MRI reveals hemodynamic changes with acute maternal hyperoxygenation in human fetuses with and without congenital heart disease†

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ABSTRACT

Objective We investigated the physiologic impact of acute maternal hyperoxygenation (MH) in human fetuses with and without congenital heart disease (CHD) using fetal cardiac magnetic resonance (CMR) in order to explore the potential therapeutic benefits of chronic MH.

Methods We examined 17 normal and 20 late gestation human fetuses with CHD on a 1.5 T CMR system. Flows were measured in major fetal vessels using phase contrast MRI. The T2 of umbilical venous blood was measured using T2 mapping. The measurements were repeated during acute MH. The results were compared using a Student’s t-test, with p-value ≤0.05 considered statistically significant.

Results At baseline, the umbilical venous T2 (oxygen saturation) was lower in CHD fetuses than in normals, with significant increase with MH (p = 0.01). Both groups showed significant increase in pulmonary blood flow during MH, which was more dramatic in CHD (p = 0.005). There was a reduction in ductus arteriosus flow in CHD during MH (p = 0.04). There was no significant difference in blood flow in any of the other major vessels.

Conclusion This study suggests that fetal MR identifies the expected hemodynamic changes associated with acute MH. MRI could be useful as a method for monitoring the impact of chronic MH in fetuses with CHD. © 2015 John Wiley & Sons, Ltd.

INTRODUCTION

A number of investigators have reported an increase in human fetal oxygen (O2) levels during maternal O2 inhalation,1-4 and maternal hyperoxygenation (MH) has been used in the setting of hypoplastic left heart syndrome as a diagnostic test to improve the identification of atrial septal restriction, which impairs the usual pulmonary vasodilatory effect of increased pulmonary artery O2 content.5 MH was associated with growth of the aortic arch in a fetus with coarctation of aorta.6 The use of MH has also been investigated as a potential therapy for augmenting ventricular growth in fetuses with congenital heart disease (CHD) associated with underdeveloped cardiac chambers,5,7-9 where improvements in the dimensions of left-sided heart structures were detected on fetal echocardiography following MH. Fetal lamb experiments reveal an increase in umbilical venous (UV) O2 saturation (SaO2)10 and a reduction in pulmonary vascular resistance (PVR) during MH.11-13 In fetal lambs, the decrease in PVR associated with higher O2 tensions of blood in the pulmonary circulation is more pronounced closer to term.11 Doppler studies in late gestation human fetuses have suggested a similar increase in fetal pulmonary blood flow (PBF) during MH.14 However, ultrasound flow measurements are inherently less accurate15 than phase contrast (PC) cardiac magnetic resonance (CMR). Furthermore, T2 mapping provides the potential to directly measure changes in the O2 content of fetal blood using CMR.

High-resolution fetal cine PC CMR can be achieved with metric optimized gating (MOG), a retrospective technique that acquires temporally oversampled data and then iteratively sorts the data using hypothetical electrocardiogram trigger times until artifact in the associated images is minimized.16-19 This technique has been validated using flow phantoms16 and in adult volunteers. Reference ranges for the distribution of the fetal circulation in the normal late gestation fetus by PC CMR with MOG have recently been published,19 and the technique has been used to examine circulatory redistribution in the setting of CHD20-22 and intrauterine growth restriction.23,24

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Magnetic resonance oximetry is a technique first developed more than 20 years ago that takes advantage of the different magnetic properties of oxygenated and deoxygenated hemoglobin. For a given hematocrit, the T2 of blood varies characteristically with the SaO2 because of the paramagnetic effect of deoxyhemoglobin so that higher SaO2 is associated with higher T2. Good agreement has been demonstrated between SaO2 measured using a T2 preparation approach with conventional blood gasses in the vessels of children with CHD. Furthermore, the feasibility of prenatal T2-based oximetry has been shown in the cardiac ventricles of fetal lambs. We have recently modified a T2 mapping sequence designed for myocardial imaging that incorporates a fast steady-state free precession (SSFP) readout and a non-rigid registration motion correction algorithm in order to measure vessel T2 in the late gestation human fetus, revealing a mean umbilical vein SaO2 of 73% in fetuses with CHD compared with 79% in normal controls.

