Developmental Changes in Aortic Mechanical Properties in Normal Fetuses and Fetuses with Cardiovascular Disease

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Received Dec 16, 2015; received in revised form Apr 22, 2016; accepted May 26, 2016
Available online

Key Words
aortic compliance; congenital heart disease; fetal cardiology; pregnancy; uteroplacental Doppler flow

Background: We hypothesized that fetal aortic mechanical properties assessed by aortic diameter (AoD) and flow show maturational changes during the gestational period, and that these properties are different in fetuses with congenital heart diseases and fetuses with normal development.

Methods: Phasic changes in ascending AoD along with Doppler flow profile were measured in 84 consecutive normal fetuses (gestational age, 18–36 weeks) and in 30 consecutive fetuses with cardiovascular diseases (gestational age, 22–39 weeks).

Results: AoD and cardiac output significantly increased with gestational age. Fetal aortic compliance (AC), assessed as (maximum AoD − minimum AoD)/stroke volume, significantly decreased with gestational age in normal fetuses, indicating maturational changes in aortic wall properties. Importantly, fetuses with Marfan syndrome and tetralogy of Fallot that exhibit "aortopathy" showed significantly lower AC than normal fetuses of the same gestational age, suggesting intrinsic abnormalities in aortic wall properties in these diseases. Fetuses with trisomy 18 and Noonan syndrome also had AC values below the normal ranges.

Conclusion: Measurements of phasic changes in fetal AoD and flow measurements can provide useful information about aortic mechanical properties and may help clarify abnormal arterial hemodynamics in pathologic conditions.

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1. Introduction

Advancements in fetal echocardiography allow assessment of the prognosis of cardiac lesions based on cardiac anatomy and function in utero. Doppler ultrasonography has enabled noninvasive examination of fetal cardiovascular pathophysiology and has been used to study hemodynamics using the flow-velocity waveform. More recently, quantification of cardiac function with new techniques, such as four-dimensional ultrasound using spatiotemporal image correlation and tissue Doppler imaging, has attracted interest. These techniques allow partial assessment of cardiac preload and myocardial performance. However, the assessment of the cardiac afterload prior to birth remains challenging because measurement of fetal blood pressure is not yet possible. The pressure pulse waveform produces a corresponding change in the diameter of the vessel, and simultaneous recording of pressure and diameter waves in human arteries has demonstrated the concordance between these features.6,7 Thus, recording the change in the vessel lumen diameter throughout the cardiac cycle, combined with measurement of the flow velocity profiles, may have the potential to provide information about the elastic properties of the fetal aorta, which is an important component of cardiac afterload. We hypothesized that fetal aortic mechanical properties assessed by aortic diameter (AoD) and flow show maturational changes during the gestational period, and that properties of fetuses with congenital heart diseases differ from those of fetuses with normal development.

2. Methods

2.1. Patients

Fetal echocardiography and Doppler ultrasound examinations of the fetal aorta were retrospectively analyzed in 84 normal fetuses between 18 weeks and 36 weeks of gestation. These fetuses were selected from 258 consecutive fetuses that had undergone echocardiographic examination. The exclusion criteria were maternal and fetal abnormalities. Maternal abnormalities for exclusion included hypertensive disease, diabetes, medicated collagen vascular diseases, and threatened premature labor, whereas fetal abnormalities for exclusion included fetal growth retardation, abnormal amniotic fluid volume, monozygotic twin, hydrops, and cardiac or extracardiac abnormalities.

We also examined 30 consecutive fetuses with abnormal heart findings (gestational age, 22–39 weeks) from the same cohort (258 patients). These abnormal heart findings included transposition of the great arteries (n = 2), single ventricle (n = 3), tetralogy of Fallot (TOF; n = 3), ventricular septal defect (VSD; n = 7), heart defect associated with trisomy 18 (n = 3; VSD in 2 and atroventricular defect in 1), coarctation of the aorta/interrupted aortic arch (CoA/IAA; n = 5), and others (n = 7; persistent left superior vena cava, small left ventricle, bicuspid aortic valve, cardiitis, cardiac tumor, multiple valve regurgitation associated with Marfan syndrome, and left ventricular hypertrophy associated with Noonan syndrome). In 12 of these 30 fetuses with an abnormal heart, we performed serial studies for follow-up, and a total of 49 studies were included in this group.

2.2. Measurements

Fetal echocardiograms were performed with a C3540 convex linear-array transducer or a 58 or 54 phased-array transducer on a Sonos 5500 (Hewlett-Packard, Agilent Technologies, Inc., Palo Alto, CA, USA) or 7500 (Philips Healthcare, Andover, MA, USA) system. Maximum and minimum AoDs at the sinotubular junction were measured from two-dimensional echo tracings in the left ventricular outflow tract view. The aortic flow velocity waveform was also recorded from the same view, and aortic velocity time integral (AoVTI) was obtained. Stroke volume (SV) was then calculated as AoVTI multiplied by aortic cross-sectional area (obtained by maximum aortic diameter), and cardiac output (CO) calculated as SV multiplied by the fetal heart rate.

