Reduced combined ventricular output and increased oxygen extraction fraction in a fetus with complete heart block demonstrated by MRI

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Introduction

Congenital complete heart block (CHB) occurs in approximately 1 in 15,000 live births.[1] It may result from an immune- or non-immune-mediated process, with immune-mediated cases usually associated with high-titer maternal anti-Ro antibodies, which cross the placenta and may result in injury to the fetal cardiac conduction tissues.[2] Autoimmune-mediated congenital CHB is associated with significant morbidity and mortality in the perinatal period.[2] One study reported a total mortality rate of CHB to be 19%, of which 27% died in utero and 45% died within the first 3 months of life.[2] Risk factors for poor fetal outcome include premature delivery, fetal hydrops, low heart rate, and ventricular endocardial fibroelastosis.[3] CHB is known to decrease cardiac output in postnatal patients.[4] However, the hemodynamics of the fetal circulation in the setting of CHB have not been well characterized. Fetal echocardiography can be used to detect and analyze fetal arrhythmias. Mechanical assessment by M mode can be used to characterize fetal bradycardia including CHB, and pulsed Doppler is also widely employed to visualize the temporal relationships of the blood flows in the heart and great vessels that delineate the timing of cardiac electrical events.[4] New magnetic resonance imaging (MRI) technology now provides an additional noninvasive method for measuring the oxygen saturation (SaO2) and flow in fetal blood vessels. The feasibility of this MRI technique, which incorporates a combination of cine phase-contrast MRI and T2 mapping, has been shown in normal fetal circulation, and in fetuses with congenital heart disease and intrauterine growth restriction, and we were interested to see what such an approach might reveal in the setting of CHB.[5–8]

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Case report

Fetal bradycardia was first noted in a 26-year-old mother with systemic lupus erythematosis during a routine obstetric anatomy scan at 19 weeks gestation. The pregnancy had otherwise been uncomplicated, although screening for autoantibodies revealed an elevated anti-Ro titer. At the first echocardiogram, the fetus was found to be in second-degree heart block, with an atrial rate of 149 beats per minute (bpm) and ventricular rate of 73 bpm without signs of cardiac dysfunction, endocardial fibroelastosis, or effusions. The estimated fetal weight was on the 40th percentile. The mother was started on a course of dexamethasone and intravenous immunoglobulin. By 20 weeks, the atrioventricular conduction had progressed to CHB (Figure 1) (Philips iE33; Philips ATL, Bothell, WA) and the fetal heart rate had dropped to 50 bpm. The patient was started on oral salbutamol at 34 weeks gestation to maintain fetal heart rates between 51 and 55 bpm until delivery. At 36 weeks gestation the fetus was delivered by cesarean section for nonreassuring biophysical profile, and was born in good condition weighing 2020 g (below 3rd percentile). The birth weight and fetal growth curve, produced using ultrasound biometry (Figure 2), were in keeping with intrauterine growth restriction (IUGR). The heart rate at birth was 50 bpm and a permanent pacemaker was placed with epicardial ventricular leads. The infant was discharged from the hospital at 8 days of age with ventricular pacing at 120 bpm, a systolic blood pressure of 62–78 mm Hg and arterial SaO2 of 96%–98%.

Fetal MRI hemodynamic assessment

After obtaining informed consent as part of a hospital ethics board–approved study, a fetal MRI scan was performed at 35

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KEY TEACHING POINTS

- Bradycardia in a complete heart block fetus is associated with a significant reduction in fetal combined ventricular output, resulting in restricted fetal growth and elevated oxygen extraction.
- Magnetic resonance imaging (MRI) confirmed the "brain-sparing physiology" that was indicated by the Doppler assessment.
- MRI hemodynamic assessment could provide a useful adjunct to conventional ultrasound parameters in the monitoring of fetal well-being in complete heart block.