In this study we aimed to investigate the physiologic impact of acute MH in human fetuses with and without CHD using a combination of PC MRI and T2 mapping to explore the potential therapeutic benefits of chronic MH.

METHODS

Study design and patient selection

This was a prospective cross-sectional case control study performed with informed consent and hospital research ethics board approval. We recruited healthy controls from the low-risk obstetric outpatient clinic at Mount Sinai Hospital in Toronto. Exclusion criteria for the control group included chronic maternal illnesses and evidence of fetal or placental disease including growth restriction, congenital anomaly, autoimmune disease or multiple pregnancy. Consecutive fetuses with CHD diagnosed prenatally between July 2013 and December 2013 that was severe enough to warrant a period of inpatient monitoring following birth or a neonatal cardiac intervention or operation were invited to participate in the study. There were no major exclusion criteria for the CHD group. Patients were invited to undergo MRI as close to 37 weeks’ gestation as possible. At this gestational age (GA), the vessel sizes are larger, facilitating the measurement of blood flow and T2, and fetal motion is more restricted, resulting in a reduction in artifact.

MRI protocol

The MRI examinations were performed on a commercial 1.5 T CMR system (Avanto, Siemens Medical Solutions, Erlangen, Germany).

Blood flow quantification

We measured blood flow in the major human fetal vessels using PC MRI with MOG and indexed the flow measurements to fetal weight according to our previously published technique. We acquired a high-resolution 3D SSFP breath-hold acquisition covering the whole fetus and segmented the fetal envelope using a combination of thresholding and other post-processing tools in order to calculate the fetal volume (Materialise, Belgium). Fetal volume was converted to fetal weight using the conversion proposed by Baker et al. [fetal weight (grams) = 120 + fetal volume (mL) × 1.03]. The blood flow measurements were indexed by fetal weight. This allowed for comparison between fetuses and with prior fetal lamb measurements. At baseline, blood flow measurements were obtained from the ascending aorta (AAo), main pulmonary artery (MPA), right and left pulmonary arteries, superior vena cava (SVC), descending aorta, ductus arteriosus (DA) and UV in all subjects. PBF was calculated as the sum of the right pulmonary artery and left pulmonary artery flows. The combined ventricular output was calculated as the sum of the MPA and AAo flows plus 3% of this sum for estimated coronary flow based on previous lamb data.

T2 mapping

T2 mapping was performed in the UV using the sequence devised by Giri et al. Our version of the sequence was composed of five T2 preparation pulses between 0 and 200 ms, followed by an SSFP readout. The individual T2 preparation images were incorporated into T2 maps, an example of which is shown in Figure 1. The sequence incorporated a non-rigid registration motion correction algorithm that helped to compensate for the small fetal movements and maternal respiratory movements that were commonly encountered during the 16-s acquisition. The images were checked during the acquisition and repeated if there was excessive fetal motion. Excessive fetal motion resulted in our inability to make an accurate T2 measurement in approximately 46% of cases at baseline. We targeted the proximal intrahepatic portion of the UV, as this is its straightest section, which should therefore reduce on partial volume artifacts. At this gestation,
the intrahepatic UV has a mean diameter of 6.6 mm (n=17, standard deviation ± 0.7 mm). With a spatial resolution of 1.56 mm, this allowed for approximately 5 pixels across the vessel area while maintaining an adequate signal-to-noise ratio with a slice thickness of 5 mm. The sequence parameters for the T2 mapping are shown in Table 1. The T2 measurement was obtained by placing a region of interest over the central 60% of the vessel diameter according to the recommended approach, which helps to ensure there was no contamination of the signal from partial volume artefact.33

Acute maternal hyperoxygenation
Maternal hyperoxygenation was achieved with a non-rebreather mask and 12 L/min of O2 to achieve a fraction of inspired oxygen of approximately 70%.7,34 We attempted to repeat all vessel flows and UV T2 after 10 min of MH, during which the mother continued to inhale the same concentration of O2.

