0.60	17	1.85 (1.02–2.43)	0.70

Discussion

PI values of preterm infants were stable during transition in the first 10 minutes after birth and no trend could be observed. Except for a decrease during the intubation procedure, the PI was generally higher in the group needing intubation when compared to the non-invasive group. Although the difference is small and in contrast to what we expected, it is quite consistent in the first 10 minutes. It is possible that this reflects the subjective assessment of the need for intubation during stabilization in the DR.

The PI in preterm infants is lower when compared to healthy term infants (1.9 (1.3–2.9), which could reflect the transitional problems in preterm infants at birth. However, the higher PI in infants needing intubation as compared to the CPAP group contradicts this. Although we have criteria for intubation, it is mostly left to the discretion to the caregiver. It is possible that the "need" for intubation does not reflect to severity of the transitional problems and that our findings emphasize the subjectivity in the decision to intubate (23). In addition, the most common problem in preterm infants at birth is inadequate lung aeration, but recently it was demonstrated that partial lung aeration does cause a significant increase in pulmonary blood flow, causing a ventilation/perfusion mismatch (24). Although this causes low SpO_2, which is compensated by increasing the fractional oxygen, no hemodynamic problems would be observed.

Similar to healthy term infants, PI was low in preterm infants, no trend was observed in the first 10 minutes after birth and all differences observed in this study were small. It is possible that this is a consequence of the peripheral vasoconstriction caused by the high surge of adrenaline around birth. This makes it unlikely that measuring PI at birth could be a valuable parameter for evaluating transition at birth.

The PI in preterm infants directly after birth is higher than later in life (13;14). Cresi *et al*. (13), Hakan *et al*. (14) and Vidal *et al*. (25) reported PI in hemodynamically stable preterm infants during the first of life was 0.9 (0.6–1.0), 1.0 (0.8–1.6) and 0.7 (0.5–1.1) respectively. It is not clear why PI would decrease after the transition, but is possible that a further decrease in pulmonary vascular resistance leading to an increase in left-to-right shunting would cause a decrease in PI in the preductally circulated right upper extremity. Indeed, in all infants in the referenced studies the ductus arteriosus was patent (13;14;25).

A significant decrease in PI was observed in the intubation group after the first minutes of life. It is possible that this decrease in PI is a consequence of the intubation itself. O'Donnell *et al*. demonstrated that the time taken for intubation is often variable and

infants frequently deteriorate during intubation attempts as determined by PO (26). The observed decrease of PI seen in our cohort of intubated infants between 4 and 7 minutes after birth corresponds to a decrease of both HR and SpO_2 and the mean time of intubation during the same time period. The decrease in PI during intubation attempts was comparable to what was observed during intubation of adults (27).

Our study has several limitations. We were unable to include sufficient valid data points in both cohorts of preterm infants in the first minute after birth. However, multiple studies have demonstrated that reliable PO signals are rarely available within the first minute after birth (28-32). In addition, as discussed above the decision of the intensity of respiratory support could have been subjective and thus could account for potential selection bias.

Conclusion

We have described PI of preterm infants during supported transition after birth. We observed that PI was stable during transition in the first 10 minutes after birth with the exception of the decrease caused by intubation. PI was generally higher in the invasively ventilated group compared to the non-invasively ventilated group. It is possible that this reflects the subjective assessment of the need for intubation in the DR. As PI could be influenced by several factors which are independent from the infants' health the clinical relevance of monitoring PI during transition is unclear.

References

1. Dawson JA, Davis PG, O'Donnell CPF, Kamlin CO, Morley CJ. Pulse oximetry for monitoring infants in the delivery room: a review. Archives of Disease in Childhood - Fetal and Neonatal Edition 2007;92:F4-F7.
2. Kamlin CO, O'Donnell CPF, Davis PG, Morley CJ. Oxygen saturation in healthy infants immediately after birth. The Journal of Pediatrics 2006;148:585-9.
3. Prasad S, Watcher D, Aitchison R, Aitchison P, Wang E, Kharasch M. Neonatal resuscitation guidelines. Disease-a-Month 2013;59:196-201.
4. Kopotic RJ, Lindner W. Assessing high-risk infants in the delivery room with pulse oximetry. Anesth Analg 2002;94:S31-S36.
5. Perlman JM, Wyllie J, Kattwinkel J, Atkins DL, Chameides L, Goldsmith JP, *et al*. Part 11: Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation 2010;122:S516-S538.
6. Vento M, Aguar M, Leone TA, Finer NN, Gimeno A, Rich W, *et al*. Using Intensive Care Technology in the Delivery Room: A New Concept for the Resuscitation of Extremely Preterm Neonates. Pediatrics 2008;122:1113-6.

7. Dawson JA, Kamlin CO, Wong C, te Pas AB, O'Donnell CPF, Donath SM, *et al*. Oxygen saturation and heart rate during delivery room resuscitation of infants <30 weeks' gestation with air or 100% oxygen. Archives of Disease in Childhood - Fetal and Neonatal Edition 2009;94:F87-F91.
8. Singh JK, Kamlin CO, Morley CJ, O'Donnell CPF, Donath SM, Davis PG. Accuracy of pulse oximetry in assessing heart rate of infants in the neonatal intensive care unit. Journal of Paediatrics and Child Health 2008;44:273-5.
9. Saugstad OD. Oxidative Stress in the Newborn Ïçô A 30-Year Perspective. Neonatology 2005;88:228-36.
10. Lima AP, Beelen P, Bakker J. Use of a peripheral perfusion index derived from the pulse oximetry signal as a noninvasive indicator of perfusion. Crit Care Med 2002;30:1210-3.
11. De Felice C, Latini G, Vacca P, Kopotic RJ. The pulse oximeter perfusion index as a predictor for high illness severity in neonates. Eur J Pediatr 2002;161:561-2.
12. Granelli A, Ostman-Smith I. Noninvasive peripheral perfusion index as a possible tool for screening for critical left heart obstruction. Acta Paediatr 2007;96:1455-9.
13. Cresi F, Pelle E, Calabrese R, Costa L, Farinasso D, Silvestro L. Perfusion index variations in clinically and hemodynamically stable preterm newborns in the first week of life. Ital J Pediatr 2010;36:6.
14. Hakan N, Dilli D, Zenciroglu A, Aydin M, Okumus N. Reference values of perfusion indices in hemodynamically stable newborns during the early neonatal period. Eur J Pediatr 2014;173:597-602.
15. Teitel DF, Iwamoto HS, Rudolph AM. Effects of Birth-Related Events on Central Blood Flow Patterns. Pediatr Res 1987;22:557-66.
16. Bhatt S, Alison BJ, Wallace EM, Crossley KJ, Gill AW, Kluckow M, *et al*. Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. The Journal of Physiology 2013;591:2113-26.
17. Richardson BS, Carmichael L, Homan J, Johnston L, Gagnon R. Fetal cerebral, circulatory, and metabolic responses during heart rate decelerations with umbilical cord compression. Am J Obstet Gynecol 1996;175:929-36.
18. Crossley KJ, Allison BJ, Polglase GR, Morley CJ, Davis PG, Hooper SB. Dynamic changes in the direction of blood flow through the ductus arteriosus at birth. The Journal of Physiology 2009;587:4695-704.
19. O'Donnell CPF, Kamlin CO, Davis PG, Morley CJ. Obtaining pulse oximetry data in neonates: a randomised crossover study of sensor application techniques. Archives of Disease in Childhood - Fetal and Neonatal Edition 2005;90:F84-F85.
20. O'Donnell CPF, Kamlin CO, Davis PG, Morley CJ. Feasibility of and Delay in Obtaining Pulse Oximetry during Neonatal Resuscitation. The Journal of Pediatrics 2005;147:698-9.
21. Masimo Corporation. Radical signal extraction pulse oximeter operator's manual. 2004. Irvine, Masimo.
22. van den Dungen FA, van Veenendaal MB, Mulder AL. Clinical practice: neonatal resuscitation. A Dutch consensus. Eur J Pediatr 2010;169:521-7.
23. Schilleman K, Siew ML, Lopriore E, Morley CJ, Walther FJ, te Pas AB. Auditing resuscitation of preterm infants at birth by recording video and physiological parameters. Resuscitation 2012;83:1135-9.
24. Lang JA, Pearson JT, Pas BT, Wallace MJ, Siew ML, Kitchen MJ, *et al*. Ventilation/perfusion mismatch during lung aeration at birth. J Appl Physiol (1985) 2014.
25. Vidal M, Ferragu F, Durand S, Baleine J, Batista-Novais AR, Cambonie G. Perfusion index and its dynamic changes in preterm neonates with patent ductus arteriosus. Acta Paediatr 2012.
26. O'Donnell CPF, Kamlin CO, Davis PG, Morley CJ. Endotracheal Intubation Attempts During Neonatal Resuscitation: Success Rates, Duration, and Adverse Effects. Pediatrics 2006;117:e16-e21.
27. Atef HM, Fattah SA, Gaffer ME, Al Rahman AA. Perfusion index versus non-invasive hemodynamic parameters during insertion of i-gel, classic laryngeal mask airway and endotracheal tube. Indian J Anaesth 2013;57:156-62.
28. Kamlin COF, Dawson JA, O'Donnell CPF, Morley CJ, Donath SM, Sekhon J, *et al*. Accuracy of Pulse Oximetry Measurement of Heart Rate of Newborn Infants in the Delivery Room. The Journal of Pediatrics 2008;152:756-60.

29. Gandhi B, Rich W, Finer N. Time to achieve stable pulse oximetry values in VLBW infants in the delivery room. Resuscitation 2013;84:970-3.
30. Rich WD, Leone T, Finer NN. Delivery Room Intervention: Improving the Outcome. Clinics in Perinatology 2010;37:189-202.
31. Dawson JA, Kamlin CO, Wong C, Te Pas AB, Vento M, Cole TJ, *et al*. Changes in heart rate in the first minutes after birth. Arch Dis Child Fetal Neonatal Ed 2010;95:F177-F181.
32. Katheria A, Rich W, Finer N. Electrocardiogram provides a continuous heart rate faster than oximetry during neonatal resuscitation. Pediatrics 2012;130:e1177-e1181.

CHAPTER 16

Pulse oximetry measures a lower heart at birth compared to electrocardiography

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Submitted

Abstract

Objective: To examine the effect of time on heart rate measured by pulse oximetry (HR_{PO}) and ECG (HR_{ECG}).

Methods: HR_{ECG} and HR_{PO} (collected at maximum sensitivity) were assessed in (pre)term infants at birth. ECG electrodes and a PO sensor were attached as soon as possible and HR_{ECG} and HR_{PO} were compared every 30 s from 1-10 minutes after birth. PO data were excluded if Signal Identification and Quality <0.30.

Results: 53 patients were included and 755 data pairs were analysed. Median (IQR) gestational age was 37 (31-39) weeks. Mean (SD) starting time of PO and ECG data collection was 99 (33) vs. 82 (26) s after birth (p=0.001). In the first 2 minutes, HR_{PO} was significantly lower from 60-450 s when compared to HR_{ECG} (94 (67-144) vs. 150 (91-153) bpm at 60 s (p<0.05), 81 (60-109) vs. 148 (83-170) bpm at 90s (p<0.001) and 83 (67-145) vs. 158 (119-176) at 120 s (p<0.001). A HR <100 bpm was more frequently observed with a PO than ECG in the first 2 minutes (64% vs. 27 % at 60 s (n.s.), 56% vs. 26% at 90 s (p<0.05) and 53% vs. 21% at 120 s (p<0.05).

Conclusion: In infants at birth HR measured by PO is significantly lower compared to ECG with clinically important differences in the first minutes.

Introduction

Heart rate (HR) measurement is the only parameter currently used for evaluating the infant's condition and effect of resuscitation at birth (1). HR is often underestimated by auscultation or palpation and currently pulse oximetry (PO) is recommended for accurate measurement of HR values (1). Reference ranges of HR of uncompromised infants receiving no resuscitation have been defined (2). Although intervention is recommended if HR is <100 beats per minute (bpm) (1), many healthy (pre)term infants were found to be bradycardic (HR <100 bpm), when measured with a PO, shortly after birth, which is followed by a rapid increase (2). In contrast, more recently, HR <100 bpm was not observed when electrocardiography (ECG) was used in uncompromised infants in the first minutes after birth. They also found that HR did not change in the first 10 minutes (3).

Although only high quality data from PO have been used to define the reference ranges (2), ECG is considered as the 'gold standard' for monitoring HR. Finer *et al*. showed that an ECG provided a reliable HR earlier than pulse oximetry during neonatal resuscitation (4). Studies testing the reliability of PO at birth have shown that HRs obtained by PO (HR_{PO}) only slightly deviated from HRs measured by ECG (HR_{ECG}) and, therefore, were considered equivalent (5;6). However, in these studies the comparison was not performed in relation to time after birth, as it is possible that when comparing all data a difference in HR between the devices during the first minutes could have been missed. To determine whether PO is a reliable clinical tool for evaluation of the infant during early transition at birth we repeated a previous study (6) but we compared HR_{PO} with HR_{ECG} in infants at specific time points over the first 10 minutes after birth.

Methods

This prospective observational study was conducted in the Department of Neonatology of the Leiden University Medical Center, Leiden, the Netherlands. Approval for the study was obtained from the institutional review board of the Leiden University Medical Center. Informed parental consent was asked before birth. In the event this was deemed not suitable (e.g., due to the clinical condition of the mother), permission to use the data was asked after birth. Permission was acquired both verbally and in writing. Term and preterm infants born vaginally or by cesarean section were eligible for study inclusion. Infants were excluded if they had congenital abnormalities or cardiac defects.

Before delivery, a set of single-use pediatric ECG electrodes (Neotrode II, ConMed Corporation, Utica, NY, USA) was connected to a heart rate monitor (Intellivue MP5, Philips, Eindhoven, the Netherlands). The PO (Masimo Radical 7, Masimo, Irvine, CA, USA) was set to acquire data with maximum sensitivity and a PO sensor (M-LNCS NeoPt-500, Masimo SET, Masimo, Irvine, CA, USA) was also readied for use prior to delivery.

Immediately following birth, an Apgar timer (Medela Apgar-Timer, Medela AG Equipment, Baar, Switzerland) was started and recording of data commenced.
As soon as possible after birth the three ECG electrodes were placed on the infant's chest and abdomen.
The PO sensor was simultaneously applied to the infant's right hand or wrist and connected to the PO by a second member of the research team (7;8). Local resuscitation guidelines were followed and positive pressure ventilation was given if the infant displayed laboured breathing, had a HR <100 bpm and/or there was apnea (1).

HR_{ECG} and HR_{PO} were continuously recorded every 2 s until 10 minutes after birth or sooner if the infant was handed over to mother or transported to the unit before 10 minutes after birth. All recorded values were stored on a laptop using the Spectra Physiological Recording Program (Spectra, Grove Medical, Hampton, UK). HR_{ECG} and HR_{PO} data were averaged for each infant at each 30 s interval (2 s of data before and after each 30 s interval). Only good quality data were included for analysis, which was defined as clear visible QRS complexes for ECG and for HR_{PO}, the Signal Identification and Quality (SIQ) value provided by the device was >0.30 and no alarm messages (low SIQ, low perfusion) were displayed. This good quality data definition was similar to previous studies (5;6;9).

