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Cerebrovascular Blood Flow Dynamic Changes in Fetuses with Congenital Heart Disease

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Key Words
Brain development · Cerebrovascular circulation · Congenital heart disease · Fetal echocardiography · Heart function

Abstract
Objective: The aim of this study was to determine whether the type of congenital heart disease (CHD) or heart function influence fetal cerebrovascular blood flow dynamics. ***Methods:*** Doppler flow velocimetry was performed in the umbilical artery (UA) and middle cerebral artery (MCA), and the ratio of the UA pulsatility index (PI) to the MCA PI (U/C PI) was determined in 45 fetuses with CHD at 20–40 weeks' gestational age. The control group consisted of 275 healthy fetuses matched for gestational age. Individual PI measurements were converted into Z-scores for statistical analysis. ***Results:*** Fetuses with CHD (n = 45) had an increased UA PI ($p = 0.001$) and U/C PI ($p < 0.001$) when compared to controls. There was no significant difference in the MCA PI between fetuses with CHD (n = 45) and controls (n = 275), while fetuses with CHD complicated by congestive heart failure (CHF) (n = 10) had a decreased MCA PI ($p < 0.001$) compared to controls. ***Conclusions:*** The lower PIs observed in the MCA of fetuses with CHD complicated by CHF represents a marker of cerebral vasodilation that is due to cerebral hypoxemia and limiting perfusion. The heart function and type of CHD have an impact on fetal cerebrovascular blood flow distribution and this may contribute to the cause of abnormal neurologic development in these fetuses.

Introduction

It has been shown that brain lesions occur in a number of patients with congenital heart disease (CHD) who have undergone surgical correction or palliation in infancy [1, 2]. Most of these studies have focused on operative or postoperative factors as predictors of outcome, such as different surgical strategies, varying duration of cyanosis, and types of medical management. However, many infants with CHD have a propensity for poor neurodevelopmental outcome that is independent of cardiac surgical intervention. Neurologic abnormalities have been identified preoperatively in many of these patients [3–8]. Neuroimaging [4], neuropathologic [2], and clinical studies [3, 5] have demonstrated postnatal, pre-surgical neurological abnormalities in neonates with CHD. Mahle et al. [6] identified structural and ischemic lesions by MRI in 17 and 24% of patients with CHD prior to surgery, respectively. Donofrio et al. [7] published a prospective study of

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Table 1. Cardiac diagnoses according to the anatomic subtypes of the study group

Diagnosis	Fetuses, n
Normal	275
LSOL	11
Hypoplastic left-heart syndrome	5
Aortic stenosis	4
Aortic arch hypoplasia/coarctation	2
RSOL	16
Pulmonary atresia	4
Tetralogy of Fallot	4
Ebstein's anomaly	4
Tricuspid atresia	2
Pulmonary stenosis	2
MTC	18
Completed endocardial cushion defect	4
Double outlet right ventricle	3
Single ventricle	4
Truncus arteriosus	2
Transposition of great arteries	3
Others	2

LSOL = Left-sided obstructive lesions; HLHS = hypoplastic left-heart syndrome; RSOL = right-sided obstructive lesions; MTC = mixed type of CHD.

36 sonographically-diagnosed fetuses with CHD. They reported a decreased umbilical artery (UA) to middle cerebral artery (MCA) pulsatility index (PI) and a reduced head circumference measurement in a significant number of fetuses due to cerebral hypoxemia.

To date, there have been few studies investigating peripheral blood flow in fetuses with congenital heart defects, and most have aimed to assess the prognostic value of an abnormal UA PI [3, 9–13]. These studies have shown that umbilical arterial blood flow velocity waveforms in fetuses with isolated CHD do not show sufficient alterations to be of diagnostic value [9]. Furthermore, UA Doppler sonography is not clinically helpful in predicting fetal outcome [10]. There is an extremely limited body of literature that pertains to the topic of CHD and the in utero cerebrovascular response. Whether cerebrovascular blood flow dynamics change in fetuses with CHD has given rise to much controversy. Meise et al. [9] compared MCA PI in fetuses with CHD to normal controls, but found no significant difference. Kaltman et al. [11] showed that the type of CHD lesion significantly impacts cerebral blood flow and substrate delivery. Donofrio et al. [7] concluded that fetuses with CHD had diminished cerebral impedance for cerebral hypoxemia and that this was due to intracardiac mixing of oxygenated and deoxygenated blood. The aim of our study was to use MCA Doppler ultrasound as a surrogate measurement to determine whether the type of CHD or heart function affects fetal cerebral blood flow.

