Investigating cerebral blood flow control to save the newborn brain

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One in every ten infants worldwide is born preterm, or before 37 weeks of gestation. Complications related to prematurity are the leading cause of death in children under 5 years of age, accounting for 1 million deaths annually. As preterm birth rates have been increasing in the United States, so have the survival rates in recent years (50–70%). Despite higher survival rates, most studies have shown that up to 50% of preterm infants will eventually develop a disability. Brain injuries, such as intraventricular haemorrhage and white matter injury, are an important underlying cause of prematurity-associated disabilities (Fyfe et al. 2014). In a recent article in The Journal of Physiology, Eiby et al. (2018) investigated how reduced blood volume in the early hours after birth subsequently decreases cerebral blood flow, which may ultimately contribute to brain injury in prematurity. This was done by studying cerebral blood flow in preterm and term piglets before and after the removal of up to 10% of their estimated blood volume.

The authors hypothesized that lower cardiac output and blood pressure, as a result of a reduction in blood volume, would compromise cerebral blood flow in preterm piglets relative to term piglets due to disparities in cerebral compensatory mechanisms. The experiments resulted in two main conclusions: (1) mean arterial pressure and cardiac output decreased to the same degree in both term and preterm piglets following blood volume reduction; (2) cerebral blood flow remained constant in term piglets but decreased significantly in preterm piglets. This indicated that cerebral compensatory mechanisms were effective in the term piglets but not in the preterm piglets.

The authors are to be applauded for conducting a thorough study on the effects of hypovolaemia on cardiovascular function and cerebral blood flow in piglets. Their approach advances the understanding of the potential effects of hypovolaemia on brain injury in preterm infants. In this Journal Club review, we present and consider some ideas about this study’s translational impact, as well as ask a few physiological questions.

First, to quantify cardiac output, Eiby et al. (2018) used the validated technique of injecting coloured microspheres into the left ventricle followed by reference blood sampling from the descending aorta. Cerebral blood flow was calculated by comparing the number of microspheres in brain tissue to the reference blood sample. This type of rigorous measurement is helpful in determining accurate absolute flows. However, as noted by the authors, the microsphere injection technique does not allow for the measurement of cerebral oxygen extraction or brain injury. From a translational perspective, it would be valuable to investigate how the experimental microsphere injection technique compares to clinically available indicators of cerebral oxygen metabolism and brain injury. The mixed-venous oxygen saturation of haemoglobin in brain tissue can be measured clinically using near-infrared spectroscopy (NIRS) (Fyfe et al. 2014). NIRS uses the difference in absorption of near-infrared light by oxy- and deoxyhaemoglobin to detect the relative concentrations of each compound. Given that only 30% of blood is intra-arterial at any given time, the measured value represents a 30/70 arterial/venous-weighted estimate of oxygen saturation. The safety and cost profile of NIRS have led to increased use of NIRS in neonates. Prospective clinical studies are now trying to establish the value of NIRS monitoring combined with standardized treatment protocols in preventing cerebral injury in preterm neonates (Hyttel-Sorensen et al. 2015). However, the clinical utility of NIRS monitoring is limited due to a lack of understanding of what the measurement represents specifically in preterm infants. Mixed-venous oxygenation correlates with measures of cerebral blood flow, but is influenced by many parameters including oxygen content of the blood, pH and metabolic demand by the tissues. Combining measurements of cerebral blood flow with NIRS monitoring in a future study would help to evaluate how NIRS monitoring can be used in the neonatal population. If future hypovolaemia experiments could be conducted as survival studies in animals, one could even assess if changes in mixed-venous oxygenation and/or cerebral blood flow are eventually related to brain injury, as measured by imaging modalities such as ultrasound or magnetic resonance imaging.

Second, the coloured microspheres’ measurements of cerebral blood flow, although accurate, only yield discrete values. Previous NIRS studies have revealed that impaired autoregulation may be a fluctuating phenomenon (Fyfe et al. 2014). Such studies in piglets have shown that cerebral tissue haemoglobin oxygen desaturation must be maintained for some time before manifest brain damage occurs (Hyttel-Sorensen et al. 2015). Having a continuous indicator allows for the analysis of the cerebral blood flow response to physiologically occurring minor changes in perfusion pressure (dynamic autoregulation; Fyfe et al. 2014). The correlation between NIRS signal and blood pressure can be calculated using either time-domain or frequency-domain analyses. A greater correlation between the two inputs in either analysis is interpreted as evidence of impaired cerebral autoregulation (greater ‘pressure-passivity’). A more pressure-passive pattern has been documented in very preterm neonates (born between 28 and 32 weeks of gestation), and it may be associated with brain injury (Fyfe et al. 2014).

