The association of fetal cerebrovascular resistance with early neurodevelopment in single ventricle congenital heart disease

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Background Children with congenital heart disease are at risk for impaired neurodevelopment (ND). We investigated the association of fetal cerebrovascular resistance with ND in patients with single ventricle lesions.

Methods In the Single Ventricle Reconstruction (SVR) and Infant Single Ventricle trials, 14-month ND was assessed using the Bayley Scales of Infant Development II. We investigated associations between ND scores and fetal middle cerebral artery pulsatility index (MCA-PI) z-scores, a Doppler-derived estimate of cerebrovascular resistance in a subset of those infants.

Results Neurodevelopment assessments were performed at age 14.3 ± 1 months in 170 (74%) of 230 Infant Single Ventricle and 321 (58%) of 555 SVR subjects. Fetal echocardiographic data were available in 119 subjects, 72 (61%) of which had ND testing. Mean Psychomotor Development Index (PDI) (76 ± 20) and Mental Development Index (MDI) (89 ± 17) scores were lower than normative means (100 ± 15, $P < .001$). Mean MCA-PI z-score was –0.95 ± 1.52. Middle cerebral artery pulsatility index z-score correlated negatively with PDI ($r = –0.27$, $P = .02$) but was not associated with MDI. When MCA-PI z-score was added to a multivariable model controlling for factors identified in the SVR trial to predict PDI, the percentage of explained variation increased from 23% to 30%, and MCA-PI z-score remained an independent predictor ($r = –3.864$, $P = .03$). Middle cerebral artery pulsatility index z-score was not an independent predictor in a model adjusting for site.

Conclusions Among fetuses with single ventricle anomalies, lower cerebrovascular resistance was associated with higher ND scores. This relationship is opposite to that observed with advanced intrauterine growth retardation and may represent a unique ability of these congenital heart disease fetuses to compensate for diminished cerebral oxygen delivery. (Am Heart J 2013;165:544-550.e1.)

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Advances in surgical techniques and perioperative care have improved survival of infants born with hypoplastic left heart syndrome (HLHS) and other single ventricle lesions. However, survivors are at high risk for neurodevelopmental (ND) delay with the percentage affected reported to be as high as 70%.[1,2] The spectrum of neurocognitive effects is wide, ranging from learning disability to attention deficit disorder to mental retardation.[3] In addition to our inability to predict the type and degree of deficit likely to be encountered, we are currently unable to predict who among our patients is at highest risk.

The healthy fetus maintains adequate cerebral oxygenation through a range of adaptive physiologic responses. This includes vasodilation of the cerebral arteries to increase brain perfusion if the fetus is exposed to acute or chronic hypoxia.[4,5] As a result of this cerebral vasodilation, the diastolic flow in the middle cerebral artery (MCA) increases, whereas the MCA pulsatility index (MCA-PI) decreases. With further deterioration, the

protective brain sparing reflex may be overwhelmed, and cerebral ischemia and metabolic acidosis may ensue leading to intraventricular hemorrhage and periventricular leukomalacia.

Although decreased cerebrovascular resistance may predict poor neurologic outcomes in fetal disease states such as intrauterine growth retardation (IUGR),[6,7] the significance of this finding in the setting of congenital heart disease (CHD) is unclear. In univentricular hearts, the fetal systemic arterial saturation is lower than usual due to intracardiac mixing of oxygenated and deoxygenated blood. In some, this is compounded by abnormal flow patterns related to either right- or left-sided outflow tract obstruction. This chronically lower arterial saturation may explain why some fetuses with CHD, particularly the group with HLHS, demonstrate aberrant cerebrovascular resistance on fetal ultrasound in the absence of placental failure.[8,9] Our aim was to investigate associations between fetal cerebrovascular resistance and early ND in patients with univentricular hearts.