In a subgroup of infants included in this study, HR was measured at 2, 5 and 10 minutes using synchronous ECG and ultrasound measurements. These infants took part in a different study focused on left ventricular changes directly after birth (3). In the previous study methods are described (3). For this study we focussed on the occurrence of left ventricular output flow by using continuous wave Doppler recording and timing with the QRS complex registered by ECG, recorded as described above.

The trial was set up as a non-inferiority study with as null hypothesis that HR measured by PO was ±28 bpm different compared to measurements collected by ECG. This difference is equal to a 2 SD interval as stated by Kamlin *et al*. (6) being -2 (± 26) bpm. With a $\alpha = 0.05$ and $\beta = 0.80$ a minimal sample size of 38 patients with good quality recordings was needed.

Statistical analysis

Analyses were performed using SPSS 20.0 for Windows (IBM, Chicago, IL). Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Data were presented as mean (SD), median (range) or median (IQR) where appropriate. HR_{ECG} and HR_{PO} were compared using a Wilkinson signed-rank test. Clinical relevance (i.e. occurrence of HR <100 bpm) was compared using a McNemar test for normally distributed nominal data. A two-sided p-value of <0.05 was considered as statistically significant. To assess agreement between HR_{ECG} and HR_{PO}, a Bland–Altman plot was constructed (10;11).

Results

Data were collected from 52 infants during the study period, of which 4 infants were excluded because of technical problems with the PO or PO data were not collected. A total of 48 infants were included in the analyses and paired HR measurements were compared every 30 s (in total 755 data pairs). In 14 infants the initiation of cardiac contraction, evidenced by a Doppler flow profile over the left ventricular outflow tract assessed using ultrasonography following an ECG-complex was evaluated. Demographics and clinical interventions are given in table 1. The mean (SD) time taken to acquire stable data from the ECG and PO was 82 (26) vs. 99 (33) s, respectively (p= 0.001). The time taken to acquire ECG and PO data after sensor application was 1 (1-2) vs. 12 (9-30) s (p= 0.001).

Table 1. Demographic and clinical characteristics of infants

Characteristic	
Gestational age, median (range)	36 (27-41)
Birth weight, median (IQR)	2848 (1694-3356) grams
Caesarean delivery	79 %
Male gender	55 %
Apgar 1 minutes (median (IQR))	8 (7-9)
Apgar 5 minutes (median (IQR))	9 (8-10)
Apgar 10 minutes (median (IQR))	10 (8-10)
Respiratory support	
None	31
Continuous positive airway pressure	11
Positive pressure ventilation	6

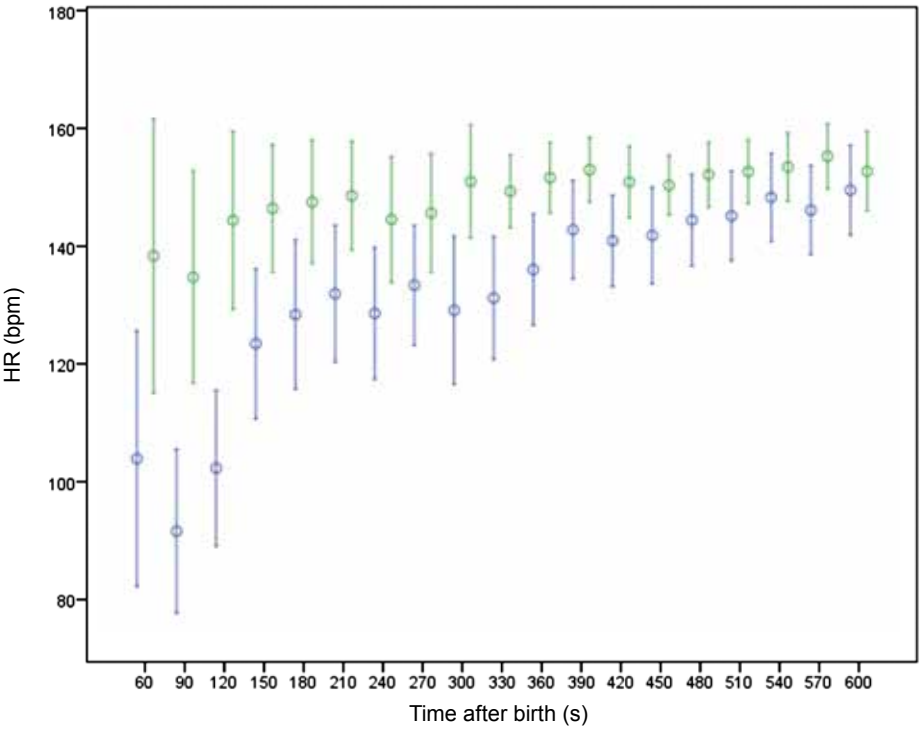

Figure 1. Heart rate (SEM) changes in the first 10 minutes after birth measured by PO (blue) and ECG (green).

HR_{PO} was significantly lower until 450 s after birth when compared to HR_{ECG} (table 2, figure 1). The largest difference was observed in the 60-120 s time interval after birth (table 2), 64% infants were bradycardic (HR <100 bpm) according to the PO, while this was 27 % according to the ECG at 60 s (n.s.), 56% vs. 26% at 90 s (p= 0.04) and 53% vs. 21% at 120s (p= 0.01). When measured by PO there was a steep increase in median (IQR) HR from 60 to 180 s after birth (94 (67-144) bpm at 60 s to 148 (90-159) bpm at 180 s), after which it remained stable (table 1). HR measured by ECG remained stable (approximately 150-160 bpm) from start of recording throughout the first 10 minutes, with no steep increase being observed.

Up to 300 s after birth a significant difference was seen between the two methods of measuring HR, which could have clinical implications as the frequency of HR <100 bpm occurred more often when measured by PO (table 3). The mean difference between both methods (HR_{PO} - HR_{ECG}) for all data pairs was -3 (1-12) bpm. For all data the 95% limit of agreement (± 1.96 SD) was 35 bpm (figure 2).

Table 2. Median (IQR) HR beats per minute (bpm) over time (**= p<0.001, *= p<0.05).

Time	HR PO	HR ECG	Number of infants
60s**	94 (67-144)	150 (91-153)	11
90s*	81 (60-109)	148 (83-170)	27
120s*	83 (67-145)	158 (119-176)	38
150s*	130 (77-158)	156 (132-174)	42
180s**	148 (90-159)	156 (118-174)	46
210s**	145 (101-162)	153 (131-172)	48
240s**	135 (95-157)	153 (117-169)	47
270s**	140 (105-161)	152 (124-170)	44
300s*	141 (102-160)	160 (134-170)	42
330s*	146 (104-157)	149 (133-163)	41
360s*	144 (124-159)	154 (136-166)	45
390s**	145 (132-160)	153 (141-164)	44
420s**	144 (133-158)	152 (142-164)	44
450s	141 (132-159)	149 (136-162)	44
480s	147 (135-160)	151 (139-162)	41
510s	147 (135-158)	151 (139-162)	41
540s	149 (137-164)	156 (140-166)	40
570s	146 (138-159)	155 (141-165)	39
600s	152 (139-163)	154 (142-166)	37

Table 3. Frequency of occurrence of HR < 100 beats per minute (bpm).

Time	HR PO below 100 bpm	HR ECG below 100 bpm	p-value
60s	64	27	n.s.
90s	56	26	0.04
120s	53	21	0.01
150s	27	13	0.04
180s	32	9	0.01
210s	24	9	0.04
240s	23	9	n.s.
270s	22	7	n.s.
300s	23	8	0.03
330s	21	0	n.s.
360s	14	0	n.s.
390s	5	0	n.s.
420s	7	0	n.s.
450s	8	0	n.s.
480s	5	0	n.s.
510s	5	0	n.s.
540s	5	0	n.s.
570s	6	0	n.s.
600s	6	0	n.s.

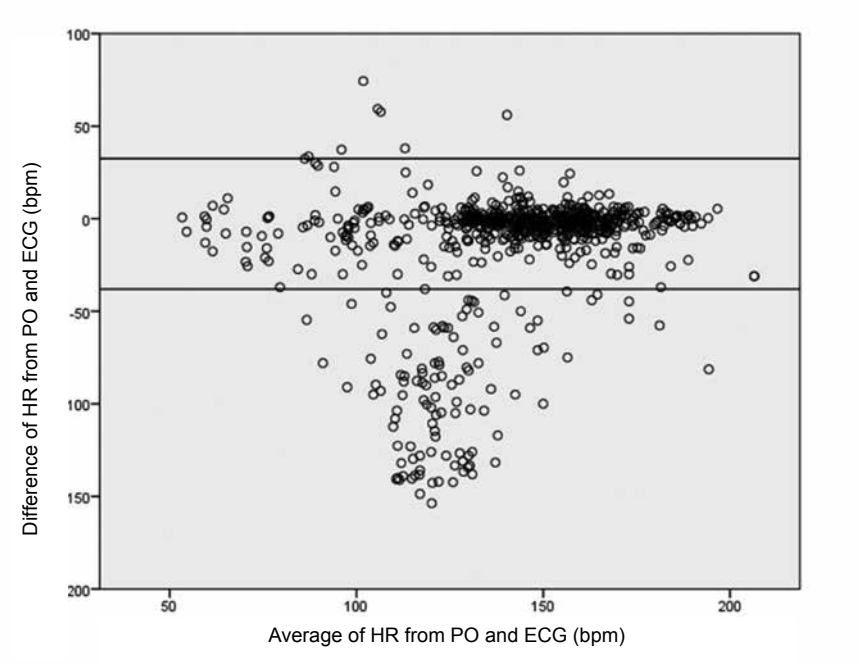

Figure 2. Bland-Altman plot of the differences in HR_{PO} and HR_{ECG} (bpm).

In the subgroup of infants (N= 14) where Doppler flow profiles over the left ventricular outflow tract were compared with ECG signals we observed that the QRS complex occurred in a 1:1 ratio. As such every QRS-complex was associated with a Doppler flow profile over the left ventricular outflow tract. This ratio was the same at all three time points.

Discussion

In this study we measured HR_{ECG} and HR_{PO} in infants during the first 10 minutes after birth. Using Doppler measurements we confirmed that each QRS complex, detected by ECG, was associated with a ventricular contraction and subsequent cardiac output. However, we observed that until 7 minutes after birth HR_{PO} was significantly lower than HR_{ECG}. As ECG is the gold standard, our findings imply that PO underestimates HR, and thus cardiac contractions, when compared to ECG in the first minutes after birth. While HR_{PO} starts low and increased after 2 minutes, HR_{ECG} remained around 150 bpm immediately after birth and was relatively stable. With all data combined, the difference is acceptable and com-

parable with what has been reported previously. However, for the first 2 minutes after birth, measured HR_{PO} values were significantly lower than HR_{ECG}. This is a clinically important difference as the observed HR_{PO} <100 bpm could have led to interventions (1) in a large proportion of the infants that would have been unnecessary according to HR_{ECG}.

This is the first study that has compared HR_{ECG} and HR_{PO} values at specific time points after birth. When all data are combined, we observed a higher mean difference (HR_{PO} - HR_{ECG}) of 3 (35) bpm than previous studies. Kamlin *et al*. observed a difference of -2 (±26) bpm whereas Dawson *et al* recently reported an even smaller mean difference of 0.2 (±9) bpm. The higher mean difference observed could be due to differences in the method used to assess the data quality. Although all studies only analysed good quality data, we assessed good quality PO data based on a SIQ >0.30 (9) whereas in previous studies (2;5;6) PO data quality was judged by visually assessing the pulse wave forms on recorded videos. Also, we compared data points every 30 s while the previous comparison studies used all data collected every 2 s. As a consequence we had less data pairs at each specific time point, resulting in a larger variability. As Kamlin *et al*. and Dawson *et al*. did not compare HR_{ECG} and HR_{PO} with respect to time after birth, we do not know whether the proportion of the data excluded was greater in the first minutes after birth. As such, it is possible that, relative to the amount of data included in the analysis from <3 minutes after birth, the amount of data included from time points >3 minutes after birth, may have obscured the large differences we observed (2;6).

The observed HR measured by ECG in this study and our previous study (3) are not consistent with currently available normograms that were based on PO data. Based on these normograms, a bradycardia is considered normal in the first minutes after birth in uncompromised infants (2). It is possible that in the first minutes of transition, not all pulse waves, emanating from cardiac contractions, can be detected by PO in the peripheral vasculature, resulting in an underestimation of HR. As we have verified in a subgroup that each contraction observed by ECG was associated with left ventricular outflow, it is clear that PO must have missed some heartbeats. This is possible, because during the first minutes large hemodynamic changes take place which could affect the ability of the pulse wave to penetrate downstream into the peripheral vessels (12). For instance, animal experiments have demonstrated that immediately after birth approximately 50% of the large increase in pulmonary blood flow is due to left-to-right ductal shunting (13). This ductal steal could have influenced the pulse wave, particularly if it is combined with peripheral vasoconstriction caused by low venous return and left ventricular output associated with umbilical cord clamping (14). Indeed, a low left ventricular output shortly after birth has recently also been observed in human infants (3). Further

studies are needed to confirm and explain our findings, as this would indicate that current recommended normal ranges, as measured by PO, are not accurate.

The timing of placement of both ECG and PO sensors was dependent on separate members of the research team and was not always simultaneous. However, we were able to include data of 11 infants at 60 s and 24 infants at 90 s. Although it has been shown that PO effectively provides SpO_2 and HR in newborns (6;15), several studies reported that at birth reliable signals were rarely available within 60 to 120 s after birth (2;4;6;16;17). However, we managed to collect data with good signal quality in a considerable number of newborns during this time period.

The use of PO for evaluation infants at birth in combination with the recommended normal ranges is now adopted worldwide. It is easy to use and the probe is much easier to apply then the electrodes of an ECG, especially in preterm infants. However, as shown in previous studies (4;18) we measured HR by ECG earlier than by PO and it was not difficult to get a reliable ECG-signal. In addition, with the frequent occurrence of poor quality data during PO measurements (2;6) and the apparent underestimation when even good quality data are used, it is difficult for clinicians to interpret whether the data are valid during resuscitation. Studies with larger sample sizes are needed to decide whether PO or ECG should be used for evaluating HR.

Conclusion

At birth HR measured by PO is lower than that measured by ECG, especially in the first minutes when a large clinical important difference occurs. These results suggest that, even with selection of good quality data, PO underestimates HR immediately after birth and values should be interpreted with caution when a bradycardia is observed.

