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Hemodynamic antecedents of peri/intraventricular hemorrhage in very preterm neonates

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SUMMARY

Novel hemodynamic monitoring technologies have contributed to the understanding of developmental cardiovascular physiology and pathophysiology in general, and of developmental hemodynamics in particular. Hemodynamic disturbances play a significant role in the pathogenesis of peri/intraventricular hemorrhage (P/IVH) in preterm infants. Immaturity of the myocardium, delayed and incomplete cardiopulmonary transition, sustained patency of the ductus arteriosus, and unintended consequences of respiratory and cardiovascular supportive care are all likely to be involved in the presentation of low cardiac output syndrome and decreased organ blood flow in a large number of very preterm neonates (gestational age \leq 28 weeks). Forebrain vessels in very preterm infants may not have achieved a "high-priority vasculature" status at the time of delivery; in these patients, forebrain perfusion is not protected during the compensated phase of shock. Reperfusion may be attenuated by the careful use of medications decreasing cerebrovascular reactivity, thus providing a potential target for the development of careful pharmacological support of transitional hemodynamics in selected patients at high risk for the development of P/IVH.

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1. Introduction

Transition from the fetal to postnatal circulation can be challenging, especially for very preterm infants (gestational age <28 weeks). Accordingly, if the process of immediate postnatal transition is significantly affected, the chances of cardiopulmonary failure and/or brain injury increase. The mechanisms of brain injury in preterm infants are complex and multifactorial but also include hemodynamic derangements as a potentially significant contributing factor. The premature cardiovascular system has inherent vulnerabilities. For instance, the immaturity of the myocardium results in, among other things, a greater sensitivity to high afterload and the persistence of fetal shunts affects the loading conditions of the heart. Furthermore, the unintended consequences of our supportive care can further compromise cardiovascular function. For example, our interventions in the delivery room, such as the timing of cord clamping, influence the effective circulating blood volume.

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http://dx.doi.org/10.1016/j.siny.2015.02.004 1744-165X/© 2015 Elsevier Ltd. All rights reserved. In addition, positive pressure ventilation can compromise ventricular function and venous return. Changes in blood oxygen and carbon dioxide (CO₂) concentrations as a result of the provision of supplemental oxygen and positive pressure ventilation, respectively, can also affect the vascular system in general and the cerebral vascular bed in particular. All of the above factors, directly or through their effects on the cardiovascular system, could alter cerebral hemodynamics and oxygen delivery, predisposing the vulnerable brain of the premature infant to peri/intraventricular hemorrhage (P/IVH). In this article, we first review the normal cardiovascular transition from fetal to postnatal life with a special focus on cerebral blood flow (CBF). We then discuss the impact of the altered immediate postnatal circulatory transition and the accompanying events that precede and likely are involved in the development of P/IVH.

2. Cardiac function and CBF during fetal life

Although much of our understanding about fetal circulation comes from studies in lamb models, recent Doppler studies in the human fetus have shed light on some of the differences of the

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circulatory adaptation between the lamb and the human. Close to half of the oxygenated blood coming from the placenta in the umbilical vein bypasses the liver via the ductus venosus, and, from the inferior vena cava it preferentially flows through the foramen ovale into the left atrium thereby supplying the most oxygenated blood to the heart and brain. Blood coming from the superior vena cava (SVC) to the right atrium mainly enters the right ventricle. However, because of the high pulmonary vascular resistance, most of the blood is diverted from pulmonary artery to the systemic circulation via the large patent ductus arteriosus (PDA). Therefore, both ventricles contribute to systemic flow. As for the CBF, animal studies show that it increases both as a proportion of cardiac output and in relation to brain weight [1]. Data from Doppler studies indicate that this is also the case in humans [2].

3. Hemodynamic changes at birth

At birth there are three major events significantly affecting the cardiovascular system: lung aeration, exposure to higher oxygen tension and separation from the placental circulation. In the fetal lamb model, ventilation with a gas mixture that does not alter blood gases results in no change in CBF [3]. Once oxygen is given, however, significant decrease in CBF occurs. Cord occlusion results in a slight but non-significant increase in CBF. Therefore, in the lamb, CBF decreases at birth, primarily because of exposure to higher blood and thus tissue oxygen concentration. Doppler studies suggest that CBF deceases at birth in the human neonate also [4]. Interestingly, timing of cord clamping could have a significant effect on the postnatal changes in CBF (see Section 5.2).