Statistics
The fetal flows are expressed in milliliters/minute and indexed to the fetal weight in kilograms. T2 is expressed in milliseconds (ms). The results are shown as means with standard deviations. A Kolmogorov–Smirnov test was used to establish that the data were normally distributed. A paired Student’s t-test was used to compare flows and T2s in fetuses at baseline and during MH (GraphPad © Prism 6, GraphPad Software, Inc., La Jolla, California, USA). Fetuses with CHD were compared with normal controls using an unpaired Student’s t-test. p-values ≤0.05 were considered statistically significant. We assessed inter-observer agreement for the T2 and PC CMR measurements using Pearson correlation and Bland–Altman plots.

RESULTS

Patients
We scanned 20 fetuses with CHD and 17 normal controls. The mean GA of normal controls (37.3 weeks ± 1 week) was similar to fetuses with CHD (36.2 weeks ± 1 week) (p=0.002). The types of CHD in the study group fetuses included tetralogy of Fallot (n=4); tricuspid atresia (n=4); borderline left ventricle (n=3); right/left ventricular disproportion (n=3); hypoplastic left heart syndrome (n=2); transposition of the great arteries (n=2); double outlet right ventricle (n=1); and interrupted aortic arch (n=1). One of the fetuses with tetralogy of Fallot also had confirmed trisomy 21, but no other genetic syndromes or congenital malformations were identified during the prenatal and postnatal period. Flow measurements were possible in each of the major vessels at baseline and during MH in total of 18 patients (11 normals and seven CHD), while in 13 patients (five normals and eight CHD), we were able to measure UV T2 during both baseline and MH. In 17 patients (ten normals and seven CHD), we were only able to measure flow in all of the vessels at baseline, resulting in failure to measure important flows in the AAo and SVC flows in 12 patients. In seven patients (two normals and five CHD), we were only able to measure T2 at baseline.

Accuracy of measurements
Figure 2 shows the level of inter-observer agreement for UV T2 (Figure 2A) and PC MRI pulmonary blood flow (Figure 2B) measurements by two observers (P. P., S. M.). There was a high level of agreement (r=0.99, p=0.0001) and UV T2 (r=0.95, p=0.0001), and the Bland–Altman plot shows no significant

Table 1 Fetal cardiovascular magnetic resonance sequence parameters

| Sequence | Type | Gating | Resp. comp. | Parallel imaging factor | NSA | TE (ms) | TR (ms) | Slice thickness (mm) | Matrix size | FOV (mm) | Temp. resol. (ms) | Scan time (s) |
|----------|------|--------|-------------|-------------------------|-----|---------|---------|---------------------|-------------|-----------|------------------|-------------|
| 3D SSFP  | 3D   | #      | Breath hold | 2                      | 1   | 1.74    | 3.99    | 2                   | 300x200     | 400       | #                | 13          |
| Static SSFP | 2D   | #      | #            | 1                      | 1.3 | 6.33    | 4       | 320x211             | 350         | 1336      | 24 (15 slices)  |
| Cine SSFP | 2D   | MOG    | #            | 2                      | 1   | 1.26    | 3.04    | 5                   | 340x310     | 340       | 46               | 55 (10 slices) |
| Phase contrasta | 2D   | MOG    | #            | 3.15                   | 6.78 | 3       | 240x240           | 240         | 54        | 36               |
| T2 mappingb | 2D   | PG     | #            | 2                      | 1   | 1.15    | 3.97b   | 5                   | 224x181     | 350       | 4000             | 16          |

NSA, number of signal averages; TE, echo time; TR, repetition time; FOV, field of view; PG, pseudo-gating (based on estimated RR interval); MOG, optimized gating; SSFP, steady-state free precession.

aVelocity encoding sensitivity tailored according to vessel: 1.50 cm/s for arteries, 100 cm/s for veins and 50 cm/s for umbilical vein. Number of segments per cardiac cycle = 4. 