Materials and Methods

Study Population

Approval for the study was obtained from the Ethics Committee and informed consent was obtained from the participants prior to beginning the study. 45 consecutive fetuses of singleton pregnancies with prenatally-diagnosed structural heart disease were included in the study between January 2002 and March 2007. The gestational age ranged from 20 to 40 weeks. In each case, the heart defect was confirmed after birth by pediatric cardiologists and/or autopsy (table 1). Fetuses with sonographically-diagnosed CHD during the aforementioned time period were designated as cases. Gestational age-matched fetuses (n = 275) in whom echocardiograms showed normal structure and function were selected as control fetuses. None of the pregnancies had signs of uteroplacental dysfunction. Inclusion for analysis was determined according to the type of CHD: (1) left-sided obstructive lesions (LSOL; n = 11); (2) right-sided obstructive lesions (RSOL; n = 16); (3) mixed type of CHD (MTC; n = 18), and whether the CHD was complicated by congestive heart failure (CHF): (1) CHD complicated by CHF (n = 10), and (2) CHD without CHF (n = 35). Exclusion criteria included the following: (1) gestational age <20 weeks or >40 weeks; (2) cardiac lesion other than one listed in the inclusion criteria; (3) identifiable extracardiac malformation; (4) identifiable chromosomal abnormality; (5) persistent non-sinus rhythm; (6) maternal condition that might affect fetal hemodynamics, such as gestational diabetes, thyroid disease, or preeclampsia; (7) monochorionic twins; (8) fetal anemia, and (9) signs of uteroplacental dysfunction (birth weight <10th percentile, small for gestational age, and/or abnormal uterine artery Doppler flow velocity waveforms). The definition of fetal CHF is similar to that after birth (i.e., inadequate tissue perfusion and inadequate cardiac output resulting in a series of complex reflexes and adaptations to improve forward flow or to direct flow to vital organs). The clinical state of CHF in the fetus can be characterized by findings in five categories obtained during the ultrasonographic examination: (1) hydrops; (2) umbilical venous Doppler; (3) heart size; (4) abnormal myocardial function, and (5) arterial Doppler (table 2). Each of these categories is assigned 2 points on a 10-point scoring system for assessment of the cardiovascular system [14]. This profile is deemed normal if the score is 10; signs of cardiac abnormalities result in a decrease in the score from normal. The average score in fetuses in the CHD with CHF group was 6.3.

Fetal Echocardiography

Doppler recordings were obtained from the UA and MCA during a fetal heart rate of 120–160 bpm using a 3.0- or 5.0-MHz phased-array sector scanner (Aloka SSD 5500; Aloka Co., Ltd.,

Table 2. Summary of cardiovascular profile score

Hydrops	
Effusion	–1 point
Skin edema	–2 points
Venous Doppler	
Atrial reversal in ductus venosus	–1 point
Atrial pulsations in umbilical vein	–2 points
Heart size	
C/T area ratio >0.35	–1 point
>0.5 or <0.20	–2 points
Cardiac function	
RV/LV shortening fraction 0.28	–1 point
Tricuspid valve regurgitation (holosystolic)	–1 point
Mitral regurgitation	–1 point
Pulmonary or aortic valve regurgitation	–1 point
Valve regurgitation dP/dt 400 mm Hg/s	–2 points
Ventricular hypertrophy	–1 point
Monophasic filling	–2 points
Umbilical artery	
Absent end-diastolic velocity	–1 point
Reversed diastolic velocity	–2 points

The maximum deduction for each category is 2 points.

