

# Delayed Cord Clamping in Preterm Infants: New Insights into the Circulation in the Transition between Intrauterine and Extrauterine Life

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## ABSTRACT

Facilitating placental transfusion in preterm infants by means of delayed cord clamping or cord milking has been recently adopted in many centres. These procedures have been shown to have short term benefits in preterm infants. There is decreased receipt of blood transfusion, significantly less use of inotropes and reduction in intra ventricular haemorrhage (of all grades). At the same time as the placental transfusion is occurring, important circulatory changes are taking place. The onset of respiration and reduction of pulmonary vascular resistance markedly affect pulmonary and systemic blood flow, including cerebral perfusion. Removal of the placental bed from the circulation before the period of transition and circulatory dynamics have stabilized may have a detrimental effect on ventricular output and subsequent cerebral perfusion. This in turn may increase the likelihood of intra ventricular haemorrhage and/or white matter injury in the preterm infant.

For this work, the animal and human preterm studies (either observational studies or randomized trials) relating to the changes in cerebral blood flow during placental transfusion have been reviewed. Recent studies of the effects of mode of delivery, gravity and use of uterotonics in relation to placental transfusion were also reviewed as they may, in turn, affect cerebral perfusion.

Cerebral blood flow (as measured directly, by echocardiogram or near infrared spectroscopy) has been shown to be increased when placental transfusion has occurred (compared to infants where immediate cord clamping has taken place). In addition, there is evidence to suggest that the onset of respiration during placental transfusion is associated with increased placental transfusion and better neonatal outcomes. Focussing attention on placental transfusion during the transitional period offers an important opportunity to improve neonatal outcomes in preterm infants.

**Keywords:** Preterm infant; Delayed cord clamping; Placental transfusion; Transitional circulation; Intraventricular haemorrhage

**Abbreviations:** **DCC:** Delayed Cord Clamping; **SVC:** Superior Vena Cava; **ECHO:** Echocardiogram; **NIRS:** Near Infra Red Spectroscopy; **IVH:** Intraventricular Haemorrhage

## INTRODUCTION

Recently, renewed attention has been focussed on the period of transition between intrauterine to extrauterine life for both term and preterm infants. Part of this attention has been directed towards augmenting placental transfusion by means of delayed cord clamping or cord milking. Evidence from meta- analysis indicates no increased risk to the mother in terms of important outcomes such as postpartum blood loss or infection [1], while at the same time there are benefits for the infant. Although there is evidence of improved outcomes in term infants, it is the preterm infant that is most likely to benefit as a result of increased placental transfusion and improved transition [2].

It appears that it is not only the increase in circulating blood volume from the placental transfusion that is beneficial, but facilitating the profound circulatory changes taking place at birth and avoiding asphyxia may also be crucial. There is evidence that retaining the low resistance vascular bed of the placenta intact whilst breathing is established and the circulation is changing from the in-utero to ex-utero pattern may be important [3,4].

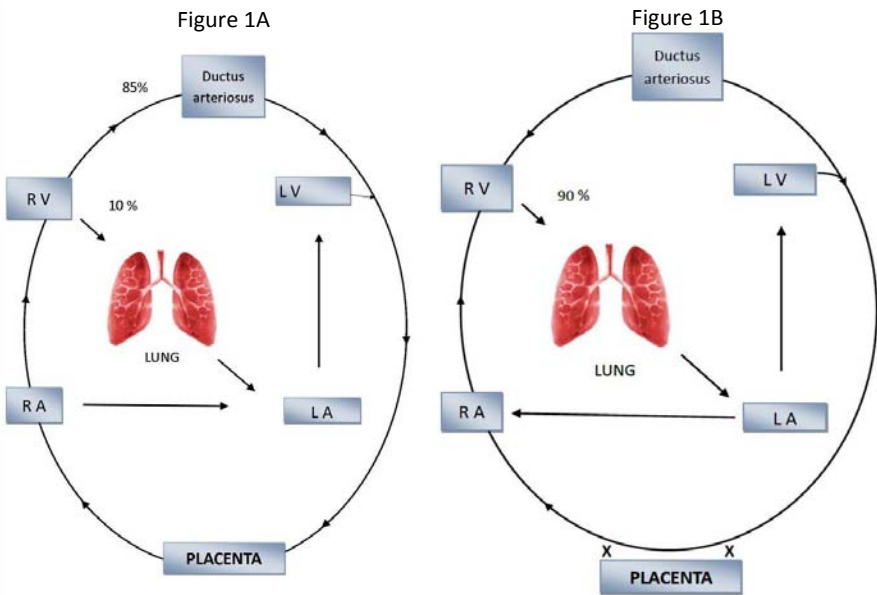
The early postnatal adaption of cardiovascular and respiratory systems may also have far reaching consequences in terms of other organs, particularly the brain [5]. In an effort to improve outcomes, increased attention has to be given to the postnatal adaption process.