References

1. Kattwinkel J, Perlman JM, Aziz K, Colby C, Fairchild K, Gallagher J, *et al*. Part 15: neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122:S909-S919.
2. Dawson JA, Kamlin CO, Wong C, Te Pas AB, Vento M, Cole TJ, *et al*. Changes in heart rate in the first minutes after birth. Arch Dis Child Fetal Neonatal Ed 2010;95:F177-F181.
3. van Vonderen JJ, Roest AA, Siew ML, Blom NA, van Lith JM, Walther FJ, *et al*. Noninvasive measurements of hemodynamic transition directly after birth. Pediatr Res 2014;75:448-52.
4. Katheria A, Rich W, Finer N. Electrocardiogram provides a continuous heart rate faster than oximetry during neonatal resuscitation. Pediatrics 2012;130:e1177-e1181.
5. Dawson JA, Saraswat A, Simionato L, Thio M, Kamlin CO, Owen LS, *et al*. Comparison of heart rate and oxygen saturation measurements from Masimo and Nellcor pulse oximeters in newly born term infants. Acta Paediatr 2013;102:955-60.
6. Kamlin CO, Dawson JA, O'Donnell CP, Morley CJ, Donath SM, Sekhon J, *et al*. Accuracy of pulse oximetry measurement of heart rate of newborn infants in the delivery room. J Pediatr 2008;152:756-60.
7. O'Donnell CP, Kamlin CO, Davis PG, Morley CJ. Obtaining pulse oximetry data in neonates: a randomised crossover study of sensor application techniques. Arch Dis Child Fetal Neonatal Ed 2005;90:F84-F85.
8. O'Donnell CP, Kamlin CO, Davis PG, Morley CJ. Feasibility of and delay in obtaining pulse oximetry during neonatal resuscitation. J Pediatr 2005;147:698-9.
9. Brockmann PE, Poets A, Urschitz MS, Sokollik C, Poets CF. Reference values for pulse oximetry recordings in healthy term neonates during their first 5 days of life. Arch Dis Child Fetal Neonatal Ed 2011;96:F335-F338.
10. Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res 1999;8:135-60.
11. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307-10.
12. van Vonderen JJ, Roest AA, Siew ML, Walther FJ, Hooper SB, Te Pas AB. Measuring Physiological Changes during the Transition to Life after Birth. Neonatology 2014;105:230-42.
13. Crossley KJ, Allison BJ, Polglase GR, Morley CJ, Davis PG, Hooper SB. Dynamic changes in the direction of blood flow through the ductus arteriosus at birth. J Physiol 2009;587:4695-704.
14. Bhatt S, Alison B, Wallace EM, Crossley KJ, Gill AW, Kluckow M, *et al*. Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. J Physiol 2013.
15. Singh JK, Kamlin CO, Morley CJ, O'Donnell CP, Donath SM, Davis PG. Accuracy of pulse oximetry in assessing heart rate of infants in the neonatal intensive care unit. J Paediatr Child Health 2008;44:273-5.
16. Gandhi B, Rich W, Finer N. Time to achieve stable pulse oximetry values in VLBW infants in the delivery room. Resuscitation 2013;84:970-3.
17. Rich WD, Leone T, Finer NN. Delivery room intervention: improving the outcome. Clin Perinatol 2010;37:189-202.
18. Mizumoto H, Tomotaki S, Shibata H, Ueda K, Akashi R, Uchio H, *et al*. Electrocardiogram shows reliable heart rates much earlier than pulse oximetry during neonatal resuscitation. Pediatr Int 2012;54:205-7.

CHAPTER 17

Discussion

Most of our knowledge on the physiological changes during the transition at birth is based on human studies performed in the early 1960s and 70s or animal studies (1-8). In the studies conducted in humans, healthy term infants were often submitted to cumbersome invasive techniques to gather data (5;9-13). After this period no more data were published, probably reflecting the difficulties in performing studies in this area. In addition, nowadays ethics committees would not allow the invasive procedures used for data collection. Currently, there is renewed interest in the physiological changes that occur during transition and improving the management of infants with transitional problems. Novel techniques are available to measure respiratory and hemodynamic function which are less cumbersome and less stressful to the infant in comparison with the methods used previously (14-17). This thesis has shown that it is feasible, even in the preterm infant, to gather respiratory and hemodynamic physiological data, allowing us to study the physiological process of transition in more detail and monitor the effect of resuscitative interventions at birth.

In most of the studies presented in this thesis we have used respiratory function monitoring (RFM) in a non-invasive manner by placing the flow meter between the mask and T-piece ventilator. With this technique flow is measured and inspiratory and expiratory volumes can be calculated (and when respiratory support is given pressures are also measured). This, in combination with a pulse oximeter, makes it possible to monitor transition and evaluate the respiratory support given by the caregivers. The RFM is now even recommended by several experts in the field of delivery room management as standard care during resuscitation or stabilization of preterm infants at birth (15;18;19). However, monitoring ventilation is not recommended in current international resuscitation guidelines as there is little evidence to support this. The question remains whether evidence is needed to use this feedback device in the delivery room, while similar measurements are daily used to monitor ventilation in the NICU.

Mask ventilation

Previous studies reported RFM measurements during face mask ventilation at birth (15;17;19). These studies have shown that face mask ventilation is difficult, the tidal volumes given are often inadequate and mask leak and obstruction occurred frequently. (15;17;19). The observed difficulties are confirmed by our studies in chapter 3 and 4 of this thesis, where we investigated the initial sustained inflation and the mask ventilation given in the MOUNTAIN trial (20) (comparison of the nasal tube with the face mask during positive pressure ventilation).

In chapter 3 we measured the effect of an initial sustained inflation (SI) during respiratory support in preterm infants at birth. An initial SI has been advocated to overcome the resistance of a liquid filled lung (21) and experimental studies have shown that an initial SI is beneficial for uniform lung aeration and establishing functional residual capacity (FRC). (22;23). The randomized clinical trial performed in Leiden, where the SI was incorporated in the approach for resuscitating preterm infants at birth, showed a decrease in the need of intubation and BPD (24). However, we now observed the direct effect of a SI given via a face mask (15;25) and the volume delivered was often inadequate with frequent occurrence of obstruction and large mask leak. The obstruction that occurred during the inflation was most likely caused by a closed glottis as we observed that infants take breaths during the SI and large volumes enter the lung. The observation that in some apneic infants breaths were taken during the SI, but that these infants remained apneic after the SI was a surprising finding. We speculate that applying a pressure on the pharynx might induce a respiratory reflex, as was demonstrated in cats (26;27) . It is also possible that we were not observing obstruction but that the starting pressures of the SI were too low to overcome the resistance of the liquid filled lung. The findings that the SI was not efficient until the infant takes a breath was also confirmed in chapter 10 where we measured volumetric CO_2 and FRC changes during mask ventilation at birth. Similar to our previous study most SIs applied were not appropriate to contribute to lung aeration and FRC.

In addition, there was very little gas exchange until the infant took a breath. We also demonstrated the ineffectiveness of the SI by observing (chapter 3 and 10) no immediate increase in heart rate (HR) or oxygen saturation (SpO_2), which is currently used as the indicator of effective ventilation. The beneficial effects of an initial SI have been shown in experimental studies, but before we can translate these effects into clinical practice, we first need to find an effective manner to apply a SI to the lungs. The non-invasive manner (face mask) seems to be the weakest link in this lung recruitment strategy.

Mask ventilation is the cornerstone for resuscitating infants at birth. Considering the difficulties described above it has been suggested to abandon the face mask and use an alternative interface, such as a nasal tube (28;29). The MOUNTAIN trial, comparing the effect of the face mask vs. a nasal tube during non-invasive ventilation at birth on clinical outcome, was recently completed (20). Based on the fact that the rate of intubation was similar and complications of using the interfaces hardly occurred, it was concluded that either interface could be used and a nasal tube was a good alternative for a face mask (20). However, we now observed, in chapter 4, respiratory function measurements and the direct effect when the interfaces were used. There were no difference in terms of HR and SpO_2 (20). However, Mask technique was considerably improved in both centers (Leiden

and RWH), as mask leak and obstruction occurred much less often when compared to previous reports of these centers (15;25). This improvement could be due to a Hawthorne phenomenon (30). However, it is also possibly the result of frequent mask technique training, which has become been an integral part of resuscitation training in both centers.

During nasal tube ventilation volumes given were more often too low, caused by leak and obstruction which occurred more frequently when compared to the face mask. Apparently it is much more difficult to perform the ventilation leak free with a nasal tube, even when contralateral nostril and mouth are closed. Also, it is possible that the tip of the tube was placed against the posterior wall of the nasopharynx, causing obstruction. Based on our findings, the use of a nasal tube as interface instead of a face mask for non-invasive ventilation in preterm infants at birth cannot be recommended.

Breathing

Previously, it has been described that breathing is difficult to observe and is therefore often missed, especially in preterm infants covered in a wrap to prevent hypothermia (15;31). The studies performed in this thesis confirm that the use of a RFM is useful in adequately detecting spontaneous breathing (32). Despite the fact that most of the ventilation we observed was inadequate, most infants were not intubated but were transported to the NICU on CPAP. In the studies reported in chapter 3, 4 and 10 we often observed spontaneous breaths during the initial SI and consecutive ventilation. Although the respiratory rate and the volumes of these breaths were not always sufficient, the spontaneous breaths produced larger tidal volumes than the inflations given. In addition, when a spontaneous breath occurred concurrent with the inflation the tidal volume increased. Not only tidal volumes were larger, but also, as demonstrated in chapter 10, breaths were more efficient in creating gas exchange (expired CO_2, (ECO_2) and creating FRC than the inflations given. The observed breathing of the preterm infants likely influenced the effect observed when ventilation is applied.

We should also be cautious about the breaths in between and coinciding with inflations. It has been shown that the observed non-synchronized ventilation, could lead to inadvertent pressures and increase the risk for lung injury and air leaks (33). In addition, Schilleman *et al*. and Schmölzer *et al*. have described that during inflations coinciding with breathing, high tidal volumes can be achieved (15;25). These excessive tidal volumes also have the potential to cause lung injury and should be avoided (34;35). In the NICU synchronized and volume guarantee ventilation is given to reduce the above men-

tioned risks (36), this could also be considered as a manner to support the spontaneous breathing of preterm infants at birth.

When considering safe tidal ventilation a distinction should be made between spontaneous breaths and inflations applied non-invasively. The current recommendation of the safe range of tidal volumes at birth is 4-8 mL/kg, but this is based on measurement of spontaneous breathing and intubated ventilated infants (18). However, during mask ventilation the complete respiratory system is pressurized and ventilated, which includes the lungs, the trachea and the nasopharynx. During an inflation given via a mask or nasal tube the nasopharynx is pressurized leading to a volume displacement in the nasopharynx, which does not occur during a breath. This volume displacement has to be taken into account when monitoring mask ventilation. In chapter 6 we investigated this both in an experimental setting as well as in preterm born infants. We demonstrated that a large proportion of the volumes measured during an inflation is caused by pressurization of the nasopharynx and part of the trachea. It is possible that ventilation will be more effective when we correct for this and aim for larger tidal volumes. A different range of safe tidal volume should therefore be defined, in order to avoid inadequate but also excessive and injurious tidal volumes. In addition to this an adequate mask technique with minimal mask leak is still a prerequisite for effective ventilation.

Breathing does not only lead to a better gas exchange than the ventilation we have given at birth, we also demonstrated in chapter 11 and 13 that breathing influences the hemodynamic transition. In fact, in chapter 13 it was shown that when large inspirations (after crying) were taken there is an increase in left-to-right shunt through the ductus arteriosus. This would then increase the pulmonary blood flow, leading to an increased preload and left cardiac output, promoting increased blood flow and oxygenation of the organs.

Based on all these findings, we speculate that stimulating and effectively supporting breathing should be the cornerstone of resuscitation of preterm infants at birth. Infants are currently supported with a continuous positive airway pressure level of 5-6 cmH_2O, but it is possible that initially a higher pressure level is needed to support spontaneous breathing and maintain FRC after lung aeration. In addition when positive pressure ventilation is considered, ventilation that synchronizes with spontaneous breathing (triggered ventilation, assist/control) and which takes the breathing effort of the infant (volume guarantee, pressure support) into account would be a better alternative than our current approach. In this way inflations asynchronous with breathing and excessive tidal volume during inflations concurrent with breathing will be avoided.

The brainstem (respiratory center) is pO_2 sensitive (37) and one of the methods to stimulate breathing at birth is to titrate the extra oxygen given to maintain an adequate SpO_2. The current thought is that low SpO_2 are well tolerated in preterm infants directly after birth and supplemental oxygen should be given with caution as hyperoxia could easily occur. However, the other side of the medal is that the accepted low saturations actually could inhibit the respiratory effort. In chapter 8 we investigated the effect of oxygenation on breathing effort of preterm infants at birth and observed that a short period of 100% oxygen improved oxygenation and effectively increased the breathing effort and respiratory rate (37). This was a retrospective analysis and it is likely that the extra oxygen was needed to compensate for the inadequate lung aeration and FRC that was created. It is possible that the increased respiratory effort improved lung aeration and FRC as we observed that once the SpO_2 and breathing effort increased inspired oxygen could be reduced quickly to 21-23% and infants were transported to the NICU on CPAP. We speculate that we should aim for a higher oxygen saturation target and an SpO_2, higher than the 10^{th} percentile, should be maintained to decrease the chance of breathing failure. Further studies are needed to investigate the effect of SpO_2 on breathing effort, as also other agents to stimulate breathing such as caffeine, glucose and doxapram might be effective in stimulating breathing at birth.

In light of this, a difficult to catch but important observation is the effect of naloxone after birth. In chapter 9 we reported an observation of an infant receiving mask ventilation after birth as she was apneic as a result of the antenatal administration of opiates to the mother. It was difficult to maintain SpO_2 within the accepted range during ventilation, but after administration of naloxone breathing effort immediately increased (a high respiratory rate and large tidal volumes were observed) with a fast increase in SpO_2. Positive pressure ventilation was stopped and inspired oxygen could be weaned. This was the first observation of the direct effect of naloxone on breathing effort. In the current literature the effect of naloxone on breathing effort was debated and no longer recommended. This case report demonstrated that in specific cases naloxone could be effective .

However, caution should be taken in stimulating breathing effort as there is always a possibility of exhausting the preterm infant. In chapter 7, we investigated whether respiratory effort and frequency of certain respiratory patterns, expiratory breaking maneuvers in particular, was related to failure of non-invasive respiratory support at a later stage. We observed that preterm infants who fail CPAP at later age and were intubated, showed early signs of fatigue in their breathing efforts and patterns shortly after birth. This information could be used to intensify the non-invasive support given to a breathing preterm infant (increase CPAP pressure) or even early identification of the infants that

need surfactant. In neonatal practice there is a trend towards a more non-invasive manner of surfactant application (38;39), and identifying respiratory fatigue creates opportunity for surfactant administration in the first ten minutes of life after birth. This early administration of surfactant would then also be beneficial for lung liquid clearance and more uniform lung aeration at birth (40). However, also here more studies are needed to see if the breathing pattern and effort can be used to assess whether infants are likely to fail non-invasive support and to use this in decision making.

Monitoring

So far, only the use of pulse oximetry (PO) is recommended as an objective manner for evaluation of the infant's condition and the effect of interventions. In this thesis we have demonstrated different parameters that can be used to evaluate the infant's condition objectively. In addition to the current used parameters (SpO_2 and HR), we have shown that it could be helpful to measure tidal volume (chapter 3, 4 and 10), ECO_2, relative FRC changes (chapter 10) and perfusion index (chapter 14 and 15). We have also demonstrated in chapter 12 that the ductal arteriosus shunt could be a good indicator whether transition is successful or not.

