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Brain hypoxia before surgery; a tale of two cells: Astrocytes and oligodendrocytes

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There is now overwhelming evidence that large numbers of survivors of infant heart surgery face significant academic and neurodevelopmental challenges that limit their quality of life and likelihood of successful independence as adults.[1,2] Early investigations into the risks of poor cognitive outcomes had focused on the conduct of surgery; however, recent pooled data drive home the notion that, despite advances in surgical technique and alternative perfusion strategies, no significant gains have been made in developmental outcomes.[3] In 2002, the keystone article from Mahle and colleagues[4] described a highly prevalent form of brain injury to the white matter of the brains of these infants (termed white matter injury–periventricular leukomalacia [WMI-PVL]).[4] This imaging finding has been the target of much research by my group and others, as it has offered a plausible surrogate marker for later cognitive outcomes. Longitudinal studies are now emerging that support the link between WMI-PVL and cognitive outcomes.[5,6] Further support comes from the recent 16-year outcomes from the Boston Circulatory Arrest Trial, where cognitive and performance deficits were associated with abnormalities in very specific white matter tracts[7] and functional deficits in connectivity.[8] At the same time, there is a growing literature on how patient factors, such as in utero brain maturation, genetic polymorphisms, and heart defect diagnoses, heavily influence risk for both WMI-PVL and poor cognitive outcomes.

In their study published in this issue of the *Journal*,[9] Ishibashi and colleagues, lead author Agematsu, have studied the effects of third-trimester hypoxia on the development of WMI-PVL after surgery. Although this model cannot be considered a fetal model in the strictest sense (it involved postnatal mice), there are some developmental and cellular similarities. The third trimester was targeted in these experiments because that is when we see the divergence from normal brain growth in human fetuses with congenital heart defects.[10] We do need to remind ourselves that brain growth is just one marker, and more subtle cellular changes resulting from the altered circulations could be happening at much earlier time points.

To study the effects of presurgical hypoxia, Ishibashi and colleagues developed a very novel rat brain-slice preparation that is supposed to mimic operative conditions of deep

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hypothermic circulatory arrest (DHCA). This includes the absence of oxygen and glucose delivery to the tissue. With this model, Ishibashi and colleagues elegantly demonstrate that hypoxia before this modeled exposure to deep hypothermic circulatory arrest, similar to what is experienced during heart surgery, results in astroglial cell death, which can be rescued with hypothermic conditions. The results of this exposure model are strikingly similar to human results, in which lower postnatal cerebral oxygen saturations before surgery with deep hypothermic circulatory arrest predicted new and worsened WMI-PVL on postoperative brain MRI.[11] One wonders whether, if Ishibashi and colleagues were to extend their study and look at variation in the duration of hypoxic exposure before surgery, their results could parallel those of Lynch and colleagues,[11] who found that increasing time to surgical correction of hypoplastic left heart syndrome was associated with a higher incidence of WMI-PVL.

WMI-PVL has been thought to result from hypoxic ischemic injury to immature oligodendrocytes, which are particularly sensitive to injury during the premyelinating stage of development.[12] The role of the astrocyte in accelerating this injury has not previously been investigated. Through the process of reactive astrogliosis, astrocytes are generally believed to be harmful to white matter repair. In a rat model of fetal intrauterine growth retardation, the expression of bone morphogenetic protein from reactive astrocytes was demonstrated to inhibit oligodendrocyte maturation.[13] Here, however, the *lack* of reactive astrogliosis seems to impart a worsening of injury to both immature and mature oligodendrocytes. This finding might not be contradictory, as the hypoxia in this experiment is postnatal, starting at P3 (equivalent to the third trimester in human beings), and not fetal, beginning late in the first trimester. Moreover, astrocyte heterogeneity is well known and often underappreciated in experimental design. Further investigation will be needed.

In the end, our interest in these studies is to plan for neuroprotective strategies. Clearly, the focus has shifted away from “tweaking” surgeries and is concentrated on presurgical and fetal care. Medical in utero interventions have started (https://clinicaltrials.gov/show/NCT02133573), but there are other potential targets. In postnatal human studies, we have found that falling cerebral oxygen saturations between birth and heart surgery predict the development of postoperative WMI-PVL. These brain-slice experiments appear to support this and raise awareness of the role of astrocytes in propagation or acceleration of this injury. These findings will have to be replicated in larger animals (Ishibashi’s team is well recognized for work in a porcine model), and the role of astroglial cells and their effect on the oligodendroglia need to be further characterized. There is still much work to be done, both clinically and in the laboratory, but this article opens new avenues for investigation.

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Central Message

Presurgical hypoxia accelerates postsurgical brain injury.