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● *Original Contribution*

CEREBRAL BLOOD FLOW CHARACTERISTICS AND BIOMETRY IN FETUSES UNDERGOING PRENATAL INTERVENTION FOR AORTIC STENOSIS WITH EVOLVING HYPOPLASTIC LEFT HEART SYNDROME

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Abstract—Children with hypoplastic left heart syndrome (HLHS) are at risk for neurodevelopmental dysfunction; prenatal factors may play a role in this predilection. Cerebral blood flow profiles are abnormal in fetuses with HLHS, raising the possibility that cerebral hemodynamics *in utero* may be related to neurodevelopmental abnormalities. Prenatal aortic valvuloplasty for fetal aortic stenosis with evolving HLHS is technically feasible and improves left heart hemodynamics. This study aimed to assess the effects of prenatal intervention on cerebral blood flow profiles and head circumference in fetuses with evolving HLHS. Seventy fetuses underwent prenatal aortic valvuloplasty for evolving HLHS (median 23 weeks gestation). Among 46 fetuses that had successful valvuloplasty and available data, middle cerebral artery (MCA) pulsatility (PI) and resistive (RI) indices were abnormal (Z-scores -1.7 ± 1.1 and -2.2 ± 1.4, $p < 0.001$). Early post-valvuloplasty ($n = 33$) and at late gestation follow-up ($n = 28$), MCA PI and RI Z-scores remained low with no difference from pre- or early postintervention. Fetal head circumference was normal, as were umbilical artery PI and RI Z-scores. Cerebral blood flow characteristics are abnormal in mid-gestation fetuses with evolving HLHS, suggesting low cerebral vascular impedance. The mechanisms and significance of these abnormalities are unknown. Prenatal aortic valvuloplasty did not have a major impact on these indices. (E-mail: doff.mcelhinney@cardio.chboston.org) © **2010 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Fetal surgery, Balloon aortic valvuloplasty, Brain sparing effect, Congenital heart disease, Hypoplastic left heart syndrome, Microcephaly.**

INTRODUCTION

Major noncardiac morbidities in patients with congenital heart disease include neurologic and developmental abnormalities (Goldberg et al. 2000; Ikle et al. 2003; Limperopoulos et al. 2000; Mahle et al. 2002, 2004; Majnemer et al. 2006; Massaro et al. 2008; Miller et al. 2007; Wernovsky et al. 2000). There is growing evidence that neurodevelopmental anomalies in the setting of congenital heart disease may be due not only to perioperative insult but also to impaired brain growth and development prenatally (Hinton et al. 2008; Limperopoulos et al. 2000; Mahle et al. 2002; Miller et al. 2007; Te Pas et al. 2005). Among the various types of congenital heart disease, hypoplastic left heart syndrome (HLHS) appears to carry a particularly high risk of abnormal neurodevelopmental outcome (Goldberg et al. 2000; Hinton et al. 2008; Ikle et al. 2003; Mahle et al. 2004; Wernovsky et al. 2000). Although factors contributing to this predilection may include hypoxic-ischemic injury incurred during surgery, as well as peripartum and neonatal hemodynamic insult, there is an emerging literature indicating that prenatal factors may play an important role in the relatively high risk of adverse neurodevelopmental outcome in individuals with HLHS. For example, several studies have documented a high prevalence of microcephaly in newborns and fetuses with HLHS (Hinton et al. 2008; Rosenthal et al. 1996; Shillingford et al. 2007), there is evidence of

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white matter injury consistent with ischemia in fetuses with HLHS (Hinton et al. 2008) and the cerebral microvasculature is abnormal in some fetuses with HLHS (Kinnear et al. 2008).

