Int J Clin Exp Med 2016;9(2):1382-1388
www.ijcem.com /ISSN:1940-5901/IJCEM0017610

Original Article

The impact of severe left heart obstruction with retrograde aortic arch flow on fetal cerebral and placental blood flow

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Received October 10, 2015; Accepted December 25, 2015; Epub February 15, 2016; Published February 29, 2016

Abstract: Purpose: The aim of this study was to explore the impact of anatomical subtypes in fetal heart disease on decreased middle cerebral artery (MCA) pulsatility index (PI) and head growth. Methods: The fetal echocardiograms of pregnancies with fetal hypoplastic left heart syndrome (HLHS; n=28) with and without anatomic coarctation, isolated severe aortic coarctation (n=28), D-transposition of the great arteries (TGA; n=28) and pulmonary outflow tract obstruction without forward flow across the pulmonary valve (POTO; n=28) were retrospectively reviewed. The data of MCA and umbilical artery (UA) PI, the cerebral placental ratio (CPR), and neonatal head circumference (HC) were collected and compared. Results: Significantly lower MCA-PI, higher UA-PI and lower CPR were found in fetuses with HLHS and isolated coarctation of the aorta. No difference was found in HLHS fetuses with or without anatomical coarctation. Positive correlation was found on between MCA-PI and HC in newborns with HLHS (r=0.232, P=0.046) or severe coarctation of aorta (r=0.418, P=0.022). Conclusions: Severe left heart obstruction with retrograde aortic arch flow influences fetal cerebral blood flow. Association was found between MCA-PI and head growth.

Keywords: Hypoplastic left heart syndrome, coarctation, fetal hemodynamics, middle cerebral artery flow

Introduction

Structural and functional brain abnormalities were observed in children with congenital heart disease (CHD), even at birth before initial surgical treatment [1-3]. Altered cerebral blood-flow pattern might be responsible for these abnormalities. Blood flow delivery to brain in utero was variable and may be influenced by different type of CHD [4-6]. The factors such as ventricle number (one or two), systemic ventricular morphology (right or left) and the nature of flow into the aorta (obstructed or unobstructed) may influence the pathways and the patterns of blood flow delivery to the aorta, and finally change the cerebral circulation.

Abnormal cerebral Doppler measurements could be found in the fetuses with severe forms CHD. It is reported cerebral to placental resistance ratio (CPR) was less than one in fetuses with complex brain-sparing CHD [5]. In the setting of Left- and right-sided obstructive lesions, reduced and increased middle cerebral artery pulsatility index (MCA PI) was respectively observed [6]. Currently, fewer evidence has been proposed that these changes may impact cerebral development frequently observed in affected infants and children [4-8].

The aim of this study was to explore the impact of anatomical subtypes in fetal heart disease on decreased middle cerebral artery (MCA) pulsatility index (PI) and head growth.

Patients and methods

All pregnancies complicated with HLHS, isolated aortic coarctation, D-transposition of the great arteries (TGA) or lesion associated with severe pulmonary outflow tract obstruction without forward flow across the pulmonary valve (POTO) from January 2011 to January 2015 were included in this study. This study was

