Cardiology in the Young

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Lung volumes are increased in fetuses with transposition of the great arteries on intrauterine MRI

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Abstract

Fetal brain size is decreased in some children with complex CHDs, and the distribution of blood and accompanying oxygen and nutrients is regionally skewed from early fetal life dependent on the CHD. In transposition of the great arteries, deoxygenated blood preferentially runs to the brain, whereas the more oxygenated blood is directed towards the lungs and the abdomen. Knowledge of whether this impacts intrauterine organ development is limited. We investigated lung, liver, and total intracranial volume in fetuses with transposition of the great arteries using MRI.

Eight fetuses with dextro-transposition and without concomitant disease or chromosomal abnormalities and 42 fetuses without CHD or other known diseases were scanned once or twice at gestational age 30 through 39 weeks. The MRI scans were conducted on a 1.5T system, using a 2D balanced steady-state free precession sequence. Slices acquired covered the entire fetus, slice thickness was 10 mm, pixel size 1.5 × 1.5 mm, and scan duration was 30 sec.

The mean lung *z* score was significantly larger in fetuses with transposition compared with those without a CHD; mean difference is 1.24, 95% CI:(0.59;1.89), $p < 0.001$. The lung size, corrected for estimated fetal weight, was larger than in the fetuses without transposition; mean difference is 8.1 cm^3/kg, 95% CI:(2.5;13.7 cm^3/kg), $p = 0.004$.

In summary, fetuses with dextro-transposition of the great arteries had both absolute and relatively larger lung volumes than those without CHD. No differences were seen in liver and total intracranial volume. Despite the small number of cases, the results are interesting and warrant further investigation.

Introduction

Some complex CHDs are associated with smaller brain size[1] and neurodevelopmental impairment.[2] The causes are not fully understood, but they may include both genetic[3] and circulatory factors.[4] Another explanation for impaired brain growth may be a lower cerebral tissue oxygenation, as seen in fetuses with specific CHDs such as dextro-transposition of the great arteries and hypoplastic left heart syndrome.[5–8] In fetuses with dextro-transposition of the great arteries, the cyanotic state is, however, not universal throughout the body. Here, the distribution of blood and accompanying oxygen and nutrients is regionally skewed. The brain receives the desaturated blood from the right ventricle, while the blood of mixed saturation supplies the abdominal circulation, and the oxygenated blood originating from the placenta supplies the pulmonary circulation.[9] Lachaud et al. also estimated an increase in global pulmonary blood flow in fetuses with transposition of the great arteries using ultrasound.[10] Brain size has been reported smaller in fetuses with complex CHDs, perhaps due to changes in fetal flow and saturation. However, in transposition of the great arteries, fetal brain size has been reported both smaller[11] and normal-sized.[12] Knowledge of how these complex circulatory changes affect the fetal development of other organs is limited.[13] The present study focuses on the non-cerebral fetal organ development, as these are supplied by blood with altered saturations in fetuses with transposition of the great arteries.

We hypothesised that extracardiac fetal organ growth would be affected in fetuses with dextro-transposition of the great arteries compared with organs in fetuses without CHD.

Materials and methods

Population

We analysed fetal MR images acquired by Lauridsen et al.,[14] using organ volumetry. Besides the fetal MR images, we also retrieved maternal and fetal characteristics, presented in Table 1.

Volumetry was done on MR images from 50 fetuses between gestational age weeks 30–39. Eight of the fetuses were prenatally diagnosed with dextro-transposition of the great arteries, and the 42 fetuses were healthy and without CHDs. The mothers were approached after their first or second normal routine prenatal ultrasound scan and then asked to enrol by e-mail. The study invited subjects to a second MRI scan, on average 5.9 weeks after the initial scan. A total of eight cases and 40 controls provided maternal and fetal characteristics.

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.

MRI acquisition

MRI was performed on a Philips 1.5 T Ingenia System, at Aarhus University Hospital between October 2014 and June 2016. The MR images used in this study were, in the original study, used to facilitate the general orientation of the fetus and placenta and plan the subsequent cerebral and transplacental images.

