Title

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Journal

Ultrasound in Obstetrics and Gynecology, 57(5)

ISSN

0960-7692

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Publication Date

2021-05-01

DOI

10.1002/uog.22024

Peer reviewed

HHS Public Access

Author manuscript

Ultrasound Obstet Gynecol. Author manuscript; available in PMC 2022 May 01.

Published in final edited form as:

Ultrasound Obstet Gynecol. 2021 May ; 57(5): 769–775. doi:10.1002/uog.22024.

Fetal Cerebral Vascular Response to Maternal Hyperoxia in Congenital Heart Disease: Effects of Cardiac Physiology

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Abstract

Objectives: Fetal cerebral vascular resistance is influenced by several factors in the setting of intact autoregulation to allow for normal cerebral blood flow and oxygenation. Maternal hyperoxia (MH) testing allows for acute alterations in fetal physiology and can be a tool to test cerebral vascular reactivity in late gestation fetuses. We utilized MH testing to evaluate cerebral vascular reactivity in fetuses with specific congenital heart disease (CHD).

Methods: This cross-sectional study compares fetuses with complex CHD to controls without CHD. CHD cases were grouped by physiology: left-sided obstructive lesion (LSOL), right-sided obstructive lesion (RSOL), and d-transposition of the great arteries (d-TGA). Subjects underwent MH testing during the 3rd trimester fetal echocardiogram. The pulsatility index (PI) was calculated for the middle cerebral artery (MCA), umbilical artery (UA) and branch pulmonary artery (PA). Comparisons were made between each CHD group and the control group at baseline and following MH.

Results: 60 pregnant women enrolled (CHD, n= 43; Control, n= 17). There were 27 fetuses with LSOL, 7 with RSOL and 9 with d-TGA. Mean gestational age was 33.9 weeks (95% CI: 33.6-34.2). At baseline, the MCA PI Z-score was lowest in the LSOL group (−1.8, 95% CI: −2.4, −1.2) compared with the control group (−0.8, 95% CI: −1.3, 0.3). In response to MH, the MCA PI Z-score increased significantly in the control and d-TGA groups but remained unchanged in the LSOL group and declined in the RSOL group. The change in MCA PI Z-score was significantly higher in the control group than the LSOL group (control= 0.9, 95% CI: 0.42, 1.4; LSOL= 0.12, 95% CI: −0.21, 0.45; p= 0.03). This difference was more pronounced in the LSOL subgroup with retrograde aortic arch flow. In all groups, the PA PI decreased at the same rate with MH and the UA PI was unchanged.

Conclusions: The fetal cerebral vascular response to MH varies based on underlying CHD diagnosis, suggesting that cardiovascular physiology may influence autoregulatory capacities of

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Financial Disclosure: The other authors have indicated they have no financial relationships relevant to this article to disclose.

Conflicts of Interest: The other authors have indicated that they have no conflicts of interest relevant to this article to disclose.

the fetal brain. Further studies are needed to determine clinical implications of these findings on long-term neurodevelopment in these at-risk children.

Keywords

congenital heart disease; maternal hyperoxia; middle cerebral artery pulsatility index; fetal cerebrovascular resistance; fetal echocardiogram

Introduction:

Cerebral vascular resistance, or impedance, is influenced by several factors including perfusion pressure,[1-3] metabolic activity,[4,5] carbon dioxide (CO2) [6-8] and oxygen.[9,10] The ability of the cerebral vasculature to respond to these factors reflects an autoregulatory function to titrate cerebral blood flow and oxygen delivery to oxygen consumption. Absence of cerebral autoregulation has been shown to be associated with increased risk of brain injury in premature neonates and is thus an important component of brain health.[11] Fetal hypoxia, that may occur in intrauterine growth restriction, leads to a decrease in fetal cerebral vascular resistance, which is thought to be a “brain-sparing” effect to compensate for decreased oxygen content and maintain adequate oxygen delivery to the brain.[12]

In the setting of complex congenital heart disease (CHD), abnormal underlying cardiovascular physiology may also influence cerebral vascular reactivity and overwhelm autoregulatory mechanisms,[13,14] which may contribute to brain immaturity and acquired brain injury observed in this population.[15-17] It remains unclear if compensatory mechanisms are adequate to maintain normal cerebral blood flow and oxygenation to the developing fetal brain. Similar to adult human studies, a prenatal provocation test can be useful to measure fetal cerebral vascular reactivity, which may shed light on the autoregulatory capacity of the fetal brain in the setting of various fetal disease states.