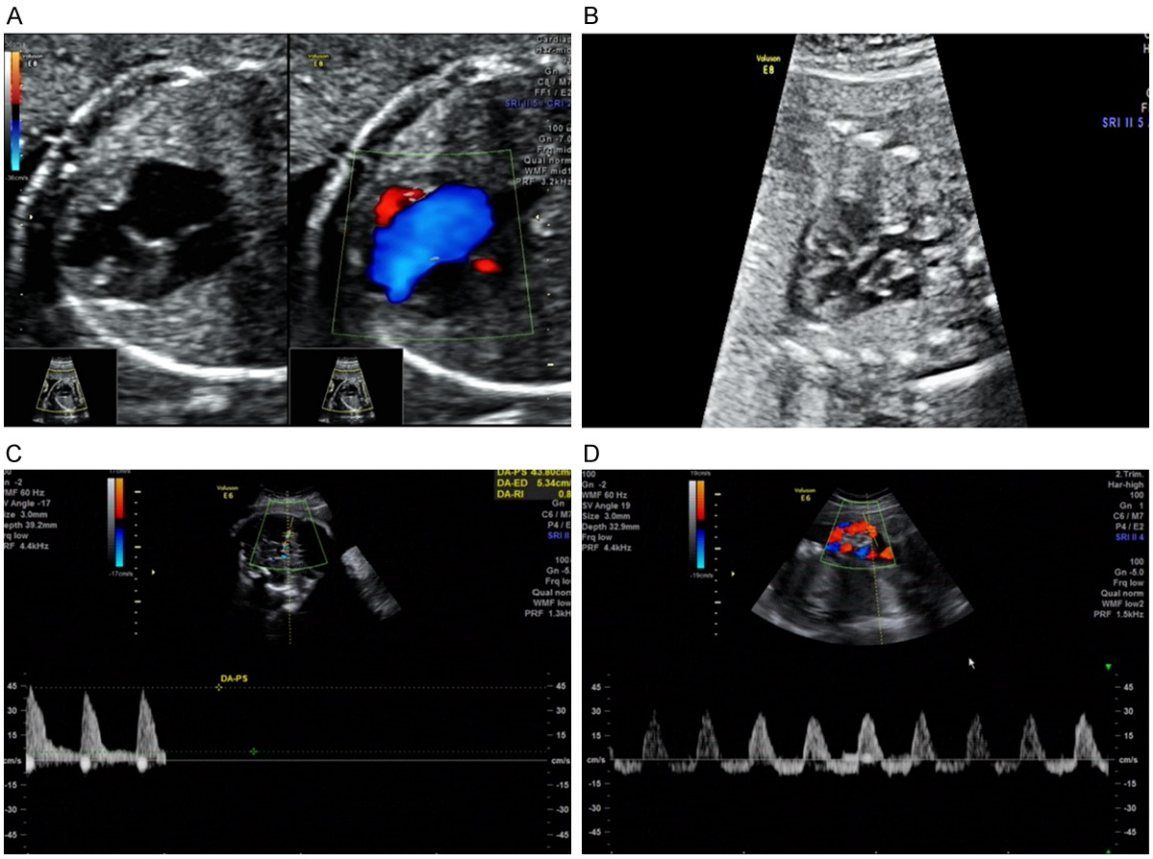

Figure 1. Echocardiographic images of fetal hypoplastic left heart syndrome (HLHS). (A) Cardiac asymmetry with smaller left atrium, left ventricle and venticular septal defect; (B) Echo enhancement with aorta dysplasia. A higher middle cerebral artery pulsatility (MCA-PI) (C) and umbilical artery (UA)-PI with reversed flow (D) were found in the same fetuses 2 weeks later.

approved by Institutional Review Board of Our hospital.

The echocardiograms data of fetal and preoperative neonatal and clinical data of maternal and neonatal were restrospectively reviewed.

Doppler velocity profiles of the umbilical artery (UA) just before cord insertion and those of the MCA were evaluated when fetal cardiac anatomy was ascertained. The PI was calculated as follows: PI = (peak systolic velocity-end-diastolic velocity)/mean velocity. The cerebroplacental ratio (CPR) was calculated as MCA-PI/UA-PI. All the data were transformed into Z-scores based on the gestational age according to previously published normalized data [9, 10]. When multiple measurements were performed in one pregnancy, the most recent data was used in the study. We also collected birth weight and head circumference (HC) at birth from the medical records and these data was also converted to a Z-score according to the normalized data [11, 12].

Statistical analysis

All the statistical analyses were performed with SPSS 18.0. Data was expressed as mean ± SD. One way ANOVA and student t test was employed to examine the difference in multiple groups and between groups, respectively. Linear regression and Pearsons correlation coefficient were used to assess the relationship between MCA-PI and HC at birth. $P<0.05$ was considered as statistical significance.