Japan). Multiple two-dimensional views were obtained to evaluate fetal heart anatomy. Doppler interrogation was performed to evaluate valve competence, stenosis, and shunting. The M-mode was used to assess cardiac rhythm and heart rate. Doppler color flow mapping was used to identify the umbilical vessels, the circle of Willis, and the MCA. Pulsed-wave Doppler was used to determine blood flow velocities in the UA and MCA. All Doppler studies were performed in the absence of gross fetal movements or breathing. The MCAs were identified using color Doppler imaging on a transverse section of the fetal head below the plane used for the biparietal diameter measurement. Pulsed Doppler studies were performed in the free loop of the UA. The Doppler sample gate was placed so that the angle of insonation was close to 0. For measurement of all PIs, the pulsed Doppler gate was placed on the vessel under investigation until the characteristic Doppler signal was obtained for a minimum of five consecutive waveforms. The images were frozen and the PI values were calculated from at least three consecutive waveforms and averaged (PI = [systolic velocity – diastolic velocity]/mean velocity). The ratio of the UA PI to the MCA PI was designated U/C PI.

Statistical Analysis

To compare Doppler results independent of gestational age, Z-score conversions were done [11, 12, 15] and individual PI measurements were converted into Z-scores based on published, normative data from a large Chinese population of healthy fetuses [16]. Because the data were not normally distributed, we used nonparametric measures of distribution (median and interquartile ranges) and Kruskal-Wallis with post-hoc Mann-Whitney U testing to determine differences between the two groups. Significance was defined at an α level of 0.05.

Table 3. Pulsatility index Z-scores of the CHD and the control group

Type of CHD	Controls	CHD group
Fetuses, n	275	45
Z-score		
UA PI	–0.25 (–0.89 to 0.33)	0.45 (–0.50 to 1.53)#
MCA PI	–0.30 (–0.83 to 0.41)	–0.50 (–1.19 to 0.40)
U/C PI	–0.27 (–0.69 to 0.46)	0.99 (0 to 1.77)*

Z-scores as quotients, data are expressed as the median (interquartile range). CHD = Congenital heart disease; MCA = middle cerebral artery; UA = umbilical artery; PI = pulsatility index; U/C PI = the ratio of UA PI to MCA PI.

# $p < 0.001$ vs. controls; * $p < 0.001$ vs. controls.

Results

The mean PI Z-scores for the UA and MCA and the mean U/C PI ratio Z-scores are shown in tables 3–5. There was a significant difference in the UA PI ($p = 0.001$) and the U/C PI ($p < 0.001$) values between the groups, with the CHD group having a higher UA PI and U/C PI compared to the controls. There was not a significant difference in the MCA PI values between the CHD groups and the controls ($p = 0.14$).

Among the diagnostic groups according to heart function, the CHD complicated by CHF group had a lower MCA PI ($p = 0.001$) when compared to the controls, while among the diagnostic groups according to the anatomic subtypes, there was not a significant difference between the diagnostic groups. Only the LSOL group had a relatively lower MCA PI than the controls, but not to a significant degree ($p = 0.10$).

Discussion

Because brain development is dependent on substrate and oxygen delivery, autoregulatory mechanisms in the fetus alter cerebrovascular impedance to counteract changes in substrate and oxygen delivery. Based on animal studies, it has been shown that fetal hypoxemia leads to blood flow redistribution [17–19]. Doppler studies in human fetuses also have confirmed this fetal adaptation to hypoxia [20]. This phenomenon, known as the 'brain-

Table 4. MCA PI Z-scores by diagnosis according to the anatomic subtypes of the study group

Type of CHD	Controls	LSOL	RSOL	MTC
Fetuses, n	275	11	16	18
Z-score				
MCA PI	–0.30 (–0.83 to 0.41)	–0.50 (–1.77 to 0.33)*	–0.20 (–0.69 to 1.35)	–0.85 (–1.36 to 0.49)

Z-scores as quotients, data are expressed as the median (interquartile range). LSOL = Left-sided obstructive lesions; RSOL = right-sided obstructive lesions; MTC = mixed type of CHD; MCA-PI = middle cerebral artery pulsatility index.