During this thesis, we have developed a monitor device that included all these parameters (except echocardiography) and a video recording. The tidal volume measurements have been discussed in detail above and currently a large international randomized trial (NTR 4104) is performed to determine whether this monitor will improve evaluating infants and ventilation at birth.

An available method to directly determine the adequacy of gas exchange and lung aeration is capnography (41). It has been described that capnography adds to the objective evaluation of the infant (42). End-tidal capnography can be used to assess gas exchange (43). Capnography has large potential for monitoring the effect of breathing and ventilation given, as shown in chapter 10, but it is not yet recommended to monitor this at birth. We demonstrated that Monitoring ECO_2 is more complex than is currently described in recent published studies (42). Pressurization and volume displacement in the nasopharynx during mask ventilation in combination with a closed larynx could lead to low ECO_2 while "adequate" tidal volume are given. Spontaneous breathing during inflations, obstruction or rebreathing due to dead space ventilation could lead to the measurement of high ECO_2 while very low tidal volumes are measured. While low ECO2 values can be measured due to the occurrence of leak (44). Using ECO_2 standardly in the delivery room

would confuse the caregiver, inexperienced with these physiological measurements, and currently should not be recommended as standard care and if used, should always be combined with volume measurements. More studies are needed to overcome the abovementioned pitfalls and make interpretation of CO_2 measurement less complicated.

The only objective parameter currently used and recommended during resuscitation is HR (45). It is advised to measure HR by PO and with this technique normograms were developed which are now used in the delivery room to evaluate the infant's condition (46). In chapter 16, we compared the HR measured by PO with HR measured by ECG, which is the golden standard. In a previous study PO was found to be comparable with ECG, but the comparison was not performed in course of time after birth (47). During the early phases of transition when pulmonary blood flow is still low and perfusion of the peripheral tissues might be hampered due to a high systemic vascular resistance. Katheria *et al*. showed that it was feasible to measure HR by using electrocardiography in preterm infants at birth (48). For these reasons we repeated the study in healthy term and preterm infants at birth, but this time compared in course of time. Overall the HR of the PO was not significantly lower than measured by the ECG, with the exception of the first minutes after birth. In the first minutes PO significantly underestimated HR. It is difficult to explain this difference, but it could be caused by the difference in which both devices determine HR. The PO uses the pulsatile waves of the contraction of the heart and the ECG uses the electric signal needed for the cardiac contraction. However, to make sure the ECG showed the true heart rate, also echocardiography was performed and confirmed that the QRS complexes were concomitant with a contraction of left ventricular output (LVO) and thus pulse wave. It is possible that the short circuit that is temporarily present when pulmonary vascular resistance decreases (blood flow directed from the left ventricle to the aorta and pulmonary artery via the ductus arteriosus) mitigated part of the pulse waves. Until this is investigated more thoroughly, HR measured by PO must be interpreted with caution, especially in the first 2 minutes after birth. In case of low HRs we would still recommend to confirm this with auscultation or palpation of the umbilical cord to make sure PO does not give an underestimation and unnecessary measures are taken. In addition with this finding the current internationally accepted normal ranges of HR at birth need to be re-evaluated.

Monitoring additional non-invasive hemodynamic parameters could be useful for evaluating the infant's condition at birth or the interventions given. We investigated the perfusion index (PI) in term (chapter 15) and in preterm infants (chapter 14). PI can be derived from the pulse oximeter by calculating the ratio of the pulsatile signal (arterial blood flow) indexed against the non-pulsatile signal (static blood flow in skin and other tissues) and is described as a non-invasive indicator for peripheral perfusion (49). Studies

performed in the NICU have shown to give extra information on the circulatory status of the infant (50;51). Also PI has been studied in term infants at birth (52), but the course of PI over time transition was not reported. We described that in healthy infants at birth very little changes occur in PI during transition. We also described that preterm infants breathing on CPAP compared to infants intubated in the delivery room had a significantly lower PI. The question remains how clinically important this is as the difference was very small. In addition the caregiver's decision to intubate in the delivery room is often based on subjective observations and this could have influenced the results. It is also possible that the respiratory problems of preterm infants at birth are not reflected by the peripheral circulation. More studies are needed before this parameter can be used for evaluating transition at birth and decision making.

Hemodynamic transition

The significant hemodynamic changes during neonatal transition are intimately linked with the respiratory changes (53). Most of the data of the hemodynamic transition are derived from animal studies. In this thesis we have provided data from human infants using echocardiography, ECG and non-invasive blood pressure. In chapter 11 we described that a successful transition in healthy term infant born after a cesarian section is characterized by a significant increase in LVO between 2 and 5 minutes after birth, which was due to an increase in preload and an increase of pulmonary blood flow (53). HR remained unchanged during this time period (53). The LVO was equivalent to values measured at later time points after birth (14). The increase in stroke volume that was observed directly after birth is in contrast to the current held belief that newborns can only increase their cardiac output by increasing HR and that stroke volume cannot be increased directly after birth. These assumptions were based on extrapolated data from fetal observations of the cardiac output, when the circulation is completely different compared to the circulation during transition (54). Clamping the cord before lung aeration will result in a 25-50% decrease in LVO as during this time the left ventricle was dependent on the venous return from the placenta. When lungs are aerated before cord clamping the sudden decrease in LVO will not occur as the left ventricle is then dependent on the pulmonary venous return. Lung aeration at birth causes a decrease in pulmonary vascular resistance and an increase in pulmonary blood flow, which then increases the preload in left ventricle (55). Most of the infants in our cohort immediately breathed and aerated their lungs before the cord was clamped, which compensated the sudden loss of venous return from the placenta (56). A reversal of shunt (from right-to-left to left-to-right) in the ductus arteriosus in ventilated newborn lambs was shown to be responsible for almost 50 % of the

increase in pulmonary blood flow and thus venous return (55). We now have demonstrated in chapter 12 that a smooth transition in spontaneously breathing human infants is also characterized by reversal of this ductal shunt (from right-to-left to left-to-right). The ductal shunt ratio (right-to-left/left-to-right) has the potential to be used as a parameter/ indicator for the success of the neonatal transition.

Blood pressures at birth were previously unknown, but we now provided (chapter 11) values of blood pressure in healthy term infant in the first minutes after birth. We observed that despite significant hemodynamic changes, blood pressures did not change in the first 10 minutes after birth and these values were similar to values measured at later time points during the first day of life. We only measured preductal blood pressure, it is possible that we would have observed different results when blood pressure was measured post-ductally. Blood pressure is the product of cardiac output and vascular resistance, and is mediated by cardiovascular reflexes, stress and relaxation and hormonal control (such as adrenalin) (57). It is possible that the decrease in pulmonary vascular resistance and increase in systemic vascular resistance (by cord clamping) mitigated the effect of cardiac output on blood pressure (55). Apparently the large hemodynamic changes after birth are not reflected in blood pressure and PI measured at the extremity. Although the stable PI and blood pressure measured in the extremity makes it likely that the systemic vascular resistance increases in the extremities, this has not been investigated. Blood pressure was easy to measure at birth and could be used as an extra parameter for evaluating the hemodynamic condition.

We also described in chapter 13 that breathing and crying has large influence on the hemodynamic observations. The large inspirations during crying caused an increase in left-to-right ductal shunt, increasing the pulmonary blood flow and therefore influencing LVO. Although we could not measure the effect of the expiratory phase of crying (the cry itself), our findings are in line with previous findings (58) that breathing is important for the hemodynamic transition. We speculate that crying at birth has more physiological function than only expressing discomfort.

It was possible to perform these hemodynamic measurement in infants born by cesarean section, as in our hospital it was standard procedure to evaluate these infants on the resuscitation table. However, this is also a limitation to this part of the thesis and we are not informed if in vaginally born infants similar measurements would have been observed. It is however much more difficult to gather reliable measurements as these infants are directly placed on the chest of their mother. Although a faster transition could take place in vaginally born infants, we expect that measurements will be comparable to the measurements we described above.

Conclusions

We have shown that it is possible to translate experimental findings to clinical setting and perform non-invasive physiological measurements in human infants at birth. We have gathered unique data of both respiratory and hemodynamic transition and during interventions when transition failed. We have demonstrated that the SI and consecutive inflations given via mask are often inadequate and not effective. This could be explained by inadequate ventilatory pressures used and inadequate mask technique, but also a closed glottis could play a role in an ineffective non–invasive ventilation. We have shown that in a trial mask technique was improved when compared to previous observations, this could be explained by a Hawthorne phenomenon or the effect of frequent training in mask technique. We also observed that a nasal tube is not a good alternative for the face mask, as more leak and obstruction occurred.

The general finding of this thesis is the importance of breathing for the neonatal transition, as it both aerates the lungs, creating FRC and causes hemodynamic changes. Breathing in preterm infants is often missed, and although it is not always sufficient, it is likely that breathing has contributed to the effect of ventilation given. This suggests that stimulating and supporting breathing might be a more efficient respiratory strategy at birth. We speculate that synchronization of inflations with breathing and supporting breathing using triggered ventilation with volume guarantee or pressure support might be a good alternative for the currently used manual positive pressure ventilation. However, still a proportion of infants are apneic and adequate mask ventilation technique should still be a focus in resuscitation training.

We demonstrated that the use of several objective parameters, other than SpO_2 and HR, will inform the caregiver how adequate the infant's breathing is and/or how adequate the ventilation is given. In addition the breathing pattern and effort observed in more detail could have the potential to show early signs of fatigue and predict respiratory failure.

We have collected important observations of hemodynamic changes in human infants at birth. We observed that newborns are capable to increase LVO by increasing the cardiac preload, not necessarily only by increasing HR. We have described the ductal shunt reversal that occurred during uneventful transitions and that the ductal shunt ratio could have the potential to be used as a parameter to monitor transition. The blood pressures values

measured in term infants can be used as an extra parameter for evaluating the infants hemodynamic condition. Measuring HR by PO at birth is currently recommended by international resuscitation guidelines and normal ranges are based on PO measurements, but we now demonstrated that the pulse oximeter significantly underestimates the heart rate in the very first minutes. The currently accepted normal ranges should be re-evaluated.

Future directions

With this thesis much progress has been made in understanding the physiological process of transition at birth and the effect of our support given when transition fails. However, many questions still need to be answered as we are not yet fully informed about the respiratory and circulatory changes taking place. Understanding the physiology of transition and the most effective way to support transitional problems is important to improve our care of the preterm infant in his/her most vulnerable period, right after birth. The following are the most important questions that need to be addressed in the near future:

1. What causes the infant to start breathing and what is the best way to stimulate this and what is the most effective way to support this?
2. Is starting a higher level of CPAP and then titrating down based on clinical parameters a better way than a SI followed by CPAP?
3. Is it feasible to use triggered ventilation and volume guarantee for ventilating preterm infants in the delivery room and what is the effect?
4. What is the lower level of SpO_2 that is acceptable and is needed to maintain respiratory effort at birth?
5. Which parameters can be used best to monitor respiratory changes or support at birth, tidal volume or capnography and which parameters should be used as standard of care?
6. Can the respiratory effort and pattern at birth predict respiratory failure and if so, can we use it to select these infants for early surfactant treatment?
7. How can we combine the support of breathing with delayed cord clamping in preterm infants at birth?
8. Can we use non-invasive parameters such as the ductus arteriosus ratio to monitor transition and does this add to the current used parameters?
9. How should we interpret and use the international accepted normal ranges of heart rate at birth measured by pulse oximeter.

These questions can be answered by conducting both experimental and observational studies as well as randomized controlled trials.

References

1. Boon AW, Milner AD, Hopkin IE. Lung expansion, tidal exchange, and formation of the functional residual capacity during resuscitation of asphyxiated neonates. J Pediatr 1979;95:1031-6.
2. Dawes GS, Mott JC, Widdicombe JG, Wyatt DG. Changes in the lungs of the new-born lamb. J Physiol 1953;121:141-62.
3. Heymann MA. Control of the pulmonary circulation in the fetus and during the transitional period to air breathing. Eur J Obstet Gynecol Reprod Biol 1999;84:127-32.
4. Karlberg P, Cherry RB, Escardo FE, Koch G. Respiratory Studies in Newborn Infants II. Pulmonary Ventilation and Mechanics of Breathing in First Minutes of Life, Including Onset of Respiration. Acta Paediatrica Scandinavica 1962;51:121-126.
5. Lind J, Peltonen T, Tornwall L, Wegelius C. Roentgenological lung findings in the newborn infant's 1st breath. Z Kinderheilkd 1963;87:568-78.
6. Milner AD, Saunders RA. Pressure and volume changes during the first breath of human neonates. Arch Dis Child 1977;52:918-24.
7. Rudolph AM, Iwamoto HS, Teitel DF. Circulatory changes at birth. J Perinat Med 1988;16:9-21.
8. Vyas H, Field D, Milner AD, Hopkin IE. Determinants of the first inspiratory volume and functional residual capacity at birth. Pediatr Pulmonol 1986;2:189-93.
9. Boon AW, Milner AD, Hopkin IE. Physiological responses of the newborn infant to resuscitation. Arch Dis Child 1979;54:492-8.
10. Bosma JF, Lind J. Roentgenologic observations of motions of the upper airway associated with establishment of respiration in the newborn infant. Acta Paediatr Suppl 1960;49:18-55.
11. Hull D. Lung expansion and ventilation during resuscitation of asphyxiated newborn infants. J Pediatr 1969;75:47-58.
12. Karlberg P, Cook CD, O'Brien D, Cherry RB, Smith CA. Studies of respiratory physiology in the newborn infant. II. Observations during and after respiratory distress. Acta Paediatr Suppl 1954;43:397-411.
13. Palme-Kilander C, Tunell R. Equipment for recording pulmonary gas exchange immediately after birth during spontaneous breathing and assisted ventilation. Med Biol Eng Comput 1993;31:67-71.
14. Noori S, Wlodaver A, Gottipati V, McCoy M, Schultz D, Escobedo M. Transitional Changes in Cardiac and Cerebral Hemodynamics in Term Neonates at Birth. J Pediatr 2012;160:943-8.
15. Schilleman K, van der Pot CJ, Hooper SB, Lopriore E, Walther FJ, Te Pas AB. Evaluating Manual Inflations and Breathing during Mask Ventilation in Preterm Infants at Birth. J Pediatr 2013;162:457-63.
16. Schmolzer GM, Kamlin CO, Dawson JA, Morley CJ, Davis PG. Tidal volume delivery during surfactant administration in the delivery room. Intensive Care Med 2011;37:1833-9.
17. Te Pas AB, Wong C, Kamlin COF, Dawson JA, Morley CJ, Davis PG. Breathing Patterns in Preterm and Term Infants Immediately After Birth. Pediatric Research 2009;65:352-6.
18. Schmolzer GM, Te Pas AB, Davis PG, Morley CJ. Reducing lung injury during neonatal resuscitation of preterm infants. J Pediatr 2008;153:741-5.
19. Schmolzer GM, Morley CJ, Wong C, Dawson JA, Kamlin CO, Donath SM, *et al*. Respiratory function monitor guidance of mask ventilation in the delivery room: a feasibility study. J Pediatr 2012;160:377-81.
20. Kamlin CO, Schilleman K, Dawson JA, Lopriore E, Donath SM, Schmolzer GM, *et al*. Mask versus nasal tube for stabilization of preterm infants at birth: a randomized controlled trial. Pediatrics 2013;132:e381-e388.
21. Te Pas AB, Davis PG, Hooper SB, Morley CJ. From liquid to air: breathing after birth5. J Pediatr 2008;152:607-11.
22. Klingenberg C, Sobotka KS, Ong T, Allison BJ, Schmolzer GM, Moss TJ, *et al*. Effect of sustained inflation duration; resuscitation of near-term asphyxiated lambs. Arch Dis Child Fetal Neonatal Ed 2013;98:F222-7.