Results

Demographic data

A total of 112 fetuses with CHD were included in this study. Among them, 28 with HLHS (16 with and 10 without anatomical coarctation, and 2 with indeterminate status of the distal

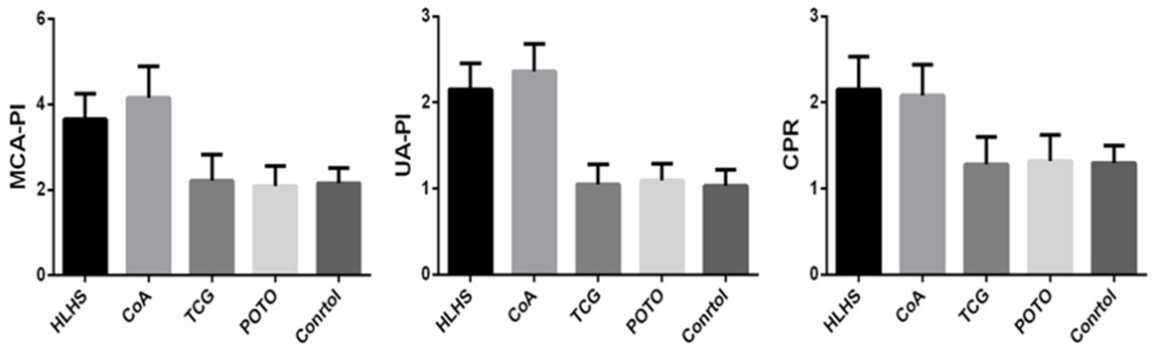

Figure 2. Comparison of the cerebral and placental blood flow parameters in fetuses with congenital heart disease and controls. Middle cerebral artery pulsatility (MCA-PI) was significantly lower in fetuses with hypoplastic left heart syndrome (HLHS) and isolated coarctation of the aorta (CoA) compared with controls. A significantly higher umbilical artery (UA)-PI was observed in fetuses with HLHS and isolated CoA than the controls. Cerebroplacental ratio (CRP) was lower in fetuses with HLHS and isolated CoA compared to the controls. POTO: severe pulmonary outflow obstruction; TGA: D-transposition of the great arteries. All the data was expressed as Z-scores.

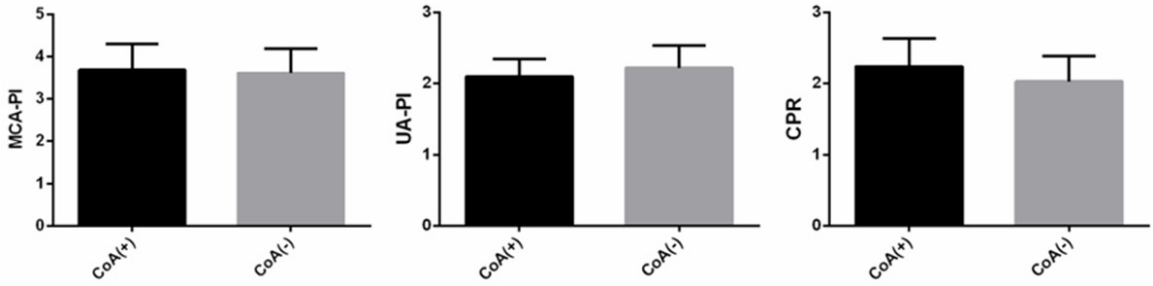

Figure 3. No significant difference was found on middle cerebral artery pulsatility (MCA-PI), umbilical artery (UA)-PI and cerebroplacental ratio (CRP) in hypoplastic left heart syndrome fetuses with or without anatomical coarctation (CoA).

arch); 28 with isolated coarctation of the aorta (18 with forward flow through the distal aortic arch, and 10 with reversed flow through distal aortic arch); 28 with TGA; and 28 with POTO (**Figure 1**). One hundred twelve gestational age-matched healthy fetuses with fetal echocardiography data were included as control. No significant difference was found on the gestational age at the time of echocardiography between CHD fetuses and controls. A significantly smaller Z-score was found on the birth weight in fetuses with HLHS and coarctation than the controls.

