Reduced Fetal Cerebral Oxygen Consumption is Associated With Smaller Brain Size in Fetuses With Congenital Heart Disease

Running title: Sun et al.; Fetal hemodynamics and brain size in CHD

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Abstract

Background—Fetal hypoxia has been implicated in the abnormal brain development seen in newborns with congenital heart disease (CHD). New magnetic resonance imaging (MRI) technology now offers the potential to investigate the relationship between fetal hemodynamics and brain dysmaturation.

Methods and Results—We measured fetal brain size, oxygen saturation and blood flow in the major vessels of the fetal circulation in 30 late gestation fetuses with CHD and 30 normal controls using phase contrast MRI and T2 mapping. Fetal hemodynamic parameters were calculated using a combination of MRI flow and oximetry data and fetal hemoglobin concentrations estimated from population averages. In fetuses with CHD, reductions in umbilical vein oxygen content (p<0.001), and failure of the normal streaming of oxygenated blood from the placenta to the ascending aorta were associated with a mean reduction in ascending aortic saturation of 10% (p < 0.001), while cerebral blood flow and cerebral oxygen extraction were no different from controls. This accounted for the mean 15% reduction in cerebral oxygen delivery (p = 0.08) and 32% reduction cerebral VO₂ in CHD fetuses (p < 0.001), which were associated with a 13% reduction in fetal brain volume (p < 0.001). Fetal brain size correlated with ascending aortic oxygen saturation and cerebral VO₂ (r = 0.37 p = 0.004).

Conclusions—This study supports a direct link between reduced cerebral oxygenation and impaired brain growth in fetuses with CHD and raises the possibility that in utero brain development could be improved with maternal oxygen therapy.

Key words: fetal cardiac magnetic resonance imaging, brain, congenital heart disease, hemodynamics
Background

The neurodevelopmental outcomes of children with congenital heart disease (CHD) remain a cause for concern. While a proportion of this morbidity is attributable to injury occurring in the peri-operative period, there is increasing evidence that CHD is associated with fetal brain dysmaturation\(^1,2\). A reduction in brain growth and maturation during the third trimester has been demonstrated in fetuses with CHD using MRI brain volumetry and magnetic resonance spectroscopy\(^1\), while term newborns with transposition of the great arteries (TGA) or with single ventricle (SV) physiology display microstructural and metabolic brain parameters more in keeping with premature infants than normal controls\(^2\). Furthermore, recent evidence suggests that this brain dysmaturation is associated with increased vulnerability to white matter injury around neonatal cardiac surgery and decrements in neurodevelopmental outcome at 2 years\(^3,4\).

Reductions in middle cerebral artery pulsatility measured by transcranial ultrasound have been observed in fetuses with CHD, raising the possibility of cerebral vasodilation in response to hypoxia\(^5\), and fetal cerebral and placental Doppler indices have recently been linked to developmental outcome in CHD\(^6\). Advances in MRI technology have provided a new approach to evaluating fetal hemodynamics\(^7\). In the present study, we sought to investigate the relationship between fetal hemodynamics and brain growth in fetuses with CHD compared with normal controls using MRI.

Methods

The study design is a prospective observational cross-sectional case-control study comparing fetal hemodynamic parameters and brain size measured by MRI in fetuses with and without CHD. A sample size of 30 subjects and 30 controls was determined based on the resources
available for the study.

**Study participants**

The research ethics board of the Hospital for Sick Children approved the study and written consent was obtained from every mother prior to study enrolment. We recruited study subjects from the Fetal Cardiac Program at the Hospital for Sick Children and controls from the low risk outpatient clinic at Mount Sinai Hospital in Toronto during a one-year period from May 2013 to May 2014. Consecutive patients with CHD severe enough to warrant a period of inpatient monitoring or neonatal cardiac surgery or intervention following birth were invited to participate in the study. Exclusion criteria in both cohorts included mothers with significant maternal medical problems including pregnancy induced hypertension, diabetes and autoimmune disease and fetal conditions including intrauterine growth restriction and anemia. Fetuses with prenatally diagnosed congenital malformations and genetic syndromes were also excluded. The CHD group underwent detailed diagnostic fetal echocardiography in the second trimester according to published guidelines.

**MRI protocol**

The same imaging protocol was used for each subject and consisted of a fetal MRI scan during the final weeks of pregnancy. The scans were performed on a clinical 1.5T MRI system (Siemens Avanto, Erlangen, Germany) without sedation.

**Blood flow quantification**

Vessel flow was quantified using cine phase contrast (PC) measurements in each of the major fetal vessels and indexed to the fetal weight according to our previously published technique.

