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## First things first: The importance of the preoperative period for neurocognitive outcomes in hypoplastic left heart syndrome

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The article by Hansen and colleagues<sup>1</sup> from the University Hospital Schleswig-Holstein investigates the relationship between perioperative cerebral oxygenation and neurodevelopmental outcomes, intelligence quotient, and cognitive function at approximately 4.5 years. The authors suggest that preoperative, not postoperative, cerebral tissue oxygenation is an important determinant of cognitive development later in life. Although other recent publications have supported the importance of the preoperative period, the correlation between preoperative cerebral tissue oxygenation and neurocognitive outcomes needs to be understood in the context of other risk factors known to be predictive of poorer cognitive function.

The report describes a study of 43 neonates who underwent a Norwood procedure with preoperative and postoperative near-infrared spectroscopy monitoring and subsequently underwent neurodevelopmental testing at 4.5 years. In agreement with previous studies, the authors found that intelligence quotient scores and cognitive functions assessed with the German “Kognitiver Entwicklungstest für das Kindergartenalter” were in the lower normal range.<sup>2–4</sup> Hansen and colleagues<sup>1</sup> report that lower preoperative cerebral tissue oxygenation was correlated with poorer neurodevelopmental outcomes at 4.5 years but found no correlation between these developmental outcomes and postoperative recovery of oxygenation.

Monitoring cerebral tissue oxygenation and perfusion in these patients is particularly important because of the high risk for developing hypoxic-ischemic white matter injury.<sup>5</sup> This type of injury, sometimes referred to as “periventricular leukomalacia,” also is seen in infants born prematurely and has been shown to correlate with poor neurodevelopmental outcomes later in life.<sup>6–8</sup> Thus, low cerebral oxygenation is thought to be a risk factor for poor neurodevelopmental outcomes. However, the exact timing and mechanism behind this risk are still up for debate, and research is now aimed toward understanding when the brain is most vulnerable to low oxygenation in these patients. The authors’ finding that preoperative, and not postoperative, cerebral tissue oxygenation correlates with

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neurocognitive outcomes is in agreement with recent studies that suggest that the brain is most vulnerable to poor oxygenation during the preoperative period.<sup>9–11</sup> This increased vulnerability in the preoperative period is likely due to the inability of the cerebral vasculature to accommodate increasing oxygen demand that occurs after birth. Prenatal studies in fetuses with hypoplastic left heart syndrome have shown lower than normal cerebral vascular resistance.<sup>12,13</sup> This sustained decreased cerebrovascular resistance during fetal life could exhaust the compensatory mechanisms that are needed to increase oxygen delivery in response to increasing demand after birth, resulting in low cerebral tissue oxygenation and, after enough time, hypoxic-ischemic lesions.

The present study from Hansen and colleagues,<sup>1</sup> along with the other recent studies mentioned, suggest that the *modifiable* risk factors for poor neurodevelopmental outcomes likely exist in the prenatal and preoperative periods. However, these studies have been limited to single institutions and exclude patients with other comorbidities, such as genetic abnormalities. Larger and more thorough studies and trials investigating the prenatal and preoperative period are essential. To fully appreciate the effect of these modifiable risk factors during the preoperative period, these factors must be understood in the context of patient-specific predictors, such as socioeconomic status and genetic abnormalities, which likely have the biggest effect on neurocognitive outcomes later in life.<sup>14,15</sup> In addition, differences in perioperative care between institutions likely contribute to the variation of incidence, severity, and risk factors for brain injury and poor neurodevelopmental outcome in these patients, making large, multi-institutional studies a necessity.

Hansen and colleagues<sup>1</sup> demonstrate the vulnerability during the preoperative period in neonates with hypoplastic left heart syndrome by reporting a correlation between preoperative cerebral tissue oxygenation and neurodevelopmental outcomes at 4.5 years. Although the significance of the preoperative period has been suggested previously, large multicenter trials are necessary to understand the effect of the modifiable risk factors in the context of socioeconomic status, perioperative care, and other predictors that likely play the biggest role in neurodevelopmental outcome in this population.

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**Central Message**

The modifiable risk factors for poor neurodevelopmental outcomes in patients with hypoplastic left heart syndrome exist mainly in the preoperative period.

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