Fetal Cardiovascular MRI

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Background and rationale

Intrauterine growth restriction (IUGR) is associated with changes in fetal cerebral, peripheral and placental vascular resistance resulting in circulatory redistribution commonly referred to as ‘brain-sparing physiology’ [1]. This is routinely identified through detection of velocity waveforms in the cerebral and umbilical arteries using Doppler ultrasound [2]. However, animal studies suggest that chronic fetal hypoxia results in a reduction in fetal oxygen consumption (VO₂) that tends to normalize blood flow distribution, but which is nevertheless associated with delayed fetal growth and development [3, 4]. The detection of chronic IUGR might therefore be improved by the identification of reduced fetal VO₂ in the setting of normal Doppler findings. This could be particularly useful towards the end of the pregnancy, when the potential benefits of delivery from in utero hypoxia and starvation outweigh the risks of premature birth.
Fetal VO$_2$ can be calculated when the oxygen content of blood in the umbilical artery and vein, and placental blood flow are known [7]. This has been achieved in human fetuses using invasive cordocentesis and ultrasound [8]. However, ultrasound measurements of vessel flow are prone to inaccuracy [9], and the risks associated with direct cordocentesis make it unsuitable for routine clinical use. We sought to develop cardiovascular magnetic resonance (CMR) techniques to assess fundamental elements of fetal cardiovascular physiology including oxygen delivery (DO$_2$), oxygen consumption (VO$_2$), and the distribution of blood flow and oxygen content in the major vessels of the fetal circulation. We present here our preliminary findings in the normal human fetal circulation.

**Theory**

Techniques for measuring blood flow using phase-contrast (PC) MRI [10] and oxygen content using quantitative T2 MRI [11, 12] are well established, but imaging fetal* vessels requires modification of the existing techniques. Specific challenges include the small size of the vessels, the virtually constant movement of the fetus, and difficulty detecting the fetal electrocardiogram for cardiac triggering.

The latter can be overcome with alternatives to ECG gating such as self-gating [13] and cardiotoxicographic gating [14], which have both been shown to be feasible in fetal animal models. Alternatively, a retrospective technique can be used that acquires temporally oversampled data and then iteratively sorts the data using hypothetical ECG trigger times until artifact in the associated images is minimized [15]. This approach, which is illustrated in Figure 1, is termed metric optimized gating (MOG) and has been used successfully for PC MRI and steady state free precession (SSFP) cine imaging [16, 17].

Regarding fetal oximetry, a novel approach to myocardial T2 mapping with non-rigid motion correction has been developed by Giri et al., which holds promise for improving fetal MR oximetry in the presence of small fetal movements [18, 19]. This approach, currently available as a work-in-progress from Siemens**, may improve T2 accuracy by aligning target vessels across images used to construct a T2 map.

For fetal MRI, short scan times are essential to reduce artifact from gross fetal motion. As a result, there is a practical limit to the spatial resolution and signal-to-noise ratio that can be achieved. However, in our experience PC MR and T2 mapping techniques perform well in the majority of late gestation fetuses, whose vessel sizes are similar to neonates and whose body motion is partly restricted by the uterine walls.

Assuming a normal hematocrit, the PC MRI and T2 data may be used to calculate fetal DO$_2$ and VO$_2$ [7]. This requires calculation of the oxygen content, C, of umbilical venous (UV) blood, which is given by the equation:

\[
C_{UV} = [Hb] \times 1.36 \times Y_{UV}
\]

where $Y_{UV}$ is the oxygen saturation of blood in the UV, and 1.36 is the amount of oxygen (ml at 1 atm) bound per gram of hemoglobin.

Fetal DO$_2$ can then be calculated from the product of UV flow ($Q_{UV}$) and $C_{UV}$. To calculate fetal VO$_2$, the arterio-venous difference in oxygen content ($\Delta C$) between the UV and umbilical artery (UA) must be calculated, as follows:

\[
\text{Fetal VO}_2 = Q_{UV} \times \Delta C_{UV-UA}
\]

Because of the small size of the UA, the T2 in the descending aorta (DAo) is used for this calculation.

If it is assumed that the majority of the flow in the superior vena cava (SVC) is venous return from the brain then fetal cerebral VO$_2$ can also be approximated:

\[
\text{Fetal cerebral VO}_2 = Q_{SVC} \times \Delta C_{AAO-SVC}
\]

**Fetal CMR methodology and protocol**

**Safety** – The American College of Radiologists recommends fetal MRI only be used when alternative imaging techniques, namely ultrasound, are considered inadequate by the responsible imaging physician [20]. Contrast agents should be avoided due to the risk of toxicity to the fetus and where possible fetal MRI should be avoided in the first trimester. We follow the Siemens recommendation to limit the specific absorption rate (SAR) to 2 watts per kilogram (‘normal mode’). A recent review reports that there is no evidence that MRI poses any risk to the mother or fetus [21].