According to the Windkessel theory, SV ejected into the distensible arterial system proceeds into a compliant arterial compartment. This compartment has an outflow resistance, which corresponds to the arterial resistance (R). At a given R, changes in volume in the compliant aortic compartment are proportionate to the compliance (AC) of the compartment and the amount of SV; changes in aortic diameter become larger when AC is greater and SV is larger, and vice versa. Thus, fetal AC can be estimated as:

\[ AC = \frac{\Delta Volume}{SV} = \frac{(maximal AoD - minimal AoD)}{SV}, \]

where \( \Delta Volume \) denotes the changes in volume in the compliant aortic compartment.

Changes in AC with gestational age both in normal fetuses and those with cardiovascular disease were examined. The study was approved by the Saitama Medical University Review Board on Clinical Investigation (No. 11-077; Saitama, Japan).

2.3. Statistical analysis

Intraobserver differences of AoD were determined with repeated measurements of AoD in 25 randomly selected fetuses, and the difference was expressed as a correlation coefficient of the paired measurements. The ratio of the SD and the mean of the two measurements were also calculated as the intraobserver variability. Developmental alterations of each parameter were assessed using linear regression analysis with the least-squares method for aortic diameter, diameter pulse, and CO. AC was logarithmically transformed and also assessed using linear regression analysis. The correlation coefficient was calculated using the Pearson product-moment method. To compare the AC in normal fetuses and in fetuses with abnormal heart, we used the Z score of AC. The Z score was calculated as described previously:

\[ Z score = \frac{\ln(\text{actual AC}) - \ln(\text{predicted AC})}{\sqrt{\text{MSE}}}, \]

where MSE is the mean square error. Predicted AC and MSE were obtained using the regression analysis of AC and
gestational age in normal fetuses. Z scores in fetuses with abnormal heart were compared with those in normal fetuses using the Mann–Whitney U test.

All statistical analyses were performed using the JMP version 9.0 software (SAS Institute Inc., Cary, NC, USA). A p value of < 0.05 was considered statistically significant.

3. Results

Intraobserver differences of maximum and minimum AoD were as follows: correlation coefficients of \( r = 0.98 \) (\( p < 0.001 \)) and \( r = 0.98 \) (\( p < 0.001 \)) with intraobserver variability of \( 4.5 \pm 3.8\% \) and \( 6.0 \pm 3.4\% \), respectively.

As expected, maximum and minimum AoDs, aortic diameter pulse (difference between maximum AoD and minimum AoD), and CO significantly increased with gestational age (Table 1), suggesting the validity of measurements for aortic diameter and flow in this study. In normal fetuses, AC decreased logarithmically with gestational age (Table 1 and Figure 1; \( \ln AC = 1.5510 - 0.0779 \times \) gestational age in weeks; \( r = 0.6798, p < 0.0001 \)), indicating maturational changes in aortic wall properties (increase in aortic stiffness) during the fetal period.

Although the majority of fetuses with heart diseases had AC values within the ranges of those in normal fetuses, fetuses with TOF, Noonan syndrome, and Marfan syndrome had lower AC values than normal fetuses (Figure 2). All fetuses with TOF had Z scores < −2.0. The Z score in fetuses with TOF was significantly lower than that in normal fetuses (\( p = 0.0034 \)). Fetuses with Noonan syndrome and Marfan syndrome also exhibited low Z scores of −4.52 and −2.65, respectively (Figure 3).

In the serial assessment of fetuses with heart diseases (12 fetuses, average time interval from the 1st assessment was 3.9 weeks), the Z score of AC in fetuses with VSD and trisomy 18 decreased from a normal range to abnormally low throughout gestation, whereas the Z score in a fetus with TOF remained low from the first examination (Figure 4).

4. Discussion

4.1. Changes in elastic properties of the fetal aorta

Elastin is an essential component of the aortic wall and increases in quantity in response to increases in blood pressure and flow during fetal development.\(^{11}\) This suggests an increase in the load-bearing nature of the aortic wall property by appropriately increasing its stiffness. This theory is supported by the results of an elegant study by Mori and Saburi.\(^{12}\) They measured the aortic stiffness in both preterm and term infants (between 29 weeks and 40 weeks of gestation) who were appropriate for gestational age and demonstrated that the stiffness index calculated from aortic diameter and pressure significantly increased with gestational age at birth. The results of the present study are consistent with these results, indicating increases in aortic wall stiffness with structural maturation during the fetal period. Furthermore, the present results

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<th>Table 1: Correlation between aortic diameters, aortic diameter pulse, cardiac output, aortic compliance, and gestational age.</th>
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<td><strong>Slope</strong></td>
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<td>Maximum AoD</td>
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AoD = aortic diameter; \( \ln AC \) = natural logarithm of aortic compliance. |
are consistent with our previous reports of the developmental increase in aortic wall stiffness in children after birth,\textsuperscript{13,14} and they importantly suggest a continuity of maturational changes in aortic wall mechanical properties in humans from the fetal to childhood stages.