23. Te Pas AB, Siew M, Wallace MJ, Kitchen MJ, Fouras A, Lewis RA, *et al*. Establishing functional residual capacity at birth: the effect of sustained inflation and positive end-expiratory pressure in a preterm rabbit model. Pediatr Res 2009;65:537-41.
24. te Pas AB, Walther FJ. A randomized, controlled trial of delivery-room respiratory management in very preterm infants. Pediatrics 2007;120:322-9.
25. Schmolzer GM, Kamlin OC, O'Donnell CP, Dawson JA, Morley CJ, Davis PG. Assessment of tidal volume and gas leak during mask ventilation of preterm infants in the delivery room. Arch Dis Child Fetal Neonatal Ed 2010;95:F393-F397.
26. Tomori Z, Benacka R, Donic V. Mechanisms and clinicophysiological implications of the sniff- and gasp-like aspiration reflex. Respir Physiol 1998;114:83-98.
27. Tomori Z, Donic V, Benacka R, Jakus J, Gresova S. Resuscitation and auto resuscitation by airway reflexes in animals. Cough 2013;9:21.
28. Capasso L, Capasso A, Raimondi F, Vendemmia M, Araimo G, Paludetto R. A randomized trial comparing oxygen delivery on intermittent positive pressure with nasal cannulae versus facial mask in neonatal primary resuscitation. Acta Paediatr 2005;94:197-200.
29. Segedin E, Torrie J, Anderson B. Nasal airway versus oral route for infant resuscitation. Lancet 1995;346:382.
30. McCarney R, Warner J, Iliffe S, van HR, Griffin M, Fisher P. The Hawthorne Effect: a randomised, controlled trial. BMC Med Res Methodol 2007;7:30.
31. O'Donnell CP, Kamlin CO, Davis PG, Morley CJ. Crying and breathing by extremely preterm infants immediately after birth. J Pediatr 2010;156:846-7.
32. Schmolzer GM, Kamlin OC, Dawson JA, te Pas AB, Morley CJ, Davis PG. Respiratory monitoring of neonatal resuscitation. Arch Dis Child Fetal Neonatal Ed 2010;95:F295-F303.
33. Greenough A, Dimitriou G, Prendergast M, Milner AD. Synchronized mechanical ventilation for respiratory support in newborn infants. Cochrane Database Syst Rev 2008;CD000456.
34. Bjorklund LJ, Ingimarsson J, Curstedt T, John J, Robertson B, Werner O, *et al*. Manual ventilation with a few large breaths at birth compromises the therapeutic effect of subsequent surfactant replacement in immature lambs. Pediatr Res 1997;42:348-55.
35. Dreyfuss D, Saumon G. Barotrauma is volutrauma, but which volume is the one responsible? Intensive Care Med 1992;18:139-41.
36. Keszler M, Abubakar KM. Volume guarantee ventilation. Clin Perinatol 2007;34:107-16.
37. van Vonderen JJ, Narayen NE, Walther FJ, Siew ML, Davis PG, Hooper SB, *et al*. The administration of 100% oxygen and respiratory drive in very preterm infants at birth. PLoS One 2013;8:e76898.
38. Dargaville PA, Aiyappan A, De Paoli AG, Kuschel CA, Kamlin CO, Carlin JB, *et al*. Minimally-invasive surfactant therapy in preterm infants on continuous positive airway pressure. Arch Dis Child Fetal Neonatal Ed 2013;98:F122-F126.
39. Kribs A, Hartel C, Kattner E, Vochem M, Kuster H, Moller J, *et al*. Surfactant without intubation in preterm infants with respiratory distress: first multi-center data. Klin Padiatr 2010;222:13-7.
40. Siew ML, Te Pas AB, Wallace MJ, Kitchen MJ, Islam MS, Lewis RA, *et al*. Surfactant increases the uniformity of lung aeration at birth in ventilated preterm rabbits. Pediatr Res 2011;70:50-5.
41. Hooper SB, Fouras A, Siew ML, Wallace MJ, Kitchen MJ, Te Pas AB, *et al*. Expired CO2 levels indicate degree of lung aeration at birth. PLoS One 2013;8:e70895.
42. van Os, Cheung PY, Pichler G, Aziz K, O'Reilly M, Schmolzer GM. Exhaled carbon dioxide can be used to guide respiratory support in the delivery room. Acta Paediatr 2014.
43. Kong JY, Rich W, Finer NN, Leone TA. Quantitative End-Tidal Carbon Dioxide Monitoring in the Delivery Room: A Randomized Controlled Trial. J Pediatr 2013;163:104-8.
44. Schmalisch G, Al-Gaaf S, Proquitte H, Roehr CC. Effect of endotracheal tube leak on capnographic measurements in a ventilated neonatal lung model. Physiol Meas 2012;33:1631-41.

45. Kattwinkel J, Perlman JM, Aziz K, Colby C, Fairchild K, Gallagher J, *et al*. Part 15: neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122:S909-S919.
46. Dawson JA, Kamlin CO, Wong C, Te Pas AB, Vento M, Cole TJ, *et al*. Changes in heart rate in the first minutes after birth. Arch Dis Child Fetal Neonatal Ed 2010;95:F177-F181.
47. Kamlin CO, Dawson JA, O'Donnell CP, Morley CJ, Donath SM, Sekhon J, *et al*. Accuracy of pulse oximetry measurement of heart rate of newborn infants in the delivery room. J Pediatr 2008;152:756-60.
48. Katheria A, Rich W, Finer N. Electrocardiogram provides a continuous heart rate faster than oximetry during neonatal resuscitation. Pediatrics 2012;130:e1177-e1181.
49. Lima AP, Beelen P, Bakker J. Use of a peripheral perfusion index derived from the pulse oximetry signal as a noninvasive indicator of perfusion. Crit Care Med 2002;30:1210-3.
50. De Felice C, Latini G, Vacca P, Kopotic RJ. The pulse oximeter perfusion index as a predictor for high illness severity in neonates. Eur J Pediatr 2002;161:561-2.
51. Latini G, Dipaola L, De FC. First day of life reference values for pleth variability index in spontaneously breathing term newborns. Neonatology 2012;101:179-82.
52. De Felice C, del Vecchio A, Criscuolo M, Lozupone A, Parrini S, Latini G. Early postnatal changes in the perfusion index in term newborns with subclinical chorioamnionitis. Arch Dis Child Fetal Neonatal Ed 2005;90:F411-F414.
53. van Vonderen JJ, Roest AA, Siew ML, Blom NA, van Lith JM, Walther FJ, *et al*. Noninvasive measurements of hemodynamic transition directly after birth. Pediatr Res 2014;75:448-52.
54. Mielke G, Benda N. Cardiac output and central distribution of blood flow in the human fetus. Circulation 2001;103:1662-8.
55. Crossley KJ, Allison BJ, Polglase GR, Morley CJ, Davis PG, Hooper SB. Dynamic changes in the direction of blood flow through the ductus arteriosus at birth. J Physiol 2009;587:4695-704.
56. Bhatt S, Alison B, Wallace EM, Crossley KJ, Gill AW, Kluckow M, *et al*. Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. J Physiol 2013.
57. Jones JE, Jose PA. Neonatal blood pressure regulation. Semin Perinatol 2004;28:141-8.
58. Te Pas AB, Davis PG, Kamlin CO, Dawson J, O'Donnell CP, Morley CJ. Spontaneous breathing patterns of very preterm infants treated with continuous positive airway pressure at birth. Pediatr Res 2008;64:281-5.

CHAPTER 18

Summary

Introduction

During the transition at birth the infant undergoes major physiological changes of both the pulmonary and hemodynamic tract which are closely linked. Most of our current knowledge of the neonatal transition is based on extrapolation from animal studies, while very little data from human infants are available. Current guidelines for neonatal resuscitation are focused on ventilation. These guidelines state that when positive pressure ventilation is necessary effect can be determined by occurrence of adequate chest movements and increase in heart rate. However, both parameters are not completely representative for the pulmonary and hemodynamic physiological changes that occur during transition at birth. The transition is much more complex than assumed by the caregiver standing ready to give support to the infant. The few parameters currently used for evaluation and to monitor the effect of therapy do not tell the complete story and inadvertent measures can easily be taken.

The general aim of this thesis was to understand what physiological changes take place in infants at birth and what the effect is of our interventions when the infant needs support during the transition. It is important to understand the transitional changes as this is the most vulnerable moment of a preterm infant's life. Several studies have shown that injury to lungs and brains can easily occur by our actions taken at birth. In this thesis, the observational physiological studies performed are divided into the three tracts considered most important in the delivery room: Airway, Breathing and Circulation

In **chapter 2** an overview of the literature is given describing the physiological measurements at birth performed in the last decades, which is the basis of our current knowledge of the respiratory and hemodynamic transition at birth. Furthermore, an outlook is given on some of the new methods for measuring physiological parameters during neonatal transition.

In **chapter 3** the direct clinical effect of a sustained inflation (SI) in preterm infants (born <32 weeks gestation) at birth was determined. An initial SI of 10 s was given to promote lung liquid clearance and lung aeration at birth. Respiratory function monitoring was used to measure airway pressures, flow, tidal volumes (VTs) and relative functional residual capacity (FRC) changes during the SI and created by breaths occurring during the SI. Pulse oximetry was used to measure oxygen saturation (SpO_2) and HR. We observed that in 20/70 infants a large leak (100 (1)%) was present during the SI. In the 14/50 infants that did not have a large leak and did not breathe during the SI caused an expiratory VT of 0.6 (0.1-2.0) mL/kg and FRC gain of 0.0 (-0.5-0.6)mL/kg. In the 36/50 infants that breathed during the SI

an expiratory VT of 3.8 (1.0-5.9) mL/kg was observed due to the SI. The inspiratory and expiratory cumulative Vts of breathing were 16.4 (6.8-23.3) mL/kg, and Vtebr 5.8 (1.2-16.8) mL/kg respectively. This resulted in a total FRC gain of 7.1 (1.7-15.9) mL/kg. The SI did not cause an immediate effect on HR and SpO_2. We concluded that the SI was only effective in infants who breathed during the SI. It is possible that active glottic adduction may be responsible for the absent effect of SI or the pressure in combination with time applied (pressure time integral) is too low to overcome the resistance of the lung liquid.

In **chapter 4** the physiological measurements of a subgroup of infants included in the MOUNTAIN-trial are presented. In this randomized trial the nasal tube (NT) as interface to provide positive pressure ventilation (PPV) was compared with the face mask (FM) for neonatal resuscitation of very preterm born infants. In the subgroup physiological parameters were recorded, including respiratory function monitoring and pulse oximetry to measure the direct clinical effect of the interface used. During inflations higher leak was found during ventilation via NT when compared to FM (98 (33-100)% vs. 14 (0-39)%; $p< 0.0001$). Furthermore we found that obstruction occurred more often during ventilation via NT compared to FM (8.2% vs. 1.1%; $p<0.0001$)). This led to lower expired VTs during ventilation via NT compared to FM (0.0 (0.0-3.1) mL/kg vs. 9.9 (5.5-12.8) mL/kg; $p<0.0001$). HR was not significantly different between both groups during the first 5 minutes after birth, a lower SpO_2 was observed in the first minutes when NT was used while the amount of FiO_2 given was similar. Breathing was frequently observed during PPV and probably influences the effect of ventilation given in both groups. We concluded that during ventilation in preterm infants at birth a NT is less effective than a FM and cannot be recommended.

In **chapter 5** the effect of volume changes of the face mask on lung volume measurements during neonatal ventilation was tested in a manikin study. Manual squeeze of the face mask, pressurization during inflation and release during expiration could cause a different in VTs measured and delivered to the lung. Furthermore, it could cause incorrect mask leak measurement during mask ventilation. Using a respiratory function monitor mask ventilation using a fixed peak inspiratory pressure and positive end expiratory pressure was tested A) with (1) consistent hand squeeze, (2) release during inflation and squeeze during expiration, (3) squeeze during inflation, release during expiration, and (4) gentle squeeze and (B) variation of VTs was studied in thirty caregivers performing mask ventilation. We found that variation in mask hold and pressurization and release during mask ventilation can influence volume measurement and leak measurements. However, when caregivers performed the mask ventilation there was little variation (coefficient of variance 9-10%) in VTs. We concluded that volume changes in the mask could influence the measurement, but this hardly occurred among the caregivers and does not have to be taken into account when VT and leak are measured during mask ventilation.

In **chapter 6** we tested the effect of distention of the airways (nasopharynx and trachea) during mask ventilation on lung volumes measured and how much volume is actually ventilating the lungs. A) In preterm lambs, volumes of the airways (oropharynx, trachea, lungs) were assessed and B) in preterm infants delta pressures, VTs and leak were measured during ventilation 2 minutes before (mask ventilation) and 2 minutes after intubation (endotracheal ventilation) in preterm infants. We observed that the combined trachea and oropharynx and the oropharynx alone significantly contributed to the total VT measured (14 and 9%). In preterm infants ventilated with equivalent pressures, inspiratory and expiratory VTs were significantly smaller during endotracheal ventilation when compared to face mask ventilation (60 (44-81)% and 54 (29-87)% of mask ventilation volume respectively). Leak and delta pressure were not significantly different before vs. after intubation. We concluded that during neonatal mask ventilation, distention of the upper respiratory tract contributes to the VTs measured and should be taken into account when targeting VTs during mask ventilation.

In **chapter 7** we investigated whether breathing pattern and effort at birth can identify infants who fail continuous positive airway pressure (CPAP) <48 hours after birth and were intubated. Recordings of respiratory function monitoring of 32 preterm infants were reviewed, of which 17 infants remained on CPAP (CPAP-success) and 15 failed CPAP < 48 hours of age (CPAP-failure). Frequency and duration of expiratory holds (EHs) and VTs (VT), peak inspiratory flows, CPAP-level and FiO2-levels were analyzed. We observed that that EH occurrence increased <6 minutes after birth and remained stable thereafter. EH occurrence, EH peak inspiratory flows and VT were similar between CPAP-fail and CPAP-success infants. At 9-12 minutes, CPAP-fail infants more frequently used smaller VTs and required higher peak inspiratory flows. VT was less variable in CPAP-fail infants. Also, CPAP-success infants often showed large VTs (>9ml/kg) with higher peak inspiratory flows than CPAP-fail infants (71.8 ±15.8 vs. 15.5 ±5.2 ml/kg.s). CPAP-fail infants required higher FiO2, higher CPAP pressures and more positive pressure-delivered inflations. We concluded that at 9-12 minutes after birth, CPAP-fail infants more commonly used lower VTs and required higher peak inspiratory flow rates while receiving greater respiratory support. VT was less variable and larger VTs were infrequently used. This indicates that CPAP-failure infants already showed signs of fatigue in the delivery room right after birth.

