Seminars in Fetal & Neonatal Medicine 20 (2015) 232–237

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Review

Hemodynamic antecedents of peri/intraventricular hemorrhage in very preterm neonates

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Keywords:
Cerebral blood flow
Cerebral oxygenation
Echocardiography
Hemodynamic monitoring
Near-infrared spectroscopy
Patent ductus arteriosus

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 ≤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.

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. In addition, positive pressure ventilation can compromise ventricular function and venous return. Changes in blood oxygen and carbon dioxide (CO_2) 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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http://dx.doi.org/10.1016/j.siny.2015.02.004
1744-165X/

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 ($CrSO_2$) increases in the first few minutes and then it plateaus by about 8 min after birth [5–7]. The increase in $CrSO_2$ coincides with an increase in arterial oxygen saturation. However, we found that $CrSO_2$ 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-to-right 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 left-to-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, $CrSO_2$ 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 $CrSO_2$ 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 $CrSO_2$ 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 $CrSO_2$ and CFOE in those who later developed P/IVH (Fig. 1). Over the first 12 h, patients in the P/IVH group had lower $CrSO_2$ and higher CFOE, whereas during the following 12 h the difference between the two groups subsided. P/IVH was only detected after normalization of $CrSO_2$ and CFOE. These findings indicate that CBF was initially low and subsequently increased toward normal before P/IVH occurred. In other words, an ischemia–reperfusion 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