Physiological measurements of the effect of cord clamping strategies

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SUMMARY

INTRODUCTION

Clamping and cutting the umbilical cord after birth is a normal and necessary procedure, but the ideal moment to do this has been the subject of debate since ancient times.[1] Delaying the moment of cord clamping (delayed cord clamping; DCC) was considered advantageous for the newborn and has been advocated for centuries. However, as soon as infants started to be born in hospitals, early cord clamping was implemented as a part of 'active management of the third stage of labour' to reduce the risk of post-partum haemorrhage.[2] In the past few decades there has been renewed interest in DCC, and several studies have been performed.[3, 4] These studies demonstrated beneficial effects if the moment of cord clamping was delayed, which led to changes in both obstetrical and neonatal guidelines recommending DCC for at least three minutes for term born infants and 30-60 seconds for preterm infants who are not compromised at birth.[5, 6] However, most preterm infants are in need of respiratory support at birth and immediate cord clamping is recommended, denying them the beneficial effects of DCC. To overcome this practice, new resuscitation tables have been developed that enable effective neonatal stabilisation at the maternal bedside, while the umbilical cord remains intact. Implementing this new approach in clinical practice will allow preterm infants to receive DCC and its accompanying beneficial effects.

The beneficial effects seen after DCC have been attributed to the net shift in blood volume from placenta to neonate, or placental transfusion.[7-9] Although this is a commonly accepted feature of DCC, the physiology causing this net increase in neonatal blood volume remains unclear. It is possible that spontaneous breathing is the driving force for placental transfusion by generating a sub atmospheric pressure during inspiration.[10] This sub atmospheric pressure is thought to create an increase of umbilical venous blood flow influx towards the neonate, resulting in a net increase in blood volume. In addition to placental transfusion, there has recently been another, perhaps even larger, benefit described.[11] Establishing lung aeration at birth, by breathing or positive pressure ventilation, causes a prompt increase in pulmonary blood flow at birth, which will have a major influence on the hemodynamic changes during neonatal transition.[12] Experimental studies demonstrated that delaying the moment of cord clamping until **after** lung aeration (physiological-based cord clamping; PBCC) leads to a more stable and gentle hemodynamic transition than immediate clamping **before** lung aeration has been established. This PBCC has been shown to lead to less bradycardia and better peripheral and cerebral oxygenation at birth.[11, 13] In an experimental setting the beneficial effects are clear and look promising for improving neonatal outcomes; this physiological effect and benefit needs to be confirmed in human infants in a clinical setting, however.

The general aim of this thesis was to investigate the physiological changes that occur with physiological and time-based delayed cord clamping strategies. To obtain a better understanding of the optimal moment of cord clamping and factors of influence, this thesis has focused on the effect of spontaneous breathing on placental transfusion as well as the effect of PBCC on preterm neonates during and directly after resuscitation.

PLACENTAL TRANSFUSION

In **chapter 1**, we investigated the effect of spontaneous breathing on umbilical venous flow and body weight in preterm lambs directly after birth. Sterile fetal surgery was performed on six pregnant ewes, which were instrumented at 132-133 days of gestational age to measure fetal pulmonary, cerebral and common umbilical venous (UV) blood flow at delivery. Both doxapram and caffeine were administered after delivery to promote spontaneous breathing, which was assessed using intrapleural pressure changes. Body weight, breathing, and blood flow measurements were continuously measured throughout the experiment. Change in body weight could be analysed in a total of 491 breaths and was found to increase in 46.6% and decrease in 47.5% of breaths with an overall mean increase of 0.02±2.5 g per breath. We did not observe net placental transfusion prior to cord clamping. In addition, we found UV flow to be influenced by breathing, however the relationship was the opposite of our hypothesis. UV flow transiently decreased and, in some cases, even ceased with inspiration before normalising during expiration. This reduction in UV flow was positively correlated with the reduction in intrapleural pressure or increase in inspiratory depth. This finding could be the result of narrowing or closure of the inferior vena cava (IVC) based on diaphragm contraction during inspiration. Although spontaneous breathing had no net effect on body weight it clearly has an effect on UV blood flow in preterm lambs, which warrants further investigation. Unravelling the exact effect of breathing on the mechanisms driving placental transfusion could lead to recommendations for a more optimal moment of cord clamping.

