Sustained Chronic Maternal Hyperoxygenation Increases Myocardial Deformation in Fetuses with a Small Aortic Isthmus at Risk for Coarctation

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Background: We aimed to assess differences in myocardial deformation in fetuses at risk for coarctation (CoA) and the effects of maternal hyperoxygenation on deformation.

Methods: Fetal echocardiography and velocity vector imaging were performed prospectively and serially in 48 fetuses with a small aortic isthmus and 48 gestation age-matched normal fetuses. Fetuses with a small aortic isthmus were randomly divided into two groups: one group with and the other group without maternal supplemental oxygen administration. The strain (S) and strain rate (SR) in the left ventricle (LV) and right ventricle (RV) were measured and compared between the groups. Regression analyses were performed to identify potential factors associated with myocardial deformation.

Results: Compared with normal fetuses, fetuses with a small aortic isthmus exhibited a lower S and SR at baseline. A negative correlation was found between aortic isthmus velocity-time integrals and S and SR at baseline ($P < .05$). In the group that received supplemental oxygen therapy, the S and SR in both the LV and RV increased as a function of time, especially 4 weeks after the initiation of oxygen therapy ($P < .05$). The duration of oxygen therapy and increased combined cardiac index were associated with increased myocardial deformation ($P < .05$).

Conclusions: Myocardial deformation appears abnormal in those at risk for CoA beginning in utero, and chronic oxygen therapy appears to increase deformation measures. These findings may improve patient counseling and perinatal management. (J Am Soc Echocardiogr 2017;30:992-1000.)

Keywords: Oxygenation, Small aortic isthmus, Cardiac function, Myocardial deformation, Strain, Strain rate

Increasing evidence has shown impaired heart function in patients with coarctation (CoA) after optimal treatment. Chen *et al.*[1] demonstrated a reduced systolic and diastolic myocardial reserve and an abnormal myocardial contractile response to exercise in CoA patients. Faganello *et al.*[2] reported that patients for whom CoA was successfully repaired commonly exhibit asymptomatic lower mitral annular peak systolic velocity (S′) associated with worse left ventricle (LV) diastolic function during long-term follow-up. Additionally, Fesseha *et al.*[3] reported that neonates with isolated CoA showed worse preoperative LV myocardial performance indexes, indicating that the cardiac dysfunction might exist in utero.

Maternal oxygenation therapy, as either a diagnostic or therapeutic tool, has been applied to various prenatal conditions. In a fetus with congenital heart disease (CHD), an increase in pulmonary venous return[4] and partial improvement of hypoplastic cardiovascular dimensions[5,6] were reported after oxygen therapy. Our recent study[7] also demonstrated that sustained maternal hyperoxygenation improved aortic arch dimensions in fetuses with CoA, but no studies have been performed on the influence of maternal hyperoxygenation on myocardium mechanics in fetuses with CHD. Rasanen *et al.*[8] demonstrated that maternal hyperoxygenation between 31 and 36 weeks causes redistribution of the right ventricle (RV) cardiac output from the systemic circulation to the pulmonary circulation in a normal fetus, although RV cardiac output and LV cardiac output remain unchanged. We hypothesized that this redistribution might alter LV preload and benefit heart function in fetuses with a small aortic isthmus.

In this study, we attempted to (1) observe myocardial deformation in fetuses with a small aortic isthmus and (2) observe the impact of chronic maternal hyperoxygenation on heart deformation in fetuses with a small aortic isthmus.

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Abbreviations

CCO = Combined cardiac output

CCOi = Combined cardiac index

CHD = Congenital heart disease

CoA = Coarctation

DA-PI = Pulsatility index of the ductus artery

EFW = Estimated fetal weight

GA = Gestation age

LV = Left ventricle

MPI = Myocardial performance index

RV = Right ventricle

S = Strain

SR = Strain rate

UA-PI = Pulsatility index of the umbilical artery

VTI = Velocity-time integral

VVI = Velocity vector imaging

METHODS

Study Population

This was a prospective, longitudinal investigation. The case group consisted of pregnant women referred for fetal echocardiography because of ventricular and/or great artery disproportion with a small left heart (mitral valve Z score less than -2) during the period from January 2012 to December 2014. The inclusion criteria were single fetuses with an isolated smaller aortic isthmus (i.e., a Z score of the aortic isthmus diameter <-2 when measured just before the descending aorta in the three-vessel and trachea view; modified three-vessel view that includes the aortic arch and isthmus) and abnormal aortic isthmus flow (retrograde or persistent diastolic blood flow at the aortic isthmus). We excluded fetuses with intrauterine growth restriction, placenta insufficiency, atrial septal restriction, hypoplastic left heart syndrome, tricuspid regurgitation, anomalous pulmonary venous return, and medium or large ventricular septal defects (>2 mm). The normal group consisted of gestation age (GA)-matched mothers from a local low-risk population. Furthermore, fetuses were excluded if they had a GA of <18 weeks or >40 weeks; were small for their GA after birth; had chromosomal defects, extracardiac abnormalities, or persistent fetal arrhythmia; or had maternal complications, including gestational diabetes, preeclampsia, and thyroid disease. This study was approved by the institutional review board at the Second Xiangya Hospital of Central South University, and written informed consent was obtained from all the families.