The purpose of this paper is to review the circulatory changes taking place during transition from foetal to extrauterine life and, in particular, to focus on the cerebral circulation and how it may be affected by establishing respiration with the cord intact and the infant attached to the placenta. This may provide important future strategies to minimize cerebral injury in preterm infants.

# PHYSIOLOGY OF THE TRANSITIONAL CIRCULATION

The foetal circulation in-utero is quite different from that after birth in that oxygenation is achieved through the placenta and most of the cardiac output by-passes the lungs [5,6]. Oxygenated blood passes from the placenta to the right atrium via the umbilical vein and ductus venosus. Most of the flow is channelled via the foramen ovale to the left atrium but some 10% passes into the right ventricle and pulmonary circulation. The majority of the right ventricular output passes through the ductus arteriosus and with some of the left ventricular output passes to the placenta (which is a low resistance vascular bed). The left ventricle pumps blood mainly to the upper body. It follows that in the foetus, the right and left heart pump predominantly in parallel rather than in series (Figure 1A).

After birth the pulmonary vascular resistance drops markedly once breathing is initiated and the right ventricular output to the lungs increases dramatically. At the same time, there is a drop in flow reaching the left ventricle from the umbilical vein. However, the left ventricular filling (preload) is maintained by the flow now coming from the pulmonary veins into the left atrium and this helps to maintain the systemic blood flow. Simultaneously, there is a potential increase in systemic vascular resistance with removal of the low resistance placenta from the circulation. This may be offset by left to right ductal shunting into the pulmonary circulation. The change in direction of ductal shunting is very rapid, occurring within a few heart beats. With removal of the placenta, right ventricular preload is maintained by the change in direction of shunting across the foramen ovale, with the major portion of flow becoming left to right [3-6]. See Figure 1B.



**Figure 1:** Transitional circulation and changes after cord clamping and lung expansion.

**Figure 1A:** Foetal circulation; **Figure 1B:** Circulation during transition.

The transitional circulation is affected by breathing, which is not surprising in view of the marked changes that take place in the pulmonary vascular resistance once the lungs are inflated. A recent series of experiments in preterm lambs have helped to clarify the physiology [3]. Ewes at 126 days gestation (term is 143 days) were anaesthetized and the lambs intubated via tracheostomy (pressure transducers had previously been placed at 123 days). In one group, consisting of 6 animals (Clamp first group), the umbilical cord was immediately clamped prior to onset of ventilation (ventilation was commenced at 2 mins). In the other group, the 6 animals were ventilated for 2 mins prior to cord clamping (Vent first group). In the Clamp first animals, the right ventricular output dropped because of decreased preload from interruption of placental return (the placental circulation receives 30-50% of the cardiac output). There was also a very rapid increase in carotid artery pressure within 1-4 heart beats, presumably in an attempt to maintain cerebral blood flow by increased vascular resistance. This was followed by a decrease in cerebral blood flow and reduction in carotid artery pressure at around 60 -120secs. In these clamp first animals there was reduced preload to both ventricles and increased afterload, particularly to the left ventricle prior to lung expansion. When the ventilation was initiated and the lungs expanded at 120 sec, cerebral blood flow and carotid artery pressure rapidly increased. This was hypothesized to be because the drop in pulmonary vascular resistance led to an increase in left ventricular preload.

Many of these changes were not seen in the Vent first group with preload from the placenta to the right ventricle being maintained and the marked drop in pulmonary vascular resistance occurring prior to cord clamping. Ductal shunting reversed to left to right within 4 beats of initiating ventilation. This limited left ventricular afterload and at the same time maintained left ventricular preload (from left atrial filling via the pulmonary circulation). The Vent first group had a more stable transitional circulation with cerebral blood flow and carotid artery pressures showing much smaller fluctuation than in the Clamp first group.

Another series of experiments on preterm lambs has provided alternative explanations for these events, however [4]. It appears that a 90 sec delay in ventilation after cord clamping induces an asphyxial state in the lambs (this is not seen in lambs after only a 30 sec delay in cord clamping prior to ventilation). Thus the rapid increase in carotid pressure following ventilation in the clamp first animals noted in the first series of experiments described above may be due to compensation for the preceding hypoxaemia (induced by 2 minutes with no cord blood flow). The smooth transition seen in the Vent first group may therefore represent the situation where there is no preceding hypoxia.

Whatever the true explanation, these results could be extrapolated to clinical practice. As described in more detail later on, most preterm infants have been shown to breathe during delayed cord clamping so that the circulatory and respiratory changes are happening at a similar time. However, if this is not the case (ie onset of respiration is delayed and the cord is clamped), a

period of cerebral circulatory instability may result. In some circumstances, the end result of this may be intraventricular haemorrhage and/ or white matter injury.

It follows that delayed cord clamping may be of clinical benefit in preterm infants.

## HISTORICAL PERSPECTIVE

DCC was the usual practice as evidenced by the quotes below:

“The common method of tying and cutting the navel string in the instant the child is born, is likewise one of those errors in practice that has nothing to plead in its favour but custom. ...”