bT2 mapping used 4 T2 preparation times, tailored to span the expected T2 of a given vessel (0 ms, 0.33* T2, 0.66*T2, 1.00*T2 and 1.33*T2), with 4000 ms of magnetization recovery between successive T2 preparations. Rapid imaging of the T2-prepared magnetization was performed using a single-shot SSFP sequence with the indicated TE/TR values. PG is based on estimated RR interval. MOG (R-R interval 545 ms).
bias. The difference in measurements was more in patients with lower pulmonary blood flow.

**Effect of maternal hyperoxygenation**

At baseline, the UV T2 was lower in CHD fetuses (158.9 ± 32.1 ms) than in normals (197.2 ± 46.1 ms), although the difference did not reach statistical significance (*p* = 0.13) (Figure 3 and Table 2). UV T2 did not increase significantly with MH in normals (208.6 ± 52.6 ms; *p* = 0.47), while we observed a 19% increase in UV T2 with MH in fetuses with CHD (188.6 ± 38.1 ms; *p* = 0.01). PBF was slightly lower in fetuses with CHD at baseline (*p* = 0.55), and the expected increase in PBF with MH was observed in both groups. PBF increased by 53% from 74.6 ± 56.3 mL/min/kg to 114.1 ± 56.0 mL/min/kg (*p* = 0.02) in normal fetuses and almost doubled from 62.4 ± 32.3 mL/min/kg to 121.0 ± 50.0 mL/min/kg in the CHD fetuses, *p* = 0.005. CHD fetuses had significantly higher DA flow compared with normals (250.1 ± 52.8 mL/min/kg versus 180.2 ± 42.9 mL/min/kg) at baseline (*p* = 0.002). While there was a significant reduction in DA flow in CHD fetuses during MH (206.5 ± 58 mL/min/kg; *p* = 0.04), there was no significant change in normals (188.5 ± 40.5 mL/min/kg; *p* = 0.38). The majority of CHD subjects in whom we were able to compare all flows at baseline and during MH had some form of left-sided obstruction, and in these fetuses, we noticed a trend towards higher ascending aortic flow during MH. This accounted for maintenance of stable descending aorta flow in the setting of the reduction in DA flow during MH. Although the number of patients in whom all of the flows could be compared was limited, we found no significant difference in blood flow in any of the other major vessels or combined ventricular output with MH.

**DISCUSSION**

The results of this study are in keeping with our previous work, suggesting that the O2 content of blood supplied to the developing fetus with CHD is lower than normals. It also reproduces the pulmonary vasodilatory effect of MH shown by previous studies in late gestation normals and CHD fetuses. We conclude that our results would therefore support the use of fetal MR to assess hemodynamic changes resulting from MH in late gestation human fetuses with and without CHD.

Our finding of lower SaO2 in the UV of fetuses with CHD may reflect abnormal placental function in fetuses with CHD, which have lower placental weights and a range of gross and histopathologic abnormalities, including eccentric placental cord insertion, abnormal maturation of villi, chorangiosis, inflammation, infarction and fetal thrombotic vasculopathy. The reason for this abnormal placentation remains uncertain but could reflect the obvious potential for hemodynamic alterations in these fetuses. Another possibility is that placental and cardiac abnormalities have common genetic origins. The reduction in UV SaO2 combines with failure of the normal
streaming of oxygenated blood from the placenta to the ascending aorta and the reduction in UV flow seen in particular in the setting of single ventricle CHD to impact the O2 content of blood supplied to the brains of fetuses with CHD. However, the higher O2 affinity of fetal hemoglobin resulting from weaker binding of 2,3-Bis-phosphoglycerate facilitates the transfer of O2 across the placenta from the maternal plasma to fetal red blood cells, and so the lower position of UV blood saturation on the O2 dissociation curve of hemoglobin may explain the higher uptake of O2 from maternal plasma we observed in CHD fetuses.