The images were acquired with a 2D balanced steady-state free precession sequence. The images were aligned in the sagittal orientation of the fetus, and 30 slices were acquired. Slice thickness was 10 mm without gap, field of view was 385 × 385 mm, and the matrix was 256 × 256, giving a pixel resolution of 1.5 ×1.5 mm. The scan duration was about 30 s.

Fetal ultrasound

Fetal ultrasound and fetal echoradiography (Voluson E8 and Voluson E10, GE Healthcare) was performed on the day of the MRI. Fetal weight was estimated using Hadlocks formula based on head circumference, abdominal circumference, and femur length, which were used to calculate estimated fetal weight.[15] The ultrasound scans were performed by an expert in fetal medicine.

Organ volumetry

All of the data were analysed in the open-source software platform, Horos (https://horosproject.org/). Lung volume was acquired by tracing regions of interest along the transition from the thorax wall, diaphragm, mediastinum, and heart to the lungs. Liver volume was obtained the same way along the transition from the diaphragm and abdominal organs to the liver. Volumetry of total intracranial volume was found by manually drawing regions of interest around the inner side of the skull covering the brain, meninges, cerebellum, and cerebrospinal fluid. The volume was calculated by multiplying areas by the slice thickness. The organ volume measurements were validated with an in vitro pilot trial, described in the supplementary material (S6).

Below are examples of defining total intracranial volume, lungs, and liver, and computing the volume in Horos.

The analysts (E.K., S.R., and P.R.) were blinded to gestational age, sex, and transposition of the great arteries ± and drew regions of interest and performed volumetry on total intracranial volume, lung, and livers in 81 fetal scans. Fetal organs were measured twice in 41 scans to assess the intra-observer variability. To determine inter-observer variability, a second observer measured the fetal organs of the first 10 fetuses.

Table 1. Characteristics of mothers and fetuses with and without TGA

	No CHD	*n*	TGA	*n*
Age, years	30 (7)	40	29 (5)	8
BMI, kg/m^2	23.1 (3.1)	40	22.8 (3.8)	8
Caucasian	38 (95%)	40	8 (100%)	8
Maternal smoking during pregnancy	0 (0%)	40	0 (0%)	8
Alcohol during pregnancy	0 (0%)	40	0 (0%)	8
Nulliparous	20 (50%)	40	4 (57%)	7
Male gender	20 (50%)	40	7 (88%)	8

Age is shown as median (interquartile range), BMI is shown as mean (standard deviation), and the remaining is shown as absolute numbers (%). n, number of fetuses. CHD = congenital heart defect; BMI = body mass index; TGA = transposition of the great arteries.

Statistics

Normally distributed data are presented with mean and standard deviation values. Differences in means were calculated and compared using an independent-samples *t*-test.

Statistical analysis was conducted using STATA16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC) for Windows and R (v4.2.2; R Core Team 2022). Lung volumes of the fetuses without transposition of the great arteries were applied to calculate the organ *z* scores of all the fetuses. The regression analysis was performed in Microsoft Excel 2016.

Results

Fetal organ size volumetry

The total number of image sets used in this study was 81; 15 from eight fetuses with transposition of the great arteries, and 66 from 42 fetuses without transposition of the great arteries.

Table 1 shows the characteristics of the included mothers and fetuses in the study.

Table 2 shows the gestational ages, and estimated fetal weights along with the organ sizes of the fetuses with and without transposition of the great arteries at the time of the MRIs.

Z scores for the lungs were calculated following the initial analysis because of the observed difference between the cases and controls. The *z* scores are used to account for differences in gestational age and thus expected organ size at the time of the MRI. Mean lung *z* score was significantly larger in fetuses with transposition of the great arteries (*z* score [SD]: 1.21 [1.21], 95% CI: [0.60; 1.81]) compared with those without CHD (*z* score [SD]: −0.03 [0.94], 95% CI: [−0.26; 0.20], mean difference 1.24, 95% CI: [0.59; 1.89], $p < 0.001$).