**Charles White: 1773 [7]**

“Another thing very injurious to the child, is the tying and cutting of the navel string too soon; which should always be left till the child has not only repeatedly breathed but till all pulsation in the cord ceases. As otherwise the child is much weaker than it ought to be, a portion of the blood being left in the placenta, which ought to have been in the child.”

**Darwin E: 1801[8]**

One may question why immediate cord clamping became established practice? In the 1950s a series of procedures was put in place to reduce the incidence of post partum haemorrhage and retained placenta [9]. This active management of the third stage included early cord clamping, controlled cord traction and use of uterotonics eg oxytocin. These measures also facilitated earlier resuscitation of the infant although the benefits of early cord clamping were unproven and the term infant was deprived of around 100ml of blood volume in the absence of placental transfusion.

## EARLY AND LATE CORD CLAMPING

Over the last 10 or more years there has been renewed interest in the normal transition around birth and placental transfusion by means of delayed cord clamping or cord milking. Recent evidence from meta- analysis indicates no increased risk to the mother in terms of important outcomes such as post partum blood loss or infection [1]. At the same time there are benefits for the infant which are described in detail in the following sections. As a result of this change in thinking and practice, various definitions of timing of cord clamping have been put in place.

- The Royal College of Obstetricians and Gynaecologists in the UK define early clamping within 30 seconds [10].
- The World Health Organization (**WHO**) defines early clamping as occurring within 1 min and late cord clamping being after 3 minutes [11].
- Some recommendations are to delay clamping until cord pulsation ceases (usually within a few minutes) [1].
- Evidence from one recent study where continuous weighing was carried out indicates that placental transfusion may continue for over 4 minutes after birth [12].

## BENEFITS IN TERM INFANTS

The benefits of placental transfusion in term infants have been summarized in recent publications [1]. The infant's increased blood volume (approximately 100ml) potentially results in an extra 100mg of iron and in several studies has been shown to reduce measures of iron deficiency in early infancy [13,14]. Although iron deficiency is potentially associated with worse neurodevelopmental outcomes, follow up studies in term infants that received placental transfusion have not shown significantly improved outcomes beyond the first year of life [15]. On the other hand, there is no evidence of harm or adverse outcome in healthy term infants who receive placental transfusion and there may be benefit in settings where iron deficiency in infancy is common.

## BENEFITS IN PRETERM INFANTS

Meta analysis of randomized trials of placental transfusion in preterm infants has indicated improved neonatal outcomes, but there have been few longer term follow up studies [2]. Blood transfusions are reduced in preterm infants receiving placental transfusion with fewer infants being transfused for anaemia (odds ratio 0.61 CI 0.46-0.81). Other reported neonatal benefits include less necrotizing enterocolitis (**NEC**), less sepsis, decreased inotrope use for blood pressure support, increased urine output and lower rates of intraventricular haemorrhage (**IVH**). Meta-analysis has shown reduction in IVH when all grades of haemorrhage are considered together (odds ratio 0.59, CI 0.41-0.85) and this result was consistent across studies with little heterogeneity [2]. However, although individual studies have shown significant reduction in more severe haemorrhage of grade 3 or 4, meta-analysis has not shown a reduction in these grades. This could be a reflection of small numbers - severe haemorrhage is relatively rare (about 5% of studied patients), so that a combined sample size of over 1000 infants would need to be randomized for a power of 80% to show a 50% reduction in incidence. Currently only around 150 infants have had the outcome of severe haemorrhage reported in relation to placental transfusion.

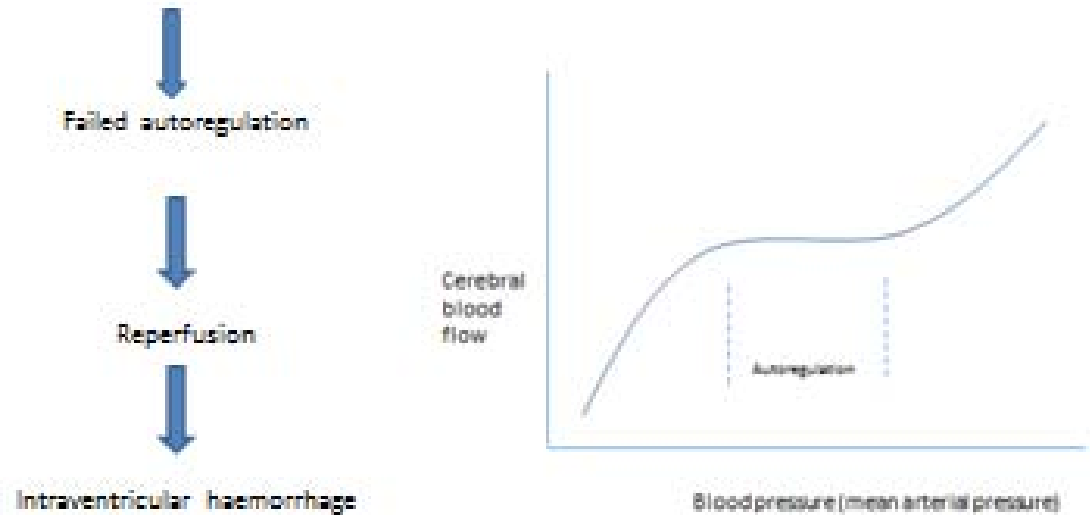
It is interesting that for many of the neonatal outcomes (such as inotrope support, urine output, IVH and possibly NEC), there is a circulatory component in the pathogenesis and this probably relates to the changes taking place in the transitional circulation highlighted above. In particular, these changes are relevant to the pathogenesis of IVH.