**Fetal brain volumetry**

The three dimensional steady state free precession (SSFP) acquisition used to measure fetal
volume was also used to measure fetal brain volume, which we converted to estimated fetal brain weight using a published conversion factor based on fetal brain density. The imaging parameters for this acquisition, which was acquired during a single maternal breathhold, are as follows: TE 1.74ms, TR 3.99ms, slice thickness 2mm, matrix size 256×205×80, field of view 400mm, 1 signal average, parallel imaging factor of 2, and average scan time of 13 seconds. Post processing of the acquisition to segment the fetal brain was performed using a combination of threshold, cutting and filling tools using a commercial software package (Mimics, Materialize, Leuven). An example of fetal brain segmentation is shown in Figure 1. We converted the fetal brain weights to gestational age appropriate Z-scores according to a previously published large autopsy series.

**Magnetic resonance oximetry**

The T2 relaxation of any tissue is a time constant derived from the exponential rate of decay of its MRI signal. The almost linear relationship between the oxygen saturation of blood and its T2 relaxation results from the proportions of diamagnetic oxygenated hemoglobin and paramagnetic deoxygenated hemoglobin. Wright et al defined this relationship as follows:

\[
\frac{1}{T2} = \frac{1}{T2o} + K \left(1 - \frac{SaO2}{100}\right)^2
\]

where \(T2o\) is the T2 of fully oxygenated blood for a given hemoglobin concentration and \(K\) is a constant that depends on the magnetic field strength and the refocusing interval of the T2 preparation pulse of the imaging sequence used to measure T2.

T2 mapping is the technique used to measure the T2 of a tissue and consists of the acquisition of a series of images with different T2 preparation times, which allow T2 curves to be calculated for each voxel and displayed as a T2 map. The T2 of blood in a vessel is measured by placing a region of interest in the center of the vessel. Spatial resolution criteria for ensuring
accurate vessel T2 quantification by avoiding contamination of the signal from blood by
surrounding tissues have been established. According to this work, the region of interest should
be less than 60% of the vessel diameter and a minimum of six pixels across the vessel diameter
with a slice thickness less than the vessel. The importance of prescribing the imaging plane
perpendicular to the long axis of the vessel to avoid partial volume artifacts is also emphasized.

The imaging technique we used for T2 mapping in this study was adapted from a new
sequence designed for myocardial T2 mapping which employs a T2 preparation pulse followed
by a rapid SSFP readout with TE 1.15ms and TR 3.97ms. An interval of 4 seconds between
the individual T2 preparation images was employed to ensure adequate magnetization recovery,
and five T2 preparation images with T2 prep times spread evenly across the expected T2 of the
vessel were obtained for each T2 map. We used a slice thickness of 5mm, matrix size of
224×181 and field of view of 300mm with 1 signal average and a parallel imaging factor of 2,
resulting in a scan time of 16 seconds and in-plane spatial resolution of 1.3mm. The diameter of
the umbilical vein (UV), descending aorta (DAo), main pulmonary artery (MPA), and ascending
aorta (AAo) are all in excess of 7mm at term, thus ensuring a minimum of 6 pixels across the
towards term results in imaging with less than the recommended spatial resolution. A critically
important innovation with regard to fetal T2 mapping that is incorporated into the sequence we
used is its non-rigid registration motion correction algorithm, which corrects for small fetal and
maternal movements occurring between each T2 preparation image. When more gross fetal
motions resulted in more significant artifact, the sequence was repeated, a situation that occurred
approximately 25% of the measurements. Examples of T2 maps of the umbilical cord and
mediastinal three-vessel view are shown in Figure 2.
Hemodynamic calculations

We used the PC and T2 measurements to calculate fetal oxygen delivery (DO₂) and consumption (VO₂) and fetal cerebral DO₂ and VO₂. The fetal and fetal cerebral oxygen extraction fractions (OEF) were calculated as fetal VO₂/DO₂ and cerebral VO₂/DO₂ respectively. The oxygen (O₂) content of the blood was estimated using the T2 measurements and gestational age appropriate population averages for blood hemoglobin concentration. As the T₂o of human fetal blood is not known, we used the previously established value of 250ms for the T₂o of adult blood. Fetal DO₂ was calculated as the product of UV flow and UV O₂ content, while fetal VO₂ was obtained from the product of UV flow and the difference between the umbilical vein and artery O₂ content. Because of the umbilical arteries’ small size, their O₂ content was estimated based on the T2 measurement made in the DAo at the diaphragm, which directly supplies them. The small size of the vessels exclusively supplying and draining the brain also makes them unsuitable for accurate PC MRI and T2 mapping. However, cerebral blood flow accounts for the majority of venous drainage to the SVC in children, so we used SVC flow and T2 values of the aortic arch and SVC to approximate cerebral DO₂ and cerebral VO₂. The blood hemoglobin concentration was measured in the CHD fetuses on the first day of life as part of a complete blood count. Hemoglobin concentration was not measured in the control group.