Brief administration of maternal hyperoxia (MH) is known to cause acute changes in fetal cardiovascular physiology based on both invasive and non-invasive measures.[18,19] Invasive studies have shown an increase in arterial oxygen content in the umbilical vein while ultrasound- based studies have shown a decrease in pulmonary vascular resistance and thus increased pulmonary blood flow, with no change in overall cardiac output. We utilized MH testing to determine the effects on cardiovascular physiology and specifically cerebral vascular reactivity in the middle cerebral artery (MCA) in fetuses with varying forms of CHD and compared them to fetuses without CHD. We hypothesized that fetuses with left sided obstructive disease would have a different response to MH testing compared with other CHD sub-types and control fetuses due to a combination of both decreased antegrade cerebral blood flow and oxygen content to the brain.

Participants and Methods:

This is a cross-sectional study conducted between March 2017-August 2019. Pregnant mothers with a fetal diagnosis of CHD requiring a neonatal intervention referred to the University of California San Francisco (UCSF) Fetal Cardiovascular Center were prospectively recruited to undergo brief MH testing in the third trimester. Exclusion criteria

consisted of known chromosomal or genetic abnormalities, twin gestation, extra-cardiac anomalies, growth restriction, significant utero-placental disease such as pre-eclampsia, and maternal disease. The control group consisted of healthy pregnant women with normal uteroplacental function, normal fetal cardiovascular anatomy and normal extracardiac anatomy. These subjects were prospectively recruited from the low-risk obstetric clinic at UCSF to undergo a voluntary fetal echocardiogram with MH testing in the 3rd trimester. Pregnancies were dated by the last menstrual period and dates confirmed by first trimester ultrasound. Informed consent was obtained from all mothers. The institutional committee on human research at UCSF approved this study protocol.

The study group consisted of fetuses with isolated CHD that would require a neonatal intervention and were sub-divided based on fetal cardiovascular physiology. The categories consisted of 1) left-sided obstructive lesions (LSOL) which included hypoplastic left heart syndrome (HLHS), coarctation or interruption of the aortic arch with or without a ventricular septal defect (VSD) and aortic stenosis, 2) d-Transposition of the great arteries (d-TGA) with or without a VSD, and 3) right-sided obstructive lesions (RSOL) resulting in either single or biventricular circulation including only fetuses with pulmonary atresia with or without a VSD. The LSOL group was further subdivided based on the predominate direction of flow in the transverse aortic arch (antegrade vs. retrograde). All fetuses with retrograde flow in the aortic arch had HLHS with aortic atresia. All cardiac lesions were confirmed after birth.

Fetal echocardiogram study:

All subjects (CHD and control) underwent a complete fetal echocardiogram in the 3rd trimester for research purposes.[20] This includes multiple tomographic views of the fetal heart according to the AIUM [21] and ISUOG guidelines[22] as well as color Doppler and pulsed-wave Doppler examination of the umbilical cord, venous structures, branch pulmonary artery (PA) and the MCA. Studies were performed on Sequoia S2000 or GE E10 ultrasound systems (Siemens, Mountain View, CA, USA and GE Medical Systems, Zipf Austria). A three-phased protocol was followed for each subject. After the complete fetal echocardiogram (baseline phase), mothers were administered 8L/min of oxygen via a non-rebreather mask at 100% FIO2 as previously described.[19,23,24] After 10 minutes of oxygen administration, additional images of the fetal heart, including color and pulsed-wave Doppler of the three circulatory beds of interest for this study: umbilical artery (UA), MCA and branch pulmonary artery (MH phase). After cessation of oxygen, additional images of the fetal heart were obtained limited to a qualitative assessment of function and color and pulsed-wave Doppler of the ductus arteriosus (recovery phase).

The branch PA with the best angle of insonation was sampled (right or left) as it entered the lung parenchyma with the same side being sampled during the MH phase. The images were stored digitally in standard DICOM format. A fetal cardiologist (S.P.) and an experienced fetal sonographer (Y.Z.) reviewed the echocardiograms. Vascular impedance, expressed as the pulsatility index (PI) was obtained from the MCA, PA and UA using the following equation: PI= (peak systolic velocity – end- diastolic velocity)/time averaged velocity, averaged over three cardiac cycles. The PI was calculated at baseline and the MH phase. The

MCA PI was converted to a Z-score for gestational age based on published normative data.[25] A higher PI denotes higher resistance or vasoconstriction, while a lower PI represents lower resistance or vasodilation. Combined cardiac output (CCO) was calculated using the following equation: CO= heart rate x (velocity time integral x valve area) at baseline and MH phase. The value was indexed to estimated fetal weight. Aortic and pulmonic valve annulus measurements were obtained by measuring from inner edge to inner edge at end-systole. Aortic and pulmonic velocity time integrals were planimetered and averaged over three cardiac cycles.

