Feature Review

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Congenital cardiac anomalies and white matter injury

Paul D. Morton, Nobuyuki Ishibashi, Richard A. Jonas, and Vittorio Gallo

Center for Neuroscience Research and Children's National Heart Institute, Children's National Medical Center, Washington, DC 20010, USA

Cardiac abnormalities are the most common birth defects. Derangement of circulatory flow affects many vital organs; without proper supply of oxygenated blood, the brain is particularly vulnerable. Although surgical interventions have greatly reduced mortality rates, patients often suffer an array of neurological deficits throughout life. Neuroimaging provides a macroscopic assessment of brain injury and has shown that white matter (WM) is at risk. Oligodendrocytes and myelinated axons have been identified as major targets of WM injury, but still little is known about how congenital heart anomalies affect the brain at the cellular level. Further integration of animal model studies and clinical research will define novel therapeutic targets and new standards of care to prevent developmental delay associated with cardiac abnormalities.

Why congenital cardiac anomalies and WM injury?

Congenital heart disease (CHD) is the most common major birth defect; nearly 8 in every 1000 infants born each year suffer a cardiac abnormality [1]. Although significant advances have greatly reduced hospital mortality risk [2], patients with CHD frequently suffer from a broad spectrum of subsequent neurological deficits; including motor, cognitive, behavioral, social, and attention abnormalities [3–6]. Owing to improvements in the mortality rate, it is estimated that 1 in every 150 young adults will be affected by some form of CHD within the next decade [7]. The personal, familial, and societal costs/hardships of neurological morbidity within this expanding population are inestimable. Therefore, as stated by the Pediatric Heart Network of the National Heart, Lung, and Blood Institute [8], 'one of the most important challenges in the 21st century for CHD patients is to improve neurological deficits.'

Neurological outcome in CHD patients is governed by multiple factors, including unusual fetal cerebral blood flow and oxygen saturation [9]. In normal fetuses, highly oxygenated blood is preferentially streamed to the developing brain; however, severe/complex CHD often alters blood flow (Figure 1), resulting in delivery of de-saturated blood to the brain [9,10]. These alterations have been shown to cause immature and delayed brain development in newborns [11–15]. Recent magnetic resonance imaging (MRI) studies demonstrate a high frequency of WM injury (25–55%) in CHD patients [14,16–18]. In addition to the prenatal insults to WM development, clinical trials and animal models have identified perioperative factors – such as cardiopulmonary bypass surgery (CPB) – that contribute to brain injury [17,19–22]. Cellular events associated with CHD-induced WM injury are largely unknown and unexplored, partly due to the technical and ethical difficulties of studying human tissue. Although several large and small animal models have been designed to mimic CHD, they are rarely utilized to study the impact of CHD on WM development, particularly at the cellular level. The purpose of this review is to summarize current knowledge in this field and highlight an urgent need to create a truly translational area of research in CHD-induced WM injury through further exploration and integration of animal models with findings in human subjects and in postmortem human tissue.

Congenital heart disease

Worldwide, approximately 1.3 million infants are born with CHD each year and this population is steadily rising [23]. More than 75% of CHD children who survive the first year of life, including those with complex cardiac malformations, will live into adulthood [24]. Prolonged neurological deficits are commonly observed in patients with CHD, and pose substantial socioeconomic and management challenges for patients, families, and society. Elucidating the cellular events underlying CHD-induced neurological deficits is not only a fundamental research endeavor: it is vital for the healthcare of this growing community of patients.

Several complex factors, often combinatorial and cumulative, contribute to neurological outcomes in patients with CHD (Figure 1), including (i) preoperative factors, such as unusual fetal cerebral blood flow; (ii) perioperative factors involved with heart surgery; and (iii) postoperative factors, such as length of hospital stay and parental stress [4,19,25]. Sophisticated imaging techniques are bringing prenatal events associated with neurological injury into focus [4,10]. Fetal cerebral blood flow involves preferential streaming of the most highly oxygenated blood to the developing brain [9]. However, heart abnormalities can alter these beneficial patterns, resulting in less or oxygen-deficient cerebral blood flow [9,10] (Figure 1). The first organ to form during embryonic development is the heart; through shared morphogenic programs, there is great time-overlap between heart and brain development in

Corresponding author: Gallo, V. (vgallo@cnmc.org).
Keywords: neuroimaging; heart; glial cells; myelin; oligodendrocyte.