weeks using a 1.5 Tesla clinical MRI system (Siemens Avanto, Erlangen, Germany) according to our previously published technique.[5,6] Three-dimensional volumetry provided an estimation of fetal weight of 1950 g, which was at the 2nd percentile for gestational age. The fetal heart rate was at about 50 bpm at the time of the MRI scan. A reconstruction technique called metric optimized gating was used for retrospective cardiac triggering, allowing high-resolution time-resolved phase-contrast MRI measurements of fetal blood flow. An example of flow measurement in the fetal descending aorta (DAo) is shown in Appendix 1 (supplemental material available online). The phase-contrast results were compared with reference ranges (mean ± 2 standard deviations).[5] The results showed low normal flow in the pulmonary arteries, ductus arteriosus, and superior vena cava (SVC), and significantly reduced flows in ascending aorta, DAo, and umbilical vein (UV). The combined ventricular output (the sum of ascending aortic and main pulmonary artery flows; CVO) was significantly reduced. T2, an MRI parameter related to blood SaO2, was normal in the UV but low in all other measured vessels compared to values in normal fetuses (Figure 3A). Estimating fetal hematocrit according to gestational age–appropriate reference ranges and assuming the relationship of the T2 of blood with fetal SaO2 to be the same as exists for adult blood, the SaO2 and oxygen content of blood in fetal vessels was calculated according to our previously published technique.[5,6] The SaO2s across the fetal circulation in this case, compared with reference ranges, are shown in Figure 3B. By combining oxygen content measurements in the UV and DAo with UV flow, fetal oxygen delivery (DO2), consumption (VO2), and oxygen extraction can be calculated.[9,10] The fetus had normal VO2 (6.9 mL/min/kg, reference: 3.7–10.4) and reduced DO2 (13.3 mL/min/kg, reference: 12–28.8), which was associated with a high oxygen extraction fraction (52%, reference: 21%–49%) (Figure 3C).[7]

Discussion

By using the novel MRI methods, this study provides new insight into the hemodynamic impact of a persistently slow heart rate and atrioventricular dissociation. Our findings reveal that the bradycardia was associated with an increase in oxygen extraction to maintain fetal VO2 within the normal range, despite the reduction in fetal DO2 that is caused by diminished umbilical flow. In keeping with the association between CHB and low birth weight reported by Eronen et al, our fetal biometric measurements were consistent with IUGR, which may have been due to a combination of decreased fetal DO2 and transplacental steroid administration.[11,12]

Doppler findings are helpful in the setting of IUGR as changes in cerebral and placental resistance reflect redistribution of the circulation in response to hypoxia, although the interpretation of fetal Dopplers is problematic in the setting of CHB, as the prolonged diastolic time results in reduced end-diastolic velocities.[5,13,14] However, the cerebroplacental ratio (CPR), which overcomes this problem because it is a ratio of middle cerebral artery and umbilical artery (UA) pulsatility index (PI), has been shown to have prognostic value in the setting of CHB.[15] The Doppler findings therefore support a hypothesis that the fetal growth restriction had a cardiovascular etiology in this case, in which the UA PI was high and middle cerebral artery PI was in the normal range resulting in a CPR below the 5th percentile throughout the pregnancy. This impression is supported by the MRI flow measurements, which indicate that at 47%, the percentage of the CVO present in the SVC was significantly higher than in normal fetuses (reference range: 15%–43%).[5]

Fetal DO2 is determined by umbilical blood flow and the oxygen content of UV blood.[10] DO2 can drop when there is decreased DO2 from the maternal circulation to the placenta, interference in diffusion of oxygen across the placenta, or decreased umbilical blood flow.[10] In our case, the low normal DO2 was caused by reduced UV flow, with normal UV T2 SaO2 in keeping with normal placental oxygenation and adequate oxygen exchange. By contrast, fetal VO2 was unaffected owing to an increase in the arteriovenous difference in SaO2 between the UV and UA. This adaptation was also observed in fetal animal models of acute hypoxia, whereby oxygen extraction increases from 30% to 70%, so that DO2 can be reduced acutely by almost 50% with no fall in VO2.[16]

Limitations

The conversion of T2 to SaO2 is derived from adult blood experiments, and does not account for the slightly longer T2 of fetal hemoglobin. Furthermore, hemoglobin concentration [Hb] could also influence the relationship between T2 and SaO2. Because fetal [Hb] cannot be directly measured, we estimated [Hb] based on population averages.[17] A high [Hb] would shorten T2, which could exaggerate desaturation. However, we propose this is unlikely in this case, as the neonatal [Hb] was close to the normal mean at 17.9 g/dL. Finally, our T2 mapping technique has not been fully validated for performing oximetry in blood flowing in fetal