**Field strength** – Fetal cardiovascular MRI can be performed on 1.5T and 3T systems. 1.5T systems are less prone to SSFP banding artifacts from field inhomogeneity. However, the increased SNR available at 3T makes PC imaging more robust, and facilitates MOG reconstruction. An important consideration is the effect of field strength on the relationship between T2 and blood oxygenation, with shorter T2 values encountered at 3T [22].

**Patient positioning and coil selection** – A body-matrix coil placed on the maternal abdomen, as close to the fetal thorax as possible, provides the best signal for fetal imaging. The addition of a second coil may help to improve signal across the whole field-of-view, particularly if the mother is in a lateral decubitus position, which many women find most comfortable in later on in pregnancy.

**Gating** – For MOG, an artificial gating trace is used in place of the actual fetal waveform. On Siemens systems this may be controlled using the IDEA command tool menu to define an R-R interval. For most fetuses an R-R interval of 545 ms, which corresponds to a heart rate of 110 beats per minute, will ensure that every heartbeat is oversampled.

**Sequences** – With the exception of the T2 mapping WIP**, the sequence parameters shown in Table 1 are based on commercially available Siemens
cardiac MRI sequences, and represent a possible approach to fetal CMR at 1.5T. For PC vessel flow quantification, we use a minimum of eight voxels over the vessel area and a temporal resolution of 50 ms. Adequate spatial resolution is also required for T2 measurements to avoid partial volume artifacts [23]. We use an interval of ~4 seconds (8 cardiac cycles) between T2 preparation pulses for T2 mapping to ensure adequate recovery of magnetization. Figure 1 shows how we orient the PC and T2 acquisitions for the target vessels.

Maternal hyperoxygenation – Investigators have used a trial of maternal hyperoxygenation (MH) to enhance fetal hemodynamic assessment, and maternal oxygen therapy has been proposed as a treatment for cardiac ventricular hypoplasia and IUGR. MH does not appear to be associated with any risk to the fetus or mother. One approach is to use a non-rebreather mask with 12 L/min of oxygen to administer an FiO2 of 60–70%. Previous studies suggest oxygen should be given for 5–10 minutes prior to and during imaging [24].

Post processing

Flow – The MOG technique currently requires transfer of the raw data from the MRI to a computer for offline reconstruction using stand-alone software developed at our institution (MATLAB, Mathworks, USA). This software is available from our laboratory upon request. To quantify flow from the resulting PC MRI reconstructions, commercially available software is used (Q-flow, Medis, Netherlands).

Fetal weight – Flows are indexed to fetal weight based on a high-resolution 3D SSFP breath-hold acquisition covering the whole fetus to calculate the fetal volume. We use a combination of thresholding and other tools in Mimics (Materialise, Belgium) to segment the fetus. Fetal volume is converted to fetal weight using the conversion proposed by Baker (fetal weight (g) = 120 + fetal volume (ml) \times 1.03) [25]. The same 3D SSFP acquisition can be used to calculate the volume and weight of individual fetal organs including the fetal brain, where brain weight (g) = brain volume \times 1.04 [26].
Table 1:

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Type</th>
<th>Gating</th>
<th>Resp. comp.</th>
<th>Parallel imaging factor</th>
<th>NSA</th>
<th>TE (ms)</th>
<th>TR (ms)</th>
<th>Slice thick (mm)</th>
<th>Matrix size</th>
<th>FOV (mm)</th>
<th>Temp. resol. (ms)</th>
<th>Scan time(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D-SSFP</td>
<td>3D</td>
<td>–</td>
<td>Breath-hold</td>
<td>2</td>
<td>1</td>
<td>1.74</td>
<td>3.99</td>
<td>2</td>
<td>256 x 205 x 80</td>
<td>400</td>
<td>–</td>
<td>13</td>
</tr>
<tr>
<td>Static SSFP</td>
<td>2D</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>1</td>
<td>1.3</td>
<td>6.33</td>
<td>4</td>
<td>320 x 211</td>
<td>350</td>
<td>1336</td>
<td>24</td>
</tr>
<tr>
<td>Cine SSFP</td>
<td>2D</td>
<td>MOG</td>
<td>–</td>
<td>2</td>
<td>1</td>
<td>1.26</td>
<td>3.04</td>
<td>5</td>
<td>340 x 310</td>
<td>340</td>
<td>46</td>
<td>55</td>
</tr>
<tr>
<td>Phase contrast†</td>
<td>2D</td>
<td>MOG</td>
<td>–</td>
<td>2</td>
<td>1</td>
<td>3.15</td>
<td>6.78</td>
<td>3</td>
<td>240 x 240</td>
<td>240</td>
<td>54</td>
<td>36</td>
</tr>
<tr>
<td>T2 mapping†</td>
<td>2D</td>
<td>PG</td>
<td>–</td>
<td>2</td>
<td>1</td>
<td>1.15†</td>
<td>3.97†</td>
<td>6</td>
<td>224 x 181</td>
<td>350</td>
<td>4000</td>
<td>12</td>
</tr>
</tbody>
</table>

† Velocity encoding sensitivity tailored according to vessel: 150 cm/s for arteries, 100 cm/s for veins and 50 cm/s for umbilical vein.
Number of segments per cardiac cycle = 4

† T2 mapping used 4 T2 preparation times, tailored to span the expected T2 of a given vessel (0 ms, 0.33*T2, 0.66*T2, and 1.00*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.