Statistical Analysis:

Characteristics of the four study groups (control, LSOL, RSOL, d-TGA) were compared using ANOVA including baseline PI values. Within each group, a paired t-test was performed to assess the change in PI from baseline to MH. The primary comparison measure was the change in PI from baseline to MH between each CHD group and the control group using unadjusted linear regression. A multi-variable analysis was then performed to compare the change in MCA PI between each CHD group and the control group adjusting for baseline MCA PI. This was performed *a priori* due to prior literature demonstrating a significant relationship between baseline MCA PI and change with MH in fetuses with HLHS.[23] A sub-analysis was performed comparing those with antegrade or retrograde flow in the aortic arch (among the LSOL group) to controls. Finally, given that each subject had two measurements for the MCA PI (baseline and MH), a repeated measures analysis was performed using generalized estimating equations adjusting for baseline MCA PI to compare the magnitude of change in MCA PI between each CHD group and the control group. P-values < 0.05 were considered statistically significant. All analyses were performed with STATA version 14.2 (Stata Statistical Software: Release 14, College Station, TX: Stat Corp LP).

Results:

During the study period a total of 60 pregnant women participated in the study (CHD, n= 43; Control, n= 17). In the CHD group 27 subjects had LSOL, 7 subjects had RSOL and 9 subjects had d-TGA. The specific CHD diagnoses included in this study are described in the supplemental table. Table 1 lists the demographic data by study group. The mean gestational age for all participants at the time of the fetal echocardiogram was 33.9 weeks (95% CI: 33.6-34.2). There was no significant difference in gestational age (p= 0.83) or estimated fetal weight (p= 0.18) at the time of the fetal echocardiogram among the four groups.

Table 2 lists the mean PI for the MCA, UA and branch PA at baseline and during the MH phase as well as the change in PI. Compared with the control group (mean MCA PI Z-score = −8, 95% CI: −1.3, −0.3), the baseline MCA PI Z-score was significantly lower in the LSOL group (mean MCA PI Z-score = −1.8, 95% CI: −2.4, −1.2; p= 0.01). The MCA PI Z-score increased significantly with MH in the control and d-TGA groups while it remained unchanged in the LSOL and RSOL groups. When comparing between groups, the change in MCA PI Z-score was significantly higher in the control group compared with the LSOL group (Control= 0.9, 95% CI: 0.42, 1.4; LSOL= 0.12, 95% CI: −0.21, 0.45; p= 0.03).

Similarly, the change in MCA PI Z-score was significantly different between the control and RSOL groups (control = 0.9, 95% CTO.42, 1.4; RSOL= −0.7, 95% CI: −2.1, 0.75, p= 0.002). The baseline PI in the branch PA (i.e. pulmonary vascular resistance) was similar among the four study groups as was the reactivity in response to MH. Among all four groups, the branch PA PI decreased significantly with MH at the same rate (Table 2). The UA PI was similar at baseline for all four study groups with no significant change noted in response to MH in any of the groups.

After adjusting for MCA PI Z-score at baseline, the change in MCA PI Z-score remained significantly different in the LSOL and RSOL group compared with controls. In particular, the absolute change in the LSOL group was 1.2 points lower (95% CI: −1.8, −0.6) compared with the control group (p< 0.001), while the absolute change in the RSOL group was 1.6 points lower (95% CI: −2.4, −0.74) compared with the control group (p< 0.001). To assess the magnitude of change in the MCA PI Z-score from the baseline to MH phase, a repeated measures analysis was performed for each group after adjusting for baseline MCA PI Z-score. Figure 1 depicts the change in MCA PI Z-score from baseline to MH. The degree of increase in MCA PI Z-score was significantly greater in the control group compared with the LSOL group (74.2% increase in the difference from baseline to MH, 95% CI: 0.18, 1.3, p= 0.01). The direction of change in the RSOL group was the opposite of the control group with a 60% decline in MCA PI Z-score from baseline to MH compared with controls (95% CI: −3.0, −0.2, p= 0.025). One subject in the RSOL group had heterotaxy with single ventricle anatomy, pulmonary atresia and infradiaphragmatic total anomalous pulmonary venous connections (TAPVC). Given that the response to MH may vary in the presence of TAPVC, we repeated the analysis by excluding this subject from the RSOL group and our results remained unchanged. In particular, the absolute change in the MCA PI z-score was 1.9 points (95% CI: −2.9, −0.1) lower compared with the control group (p< 0.001).