Comparison of MCA-PI, UA-PI and CPR in different group of fetuses

A significant difference on MCA-PI, UA-PI and CPR was observed among different types of CHD and controls (all $P<0.01$). A significant lower MCA-PI ($P<0.01$), higher UA-PI ($P<0.01$) and lower CPR ($P<0.05$) Z-score was found in fetuses with HLHS or isolated coarctation of the aorta than the controls (**Figure 2**). Our results further showed that no significant difference was found on MCA-PI, UA-PI and CPR in the fetuses with or without anatomical coarctation (**Figure 3**). Moreover, we divided the fetuses with isolated coarctation of the aorta with retrograde distal aortic arch flow and antegrade distal arch flow, and our results showed that a significantly lower MCA-PI, higher UA-PI and lower CPR was found in the fetuses with reversed flow in the distal aortic arch flow compared with controls (all $P<0.05$), whereas significantly higher UA-PI and lower CPR was found between the fetuses with forward and reversed flow ($P<0.05$ for both, **Figure 4**).

HC at birth in different group of fetuses

Among all the groups, a significantly smaller HC at birth was found in newborns with isolated coarctation of the aorta and TGA when com-

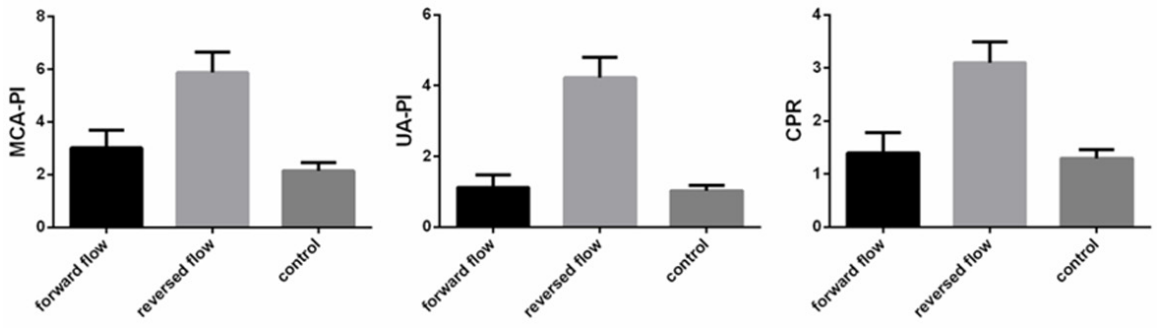

Figure 4. Z-score of middle cerebral artery pulsatility (MCA-PI), umbilical artery (UA)-PI and cerebroplacental ratio (CRP) in fetuses with coarctation, with or without forward flow through distal aortic arch. MCA-PI and CPR were decreased and UA-PI was increased () in fetuses with reversed flow in the distal aortic arch.

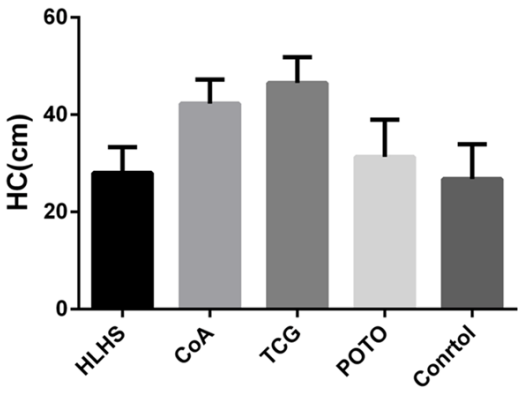

Figure 5. Head circumference (HC) at birth. Smaller HC at birth was found in newborns with coarctation of the aorta (CoA) and those with D-transposition of the great arteries (TGA) than the controls. HLHS: hypoplastic left heart syndrome; POTO: severe pulmonary outflow obstruction.

pared to the controls (P<0.01, **Figure 5**). The mean HC at birth in newborn with POTO was smaller than the controls, but no significant difference was found. We further performed the correlation analysis, weak correlation was found between MCA-PI and HC at birth in fetuses with HLHS (r=0.232, P=0.046) or severe coarctation of aorta (r=0.418, P=0.022) (**Figure 6**).

