Cerebral Oxygenation Measurements by Magnetic Resonance Imaging in Fetuses With and Without Heart Defects

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Background—Children with major congenital heart defects are risking impaired cerebral growth, delayed cerebral maturation, and neurodevelopmental disorders. We aimed to compare the cerebral tissue oxygenation of fetuses with major heart defects to that of fetuses without heart defects as estimated by the magnetic resonance imaging modality T2*. T2* is low in areas with high concentrations of deoxyhemoglobin.

Methods and Results—At gestational age mean 32 weeks (early) and mean 37 weeks (late), we compared the fetal cerebral T2* in 28 fetuses without heart defects to that of 15 fetuses with major heart defects: transposition of the great arteries (n=7), coarctation of the aorta/hypoplastic aortic arch (n=5), tetralogy of Fallot (n=1), hypoplastic right heart (n=1), and common arterial trunk (n=1). The women were scanned with a 1.5 T Philips scanner using a breath-hold multiecho gradient echo sequence. Among fetuses without heart defects, the mean T2* value was 157 ms (95% confidence interval [CI], 152–163) early and 125 ms (95% CI, 120–130) late. These figures were significantly lower (mean 14 ms; 95% CI, 6–22; $P<0.001$) among fetuses with heart defects 143 ms (95% CI, 136–150) early and 111 ms (95% CI, 104–118) late.

Conclusions—Our findings indicate that fetal cerebral T2* is measurable and that fetal cerebral tissue oxygenation measured by T2* is lower in fetuses with heart defects compared with fetuses without heart defects. This corroborates the hypothesis that tissue hypoxia may be a potential pathogenic factor that possibly affects brain development in fetuses with heart defects. **(*Circ Cardiovasc Imaging*. 2017;10:e006459. DOI: 10.1161/CIRCIMAGING.117.006459.)**

Key Words: deoxyhemoglobin ■ fetus ■ gestational age ■ heart diseases ■ hypoxia ■ magnetic resonance imaging ■ prognosis

Congenital heart disease is the most common birth defect, affecting 6 to 8 per 1000 live births.[1] Most of these children survive,[2] but 33% to 43% experience impaired neurodevelopment,[3,4] which can only be explained in part by genetic and chromosomal disorders and cardiac surgery complications.[5] Consequently, impaired brain development during late gestation has been suggested as an important cause of these disorders[6–10] as head size and brain maturation are affected at birth.

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In fetuses without heart defects, the brain is supplied by oxygenated and nutrient-rich blood directly from the placenta. In fetuses with heart defects, because of abnormal mixing of oxygenated blood from the placenta and deoxygenated blood from the fetal body, the brain is often supplied with blood that has reduced oxygen and nutritional content. Furthermore, reduced perfusion pressure may be a significant factor. Several studies document a compensatory increase in cerebral blood flow in fetuses with heart defects,[11–13] as demonstrated by a reduced resistance index in the middle cerebral artery. In spite of this brain-sparing effect, cerebral blood flow may still be inadequate to secure the oxygen supply needed for optimal brain development,[12] and brain-sparing has been associated with impaired neurodevelopment in children with congenital heart defects.[13]

Cross-sectional measurements of the blood flow and oxygen saturation in the major vessels supplying and draining the fetal brain after 35 weeks of gestation indicate reduced cerebral oxygen supply and consumption in fetuses with heart defects.[14]

In the present study, we estimated fetal cerebral tissue oxygenation using the magnetic resonance (MR) transversal relaxation time (T2*), which depends on the tissue concentration of deoxyhemoglobin.[15] T2* is measured by a gradient echo sequence with multiple echo times (TEs). The measured intensity as a function of TE is fitted to an exponential

Received March 20, 2017; accepted September 29, 2017.

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function, which has a characteristic decay time of T2*. This decay time is partly defined by the tissue microstructure (T2) and partly by the amount of deoxyhemoglobin.[16]

We chose to measure T2* since this technique has recently been used and validated at our institution as a measure of oxygenation in a fetal sheep model,[17] as well as in human kidneys and placenta.[18–20]

We hypothesized that reduced cerebral tissue oxygenation would be present before 35 weeks of gestation. We therefore aimed to measure serially the cerebral T2* values in fetuses with major heart defects and compare these values to those of fetuses without heart defects.

Methods

Recruitment took place at Aarhus University Hospital from October 2014 to June 2016. All fetuses were scanned using MR imaging (MRI) and ultrasound between gestational weeks 29 to 34 (early) and again between 35 to 40 weeks (late). The interval between the scans was 3 to 7 weeks (median 42 days). The scans of fetuses with heart defects took place at the time of the planned visits in the outpatient clinic. We included 16 of 47 potential participants (Figure 1) with a heart defect that was believed to cause disturbances in the flow of oxygenated blood to the fetal brain: transposition of the great arteries (n=8), coarctation of the aorta or hypoplasia of the aortic arch (n=5), tetralogy of Fallot (n=1), hypoplastic right heart syndrome (n=1), and common arterial trunk (n=1). Thirteen of the 16 women accepted chorionic villous biopsy and karyotyping (n=2), amniocenteses and chromosomal microarray (n=10), or noninvasive prenatal test (n=1). One of these tests showed a small deletion of 1 X chromosome, which was considered to be of no clinical significance.

During the same time period, we included 40 singleton fetuses without heart defects from 115 pregnant women. These women were randomly approached after the first or at the second routine prenatal ultrasound scan. They received written information and provided an e-mail address for further information. We excluded 73 women who did not reply to the subsequent e-mail invitation. One woman declined after receiving oral information, and 1 was excluded because of claustrophobia. None of the 40 included women had undertaken prenatal genetic testing.

The study was approved by the Danish Data Protection Agency (1-16-02-86-14) and by the Institutional Review Committee (journal number 1-10-72-61-14). All participating subjects gave written informed consent.