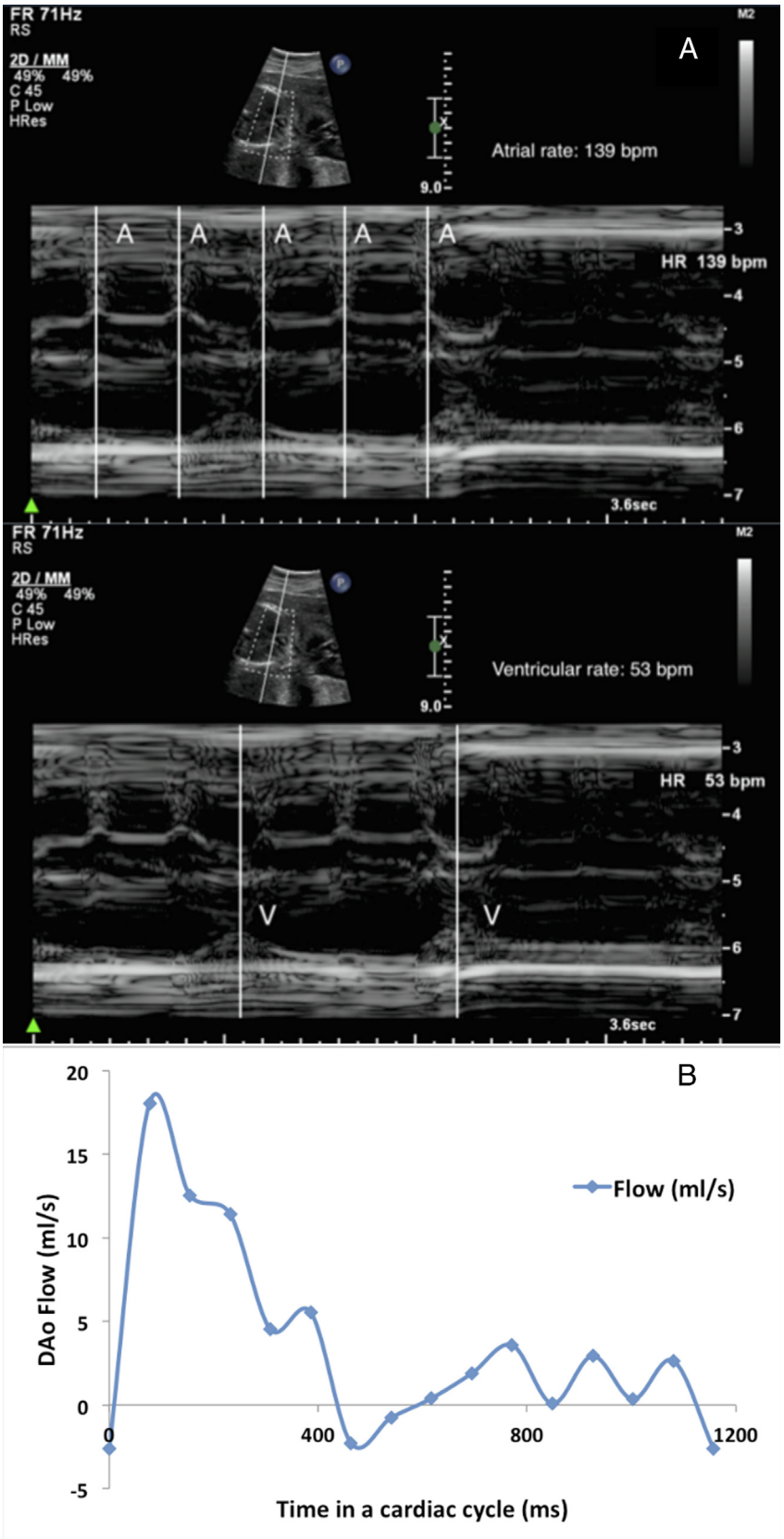

Figure 1 **A:** M mode at 36 weeks gestation demonstrates a slow ventricular rate and complete dissociation between atrial and ventricular contraction. V = ventricular; A = atrial. **B:** Fetal descending aortic flow curve measured by phase-contrast magnetic resonance with metric optimized gating at 35 weeks gestation. Fetal cardiac cycle was 1157 ms, corresponding to heart rate 52 beats per minute.