In **chapter 2**, the effect of spontaneous breathing on systemic venous return and flow in the ductus venosus (DV) in healthy term born infants directly after birth was evaluated. Echocardiographic recordings were obtained from infants born between 37 and 42 weeks of gestational age, after an uncomplicated and low-risk pregnancy, if parental consent was obtained prior to birth. A subcostal view was used to obtain an optimal view of the IVC entering the right atrium (RA), including both the DV and hepatic vein (HV). Spontaneous breathing was assessed by diaphragm movements visible in all recordings. Measurements continued until the umbilical cord was clamped at the discretion of the midwife. Flow measurements were observed to be antegrade (towards the infant) in the DV and HV during inspiration in 98% and 82%

respectively, with an increase in flow in 74% of inspirations. Retrograde flow in the DV was observed sporadically and only occurred during expiration. Collapse of the IVC was consistently located caudal of the DV inlet into the subdiaphragmatic venous vestibulum and occurred in the majority of inspirations (58%). These findings clearly demonstrate the association between spontaneous breathing and IVC collapse as well as the increased antegrade flow in the DV and HV during inspiration. Inspiration appears to preferentially direct blood flow from the DV into the RA, indicating that it could be a factor driving placental transfusion.

Chapter 3 describes an observational study investigating the feasibility of measuring heart rate (HR) with the use of umbilical pulse oximetry (PO) and whether reliable HR measurements can be obtained faster when compared to preductal PO in infants who need stabilisation at birth. Both preductal and umbilical HR measurements were obtained in infants >25 weeks of gestational age. During stabilisation, but after cord clamping, a PO sensor was placed around the umbilical cord to obtain measurements in addition to the standard preductal PO measurements. Umbilical PO measurements were shielded and alarms were muted, so caregivers were not informed or distracted by umbilical measurements. HR data of the first ten minutes after birth were reviewed and compared. A HR signal was considered reliable when signal identification and quality >30% and a stable plethysmograph pulse wave was observed. Measurements were obtained from a total of 18 infants, who needed respiratory support at birth. Reliable HRs from umbilical PO were obtained in all infants, but the time between sensor application and obtaining a reliable HR signal was longer than with preductal PO (19 [16-55] seconds vs. 15 [11-17] seconds; p=0.01). Umbilical HR was consistently lower than preductal HR (mean(±SD) difference 36 (±22) bpm; Intraclass Correlation Coefficient (95% CI): 0.1 (0.03-0.22)). Although it is feasible to obtain reliable HRs when using umbilical PO in infants needing stabilisation at birth, obtaining reliable measurements takes longer when compared to preductal PO. The lower HR measured at the umbilical cord compared to preductal HR measurements warrants further studies to confirm this but, if correct, evaluation of the infant's clinical condition using HR by palpating the cord should be reconsidered.

PHYSIOLOGICAL-BASED CORD CLAMPING

In **chapter 4**, we evaluated the feasibility of the PBCC approach in preterm born infants using a new purpose-built resuscitation table (Concord). Infants born <35 weeks of gestational age were stabilised on the Concord resuscitation table, which was supplied with the standard equipment needed for stabilisation. Cord clamping was performed when the infant was considered to be stable according to predefined criteria (HR >100 bpm, spontaneous breathing on continuous positive airway pressure (CPAP) with tidal volumes >4 mL/kg, oxygen saturation (SpO_2) ≥ 25th percentile and fraction of inspired oxygen (FiO_2) <0.4). The PBCC approach was successfully performed in 33 of 37 infants (89.2%) and resulted in a median cord clamping time of 4:23 [3:00–5:11] min after birth. Measurements on HR and SpO_2 were adequate for analysis in 26 of 37 infants. HR was 113 [81-143] bpm and 144 [129-155] bpm at 1 min and 5 min after birth. SpO_2 levels were 58% [49%-60%] and 91% [80%-96%], while median FiO_2 given was 0.30 [0.30-0.31] and 0.31 [0.25-0.97], respectively. Considering the success percentage in performing PBCC, a more stable HR and faster increase in oxygenation as well as the absence of reported serious adverse events, we consider the PBCC approach in preterm infants using the Concord feasible. Importantly, HR remained stable during and around the moment of cord clamping, which makes it likely that PBCC may result in optimal timing of cord clamping and in optimal pulmonary and cardiovascular transition.