Clinical Assessment and Follow-up

A chart review was performed for each patient at the end of the study period, which resulted in a period of follow-up of between one and 12 months. All newborns with antenatally diagnosed CHD underwent neonatal echocardiograms to confirm the cardiac diagnosis. The diagnosis of any associated congenital abnormality or genetic syndrome was recorded. Those infants with CHD associated with dysmorphic features or additional lesions underwent microarray genetic
testing. The approach to managing the CHD was noted, as were the overall outcomes at follow-up in terms of mortality and morbidity.

**Statistical analysis**

The initial analysis was comprised of a comparison between fetal hemodynamic parameters and brain size in normal versus CHD fetuses. We then compared the same parameters in subgroups of CHD fetuses against controls, with subgroups defined as those with single ventricle (SV) versus biventricular (BV) hearts and those with the two most commonly encountered individual cardiac lesions, Transposition of the Great Arteries (TGA) and Tetralogy of Fallot (TOF).

Finally, we correlated specific hemodynamic parameters with fetal brain size. Fetal brain size, DO$_2$, OEF, VO$_2$, and cerebral DO$_2$, OEF and VO$_2$ were all confirmed to be normally distributed using the Kolmogorov-Smirnov test in the CHD and control fetuses. A Student t-test was used to compare variables between controls and CHD fetuses, and a one-way ANOVA with a Dunnett’s multiple comparison test was used to compare the variables between the control group and subgroups of CHD. A Mann Whitney test was used to compare variables in fetuses with and without genetic syndromes. Pearson’s correlation was used to examine the relationships between the listed variables. Inter-observer agreement for the phase contrast and T2 measurements was compared using Pearson’s correlation and Bland Altman plots. P-values of less than 0.05 were considered statistically significant. Statistical analysis was performed using GraphPad Prism 6.0e, USA.

**Results**

A complete set of individual measured and calculated variables is given in the supplementary material. We enrolled 30 subjects with CHD and 30 controls and performed fetal cardiovascular
MRI at a mean gestational age of 36 weeks (SD 1.0). There was no significant difference in
gestational age between the normal and CHD groups (p = 0.5). There were eight fetuses with SV
hearts and 22 fetuses with BV hearts, of which seven had TGA and seven had TOF. Table 1 shows
the demographic details of the CHD study subjects including their cardiac diagnosis, associated
congenital abnormalities, genetic diagnoses, the type of surgery they underwent and their clinical
status at the completion of the study period. Figure 3 shows the high level of agreement and lack
of bias between two observers for fetal vessel blood flow and T2 measurements (r = 0.97, p =
0.0001). The mean hemoglobin concentration on the first day of life in the newborns with CHD
was 16.3 g/dL with a range of 13.0-19.4 g/dL, which is similar to published reference ranges
(mean 17, range 14-20)20. Table 2 shows measured and calculated variables for normal and CHD
fetuses, while Table 3 shows a comparison of these variables between controls and individual
subgroups of CHD. The results are also illustrated in Figures 4-6.

When the CHD fetuses where collectively compared with controls we found a mean 10% reduction in the SaO2 of blood supplied to the developing brain (p < 0.0001). As there was no
difference in cerebral blood flow (SVC flow p – 0.6) this resulted in an almost statistically
significant 15% reduction in cerebral DO2 (p = 0.08). As there was no difference in the extraction
of oxygen by the brain (p = 0.5), the result was a mean 32% reduction in cerebral VO2 in CHD
fetuses (p < 0.001). This was associated with a mean 13% reduction in brain volume (p < 0.001)
or full standard deviation reduction in estimated brain weight Z-score (p < 0.001). We found a
mean 6% reduction in UV SaO2 (p = 0.0004), which was associated with a mean 17% reduction
in fetal DO2. In normal controls the mean AAO SaO2 was 7% higher than the MPA, while in
CHD fetuses the mean AAO SaO2 was only 2% higher than the MPA SaO2 so that streaming was
responsible for a significant increment in AAO SaO2 compared with MPA SaO2 in controls but
not in CHD fetuses (p = 0.03). There was a 30% reduction in CVO in SV fetuses compared with BV CHD (p=0.003), and this was associated with a 20% reduction in UV flow (p=0.002). UV flow correlated with CVO across the whole study group (r = 0.27, p = 0.03) as shown in Figure 4. The combination of lower UV SaO2 and lower UV flow in CHD fetuses as a whole resulted in a 17% reduction in DO2 (p = 0.006), which was associated with a 17% reduction in fetal VO2 (p = 0.007). Fetal DO2 was further reduced in SV fetuses compared with fetuses with BV CHD (p = 0.03) and SV fetuses also had the lowest AAo SaO2, although AAo SaO2 was significantly lower than controls for all of the subgroups of CHD except TOF (p=0.0001). Cerebral VO2 was lower in all subgroups of CHD than controls except SV (p=0.0001), while brain volume was lower than controls in all CHD subgroups except TGA and SV fetuses (p=0.0001). There were no significant differences between subgroups of CHD and controls in terms of SVC flow, cerebral DO2, cerebral OEF or OEF. There were no significant differences between the three syndromic and 27 non-syndromic fetuses with CHD in terms of brain volume (p = 0.9) or cerebral VO2 (p = 0.7).