## IVH PATHOGENESIS

Cerebral blood flow is related to cerebral perfusion pressure (generally regarded as the mean arterial blood pressure). The flow-pressure relationship is shown in Fig 2 and there is a plateau where changes in blood pressure do not result in changes in flow and this is brought about by altered diameter of small blood vessels which affects resistance to flow. The autoregulatory plateau is relatively narrow in the preterm infant and may be absent or impaired, giving rise to a pressure passive circulation [16,17]. The germinal matrix (where the developing neuronal plate

is located) is particularly vulnerable to haemorrhage [17]. Periods of reduced perfusion may be followed by increased perfusion and bleeding (Figure 2). The area is highly vascularized and the developing capillary network is lined by a thin layer of endothelial cells with little supporting tissue. Haemorrhage in the area often spreads to the ventricles which may become distended with blood (grade 3) and can lead to impaired venous return and venous infarction of cerebral parenchyma (grade 4).

Decreased cerebral blood flow



**Figure 2:** Autoregulation of cerebral blood flow and intraventricular haemorrhage.

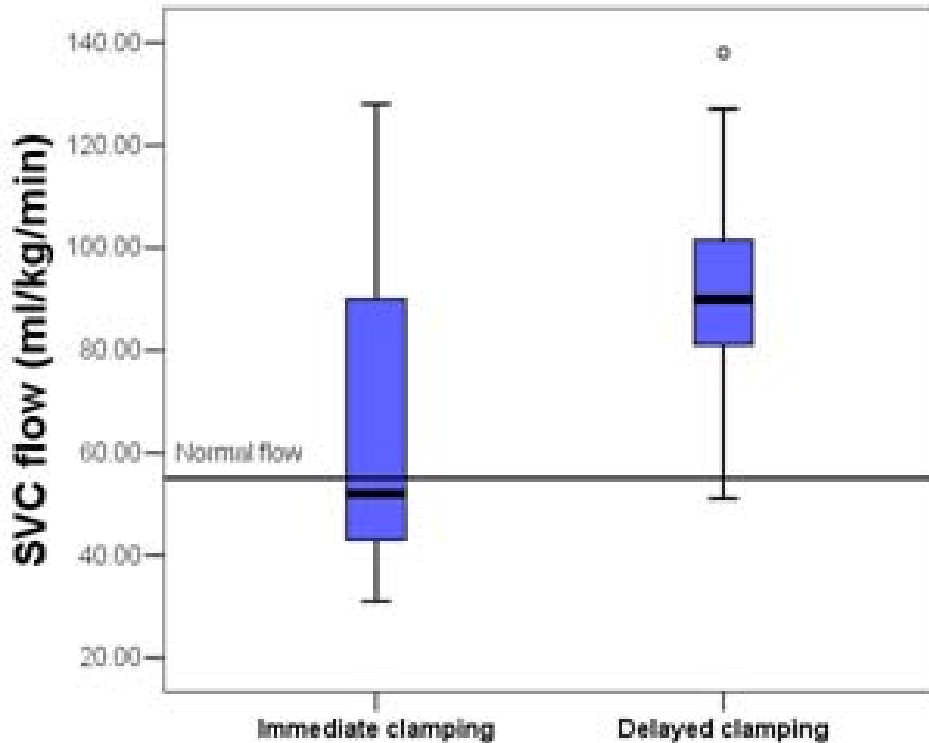
The pattern of cerebral blood flow after birth has been studied by a number of methods, including measuring blood flow in the superior vena cava and by determining regional cerebral oxygen saturations.

Blood flow in the superior vena cava (**SVC**) can be measured with echocardiography (**ECHO**). SVC flow measures blood returning from the upper part of the body and is a better measure of cerebral blood flow than measuring left ventricular output because it is not influenced by left to right shunting through the ductus arteriosus or foramen ovale. For the measurement of SVC flow, the diameter of the SVC is measured as it enters the right atrium and the flow measured by Doppler. A period of low SVC flow is strongly associated with IVH and the lowest flow occurs in the first 12-24hrs of life [18].