Additionally, the present study demonstrates the importance of identifying hypovolaemia as a contributor to poor cerebral perfusion and potential brain injury during the first day of life in preterm infants. The authors also point out that hypovolaemia is difficult to detect and treat in preterm neonates. The aforementioned clinical trial on
NIRS monitoring (Hyttel-Sorenson et al. 2015) included a standardized treatment algorithm addressing the underlying causes of poor cerebral regional tissue oxygen saturation of haemoglobin. In addition to assessing volume status, systemic vascular resistance, cardiac output and respiratory status, Hyttel-Sorenson et al. call for the assessment of the status of the ductus arteriosus as a potential cause of reduced effective systemic blood flow. After birth, the initial functional closure of the ductus arteriosus usually occurs within a few hours due to smooth muscle contraction, but this may take longer in the preterm neonate. Previous studies have found that a patent ductus arteriosus can redistribute blood flow causing decreased blood pressure and cerebral blood flow (Hyttel-Sorenson et al. 2015). In premature lambs in the early hours after birth, it has been reported that cerebral blood flow increases by ~40% after experimental closure of a patent ductus arteriosus (Baylen et al. 1983). We wonder if evaluation of coloured microspheres in a lung sample could provide insight into the extent of left-to-right shunting during both the baseline and hypovolaemic measurements in the present study. Perhaps increased left-to-right shunting in the preterm vs. term piglets contributed to their inability to maintain cerebral blood flow after the reduction in blood volume.

Finally, as discussed by the authors, it has been suggested that cerebrovascular control in neonates operates close to the point at which further reductions in blood pressure and cardiac output will result in inadequate cerebral blood flow. We have previously studied the effect of experimental central hypovolaemia on static and dynamic measures of cerebral blood flow control in adults. We found that both static and dynamic measures of cerebral blood flow are controlled just up until the point that adequate cerebral oxygenation can no longer be maintained due to profound hypovolaemia (van Helmond et al. 2018). Measurements of dynamic cerebral blood flow control demonstrated increased correlation between cerebral blood flow and blood pressure. This has been a consistent finding in haemorrhage studies in adults, and we proposed that increased pulsatile cerebral blood flow may be a mechanism to help maintain overall cerebral blood flow, despite lower blood pressures and cardiac output. The underlying mechanism may be that less energy is required to maintain forward flow if the flow is pulsatile versus continuous. Similarly, preterm neonates seem to respond with overall decreased cerebral blood flow (Eiby et al. 2018) and increased ‘pressure-passivity’ (Fyfe et al. 2014) just below the lower limit of their capability to compensate for further reductions in blood volume. Rather than focusing on the primary detection of hypovolaemia, perhaps monitoring trends in absolute cerebral blood flow, conductance and dynamic components of regulation, with a continuous measurement, could be used to detect hypovolaemia in preterm neonates. In that case, an improvement in continuous static and dynamic measures of cerebral blood flow after volume expansion would support a diagnosis of hypovolaemia. However, there may be a lack of cerebral blood flow response to saline infusions due to the reduced ability of saline to remain in the intravascular space in neonates, as a result of the leakiness of their capillaries (Eiby et al. 2018). Transfusion of packed red blood cells may be more appropriate to test for, and subsequently treat, hypovolaemia. Ultimately, the goal of haemodynamic interventions in preterm neonates is to ensure adequate tissue perfusion, but volume expansion should be used with caution, as reperfusion of the brain has been associated with an increased risk of intraventricular haemorrhage. Excess volume expansion in preterm neonates, in particular very low birth weight neonates, is also associated with other undesirable end organ outcomes including maintaining a patent ductus arteriosus, pulmonary oedema, broncho-pulmonary dysplasia, as well as congestive heart failure.

In conclusion, as more infants are born prematurely, the topic of cerebral blood flow control during hypovolaemia and its relationship to brain injury is critically important. The study by Eiby et al. (2018) helps provide further insight into the significant role of hypovolaemia in compromising cerebral blood flow in premature infants; however, many physiological questions still remain. More preclinical and clinical studies are needed to eventually develop diagnostic and treatment algorithms to prevent brain injury in premature neonates.

References

Additional information
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