We found no relationship between fetal VO2 and fetal cerebral VO2 (p=0.62) and no correlation between CVO and SVC flow for the whole cohort or for any individual group. SVC flow comprised 30% of the CVO in controls and 31% of the CVO in fetuses with CHD and there was no significant difference between the proportion of the CVO devoted to cerebral perfusion in any of the subgroups of CHD (p=0.17). There were significant correlations between both AAo SaO2 (r = 0.33, p = 0.01) and fetal cerebral VO2 (r = 0.37, p = 0.004) with estimated fetal brain weight Z-score across the whole study population, as shown in Figure 7. However, the correlations between AAo SaO2 fetal CVO2 and brain volume were not statistically significant.
Discussion

Fetal cerebral oxygenation and brain growth and development

The abnormal connections and obstructions of flow present in fetuses with CHD have long been suspected of causing a reduction in the nutritional content and oxygen saturation of blood supplied to the developing fetal brain\(^{18}\). Reductions in middle cerebral artery pulsatility index found in CHD (5) are in keeping with the “brain-sparing physiology” seen in animals exposed to acute hypoxia and human pregnancies affected by placental insufficiency\(^{18,21}\). However, fetal animal models suggest that following prolonged periods of hypoxia cerebral vascular tone tends to normalize, with down-regulation of neuronal and glial metabolism that results in reduced cerebral VO\(_2\) and associated changes in brain growth and development\(^{22}\). In our study the mean SVC flow was the same in each of the groups despite the lower oxygen content of the blood supplied to the brain in fetuses with CHD. Our findings would therefore be more in keeping with a model of reduced cerebral VO\(_2\) resulting from chronic hypoxia than the brain-sparing physiology seen in acute fetal hypoxia. An alternative explanation of our findings is that fetal cerebral VO\(_2\) is reduced in fetuses with CHD for some other reason than reduced cerebral DO\(_2\) that was not captured by our study. The fact that the mean 15% reduction in cerebral DO\(_2\) we found in CHD fetuses did not reach statistical significance, while the reduction in cerebral VO\(_2\) was highly significant would be in keeping with additional factors affecting fetal brain metabolism and growth than simply cerebral DO\(_2\). However, the lack of difference between the syndromic and non-syndromic CHD fetuses in terms of brain size and cerebral VO\(_2\) would suggest that in this cohort at least, genetic diagnoses were not responsible for the abnormal cerebral hemodynamics and brain growth we found in the CHD group.

At least three circulatory mechanisms appear to be impacting the oxygen content of blood
supplied to the brain in fetuses with CHD. **Figure 8** shows the oxygen saturations across the circulations of representative examples of a normal fetus and fetuses with hypoplastic left heart syndrome, TGA and TOF by MRI. In the normal fetal circulation, there is streaming of oxygenated blood from the placenta to the fetal cerebral circulation via the ductus venosus and foramen ovale. In each of the examples of CHD, this pathway is disrupted. In TGA, streaming results in well oxygenated blood being directed to the pulmonary circulation, while the blood supplied to brain is largely derived from more deoxygenated blood returning from the caval veins. In TOF, the oxygenated blood crossing the foramen ovale passes into the aorta in the normal way but is diluted by more doxygenated blood shunting from right to left across the ventricular septal defect. In hypoplastic left heart syndrome, no streaming of oxygenated blood is possible, as there is essentially only one outlet of the heart, so that the entire fetal circulation is supplied by blood with the same oxygen content. In addition to the disruption of streaming of oxygenated blood towards the brain, in single ventricle hearts oxygen delivery to the fetus as a whole is affected by a reduction in combined ventricular output. Fetal animal models indicate that the principle determinant of placental blood flow is fetal blood pressure, and that blood pressure is dependent on cardiac output. We conclude that the lack of two functioning ventricles is the driver behind the reductions in UV flow and the resulting drop in fetal DO2 in SV hearts. The impact of ventricular hypoplasia on CVO is likely to be further compounded by the presence of atrio-ventricular valve regurgitation. In our study, there were two SV fetuses with significant atrio-ventricular valve regurgitation, and the mean CVO was 25% lower in these fetuses than SV fetuses without regurgitation. Although this was not statistically significant, this was likely because of the small sample size. Finally, a third factor contributing to lower oxygen saturations in fetuses with CHD was the reduction in UV SaO2, which is suggestive of abnormal
placental function and results in lower fetal DO\textsubscript{2} even in the setting of normal CVO and UV flow. This interpretation is supported by the high incidence of placental abnormalities found in the setting of CHD on gross pathology and histopathology\cite{23}. The reason for the higher cerebral VO\textsubscript{2} we observed in fetuses with SV hearts than BV hearts is not certain, and we suspect this is a spurious result resulting from our small sample size. Indeed, the small size of the subgroups of CHD in general means that caution should be exercised in the interpretation of differences between these groups and further studies with larger sample sizes would be necessary to convincingly characterize the fetal hemodynamics of each subtype of CHD.