To determine descriptive differences in fetal organ size when corrected for estimated fetal weight, crude comparisons and simple linear regression were used. The difference in mean organ volumes is shown in Supplementary Material S1.

Organ size divided by estimated fetal weight was plotted as a function of the gestational age of the fetus for a graphical representation of the data. This was done separately for the lungs (Figure 2), total intracranial volume (Supplementary material S2),

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Table 2. GA, EFW, and organ volume measurements in fetuses with and without TGA

	No CHD	*n*	TGA	*n*	*p*
GA, weeks	34.3 (3.2)	66	34.6 (3.2)	15	0.74
EFW, kg	2.4 (0.7)	64	2.5 (0.8)	15	0.66
TICV, cm^3	317.5 (68.1)	66	315.1 (62.5)	15	0.90
Lung, cm^3	76.9 (24.1)	66	103.3 (33.2)	15	0.004*
Liver, cm^3	107.7 (38.4)	66	116.2 (44.8)	15	0.50

Values are shown as mean (standard deviation). Differences in means were compared using an independent-samples *t*-test. n, number of fetal scans. GA = gestational age, EFW = estimated fetal weight; TGA = transposition of the great arteries; CHD = congenital heart defect; TICV = total intracranial volume; Lung = lung volume; Liver = liver volume; *, statistical significance at $p < 0.05$.

and liver (Supplementary material S3). The regression lines for lung volumes corrected for estimated fetal weight visualised larger volumes in the transposition of the great arteries group as compared with controls (Figure 2).

Likewise, figures were created for total intracranial volume and liver volumes for the two groups throughout gestational ages 30–39 (Supplementary materials S2 and S3). The difference was not statistically significant.

Division of the study population into two groups, an "Early" group from gestational ages 29–34 and a "Late" group with gestational ages 35–39, ensured that fetuses were only present with one scan in each group. This division is shown in boxplots of the organ volumes, with and without correction of estimated fetal weight, found in the Supplementary Material S4. Lung volume in fetuses with transposition of the great arteries was larger than controls in both "Early" gestational age and "Late" gestational age, but only in the "Late" GA, when corrected for estimated fetal weight. No significant differences were found in the other organs. Comparison of the gestational age, estimated fetal weight, and raw organ volumes in "Early" and "Late" gestational age is presented in Supplementary Material S5.

Intra- and inter-observer variation

The measured intraclass correlation coefficient values for intra-observer variation between the first and second analysis of the organs are regarded as "excellent" reliability (intraclass correlation coefficient: 0.96–0.99). The measured intraclass correlation coefficient values for inter-observer variation between the two observers were regarded as "good" reliability (intraclass correlation coefficient: 0.79–0.83). This is based on a definition originating from the article "A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research."[16]

Fetal echocardiography

Ultrasound of the outflow tracts in our fetuses with transposition of the great arteries was without notable obstruction, and all of them presented with antegrade ductal flow. Four of the eight fetuses with transposition of the great arteries had a ventricular septal defect, and the rest were with intact ventricular septum.

Discussion

In this small prospective case-control study of fetal organ size in fetuses with and without transposition of the great arteries, we measured fetuses with transposition of the great arteries to have larger lung volumes relative to fetal weight and greater lung volume *z* scores as compared with fetuses without CHD. There was no observed difference regarding liver volume or total intracranial volume. These are interesting findings, underlining the need for more elaborate studies, and raising the question of any potential long-term consequences of affected organ development.

Apart from the brain, organ size and development in fetuses with CHD are largely undescribed. Smaller lungs for CHD individuals with decreased pulmonary blood flow such as tetralogy of Fallot and pulmonary atresia have been reported.[13,17] As fetuses with tetralogy of Fallot and pulmonary atresia have restricted flow through the main pulmonary artery, the smaller size may be thought to be due to a decrease in blood supply and perfusion. Although the effect of a potential compensatory increase through the duct remains unknown, the finding adds some support to a potential hypothesis about an association between blood flow and organ growth. To the best of our knowledge, no studies on fetal lung volumes in fetuses with transposition of the great arteries have been conducted.