Until very recently, virtually no data existed on the immediate transitional changes of the circulation in humans. With advances in our ability to non-invasively monitor changes in blood flow and oxygen delivery, we now understand that in normal term neonates, cerebral regional tissue oxygen saturation (CrSO₂) increases in the first few minutes and then it plateaus by about 8 min after birth [5-7]. The increase in CrSO₂ coincides with an increase in arterial oxygen saturation. However, we found that CrSO₂ subsequently decreases despite the continued rise in arterial oxygen saturation [6]. This period is associated with an increase in cerebral fractional oxygen extraction (CFOE) and a decrease in middle cerebral artery mean velocity (MCA-MV), indicating a decrease in CBF after the first few minutes of postnatal life [6]. The underlying cause of reduction in CBF is unknown. A number of factors may play a role in the postnatal decrease in CBF, including the elevated blood oxygen saturation and the coinciding progressive increase in net left-toright PDA flow [6]. Although left ventricular stroke volume increases during this period [6,8], the modest increase is less than the increase in left-to-right PDA shunt [6]. This observation, together with the strong inverse linear relationship between MCA-MV and left-to-right PDA flow, highlights a possible role of increasing leftto-right shunting through the PDA in the reduction of CBF during the immediate transitional period (see Section 5.3) [6].

In general, there is a paucity of information on changes in cardiovascular function and cerebral hemodynamics in preterm infants at birth. However, it is well documented that compared to a few hours after birth, CBF increases over the second and third postnatal days. When measured by near-infrared spectroscopy (NIRS), most of the subjects demonstrate an increase in CBF over the first three days [9]. Changes in SVC flow, a surrogate for CBF, also reveal a rise in CBF from 5 h after birth throughout the first two postnatal days [10]. Studies that used CFOE, as a surrogate for CBF, also demonstrated a similar pattern [11]. In summary, the initial decrease in CBF immediately after delivery is followed by a robust rise during the first few days. Thereafter, volumetric ultrasonographic data reveal a more gradual increase in CBF over next two weeks [12].

4. Cerebral blood flow and oxygenation and P/IVH

The pattern of changes in CBF in extremely preterm infants who later develop P/IVH is different from those who do not. When CBF was measured by NIRS on the first postnatal day, the infants who later developed severe P/IVH had significantly lower CBF than the controls [13]. Studies of SVC flow also indicate that low SVC flow, a surrogate of CBF, is a risk factor for developing P/IVH [14]. Furthermore, changes in CFOE reveal that preterm infants who later develop P/IVH have a greater rise in CBF on the second postnatal day than those who do not [11].

With more widespread use of NIRS and functional echocardiography in recent years, the role of cardiovascular compromise in the pathogenesis of P/IVH has increasingly been recognized. A prospective study of cerebral oxygenation in 63 extremely preterm neonates using NIRS during the first postnatal day revealed that CBF is low in those who later develop severe P/IVH [15]. In one case-control study, CrSO₂ and CFOE were compared between patients with and without P/IVH during the first 15 days after birth [16]. Although NIRS measurements were performed for 2 h per day only, the authors found that CrSO₂ was lower and CFOE was higher in the P/IVH group during the first eight days. These findings suggest that CBF is low in patients who develop P/IVH from postnatal day 1 and that it stays low for more than two weeks. By contrast. another case-control study demonstrated that CrSO₂ was higher and that CFOE was lower during the 24 h preceding P/IVH compared to the control group [17]. The findings of this study suggest that CBF is higher in preterm infants before they develop severe brain hemorrhage – a finding that is contrary to the observation of persistently low CBF for two weeks [16,17].

In a comprehensive study, we recently investigated the temporal relationship of P/IVH with changes in cerebral hemodynamics and cardiac function in extremely preterm infants. After initial screening for P/IVH at 4–6 h after birth, subjects without an early P/ IVH were monitored closely with continuous NIRS and, every 12 h, with echocardiography and head ultrasound for 72 h, the period when >90% of P/IVH occur [18]. We noted a particular pattern of changes in CrSO₂ and CFOE in those who later developed P/IVH (Fig. 1). Over the first 12 h, patients in the P/IVH group had lower CrSO₂ and higher CFOE, whereas during the following 12 h the difference between the two groups subsided. P/IVH was only detected after normalization of CrSO2 and CFOE. These findings indicate that CBF was initially low and subsequently increased toward normal before P/IVH occurred. In other words, an ischemiareperfusion injury appears to have preceded and perhaps contributed to the occurrence of P/IVH. Therefore, whereas the previous studies only detected either the ischemic or the reperfusion state. with our study design using continuous NIRS monitoring for the first three days along with the regular evaluations to document the timing of P/IVH by head ultrasonography every 12 h, we were able to detect both the ischemic phase and the subsequent reperfusion phase.