## MEASUREMENT OF SVC FLOW IN RELATION TO CORD CLAMPING

An observational study was carried out when delayed cord clamping was introduced at Middlemore Hospital in New Zealand [19]. Thirty infants <30 weeks gestation were eligible for

the study. There were 17 in the control group who did not receive DCC and 13 in the group who received 30-45sec DCC. Overall this was a group of extremely preterm infants with median gestation in both groups of 26 weeks and median birth weight <1000g. Less than 50% of patients had completed antenatal steroids prior to delivery. ECHO was performed within 24hrs of birth at a median age of 16hrs in both groups. Overall, SVC flow was significantly lower in the group with immediate cord clamping (52 ml/kg/min IQR 42-100 compared to 91ml/kg/min IQR 81-101 in the DCC group ( $p=0.02$ ). Low SVC flow (<55ml/kg/min) was present in 53% of the infants in the ICC group and 8% in the DCC group ( $p <0.02$ ; Figure 3). All 3 infants with IVH had low flow and this included one in the DCC group.



**Figure 3:** Blood flow in the superior vena cava in relation to immediate or delayed cord clamping.

An increase in SVC flow following DCC was confirmed in a nested randomized controlled trial [20]. Overall 51 patients were randomized to either DCC (45 sec) or immediate cord clamping. ECHO measurements were done at 6hrs and 24hrs and two later time periods and were performed by a single operator. Mean gestations in the 2 groups were approximately 28 weeks and the mean birth weight was >1000g. The mean increase in flow was 20-25ml/kg/min in the first 24hrs with a larger difference being recorded at 48hrs and beyond ( $p=0.002$ ).



Another study examined the effect of cord milking and immediate cord clamping on SVC flow. Enrolled infants were <32 weeks gestation and randomized to cord milking or control groups (immediate clamping). The cord was milked three times at a rate of 20cm over 2 sec. SVC flows were measured by a single operator at several time points. Flows were significantly greater at 6h and 30h of age with a mean increase of approximately 30ml/kg/min at 6 hrs [21].

Takami, et al [22] carried out an observational study of 50 preterm infants <29 weeks gestation and measured SVC flow following cord milking. Infants admitted prior to the period of cord milking were studied as controls. The mean gestation was 25 weeks, with less than half receiving antenatal steroids. A number of measurements were obtained including SVC flow and cerebral near infra red spectroscopy (**NIRS**). SVC readings were obtained by a single operator. In the cord milking group, SVC flow increased in the first 12-24hrs as did the cerebral total oxygenation index (**TOI**) with a decrease in fractional total oxygen extraction (**FTOE**). The left ventricular diastolic dimension (an index of left ventricular preload) increased over the first 16hrs compared to controls. Left ventricular systolic and diastolic dysfunction were also measured. Values in both groups decreased over the first 24hrs. However, the decrease was more marked in the milked group, likely due to improvement in the LV diastolic function from increased preload. Although these measurements were not specifically linked to IVH, an improvement in left ventricular function could conceivably improve cerebral blood flow in this vulnerable period.

The above studies have all shown an improvement in SVC flow of around 25 to 40mls/kg/min following placental transfusion. These findings seem to be consistent across a range of gestations. The repeatability coefficient for single observer studies is reasonable and was found to be 30ml/kg/min; values reported in 2 of the above studies were consistent with this. Therefore, we can have a degree of confidence in these findings. However, between-observer repeatability has been noted to be very poor, with a repeatability coefficient of 85ml/kg/min, so that direct comparison of absolute flow values between studies may be of limited value with the current methods employed [23].

Severe IVH (grade 3 or 4) was reduced in the studies recording SVC flow described above, with a total of 7/71 in the group not receiving placental transfusion vs 3/69 in the group that did receive placental transfusion but this difference was not statistically significant.

## **NEAR INFARED SPECTROSCOPY (NIRS)**

In infants who went on to develop IVH, studies have indicated lower LV output and lower regional cerebral saturations in the first 12hrs of life followed by an increase in these measures [24,25]. These changes are consistent with decreased cerebral perfusion followed by reperfusion injury.

In a RCT which was part of a larger study, Baenziger, et al [26] randomized 15 infants to DCC of 60-90 sec and 24 infants to immediate cord clamping<20 sec. Regional cerebral saturations were measured at 4hrs of age and again at 24 hrs, 72 hrs and 36 weeks corrected gestation. Mean

gestational ages were 29-30 weeks at the time of study. The regional cerebral saturations were higher in the DCC group at the 4 hr and 24 hr time periods and mean blood pressure was higher in the DCC group at 4hrs of age. These changes suggest improved cerebral perfusion with DCC.

Although the above studies have not shown a direct link between DCC, improved cerebral regional saturation (likely related to increased perfusion) and reduced IVH, the mechanism is certainly plausible.