NSA: number of signal averages, TE: echo time, TR: repetition time, FOV: field-of-view, PG: pseudo-gating (based on estimated R-R interval), MOG: metric optimized gating (R-R interval 545 ms)
How-I-do-it

T2 mapping – Regions-of-interest covering the central 50% of the vessel area are used for measuring T2. We currently convert the T2 values to saturations using the relationship described by Wright et al. for adult blood [11]. The accurate conversion of the T2 of blood to oxygen saturation is dependent on hemoglobin concentration \([Hb]\). We assume a fetal \([Hb]\) of 15g/dL at 36-37 weeks [27].

Results

Tables 2 and 3 show the mean vessel flows and ranges of flows in 30 subjects (mean gestational age – 37 weeks, SD 1.2) by phase contrast MRI. We also present preliminary mean oxygen saturations, fetal \(DO_2\) and \(VO_2\) for eight subjects based on our preliminary experience with fetal vessel T2 mapping. Figure 3 represents the mean flows and oxygen saturations across the circulation. The findings are in keeping with previous estimations made regarding the human fetal circulation based on results of invasive measurements in fetal lambs and human ultrasound and cordocentesis results [7, 8].

Discussion

Interpretation of fetal cardiovascular MRI is currently limited to a few preliminary observations. Understanding the findings requires knowledge of normal fetal cardiovascular physiology. The normal fetal circulation operates in parallel with shunts at the foramen ovale and ductus arteriosus resulting in blood bypassing the fetal lungs. This is tolerated in the fetal circulation because gaseous exchange occurs at the placenta. The fetus exists in a relatively low oxygen environment, but also has lower oxygen consumption than the newborn due to lower demands for thermoregulation [7].

In fetal lambs, the oxygen saturation of blood in the left side of the fetal heart is approximately 10% higher than the right due to a remarkable streaming mechanism where oxygenated blood returning from the placenta is preferentially directed across the foramen ovale via the left liver and ductus venosus. This is presumably to ensure a reliable source of oxygen to the developing brain and coronary circulation. The less well-oxygenated blood returning from the SVC and lower body is preferentially routed towards the tricuspid valve and then on to the ductus arteriosus and pulmonary circulation. As pulmonary vascular resistance in the third trimester is inversely proportional to the oxygen content of the blood in the pulmonary arteries, a high pulmonary vascular resistance is maintained in the fetal lamb. Pulmonary vascular resistance is also high in the human fetus, although there is higher pulmonary blood flow compared with lambs [7]. There is also higher flow in the SVC in the human, likely reflecting the larger brain size, and lower flow in the umbilical vein, probably made possible by the higher hematocrit present in human fetuses. In fetal lambs exposed to chronic hypoxia there is an adaptive response where a 20% increase in hematocrit increases the oxygen carrying capacity of fetal blood [4]. Interestingly, T2 is inversely proportional to hematocrit, so that chronic hypoxia may result in a further reduction in the T2 of blood resulting from polycythemia [28].

The term ‘brain-sparing’ refers to an important mechanism in fetal circulatory physiology. This acute response to fetal hypoxia has been well studied in...
animal models and observed in human fetuses and is characterized by a reduction in the vascular resistance of cerebral and coronary vessels and increase in peripheral and pulmonary vascular resistance [1]. The result is a dramatic increase in cerebral and coronary blood flow, so that oxygen delivery to the brain and heart is maintained despite a fall in the oxygen content of the blood supplied to those organs. We have noted SVC flows greater than 250 ml/min/kg, or 50% of the CVO in fetuses with antenatal and postnatal evidence of placental insufficiency [29].

Limitations of this work include the absence of any attempt as yet to validate this T2 mapping technique for fetal blood in fetal vessels and our current dependence on an estimation of fetal hematocrit. Fetal hemoglobin may differ from adult hemoglobin in terms of its magnetic properties, and the small size of the fetal vessels of interest may render our T2 measurements subject to partial volume artifacts. With further investigation and a larger sample size we aim to gain a better understanding of these factors and show that oximetry can be successfully combined with the more established flow quantification.

Conclusion

We have speculated about the clinical significance of our preliminary observations regarding the distribution of flow in fetuses with CHD and IUGR [26, 30, 29], and hope that with more experience and development, fetal CMR may gain acceptance amongst clinicians as an additional tool to help guide obstetric management in these and other fetal conditions.

References


*Siemens disclaimer: MR scanning has not been established as safe for imaging fetuses and infants less than two years of age. The responsible physician must evaluate the benefits of the MR examination compared to those of other imaging procedures.

**WIP, the product is currently under development and is not for sale in the US and other countries. Its future availability cannot be ensured.

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