The pulmonary vasodilatory effect of O2 has been studied extensively, and in our study, the expected increase in PBF with MH was observed in both groups. This finding is consistent with human fetal Doppler studies, and its biochemical basis has been investigated using animal models. In fetal lambs, prostacyclin (PGI2) is synthesized primarily in vascular endothelial cells and vasodilates by activating adenylyl cyclase. In fetal lambs, prostacyclin (PGI2) is synthesized primarily in vascular endothelial cells and vasodilates by activating adenylyl cyclase.

A maturational increase in PGI2 production with advancing gestation parallels the decrease in pulmonary vascular resistance. Nitric oxide (NO) is synthesized in the endothelial cell of the fetus by activation of endothelial cell-derived NO synthetase in response to stimuli, such as shear stress, or receptor binding of endothelium-dependent vasodilators. NO production is also stimulated by activation of ATP-dependent K+ channels by stretch or increased shear forces on the pulmonary vascular endothelium. NO activates production of guanosine-3′-5′-cyclic monophosphate, which initiates a cascade that results in smooth muscle relaxation. Studies of intrapulmonary arteries and isolated lung preparations from fetal lambs reveal increases in NO-mediated relaxation with increasing gestation. O2 modulates the production of both PGI2 and endothelin-derived NO, the two potent vasodilators that may underlie, in part, the responses of the developing pulmonary circulation to changes in oxygenation.

Table 2

|                         | Normals | CHD     |
|-------------------------|---------|---------|
| **Baseline**            |         |         |
| UV T2 (n = 5)           | 197.2   | 158.88  |
| PBF (mL/kg/min, n = 14) | 74.57   | 62.36   |
| DA (mL/kg/min, n = 13)  | 180.23  | 250.09  |

| MH    |         |         |
|-------|---------|---------|
| UV T2 (n = 5) | 208.6 | 188.63 |
| PBF (mL/kg/min, n = 14) | 114.1 | 121 |
| DA (mL/kg/min, n = 13) | 188.46 | 206.45 |

| p     |         |         |
|-------|---------|---------|
|       | 0.47    | 0.01    |
|       | 0.02    | 0.005   |
|       | 0.38    | 0.04    |

CHD, congenital heart disease; MH, maternal hyperoxygenation; UV, umbilical venous; PBF, pulmonary blood flow; DA, ductus arteriosus. p ≤ 0.05 statistically significant.
pronounced in fetuses with CHD when compared with normal controls, possibly reflecting the greater increase in the O₂ content of fetal blood in the setting of CHD. We also observed a reduction in DA flow in fetuses with CHD. As DA flow is dependent on MPA flow and PBF, and MPA flow remained constant, the more dramatic increase in PBF seen in fetuses with CHD partly explains the greater reduction we observed in DA in CHD fetuses.

There is increasing evidence that CHD is associated with fetal brain dysmaturation,⁴⁹ and recent evidence suggests that this is associated with increased vulnerability to white matter injury around neonatal cardiac surgery and decrements in neurodevelopmental outcome at 2 years.⁵⁰,⁵¹ Our previous findings support the hypothesis that delayed fetal brain development in CHD may be caused by reductions in fetal cerebral O₂ delivery and consumption.²² Other groups have also noted a degree of lung hypoplasia in fetuses with CHD and attributed this to reduced lung perfusion.⁵² Our finding of lower baseline PBF in fetuses with CHD compared with controls would be in keeping with this hypothesis. In our study, MH resulted in an increase in UV T₂ and PBF with no change in UV flow, findings which are in keeping with an increase in fetal O₂ delivery and pulmonary vasodilatation. It would therefore seem reasonable to expect that MH is associated with increases in O₂ delivery to all fetal organs, including the lungs and brain. In conclusion, we propose that our study supports the investigation of MH as a treatment to promote lung and brain development in CHD.