Maternal Hyperoxygenation Protocol

A complete standard fetal echocardiogram was performed in room air using an Acuson Sequoia 512 system (Siemens Medical, Olympia, WA) coupled with a 6C2 transducer. After confirming the presence of LV/RV size discrepancy in fetuses with a small aortic isthmus and abnormal flow, pregnant women were randomly assigned to two groups, one of which received supplemental oxygen. In patients who received supplemental oxygen, 45% oxygen (6 L/min) was administered via a face mask for 3 hours, twice a day until delivery. This regimen was modified from Kohl's previous reports[9] and was identified as useful in our unpublished preliminary research. All fetuses were monitored once every 4 weeks by obstetric ultrasound, fetal echocardiography, and cardiotocography, and the mothers were also questioned by an obstetrician. After delivery, ocular fundus examinations were performed in babies in the group that received oxygen, and chest x-rays were collected from participants in the oxygen group.

Measurements

For all the fetuses, routine obstetrical ultrasound and fetal echocardiography examinations were performed serially by one expert (Q.C.). The pregnancy duration was estimated from the day of the last menstrual period and was confirmed by ultrasound measurement during the first trimester. Fetal biometry, including the biparietal diameter, head circumference, abdominal circumference, and femoral length, was performed and used to calculate the estimated fetal weight (EFW). The pulsatility indexes of the umbilical artery (UA-PI) were obtained in the absence of fetal movements. The heart structure dimensions were measured from inner edge to inner edge using two-dimensional ultrasonography. The aortic isthmus was measured in the three-vessel and trachea view (Figure 1). The Doppler sweep speed was set to the maximum value (10 cm/sec), and the angle was maintained below 10°. The flow pattern at the aortic isthmus was recorded as normal (forward flow) or abnormal (persistent diastolic blood or reverse flow; Figure 2). The peak gradient at the aortic isthmus and the pulsatility index of the ductus artery (DA-PI) were recorded. The velocity-time integrals (VTIs) of the aortic valve, pulmonary artery valve, and aortic isthmus were obtained. Only forward flow measurements were reported for the aortic isthmus VTI in fetuses with reversal flow. The combined cardiac output (CCO) was calculated using the following formulas: CCO = left ventricular output + right ventricular output = $3.14 \times (\text{AV diameter}/2)^2 \times \text{VTI AV} \times \text{heart rate} + 3.14 \times (\text{PV diameter}/2)^2 \times \text{VTI PV} \times \text{heart rate}$. The CCO was then indexed to EFW and was expressed as the combined cardiac index (CCOi) in mL/min/kg. The LV and RV myocardial performance indexes (MPIs) were calculated using pulse Doppler methods[10]: $\text{MPI} = (a - b)/b$, where a is the interval from the closure click to the aperture click of the mitral/tricuspid valve and b equals the time from the aperture click to the closure click of the aortic/pulmonary valve.

Myocardial deformation was assessed by one observer (S.Z.) who was blinded to the clinical characteristics and echocardiogram results and used vector velocity imaging software (VVI; Siemens Medical Solutions, Olympia, Washington). After acquiring high-quality cine loop clips (40-50 frames/sec) in an apical four-chamber view in the absence of maternal breathing and fetal movement, a single still frame with optimal endocardial visualization was chosen for analysis. As previously reported,[11,12] the endocardium of the LV and RV was traced at end diastole during the same cardiac cycle, and myocardial deformation analysis was then performed. Regional and global strain (S) and the strain rates (SRs) for systole and diastole were automatically calculated and displayed. In this study, only S and SR were recorded. Each value was measured three times and averaged.

Deformation Reliability

To assess interobserver variability, the global S and SR were independently measured by a third reader (Y.Z.) who was blinded to the clinical data of 20 fetuses with a small aortic isthmus (21% of the total cohort).

Statistical Analyses

The data are reported as the means with SDs or frequencies with percentages, as appropriate. An unpaired two-tailed Student's t test or the χ^2 test was performed to compare clinical characteristics between fetuses with a small aortic isthmus and normal controls. The time-course changes in myocardial deformation in all the groups were assessed using the post hoc Games-Howell test for multiple