PATHOPHYSIOLOGY AND NATURAL HISTORY

FETAL PHYSIOLOGY

Changes in intracardiac blood flow velocities and right and left ventricular stroke volumes with gestational age in the normal human fetus: a prospective Doppler echocardiographic study


ABSTRACT We used Doppler echocardiography to quantitate the changes in intracardiac blood flow velocities and right and left ventricular stroke volumes in 80 normal human fetuses from 19 to 40 weeks gestation. Blood flow velocity spectra across the aortic, pulmonary, tricuspid, and mitral valves were digitized to obtain peak velocities (m/sec) and flow velocity integrals. Aortic and pulmonary diameters were measured at valve level from two-dimensional echocardiographic images and cross-sectional area was calculated assuming a circular orifice. Ventricular stroke volume was calculated as the product of the cross-sectional area of a great vessel and the flow velocity integral through that vessel. The pulmonary arterial and aortic diameters increased linearly with gestational age (r = .82, r = .84), and pulmonary arterial diameter consistently exceeded aortic diameter. There was a positive relationship between stroke volume and gestational age: stroke volume increased exponentially from 0.7 ml at 20 weeks to 7.6 ml at 40 weeks for the right ventricle (r = .87) and from 0.7 ml at 20 weeks to 5.2 ml at 40 weeks for the left ventricle (r = .91). Similar results were obtained for right and left ventricular and combined cardiac outputs. In 44% of the fetuses it was possible to quantitate both right and left ventricular stroke volumes. There was a close correlation between right and left ventricular stroke volumes in these fetuses (r = .96) and right ventricular stroke volume exceeded left ventricular stroke volume by 28%. Flow velocity across the tricuspid and mitral valves was consistently greater during atrial systole (A wave) than during rapid ventricular filling (E wave) (0.52 ± 0.07 vs 0.37 ± 0.08 m/sec and 0.45 ± 0.07 vs 0.33 ± 0.06 m/sec). The E/A ratios for the mitral and tricuspid valves were similar throughout the period of gestation studied, indicating equivalent diastolic ventricular function. This study demonstrates that right and left ventricular stroke volumes increase by approximately 10-fold from 20 to 40 weeks gestation in the normal human fetus. It also demonstrates, within the limitations of the equipment, that right ventricular stroke volume exceeds that of the left ventricle, thus confirming right ventricular dominance in utero.

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TWO-DIMENSIONAL echocardiographic imaging of the fetal heart has permitted accurate definition of intracardiac anatomy and characterization of the growth patterns of the four cardiac chambers throughout the second and third trimesters. Echocardiography has also enabled recognition of cardiac rhythm disturbances, and allowed sequential chamber analysis, determination of ventricular morphology, and recognition of structural heart disease during prenatal life. The echocardiographic diagnoses of complex cardiac abnormalities in utero have correlated closely with the anatomic findings at postpartum cardiac catheterization and autopsy.

Although echocardiography provides detailed anatomic information, evaluation of cardiac function is limited to assessment of fractional shortening of the two ventricles. The application of Doppler echocardiography, however, permits a more detailed assessment of cardiac function. Initial studies in normal and abnormal fetuses have demonstrated that blood flow
velocities can be measured in utero, and have provided unique physiologic insights into fetal cardiac physiology.\textsuperscript{13-15} Although a few studies have attempted to quantitate blood flow velocity and calculate right and left heart outputs with the use of Doppler measurements of blood flow, information regarding the changes with gestational age is limited.

The purpose of this prospective study using Doppler echocardiography was to characterize in greater detail the changes in cardiac blood flow velocities and to quantitate and compare the changes in right and left ventricular stroke volumes with gestational age. In addition, we attempted to determine the relative dominance of the two ventricles by determining which ventricle had the greater stroke volume through the second and third trimesters.