0166-2236/
 http://dx.doi.org/10.1016/j.tins.2015.04.001

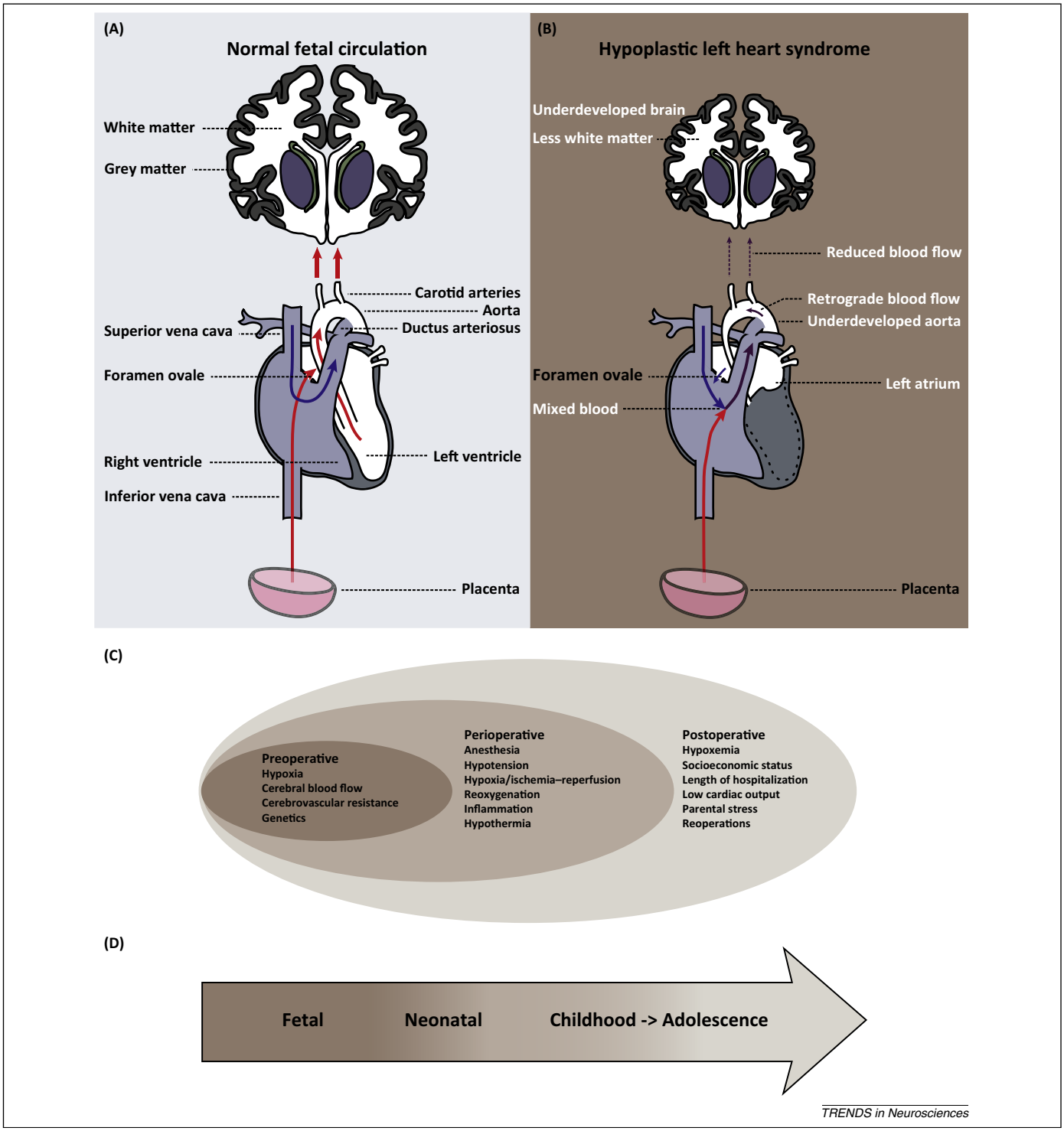

Figure 1. Fetal cerebral circulation, white matter (WM) damage, and risk factors associated with neurological outcomes in congenital heart disease (CHD). (A,B) Cartoon illustrating fetal cerebral blood flow. In normal fetuses **(A)**, oxygenated blood (red arrows) from the placenta is preferentially pumped to the left heart, exits through the carotid arteries, and flows to the brain. In fetuses with hypoplastic left heart syndrome (HLHS) **(B)**, oxygenated and deoxygenated (blue arrows) blood mix (purple arrows), and is then misdirected to the aorta, bypassing the carotid arteries. Retrograde flow of mixed blood exits through the carotid arteries at a low flow rate to the brain. In HLHS, developing fetal brains receive less and hypoxic blood, resulting in delayed WM maturation. **(C,D)** Risk factors associated with neurological deficits in CHD patients throughout life.

human fetuses (see [14,26] for review). Because the heart is nearly fully developed by the 7th week of gestation, cardiac abnormalities can disrupt fetal cerebral oxygen and nutrient delivery for more than 7 months during a period critical for brain development.

To survive, a majority of newborns with severe/complex CHD require cardiac surgery within the first few weeks of infancy. Because surgery cannot be performed on a beating heart it is necessary to stop the heart during CPB – a technique involving mechanical circulation and oxygenation of blood throughout the body while bypassing the heart and lungs. Although CPB facilitates heart surgery, this process mounts an inflammatory response associated with WM injury to the developing brain