Fetal Ultrasound

Fetal ultrasound scans (Voluson E8 and Voluson E10, GE Healthcare) were performed by experts in fetal medicine. We measured the fetal weight,[21] the diameter of the aortic and pulmonary valves, and the diameter of the aortic isthmus.[22] We calculated weight for gestational age (GA) z scores, aortic and pulmonary valve z scores, and the aortic isthmus z score.[23,24] Furthermore, using Doppler flow, we measured the flow in the isthmus and the pulsatility indices in the umbilical artery and the middle cerebral artery.[25] The cerebroplacental ratio was calculated by dividing the pulsatility indices of the middle cerebral artery by the pulsatility indices of the umbilical artery. Cerebroplacental ratio z scores were calculated.[26]

Magnetic Resonance Imaging

An MRI scan was obtained using a Philips 1.5 T Ingenia system (Philips, Best, The Netherlands). During the MRI scan, the pregnant woman was placed in a left lateral position and a dStream Torso Coil was placed over the abdomen covering the entire uterus. Initially, a localizer (a structural T2 image) was obtained to facilitate the general orientation of the placenta and the fetus. This was followed by T2-weighted fetal cerebral examinations in 3 planes, a T1-weighted scan, and a diffusion-weighted examination in 1 plane to rule out cerebral malformations and bleeding.

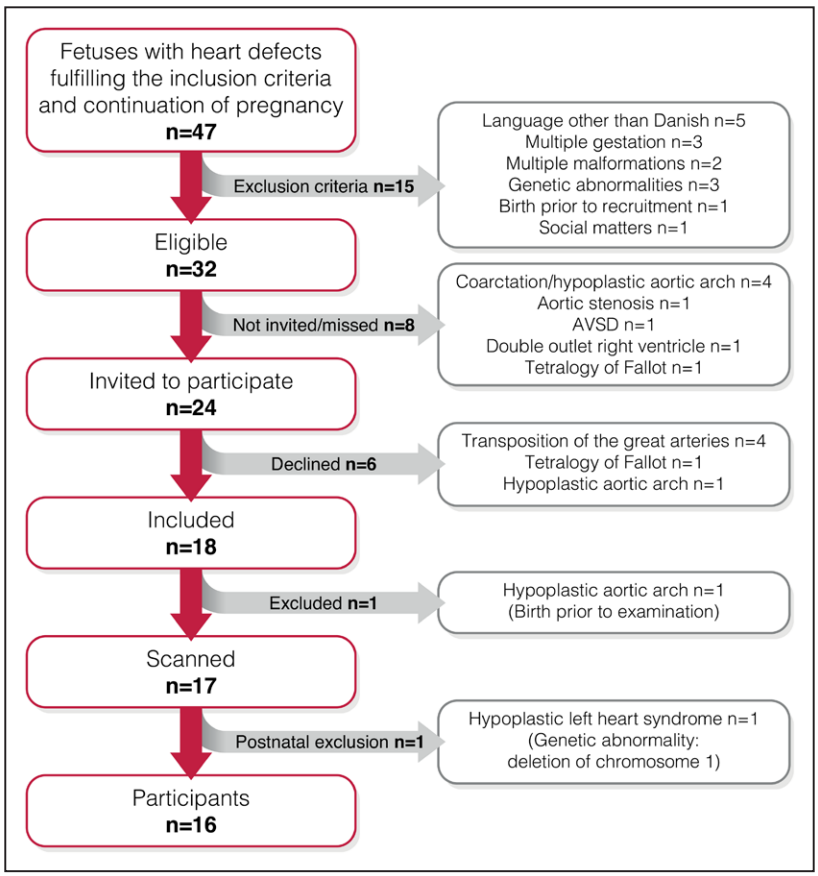

Figure 1. Flowchart illustrating the recruitment of fetuses with heart defects. AVSD indicates atrioventricular septal defect.

Fetal cerebral T2* mapping was obtained using a multiecho gradient echo sequence with the following parameters: repetition time 123 ms; 5 or 16 echoes ranging from 1.42 to 80/121.5 ms in steps of 20/25/5.2 or 8 ms, respectively; field of view 350×350 mm, and acquisition matrix 176×123 resulting in an in-plane resolution of 2.0×2.8 mm. Two 10-mm slices were placed axially through the fetal brain (Figure 2). The flip angle was 20°, and 1 average was used. Each slice was acquired within a single breath hold of 9 s.

At least 1 repeat cerebral T2* scanning was performed; more were performed if obvious artifacts were observed during the examination.

We initiated our study using a gradient echo sequence with 16 echoes ranging from 1.42 to 80 ms.[27] However, after the sixth examination, scanner software upgrades resulted in an unexpected loss of the 16-echo option, and only 5 echoes were available until a dedicated software upgrade was available.

Fourteen of the first 19 examinations were of poor quality (all fetuses without heart defects) and were discarded. The longest TE was then increased to contain the full decay of the T2* signal from the fetal brain.[28]

We have results from 13 examinations where only 5 echoes were available; 8 from fetuses without heart defects and 5 from fetuses with heart defects.

Apart from tissue oxygenation, the T2* value is also affected by elements of tissue composition (the intrinsic T2 value) such as cell density, water content, amount of hydrogen atoms, surface area,[29,30] as well as fetal and maternal movements.

T2* is a superposition of the intrinsic T2, the local susceptibility caused by deoxyhemoglobin and inhomogeneity in the magnetic field (also called background fields). Inhomogeneity was observed as signal void arising from the outer parts of field of view and growing inwards with increasing TE. This error of the T2* value is a well-known issue, and it is a fundamental problem when using T2* as an absolute value.[31]

Fetal movements made it necessary to discard a number of the early examinations, in particular.

MRI Analysis

Images were processed using an in-house developed program written in MATLAB (The MathWorks Inc, Natick, MA). Sinding and Sorensen previously used this program.[20,27] In each T2* scan, a region of interest (ROI) was drawn on each slice on the image with the longest TE covering at least half of the fetal brain in an area without visible artifacts (Figure 3). This ROI was used for all images with different TEs from each slice, and the ROI was repositioned if visible artifacts were encountered on one of the images. The slice was discarded from the analyses if artifacts affected more than half of the brain on one of the images. The T2* value was obtained by fitting the averaged signal (S) within each ROI as a function of the TE. The fitting was performed using a mono-exponentially decaying function, with equilibrium magnetization (M0) and T2* as the free parameters; $S=M0\times e^{(-TE/T2^*)}$.