In the transposition of the great artery fetal circulation, the preferential streaming from the placenta to the left atrium presumably leads to the redirection of well-oxygenated blood into the pulmonary circulation, while the blood sent to the brain contains less oxygenated blood originating from the caval veins.[9] Increased pulmonary oxygen saturation is known to decrease pulmonary vascular resistance and might, if present in transposition of the great arteries, be an explanation for the observed increase in lung volume. However, the literature reports conflicting data. A recent study from Toronto did not report significantly higher pulmonary saturation in transposition of the great arteries fetuses.[18] On the other hand, Lachaud et al. estimated increased pulmonary blood flow in fetuses with transposition of the great arteries, leading to a restricted growth of the oval foramen and a lower ductal flow during fetal life as hypothesised by Rudolph et al.[10,19] These anomalies were present from the first ultrasound scan in weeks 18–22 and became more prominent in the third trimester. In general, both blood vessel dilation and a greater blood volume present during imaging or an increased oxygen-, nutrient-, and flow-dependent growth of the lung parenchyma may cause increased lung volume on fetal MRI. In the current study, both of these factors may be hypothesised to relate to our findings; however, this remains to be explored.

Anatomical factors other than the aortopulmonary transposition could alter the fetal haemodynamics in these fetuses. Ultrasound of the outflow tracts in our fetuses was without notable obstruction, and all of them presented with antegrade ductal flow. Four of the eight fetuses with transposition of the great arteries had a ventricular septal defect, and the rest had intact ventricular septum. Studies on the differences in haemodynamics between transposition of the great arteries + ventricular septal defect and transposition of the great arteries with intact ventricular septum are sparse. Charbonneau et al. reported that late-gestation fetuses with transposition of the great arteries + ventricular septal defect exhibited normal transpulmonary flow, while fetuses with transposition of the great arteries with intact ventricular septum had higher transpulmonary flow throughout gestation.[20] With this sparse information, one could hypothesise that fetuses with transposition of the great arteries + intact ventricular septum have a larger pulmonary blood flow than fetuses with transposition of the great arteries + ventricular septal defect. Our study population was too small to do subgroup analysis regarding the above.

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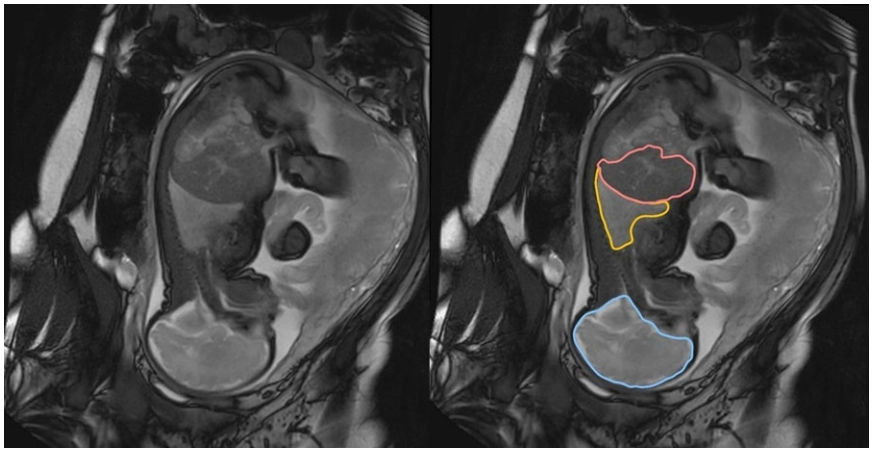

Figure 1. (***a***). 2D balanced steady-state free precession image of a fetus, captured in the coronal plane of the mother, duplicated to illustrate the process of organ volume measurement. The image on the left illustrates identifying the fetal organs, and the image on the right shows the drawing of regions of Interest around the total intracranial colume (blue line), the lungs (yellow line), and the liver (pink line).