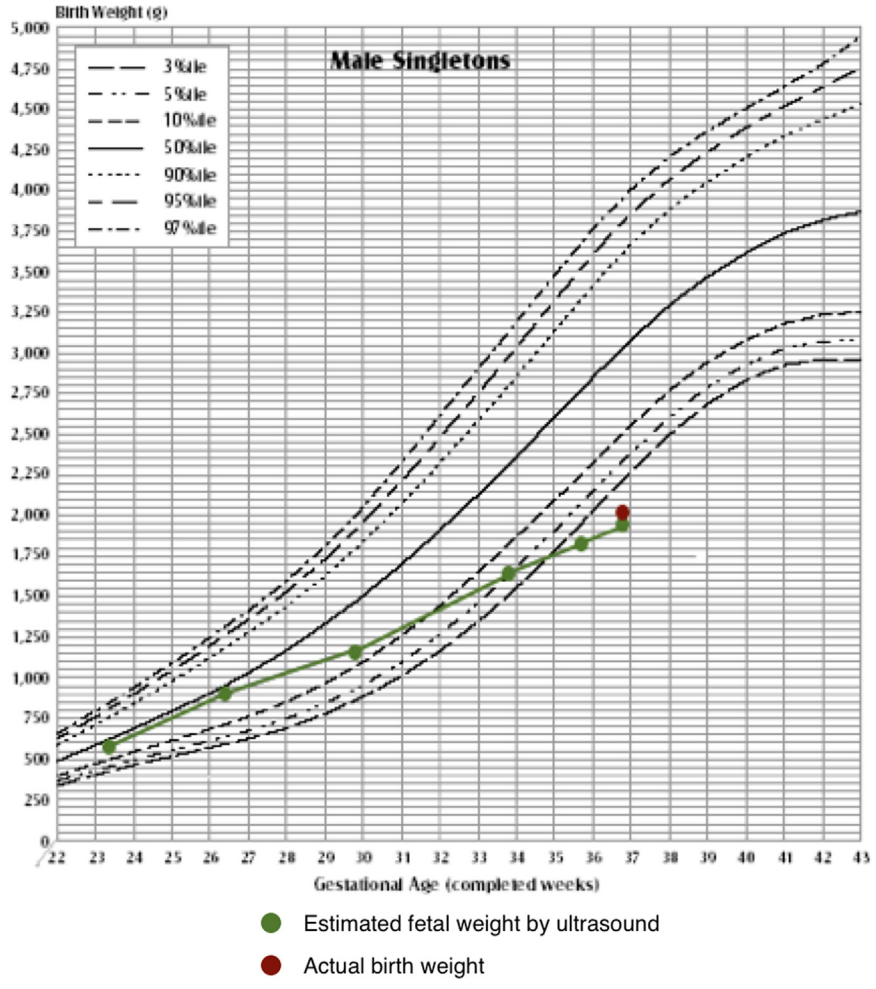

Figure 2 Ultrasound-estimated fetal weight plotted on a reference male singleton weight chart. The fetal weight percentile dropped from 26 weeks to 36 weeks. (23 wk: 35th; 26 wk: 45th; 29 wk: 15th; 33 wk: 10th; 35 wk: 3rd; 36 wk: 2nd).[18]