Our demonstration of reduced fetal brain size in third trimester fetuses with CHD is in keeping with a previous study which also demonstrated changes in fetal brain metabolism using magnetic resonance spectroscopy that were attributed to reduced cerebral DO\textsubscript{2}\cite{1}. As brain dysmaturation appears to confer increased susceptibility to white matter injury in the perioperative period and neurodevelopmental deficits at 2 years, the identification of fetal hypoxia as a potentially modifiable cause of delayed fetal brain development may be clinically significant\cite{3,4}. For example, previous authors have shown that oxygen saturations in the fetal circulation can be augmented through increases in the oxygen concentration of maternal inhaled air\cite{18}. This also appears to be the case in normal humans, where maternal hyperoxygenation results in oxygen mediated pulmonary vasodilation\cite{24}.

While fetal brain volumetry by MRI provides a ready marker of fetal brain growth, it is a crude tool compared with the array of measures of brain maturation now available with neonatal brain MRI. Further investigation of the relationship between fetal hemodynamics and brain development should include correlation of fetal cerebral DO\textsubscript{2} and VO\textsubscript{2} with a range of imaging parameters of brain maturation. Most importantly, fetal hemodynamic parameters measured by
MRI should be correlated with long-term neurodevelopmental outcomes in order to fully evaluate the importance of any relationship between prenatal hemodynamics and brain development. Furthermore, a single late gestation fetal hemodynamic assessment is not likely to capture a comprehensive picture of how hemodynamics impact brain development throughout the prenatal period, and in future it will be important to develop new techniques to allow a similar approach to be applied earlier in the pregnancy so that serial measurements can be performed.

**Discussion of Methodology**

The techniques used to obtain the results reported in this study are not well-established and a discussion of their validity is warranted. PC MRI is widely used in the non-invasive quantification of vessel flow in postnatal subjects and is more accurate than ultrasound. We have validated this technique in human fetuses and published reference values for the distribution of blood flow in the normal late gestation human fetus.

MR oximetry using quantitative T2 mapping of blood was developed by Wright et al and initially reported in 1991. We have since shown the fidelity of magnetic resonance oximetry compared with conventional blood gases in children with CHD and Wedergartner et al showed that T2 fetal MRI oximetry was feasible in the cardiac ventricles of fetal lambs. The magnetic properties of human fetal blood have not been determined and further validation work to establish the exact relationship between T2 and SaO2 in blood that contains a high proportion of the fetal form of hemoglobin is warranted. However, while any inaccuracy of our technique introduced by differences in the magnetic properties of fetal and adult blood might affect our absolute SaO2 values, it would not be expected to have a major impact on the comparison of normal and CHD fetuses. The conversion of T2 to SaO2 also depends on the hemoglobin
concentration of blood, and unfortunately there is currently no way to measure hemoglobin concentration non-invasively in the fetus. Our approach to this problem was to estimate the fetal hemoglobin concentration based on population averages, which have been more thoroughly characterized in the late second trimester than third trimester, and the lack of convincing data for the normal fetal hemoglobin concentration of late gestation fetuses is an important potential source of inaccuracy in our study. However, we suspect that such variations will cancel out when the result of a large sample are combined. The agreement between our technique and estimations of the distribution of blood flow, SaO₂, DO₂ and VO₂ in the normal human fetal circulation with those made using invasive techniques in fetal lambs as well as cordocentesis measurements made in human fetuses supports the accuracy of our technique\textsuperscript{18,28}.

The application of normal ranges for estimating hemoglobin concentration to fetuses with CHD is also problematic. There are no published ranges for fetal hemoglobin in fetuses with CHD, although previous studies have shown that hematologic indices in newborns with CHD are within the normal range\textsuperscript{29}. However, chronic hypoxia leads to fetal polycythemia, with increases in hemoglobin concentration in the 20\% range seen in fetuses with significant placental insufficiency\textsuperscript{30}. Polycythemia results in a reduction in the T2 of blood due an increase in paramagnetic deoxyhemoglobin\textsuperscript{12}. If the fetuses with CHD in our study were polycythemic because of chronic \textit{in utero} hypoxia this could have exaggerated the reductions in DO₂ we found. However, inaccuracies in the estimation of hemoglobin concentration would have a negligible effect on measurements of VO₂ because VO₂ is primarily determined by flow and the \textit{difference} in T2. Furthermore, in our study the mean hemoglobin concentration of the newborns with CHD was just below the normal mean, with nearly all of the measurements falling within the normal range and we conclude that the hemoglobin concentration in these fetuses was not responsible
for the reductions we found in vessel T2s. In future, it may be possible to improve the accuracy of fetal MR oximetry with the addition of T1 mapping to measure the hemoglobin concentration of fetal blood, as a strong relationship exists between T1 and hematocrit³¹.