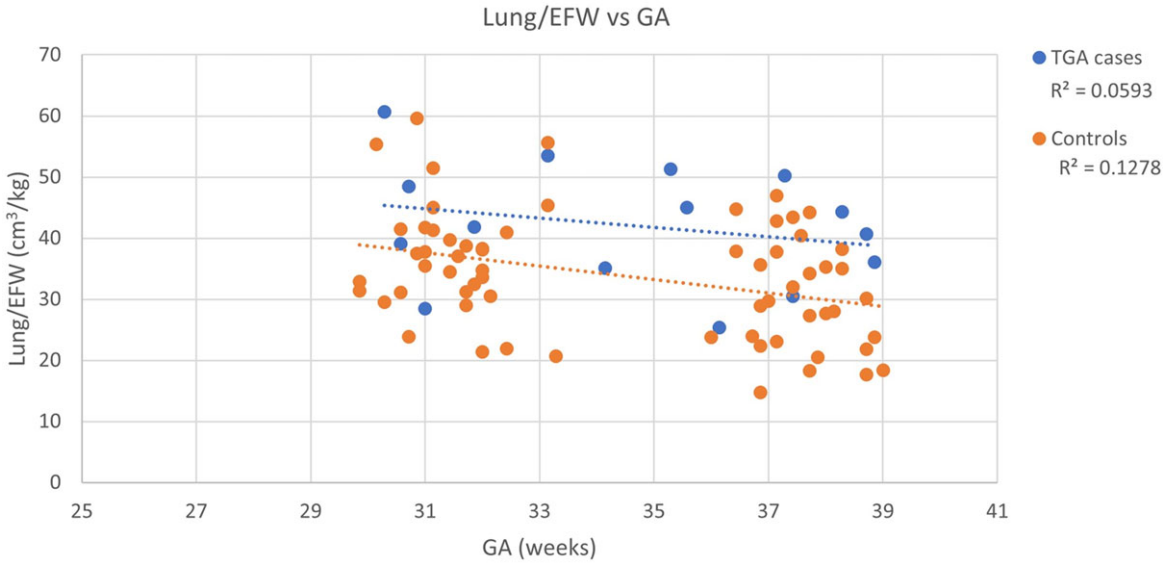

Figure 2. Lung volume corrected for EFW as a function of GA with (blue dots) and without (red dots) TGA. The dotted lines represent simple linear regressions over the measured organ volumes. EFW = estimated fetal weight; GA = gestational age; TGA = transposition of the great arteries.

Stratifying for the presence or absence of a ventricular septal defect in larger populations in the future will be of interest in exploring this matter.

No difference was observed in total intracranial volume or liver size. Some studies have reported smaller total intracranial volume in fetuses with transposition of the great arteries in late gestation,[8,21–23] and Lauridsen et al. found no difference in head size between healthy controls in a large Danish cohort study, so the literature presents conflicting results.[12] The fetal liver size in fetuses with dextro-transposition of the great arteries did not differ from the healthy controls, and this is in line with existing research.[24] A larger percentage of boys (88%) in the transposition of the great arteries fetuses compared with the equal sex distribution among control fetuses could potentially skew our results. Total intracranial volume has been measured to be larger in late gestation for male fetuses,[25] but for lungs and liver, no male–female differences have been found[26,27] However, by dividing fetal organ size with estimated fetal weight, we believe we have compensated for the difference in gender distribution. We divided our study population into two groups in the early and late gestational age (S4), so that a fetus was only present by only one scan per group. When we did this, the difference in lung volume corrected for estimated fetal weight between fetuses with and without transposition of the great arteries was significant only in the "Late" gestational age group. We think this underlines our findings, and it shows it is not due to the presence of one or a few very large fetuses with transposition of the great arteries skewing the results.