## **OTHER MEASURES OF CIRCULATORY DYNAMICS AND CORD CLAMPING**

Hosono, et al [27] randomized 40 preterm infants (24-28 weeks gestation) to either cord milking or control groups. Heart rate, blood pressure and urine output were measured over 120 hrs. Systolic and diastolic pressures were significantly higher in the milked group during the first 24 hrs of life. Infants in the control group were more likely to receive treatment with volume expanders and/or inotropes. Urine output was likewise increased in the milked group in the first 72 hrs of life. No significant differences were observed in relation to heart rate.

Meta analysis of 2 studies reporting mean arterial pressure after birth and 2 different studies reporting mean arterial pressures at 4 hrs of age showed significantly higher values in the group receiving placental transfusion. Although the mean differences in blood pressure were small (<5mm Hg), meta analysis of 4 other studies showed significantly reduced use of inotropes in the group receiving placental transfusion [2].

## **EFFECT OF RESPIRATION ON PLACENTAL TRANSFUSION AND TRANSITIONAL CIRCULATION**

The onset of breathing and lung expansion play a central and critical role in the changes occurring during transition. These events have been highlighted by Bhatt, et al [3] and have been described in detail in the physiology section above. It should be noted that these changes occurred in anaesthetized preterm animals that were ventilated and not spontaneously breathing. It is unclear whether the findings from the model can be extrapolated to preterm deliveries. In fact there are few studies or descriptions of respiration during delayed cord clamping [2,28].

Redmond, et al [28] studied uncomplicated term vertex singleton deliveries. In a retrospective grouping, there were 55 infants whose cords were clamped 10 seconds or more before the onset of respiration and 97 where the cord was clamped 10 sec or more after the onset of respiration. The main outcome was the amount of blood retained in the placenta, thus giving an indirect measure of placental transfusion. There were significantly greater residuals in those where the cord was clamped before the onset of respiration compared to those whose cords were clamped after breathing commenced. (mean residual volumes were 85ml and 40ml respectively). In those whose cords were clamped 10 sec or more after the onset of respiration the placental residuals did not decrease much when those clamped 1 min later were compared to those clamped

at 3min. This implies that it is the onset of respiration that is most important in determining placental transfusion rather than defining DCC simply on the basis of time elapsed after birth. It was suggested that as infants with respiratory distress syndrome often had delayed onset of respiration and likely received less placental transfusion they may have poorer transition [29].

Kjeldsen and Pedersen [30] performed an observational study investigating residual placental volumes in term and low birth weight infants undergoing cord clamping before or after establishment of respiration. They studied 10 term infants that were breathing. The residual placental blood volume in 5 infants whose cords were clamped at a mean of 133 sec was similar to 5 infants whose cords were clamped later (mean of 236 sec). This finding in term infants was similar to that of Redmond and co-workers above [28] and probably indicated that the term infants established respiration quickly which facilitated the transfusion. Delaying cord clamping and waiting longer did not add to transfer of placental blood. The findings in preterm and low birth weight infants was also described in the same study and showed some differences to the term infants. Of 26 low birth weight infants (the majority of whom had a birth weight of 2001-2500g), approximately 1/3 (8/26) established respiration prior to clamping. Residual placental volumes were lower (by about 50%) in those who breathed prior to clamping. There was also a decrease in residuals with time (unlike the term infants). This could reflect the longer time required to establish respiration in the preterm. However, the numbers were small, the groups were heterogeneous and preterm infants were not exposed to antenatal steroids. The lack of antenatal steroid use could be important as it is likely that respiratory distress syndrome would be more severe in these preterm infants and breathing take longer to establish at birth.

In term infants, Philip [31] also noted that the residual placental volume was more closely related to timing of the onset of regular respiration than timing of delayed cord clamping. In addition, the haematocrit was significantly higher at 24hr, 72hr and on day 5 in those clamped after onset of breathing.

In a more recent descriptive study, infants <30 weeks undergoing DCC were compared to historic controls who had immediate clamping. Of those receiving DCC, 34 established regular respiration before the cord was clamped, whilst 12 did not. Antenatal characteristics in the two groups were similar, including the percentage receiving antenatal steroids. Those who did not breathe were more likely to be males and to be intubated in delivery room. In addition, infants in this group had significantly lower haemoglobin levels on day 1, were more likely to have grade 3 or 4 IVH and were more likely to develop chronic lung disease. It was hypothesized that the infants who did not breathe had less compliant lungs due to surfactant deficiency, were unlikely to receive a significant placental transfusion, had a less stable transitional circulation and were prone to develop severe IVH [32].

In a large observational study, over 15000 neonates were studied in a rural hospital in Tanzania [33]. The majority of infants established respirations at a median of 5 sec and had cord

clamping performed at a median of 54 sec after birth. (The hospital guideline was for clamping 1-3 mins after breathing was established). The main outcome measure was death or admission to the nursery and there were significantly more infants with these outcomes where the cord was clamped before the onset of respiration compared to those whose cords were clamped after the onset of respiration (OR 4.53 95% CI 1.92-9.58). These outcomes applied to infants with birth weights  $\geq 2500\text{g}$  as well as those with birth weight below 2500g. The longer the cord was left intact after respiration was established, the less the risk of adverse outcome. Of note, the time interval between birth and spontaneous respiration was not independently associated with outcome, suggesting adequate perfusion and oxygenation from the placenta before clamping. This study highlights the interaction between breathing and cord clamping during transition.