LIMITATIONS

One of the major limitations of this study is the small number of patients. The measurement of flow and T₂ in small fetal vessels is challenging and limited by the tradeoff between spatial resolution, signal-to-noise ratio and scan time, and this resulted in our failure to make every measurement in every subject. However, our technique does meet the criteria for accurate vessel oximetry using T₂ relaxometry³³ and adequate spatial and temporal resolution to make accurate flow measurements in small vessels as defined by Hofman et al.⁵³

The known relationship between T₂ and SaO₂ resulting from the paramagnetic properties of deoxygenated hemoglobin has been defined for adult blood with a known hematocrit.⁵⁴ As fetal and adult forms of hemoglobin have different physical properties, the relationship between their T₂ and SaO₂ is likely to be different. Furthermore, the previously defined relationship between adult blood and T₂ is also dependent on hematocrit, with polycythemia resulting in a shorter T₂ for the same SaO₂. In theory, this could have impacted our results if the fetuses with CHD had higher hemoglobin concentrations. However, newborns with CHD reveal a normal range of hemoglobin concentration,⁵⁵ and our most important observation was the change in T₂, which would not be expected to be influenced by hemoglobin concentration. In future, it may be possible to take advantage of the strong relationship between hematocrit and T₁ and combine T₁ and T₂ mapping in order to measure both SaO₂ and hemoglobin concentration,⁵⁶ thus improving the accuracy of fetal MR oximetry.

The fetuses in the CHD group were on average approximately a week younger than the normal fetuses. Previous studies have shown that the fetal pulmonary vasodilatory response to O₂ content becomes more pronounced with advancing GA, while there is a gradual increase in PVR between 30 and 38 weeks of GA.¹¹,¹⁴,⁵⁷ We would therefore expect an even more dramatic response to MH in fetuses with CHD if they were as old as the normal fetuses at the time of MH, and that they would have even lower PBF at baseline. Similarly, UV O₂ is known to decrease with advancing GA.⁵⁸ Therefore, the differences between the groups cannot be attributed to the small difference in GA.

Ideally, we would have studied the effect of MH on fetal cerebral O₂ delivery. However, the smaller size and more curved course of the fetal AAo and SVC result in a greater risk of partial volume artifacts affecting T₂ measurements made in these vessels. Furthermore, in common with other investigators, we noted an increase in fetal movements during MH and found the combination of more significant motion and partial volume artifacts during MH made the measurement of cerebral O₂ delivery unusable using our technique. This is an important limitation of this approach, although advances in MR technology such as accelerated imaging acquisitions and higher field strength may overcome these limitations in the future.⁵⁹,⁶⁰

With regard to the implications of these and others’ findings regarding the impact of MH on fetal oxygenation, it is worthwhile noting that the majority of the data refer to acute MH. Additional information regarding the hemodynamic impact of chronic MH would also therefore be helpful to inform the consideration of the utility of long-term transplacental O₂ therapy aimed at improving fetal growth. Furthermore, chronic treatment with a fraction of inspired oxygen of 70% may not be very feasible because this concentration of O₂ can only be delivered with a non-rebreather mask and would potentially be inconvenient and uncomfortable. Further investigations to assess the fetal hemodynamic effects of lower concentrations of inhaled O₂ that could be administered via nasal prongs would therefore also be desirable.

CONCLUSION

We report an increase in umbilical vein T₂, indicating an improvement in the SaO₂ of umbilical venous blood, and pulmonary vasodilatation in fetuses with CHD during acute MH. Our results therefore suggest that fetal MR provides an additional tool to assess hemodynamic changes resulting from MH and could provide useful additional fetal monitoring if chronic MH is being used for therapy.

WHAT’S ALREADY KNOWN ABOUT THIS TOPIC?

Doppler and invasive techniques have revealed fetal hemodynamic changes during maternal hyperoxygenation (MH). Chronic MH has been used as a treatment for intrauterine growth restriction and to encourage ventricular growth in fetuses with congenital heart disease.

WHAT DOES THIS STUDY ADD?

Fetal MR provides a non-invasive tool to assess hemodynamic changes resulting from MH and could provide useful additional fetal monitoring if chronic MH is being used for therapy.
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