Physiological measurements of transition and resuscitation at birth

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Title: Physiological measurements of transition and resuscitation at birth
Issue Date: 2014-09-11

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 mentioned 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 10th 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.