In summary, evidence from the animal studies and observational studies described above, indicates the central role of respiration in relation to transition and cord clamping. More studies are underway.

## MODE OF DELIVERY AND TYPE OF PLACENTAL TRANSFUSION

There is some evidence that placental transfusion is less in infants undergoing cesaerean section (**CS**). Aladangady et al [34] measured blood volume in preterm infants with gestational ages of 24-32 weeks. Forty six infants were randomized to either DCC (30 sec or more) or early cord clamping. The mean blood volume increased significantly in the vaginal births randomized to DCC (the mean increase was 12ml) but the mean increase of 6ml in the cesaerean deliveries undergoing DCC was not significant. However, this was a small study not powered for subgroup analyses.

Katheria et al compared DCC (45 sec) and cord milking (4 milkings) in preterm infants 23-31 weeks gestation [35]. There were 79 infants delivered by cesaerean section in the DCC group and 75 cesaerean deliveries in the milking group. The group that underwent milking had a higher mean hemoglobin at birth (7g/L), higher SVC flow and higher urine output. However, the significance of these differences is unclear as all measured values in both groups were within normal limits. Rates of any IVH were lower (7% vs 13%) but this difference was not statistically significant and the rates of severe IVH were the same in both groups. Overall it does appear that the group delivered by cesaerean section received a greater placental transfusion following milking, but the clinical significance of this is uncertain. A further confounding factor could be the extent to which the infants were breathing at the same time as the milking was taking place.

A number of other factors may affect placental transfusion and hence the transitional circulation.

## GRAVITY AND USE OF UTEROTONICS

The effect of gravity on placental transfusion was examined in a randomized clinical trial [36]. This non-inferiority trial compared placental transfusion with the infant at the level of the

introitus with that with the infant on the maternal abdomen or chest. Normal term deliveries were selected (caesarean deliveries were not eligible) and there were 197 positioned at the level of the introitus and 194 on the abdomen or chest. Placental transfusion was assessed in terms of weight difference between birth and 2 mins of age when the cord was clamped. Mean weight gains in the 2 groups were not significantly different with a mean difference between groups of 3g ( $p=0.45$ ). In addition, multivariate analysis indicated no significant difference in weight gain between those who received early oxytocin (within 1 min of birth) and those who received it later (at 2 mins).

Similar results were obtained in another study, also performed on full term normal births in India. Infants were randomized to be positioned on the abdomen ( $n=97$ ) or 20cm below ( $n=102$ ). Delayed cord clamping was performed at 90 sec. Primary outcome was the hemoglobin at birth and this was repeated at 3 months together with measures of iron status. There were no significant differences noted [37].

In addition, in a study done on preterm lambs after the onset of ventilation, the position of the lamb above or below the placenta did not affect blood transfer between lamb and placenta [38].

Another preterm lamb study examined the effect of oxytocin during caesarean section. There were 5 animals studied in each group. A rapid decrease in umbilical arterial pressure was found, with an increase in carotid artery pressure in the group receiving oxytocin. This was associated with decreased arterial and cerebral oxygenation. The authors recommended withholding oxytocin until cord clamping was complete [39].

Overall, the effects of uterotonics such as oxytocin have not been adequately studied. The results of Vain et al study suggest there is no effect on placental transfusion in vaginal births [36]. More studies are needed for caesarean births.

## **ULTRASOUND OF FLOW IN CORD BLOOD VESSELS DURING DELAYED CORD CLAMPING**

A study in healthy term infants undergoing DCC showed considerable variability in flow in the cord vessels. In 10% there was no venous flow, while in 60% the venous flow had stopped by 4.5min. Venous flow was still present in 30% of cases by 5 min. There was no arterial flow in 17%, with 40% having stopped by 4 mins. Arterial flow was bidirectional in 72% and in some cases there was a pulse with no flow. Respiration had a marked effect on the venous flow, with a marked increase being noted [40]. At the same time vigorous crying was associated with decreased umbilical venous flow.

These observations suggest that the amount of flow in the umbilical vessels is determined by the relevant pressure gradients and resistance to flow. If abdominal pressure is high, it follows less blood will flow in the umbilical vein towards the baby. Likewise vasoconstriction of umbilical arteries will be associated with reduced flow from the baby to the placenta (as may occur for example in growth restricted infants).