5. Underlying causes of the initial postnatal cerebral ischemia

The exact cause or causes of the observed cerebral ischemia during the first few hours after birth in the subset of the extreme preterm infants who later develop P/IVH is unknown. It is possible that structural immaturity of the brain and/or its response to extreme transitional changes lead to ischemia. However, accumulating evidence implicates circulatory impairment as the primary

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Fig. 1. Changes in cerebral tissue oxygen saturation (rSO₂) and cerebral fractional oxygen extraction (CFOE) in the two groups during the study. The No-P/IVH (no peri/intraventricular hemorrhage (P/IVH) group exhibited stable cerebral rSO₂ (a) and CFOE (b) values whereas the group of patients developing P/IVH presented with a characteristic pattern of changes. The P/IVH group had lower cerebral rSO₂ and higher CFOE during the first 12 h of the study followed by normalization of these parameters just before the study periods (shaded area) when P/IVH was detected. Again, these findings suggest initial cerebral hypoperfusion followed by a period of reperfusion before the occurrence of cerebral bleeding. After the second study period, cerebral rSO₂ decreased and CFOE increased, suggesting a decrease in CBF during and after the development of P/IVH. Statistically significant differences between the two groups: **P* < 0.005, #*P* < 0.04 and ⁵*P* < 0.05. The values represent the mean ± SD of the data obtained in each 12 h data collection period. Shaded area represents the period when P/IVH

cause of low perfusion with immaturity of the brain likely playing a mostly permissive role.

Using SVC flow as a surrogate for cardiac output, low systemic flow has been suggested as a possible antecedent of P/IVH [14]. Using echocardiographic assessment of cardiac output, we have recently confirmed that systemic blood flow is low during the first postnatal day in very preterm infants who later develop P/IVH [18]. However, despite evidence for the possible role of myocardial dysfunction, low preload and PDA, the exact underlying pathophysiology of the circulatory compromise leading to low cardiac output and systemic flow remains to be elucidated.

5.1. Myocardial dysfunction and afterload

The preterm myocardium is anatomically and functionally immature, putting the infant at a disadvantage in terms of contractility. Indeed, even in term neonates, the myocardium is more sensitive to changes in afterload than in older children and adults. There is a normal inverse linear relationship between heart rate-corrected velocity of circumferential shortening (VCF_C, an index of contractility) and wall stress (WS, an index of afterload). The slope of the regression line between VCF_C and WS is much steeper in neonates [19]. This can potentially pose a significant hurdle for

normal transition as, after birth and with the removal of the lowresistance placental circulation, systemic vascular resistance abruptly increases, resulting in a higher afterload. It appears that, for unknown reasons, the myocardium of a subset of preterm infants may even be more sensitive to changes in afterload. Using SVC flow as a surrogate for CBF, it has been shown that the slope of the negative linear relationship between contractility and afterload is even steeper in patients with low SVC flow (a predictive marker for P/IVH) [20]. However, a recent study showed normal contractility as measured by VCF_C and stress–velocity index in a group of preterm infants who later developed P/IVH, and there was no difference in these indices between patients with and without P/IVH [18].

5.2. Low preload

Although available data suggest a lack or a weak correlation between blood volume and blood pressure in preterm infants during the first postnatal days, findings of recent studies on delayed cord clamping (DCC) and cord milking suggest a possible role for low preload in circulatory compromise in this patient population during early transition (see also M. Klukow and M.B. Cooper in this issue).