Furthermore, our study demonstrated for the first time that aortic compliance (AC; inverse of stiffness) assessed by the relationship between SV and corresponding aortic diameter changes was lower in fetuses with Marfan syndrome and TOF than in normal fetuses of the same gestational age. Interestingly, histological abnormalities in the aortic media, represented by elastic fiber disruption, have been well documented in these diseases\textsuperscript{15,16} and such abnormalities are mirrored by the abnormal mechanical property of increased aortic stiffness.\textsuperscript{17–19} Importantly, these structural and functional abnormalities in the aortic wall in Marfan syndrome and TOF have been postulated as intrinsic because they are observed even during early infancy.\textsuperscript{20,21} However, whether aortic stiffness, possibly reflecting histological abnormalities, is already increased prior to birth has never been explored in these diseases. Our data are the first to clarify this, and they further support the notion of “intrinsic” abnormalities of aortic wall properties in Marfan and TOF patients. In addition to these two representative diseases of “aortopathy,” we also demonstrated that fetuses with VSD and trisomy 18 had “stiff” aortas prior to birth. To our knowledge, there have been no data about aortic wall properties in this chromosomal abnormality, and our data may set the basis for future studies in this regard. We also showed that one fetus with Noonan syndrome had low AC. This may be consistent with recent reports of aortic dilation in this syndrome.\textsuperscript{22,23} Whether “aortopathy” is a potential complication associated with Noonan syndrome warrants further investigation.

Decreased arterial elasticity has adverse effects on cardiac performance because of the increased workload on the left ventricle and/or decreased coronary flow caused by a decrease in diastolic aortic pressure.\textsuperscript{24,25} Adverse effects of increased arterial stiffness and thus increased pulsatile load on the left ventricular wall have been emphasized in TOF,\textsuperscript{17,24} Marfan syndrome,\textsuperscript{27,28} and bicuspid aortic valve.\textsuperscript{29} Given the limited cardiac functional reserve in fetuses, even a modest increase in left ventricular afterload may induce a profound decrease in CO\textsuperscript{30} or a change in fetal cardiac flow distribution that may affect the cardiovascular development. Further longitudinal assessment in individual fetuses may elucidate the developmental aortic features of these diseases and their pathophysiological significance.

4.2. Study limitations

Although our results were consistent, small sample size, particularly in heart diseases, is an important limitation of this study, and large-scale studies are necessary to confirm our results. Measurements were reproducible as shown by intraobserver error of maximum AoD and minimum AoD, and CO and AoD showed expected changes with gestational age differences (Table 1). Although these findings support the validity of measurement accuracy in the present study, we have to recognize that the small size of the fetal aorta results in an inherent limitation on accurate measurement because of the relatively low signal/noise ratio and that fetal cardiac movement can be a significant source of errors in the measurement.

SV is one of the components of the AC formula, and it can influence the AC value. Fetuses with TOF or Marfan syndrome and aortic regurgitation may have lower AC because of high SV. To clarify the effect of SV on AC, we compared the ratio of actual AC to predicted AC obtained by the regression analysis of AC and SV in normal fetuses. The ratio in fetuses with TOF was significantly lower than that in normal fetuses (range, 0.59–0.67 vs. median 1.02,
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5th percentile of 0.74 and 95th percentile of 1.59; \( p = 0.0036 \), and fetuses with Marfan syndrome and Noonan syndrome also showed low values (0.63 and 0.29, respectively). However, the ratios in fetuses with other heart diseases were within normal range. Interestingly, the ratio in a fetus with pulmonary atresia with intact septum, in which SV should be much higher than normal, was similar to the values in normal fetuses (1.05). Thus, decreased AC observed in TOF or Marfan fetuses did not exist because of the increased SV. To further validate the physiological meaning of AC used in this study, we examined the relationship between AC and pulse wave velocity (an index of arterial stiffness) in 37 children who underwent echocardiography at our outpatient clinic but had only a minimum hemodynamic abnormality (i.e., small atrial septal defect, small VSD, or mild pulmonary stenosis; age, 1.4 ± 0.2 years). AC was significantly and inversely correlated with pulse wave velocity measured from the ascending aorta to the thoracic aorta at the diaphragm level (\( p < 0.05, r = 0.40 \)). These results strongly suggest the validity of our AC calculation, together with the results that are consistent with the structural maturation of the aortic wall during the fetal period (Figure 1).

5. Conclusion

Phasic change of fetal aortic dimension, coupled with information about aortic flow, provides useful information about fetal aortic mechanical properties. With this methodology, we found maturational changes in aortic mechanical properties with gestational age in normal fetuses. Furthermore, fetuses with congenital heart diseases that exhibit “aortopathy” after birth may already have abnormal aortic mechanical properties. Future studies investigating whether abnormal aortic mechanical properties detected during fetal life have diagnostic and prognostic value are of particular importance to further establish its clinical usefulness.

Conflicts of interest

The authors have no conflicts of interest to disclose.

References