A nonlinear least squares fitting algorithm was used, and each time point was weighted using the signal SD in the ROI, thereby giving less significance to images with a high SD. The resulting T2* values were obtained by averaging the calculated T2* measurements of all the available slices.

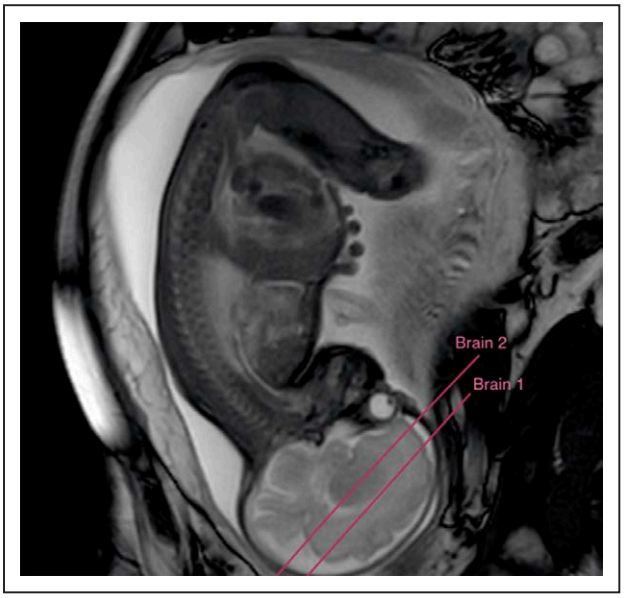

Figure 2. Two 10-mm slices axially through the fetal brain.

Blood Work

As part of the routine work up, the newborns with heart defects had hemoglobin concentrations measured within the first 12 hours of life. Hemoglobin concentrations were not measured in the children without heart defects.

Statistical Analyses

Multilevel mixed-effects linear regression that accounted for repeated measurements within each fetus was used to estimate the relationship between GA and the fetal cerebral T2* value. We present the linear regressions with 95% prediction intervals (Figure 4). The mean difference in cerebral T2* values between fetuses with heart defects and fetuses without heart defects are presented with 95% confidence intervals (CI) and corresponding *P* values. Fetal ultrasound characteristics, birth weight, and head circumference at birth are presented as *z* scores; Student *t* test and linear regression were used to compare *z* scores between groups. The cerebral T2* values of the fetuses without heart defects were applied to calculate the cerebral T2* *z* scores of all the fetuses. Wilcoxon rank-sum test was used to compare parameters that were not normally distributed. Categorical variables were compared using the χ^2 test.

Twenty-four of the examinations were randomly chosen for the repeated, blinded analyses for interobserver and intraobserver reproducibility of the segmentation. The reproducibility of the method was estimated using the variation in T2* obtained by repeat scans of a single cerebral slice in the fetuses without heart defects. In 10 examinations, the T2* value was estimated using both 5 and 16 of the available TEs. We used Bland–Altman plots to depict the reproducibility and reliability of the method and calculated the mean difference with 95% limits of agreement as suggested by Bland and Altman.[32]

The statistical software package Stata 13.1 (StataCorp LP, College Station, TX) was used for all analyses.

Results

We obtained at least 1 T2* measurement from 15 of the 16 fetuses with heart defects and from 28 out of the 40 fetuses without heart defects.

Maternal and fetal characteristics are presented in Table 1. We found no statistically significant differences between pregnancies with fetal heart defects and pregnancies without fetal heart defects (Table 1).

Twelve fetuses were only examined once. Among the fetuses with heart defects, 3 were recruited later than 35 weeks of gestation, and the second examination was cancelled by 1 participant because of maternal discomfort. The reasons that only 1 examination was performed in some fetuses without heart defects were onset of labor before the second examination (n=2), gestational hypertension (n=3), and maternal discomfort (n=3).

In 6 fetuses with heart defects and in 13 fetuses without heart defects, we obtained T2* measurements at both the early and late examinations (Figure 4; Table 2).