A randomized control trial (RCT) of immediate cord clamping (ICC, <20 s) versus DCC (60–90 s) in preterm infants showed higher cerebral oxygen saturation in the DCC group during the first 24 h [21]. Another RCT comparing ICC (5 s) versus DCC (45 s) found a higher SVC flow in the DCC group throughout the first few postnatal days [22]. Taken together, the results of these two studies indicate a higher CBF in the setting of DCC. The observed higher CBF with DCC could be due, at least in part, to a higher preload as a result of placental transfusion. Indeed, in term neonates delaying cord clamping by 60 and 180 s results in a 16 and 23 mL/kg increase in blood volume, respectively [23,24]. An RCT of milking of the cord versus ICC showed higher blood pressure in the first 12 h and less hypotension and a decreased need for high-dose vasopressor treatment throughout the transitional period in the cord milking group [25]. Another RCT showed higher cerebral oxygenation and SVC flow during the first 18 h after birth in the cord milking group compared to the infants undergoing ICC [26]. The finding of improved hemodynamic status after cord milking supports the notion that hypovolemia plays a role in the early postnatal circulatory compromise, especially in very preterm neonates, and that the hemodynamic benefit of DCC is likely primarily through an improved preload. However, other mechanisms may also play a role in the observed beneficial effects of DCC. As mentioned earlier, a sudden increase in afterload may result in worsening myocardial dysfunction in the preterm neonate. Therefore, by allowing a more gradual rise in afterload, DCC may reduce this burden on the immature myocardium. The gradual rise in afterload without ICC could be an important natural adaptive process that is prematurely terminated by our present practice of management of the third stage of labor. This notion is supported by recent evidence showing that blood does flow through the umbilical cord for 5 min in many cases when the cord is unclamped [27]. Another possible mechanism of the adverse effect of ICC is the resultant significant fluctuation in brain blood flow and blood pressure, as shown in the lamb model [28]. Regardless of the underlying mechanism, DCC appears to attenuate the ischemic phase of the ischemia-reperfusion cycle described earlier. Indeed, findings of a meta-analysis of RCTs on DCC and cord milking versus ICC reveal a reduction in the overall incidence of P/IVH when placental transfusion is allowed to take place [29]. Despite the recent evidence of improvement in transitional hemodynamics and the possible decrease in P/IVH with DCC and cord milking in preterm infants, further studies are needed

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to define the best approach in optimizing placental transfusion and the population of infants that benefits the most from it.

In addition to hypovolemia, diastolic dysfunction due the decreased compliance of the immature myocardium and high intrathoracic pressure as a result of the use of an inappropriately high mean airway pressure could also decrease the preload and therefore play a role in the observed presentation of low cardiac output syndrome during early transition in a subset of preterm infants at risk for P/IVH.

5.3. Shunting through the PDA

Another factor that likely contributes to altered transitional hemodynamics and the documented reduced CBF is PDA. As mentioned earlier, even in term neonates, PDA flow rapidly changes with the net flow becoming left-to-right after 5 min of birth [6]. Furthermore, there is a strong inverse linear relationship between the degree of left-to-right shunting and MCA-MV, another surrogate of CBF [6]. When examined at 5 h after birth, the vast majority of preterm infants had completely or predominantly left-to-right shunting through the PDA. During this early phase of postnatal transition, the compensatory increase in left ventricular output may not be fully effective and the left-to-right shunt may contribute to the reduced CBF. Indeed, preterm infants with low SVC flow have a larger PDA than those with normal SVC flow during the first 12 h after birth but not afterward. This finding implies that the most vulnerable period when PDA shunting significantly contributes to low CBF is the first few hours after birth. Indeed, in preterm infants, the presence of an early, large PDA is an independent predictor of low SVC blood flow, a surrogate for low systemic blood flow [14].

5.4. Other factors

Ventilatory management can affect CBF. As mentioned earlier, inappropriately high mean airway pressure can decrease cardiac output/SVC flow. Systemic hypotension, especially in the setting of impaired CBF autoregulation, also results in decreased cerebral perfusion (see Chapter 5). Finally, hypocarbia and hyperoxia, via a direct effect on the vasomotor tone of the cerebral vasculature, will also lead to a decrease in CBF.

6. Underlying causes of reperfusion

With the resolution or correction of the initial physiologic and/ or iatrogenic events resulting in systemic and/or cerebral hypoperfusion, CBF increases. Accordingly, following the early, low cardiac output state in the immediate postnatal period (first 12–24 h), cardiac function normalizes and CBF increases in most very preterm neonates [18]. In a subset of extremely preterm infants with a more immature and thus vulnerable cardiovascular and cerebral status and/or who are born depressed following delivery, myocardial recovery and the ensuing systemic and cerebral reperfusion are often associated with an increased risk of P/IVH. However, the presence of other factor such as hypercarbia, hypoxia and impaired CBF autoregulation, especially during the period when myocardial recovery takes place, can further enhance cerebral reperfusion and thus also increase the risk for P/IVH.