Among the LSOL group, 12 subjects had antegrade flow in the aortic arch while 15 subjects had retrograde flow. Within these groups, the MCA PI Z-score did not change among those with retrograde flow but did increase significantly in the group with antegrade flow similar to the control group (Table 3). Compared to the control group, the change in MCA PI Z-score was 1.6 points lower (95% CI: −2.2, −1.0) in the LSOL subgroup with retrograde flow (p < 0.001) after adjusting for baseline MCA PI Z-score. Similarly, the magnitude of change in MCA PI Z-score was significantly less in the LSOL subgroup with retrograde flow in the aorta as compared to the control group (Figure 2).

The pulmonary, aortic and combined cardiac outputs at baseline and with MH are listed in Table 4. Although not reaching statistical significance, the indexed combined cardiac output was lowest in the LSOL subgroup with retrograde aortic arch flow compared to controls (LSOL-retrograde= 342.9 cc/kg/min (95% CI: 281.3-404.6) vs. Controls= 423.2 cc/kg/min (95% CI: 281.3-404.6), p= 0.06). No significant difference was noted in indexed combined cardiac output or in the pulmonary and aortic output as a percentage of the combined cardiac output from baseline to MH for each group.

Discussion:

In this cross-sectional study, we demonstrate that the underlying structural anatomy and cardiovascular physiology play an important role in the cerebral vascular response to MH in the late gestation human fetus. In particular, fetuses with LSOL had very little cerebral vasoconstriction to maternal oxygen compared with controls, while fetuses with RSOL had a paradoxical response with evidence of vasodilation. These findings provide insight into the regulatory capacities of the fetal brain using brief oxygen administration to the mother as a tool to acutely alter physiology.

In the fetus without structural heart disease, chronic hypoxia as seen in fetal growth restriction (FGR) leads to development of the "brain-sparing" effect, characterized by low cerebral vascular resistance in the MCA[26] with high resistance in the UA. Brain-sparing pattern on Doppler interrogation has been shown to correlate directly with low umbilical venous PaO2 sampled immediately before delivery, [12] suggesting a direct link between low aortic PaO2 and decreased cerebral resistance. Consistent with our findings, fetuses with LSOL are known to exhibit similar MCA patterns with decreased cerebral vascular resistance compared to normal fetuses.[13,14] In both FGR and LSOL, decreased MCA pulsatility is thought to be a compensatory or auto-regulatory mechanism to maintain adequate cerebral oxygen delivery—allowing an increase in flow to compensate for the lower oxygen content. Though cerebral autoregulation has been shown to be intact in the late gestation lamb, [27] it remains challenging to determine the autoregulatory capacity of the human fetal brain using non-invasive tools, such as estimating resistance within the MCA by measuring the PI at a single timepoint. By direct sampling of human umbilical cord blood, it has been shown that maternal administration of oxygen can increase human fetal oxygen partial pressure.[28,29] Though administration of oxygen to mothers may also lead to decreased maternal pCO2, these changes are minimal and do not appear to transmit to the fetus. [30] Thus, the effects of MH appear to be related primarily to increasing circulating fetal oxygen tension. Temporarily manipulating the fetal blood oxygen content to raise the Pa02 of blood perfusing the brain may be expected to lead to cerebral vasoconstriction, and may thus give insight into the autoregulatory capacity in the brain of the CHD fetus.