Discussion

Multiple factor such as resistance difference between vascular beds upstream and downstream of the artery, artery properties, fetal heart rate and cardiac output could influence the arterial blood flow pulsatility, which was assessed by Doppler [13, 14]. In the setting of structural heart disease, decreased cerebral oxygen content, abnormal cardiac output, cerebral blood flow could be impeded by the anatomical substrate and difference vasular resistance between body and placenta could result in the change of MCA-PI. In present study, we found that significantly lower MCA-PI, higher UA-PI and lower CPR n fetuses with HLHS and isolated coarctation of the aorta compared to the controls. Moreover, associations were found between MCA-PI and HC in newborns with HLHS or severe coarctation of aorta. Our results demonstrated that severe left sided heart obstruction with retrograde aortic arch flow influences fetal cerebral blood flow.

Consistent with previous report, we did not obeserve a significant difference on MCA-PI between those with and without distal arch obstruction in HLHS. Our results suggested that retrograde arch flow could result in less blood flow to the fetal brain, causing a potential brain-sparing phenomenon. Increased UA-PI, which may be caused by placental pathology [15] or reduced fetal cardiac output [16] in HLHS, may contribute further on MCA-PI reduction.

Previous reports have shown that left heart obstruction is associated with reduced fetal MCA-PI [17], and our results here demonstrated a consistent conclusion on the relationship between between the direction of distal arch flow and cerebral arterial flow. Moreover, association was also observed between isolated coarctation with retrograde distal arch flow and reduced MCA-PI, which was comparable to that of fetuses with HLHS. These results combing with reduced cardiac output in fetal HLHS could suggest that reduced blood flow to the fetal brain itself may be important in cerebral vascu-

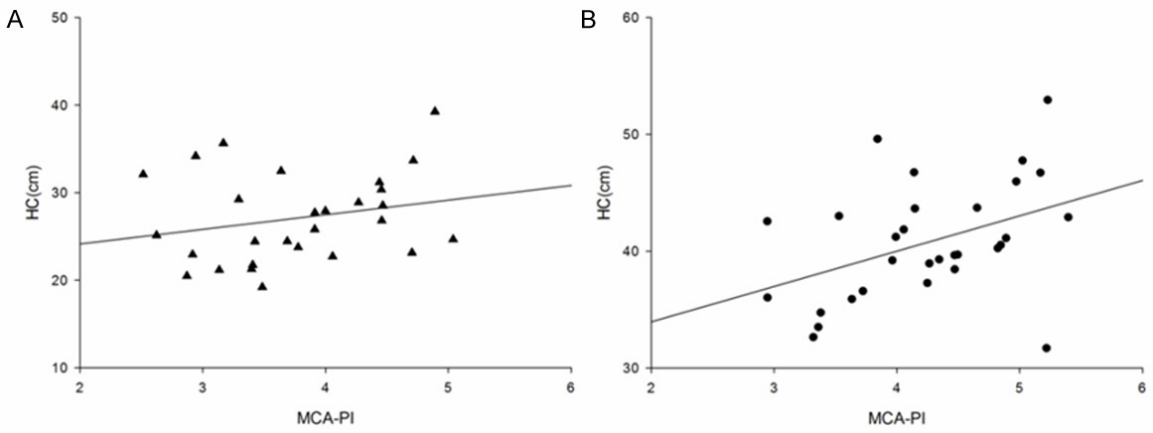

Figure 6. Correlation between middle cerebral artery pulsatility (MCA-PI) and head circumference (HC) at birth. In fetuses with reversed flow in the distal aortic arch including hypoplastic left heart syndrome (HLHS) (A) and severe coarctation alone (B).

lar regulation. Consistent with this conclusion, previous study has demonstrated that reduced output to the fetal brain alone results in the brain-sparing phenomenon [18]. However, we did not measure the oxygen delivery, hence we could not confirm that change in cerebral blood flow in severe left heart obstruction could result in sufficient oxygen delivery.