# RECENTLY COMPLETED AND ONGOING STUDIES

## Resuscitation with an Intact Cord

Katheria, et al [41] recently completed a randomized trial of preterm infants <32 weeks undergoing delayed cord clamping. Infants received either 60 sec of DCC with breathing support in the form of face mask CPAP (or positive pressure ventilation if needed) or DCC with gentle tactile stimulation only. One hundred and fifty infants were randomized with a final tally of 71 in each group. The majority of infants (almost 90% in each group) were delivered by caesarean section. Median gestation (28 weeks) and birth weights were similar in both groups. Ninety five percent of infants in the study received at least 60 seconds of DCC. Extensive monitoring in the first minutes of life as well as haemodynamic assessments including echocardiograms were carried out. There were no significant differences in any important outcomes, including the primary outcome of haematocrit in the first 24hrs. There were 137 infants who breathed during the DCC and 13 who did not. Comparing outcomes in these groups indicated more positive pressure ventilation in the non breathing group but similar rates of death and severe IVH. Conclusions from this work were that a high proportion of infants were delivered by caesarean section, most (>90%) established regular respiration with minimal stimulation and the outcomes (in the small group) who did not establish respiration during DCC were no worse than in those who did breathe regularly. Of interest, the haematocrit was not significantly different between these groups. The results are interesting as they come from the first randomized study of its kind but the numbers of infants who did not breathe during DCC are probably too small to reach definite conclusions. Similarly, it is not clear how many infants were <27 weeks gestation, and these may be the most likely to benefit from a more stable transition process.

## Australian Placental Transfusion Study

The Australian Placental Transfusion study [42] randomized preterm infants <30 weeks to 60 sec or more of DCC compared to immediate cord clamping. Although the main trial has not been published, a sub study investigating the effect of DCC on flow in the SVC in the first 24hrs has been reported. A total of 133 infants were assigned to each group, although over 20% in the DCC group did not receive the intervention; in many cases due to caregiver concerns. There were no significant differences in SVC flow between groups. The lowest mean SVC flow was approximately 70 mls/kg/min in both groups. Approximately 30% of infants in each group had flows below 55ml/kg/min, which was regarded as the lower limit of normal. For reasons that are unclear, these results are at variance with those in the smaller studies described previously. The studies of Meyer, et al [19] and Takami, et al [22] enrolled lower gestational age infants with median gestations of 25-26 weeks compared to 28 weeks in the APTS. The percentage of infants with low SVC flow was higher in the control group of the the former (observational) study than in the APTS. All four prior studies noted an increase in SVC flow following placental transfusion and have had echocardiograms performed largely by single operators. As noted previously, the

high inter-observer variability found with measurements of SVC flow may have obscured any true differences. It is not stated how many operators were involved in the APTS but with 5 sites involved over several years this could have been a significant factor. Perhaps, in retrospect, a continuous non-invasive measure of cerebral blood flow such as NIRS may be more useful.

## Ongoing Studies

Currently, other randomized studies investigating the effects of respiratory support during DCC are underway. One such study in Auckland, New Zealand is examining breathing support given to babies not breathing during DCC (ANZCTRN12615001026516). A multicentre study is also proposed in the USA (VENTFirst study) NCT02391389 and another in the UK (UK CORD trial) [43]. In these studies breathing support is given to all preterm infants in the DCC intervention group.

## Future Directions

There is evidence that both DCC and cord milking result in placental transfusion. It is unclear whether both interventions have similar effects on the circulation during transition, the main difference being the onset of breathing and reduction in pulmonary vascular resistance with the cord intact during DCC. Most of the apparently beneficial circulatory changes observed with DCC have also been recorded with cord milking. Both are associated with reduction in all grades of IVH, improved SVC flow, blood pressure and urine output. As cord milking allows rapid attention to resuscitation, are there benefits attributable to DCC that are not seen with milking?

Potentially, for the majority of preterm infants it may be that both are beneficial. However, there is a need to reduce the more severe grades of IVH in the extremely preterm infant. It may be that in this group, DCC and the establishment of respiration and a more stable transitional circulation could lead to improved outcomes.

## CONCLUSION

The period of transition to extra uterine life is critical. Major changes take place in respiratory and circulatory systems. The preterm infant is especially vulnerable to alterations in cerebral blood flow which can predispose to intraventricular haemorrhage and white matter changes with potential profound effects on neurodevelopmental outcome. A period of delayed cord clamping in preterm infants appears to aid the postnatal circulatory adaption. The placental reservoir provides a source of volume to maintain pre load to both ventricles and also reduce afterload. These changes result in a more stable cerebral circulation in experimental conditions. This state of affairs is apparent in the majority of preterm infants who breathe and are vigorous during the period of delayed cord clamping. However, for infants that are not breathing, there is insufficient evidence to indicate whether breathing support should be given or whether cord milking would be beneficial. Studies are currently underway to answer these questions. The words of Redmond et al (1965) were prescient [28]:

“In view of the relation of initial pulmonary ventilation to placental transfusion, we must now revise our concept of neonatal resuscitation: raising the intact placenta and cord must be regarded as an essential phase in artificial ventilation. During delivery, cord clamping should be delayed until spontaneous or induced breathing has begun”.

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