Additional concerns regarding the accuracy of fetal vessel oximetry based on T2 quantification arise from the small size of the vessels of interest. In particular the SVC measurements could be subject to partial volume artifacts, which would affect the accuracy of cerebral VO₂ quantification and therefore the whole basis of our analysis. However, if partial volume artifacts were significantly affecting the SVC T2, the high T2 of adjacent lung might be expected to result in erroneously high T2 values, while in practice the SVC T2 values we obtained with T2 mapping were consistently the lowest in the fetal circulation. Nevertheless, additional validation of the current approach to fetal oximetry in small vessels is warranted. Future advances in MRI technology are likely to improve the accuracy of fetal MR oximetry in the future. For example, in another approach to reducing partial volume artifacts called “TRUST”, the blood is labeled so that its signal can be better discriminated from the surrounding tissues³².

Our conversion of fetal brain volume to fetal brain weight and estimation of fetal brain weight Z-score based on autopsy normal ranges was an attempt to correct this measure of brain growth for variation in gestational age across the study cohort. While we recognize that ideally we would have performed this analysis using Z-scores for fetal brain volume, these are currently not available. The technique we used for fetal brain volumetry is comprised by segmentation of a high-resolution three-dimensional steady state free precession acquisition. This sequence has been used to good effect for fetal volumetry and for making three-dimensional fetal models and is equally well suited to performing volumetry of the fetal brain⁹,³³. Its advantages over
conventional single shot fast spin echo techniques include its three-dimensional nature, the high contrast between the bright cerebrospinal fluid and dark brain parenchyma, and the shorter scan time, which allows the whole acquisition to be acquired during a single maternal breath-hold. As the duration of the sequence is invariably 15 seconds or less, it can easily be repeated if fetal motion results in artifact at the first attempt, resulting in a high-resolution three-dimensional dataset that is straightforward to segment and free from motion artifact in almost every case. Unlike previously described spin echo techniques for fetal brain volumetry, this fast imaging approach avoids reliance on motion correction algorithms, which may not correct for fetal movement in every axis.

Conclusion

In summary, this study provides further evidence of a link between abnormal fetal hemodynamics and abnormal brain development in fetuses with CHD. While reduced cerebral oxygen delivery and consumption have been suspected as the cause of fetal brain dysmaturity in fetuses for CHD for some time, our results are the first to confirm this principle. As brain dysmaturity in CHD newborns confers increased vulnerability to brain injury in the neonatal period and adverse neurodevelopmental outcome, a fetal intervention to improve it would be desirable. It is possible that maternal hyperoxygenation, which increases the oxygen content of umbilical venous blood and has been shown to be a safe intervention in fetuses with intrauterine growth restriction, could result in improved fetal brain oxygen consumption in fetuses with CHD.
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Conflict of Interest Disclosures: None.

References:


Table 1. Demographic features of fetuses with congenital heart disease.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Associated anomalies</th>
<th>Genetic diagnosis</th>
<th>Management approach</th>
<th>Outcome</th>
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<tr>
<td>Tricuspid atresia</td>
<td>None</td>
<td>N/A</td>
<td>BCPS</td>
<td>Alive and well</td>
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<td>Tricuspid atresia, PA</td>
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<td>Normal</td>
<td>BT shunt</td>
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<td>HLHS, DORV, AS</td>
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<td>Normal</td>
<td>Norwood operation</td>
<td>Died prior to BCPS</td>
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<td>Norwood operation</td>
<td>Alive and well</td>
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<td>Alive and well</td>
</tr>
<tr>
<td>TOF, PA, MAPCAs</td>
<td>None</td>
<td>Normal</td>
<td>Central shunt</td>
<td>Alive and well</td>
</tr>
<tr>
<td>TGA</td>
<td>None</td>
<td>N/A</td>
<td>ASO</td>
<td>Alive and well</td>
</tr>
<tr>
<td>TOF</td>
<td>None</td>
<td>T21</td>
<td>TOF repair</td>
<td>Alive and well</td>
</tr>
<tr>
<td>TGA</td>
<td>None</td>
<td>N/A</td>
<td>TOF repair</td>
<td>Alive and well</td>
</tr>
<tr>
<td>DORV, TGA type</td>
<td>None</td>
<td>N/A</td>
<td>TOF repair</td>
<td>Alive and well</td>
</tr>
<tr>
<td>IAA, VSD</td>
<td>TEF</td>
<td>Deletion chromosome 1</td>
<td>Repair of IAA</td>
<td>Died following surgery</td>
</tr>
<tr>
<td>TOF with PA</td>
<td>None</td>
<td>Normal</td>
<td>TOF repair</td>
<td>Alive and well</td>
</tr>
<tr>
<td>TOF</td>
<td>None</td>
<td>Normal</td>
<td>TOF repair</td>
<td>Alive and well</td>
</tr>
<tr>
<td>LAI, AVSD</td>
<td>Abdominal heterotaxy, polysplenia</td>
<td>Normal</td>
<td>PAB, repair of AVSD and systemic vein baffle</td>
<td>Alive, AVVR, HF</td>
</tr>
<tr>
<td>TGA, VSD</td>
<td>None</td>
<td>N/A</td>
<td>ASO, VSD closure</td>
<td>Alive and well</td>
</tr>
<tr>
<td>CoA</td>
<td>None</td>
<td>N/A</td>
<td>Coarctation repair</td>
<td>Alive and well</td>
</tr>
<tr>
<td>TGA</td>
<td>None</td>
<td>N/A</td>
<td>Coarctation repair</td>
<td>Alive and well</td>
</tr>
<tr>
<td>TGA</td>
<td>Single kidney</td>
<td>Normal</td>
<td>ASO</td>
<td>Alive and well</td>
</tr>
<tr>
<td>CoA</td>
<td>None</td>
<td>Turner syndrome</td>
<td>Coarctation repair</td>
<td>Alive and well</td>
</tr>
<tr>
<td>TOF</td>
<td>None</td>
<td>N/A</td>
<td>TOF repair (planned)</td>
<td>Alive and well</td>
</tr>
</tbody>
</table>

Table 2. Comparison of hemodynamic parameters and brain size in congenital heart disease versus normals.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CHD (n=30)</th>
<th>Normal (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean gestational age at MRI</td>
<td>36 (1.0)</td>
<td>36 (1.0)</td>
<td>0.5</td>
</tr>
<tr>
<td>Mean estimated fetal weight (kg)</td>
<td>2.9 (0.5)</td>
<td>3.1 (0.3)</td>
<td>0.16</td>
</tr>
<tr>
<td>Mean fetal brain volume (ml)</td>
<td>279 (46)</td>
<td>319 (30)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mean combined ventricular output (ml/min/kg)</td>
<td>433 (81)</td>
<td>459 (46)</td>
<td>0.14</td>
</tr>
<tr>
<td>Mean superior vena caval flow (ml/min/kg)</td>
<td>132 (35)</td>
<td>137 (33)</td>
<td>0.6</td>
</tr>
<tr>
<td>Mean ascending aortic saturation (%)</td>
<td>48 (9)</td>
<td>58 (6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mean umbilical vein SaO2 (%)</td>
<td>73 (9)</td>
<td>79 (5)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Mean umbilical vein flow (ml/min/kg)</td>
<td>115 (29)</td>
<td>129 (28)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean fetal oxygen delivery (ml/min/kg)</td>
<td>17.1 (4.4)</td>
<td>20.4 (4.2)</td>
<td>0.006</td>
</tr>
<tr>
<td>Mean fetal oxygen extraction fraction (%)</td>
<td>36 (8)</td>
<td>35 (7)</td>
<td>0.93</td>
</tr>
<tr>
<td>Mean fetal oxygen consumption (ml/min/kg)</td>
<td>5.8 (1.4)</td>
<td>6.9 (1.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Mean cerebral oxygen delivery (ml/min/kg)</td>
<td>10.2 (4.2)</td>
<td>12.0 (3.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>Mean cerebral oxygen extraction fraction (%)</td>
<td>32 (20)</td>
<td>34 (8)</td>
<td>0.53</td>
</tr>
<tr>
<td>Mean cerebral oxygen consumption (ml/min/kg)</td>
<td>2.7 (1.2)</td>
<td>4.0 (1.2)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Statistical analysis performed with Student t-test.
Table 3. Comparison of hemodynamic parameters and brain size in subgroups of congenital heart disease versus normals.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (n=30)</th>
<th>All CHD (n=30)</th>
<th>BV CHD (n=22)</th>
<th>SV CHD (n=8)</th>
<th>TGA (n=7)</th>
<th>TOF (n=7)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean gestational age at MRI</td>
<td>36</td>
<td>36</td>
<td>36</td>
<td>37</td>
<td>36</td>
<td>36</td>
<td>0.33</td>
</tr>
<tr>
<td>Mean fetal weight (kg)</td>
<td>3.1</td>
<td>2.9</td>
<td>2.9</td>
<td>3.1</td>
<td>3.1</td>
<td>3.1</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean brain volume (ml)</td>
<td>319</td>
<td>279***</td>
<td>277**</td>
<td>281</td>
<td>285</td>
<td>245***</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean combined ventricular output (ml/min/kg)</td>
<td>459</td>
<td>433</td>
<td>458</td>
<td>365**</td>
<td>443</td>
<td>467</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean superior vena caval flow (ml/min/kg)</td>
<td>137</td>
<td>132</td>
<td>133</td>
<td>130</td>
<td>149</td>
<td>112</td>
<td>0.68</td>
</tr>
<tr>
<td>Mean oxygen delivery (ml/min/kg)</td>
<td>20.4</td>
<td>17.1*</td>
<td>18.1</td>
<td>14.5**</td>
<td>20.1</td>
<td>16.9</td>
<td>0.006</td>
</tr>
<tr>
<td>Mean umbilical vein SaO2 (%)</td>
<td>79</td>
<td>73**</td>
<td>72**</td>
<td>75</td>
<td>74</td>
<td>72</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean umbilical vein flow (ml/min/kg)</td>
<td>129</td>
<td>115</td>
<td>123</td>
<td>92**</td>
<td>131</td>
<td>116</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean oxygen extraction fraction (%)</td>
<td>35</td>
<td>35</td>
<td>34</td>
<td>38</td>
<td>32</td>
<td>33</td>
<td>0.74</td>
</tr>
<tr>
<td>Mean oxygen consumption (ml/min/kg)</td>
<td>6.9</td>
<td>5.8*</td>
<td>6.0</td>
<td>5.3*</td>
<td>6.5</td>
<td>5.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean cerebral oxygen delivery (ml/min/kg)</td>
<td>12.0</td>
<td>10.2</td>
<td>10.4</td>
<td>9.2</td>
<td>12.0</td>
<td>8.2</td>
<td>0.16</td>
</tr>
<tr>
<td>Mean cerebral oxygen extraction fraction (%)</td>
<td>34</td>
<td>32</td>
<td>27</td>
<td>44</td>
<td>23</td>
<td>30</td>
<td>0.08</td>
</tr>
<tr>
<td>Mean cerebral oxygen consumption (ml/min/kg)</td>
<td>4.0</td>
<td>2.7***</td>
<td>2.5****</td>
<td>3.3</td>
<td>2.4**</td>
<td>2.5*</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Statistical analysis performed with ANOVA with Dunnett’s multiple comparison test. * denotes degree of significance.
Figure Legends:

Figure 1. Fetal brain volumetry in a normal term fetus by MRI using segmentation of a three dimensional steady state free precession acquisition.

Figure 2. T2 mapping of fetal vessels in a normal term fetus. Umbilical vein (UV), umbilical arteries (UA), ascending aorta (AAo), main pulmonary artery (MPA), superior vena cava (SVC).

Figure 3. Interobserver variation in fetal phase contrast flow and vessel T2 measurements.

Figure 4. Comparison of measured variables in fetuses with congenital heart disease (CHD) versus normal controls. Umbilical vein (UV), ascending aorta (AAo) superior vena caval (SVC), combined ventricular output (CVO), umbilical vein (UV) single ventricle (SV), biventricular (BV).

Figure 5. Comparison of calculated fetal cerebral hemodynamic parameters and brain volume in fetuses with congenital heart disease (CHD) versus normal controls. Cerebral oxygen delivery (DO2), oxygen extraction fraction (OEF) oxygen consumption (VO2).

Figure 6. Comparison of calculated fetal hemodynamic parameters in fetuses with congenital heart disease (CHD) versus normal controls. Oxygen delivery (DO2) oxygen extraction fraction (OEF), oxygen consumption (VO2), estimated fetal weight (EFW).
Figure 7. Correlations between estimated brain weight (EBW) Z-score and cerebral oxygen consumption (VO$_2$) and ascending aortic oxygen saturation (AAo SaO$_2$).

Figure 8. Fetal hemodynamics in representative examples of transposition (TGA), hypoplastic left heart syndrome (HLHS), and Tetralogy of Fallot (TOF) by MRI.
**Figure 3**
Figure 4
Figure 6
Figure 7

- Cerebral VO2 (ml/min/kg)
  - $r = 0.37$
  - $p = 0.004$

- AAo $SaO_2$
  - $r = 0.33$
  - $p = 0.01$
Reduced Fetal Cerebral Oxygen Consumption is Associated With Smaller Brain Size in Fetuses With Congenital Heart Disease

Liqun Sun, Christopher K. Macgowan, John G. Sled, Shi-Joon Yoo, Cedric Manlhiot, Prashob Porayette, Lars Grosse-Wortmann, Edgar Jaeggi, Brian W. McCrindle, John Kingdom, Edward Hickey, Steven Miller and Mike Seed

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