Chapter 5 describes a randomised controlled non-inferiority study to evaluate whether stabilising very preterm infants according to the PBCC approach is at least as effective as the standard approach of time-based DCC. Infants were eligible for inclusion if they were born < 32 weeks of gestational age and if antenatal parental consent was obtained. Infants were either allocated to PBCC and stabilised with an intact cord or allocated to standard DCC. In infants who received PBCC the umbilical cord was clamped when they were deemed stable (regular spontaneous breathing, HR ≥100 bpm and SpO_2 >90% while using FiO_2 <0.40). In infants receiving DCC, the cord was clamped at 30-60 s after birth before they were transferred to the standard resuscitation table for further treatment and stabilisation. The non-inferiority limit was set at 1:15 min. A total of 37 infants (mean gestational age 29+0 weeks) were included. Mean cord clamping time was 5:49 ± 2:37 min in the PBCC (n=20) and 1:02 ± 0:30 min in the DCC group (n=17). Infants receiving PBCC needed less time to reach respiratory stability (PBCC 5:54 ± 2:27 min; DCC 7:07 ± 2:54 min). The mean difference, corrected for gestational age, in time needed to reach respiratory stability was -1:19 min, 95% CI [-3:04 - 0:27]), demonstrating the non-inferiority of the PBCC approach as the pre-defined limit of 1:15 min falls outside of this confidence interval. Stabilisation of very preterm infants with the PBCC approach is therefore at least as effective as with standard DCC.

In **chapter 6,** the correlation between ductus arteriosus (DA) flow ratio and oxygenation parameters (as a measure of the infant's transitional status) were evaluated. Echocardiography was performed in preterm infants at 1 hour after birth, as part of an ancillary study to the previously described cord clamping studies of ABC 2 and 3. The DA flow ratio was calculated and correlated with FiO_2 given, SpO_2 and SpO_2/FiO_2 ratio (SF) in a total of 16 infants. The DA flow ratio of infants receiving PBCC and standard DCC were compared. All infants received CPAP of 7-8 cmH_2O at the time of measurements, except for one infant who did not receive any respiratory support.

Right-to-left DA shunting was 16 [17-27] ml/kg/min and left-to-right shunting was 110 [81 – 124] ml/kg/min. The DA flow ratio was 0.18 [0.11-0.28], SpO_2 was 94 [93-96] %, FiO_2 was 23 [21-28] % and SF ratio 4.1 [3.3-4.5]. There was a moderate correlation between DA flow ratio and SpO_2 (correlation coefficient (CC) -0.415; p=0.110), FiO_2 (CC 0.384; p=0.142) and SF ratio (CC -0.356; p=0.175). There were no differences in any of the DA flow measurements between infants who received PBBC or time-based DCC. In this pilot study DA flow ratio at 1 hour after birth seems to be correlated with oxygenation parameters in preterm infants at birth and could reflect transition in preterm infants at birth. DA flow ratio as a measure of transitional status at different moments after birth could be of use to predict adverse outcome.

CONCLUSION

In the **general discussion** we reviewed spontaneous breathing as a possible driving force for placental transfusion, the implementation of PBCC in a clinical setting, and the physiological changes during neonatal transition when PBCC is performed. Placental transfusion is a widely accepted feature of DCC, however the physiological mechanisms driving this net increase in neonatal blood volume remain unclear. The negative sub atmospheric pressures generated during spontaneous inspiration have been suggested as the driving force for placental transfusion. Indeed, we demonstrated that spontaneous breathing greatly influences umbilical blood flow, as inspiration was associated with an increase in umbilical venous blood flow in humans. When combined with the association between inspiration and collapse of the IVC, this potentially creates a preferential placental blood flow towards the RA. Anatomical differences between humans and animal models used have prevented experimental studies from demonstrating a similar association. In addition, we found spontaneous breathing to not only influence umbilical and pulmonary blood flow, but also a disruption of the systemic blood flow to the lower body while the DA remains intact. We concluded that spontaneous breathing is likely to be a force influencing placental transfusion.

Both the physiological effect and the beneficial effects of PBCC are clear in an experimental setting. Lung aeration and the subsequent increase in pulmonary blood flow are vital for the success of this approach. When successfully translating PBCC to human infants it is pivotal that the lungs have been aerated. Hence, the moment of cord clamping should not be at a fixed time but rather based on the infant’s transitional status. With the studies performed in this thesis we demonstrated that it is safe and feasible to perform PBCC, and that it has a similar effect to that shown in the experimental setting. We also demonstrated that resuscitation on the cord is at least as effective as the standard approach, while allowing much longer and variable cord clamping times.

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