Materials and methods

Our study population consisted of 80 normal mothers who were recruited from patients referred for obstetrical ultrasound examination. Indications for ultrasound included estimation of gestational age and fetal weight and determination of placental location. Mothers with diabetes mellitus, hypertension, pre-eclampsia, Rh incompatibility, multiple gestations, or who had previous pregnancies in which congenital malformations were noted were excluded from the study. Doppler echocardiograms were obtained from the fetuses from 19 weeks gestation to term. Gestational age was assessed from the first day of the last menstrual period, and was corroborated with ultrasound measurements of biparietal diameter, which has been shown previously to correlate closely with fetal gestational age.\textsuperscript{16, 17}

The study protocol was approved by the Brigham and Women's Hospital Human Subjects Committee, and written informed consent was obtained from each mother. Only one pulsed Doppler echocardiographic examination was performed on each mother to minimize any potential harmful effects of repeated ultrasound examinations.\textsuperscript{18}

Procedures. Studies were performed with a Hewlett-Packard 77020 AC/AR ultrasound system with 3.5 or 5.0 MHz transducers (5 MHz was used in the youngest fetuses). The 3.5 MHz transducer has an axial resolution of 1.0 mm and a lateral resolution of 1.6 mm and the 5 MHz transducer has an axial resolution of 0.7 mm with a lateral resolution of 1.2 mm. The fetal heart was located with use of the spine and liver as easily recognizable anatomic landmarks. The orientation of the heart with respect to the transducer was determined by identifying the right heart chambers by the more apical position of the tricuspid valve, the presence of the moderator band, and the insertion of the inferior vena cava.

A systematic two-dimensional echocardiographic examination of each fetal heart was performed to exclude any structural abnormality. The presence of two normal atrioventricular valves, two normal semilunar valves, and concordant atrioventricular and ventriculoarterial connections was established in each fetus. The great vessels were identified by their characteristic pattern of major branches.

Two-dimensional echocardiographic imaging was used to position the Doppler sample volume in the region of interest, where blood flow velocity was to be measured. Attempts were made in each fetus to obtain blood flow velocities across the right and left atrioventricular and semilunar valves. Doppler blood flow velocities across the tricuspid and mitral valves were obtained from the apical four-chamber view with the sample volume positioned in the ventricles immediately distal to the valves where the ultrasound beam was parallel to the direction of blood flow. For atrioventricular valves the direction of flow was assumed to be at right angles to the annulus of the valves and parallel to the long axis of the ventricles. Doppler records of aortic blood flow velocity were obtained from the five-chamber view. Pulmonary blood flow velocities were recorded from the conventional two-dimensional echocardiographic short-axis view. Doppler sample volumes were located in the great vessels immediately distal to the semilunar valves with the ultrasound beam parallel to the direction of blood flow. The direction of blood flow for the semilunar valves was assumed to be parallel to the long axis of that portion of the pulmonary artery or aorta just distal to the valve. Two-dimensional images and Doppler flow velocity spectra were recorded on standard ½ inch videotape for subsequent analysis. To minimize any possible risk to the fetus, only one Doppler study was performed on each fetus, and total scanning time was limited to 15 min with Doppler recordings limited to 2 min; gain control was reduced to the minimum necessary to record adequate flow velocity spectra. All fetuses were subsequently delivered at Brigham and Women's Hospital without apparent fetal abnormalities.

In recording flow velocity spectra the Doppler cursor was positioned parallel to the direction of blood flow. If the angle between the Doppler cursor and the assumed direction of flow was greater than zero, then the "angle correction cursor" or "flow direction indicator" was positioned along the assumed direction of blood flow to estimate the angle of incidence between flow and the Doppler beam. The angle between this flow direction indicator and the Doppler ultrasound beam was determined by the instrument and its cosine used to recompute flow velocity. If there appeared to be any visual discrepancy between the angle between the direction of blood flow and the flow direction indicator, this angle was checked manually with a protractor.