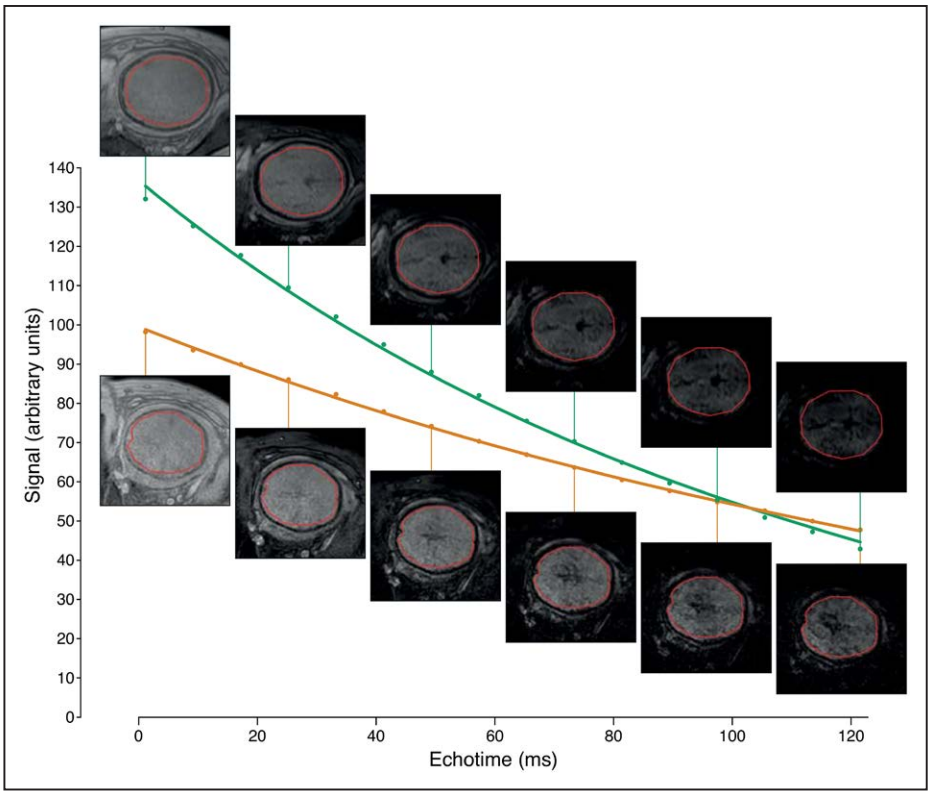

Figure 3. The figure shows the mean magnetic resonance imaging signal of each cerebral region of interest (*y* axis) plotted at the 16 different echo times (TE; *x* axis). The orange line depicts the T2* decay from the early scan (week 32) and the green line depicts the T2* decay from the late scan (week 39) of the same fetus. For each fetus, the T2* decay curve is obtained using a nonlinear least squares fitting algorithm ($S=M0\times e^{(-TE/T2^*)}$), where M0 is the equilibrium magnetization. Six of the corresponding T2* weighted images of the fetal brain and regions of interest (red circle) are depicted for each of the 2 scans.

Cerebral T2* Value

Among fetuses without heart defects, the mean T2* value decreased with increasing GA; the mean T2* value was 157 ms (CI, 152–163) in GA week 32 (early) and 125 ms (CI, 120–130) in GA week 37 (late). The cerebral T2* values were significantly lower among fetuses with heart defects; 143 ms (CI, 136–150) at the early scan and 111 ms (CI, 104–118) at the late scan. The average cerebral T2* decline was 5.7 ms per gestational week in both groups. On average, the fetuses with heart defects had cerebral T2* values 14 ms lower than the fetuses without heart defects (95% CI, 6–22; $P<0.001$; Figure 4).

Cerebral T2* Value in Relation to Fetal Measures and Neonatal Hemoglobin Concentrations

None of the fetuses without heart defects had cerebral T2* measurement *z* scores <–2.0 at the late examination as opposed to 4 fetuses with heart defects (transposition of the great arteries [n=2] and coarctation of the aortic arch [n=2]).

One fetus without a heart defect and 3 fetuses with a heart defect (coarctation of the aortic arch [n=2] and transposition of the great arteries [n=1]) had cerebroplacental ratio *z* scores <–2 at the late examination. The mean cerebroplacental ratio *z* score did not correlate with the T2* *z* score in the fetuses without heart defects or in the fetuses with heart defects.

Two of the newborns with heart defects had hemoglobin concentrations above the normal range of our laboratory (9.1–14.9 mmol/L) measured within the first 12 hours of life. Increasing the hemoglobin concentration results in a slightly, but not statistically significant, reduction in the cerebral T2* *z* score; $-0.29/mmol^{-1}$ (CI, −0.9 to 0.3; $P=0.3$; Figure 5).

Fetal ultrasound measures and neonatal outcomes are presented in Table 2.

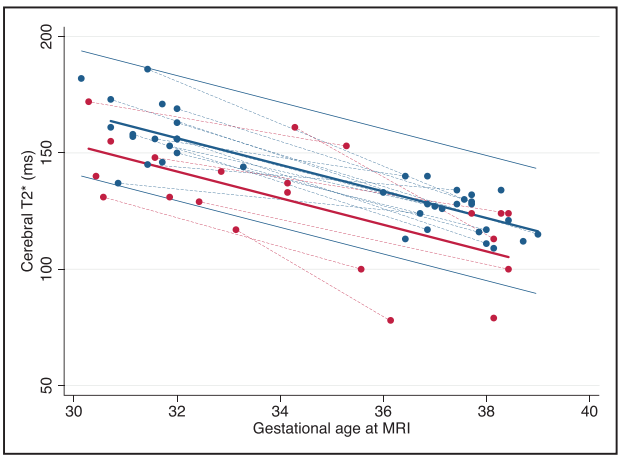

Figure 4. Fetal cerebral T2* (ms; *y* axis) by gestational age (weeks; *x* axis); the blue dots represent the fetuses with no heart defects and the red dots represent the fetuses with heart defects. The thick blue and the thick red line represent the regression line of the fetuses without and with heart defects, respectively. The thinner blue lines represent the 95% prediction interval for the fetuses without heart defects. A very thin dashed line connects results from 2 scans of the same fetus. MRI indicates magnetic resonance imaging.

Table 1. Maternal and Fetal Characteristics

	No Heart Defect (n=28)	Heart Defect (n=15)
Maternal characteristics		
Age, y	29 (26–33)	29 (27–33)
Body mass index, kg/m^2	22 (21–24)	23 (21–27)
White, n	28/28 (100)	15/15 (100)
Maternal smoking during pregnancy, n	0/28 (0)	1/15 (7)
Nulliparous, n	14/28 (50)	5/15 (33)
Fetal characteristics		
Male gender, n	14/28 (50)	9/15 (60)

Maternal and fetal characteristics in 15 pregnancies with fetal heart defects and 28 pregnancies without fetal heart defects, Aarhus, Denmark, 2014–2016. Data are presented as median (interquartile range) or n (%).

Besides lower cerebral T2* values and reduced mean head circumferences at birth, the fetuses and neonates with heart defects did not differ significantly from the fetuses and neonates without heart defects. None of the scanned fetuses had reversed flow in the aortic isthmus.

The cardiac measures of the fetuses with heart defects are presented in more detail in Table 3.

Reproducibility

We used Bland–Altman plots to depict the reproducibility and the reliability of the method. The mean difference and 95% limits of agreement for the slice-to-slice reproducibility were –0.05±12.3 ms. The mean difference and 95% limits of agreement for the intraobserver and interobserver variability were 0.0±20.7 ms and –2.4±26.2 ms, respectively. The mean difference and 95% limits of agreement between using 5 or 16 of the available echoes were –3.6±6.4 ms (plots not shown).