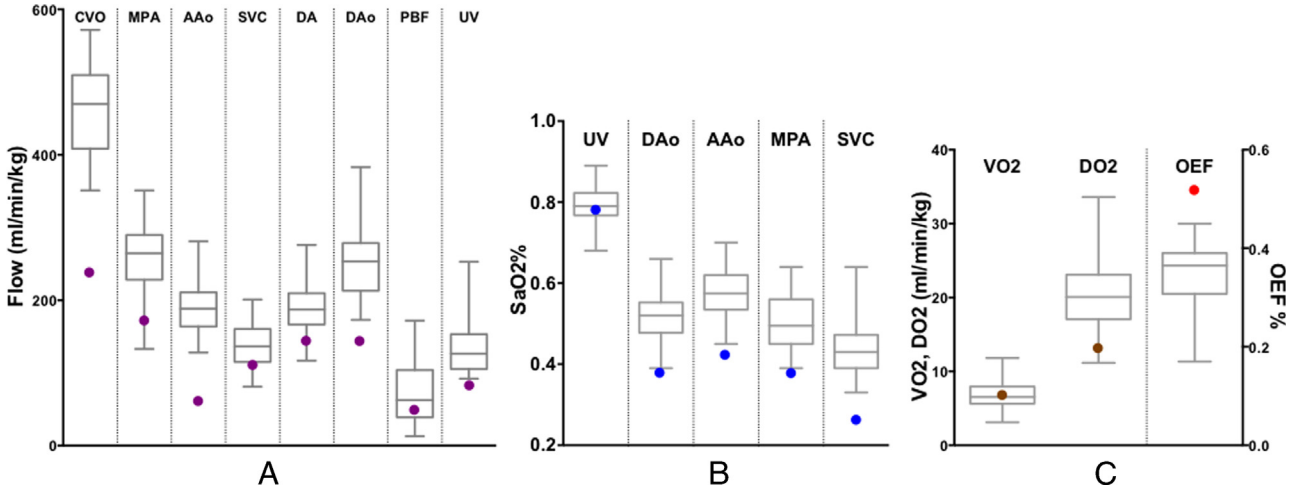

Figure 3 **A:** Magnetic resonance imaging measured flow in major fetal vessels. **B:** Oxygen saturation calculated based on T2 relaxation time in major fetal vessels. **C:** Calculated oxygen consumption (VO2), oxygen delivery (DO2), and oxygen extraction fraction (OEF). Reference ranges for each parameter for normal fetuses are also shown.[5,7] CVO = combined ventricular output; MPA = main pulmonary artery; AAo = ascending aorta; SVC = superior vena cava; DA = ductus arteriosus; DAo = descending aorta; PBF = pulmonary blood flow; UV = umbilical vein.

vessels, although good agreement has been shown between T2 oximetry and conventional blood gases in the vessels of children with congenital heart disease and in fetal lambs.[19,20] Despite the limitations of our technique, its potential value lies in the fact that there is currently no noninvasive alternative for making oximetry measurements. The limitations of ultrasound measures of the relative resistance of different fetal vascular territories have been referred to above, while flow measurements made using Doppler and vessel diameters are prone to inaccuracies in measurement of vessel area, problems with obtaining an adequate angle of insonation, and problems accounting for the different blood flow velocities encountered across the lumen of the vessel.[21] By contrast, phase-contrast MRI is the noninvasive gold standard for the quantification of flow in fetal vessels, and is routinely used in postnatal clinical practice for measuring cardiac output, QP:QS, etc.[22] However, the technical challenges of fetal cardiovascular MRI currently limit this approach to late gestation, and the hemodynamic measurements obtained in a single "snapshot" may not be reflective of diurnal or gestational age-related changes in fetal cardiovascular physiology.

Conclusion

In conclusion, this is the first report of fetal hemodynamic measurements by MRI in the setting of congenital CHB. MRI confirmed the "brain-sparing physiology" that was indicated by the Doppler assessment. Our data provide the evidence of a cardiac hemodynamic basis for growth restriction, which may be accentuated by the use of prenatal steroids in this CHB fetus. Our case also provides evidence to suggest that despite an increase of approximately 70% in stroke volume, the bradycardia is associated with a significant reduction in fetal CVO, resulting in restricted fetal growth and elevated oxygen extraction. Of interest, the dramatic increase in oxygen extraction fraction seen here is similar to our results in other fetuses with IUGR and those with forms of congenital heart disease associated with the lowest CVO, namely severe forms of Ebstein's anomaly or tricuspid valve dysplasia, while most forms of congenital heart disease are associated with normal oxygen extraction fraction.[7] In this case, the heart rate was particularly low, and it is possible that fetuses in CHB with higher ventricular rates are able to maintain more normal CVO. We propose that in future this kind of hemodynamic assessment could provide a useful adjunct to conventional ultrasound parameters in the monitoring of fetal well-being in the setting of CHB. A prospective study with a larger number of CHB patients will be required to further clarify the physiological changes and adaptation in CHB fetuses and also the role of MRI in monitoring CHB fetuses.

Appendix

Supplementary data

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.hrcr.2015.12.010.

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