6.1. Hypercarbia

The direct relationship between CO_2 and CBF is well known; accordingly CBF increases with a rise in the partial pressure of blood CO_2 (PaCO₂). Therefore, hypercarbia can potentiate reperfusion following ischemia. Indeed, epidemiological studies have

demonstrated a strong association between hypercarbia and P/IVH [30,31]. We have recently reported a bilinear relationship between arterial PaCO₂ and MCA-MV, a surrogate for CBF [32]. In hemodynamically stable preterm infants of 1-3 days of age, we have found a breakpoint in the CBF-PaCO₂ relationship at a PaCO₂ value of ~52 mmHg. Below the breakpoint, there is no relationship between MCA-MV and PaCO₂, whereas a very strong, positive linear relationship exists above the cut-off value (Fig. 2). This finding suggests that once the PaCO₂ value is above the low 50s, CBF significantly increases with higher PaCO₂ values. In addition to the increase in CBF, higher PaCO₂ also attenuates CBF autoregulation [32–34]. Indeed, it has been shown that the higher the PaCO₂ above the normal level, the more attenuated the CBF autoregulation becomes [33]. Interestingly, however, there may be no or only a weak association between PaCO₂ and CBF during the first postnatal day [32,35,36]. The subsequent restoration of cerebral vascular reactivity to PaCO₂ by the second or third postnatal day along with the practice of permissive hypercapnia [37] could contribute to the pathogenesis of P/IVH, as systemic and cerebral reperfusion also occurs on these days [18,32]. The cause of the diminished cerebral vascular reactivity during the first postnatal day is unknown. However, we speculate that the postnatal increase in PaO₂ and the proposed delay in vital organ assignment of the forebrain of the very preterm neonate [38] are factors likely to explain, at least in part, the diminished cerebral vascular reactivity to PaCO₂ during the first postnatal day.

6.2. Impaired CBF autoregulation

Although even the most immature preterm infants have established CBF autoregulation, their autoregulatory plateau is quite narrow. Furthermore, independent of gestational age, critically ill neonates in general do have impaired CBF autoregulation [39]. In addition, factors such as hypercarbia can further enhance the impairment of CBF autoregulation. In the setting of a pressure-



Fig. 2. Piece-wise bilinear regression identifying a breakpoint in the middle cerebral artery mean flow velocity (MCA-MV)–arterial carbon dioxide (PaCO₂) relationship. (A) Breakpoints at a PaCO₂ value of 52.7 mmHg for day 2 (broken line, $R^2 = 0.74$, P < 0.0001), 51.0 mm Hg for day 3 (dotted line, $R^2 = 0.60$, P < 0.034) and 53.2 mmHg for days 2 and 3 combined (solid line, $R^2 = 0.66$, P < 0.0001). (B) Breakpoint at PaCO₂ of 51.7 mmHg ($R^2 = 0.49$, P < 0.0001) for all data points, including day 1.

passive cerebral circulation, fluctuations in blood pressure and/or cardiac output lead to similar fluctuations in CBF. Therefore, loss of CBF autoregulation may contribute to both ischemic and hyperperfusion phases of brain injury preceding the development of P/ IVH [40,41]. Unfortunately, our ability to assess autoregulation is limited and the currently available tools need to be further studied before their routine clinical use can be recommended [42].

6.3. Inappropriate use of vasopressor-inotropes, inotropes and lusitropes

Most studies have found an association between hypotension and poor neurodevelopmental outcome. As the common clinical practice is to correct hypotension, the cause of the associated poor outcome is unclear and might be hypotension itself, the inappropriate use of vasoactive medications, or both (see Chapter 5). In the context of cerebral reperfusion, inappropriate use of vasoactive medications can indeed play a significant role. As hypotensive, critically ill neonates have pressure-passive cerebral circulation, inappropriate use and/or titration of vasoactive medications can result in relatively rapid blood pressure changes resulting in similar changes in CBF [43]. Indeed, it has been documented that the use of cardiovascular medications in the neonatal intensive care unit is associated with increases in both blood pressure and CBF [44]. Although it is desirable to prevent or reverse cerebral ischemia, one has to be extremely careful how to approach a hypotensive very preterm neonate and avoid under- or overshooting with the titration of the drug(s) and thus with the resultant changes in cardiac output and blood pressure. Whereas it has been advocated by many, especially by the authors, to pay close attention to carefully titrating cardiovascular medications to reduce the risk of ongoing hypo- or potential sudden hyperperfusion, validation and use of emerging novel hemodynamic monitoring tools will be necessary to better judge the adequacy of systemic circulation in general and cerebral circulation and oxygenation in particular in critically ill neonates treated with vasoactive medications (see articles in this issue by T. Azhibekov et al. and A. Sullivan and K.D. Fairchild).