High-quality two-dimensional echocardiographic images of the aorta and pulmonary artery were recorded from the short-axis view or the five-chamber view oriented as orthogonally as possible to the axial plane of the ultrasound system to determine vessel diameters. Echocardiographic images were transferred to the video digital disk of a Franklin Quantic 1200 ultrasound analysis system and digitized with the electronic cursor. Measurements were made of the aortic and pulmonary arterial diameters at the level of the anulus from the systolic frame showing maximum diameter. A minimum of five separate cycles were measured and mean values were calculated. Measurements of the internal diameters of both vessels were made from where the semilunar valves were clearly visible and the gain controls were adjusted to minimize the "blooming" of the vessel wall echoes.\textsuperscript{19, 20}

Doppler flow velocity spectra were also analyzed with the Franklin Quantic 1200 analysis system. The flow velocity spectra from a minimum of three consecutive cardiac cycles were digitized through the middle of the densest portion of the flow velocity envelope to obtain peak flow velocities and the flow velocity integrals. Doppler flow velocity spectra were not analyzed when the angle between the ultrasound beam and direction of blood flow was greater than 25 degrees and those spectra that were not clearly defined or in which there was considerable variation in amplitude were also not analyzed.

Measurements of the following variables were made: (1) Heart rate (beats/min). (2) Pulmonary arterial and aortic diameters, rounded off to the nearest millimeter because of the limits of resolution of equipment, from which cross-sectional area was calculated assuming a circular cross section. (3) Aortic valve and pulmonary valve flow velocities, including peak velocity
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stroke volume outputs area, and the cardiac output was determined as

arterial blood flow was 14 ± 8 degrees in the pulmonary artery and 12 ± 8 degrees in the aorta.

Right and left ventricular stroke volume outputs were calculated as the product of the respective great vessel cross-sectional areas and the blood flow velocity integrals. There was a positive correlation between right

FIGURE 1. Relationship between pulmonary arterial diameter (cm) measured at valve level and gestational age (weeks) and between aortic diameter and gestational age.

Reproducibility. The reproducibility of Doppler measurements of pulmonary and aortic diameters and flow velocity integrals were assessed in 20 studies chosen at random by two observers blinded to gestational age and patient serial number.

Data analysis. Doppler and echocardiographic variables were plotted against gestational age and the respective correlations were determined by regression analysis.

Results

Although heart rate varied from 125 to 160 beats/min in individual fetuses, mean heart rate decreased from 150 ± 5 beats/min at 20 weeks to 140 ± 11 beats/min at 40 weeks. Heart rate (HR) was inversely related to gestational age (GA) by the regression equation HR = -0.35GA + 151; r = - .27 , p < .05 . Heart rates were stable throughout the examination in each fetus and did not vary by more than 5 beats/min.

High-quality images of the pulmonary artery were obtained in 90% of fetuses. Pulmonary arterial diameter increased linearly with gestational age from 0.40 ± 0 cm at 20 weeks to 0.85 ± 0.13 cm at 40 weeks (r = .82 , p < .001; figure 1). In 94% of fetuses the aortic diameter was measured and it also increased linearly with gestational age from 0.35 ± 0.05 cm at 20 weeks to 0.76 ± 0.11 cm at 40 weeks (r = .84 , p < .001; figure 1). There was a close linear correlation between pulmonary arterial diameter and aortic diameter (r = .97 , p < .001; figure 2). The pulmonary arterial diameter was approximately 12% greater throughout the period of gestation studied, with mean pulmonary arterial diameter (0.65 ± 0.16 cm) being significantly greater than mean aortic diameter (0.58 ± 0.15 cm, p < .001).