Patients and methods

This was an approved ancillary study to the Pediatric Heart Network's (PHN) Single Ventricle Reconstruction (SVR) and Infant Single Ventricle (ISV) trials. All PHN sites that contributed patients to the SVR or the ISV trial and had fetal echocardiograms available for these patients were invited to participate. Local approval from the institutional review board or its equivalent was obtained at each site; institutional review board approval for the SVR and ISV trials along with written parental informed consent had been obtained previously. Pediatric Heart Network's studies were supported by U01 grants from the National Heart, Lung, and Blood Institute (HL068270, HL068279, HL068281, HL068285, HL068290, HL068288, HL085057) and the FDA Office of Orphan Products Development. In addition, Dr Williams received support from grant number 1K23HD061601 from the National Institute of Child Health & Human Development of the National Institutes of Health.

Although this study was designed to allow for the prospective collection of data among fetuses likely to be eligible for SVR or ISV enrollment, final determination of PHN study eligibility could not be conducted until after birth. Therefore, although some centers enrolled fetuses and prospectively collected data in a standardized fashion, the majority of fetal data were obtained retrospectively from clinically indicated fetal echocardiograms of patients who were subsequently enrolled in the PHN trials. These retrospective echocardiograms were recorded according to local center practice guidelines.

SVR and ISV trials

Details of the SVR and ISV trials have been published.[10,11] In brief, the SVR trial prospectively enrolled infants with HLHS and other complex single right ventricle lesions at 15 centers from May 2005 to July 2008, with the goal of assessing the impact of the modified Blalock-Taussig (subclavian-to-pulmonary artery) versus Sano (right ventricle–to–pulmonary artery) shunt during the Norwood procedure on 12-month transplant-free survival. The ISV trial prospectively enrolled infants at 10 centers with any form of single ventricle lesion from August 2003 to May 2007 to assess the effect of angiotensin-converting enzyme inhibition on growth at 14 months of age. Both trials recorded subject characteristics in a standardized fashion at all hospitalizations and through 14 months of age. Medical and surgical data collected included cardiac anatomical details, surgeries performed, type and length of intraoperative and postoperative cardiac and respiratory support, perioperative and postoperative complications, and length of hospital stay. Demographic factors such as socioeconomic status and maternal education level were also recorded.

Fetal echocardiography

Subjects from either trial with available fetal echocardiograms were eligible for this ancillary study. Fetal MCA Doppler flow patterns were reviewed centrally by 1 of 2 investigators (I.W. and A.S.) blinded to ND scores for tracing quality. The peak systolic, end-diastolic, and the time averaged maximum velocities were remeasured, and the MCA-PI was calculated using a standard formula (see the online Appendix).

To account for differences attributable to gestational age (GA), MCA-PI z-scores were calculated using published norms[12] as previously described.[9] The MCA-PI is a surrogate measure for resistance within the cerebral vasculature with a lower PI estimating lower resistance. The MCA-PI was selected as the primary predictor instead of the resistance index, another commonly used measure (see the online Appendix), due to the availability of normal data allowing for z-score calculation, which is not available for the resistance index.

Neurodevelopmental testing

Subjects participating in the ISV and/or the SVR trial underwent standardized 14-month ND testing using the Bayley Scales of Infant Development, Second Edition (BSID-II).[13] To ensure consistency in testing across PHN sites, all local psychologists underwent centralized training and were certified by a single expert via review of videotaped sessions before study participation. The BSID-II is approved for the assessment of children ages 1 to 42 months and provides 2 summary scores: the Psychomotor Development Index (PDI) and the Mental Development Index (MDI). The normative mean ± SD for both the MDI and the PDI is 100 ± 15.

Statistical analysis

Data are reported as means with SDs or medians with ranges as appropriate. Preliminary associations between fetal cerebrovascular resistance and ND were assessed using the Pearson correlation coefficient between MCA-PI z-score from the initial fetal echocardiogram and MDI and PDI scores. To account for the variable number of fetal echocardiograms per subject and to minimize the likelihood of a type I error while maximizing our sample size, we limited these primary analyses to data recorded at the time of the first fetal echocardiogram. Differences in mean MDI and PDI scores among subjects with an MCA-PI z-score of less than −2 and subjects who always had an MCA-PI z-score of −2 or higher were evaluated using the Student *t* test. To control for variables that could confound or mediate the relationship between fetal cerebrovascular resistance and ND, we entered MCA-PI z-score into a multivariable regression model that included