Moreover, the findings in fetuses with POTO and TGA further suggested that oxygen content itself is not the sole driving force to cerebral vasodilation in severe left heart obstruction. In the setting of severe POTO with retrograde ductal flow and intracardiac mixing, the cerebral oxygen content might be comparable with that of HLHS; however, normal cerebral blood flow through the large fetal aorta could be expected due to the full combined cardiac output. A recent study revealed elevated MCA-PI compared with normal fetuses in the setting single ventricles with POTO [19]. Normal aortic outputs and driving force of blood flow to the fetal brain, but lowest PaO_2 was expected in fetuses with TGA. However, normal cerebral Doppler profiles in fetal TGA were found in our study, which was consistent with the work of others [4]. However, study by Jouannic et al showed lower PI in fetal TGA [20]. Furthermore, several early studies have demonstrated that changes in blood flow when the cerebral vascular bed responds significantly to severe fetal hypoxia, suggesting of brain-sparing [18, 21, 22], however, it is uncertain that the difference in PaO_2 of the cerebral vascular blood is sufficient in TGA to consistently alter cerebral blood flow.

Since altered MCA-PI before birth in the setting of structural heart disease may contribute to adverse neurodevelopmental outcomes and a previous fetal magnetic resonance imaging (MRI) study has shown the association between the absence of antegrade blood flow in the distal arch inHLHS and significantly lower levels of N-acetylaspartate/choline [23]. Therefore, we tried to determine there was a relationship between altered cerebral Doppler and head growth. In severe left heart obstruction, a weakpositive correlation was found between fetal MCA-PI and HC at birth. This result suggests that there is a relationship between cerebral blood flow and cerebral development in this anatomic subgroup. We assume that the changes in MCA-PI in severe left heart obstruction reflect cerebral vasodilation that occurs in an effort to maintain sufficient blood flow; however, Szwast et al recently suggested that inadequate flow in late gestation could be presented when MCA-PI is the lowest relative to normal fetuses during a time when keycerebral maturational processes are occurring [19]. Although we did not observe a significantly smaller HC in the neonates with HLHS than the other type of CHD, correlation between reduced MCA-PI and neonatal HC suggests that the changes observed before birth in cerebral blood flow could result in at least the preoperative changes in HLHS.

There are also some limitations in our study. Relative smaller could result in data bias. The properties of retrospective review of this study could lead to incomplete information on long-

term effect on the neurodevelopment, and what we presented here were only immediate results. Further translational and clinical studies are needed at this time to examine the influence of blood flow, PaO_2 content of cerebral blood and O_2 delivery on fetal brain metabolism and long-term neurodevelopmental outcome.

In conclusion, our results demonstrated that severe left heart obstruction with retrograde aortic arch flow in utero could result in MCA-PI decreasing, which positively correlates with head growth. Altered MCA flow in fetal HLHS was not caused by anatomical arch obstruction in HLHS fetuses. Moreover, retrograde arch flow reflecting brain-sparing and reduced left heart output is also correlated with lower MCA-PI in the setting of isolated coarctation. It is necessary to perform neurodevelopmental follow up to determine the clinical relevance of MCA changes in severe fetal left heart obstruction.

Acknowledgements

This work was supported by grants from the Special Foundation of clinical disease diagnosis and treatment technology of Suzhou City (LCZX201302); the Medical Scientific Research Project of Jiangsu Provincial Bureau of Health (H201311); Key Disciplines of Suzhou Municipal Government (Reproductive Medicine); the Science and Education for Health Foundation of Suzhou for Youth (KJXW2012006).

Disclosure of conflict of interest

None.

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