7. Conclusions

Extremely preterm infants are in the state of compensated shock at and immediately after birth. A subset of these patients is especially vulnerable to the development of P/IVH, likely due to an unappreciated severity of immaturity and/or the clinical presentation upon delivery. There is growing evidence that the cardiovascular compromise in these patients is not easily recognizable and that the shock is multifactorial in etiology involving hypovolemia, myocardial compromise, abnormal vasoregulation and/or a combination of these pathophysiological factors. Therefore, it might be extremely difficult to establish the timely diagnosis of the primary etiology of the cardiovascular compromise and to select the most appropriate medication or medications and the rate of titration of the drug(s). The inherent vulnerabilities of the immature cardiovascular system in conjunction with the adverse effects of our supportive care often leave the patient in a low systemic flow state. In addition, in compensated shock with the blood pressure still being in the "normal" range, one would expect the vital organs (brain, heart, and adrenal glands) to be appropriately perfused. Yet, it appears that, unlike that of the hindbrain (brain stem and the cerebellum), the vasculature of the forebrain (including the cortex and the basal ganglia) does not have the "vital organ" assignment upon delivery in the very preterm neonate [38,45]. Therefore, as a result of the low systemic flow and the lack of vital organ assignment of the forebrain, the forebrain is hypoperfused even if perfusion pressure (blood pressure) is still in the normal range

during the first postnatal day. On the second and/or third postnatal day, when the circulatory system of the extremely preterm neonate recovers and cardiac output normalizes, CBF increases and the formerly hypoperfused forebrain might sustain a reperfusion injury even in very preterm neonates presenting with no apparent systemic hypotension after delivery. Reperfusion can then be exacerbated by a number of factors including hypercarbia (PaCO₂ above the low–mid 50s), loss of cerebral autoregulation, and inappropriate use of cardiovascular medications.

Practice points

- Low cardiac output with or without systemic hypotension predisposes the brain to ischemia in very preterm infants immediately after birth.
- Upon adaptation to the extrauterine environment, improvement in myocardial function and systemic and CBF as well as CBF regulation occurs during the second and third postnatal days.
- The hemodynamic effects of enhanced placental transfusion by delayed cord clamping or cord milking can reduce the risk of cerebral hypoperfusion and thus the development of hypoperfusion–reperfusion injuries (white matter injury and P/IVH) in very preterm infants.
- Permissive hypercarbia (PaCO₂ above the low-mid 50s) might potentiate the reperfusion phase of ischemiareperfusion cycle of the brain in very preterm infants and contribute to the development of P/IVH during the second and third postnatal days.

Research directions

- Studying the role of cardiac dysfunction and the shunting across the ductus arteriosus in cerebral hypoperfusion in the immediate postnatal period.
- Identifying the mechanisms of the beneficial hemodynamic effects of delayed cord clamping.
- Defining the best approach to enhancing placental transfusion and the population that benefits the most from it.
- Defining the role of hemodynamic and cerebral (and other organ) oxygenation monitoring in assessing the adequacy of cerebral blood flow and oxygen supply.

References

- Rudolph AM, Heymann MA. Circulatory changes during growth in the fetal lamb. Circ Res 1970;26:289–99.
- [2] Meerman RJ, van Bel F, van Zwieten PH, Oepkes D, den Ouden L. Fetal and neonatal cerebral blood velocity in the normal fetus and neonate: a longitudinal Doppler ultrasound study. Early Hum Dev 1990;24:209–17.
- [3] Iwamoto HS, Teitel D, Rudolph AM. Effects of birth-related events on blood flow distribution. Pediatr Res 1987;22:634–40.
- [4] Kempley ST, Vyas S, Bower S, Nicolaides KH, Gamsu H. Cerebral and renal artery blood flow velocity before and after birth. Early Hum Dev 1996;46: 165–74.
- [5] Urlesberger B, Kratky E, Rehak T, Pocivalnik M, Avian A, Czihak J, et al. Regional oxygen saturation of the brain during birth transition of term infants: comparison between elective cesarean and vaginal deliveries. J Pediatr 2011;159:404–8.
- [6] 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.