Discussion

Our main findings were that the fetal cerebral T2* value (a measure of tissue oxygenation) declines with increasing GA, and that it was significantly lower among fetuses with heart defects already at 32 weeks of gestation.

A limitation of the present study is the low number of included fetuses relative to the high number of different heart defects. Another limitation of the study was that we, because of the artifacts, had to discard 31% of the examinations in fetuses with heart defects and 42% of the examinations in fetuses without heart defects. The reasons for the artifacts were a combination of fetal movements and susceptibility artifacts. The loss of echoes increased the CIs of the measurements and consequently the vulnerability to artifacts, thus a higher number of the examinations with only 5 echoes were discarded. An artifact can appear bright or dark on the images, the latter being the most common in our study. Thus, hypothetically, the acceptance of a higher percentage of examinations from the fetuses with heart defects would potentially result in an overestimation of the difference between the groups. For selection bias to occur, the risk of discarding an examination would have to depend on both the presence of a heart defect (exposure) and the actual T2* value (outcome). The proportion of discarded examinations was similar in the 2 groups. Consequently, we think that the discarded examinations are unlikely to have caused selection bias.

It has been described previously that subclinical uterine contractions affect placental oxygenation[20] and may also affect fetal cerebral oxygenation. We were not able to monitor the frequency of subclinical uterine contractions in the present study; nonetheless, we assumed them to be equally distributed in the 2 groups. Furthermore, we find it unlikely that significant confounding has been introduced by the slight overweight of males among fetuses with heart defects, the slight overweight of nulliparous women among the women expecting a child without a heart defect, or yet unknown genetic mutations.

Table 2. Fetal Measures and Neonatal Outcomes

	No Heart Defect (n=28)	No. of Measurements	Heart Defect (n=15)	No. of Measurements	Difference (95% CI)
Fetal measures					
Ultrasound estimated head circumference *z* score	0.03 (1.0)	52	–0.26 (0.9)	30	0.3 (–0.2 to 0.7); *P*=0.2
Estimated fetal weight *z* score	–0.41 (0.8)	52	–0.51 (0.9)	30	0.1 (–0.3 to 0.5); *P*=0.6
Gestational age at MR1	32 (0.7)	18	32 (1.5)	12	–0.7 (–1.5 to 0.2); *P*=0.1
Gestational age at MR2	37 (0.8)	23	37 (1.3)	9	0.1 (–0.6 to 0.9); *P*=0.7
Median interval between scans, d (IQR)	41 (36 to 43)	14	35 (27 to 42)	6	
Aortic valve *z* score	–0.81 (1.0)	52	–0.72 (3.5)	20	–0.1 (–1.2 to 1.0); *P*=0.9
Isthmus *z* score	0.96 (0.9)	49	0.34 (1.9)	16	0.6 (–0.1 to 1.3); *P*=0.1
Pulmonary valve *z* score	0.08 (1.5)	51	0.82 (3.6)	19	–0.7 (–2.0 to 0.5); *P*=0.2
CPR *z* score	0.10 (1.5)	50	–0.22 (2.0)	29	0.3 (–0.5 to 1.1); *P*=0.4
Neonatal outcomes					
Birth weight *z* score	–0.08 (0.96)	28	–0.41 (0.96)	15	0.32 (–0.29 to 0.95); *P*=0.29
Head circumference *z* score	0.02 (0.95)	28	–0.68 (1.08)	15	0.69 (0.05 to 1.34); *P*=0.04*

Data are presented as mean (SD), n. Measures were compared by Student *t* test or Wilcoxon rank-sum test. CI indicates confidence interval; CPR, cerebroplacental ratio; IQR, interquartile range; MR, magnetic resonance; and n, the number of measurements in each group.

*Statistical significance at the *P*<0.05 level.

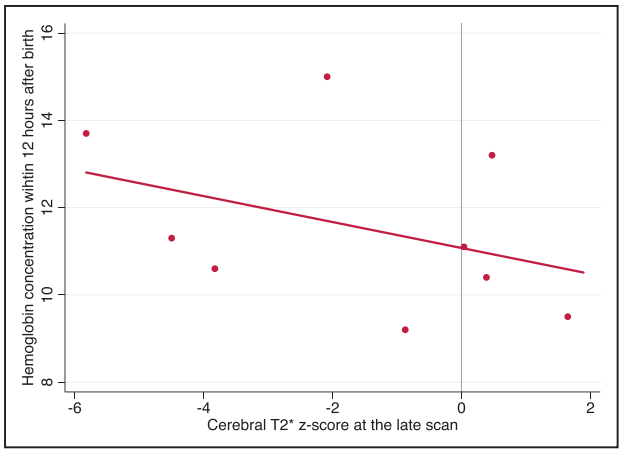

Figure 5. The relation between the hemoglobin concentration within 12 h after birth in fetuses with heart defects and the calculated cerebral T2* *z* scores at the late examination.

The association between increasing GA and the decrease in the mean T2* value may be explained by a fetal and placental hypoxic state that progresses during the third trimester of pregnancy. This is in line with Soothill et al[33] who describe a decrease in the partial pressures of oxygen in venous umbilical samples from 40 mm Hg in week 32 to 32 mm Hg in week 38. In accordance with this finding, the mean placental T2* value has been shown to decrease as pregnancy advances.[27] Alterations in the intrinsic T2 value must, however, also be taken into account as the cerebral T2 value declines with increasing GA in prematurely born infants.[30] This change is likely to be caused by changes in tissue composition along with the natural maturation of the cerebral tissues.[8] When the T2 value declines with GA, the T2* value declines correspondingly.