In **chapter 8** we describe the effect of 100% FiO_2 on SpO_2 and respiratory drive of infants <32 weeks gestation while breathing on CPAP or receiving PPV. Respiratory parameters, fraction of inspired oxygen (FiO_2) and pulse oximetry of infants before and after receiving FiO_2 1.0 were analyzed. We observed that SpO_2 increased rapidly in the first minute after FiO_2 1.0 and remained stable, SpO_2 >95% occurred more often in PPV group and lasted lon-

ger. The duration of FiO_2 1.0 tended to be shorter in the CPAP group than in the PPV group (CPAP vs. PPV: 65 (33-105) vs. 100 (40-280) s). In the CPAP group, minute volume increased significantly from 134 (76-265) at 1 minute before to 240 (157-370) mL/kg/min at 1 minute after start FiO_2 1.0 and remained stable at 2 minutes. The rate of rise to maximum VT increased in the same manner (from 13.8 (8.0-22.4) mL/kg/s to 18.2 (11.0-27.5). In the PPV group respiratory rate increased significantly from 0 (0-4) at 1 minute before to 9 (0-20) and 23 (0-34) breaths per minute at 2 minutes after start of FiO_2 1.0. We concluded that in preterm infants at birth, a rapid increase in oxygenation, resulting from a transient increase to 100% SpO_2 might improve respiratory drive, but increased the risk for hyperoxia.

In **chapter 9** the effect of naloxone on the breathing pattern after birth is described. Respiratory function monitoring and pulse oximetry were recorded of an infant who was respiratory depressed at birth after mother received maternal opiates and received naloxone. We demonstrated that before naloxone administration normal resuscitation manoeuvers had no effect on the respiratory drive. However, directly after administration of naloxone, a tachypneic breathing pattern with sporadic expiratory braking maneuvers was observed with a fast rise in SpO_2 and decrease in FiO_2. The immediate tachypnea was most likely a direct effect of the naloxone and might have caused an immediate 'rebound response' after the release of the opiate-induced inhibition of the respiratory drive.

In **chapter 10** VT, FRC changes and gas exchange during the SI, PPV and spontaneous breathing on CPAP was measured in preterm infants at birth. The following physiological measurements were performed in 15 preterm infants: 1) expired VTs (Vte (mL/kg)) using respiratory function monitoring, 2) changes in FRC (AU/kg) per breath using Respiratory Inductance Plethysmography (bands placed around the rib cage (RC) and abdomen (AB)), 3) expired CO_2 using a volumetric CO_2 monitor. We observed no difference in Vte between SI, PPV and spontaneous breathing. However, expired CO_2 was higher during breathing (32 (23-38) mm Hg) and inflations coinciding with breathing (20 (13-25) mmHg) when compared to SI (10 (2-19) mm Hg) and inflations only (2 (3-11) mm Hg). Little change in FRC occurred during the SI, PPV and breathing measured at the RC. In contrast, there was FRC gain measured at the AB during the SI, PPV and most with breathing (47 (1-146) vs. 46 (19-100) and 97 (23-221) AU/kg). We concluded that while VTs during PPV and breathing were similar, breathing was more effective in gas exchange and gaining FRC than PPV.

In **chapter 11** changes in HR, blood pressured, left ventricular dimensions and output were measured in healthy term infants born by cesarian section at 2, 5 and 10 minutes after birth. HR was measured using electrocardiography, blood pressure was measured non-invasively and cardiac measurements were performed using echocardiography. We observed that

HR and blood pressure remained unchanged during transition, but left ventricular output increased significantly from 151 (47) mL/kg/min at 2 minutes to 203 (55) mL/kg/min ($p < 0.001$) at 5 minutes and then remained equal at 10 minutes. This increase was due to a significant increase in left ventricular shortening fraction from 2 to 5 minutes of 29 (5)% to 33 (7)% ($p < 0.001$) respectively. We concluded that an uneventful transition is characterized by a swift rise in left ventricular output, which is caused by an increase in pulmonary venous return and not by increase in HR. Despite the large hemodynamic changes at birth blood pressure remained unchanged.

In **chapter 12** blood flow changes over the ductus arteriosus (DA) are quantified at 2, 5 and 10 minutes after birth for healthy term infants born via cesarian section. Blood flow was measured using echocardiography. We observed that during transition right-to-left DA shunting did not change (median (IQR) 95 (64-154) mL/kg/min to 90 (56-168) mL/kg/min and 80 (64-120) mL/kg/min respectively), whereas left-to-right shunting increased between 2 and 5 minutes (41 (31-70) mL/kg/min vs. 67 (37-102) mL/kg/min, (ns)) and increased significantly between 2 and 10 minutes (93 (67-125)) mL/kg/min; $p=0.001$). Right-to-left/left-to-right shunting ratio decreased significantly from 2.1 (1.4-3.1) at 2 minutes to 1.4 (1.0-1.8) at 5 minutes ($p<0.0001$) and to 0.9 (0.6-1.1) at 10 minutes ($p<0.0001$). We concluded that DA shunting changes swiftly from predominantly right-to-left shunting to predominantly left-to-right shunting at 10 minutes after birth, reflecting differential changes in pulmonary and systemic vascular resistance. As the increase in left-to-right shunt is correlated to the decrease in pulmonary vascular resistance, which is intimately linked to lung aeration, the ductal shunt ratio might be a useful parameter to evaluate the success of transition.

In **chapter 13** the differences in ductus arteriosus (DA) shunting during quiet breathing and crying directly after birth were assessed in healthy term infants born after a caesarian section. Velocity time integral of the DA and LVO was assessed using echocardiography. Shunting was compared within each patient during crying and quiet breathing and between time points. We observed that the velocity time integral of left-to-right shunting was significantly larger during inspiratory phase of crying than during quiet breathing (13.2 (4.5) mL/min vs. 6.4 (3.2) mL/min at 2 minutes, 16.5 (6.8) mL/min vs. 7.6 (4.4) mL/min at 5 minutes ($p<0.0001$) and 18.2 mL/min vs. 7.5 (3.6) mL/min at 10 minutes after birth). The increase in left-to-right shunting during crying was completely independent from the cardiac cycle. LVO was higher in infants who cried at 2-3 time points when compared to infants who cried at 1 time point or did not cry at all. We concluded that crying at birth significantly influences ductus arteriosus shunting and seems to have a positive influence on the increase in left ventricular output during hemodynamic transition.

In **chapter 14 and 15** the perfusion index (PI) derived from pulse oximetry of term and preterm infants is described during the first 10 minutes after birth. In term infants no trend in PI in course of time could be observed The median PI of vaginally born infants was significantly higher compared to infants born by cesarean section (2.0 (1.3–2.9) vs. 1.8 (1.2–2.6)). In preterm infants distinction is made between infants on CPAP and infants intubated during resuscitation in the delivery room. Also in the preterm infants no significant trend could be observed in median PI in time in either the intubated or CPAP groups. The PI of preterm infants was lower than in term infants, but the difference is small. There was a small, but significant difference in PI of infants receiving non-invasive support compared to the intubated infants (1.6 (1.0–3.0) vs. 1.8 (1.0–2.5); p <0.001). We concluded that the large hemodynamic changes after birth are not reflected in PI measured at the extremity, possibly due to increased systemic vascular resistance. The clinical relevance of the observed small differences in PI between groups (term vs. preterm, CPAP vs. intubated) is unclear.

In **chapter 16** HR measured by pulse oximetry (HR_{PO}) was compared with electrocardiography (HR_{ECG}) over time during the first 10 minutes after birth. HR_{ECG} and HR_{PO} were compared every 30s from 1-10 minutes. Starting time of PO and ECG data collection was 99 (33) vs. 82 (26) s after birth. HR_{PO} was significantly lower from 60 to 450 s when compared to HR_{ECG}, especially in the first 2 minutes (94 (67-144) vs. 150 (91-153) bpm at 60s ($p<0.05$), 81 (60-109) vs. 148 (83-170) bpm at 90 s and 83 (67-145) vs. 158 (119-176) at 120 s. HR_{PO} was more frequent <100 bpm than HR_{ECG} in the first 2 minutes (64% vs. 27 % at 60 s, 56% vs. 26% at 90 s and 53% vs. 21% at 120 s.
We concluded that at birth HR measured by PO is significantly lower, especially in the first minutes. This suggests that PO underestimates HR immediately after birth and values should be interpreted with caution when a bradycardia is observed.

In **chapter 17** the main findings of this thesis are discussed, conclusions are drawn and future perspectives are given.

We have shown that it is possible to perform physiological measurements in a non-invasive manner in human infants at birth. We have gathered unique data of both respiratory and hemodynamic transition and of intervention when transition failed. We have demonstrated in this thesis that ventilation at birth is often inadequate and inefficient until spontaneous breaths are taken during ventilation, which probably has contributed to the success of resuscitation of preterm infants at birth. We have shown that in preterm infants breathing not only led to higher VT, better gas exchange and gain in FRC than the inflations given, but also influenced hemodynamic transition. The findings of this thesis

suggest that stimulating and supporting breathing of preterm infants at birth might be a more efficient respiratory strategy at birth instead of delivering PPV.

Another important part of this thesis are the observations of hemodynamic changes at birth that:

a) in contrast to the current beliefs, infants are capable to increase the left ventricular output by increasing the preload and thus stroke volume;
b) HR and blood pressure and PI remains stable;
c) an uneventful transition in spontaneous breathing infants is characterized by swift increase in LVO and an increase in left-to-right shunt through the DA;
d) HR measured by pulse oximetry should be interpreted with caution when a bradycardia is observed.

With this thesis much progress has been made in understanding the physiological process of transition at birth and the effect of our support given when transition fails, but this thesis also led to more research questions.

CHAPTER 19

Samenvatting

Introductie

Onze huidige kennis over de transitie bij geboorte is grotendeels gebaseerd op dierexperimenten, maar het is mogelijk dat dit niet direct representatief is voor de transitie van humane pasgeborenen. De huidige richtlijnen voor de neonatale transitie zijn met name gericht op longaeratie, het luchthoudend maken van de longen. In deze richtlijnen wordt aanbevolen dat wanneer beademing noodzakelijk is, de effectiviteit van de beademing moet worden beoordeeld door het observeren van adequate thoraxexcursies en een toename van de hartslag. Echter, beide parameters zijn niet volledig representatief voor de fysiologische veranderingen van de long en circulatie die plaatsvinden tijdens de transitie. De transitie is veel complexer dan op dit moment wordt aangenomen door de zorgverlener die klaarstaat om respiratoire ondersteuning aan de pasgeborene te geven. De parameters die zij gebruiken voor evaluatie en effect van de interventie vertellen niet het volledige verhaal en op basis hiervan kunnen onjuiste handelingen worden verricht.

De algemene doelen van dit proefschrift zijn door middel van non-invasieve fysiologische metingen 1) de veranderingen tijdens de transitie bij de geboorte beter te begrijpen en 2) het effect van onze interventies te meten wanneer de pasgeborene ondersteuning krijgt tijdens de transitie. Dit kan ons helpen om betere strategieën te ontwikkelen die te vroeg geborenen helpt om door deze zeer kwetsbare periode heen te komen zonder schade te geven. Meerdere studies hebben aangetoond dat onze interventies bij geboorte al snel schade aan long en hersenen kan aanrichten. Het proefschrift bestaat uit observationele fysiologische studies die zijn onderverdeeld in de drie tracti die het meest belangrijk zijn in de verloskamers: Airway, Breathing en Circulation.

In **hoofdstuk 2** wordt een overzicht gegeven van de beschikbare literatuur over de toegepaste fysiologische metingen gebruikt in de afgelopen decennia. Dit is de basis van onze kennis over de respiratoire en hemodynamische veranderingen die plaatsvinden tijdens de geboorte. Ook wordt een toekomstperspectief gegeven waarin nieuwe methoden worden beschreven die gebruikt kunnen worden voor het meten van fysiologische parameters tijdens de geboorte.

In **hoofdstuk 3** wordt een studie beschreven waarbij bij premature pasgeborenen (gestatieduur <32 weken) het directe klinische effect is gemeten van een initieel verlengde inflatie van de long direct na de geboorte gegeven via een beademingsmasker. Een initieel verlengde inflatie van 10 s werd gegeven voor de klaring van longvocht en longaeratie direct na de geboorte. Longfunctie werd gemeten om de gegeven beademingsdrukken, luchtstroom, teugvolumes (TVs) en de functioneel residuale capaciteit

(FRC) te bepalen ten tijde van de verlengde inflatie. Een zuurstofsaturatiemeter werd gebruikt om de zuurstofsaturatie (SpO_2) en hartslagfrequentie (HF) te meten. Wij observeerden dat er in 20/70 pasgeborenen sprake was van een groot maskerlek (100 (1)%) tijdens de verlengde inflatie. In 14/50 van de pasgeborenen die niet ademden en waarbij geen groot lek was tijdens de verlengde inflatie werd een expiratoire TV gemeten van 0.6 (0.1-2.0) mL/kg en een FRC toename van 0.0 (-0.5-0.6) mL/kg. In 36/50 pasgeborenen die ademden tijdens de verlengde inflatie werd een totale expiratoire TV van 3.8 (1.0-5.9) mL/kg gemeten. De cumulatieve inspiratoire en expiratoire TVs als gevolg van de ademhaling waren respectievelijk 16.4 (6.8-23.3) mL/kg en 5.8 (1.2-16.8) mL/kg. Dit resulteerde in deze kinderen tot een totale FRC toename van 7.1 (1.7-15.9) mL/kg. De verlengde inflatie had geen direct effect op de SpO_2 en HF. We concludeerden daarom dat de verlengde inflatie alleen effectief was indien pasgeborenen die ademteugen namen tijdens de verlengde inflatie. Wij speculeren dat naast vaak voorkomende hoge maskerlek, het gesloten houden van de stembanden een grote rol speelt waarom de verlengde inflatie bij deze premature pasgeborenen niet effectief kan zijn. Tevens kan het zijn dat de druk in combinatie met de tijdsduur van de SI (druk-tijd integraal) niet voldoende was om de luchtwegweerstand van de met vocht gevulde longen te overwinnen.