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- [7] Pichler G, Binder C, Avian A, Beckenbach E, Schmölzer GM, Urlesberger B. Reference ranges for regional cerebral tissue oxygen saturation and fractional oxygen extraction in neonates during immediate transition after birth. J Pediatr 2013;163:1558–63.
- [8] Van Vonderen JJ, Roest AAW, 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.
- [9] Meek JH, Tyszczuk L, Elwell CE, Wyatt JS. Cerebral blood flow increases over the first three days of life in extremely preterm neonates. Archs Dis Childh Fetal Neonatal Ed 1998;78:F33-7.
- [10] Kluckow M, Evans N. Superior vena cava flow in newborn infants: a novel marker of systemic blood flow. Archs Dis Childh Fetal Neonatal Ed 2000;82: F182-7.
- [11] Kissack CM, Garr R, Wardle SP, Weindling AM. Postnatal changes in cerebral oxygen extraction in the preterm infant are associated with intraventricular hemorrhage and hemorrhagic parenchymal infarction but not periventricular leukomalacia. Pediatr Res 2004;56:111–6.
- [12] Kehrer M, Blumenstock G, Ehehalt S, Goelz R, Poets C, Schöning M. Development of cerebral blood flow volume in preterm neonates during the first two weeks of life. Pediatr Res 2005;58:927–30.
- [13] Meek JH, Tyszczuk L, Elwell CE, Wyatt JS. Low cerebral blood flow is a risk factor for severe intraventricular haemorrhage. Archs Dis Childh Fetal Neonatal Ed 1999;81:F15–8.
- [14] Kluckow M, Evans N. Low superior vena cava flow and intraventricular haemorrhage in preterm infants. Archs Dis Childh Fetal Neonatal Ed 2000;82: F188–94.
- [15] Sorensen LC, Maroun LL, Borch K, Lou HC, Greisen G. Neonatal cerebral oxygenation is not linked to foetal vasculitis and predicts intraventricular haemorrhage in preterm infants. Acta Paediatr 2008;97:1529–34.
- [16] Verhagen EA, Ter Horst HJ, Keating P, Martijn A, Van Braeckel KNJA, Bos AF. Cerebral oxygenation in preterm infants with germinal matrix–intraventricular hemorrhages. Stroke J Cereb Circ 2010;41:2901–7.
- [17] Alderliesten T, Lemmers PMA, Smarius JJM, van de Vosse RE, Baerts W, van Bel F. Cerebral oxygenation, extraction, and autoregulation in very preterm infants who develop peri-intraventricular hemorrhage. J Pediatr 2013;162: 698–704. e2.
- [18] Noori S, McCoy M, Anderson MP, Ramji F, Seri I. Changes in cardiac function and cerebral blood flow in relation to peri/intraventricular hemorrhage in extremely preterm infants. J Pediatr 2014;164:264–70. e1–3.
- [19] Rowland DG, Gutgesell HP. Noninvasive assessment of myocardial contractility, preload, and afterload in healthy newborn infants. Am J Cardiol 1995;75:818–21.
- [20] Osborn DA, Evans N, Kluckow M. Left ventricular contractility in extremely premature infants in the first day and response to inotropes. Pediatr Res 2007;61:335–40.
- [21] Baenziger O, Stolkin F, Keel M, von Siebenthal K, Fauchere J-C, Das Kundu S, et al. The influence of the timing of cord clamping on postnatal cerebral oxygenation in preterm neonates: a randomized, controlled trial. Pediatrics 2007;119:455–9.
- [22] Sommers R, Stonestreet BS, Oh W, Laptook A, Yanowitz TD, Raker C, et al. Hemodynamic effects of delayed cord clamping in premature infants. Pediatrics 2012;129:e667–72.
- [23] Yao AC, Moinian M, Lind J. Distribution of blood between infant and placenta after birth. Lancet 1969;2(7626):871–3.
- [24] Raju TNK. Timing of umbilical cord clamping after birth for optimizing placental transfusion. Curr Opin Pediatr 2013;25:180–7.
- [25] Hosono S, Mugishima H, Fujita H, Hosono A, Okada T, Takahashi S, et al. Blood pressure and urine output during the first 120 h of life in infants born at less than 29 weeks' gestation related to umbilical cord milking. Archs Dis Childh Fetal Neonatal Ed 2009;94:F328–31.