In the present study, fetuses with heart defects had a mean cerebral T2* value that was lower than the normal level. This finding may be explained by reduced tissue oxygenation. Consequently, our results support the findings of previous studies based on MR oximetry and blood flow quantification by phase contrast MRI in ascending aorta and the superior caval vein.[34] These studies report a 15% reduction of cerebral oxygen delivery and a 32% reduction of cerebral oxygen consumption in fetuses with congenital heart disease compared with fetuses without heart disease.[14] Potentially, a slightly elevated hemoglobin concentration in fetuses with heart defects can influence the mean cerebral T2* value caused by an increased level of deoxyhemoglobin at the same saturation level. Portnoy et al[35,36] from Toronto recently published their in vitro MRI T1 and T2 measurements of fetal hematocrit and oxygen saturation. They found that T2 in fetal blood increases with increasing oxygen saturation and decreases slightly with increasing hematocrit. Taking into account the range of the expected fetal cerebral saturation (40% to 70%[14,37]) and the range of the expected fetal hematocrit (0.3 in GA week 17 raising to 0.45 in GA week 40[38]) we expect the influence of higher hematocrit on T2 (and thus T2*) to be negligible as the T2 of fetal blood is barely affected by hematocrit in the 0.35 to 0.45 range.[36]

In the present study, we found that the fetal cerebral T2* values on average decrease by almost 6 ms per gestational week. We know from other studies that fetuses with heart defects often have delayed cerebral maturation.[7] If cerebral maturation in the fetuses with heart defects in our study was delayed by just 1 week, this could result in a possible overestimation of the cerebral T2* value in fetuses with heart defects of ≈6 ms. This would result in an underestimation of the difference between the fetuses without heart defects and the fetuses with heart defects. Consequently, the phenomenon does not explain our results.

Conclusions

Our findings indicate that fetal cerebral T2* can be measured and that, already at 32 weeks of gestation, fetal cerebral T2* as a measure of fetal cerebral tissue oxygenation is lower in fetuses with heart defects than in fetuses without heart defects. Our sample size is small and the congenital heart defects included in the study are heterogeneous. Consequently the results of this study should be interpreted as preliminary and hypothesis generating only. However, the present results corroborate the hypothesis that tissue hypoxia may be a potential

Table 3. Fetal Cardiac Measures

Fetal Heart Defects	Scan No	Aortic Valve *z* Score	Isthmus *z* Score	Pulmonary Valve *z* Score	CPR *z* Score
TGA (n=7)	Early	1.7 (1.3)	1.2 (0.9)	1.3 (1.3)	0.5 (1.6)
	Late	1.9 (3.4)	1.4 (1.5)	−0.3 (0.8)	0.5 (2.4)
CoA (n=5)	Early	−3.5 (1.4)	−2.7 (0.4)	1.2 (1.8)	−1.6 (0.7)
	Late	−5.4 (1.5)	−0.7 (0.3)	2.3 (0.3)	−1.1 (2.1)
HRHS (n=1)	Early	−0.4	…	−5.5	0.4
	Late	…	1.1	…	−0.2
Fallots tetralogy (n=1)	Early	−0.8	…	−6.1	−0.4
	Late	…	…	…	−0.6
Common arterial trunk (n=1)	Early	…	0.9	…	−2.0
	Late	4.1	2.8	11.4	3.9

Fetal cardiac measures and the CPR are presented as mean *z* scores (SD) and are divided into the different groups of fetal heart defects. CoA indicates coarctation/hypoplasia of the aortic arch; CPR, cerebroplacental ratio; HRHS, hypoplastic right heart syndrome; n, the number of participants in each group; and TGA, transposition of the great arteries.

pathogenic factor that may possibly affect brain development in fetuses with heart defects.

Sources of Funding

This research was supported by The Danish Children's Heart Foundation, Dagmar Marshalls Fund, and Eva and Henry Frænkels Memorial Fund.

Acknowledgments

We thank research student, Dr Camilla Lindahl, Department of Obstetrics and Gynecology, Aarhus University Hospital, Aarhus, Denmark, for recruiting patients, and research student, Dr Zarmiga Karunanithi, Department of Cardiohoracic and Vascular Surgery, Aarhus University Hospital, Aarhus, Denmark, for performing some of the analysis. We thank radiographer Anja Harbøll and staff, Department of Medical Physics, Aarhus University Hospital, Denmark for the generous use of the MR-scanner, radiographer Ole Christiansen, Department of Radiology, Aarhus University Hospital, Aarhus, Denmark, for performing some of the scanning, and Clinical Science Manager Jørn Kværness, Phillips, for the permission to use the Starquant license free of charge. We thank the many pregnant women who volunteered to participate in the study.

Disclosures

None.