In **hoofdstuk 4** wordt een analyse gepresenteerd van een subgroep van pasgeboren kinderen die zijn geïncludeerd in de MOUNTAIN-trial. Tijdens deze gerandomiseerde studie werd de nasale tube (NT) vergeleken met het beademingsmasker (BM) tijdens het geven van positieve druk beademing aan extreem premature pasgeborenen. In de subgroep werden fysiologische parameters opgenomen, waaronder longfunctiemetingen, HF en SpO_2. Met deze metingen werd de effectiviteit van beide interfaces vergeleken. Tijdens beademing werd een hoger lek gemeten wanneer de NT werd gebruikt in vergelijking met het BM (98 (33-100)% t.o.v. 14 (0-39); $p<0.0001$). Ook obstructie kwam vaker voor tijdens gebruik van de NT (8.2% t.o.v. 1.1%; $p<0.0001$)). Dit zorgde voor lagere expiratoire TVs gedurende beademing met NT wanneer dit vergeleken wordt met BM (0.0 (0.0-3.1) mL/kg t.o.v. 9.9 (5.5-12.8) mL/kg; $p <0.0001$). HF was niet significant verschillend tussen beide groepen gedurende de eerste 5 minuten na geboorte. Wel werd een lagere SpO_2 gemeten in de eerste minuten na geboorte in de NT groep terwijl de hoeveelheid toegevoerde zuurstof (FiO_2) die gegeven werd gelijk was. Ademhaling werd frequent geobserveerd tijdens de beademing wat waarschijnlijk het effect van de beademing ook heeft beïnvloed. We concludeerden dat het gebruik van een NT tijdens beademing van prematuur pasgeborenen minder effectief is dan een BM en dat gebruik hiervan daarom niet kan worden aanbevolen.

In **hoofdstuk 5** werd het effect van volume veranderingen van het BM op de volumemetingen tijdens beademing bij de geboorte vastgesteld met behulp van een aangepaste reanimatiepop. Manuele druk die wordt uitgeoefend op het BM, drukopbouw tijdens inspiratie in het BM en drukdaling in het BM tijdens expiratie zouden ervoor kunnen zorgen dat andere TVs worden gemeten dan wat werkelijk wordt toegediend aan de pasgeborene. Ook zou het ertoe kunnen leiden dat lek tussen het gezicht en het masker overschat of juist onderschat wordt. Dit werd getest met behulp van een respiratoire functie monitor waarbij een lekvrije reanimatiepop met een constante inspiratoire druk en positief eind expiratoire druk beademd werd. Tijdens de beademing werd tijdens experiment A (1) een consistente manuele druk uitgeoefend op het BM, (2) het BM losgelaten tijdens inflatie en vervolgens manuele druk uitgeoefend tijdens expiratie, (3) manuele druk uitgeoefend op het BM tijdens inflatie en vervolgens het BM losgelaten tijdens expiratie en (4) licht manuele druk uitgeoefend op het BM tijdens inflatie en expiratie. Bij experiment B werd de variatie van TVs gemeten wanneer 30 artsen en verpleegkundigen maskerbeademing aan de reanimatiepop gaven. Wij observeerden dat een variatie in het vasthouden van het BM en het drukken op het masker tijdens inflatie en loslaten tijdens expiratie de volume- en lekmetingen sterk beïnvloeden. Echter tijdens beademing van de reanimatiepop door artsen en verpleegkundigen was er maar een beperkte variatie (coëfficiënt van variantie 9-10%) in TVs. We concludeerden daarom dat volumeveranderingen van het BM metingen kunnen beïnvloeden, maar dat dit waarschijnlijk maar zelden gebeurd tijdens de beademing van een pasgeborene. Daarom hoeft er tijdens TV en lekmetingen tijdens beademing geen rekening met de manier van vasthouden van het masker en de manuele druk gehouden worden.

In **hoofdstuk 6** hebben wij het effect gemeten van luchtwegdistensie (nasofarynx en trachea) op gemeten volumes tijdens beademing met een masker. Ook hebben wij gemeten welk volume daadwerkelijk in de longen aankomt t.o.v. het deel dat in de luchtwegen achterblijft. In A) prematuur geboren lammeren zijn luchtwegvolumes (orofarynx, trachea, longen) gemeten en in B) premature pasgeborenen zijn tijdens beademing 2 minuten voor (tijdens maskerbeademing) en 2 minuten na intubatie (tijdens endotracheale beademing) beademingsdrukken, TVs en lek gemeten. Wij observeerden dat het gecombineerde volume van de trachea en orofarynx gemeten tijdens beademing en dat van de orofarynx alleen, significant bijdraagt aan het gemeten volume (14% en 9% van het totaal). In prematuur geboren kinderen werden significant lagere inspiratoire en expiratoire TVs gemeten tijdens endotracheale beademing wanneer dit vergeleken wordt met maskerbeademing (dit was respectievelijk 60 (44-81)% en 54 (29-87)% van het TV gemeten bij maskerventilatie). Lek en beademingsdrukken waren niet significant verschillen voor en na intubatie. We concludeerden dat, gedurende BM beademing,

distensie van de bovenste luchtwegen bijdraagt aan de gemeten TVs en dat hiermee rekening moet worden gehouden wanneer men tijdens beademing naar bepaalde TVs streeft.

In **hoofdstuk 7** hebben we onderzocht of ademhalingspatronen direct na de geboorte patiënten kunnen identificeren die binnen 48 uur na geboorte respiratoir insufficiënt worden bij non-invasieve respiratoire ondersteuning (continue positieve luchtwegdruk (CPAP)). Longfunctiemetingen van 32 prematuur geboren kinderen werden beoordeeld, hiervan konden 17 kinderen in de eerste 48 uur na geboorte op CPAP blijven ademen (CPAP-succes) en 15 werden respiratoir insufficiënt (CPAP-falen) en werden daarom geïntubeerd Frequentie en duur van het afremmen van de uitademing en TVs, de piek inspiratoire flow, CPAP-niveau en FiO_2-niveaus werden geanalyseerd. We observeerden in de gehele groep dat de frequentie van het afremmen van de uitademing toenam in de eerste 6 minuten na geboorte en daarna stabiel bleef. Frequentie van het afremmen van de uitademing, de piek inspiratoire flow en TVs waren gelijk in de CPAP-succes en CPAP-falen groep. Tussen 9-12 minuten, gebruikten kinderen in de CPAP-falen groep meer frequent kleinere TVs en zij hadden voor deze TVs een hogere piek inspiratoire flow nodig. TVs waren minder variabel in de CPAP-falen groep. Ook observeerden wij vaker hoge TVs (>9ml/kg) met grotere piek inspiratoire flows in de CPAP-succes t.o.v. de CPAP-falen groep (71.8 ±15.8 t.o.v. 15.5 ±5.2 ml/kg.s). De CPAP-falen groep had een hogere FiO_2 behoefte, hogere CPAP drukken en langer beademing nodig dan de CPAP-succes groep. We concludeerden dat premature pasgeborenen die falen op CPAP binnen 48 uur vaker ademden met lagere TVs, een hogere piek inspiratoire flow gebruikten tussen 9-12 minuten na geboorte en meer respiratoire ondersteuning nodig hadden. Ook waren TVs waren minder variabel en hogere TVs werden minder frequent gebruikt. Dit impliceert dat pasgeborenen die falen op CPAP al vroeg na de geboorte in de verloskamer symptomen van respiratoire vermoeidheid laten zien.

In **hoofdstuk 8** beschrijven we het effect van 100% FiO_2 op de SpO_2 en de ademhalingsinspanning bij pasgeborenen geboren <32 weken gestatieduur terwijl zij ademden op CPAP of maskerbeademing kregen. Longfunctieparameters, FiO_2, HF en SpO_2 werden geanalyseerd voor en na de start van FiO_2 1.0. We ontdekten dat de SpO_2 snel steeg in de eerste minuut na de start van 100% FiO_2 en daarna stabiel bleef, SpO_2 >95% kwam vaker voor in de beademde groep en duurde langer. De duur van 100% FiO_2 was korter in de CPAP-groep dan in de beademde groep (65 (33-105) t.o.v. 100 (40-280) s). Het ademminuutvolume nam significant toe in de CPAP-groep van 134 (76-265) mL/kg/min in de minuut voor tot 240 (157-370) mL/kg/min in de minuut na start van 100% FiO_2, daarna bleef deze stabiel. De snelheid van de flow die nodig was voor het bereiken van

een maximaal TV steeg op een vergelijkbare manier (van 13.8 (8.0-22.4) mL/kg/s tot 18.2 (11.0-27.5) mL/kg/s. In de beademde groep steeg de ademfrequentie significant van 0 (0-4) in de minuut voor tot 9 (0-20) en 23 (0-34) ademteugen per minuut in de eerste en tweede minuut na start van 100% FiO_2. We concludeerden dat een FiO_2 van 100% in prematuur geboren kinderen zorgt voor een snelle verbetering van oxygenatie, wat de respiratoire "drive" ten goede komt maar wel een risico geeft op hyperoxie.

In **hoofdstuk 9** wordt het effect van Naloxon op het ademhalen beschreven. Bij een pasgeborene die respiratoir onderdrukt was na maternale toediening van een opiaat werden longfunctiemetingen verricht en HF en SpO_2 gemeten. Tijdens de opvang werd Naloxon toegediend. Wij observeerden dat de beademing weinig effect had op het herstel van de spontane ademhaling. Echter, direct na de toediening van Naloxon werd het kind tachypnoeisch en observeerden we sporadisch dat het kind de adem vasthield. Dit ging gepaard met een snelle stijging van de SpO_2 terwijl de FiO_2 kon worden afgebouwd. Het tachypnoeïsche ademhalingspatroon was waarschijnlijk een direct effect van de Naloxontoediening wat 'onthoudingsverschijnselen' kan hebben veroorzaak doordat de opiaten geen invloed meer hadden op het ademhalingscentrum.

In **hoofdstuk 10** werden TVs, FRC veranderingen en gasuitwisseling gemeten tijdens de beademing en spontane ademhaling op CPAP bij premature pasgeborenen direct na de geboorte. De volgende fysiologische parameters werden bepaald in 15 prematuur geboren kinderen: 1) expiratoire TVs (TVe (mL/kg)) gemeten door middel van longfunctiemetingen, 2) veranderingen in FRC (AU/kg) per ademteug/inflatie gemeten door middel van "Respiratory Inductance Plethysmography" (met bandjes geplaatst rondom borstkas en buik), 3) gasuitwisseling door middel van de expiratoire CO_2 gemeten met behulp van een volumetrische CO_2 monitor. We vonden dat er geen statistisch significant verschil in TVe was tussen de initieel verlengde inflatie, de daaropvolgende inflaties en spontane ademhaling. Echter expiratoire CO_2 was hoger gedurende spontane ademhaling (32 (23-38) mm Hg) en bij inflaties die samenvielen met ademhaling (20 (13-25) mmHg) wanneer vergeleken werd met de verlengde inflatie (5 (2-15) mm Hg) en de daaropvolgende inflaties alleen (2 (3-11) mm Hg). Er was weinig verandering in FRC gemeten bij de thorax wanneer de beademing en spontane ademhaling werden vergeleken. Echter een FRC toename werd gemeten bij de buik gedurende de verlengde inflatie en daaropvolgende inflaties, maar vooral tijdens eigen ademhaling (47 (1-146) vs. 46 (19-100) en 97 (23-221) AU/kg). We concludeerden dat terwijl TVe gedurende beademing en ademhaling gelijk waren in grootte, gaswisseling tijdens ademhaling meer effectief is vergeleken met beademing en dat dit ook gepaard gaat met meer FRC toename.

In **hoofdstuk 11** worden veranderingen in HF, bloeddruk, grootte en contractie van de linker ventrikel en het hartminuutvolume van de linker ventrikel gemeten op 2, 5 en 10 minuten na de geboorte in gezonde a-terme pasgeborenen geboren na een sectio caesarea. HF werd gemeten met elektrocardiografie, bloeddruk werd non-invasief gemeten en de metingen van het hart werden verkregen door middel van echocardiografie. We observeerden dat HF en bloeddruk onveranderd bleven tijdens deze periode, maar dat hartminuutvolume significant toenam van 151 (47) mL/kg/min op 2 minutes tot 203 (55) mL/kg/min ($p < 0.001$) op 5 minuten na de geboorte waarna het stabiel bleef op 10 minuten na de geboorte. Deze toename werd veroorzaakt door een significante stijging in de contractie van de linker ventrikel (de verkortingsfractie) tussen 2 en 5 minuten (respectievelijk 29 (5)% tot 33 (7)% ($p<0.001$)) voornamelijk door een toename in preload. We concludeerden dat een normale transitie gekenmerkt wordt door een snelle stijging in het hartminuutvolume van de linker ventrikel, wat wordt veroorzaakt door een toegenomen preload (als gevolg van toename van de veneuze return vanuit de longen) en niet zozeer door een stijging van de HF. Ondanks deze grote hemodynamische veranderingen blijft de bloeddruk constant.

In **hoofdstuk 12** werd de bloedstroom (shunten) over de ductus arteriosus (DA) en de richting gemeten op 2, 5 en 10 minuten na de geboorte in gezonde a-terme kinderen geboren na een keizersnede. Bloedstroom in de ductus arteriosus werd gemeten met behulp van echocardiografie. Wij vonden dat de rechts-links shunt tijdens de transitie gelijk blijft (respectievelijk, 95 (64-154) mL/kg/min, 90 (56-168) mL/kg/min en 80 (64-120) mL/kg/min op 2, 5 en 10 minuten). Echter, de links-rechts shunt nam significant toe tussen 2 en 5 minuten na de geboorte (41 (31-70) mL/kg/min t.o.v. 67 (37-102) mL/kg/min, $p=0.01$) en tussen 2 en 10 minuten naar 93 (67-125)) mL/kg/min ($p<0.001$). De ductus shunt ratio (Rechts-links/links-rechts) nam significant af van 2.1 (1.4-3.1) op 2 minutes naar 1.4 (1.0-1.8) op 5 minuten ($p<0.0001$) en naar 0.9 (0.6-1.1) op 10 minutes ($p<0.0001$). We concludeerden dat de bloedstroomomkering in de DA snel verloopt, waarbij ze kort na de geboorte voornamelijk rechts-links zijn, maar dat dit op 10 minuten na de geboorte al voornamelijk links-rechts is. Dit wordt veroorzaakt door de veranderingen in de pulmonaire en systemische vaatweerstand. Omdat de toename in links-rechts shunt direct gecorreleerd is aan de daling in pulmonaire vaatweerstand die veroorzaakt wordt door het luchthoudend worden van de long, is de ductusshuntratio mogelijk een waardevolle parameter om het succes van de transitie te monitoren.

In **hoofdstuk 13** zijn bloedstroomveranderingen over de DA tijdens rustige ademhaling vergeleken met huilen direct na de geboorte bij gezonde a-terme pasgeborenen geboren na een keizersnede. De snelheid van de bloedstroom (de "velocity time inte-

gral") over de DA en het hartminuutvolume van de linker ventrikel werden gemeten met behulp van elektrocardiografie. De richting en snelheid van de bloedstroom over de DA werden vergeleken binnen iedere patiënt tijdens huilen en rustige ademhaling tussen de verschillende tijdspunten. We hebben gemeten dat de velocity time integral van de links-rechts shunt significant groter was tijdens de inademing bij het huilen wanneer vergeleken met de links-rechts shunt tijdens rustig ademhalen (13.2 (4.5) mL/min t.o.v. 6.4 (3.2) mL/min op 2 minuten, 16.5 (6.8) mL/min t.o.v. 7.6 (4.4) mL/min op 5 minuten ($p<0.0001$) en 18.2 mL/min t.o.v. 7.5 (3.6) mL/min op 10 minuten na de geboorte. De toename in links-rechts shunt tijdens de inademing bij het huilen was volledig onafhankelijk van de hartcyclus. Het hartminuutvolume was groter bij pasgeborenen die huilden tijdens 2-3 tijdspunten wanneer dit vergeleken werd met pasgeborenen die niet of maar op 1 tijdspunt huilden. We concludeerden dat huilen significant de bloedstroom over de DA beïnvloed en ook een positieve invloed lijkt de hebben het hartminuutvolume tijdens de neonatale transitie.

