International Journal of Cardiology 291 (2019) 50–51

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Editorial

Searching for modifiable risk factors for neurodevelopment in congenital heart disease: Lessons from the Giessen/Zurich hypoplastic left heart syndrome experience

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In 1980, William Norwood described the survival of three patients with hypoplastic left heart syndrome (HLHS), who had undergone palliative surgery comprising the creation of a conduit from the right ventricle to the descending aorta and banding of the main pulmonary artery [1]. Eight years later, Norwood reported a cohort of 104 consecutive HLHS patients treated with pulmonary artery homograft augmentation of the ascending aorta and aortic arch and a modified right Blalock-Taussig shunt in which there were 30 early and 11 late deaths [2]. Since then the "Norwood procedure" has become the primary approach to managing HLHS, as evidenced by the "single ventricle reconstruction trial", which randomized 555 HLHS newborns from 15 North American centers to a Norwood procedure with a Blalock-Taussig shunt versus a right ventricle to pulmonary artery conduit, which reported transplantation-free survival at 12 months of 64% and 74% respectively [3]. Goldberg et al. studied the neurodevelopmental (ND) outcomes of patients enrolled in the single-ventricle reconstruction trial revealing that children with single right-ventricle anomalies have significantly impaired neurodevelopment at 3 years of age, with 51% scoring more than 2 SDs below the normal mean in at least one developmental domain [4]. Risk factors for developmental delay in children undergoing the Norwood procedure included a more complex medical course, growth impairment, feeding problems, and vision and hearing problems.

An alternative approach to the initial palliation of HLHS consisting of stenting of the arterial duct combined with banding of the pulmonary arteries and atrial septostomy was first described in four patients by John Gibbs [5]. The "Hybrid procedure", which achieves the same objective as the Norwood procedure, that is to balance systemic and pulmonary blood flow in a newborn with HLHS while deferring reconstruction of the aortic arch to the second stage of Fontan palliation, when it can be combined with the creation of a superior cavo-pulmonary anastomosis. The "Hybrid" therefore offers a potential advantage from a ND perspective, as it avoids the cardiopulmonary bypass and deep hypothermic circulatory arrest that is required to achieve the aortic arch reconstruction involved in the Norwood procedure. There is pre-clinical and clinical evidence suggesting the immature brain is particularly vulnerable to ischemia compared to a more mature brain due to age-dependent alterations in neuronal and non-neuronal cellular signaling, vasodilatory responses to nitric oxide, cerebral oxidation and metabolism, neuronal plasticity and excitotoxic or apoptotic cell death pathways [6]. Over recent years, a number of centers have adopted the Hybrid as their primary approach to the surgical management of HLHS. Initial data would suggest that survival and suitability for Fontan completion are comparable between the two approaches [7]. Of note, there are certain aspects of the Hybrid procedure which may adversely affect neurodevelopment. Hybrid physiology essentially maintains the fetal circulatory pattern, whereby a substantial proportion of cerebral blood flow is achieved through retrograde aortic arch flow via the stented ductus arteriosus. Therefore, any anatomical obstruction of the aortic isthmus, which may be exacerbated by the stent, could threaten cerebral perfusion and brain growth and development.

Delay in reaching developmental milestones in early childhood and long-term ND deficits including mild cognitive impairment, impaired social interaction and communication skills, inattention, impulsive behaviour and impaired function are now recognized by the AHA as important complications of congenital heart disease (CHD) [8]. The etiology of ND problems in children undergoing surgical repair of CHD in infancy is thought to be multifactorial, with innate patient factors including genetic abnormalities and disruption of substrate supply to the developing brain in utero now thought to be as important as perioperative brain injury. Intraoperative risk factors for neurologic injury and adverse ND outcomes include longer durations of circulatory arrest and excessively low hematocrit. However, despite careful attention to intraoperative brain protection there has been little impact on ND outcomes in children undergoing infant heart surgery over the past two decades [9].

While the most meaningful measures of ND outcome in patients with CHD have been obtained by long-term follow-up studies employing detailed ND testing [4], magnetic resonance imaging (MRI) studies have provided a useful means of examining brain injury and development in children with CHD. Quantitative metrics of brain development have revealed immaturity of the brain at the time of birth, while total and regional brain volumetry have been correlated with ND delays in infants and adolescents [10]. Thus, quantitative brain MRI may represent a useful short term surrogate

DOI of original article: https://doi.org/10.1016/j.ijcard.2019.03.055.
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https://doi.org/10.1016/j.ijcard.2019.05.038

for longer term ND outcome in studies investigating new neuroprotective strategies.

In the current issue, a group of investigators from two large centers treating CHD report a comparison of MRI brain volumetry in 2-year-olds with HLHS treated with Hybrid versus Norwood strategies. The results indicate more significant impairment of brain growth in patients undergoing Norwood than Hybrid, in keeping with the concept that the avoidance of a "big" operation in the neonatal period may represent a neuroprotective approach. There are some limitations of this analysis, including the relatively small number of Norwood patients. Future studies aiming to investigate this question should attempt to compare Hybrid neurodevelopmental outcomes with Norwood outcomes from centers that undertake a large volume of Norwood operations. However, despite these limitations, the avoidance of cardiopulmonary bypass and deep hypothermic circulatory arrest in the neonatal period represents a plausible biologic mechanism to account for the findings of the study. Given the similar long-term survival reported by other groups for the two approaches when they are used for HLHS patients with the same demographic characteristics, the consistent demonstration of a meaningful neuroprotective effect of the Hybrid strategy would represent a strong argument for other centers to adopt the Hybrid as their primary approach. The current study should therefore encourage other centers using Norwood or Hybrid as their primary approach to share their data on ND outcomes to look into this specific question in more detail. The efforts of registry-based data collection efforts are likely to be helpful in this regard. Moreover, it is tempting to hypothesise that other CHD subtypes might be amenable to the approach employed by this study, particularly when there is equipoise regarding contrasting treatment strategies.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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