References

1. Erdogan F, Larsen LA, Zhang L, Tümer Z, Tommerup N, Chen W, Jacobsen JR, Schubert M, Jurkatis J, Tzschach A, Ropers HH, Ullmann R. High frequency of submicroscopic genomic aberrations detected by tiling path array comparative genome hybridisation in patients with isolated congenital heart disease. *J Med Genet*. 2008;45:704–709. doi: 10.1136/jmg.2008.058776.
2. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, Mussatto KA, Uzark K, Goldberg CS, Johnson WH Jr, Li J, Smith SE, Bellinger DC, Mahle WT; American Heart Association Congenital Heart Defects Committee; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing, and Stroke Council. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. *Circulation*. 2012;126:1143–1172. doi: 10.1161/CIR.0b013e318265ee8a.
3. Khalil A, Suff N, Thilaganathan B, Hurrell A, Cooper D, Carvalho JS. Brain abnormalities and neurodevelopmental delay in congenital heart disease: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2014;43:14–24. doi: 10.1002/uog.12526.
4. Bellinger DC, Wypij D, Rivkin MJ, DeMaso DR, Robertson RL Jr, Dunbar-Masterson C, Rappaport LA, Wernovsky G, Jonas RA, Newburger JW. Adolescents with d-transposition of the great arteries corrected with the arterial switch procedure: neuropsychological assessment and structural brain imaging. *Circulation*. 2011;124:1361–1369. doi: 10.1161/CIRCULATIONAHA.111.026963.
5. Tabbutt S, Gaynor JW, Newburger JW. Neurodevelopmental outcomes after congenital heart surgery and strategies for improvement. *Curr Opin Cardiol*. 2012;27:82–91. doi: 10.1097/HCO.0b013e328350197b.
6. Donofrio MT, Duplessis AJ, Limperopoulos C. Impact of congenital heart disease on fetal brain development and injury. *Curr Opin Pediatr*. 2011;23:502–511. doi: 10.1097/MOP.0b013e32834aa583.
7. Clouchoux C, du Plessis AJ, Bouyssi-Kobar M, Tworetzky W, McElhinney DB, Brown DW, Gholipour A, Kudelski D, Warfield SK, McCarter RJ, Robertson RL Jr, Evans AC, Newburger JW, Limperopoulos C. Delayed cortical development in fetuses with complex congenital heart disease. *Cereb Cortex*. 2013;23:2932–2943. doi: 10.1093/cercor/bhs281.
8. Limperopoulos C, Tworetzky W, McElhinney DB, Newburger JW, Brown DW, Robertson RL Jr, Guizard N, McGrath E, Geva J, Annese D, Dunbar-Masterson C, Trainor B, Laussen PC, du Plessis AJ. Brain volume and metabolism in fetuses with congenital heart disease: evaluation with quantitative magnetic resonance imaging and spectroscopy. *Circulation*. 2010;121:26–33. doi: 10.1161/CIRCULATIONAHA.109.865568.
9. Matthiesen NB, Henriksen TB, Gaynor JW, Agergaard P, Bach CC, Hjortdal VE, Østergaard JR. Congenital heart defects and indices of fetal cerebral growth in a nationwide cohort of 924 422 liveborn infants. *Circulation*. 2016;133:566–575. doi: 10.1161/CIRCULATIONAHA.115.019089.
10. Masoller N, Sanz-Cortés M, Crispi F, Gómez O, Bennasar M, Egaña-Ugrinovic G, Bargalló N, Martínez JM, Gratacós E. Severity of fetal brain abnormalities in congenital heart disease in relation to the main expected pattern of in utero brain blood supply. *Fetal Diagn Ther*. 2016;39:269–278. doi: 10.1159/000439527.
11. Arduini M, Rosati P, Caforio L, Guariglia L, Clerici G, Di Renzo GC, Scambia G. Cerebral blood flow autoregulation and congenital heart disease: possible causes of abnormal prenatal neurologic development. *J Matern Fetal Neonatal Med*. 2011;24:1208–1211. doi: 10.3109/14767058.2010.547961.
12. Donofrio MT, Bremer YA, Schieken RM, Gennings C, Morton LD, Eidem BW, Cetta F, Falkensammer CB, Huhta JC, Kleinman CS. Autoregulation of cerebral blood flow in fetuses with congenital heart disease: the brain sparing effect. *Pediatr Cardiol*. 2003;24:436–443. doi: 10.1007/s00246-002-0404-0.
13. Masoller N, Martínez JM, Gómez O, Bennasar M, Crispi F, Sanz-Cortés M, Egaña-Ugrinovic G, Bartrons J, Puerto B, Gratacós E. Evidence of second-trimester changes in head biometry and brain perfusion in fetuses with congenital heart disease. *Ultrasound Obstet Gynecol*. 2014;44:182–187. doi: 10.1002/uog.13373.
14. Sun L, Macgowan CK, Sled JG, Yoo SJ, Manlhiot C, Porayette P, Grosse-Wortmann L, Jaeggi E, McCrindle BW, Kingdom J, Hickey E, Miller S, Seed M. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. *Circulation*. 2015;131:1313–1323. doi: 10.1161/CIRCULATIONAHA.114.013051.
15. Chavhan GB, Babyn PS, Thomas B, Shroff MM, Haacke EM. Principles, techniques, and applications of T2*-based MR imaging and its special applications. *Radiographics*. 2009;29:1433–1449. doi: 10.1148/rg.295095034.
16. Wedegärtner U, Kooijman H, Andreas T, Beindorff N, Hecher K, Adam G. T2 and T2* measurements of fetal brain oxygenation during hypoxia with MRI at 3T: correlation with fetal arterial blood oxygen saturation. *Eur Radiol*. 2010;20:121–127. doi: 10.1007/s00330-009-1513-4.
17. Sørensen A, Pedersen M, Tietze A, Ottosen L, Duus L, Uldbjerg N. BOLD MRI in sheep fetuses: a non-invasive method for measuring changes in tissue oxygenation. *Ultrasound Obstet Gynecol*. 2009;34:687–692. doi: 10.1002/uog.7322.
18. Pedersen M, Dissing TH, Mørkenborg J, Stødkilde-Jørgensen H, Hansen LH, Pedersen LB, Grenier N, Frøkiaer J. Validation of quantitative BOLD MRI measurements in kidney: application to unilateral ureteral obstruction. *Kidney Int*. 2005;67:2305–2312. doi: 10.1111/j.1523-1755.2005.00334.x.
19. Khatir DS, Pedersen M, Jespersen B, Buus NH. Reproducibility of MRI renal artery blood flow and BOLD measurements in patients with chronic kidney disease and healthy controls. *J Magn Reson Imaging*. 2014;40:1091–1098. doi: 10.1002/jmri.24446.
20. Sinding M, Peters DA, Frøkjær JB, Christiansen OB, Uldbjerg N, Sørensen A. Reduced placental oxygenation during subclinical uterine contractions as assessed by BOLD MRI. *Placenta*. 2016;39:16–20. doi: 10.1016/j.placenta.2015.12.018.
21. Snijders RJ, Nicolaides KH. Fetal biometry at 14-40 weeks' gestation. *Ultrasound Obstet Gynecol*. 1994;4:34–48. doi: 10.1046/j.1469-0705.1994.04010034.x.
22. Sharland GK, Allan LD. Normal fetal cardiac measurements derived by cross-sectional echocardiography. *Ultrasound Obstet Gynecol*. 1992;2:175–181. doi: 10.1046/j.1469-0705.1992.02030175.x.
23. Marsál K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr*. 1996;85:843–848.
24. Pasquini L, Mellander M, Seale A, Matsui H, Roughton M, Ho SY, Gardiner HM. Z-scores of the fetal aortic isthmus and duct: an aid to assessing arch hypoplasia. *Ultrasound Obstet Gynecol*. 2007;29:628–633. doi: 10.1002/uog.4021.
25. Parra-Cordero M, Lees C, Missfelder-Lobos H, Seed P, Harris C. Fetal arterial and venous Doppler pulsatility index and time averaged velocity ranges. *Prenat Diagn*. 2007;27:1251–1257. doi: 10.1002/pd.1868.
26. Baschat AA, Gembruch U. The cerebroplacental Doppler ratio revisited. *Ultrasound Obstet Gynecol*. 2003;21:124–127. doi: 10.1002/uog.20.
27. Sinding M, Peters DA, Frøkjaer JB, Christiansen OB, Petersen A, Uldbjerg N, Sørensen A. Placental magnetic resonance imaging T2* measurements in normal pregnancies and in those complicated by fetal growth restriction. *Ultrasound Obstet Gynecol*. 2016;47:748–754. doi: 10.1002/uog.14917.