* p = 0.10 vs. controls.

Table 5. PI Z-scores by diagnosis according to the heart function

Type of CHD	Controls	CHD with CHF	CHD without CHF
Fetuses, n	275	10	35
Z-score			
MCA-PI	–0.30 (–0.83 to 0.41)	–1.69 (–2.70 to 1.31)*	–0.10 (–0.74 to 0.66)

Z-scores as quotients, data are expressed as the median (interquartile range). CHF = Congestive heart failure; other abbreviations as in tables 1 and 3.

* p < 0.001 vs. controls.

sparing effect', is characterized by an increase in blood flow to the brain, heart, and adrenal glands. A similar cerebral autoregulatory mechanism may also be induced in fetuses with CHD, resulting in a compensatory increase in blood flow which could be documented by Doppler ultrasound.

The fetus with CHD displayed changes in cerebral impedance for two reasons. First, the lower oxygen content of blood delivered to the brain. The CHD lesions potentially cause intracardiac mixing of oxygenated and deoxygenated blood. As a result, the oxygen content of blood delivered to the brain is low and the cerebral vasodilation that occurs in the fetus with CHD is an attempt to compensate for cerebral hypoxemia. Modena et al. [12] reported that fetuses with congenital heart defects are significantly more likely to have decreased cerebrovascular impedance due to intracardiac mixing of oxygenated and deoxygenated blood (p = 0.023). The relatively small number of patients in the non-mixing group prevented demonstrating statistical significance. Jouannic et al. [21] found the lower PIs (p < 0.001) observed in the MCA of fetuses with transposition of the great arteries was an indicator of hypoxemia and/or hypercapnia restricted to areas perfused by the preisthmus aorta. The second possible reason may be related to decreased cerebral perfusion. In the fetus with a normal two-ventricle cardiac anatomy, intracardiac streaming results in the preferential delivery of highly oxygenated ductus venosus blood across the foramen ovale to the left ventricle, ascending aorta, and cerebral circulation. This phenomenon is absent or limited in the fetus with obstructive lesions. In a cross-sectional study, Kaltman et al. [11] studied 58 fetuses with CHDs and found that fetuses with a hypoplastic left heart (HLHS), which had lower MCA PIs (p = 0.001), demonstrated decreased cerebrovascular impedance.

We also differentiated heart lesions in the CHD group according to the various anatomic subtypes: (1) LSOL; (2) RSOL, and (3) MTC; however, we found no significant difference in MCA PI values between these diagnostic groups (p = 0.10). We only found that in fetuses with LSOL, the MCA PI was lower than in normal fetuses, but not to a significant degree (p = 0.10), while Kaltman et al. [11] found that fetuses with HLHS had a lower MCA PI

($p = 0.001$). We postulated that this was due to the severity of obstructive lesions, which was inversely proportional to the amount of cerebral blood delivery. For example, fetuses with LSOLs with antegrade blood flow in the ascending aorta have cerebrovascular impedance intermediate between normal fetuses and fetuses with HLHS. With preservation of some antegrade blood flow, there is a need for some degree of autoregulatory compensation, but not to the extent seen in fetuses with HLHS [11].

Based on heart function, fetuses with CHD complicated by CHF were shown to have a significantly lower MCA PI than controls ($p < 0.001$). The definition of fetal CHF is similar to that after birth (i.e., inadequate tissue perfusion and inadequate cardiac output results in a series of complex reflexes and adaptations to improve forward flow or to direct flow to vital organs, such as the brain) [14]. This state can be described as a deficiency of flow of blood to the tissues and certain reflexes are triggered for the survival of the fetus, such as an increase in blood flow to the brain. Therefore, we postulated that heart function in fetuses with CHD significantly impacts cerebrovascular blood flow dynamics. The first reason for this effect on cerebrovascular blood flow dynamics is that cerebral perfusion decreases proportionally to the limiting perfusion to the whole body; the second reason is the lower oxygen content of blood delivered to the brain. Due to the pulsation of the umbilical vein and tricuspid regurgitation, the highly oxygenated ductus venosus blood across the foramen ovale to the left ventricle, ascending aorta, and cerebral circulation is limited, which contributes to cerebral hypoxemia.