In the present study, fetuses with LSOL and retrograde flow in the aortic arch had the least response to acute MH testing in the MCA PI compared with controls. Our study demonstrates that overall baseline cardiac output is lower in these fetuses as has been observed in fetal cardiac MRI studies.[31] In addition, fetuses with retrograde flow in the aortic arch lack the normal perfusion pressure or pulsatility to the brain provided by a ventricle, all of which can influence baseline cerebral vascular resistance and reactivity to oxygen. The lack of response to MH seen in this subgroup may be a result of low baseline cardiac output and reduced pulsatility resulting in a chronic state of maximal or near-maximal cerebral vasodilation in addition to decreased oxygen content. In this state, oxygen induced vasoconstriction (or autoregulatory capacity) is overwhelmed by the effects of changes in pressure rather than oxygen. In contrast, fetuses with normal cardiac output, pulsatility and perfusion pressure such as d-TGA[32] and controls, exhibit the normal response to oxygen in the MCA (i.e. vasoconstriction as noted by an increase in MCA PI). However, there is likely significant variability within the HLHS group as some may have adapted to a

chronic hypoxic and low output state with changes in cerebral oxygen consumption. A recent study utilizing acute MH testing among fetuses with HLHS found that baseline MCA PI strongly influences cerebral vascular reactivity to oxygen[23] and that some fetuses with HLHS can exhibit the normal response to oxygen (i.e. vasoconstriction with an increase in MCA PI), though there was a wide spectrum of HLHS variants and gestational age in the cohort studied.

Decreased cerebral vascular resistance with MH in the RSOL group was an unexpected finding but may have a physiologic explanation. In fetuses with RSOL, fetal echocardiographic studies demonstrate a lower than normal pulmonary vascular resistance, likely related to increased oxygen content of blood reaching the lungs.[33] Increased fetal circulating oxygen tension during MH testing may further decrease pulmonary vascular resistance, which leads to increased retrograde ductal shunting and a resulting steal phenomenon from the cerebral vasculature. This may be more pronounced in RSOL as compared to d-TGA given the lower baseline cardiac output in the RSOL group, particularly in fetuses with single ventricle anatomy. The decline in cerebral vascular resistance in this group may reflect a compensatory mechanism to maintain a normal degree of cerebral blood flow and suggests intact cerebral autoregulation.

Cerebral autoregulation in early neonatal life has been studied in the premature population. Utilizing a combination of blood pressure and cerebral saturations with near-infrared spectroscopy (NIRS) has allowed clinicians to non-invasively measure cerebral autoregulation at the bedside.[11] These tools have led to several studies identifying an association between abnormal cerebral autoregulation and different forms of brain injury in the preterm population, such as intraventricular hemorrhage and white matter injury secondary to a cycle of ischemia and reperfusion.[11,34] Recent studies utilizing similar techniques in full-term newborns with CHD have suggested absence of cerebral autoregulation in this population as well.[35] Furthermore, full-term newborns with CHD are known to have similar patterns of brain injury as premature newborns, namely white matter injury, even before undergoing cardiac surgery.[17,36]

Our study has some limitations. First, calculating cardiac output in a fetus by echocardiography is challenging and is open to measurement error due to the nature of the measurements and small structures. Second, pathologic studies of the placenta in the setting of severe CHD have revealed vascular and morphologic abnormalities[37,38]. These issues can theoretically affect placental delivery of oxygen and influence our findings. Finally, although this is the largest study evaluating fetal cerebral vascular response to maternal hyperoxia in different types of CHD, the sample size in each cardiac group remains small, limiting our ability to translate these findings into the clinical setting. However, our study contributes to the growing body of literature in utilizing non-invasive measures to elucidate the characteristics of the cerebral vasculature in the fetus with CHD. Taken together, our findings begin to explore the possibility of abnormal cerebral autoregulation beginning in the 3rd trimester of gestation in fetuses with CHD, particularly those with HLHS and retrograde flow in the aortic arch.

Future studies by our group will involve testing the association of our findings with postnatal neurologic findings, specifically the risk of postnatal brain injury. Further validating oxygen as a non-invasive tool to provide insight into cerebral adaptation and autoregulation in the late gestation fetus with CHD will allow for a more personalized approach to management in the delivery room and pre-operative period in order to minimize adverse neurologic sequalae and ultimately improve neurodevelopmental outcomes in this patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

The authors would like to thank Dr. Abraham Rudolph for his expertise, advice and input during the design, data analysis and interpretation of the findings in this study.

Funding Source: Dr. Peyvandi is funded by K23 NS099422 from the National Institute of Health

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What are the novel findings of this work?

Our findings reveal that underlying cardiovascular physiology leads to varying cerebral vascular response to maternal hyperoxia and that there are impairments in cerebral autoregulation in certain congenital heart disease groups.

What are the clinical implications of this work?