We found that our lung volume measurements were in line with existing literature.[28] Our measurements of total intracranial volume in both groups was consistently smaller than mentioned in previous literature.[29] We believe that this variance is because of heterogeneity in measuring methodology. The heterogeneity between organ volume measurements in fetal MRIs between studies is already described in literature reviews for lung volumes and total intracranial volume, respectively.[30,31] To our knowledge, no studies have been published on normative volumes of the fetal liver, measured by MRI. We believe that it is better methodology to compare organ volumes in fetuses with transposition of the great arteries to our own healthy controls that were scanned and measured with the same protocol as our cases than comparing with a reference organ volume varying as much as mentioned above.

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MRI allows for imaging of the entire fetus with high resolution and clear contrast between tissues,[32] making it feasible in measuring organs, compared with ultrasound, that has difficulties in seeing through denser tissues, like the bone. Furthermore, it has previously been proven useful in detecting extracardiac abnormalities in fetuses with CHD.[33] One of the challenges of fetal MRI encounters is motion-induced artefacts, thereby increasing the likelihood of measurement error in defining the organs. Fetuses at later gestational ages tend to move less, making it easier to obtain clearer sequences compared with younger fetuses. All MRI sequences used in this study were found adequate for organ volumetry. The MRI scan duration in this study is only 30 s, making it easier to acquire sequences without motion-induced artefacts and enable motion degraded images to be repeated when necessary. The variation in other studies considered, the use of MRI and the very low intra-observer variability should be considered a core strength of this study.

The full extent of the changes and the potential clinical implications of having larger lung volumes during the fetal period are still to be explored. Much attention has been directed to the intrauterine development of the brain and the potential damage of the cyanotic blood flow. We do know that children with CHD may experience complications from other organs either in the immediate postoperative phase such as kidney insufficiency or more long-term complications, such as pulmonary hypertension.[34–36] In the long run, patients with transposition of the great arteries corrected by an arterial switch operation have reduced exercise capacity.[37] Proposed factors causing this impairment range from chronotropic incompetence, narrowing of the main pulmonary artery with or without branch obstruction, coronary abnormalities, and/or ventricular dysfunction.[38] Could a minor part of this decrease in fitness be associated with altered lung development during fetal life? Many unanswered questions remain. With the new finding of larger lung volumes, we also need to evaluate if the size is at the expense of smaller hearts, larger thorax cavities, or more caudally positioned diaphragms.

This study has a number of limitations.

The MR images used in this study were acquired to determine the general orientation of the fetus before other MR sequences were introduced. Although the low resolution allowed for short image acquisition periods, preventing artefacts of movement, the spatial resolution, and in particular the slice thickness, could have been better. After the first round of analysis, it was decided to exclude the kidneys from the analyses because they turned out to be too small for the applied image resolution. In some fetal scans, the kidney was only visible on a single slice. Unfortunately, due to the MR sequences applied and the retrospective nature of this study, it was not methodologically feasible to measure pulmonary blood flow and/or saturation in the fetuses. Sun et al. recently used cine phase contrast MRI and T2 preparation oximetry technique that allowed them to measure fetal blood flow and vessel oxygen saturation.[18] For future studies, it may be possible to set up an MR sequence with higher resolution making distinction between organs feasible and with a protocol that allows for measuring fetal haemodynamics.

Another limitation of this study is that we chose to measure the total intracranial volume instead of brain volume. This was decided for the sake of simplicity but may mask a possible association between transposition of the great arteries and smaller brains. Studies have previously shown increased cerebrospinal fluid volume in late gestation CHD fetuses[21,33] along with decreased brain volume.

A total of eight cases with transposition of the great arteries is a small case population and a main limitation of this study. Larger studies should seek to accommodate alternative explanatory factors and consider the previously documented approximated exponential growth of fetal lungs[28,39] to enhance the generalisability of the findings to all fetuses with this type of CHD.

Conclusion

In the present study, we found that fetuses with dextro-transposition of the great arteries have bigger lung volumes than those of the control group when correcting for gestational age, estimated fetal weight, and lung volume *z* score. Total intracranial and liver volumes were unaffected. The findings warrant further investigation from larger and more elaborate studies and raise the question of any potential long-term consequences of affected non-cardiac organ development.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1047951124026398.

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