Our research demonstrates a significant difference between the UA PI of all fetuses with CHD compared to healthy fetuses ($p < 0.001$), which confirms the results of Meise et al. [9] and Al-Gazali et al. [10]. Fetuses with chromosomal, other extracardiac, or placental abnormalities showed significantly higher UA PI values [9]. These cases were excluded from the study group so that the abnormal UA flow profiles were most likely attributable to the upstream problems of the cardiac defect. We presume that the pulsatile flow towards the placenta is altered by retrograde perfusion of the obstructed arterial system via the ductus arteriosus, resulting from severe left- [9] or right-sided [15] obstruction of the outflow tracts. Under these circumstances, the percentage of reverse perfusion may diminish the diastolic blood flow in the descending aorta and UA to an extent that the umbilical PI becomes elevated. The other reason is associated with semilunar valve insufficiencies leading to increased pulsatility in the descending aorta and UA by an impaired 'windkessel function'. For example, fetuses with Ebstein's anomaly and severe pulmonary insufficiency had diastolic reversed blood flow in the pulmonary trunk, ductus arteriosus, descending aorta, and UA. Similarly, fetuses with an insufficient truncal valve had systolic forward flow and significant reversed flow in the descending aorta and the UA. It is important to note that the UA PI cannot be used as a predictor for fetal outcome [10], which was confirmed by Copel et al. [13], who found that all 3 fetuses with elevated UA PIs included in their study had fatal disease, while 5 of 8 fetuses with fatal anomalies had normal UA PI values.

Elevation in the U/C PI has been suggested to be a sensitive marker of the 'brain-sparing effect' in fetuses with placental insufficiency and intrauterine growth restriction [22]. Similarly, the current study supports a trend towards a significant elevation in the U/C PI ($p < 0.001$) when compared to controls. However, it is not known whether this represents a 'brain-sparing effect' in the traditional sense. The fetuses with placental insufficiency or intrauterine growth restriction had structurally normal hearts, and downstream resistance was not influenced by the hemodynamic effects of upstream obstructive cardiac lesions. To mathematically elevate the U/C PI ratio to the point at which the value becomes abnormal, a fetus must have either a significant decrease in cerebrovascular impedance while the umbilical impedance remains stable, or a significant increase in umbilical impedance while the cerebral impedance remains stable. We observed a significant elevation of the UA PI ($p < 0.001$), but no significant difference in the MCA PI ($p = 0.10$) in fetuses with CHD compared to normal controls. Thus, the elevation of the U/C PI is due to an increase in umbilical impedance, not to a decrease in cerebrovascular impedance. The use of the elevation in the U/C PI as an indication of the 'brain-sparing effect' may be inappropriate when considering cases of CHD. The use of relative resistance in the cerebral versus umbilical arterial vasculature as an indication of the 'brain-sparing effect' may be inappropriate in the setting of CHD and should be studied in a larger sample.

There were several limitations to this study, one of which was that the subgroups were relatively small and may have prevented of the demonstration of statistical significance in certain comparisons. In addition, outcome data, such as head circumference, birth weight, and the MRI scans of the brain, were not obtained due to our inability to follow the antenatal and postnatal progress of these fetuses, which limited conclusions regarding the

neurologic aspect of infant development. We conclude that fetuses with CHDs are more likely to show decreased cerebrovascular impedance than fetuses with normal cardiac structure.

Presumably, our findings represent diminished cerebral oxygenation and decreased cerebral perfusion in fetuses with CHD. The function of the heart and the type of obstructive lesions modify fetal cerebrovascular impedance. These alterations in cerebrovascular blood flow distribution may be associated with the postnatal, preoperative neurologic abnormalities found in some newborns with complex CHD. Further study that would include a large multicenter prospective study that follows these fetuses through their early school years would be important in establishing the values of the MCA PI of specific cardiac lesions and allow for the correlation of the values of the MCA PI of specific cardiac lesions with appropriate neurodevelopmental evaluation of the infant.

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