Given the recent interest in studying maternal hyperoxia as a therapeutic tool to optimize brain development in fetuses with CHD, our findings provide important physiologic data that should be incorporated in future clinical trials.

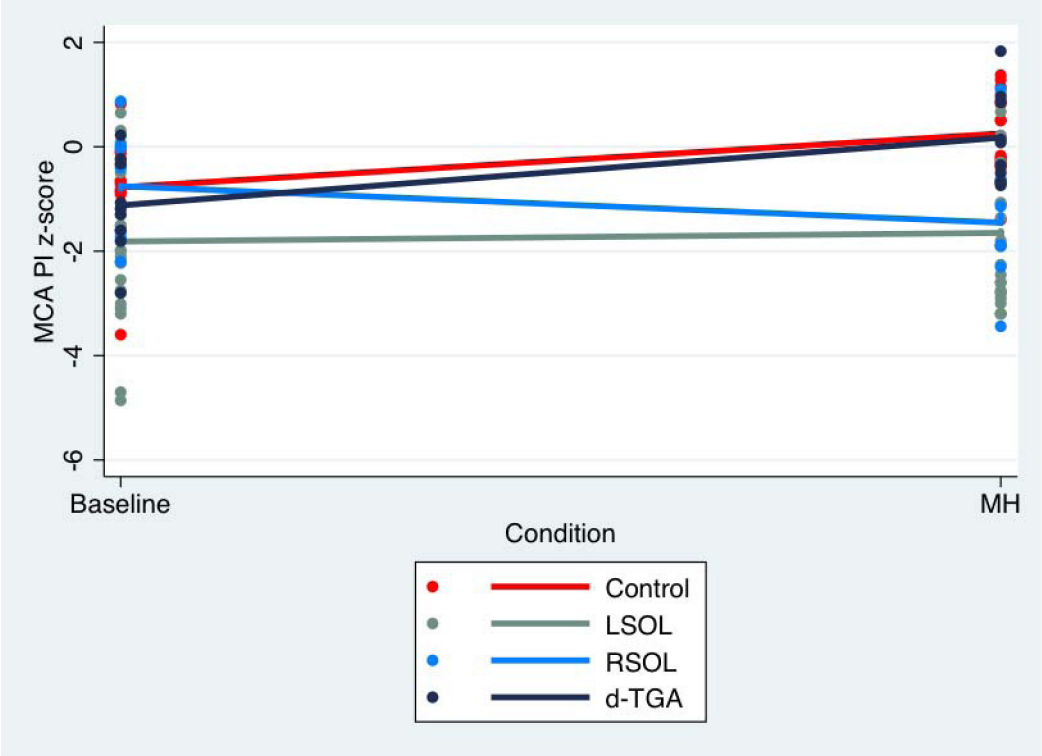

Figure 1.

Middle cerebral artery (MCA) pulsatility index (PI) Z-score at baseline and after maternal hyperoxia (MH) by study group. Fetuses with Left-sided obstructive lesions (LSOLgreen line) had the least response to maternal hyperoxia compared with the control group (red line). The absolute change in MCA PI was 1.2 points lower (95% CI: −1.8, −0.6) in the LSOL group compared with the control group after adjusting for baseline MCA PI ($p < 0.001$). RSOL= right-sided obstructive lesion; d-TGA= d- transposition of the great arteries.