Cross-sectional studies using Doppler ultrasound have shown that cerebral blood flow velocity profiles are abnormal in third-trimester fetuses with established HLHS (Donofrio et al. 2003; Kaltman et al. 2005; Modena et al. 2006). In particular, diastolic blood flow velocity in the middle cerebral artery (MCA) is relatively high and the pulsatility (PI) and resistive indices (RI) are accordingly low, suggestive of low cerebral vascular impedance presumably due to cerebral vasodilation. Abnormal cerebral vasodilation in fetuses with HLHS might be explained as part of an autoregulatory process by which the cerebral circulation responds to abnormal flow characteristics and/or abnormal oxygen or metabolic substrate content (Donofrio et al. 2003; Pearce 1987; Vyas et al. 1990; Wladimiroff et al. 1987). In the physiologically normal fetus, highly oxygenated blood returning from the placenta is preferentially directed right-to-left through the foramen ovale, into the left ventricle (LV) and out the aortic valve to the myocardial and cerebral circulations, with relatively little mixing with poorly oxygenated systemic venous return (Edelstone and Rudolph 1979). In contrast, in fetuses with HLHS or evolving HLHS, the oxygen content of cerebral arterial blood is likely decreased due to elimination of the normal intracardiac streaming patterns and preferential flow of umbilical venous return to the cerebral circulation. In addition to the relatively low oxygen content, fetal cerebral blood flow in the setting of HLHS is derived from right ventricular output, which must pass through the ductus arteriosus and retrograde around the aortic arch before flowing to the brain. However, the role and mechanisms of cerebral autoregulation in the mid-gestation fetus are debatable (Ashwal et al. 1980; Chihara et al. 2003; Gleason et al. 1990; Papile et al. 1985; van Bel et al. 1995). Exactly how and why cerebral arterial velocity profiles are abnormal in fetuses with HLHS is unclear, as is the relationship of such abnormalities to prognosis.

In mid-gestation fetuses with aortic stenosis, a normal size or dilated LV and depressed LV function, a constellation of physiologic features, including retrograde blood flow in the transverse aortic arch, left-to-right flow across the foramen ovale and abnormal left ventricular (LV) inflow, predicts evolution to HLHS postnatally (Makikallio et al. 2006). Eight years ago, we undertook a program of mid-gestation fetal aortic valvuloplasty in an effort to alter the natural history of evolving HLHS *in utero* (Tworetzky et al. 2004; McElhinney et al. 2009). The basic hypothesis behind this undertaking was that relieving obstruction to LV outflow in fetuses with aortic stenosis and evolving HLHS, regardless of the cause(s) of the disease, will facilitate growth and enhanced function of the left heart. As previously reported, technically successful *in utero* aortic valvuloplasty results in altered left heart physiology, with improved LV inflow, systolic function and antegrade flow in the ascending aorta and arch (Selamet Tierney et al. 2007). Although successful aortic valve dilation leads to improvement in fetal hemodynamics, it also causes aortic regurgitation (AR) in some cases, which is of uncertain physiologic significance but seems to be well tolerated. While the main objective of prenatal aortic valvuloplasty for evolving HLHS is to alter the natural history of the disease and facilitate postnatal survival with a biventricular circulation, it is possible that there are physiologic advantages as well, even if the patient does not achieve a biventricular circulation. One of the potential physiologic benefits of improved flow through the left heart and antegrade aortic outflow is normalization of cerebral hemodynamics. To study this possibility, however, it will be necessary to determine the characteristics of cerebral blood flow in mid-gestation fetuses with evolving HLHS, as well as the effects of prenatal aortic valvuloplasty and AR on cerebral blood flow, which is the purpose of the present investigation.

METHODS

Patients and prenatal aortic valvuloplasty

Since 2000, mid-gestation (20–31 weeks) fetuses with aortic stenosis were considered for prenatal aortic valvuloplasty if progression to HLHS was considered to be highly likely on the basis of previously published criteria (Makikallio et al. 2006) and LV size was considered potentially sufficient to sustain a biventricular circulation. The procedure was performed with ultrasound guidance and direct left ventricular (LV) puncture, using previously reported techniques (Marshall et al. 2005; Tworetzky et al. 2004). A technically successful aortic valvuloplasty procedure was defined as one in which the aortic valve was crossed and a balloon inflated, with clear evidence of increased flow across the valve and/or new AR. Procedures were performed according to compassionate use protocols that were approved by the institutional review boards of Children's Hospital and the Brigham and Women's Hospital. Parents were extensively counseled about the risks and benefits of this experimental procedure and provided written informed consent.

Ultrasound evaluation

Complete cross-sectional and Doppler fetal echocardiograms were performed according to standard clinical practice at our center 1 to 2 days prior to intervention, early (12–24 hours) postintervention and at late-gestation follow-up. All studies were read and measurements

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