- [26] Takami T, Suganami Y, Sunohara D, Kondo A, Mizukaki N, Fujioka T, et al. Umbilical cord milking stabilizes cerebral oxygenation and perfusion in infants born before 29 weeks of gestation. J Pediatr 2012;161:742-7.
- [27] Boere I, Roest AA, Wallace E, Ten Harkel ADJ, Haak MC, Morley CJ, et al. Umbilical blood flow patterns directly after birth before delayed cord clamping. Archs Dis Childh Fetal Neonatal Ed 2015;100:F121-5.
- [28] Bhatt S, Alison BJ, Wallace EM, Crossley KJ, Gill AW, Kluckow M, et al. Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. J Physiol 2013;591(Pt 8):2113–26.
- [29] Rabe H, Reynolds G, Diaz-Rossello J. A systematic review and meta-analysis of a brief delay in clamping the umbilical cord of preterm infants. Neonatology 2008;93:138–44.
- [30] Kaiser JR, Gauss CH, Pont MM, Williams DK. Hypercapnia during the first 3 days of life is associated with severe intraventricular hemorrhage in very low birth weight infants. J Perinatol Off J Calif Perinat Assoc 2006;26:279–85.
- [31] Fabres J, Carlo WA, Phillips V, Howard G, Ambalavanan N. Both extremes of arterial carbon dioxide pressure and the magnitude of fluctuations in arterial carbon dioxide pressure are associated with severe intraventricular hemorrhage in preterm infants. Pediatrics 2007;119:299–305.
 [32] Noori S, Anderson M, Soleymani S, Seri I. Effect of carbon dioxide on cerebral
- [32] Noori S, Anderson M, Soleymani S, Seri I. Effect of carbon dioxide on cerebral blood flow velocity in preterm infants during postnatal transition. Acta Paediatr 2014;103:e334–9.
- [33] Kaiser JR, Gauss CH, Williams DK. The effects of hypercapnia on cerebral autoregulation in ventilated very low birth weight infants. Pediatr Res 2005;58:931–5.
- [34] Pryds A, Tønnesen J, Pryds O, Knudsen GM, Greisen G. Cerebral pressure autoregulation and vasoreactivity in the newborn rat. Pediatr Res 2005;57: 294–8.
- [35] Levene MI, Shortland D, Gibson N, Evans DH. Carbon dioxide reactivity of the cerebral circulation in extremely premature infants: effects of postnatal age and indomethacin. Pediatr Res 1988;24:175–9.
- [36] Pryds O, Greisen G, Lou H, Friis-Hansen B. Heterogeneity of cerebral vasoreactivity in preterm infants supported by mechanical ventilation. J Pediatr 1989;115:638–45.
- [37] Van Kaam AH, De Jaegere AP, Rimensberger PC, Neovent Study Group. Incidence of hypo- and hyper-capnia in a cross-sectional European cohort of ventilated newborn infants. Archs Dis Childh Fetal Neonatal Ed 2013;98: F323-6.
- [38] Noori S, Stavroudis TA, Seri I. Systemic and cerebral hemodynamics during the transitional period after premature birth. Clin Perinatol 2009;36:723–36. v.
- [39] Soul JS, Hammer PE, Tsuji M, Saul JP, Bassan H, Limperopoulos C, et al. Fluctuating pressure-passivity is common in the cerebral circulation of sick premature infants. Pediatr Res 2007;61:467–73.
- [40] O'Leary H, Gregas MC, Limperopoulos C, Zaretskaya I, Bassan H, Soul JS, et al. Elevated cerebral pressure passivity is associated with prematurity-related intracranial hemorrhage. Pediatrics 2009;124:302–9.
- [41] Riera J, Cabañas F, Serrano JJ, Bravo MC, López-Ortego P, Sánchez L, et al. New time-frequency method for cerebral autoregulation in newborns: predictive capacity for clinical outcomes. J Pediatr 2014;165:897–902. e1.
- [42] Greisen G. Cerebral autoregulation in preterm infants. How to measure it and why care? J Pediatr 2014;165:885–6.
- [43] Munro MJ, Walker AM, Barfield CP. Hypotensive extremely low birth weight infants have reduced cerebral blood flow. Pediatrics 2004;114:1591–6.
- [44] Pellicer A, Valverde E, Elorza MD, Madero R, Gayá F, Quero J, et al. Cardiovascular support for low birth weight infants and cerebral hemodynamics: a randomized, blinded, clinical trial. Pediatrics 2005;115:1501–12.
- [45] Hernandez M, Hawkins R, Brennan R. Sympathetic control of regional cerebral blood flow in the asphyxiated newborn dog. In: Heistad D, Marcus M, editors. Cerebral blood flow, effects of nerves and neurotransmitters. Amsterdam: Elsevier; 1982. p. 359–66.