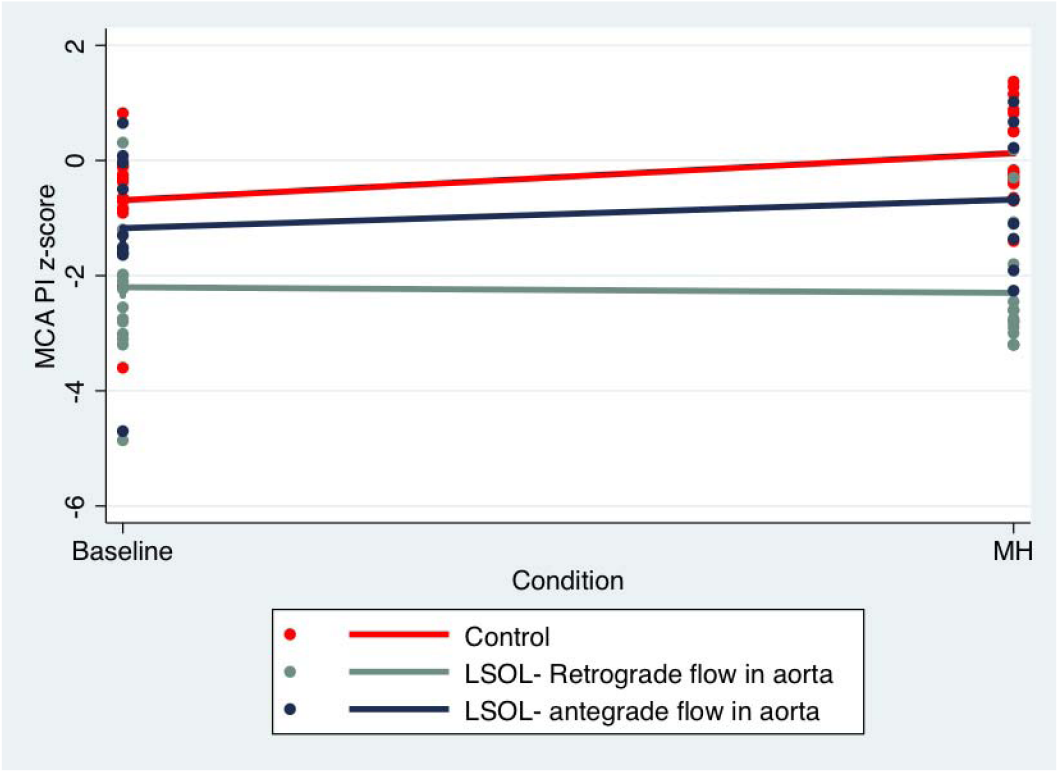

Figure 2.

Middle cerebral artery (MCA) pulsatility index (PI) Z-score at baseline and after maternal hyperoxia (MH) by direction of flow in the aortic arch among fetuses with left sided obstructive lesions (LSOL) compared with control fetuses. Fetuses with retrograde flow in the aortic arch (green line) had the least response to maternal hyperoxia compared to normal fetuses (red line). The change in MCA PI Z-score was 1.6 points lower (95% CI: −2.2, −1.0) in the LSOL-retrograde group compared with the control group after adjusting for baseline MCA PI ($p < 0.001$).

Table 1.

Baseline demographics by cardiac group (total N= 60)

	LSOL	RSOL (pulmonary atresia)	d-TGA	Control
N (%)	27 (45%)	7 (11.7%)	9 (15%)	17 (28.3%)
GA at fetal echo * Mean, 95% CI	33.9 (33.4-34.4)	33.5 (32.0-34.9)	34.2 (33.3-35.1)	33.8 (33.5-34.3)
EFW (kg) * Mean, 95% CI	2298.1 (2119.7-2476.5)	2006.2 (1599.9-2412.5)	2465 (2175.0-2754.9)	2341.5 (2129.1–2491.8)
Transverse aortic arch Flow		NA	NA	NA
Antegrade, N (%)	12 (44.4%)			
Retrograde, N (%)	15 (55.6%)			

* Gestational age (GA), mean (95% CI) and birthweight, mean (95%CI) were not significantly different between groups by one-way ANOVA (p= 0.83).

LSOL: left-sided obstructive lesion; RSOL= right-sided obstructive lesion; d-TGA= d- transposition of the great arteries; EFW= estimated fetal weight. For listing of individual lesions, see Supplement

Table 2.

Cerebral, pulmonary and placental pulsatility indices at baseline and with maternal hyperoxia

	LSOL (n= 27)	RSOL (n= 7)	d-TGA (n= 9)	Control (n= 17)
Mean MCA PI Z-score				
Baseline	−1.8 (−2.4, −1.2)	−0.75 (−1.6, 0.12)	−1.1 (−1.7, −0.51)	−0.8 (−1.3, −0.3)
MH	−1.6 (−2.2, −1.1)	−1.4 (−2.5, −0.37)	0.18 (−0.41, 0.76)	0.13 (−0.27, 0.54)
Change	0.12 (−0.21, 0.45)	−0.7 (−2.1, 0.75)	1.3 (0.60, 2.0) *	0.9 (0.42, 1.4) *
Mean PA PI				
Baseline	3.9 (3.6-4.1)	3.7 (3.3-4.1)	3.5 (3.2-3.8)	3.4 (3.1-3.8)
MH	3.3 (2.9-3.6)	3.2 (2.8-3.5)	2.7 (2.4-3.0)	2.8 (2.6-3.0)
Change	−0.7 (−0.9,−0.4) *	−0.8 (−1.3, −0.3) *	−0.8 (−1.1, −0.5) *	−0.7 (−0.9,−0.4) *
Mean UA PI				
Baseline	1.0 (0.9-1.1)	1.2 (0.91-1.4)	0.9 (0.8-1.1)	0.8 (0.7-0.90)
MH	1.1 (1.0-1.2)	1.1 (0.78-1.3)	1.0 (0.9-1.2)	1.5 (0.3-2.6)
Change	0.05 (− 0.03, 0.2)	−0.2 (−0.5, 0.07)	0.1 (−0.08, 0.28)	0.6 (−0.5, 1.8)