28. Rivkin MJ, Wolraich D, Als H, McAnulty G, Butler S, Conneman N, Fischer C, Vajapeyam S, Robertson RL, Mulkern RV. Prolonged T*2 values in newborn versus adult brain: implications for fMRI studies of newborns. *Magn Reson Med*. 2004;51:1287–1291. doi: 10.1002/mrm.20098.
29. Cameron IL, Ord VA, Fullerton GD. Characterization of proton NMR relaxation times in normal and pathological tissues by correlation with other tissue parameters. *Magn Reson Imaging*. 1984;2:97–106.
30. Counsell SJ, Kennea NL, Herlihy AH, Allsop JM, Harrison MC, Cowan FM, Hajnal JV, Edwards B, Edwards AD, Rutherford MA. T2 relaxation values in the developing preterm brain. *AJNR Am J Neuroradiol*. 2003;24:1654–1660.
31. Wen Y, Zhou D, Liu T, Spincemaille P, Wang Y. An iterative spherical mean value method for background field removal in MRI. *Magn Reson Med*. 2014;72:1065–1071. doi: 10.1002/mrm.24998.
32. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1:307–310.
33. Soothill PW, Nicolaides KH, Rodeck CH, Campbell S. Effect of gestational age on fetal and intervillous blood gas and acid-base values in human pregnancy. *Fetal Ther*. 1986;1:168–175.
34. Al Nafisi B, van Amerom JF, Forsey J, Jaeggi E, Grosse-Wortmann L, Yoo SJ, Macgowan CK, Seed M. Fetal circulation in left-sided congenital heart disease measured by cardiovascular magnetic resonance: a case-control study. *J Cardiovasc Magn Reson*. 2013;15:65. doi: 10.1186/1532-429X-15-65.
35. Portnoy S, Osmond M, Zhu MY, Seed M, Sled JG, Macgowan CK. Relaxation properties of human umbilical cord blood at 1.5 Tesla. *Magn Reson Med*. 2017;77:1678–1690. doi: 10.1002/mrm.26231.
36. Portnoy S, Seed M, Sled JG, Macgowan CK. Non-invasive evaluation of blood oxygen saturation and hematocrit from T1 and T2 relaxation times: in-vitro validation in fetal blood [published online ahead of print February 12, 2017]. *Magn Reson Med*. doi: 10.1002/mrm.26599. http://onlinelibrary.wiley.com/doi/10.1002/mrm.26599/abstract;jsessionid=33B5A955A8D768EEF731F9F9A6083132.f03t02. Accessed November 7, 2017.
37. Neelavalli J, Jella PK, Krishnamurthy U, Buch S, Haacke EM, Yeo L, Mody S, Katkuri Y, Bahado-Singh R, Hassan SS, Romero R, Thomason ME. Measuring venous blood oxygenation in fetal brain using susceptibility-weighted imaging. *J Magn Reson Imaging*. 2014;39:998–1006.
38. Nicolaides KH, Soothill PW, Clewell WH, Rodeck CH, Mibashan RS, Campbell S. Fetal haemoglobin measurement in the assessment of red cell isoimmunisation. *Lancet*. 1988;1:1073–1075.

CLINICAL PERSPECTIVE

The vast majority of children with major congenital heart defects survive, but 33% to 43% experience impaired neurodevelopment. In fetuses with congenital heart defects, disturbed hemodynamics has long been suspected to affect the developing brain. Magnetic resonance (MR) imaging studies of near term hemodynamics in fetuses with major congenital heart disease have reported reduced oxygen saturations in the ascending aorta without an increase in the cerebral blood flow or oxygen extraction extrapolated from flow and oxygen saturation measures in the superior vena cava. Accordingly these findings indicate a reduced cerebral oxygenation in fetuses with congenital heart defects. In the present study, we estimated the fetal cerebral tissue oxygenation by the MR transversal relaxation time (T2*), which depends on the tissue concentration of deoxyhemoglobin. Already at 32 weeks of gestation, we found that fetal cerebral T2* as a measure of fetal cerebral tissue oxygenation was lower in fetuses with heart defects than in fetuses without heart defects. The lower cerebral tissue oxygenation persisted at 37 weeks of gestation. Our sample size is small and the included congenital heart defects are heterogeneous. Consequently, the results of the study should be interpreted as preliminary and hypothesis generating only. However, this finding corroborates the hypothesis that tissue hypoxia may be a potential pathogenic factor that may possibly affect brain development in fetuses with heart defects.

Cerebral Oxygenation Measurements by Magnetic Resonance Imaging in Fetuses With and Without Heart Defects

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Circ Cardiovasc Imaging. 2017;10:e006459
doi: 10.1161/CIRCIMAGING.117.006459
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-9651. Online ISSN: 1942-0080