In **hoofdstuk 14 and 15** werd de perfusie index (PI) gemeten met behulp van pulse oximetrie bij a-terme en premature pasgeborenen in de eerste 10 minuten na de geboorte. Bij a-terme pasgeborenen werd in de loop van de tijd geen toename van PI geobserveerd. De gemiddeld gemeten PI van vaginaal geboren pasgeborenen was echter significant hoger dan die van a-terme pasgeborenen geboren na een sectio caesarea (2.0 (1.3–2.9) t.o.v. 1.8 (1.2–2.6)). Bij de prematuur pasgeborenen werd een onderscheid gemaakt tussen pasgeborenen ademend op CPAP en pasgeborenen die geïntubeerd werden in de verloskamers. Ook bij de prematuur pasgeborenen kon geen trend waargenomen worden in de verandering van de PI over de tijd. De PI van prematuur pasgeborenen was lager dan die van de a-termen, het verschil was echter klein. Er was een klein, maar significant, verschil tussen pasgeborenen die non-invasieve beademing kregen in vergelijking met de kinderen die geïntubeerd werden tijdens de eerste 10 minuten (1.6 (1.0–3.0) t.o.v. 1.8 (1.0–2.5); $p <0.001$). We concludeerden dat de grote hemodynamische veranderingen na de geboorte niet zorgen voor een verandering in de PI gemeten aan de extremiteiten. De klinische waarde van de geobserveerde kleine verschillen (a-terme t.o.v. prematuur pasgeborenen, CPAP t.o.v. geïntubeerd) is onduidelijk.

In **hoofdstuk 16** is de verandering in HF bij pasgeborenen gemeten door middel van pulse oximetrie (HF_{PO}) vergeleken met HF gemeten door elektrocardiografie (HF_{ECG}) in de loop van de tijd, gedurende de eerste 10 minuten na de geboorte. HF_{ECG} en HF_{PO} werden elke 30 s vergeleken gedurende 1-10 minuten. Startpunt van het verzamelen van de gegevens met PO en ECG was 99 (33) en 82 (26) s na de geboorte. HF_{PO} was significant lager bij 60 tot 450 s na de geboorte wanneer vergeleken met HF_{ECG}. Het grootste verschil

werd gemeten gedurende de eerste 2 minuten (94 (67-144) t.o.v. 150 (91-153) slagen per minuut (spm) op 60 s, 81 (60-109) t.o.v. 148 (83-170) spm op 90 s en 83 (67-145) t.o.v. 158 (119-176) op 120 s. HF_{PO} was frequenter <100 spm dan HF_{ECG} in de eerste 2 minuten na geboorte (64% t.o.v. 27 % op 60 s, 56% t.o.v. 26% op 90 s en 53% t.o.v. 21% op 120 s). We concludeerden dat HF gemeten met PO bij geboorte significant lager is, vooral in de eerste minuten. Wij concludeerden dat PO HF kan onderschatten direct na de geboorte en dat de waarden gemeten met PO voorzichtig geïnterpreteerd moeten worden wanneer gedurende deze tijd een bradycardie wordt gemeten.

In **hoofdstuk 17** worden de belangrijkste bevindingen van dit proefschrift besproken, conclusies worden getrokken en een toekomstperspectief wordt geschetst.

In conclusie, hebben wij laten zien dat het mogelijk is om meerdere fysiologische non-invasieve metingen te verzamelen bij pasgeborenen direct na de geboorte. Wij hebben unieke data verzameld van zowel de respiratoire als de hemodynamische transitie en gedurende interventies wanneer deze transitie faalde. In dit proefschrift hebben wij gedemonstreerd dat maskerbeademing direct na de geboorte vaak inadequaat is totdat er spontane ademteugen tijdens de beademing optreedt en dan bijdraagt aan het succes van resuscitatie. Zo hebben wij laten zien dat ademhaling van prematuur geboren kinderen niet alleen leidde tot hogere TVs, maar ook betere gasuitwisseling en toename in FRC. Ademhaling heeft waarschijnlijk ook een positieve invloed op de hemodynamische transitie. Deze bevindingen suggereren dat stimulatie en ondersteuning van de eigen ademhaling mogelijk effectiever is dan het overnemen van de ademhaling met beademing.

De andere belangrijke bevindingen gerapporteerd in dit proefschrift zijn de observaties van de hemodynamische veranderingen tijdens de transitie namelijk: a) in tegenstelling tot de huidige inzichten zijn kinderen in staat om het hartminuutvolume te laten toenemen door een toename van het slagvolume, b) HF, bloeddruk en PI blijven constant, c) tijdens een normale transitie kan een snelle stijging van het hartminuutvolume van de linker ventrikel en de links-rechts shunt van de DA worden gemeten snel na de geboorte, d) HF metingen met PO moeten voorzichtig worden geïnterpreteerd wanneer een bradycardie wordt gezien.

Dit proefschrift heeft geleid tot het vergroten van ons begrip van de fysiologische processen die plaatsvinden tijdens de neonatale transitie en wanneer de transitie faalt en ondersteuning gegeven moet worden. Het heeft echter ook geleid tot nieuwe onderzoeksvragen.

List of Abbreviations
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List of abbreviations

AoAnn	Aorta annulus
AQPs	Aquaporines
BP	Blood pressure
BPD	Bronchopulmonary dysplasia
BPM	Beats per minute
CO	Cardiac output
CPAP	Continuous positive airway pressure
CV	Coefficient of variation
DA	Ductus arteriosus
DaDiam	Ductus arteriosus diameter
EBM	Expiratory breaking maneuver
ECG	Electrocardiography
ECO_2	Expiratory CO_2
EH	Expiratory hold
FBM	Fetal breathing movements
FiO_2	Fraction of inspired oxygen
FRC	Functional residual capacity
HR	Heart rate
IQR	Interquartile range
LVO	Left ventricular output
LVedd	Left ventricular end diastolic diameter
LVesd	Left ventricular end systolic diameter
LVSV	Left ventricular stroke volume
LtoR	Left-to-right
NICU	Neonatal Intensive Care Unit
NS	Not significant
PEEP	Positive end expiratory pressure
PIP	Peak inspiratory pressure
PO	Pulse oximetry
PPV	Positive pressure ventilation
PVR	Pulmonary vascular resistance
RDS	Respiratory distress syndrome
RFM	Respiratory function monitor
RtoL	Right-to-left
RVO	Right ventricular output
SF	Shortening fraction
SI	Sustained inflation
SpO_2	Oxygen saturation
SVR	Systemic vascular resistance
Vt	Tidal volume
Vte	Expired tidal volume
Vti	Inspired tidal volume
VTI	Velocity time integral

Curriculum Vitae

Jeroen van Vonderen was born on the 15th of March 1987 in the Academisch Ziekenhuis Leiden (Leiden University Medical Center) at 30^{+0} weeks. He graduated from the Zandvliet College secondary school in 2005 and started to study bio-pharmaceutical sciences in the same year. He continued this study until he received his Bachelor of Science in 2012. In September 2007 he started to study medicine at the Leiden University Medical Center. He received his Bachelor of Science in medicine in 2011. From 2009 until 2011 he worked as a student assistant for dr. Kim Schilleman and dr. Arjan te Pas to collect data for the MOUNTAIN trial. In 2011 he started his PhD-training under the supervision of Dr. Arjan te Pas. During his PhD-training he also spent some time in the Monash Institute of Medical Research to perform research with the group led by prof. Stuart Hooper. In November 2014 he will start his internships which are part of the regular medical curriculum.

Publications

1. Auditing documentation on delivery room management using video and physiological recordings. Schilleman K, Witlox RSGM, van Vonderen JJ, Roegholt E, Walther FJ, te Pas AB.
   Arch Dis Child Fetal Neonatal Ed. 2014;[in press].

2. The direct effect of a sustained inflation in preterm infants at birth. van Vonderen JJ, Lista G, Cavigioli F, Hooper SB, te Pas AB.
   J Pediatr. 2014 [in press].

3. Non-invasive measurements of ductus arteriosus flow directly after birth. van Vonderen JJ, te Pas AB, Kolster-Bijdevaate C, van Lith JM, Blom NA, Hooper SB, Roest AA.
   Arch Dis Child Fetal Neonatal Ed. 2014 [Epub ahead of print].

4. Accuracy of a disposable compared to a non-disposable infant T-piece resuscitator. Krabbe VB, van Vonderen JJ, Roehr CC, te Pas AB.
   Eur J Pediatr. 2014 [Epub ahead of print].

5. Measuring Physiological Changes during the Transition to Life after Birth. van Vonderen JJ, Roest AA, Siew ML, Walther FJ, Hooper SB, te Pas AB.
   Neonatology. 2014;105:230-42.

6. Noninvasive measurements of hemodynamic transition directly after birth. van Vonderen JJ, Roest AA, Siew ML, Blom NA, van Lith JM, Walther FJ, Hooper SB, te Pas AB.
   Pediatr Res. 2014;75:448-52.

7. The administration of 100% oxygen and respiratory drive in very preterm infants at birth. van Vonderen JJ, Narayen NE, Walther FJ, Siew ML, Davis PG, Hooper SB, te Pas AB.
   PLoS One. 2013 18;8:e76898.

8. The influence of the hand squeeze and mask distensibility on tidal volume measurements during neonatal mask ventilation. van Vonderen JJ, Kamar R, Schilleman K, Walther FJ, Hooper SB, te Pas AB.
   Neonatology, 2013;104:216-21.

9. Do We Deliver the Pressures We Intend to When Using a T-Piece Resuscitator? Roegholt E, van Vonderen JJ, Walther FJ, Roehr CC, te Pas AB.
   PlosOne, 2013;22;8:e64706.

10. Nitroglycerin for severe ischaemic injury after peripheral arterial line in a preterm infant. Kamar R, van Vonderen JJ, Lopriore E, te Pas AB.
    Acta Paediatr. 2013;102:e144-5.

11. Effects of Naloxone on the Breathing Pattern of A Newborn Exposed to Maternal Opiates. van Vonderen JJ, Siew ML, Hooper SB, de Boer MA, Walther FJ, te Pas AB. *Acta Paediatr. 2012;101:e309-12*.

12. Compressive force applied to a manikin's head during mask ventilation. van Vonderen JJ, Kleijn TA, Schilleman K, Walther FJ, Hooper SB, Te Pas AB.
    Arch Dis Child Fetal Neonatal Ed. 2011;97:F254-8.

Dankwoord

Als “Fred” begon ik tijdens het eerste jaar van de studie Geneeskunde mijn tijd bij de afdeling neonatologie met het verzamelen van metingen bij prematuur geboren kinderen. Ik werd al snel gegrepen door dit onderzoek en vlak voor de start van de co-schappen deed zich de kans voor om zelf (promotie)onderzoek te doen, iets wat ik zelf niet voor mogelijk had gehouden. Na 3 jaar en veel verschillende projecten is dit proefschrift tot stand gekomen. Dit had ik niet kunnen bereiken door hulp van velen. Hen ben ik allemaal zeer dankbaar.

Allereerst wil ik alle patiënten en ouders bedanken die mee hebben gedaan aan één van deze onderzoeken. Daarnaast wil ik alle neonatologen, fellows neonatologie, arts-assistenten en verpleegkundigen bedanken voor hun deelname aan en medewerking met de studies. Bedankt dat jullie bereid waren mee te helpen tussen alle drukke werkzaamheden door.

Mijn co-promotor, dr. A.B. te Pas ben ik zeer dankbaar voor de kans die hij mij gegeven heeft. Beste Arjan, zonder jouw onuitputtelijke stroom aan ideeën was ik nooit zo ver gekomen. Ook heb ik van jou geleerd om altijd in oplossingen te denken, maar wanneer er echter niet direct een oplossing was, kon ik er altijd wel op vertrouwen dat “alles goed komt”. Bedankt dat je mij je kennis over dit onderwerp, en velen dingen meer hebt willen bij brengen, de vrijheid die je mij gegeven hebt en me hebt afgeremd wanneer dat nodig was.

Prof. Dr. F.J. Walther, beste Frans, dank voor de mogelijkheid die u mij gegeven heeft om onderzoek te doen. Zonder uw hulp was het moeilijk geweest om dit onderzoek in zo’n korte tijd tijdens mijn opleiding voor elkaar te krijgen.

Many thanks also goes to prof. S.B. Hooper. Dear Stuart, thank you very much for giving me the opportunity to do research with your group in Melbourne. Being there has helped me very much to see things “from a scientific point of view”. Also, thank you very much for your help with most of the studies published in this thesis.

Dr. A.A.W. Roest, beste Arno, heel erg bedankt voor alle tijd die je vrij hebt gemaakt om onderzoek te doen met mij. Jouw hulp was onmisbaar bij het verzamelen van data en het schrijven van deel C van dit proefschrift.

Dr. E. Lopriore, beste Enrico, heel erg bedankt voor het mogelijk maken van het laatste deel van mijn onderzoek en de kritische, maar constructieve blik op sommige van mijn studies.

I would like to express my gratitude to all the co-authors and others who helped performing research, sharing their knowledge and improving our studies and manuscripts: dr. Melissa Siew, dr. Kim Schilleman, dr. Omar Kamlin, dr. Jeniffer Dawson, Prof. Peter Davis, dr. Nadia Narayen, dr. Ilona Narayen, dr. Marjon de Boer, dr. Gianluca Lista, dr. Francesco Cavigioli, Prof. dr. Jan van Lith, Prof. dr. Nico Blom(f), dr. Erik van Zwet, Dipl.-Ing. Hilbert Koetsier, miss Clara Kolster-Bijdevaate, miss Marjolein Verhart, mister Dick Quick and mister Michael Boonekamp.

Ook wil ik alle wetenschapsstage studenten bedanken voor hun hulp met het verzamelen van gegevens: Jacco Kroese, Rita Kamar, Vera Krabbe, Sascha Kraaij, Evelien Roegholt en Charlotte Verbeek.

Kim Schilleman, Mirjam Rath, Marita de Waard, Margot Visser, Ilona Narayen en Henriëtte van Zanten, Ratna Tan, Estelle Mulder, Sandra Prins en Remco Visser wil ik danken voor hun samenwerking en de gezellige tijd die we hadden (deels) op de fellow/onderzoekskamer.

Beste Thessa en Constantijn heel erg bedankt dat jullie mij tijdens deze dag bij willen staan als paranimfen. Ook wil ik jullie bedanken voor jullie vriendschap de afgelopen jaren.

Als laatste bedank ik Karen en mijn ouders voor hun steun tijdens de afgelopen 3 jaar. Zonder jullie had ik het niet gered!