* Change in PI was significantly different from baseline to MH by paired t-test ($p < 0.05$). All values are mean (95% CI).

LSOL= left sided obstructive lesion; RSOL= right sided obstructive lesion; d-TGA= d- transposition of the great arteries; MCA= middle cerebral artery; PI= pulsatility index; MH= maternal hyperoxia; PA= pulmonary artery; UA= umbilical artery

Table 3.

Cerebral, pulmonary and placental pulsatility indices at baseline and with MH by direction of flow in transverse aorta compared with control

	LSOL (Antegrade flow; n= 12)	LSOL (Retrograde flow; n= 15)	Control (n= 17)
Mean MCA PI Z-score			
Baseline	−1.2 (−2.2, −0.1)	−2.2 (−2.9, −1.5)	−0.8 (−1.3, −0.3)
MH	−0.7 (−1.3, 0.003)	−2.3 (−2.6, −1.7)	0.13 (−0.3-0.5)
Change	0.5 (−0.04, 1.0)	−0.1 (−0.5, 0.3)	0.9 (0.4-1.4) *

* Change in PI was significantly different from baseline to MH by paired t-test ($p < 0.05$). All values are mean (95% CI).

LSOL= left sided obstructive lesion; MCA= middle cerebral artery; PI= pulsatility index; MH= maternal hyperoxia

Table 4.

Cardiac outputs at baseline and with maternal hyperoxia (MH) by cardiac group *.

	LSOL Antegrade (n= 12)		LSOL Retrograde (n= 15)		RSOL (n= 7)		d-TGA (n= 9)		Controls (n= 17)	
	Baseline	**MH**	**Baseline**	**MH**	**Baseline**	**MH**	**Baseline**	**MH**	**Baseline**	**MH**
Pulmonary CO	759.9 (582.1-937.9)	682.0 (522.4-841.7)	785.3 (655.1-915.5)	874.1 (731.5-1016.7)	--	--	501.0 (374.1-627.9)	508.2 (256.5-759.8)	489.1 (308.8-669.3)	574.0 (477.3-670.8)
Aortic CO	238.6 (122.9-354.3)	239.7 (162.7-316.7)	--	--	734.1 (584.5-919.7)	669.6 (384.4-954.8)	579.4 (304.8-854.0)	489.4 (295.0-683.8)	405.8 (343.4-468.1)	450.5 (390.8-510.2)
CCOi	414.6 (339.8-489.4)	431.6 (315.9-547.4)	342.9 (285.5-400.4)	411.1 (342.9-479.1)	419.4 (312.3-526.4)	446.4 (277.9-614.9)	478.5 (314.5-642.6)	455.6 (355.0-556.3)	423.2 (358.3-488.1)	437.7 (378.7-496.6)
PCO/CCO (%)	0.80 (0.74-0.84)	0.74 (0.66-0.83)	--	--	--	--	0.46 (0.39-0.52)	0.50 (0.30-0.71)	0.58 (0.54-0.62)	0.55 (0.53-0.58)
AoCO/CCO (%)	0.21 (0.16-0.26)	0.26 (0.17-0.34)	--	--	--	--	0.54 (0.48-0.61)	0.49 (0.29-0.70)	0.42 (0.38-0.46)	0.44 (0.42-0.47)

CO= cardiac output; CCOi= Combined cardiac output indexed to fetal weight; PCO/CCO= the percentage of pulmonary cardiac output as a fraction of the combined cardiac output; AoCO/CCO= the percentage of the aortic cardiac output as a fraction of the combined cardiac output.

* Paired t-test was used to compare each measure at baseline to the value after MH testing. All comparisons were non-significant.

Ultrasound Obstet Gynecol. Author manuscript; available in PMC 2022 May 01.