Doppler blood flow velocity spectra were obtained from the pulmonary arteries of 47 fetuses (59%) and from the aorta of 52 fetuses (65%), with an angle between the ultrasound beam and the direction of blood flow of less than 25 degrees. There was a trend toward increased peak flow velocity in the pulmonary artery with gestational (0.46 m/sec at 20 weeks to 0.8 m/sec at 40 weeks) and peak velocity was related to gestational age by the regression equation y = 0.009x + 0.43 , r = 0.41 . A similar trend existed in the aorta,
ventricular stroke volume and gestational age, with right ventricular stroke volume increasing exponentially from 0.7 ml at 20 weeks to 7.6 ± 1.6 ml at 40 weeks (r = .87, p < .001; figure 3). There was a similar positive correlation between left ventricular stroke volume and gestational age, with left ventricular stroke volume increasing exponentially from 0.7 ± 0.3 ml at 20 weeks to 5.2 ± 2.0 at 40 weeks (r = .91, p < .001; figure 3). Similar positive correlations existed for right and left ventricular cardiac outputs and gestational age (figure 4). In the 35 fetuses in whom both right and left ventricular stroke volumes could be determined there was a very close relationship between the two (r = .96), with the slope of the regression line indicating that right ventricular stroke volume exceeded left ventricular stroke volume by approximately 28% (p < .001; figure 5). Mean right ventricular stroke volume (3.4 ± 2.2 ml) was significantly greater than left ventricular stroke volume (2.6 ± 1.8 ml, p < .001). In these 35 fetuses, combined cardiac output was calculated and it also increased exponentially with gestational age from 20 to 40 weeks (r = .91, p < .001; figure 4). In this study we did not attempt to measure fetal weight by ultrasound, but in figure 4, D, we plotted fetal weight against gestational age for the latter part of pregnancy using a previously published equation.21 When this relationship was compared with the regression line derived from combined cardiac output and gestational age in our study it was noted that combined cardiac output was approximately 450 ml/kg/min at the end of the last trimester.

Doppler blood flow velocity spectra showing clearly defined E and A waves were obtained from the tricuspid valve in 48% and from the mitral valve in 60% of the fetuses studied. Peak blood flow velocities across the tricuspid and mitral valves during rapid ventricular filling (E wave) and during atrial systole (A wave) are illustrated in table 1. A higher peak flow velocity across the right-sided atrioventricular valve was in contrast to the higher peak flow velocity across the left-sided semilunar valve. The peak velocities during atrial systole across both the mitral and tricuspid valves were greater than the peak velocity during rapid filling and the E/A ratio for the tricuspid valve increased from 0.52 at 20 weeks to 0.84 at 40 weeks and was related to gestational age by the regression equation y = 0.01x + 0.43, r = .59, p < .01. The E/A ratio from the mitral valve was similar, increasing from 0.63 at 20 weeks to 0.83 at 40 weeks, and it was related to gestational age by the regression equation y = 0.01x + 0.49, r = .46, p < .01.

Interobserver variability in the measurements of pulmonary arterial and aortic vessel diameters and flow velocity integrals was assessed by comparing the data generated by one observer with those of another by linear regression analysis. The correlation coefficient between the two observers for measurements of pulmonary arterial and aortic diameters was .98 and
Right and left ventricular stroke volumes can be quantitated by Doppler echocardiography as the product of the integral of the blood flow velocity spectra and the cross-sectional area of the orifice of either an atrioventricular valve or of a great vessel. The major difficulties encountered in calculating stroke volume are in the measurement of great vessel or atrioventricular valve orifice diameters, and not in obtaining Doppler flow velocity spectra. This problem relates to the use of azimuthal resolution to record diameter measurements, the variation in the methods used for measuring these diameters, the location at which the measurements are made, the changes in orifice diameters during the cardiac cycle, and also the assumption that the orifices are circular. When these diameters are used to calculate cross-sectional areas, minor differences are magnified by a square power function. In this study we measured the diameters of the great vessel at the level of the valve to calculate stroke volumes. Our rationale for making measurements at these sites was twofold. First, a previous study has demonstrated that such measurements show the least variability, and second, left ventricular stroke volumes calculated at this level in experimental animals have been shown to correlate best with roller pump outputs.

Although echocardiography has been frequently used to measure fetal cardiac chamber sizes, there is little information regarding concomitant measurements of changes in great vessel dimensions with gestational age. This study shows that pulmonary arterial and aortic diameters both increase linearly with gestational age. However, the pulmonary arterial diameter was approximately 12% greater than that of the aorta, resulting in a 25% larger cross-sectional area, which increased fourfold from 20 to 40 weeks. In the very youngest fetuses included in this study the pulmonary arterial and aortic diameters were within the range of the azimuthal resolution of the equipment used and thus differences in great vessel diameter were difficult to detect. However, despite the limitations of the technology used, the dimensions obtained in this study are in accord with those from previously published studies.

**TABLE 1**

<table>
<thead>
<tr>
<th>Peak A and E wave velocities and flow velocity integrals of the tricuspid and mitral valves (mean ± SD)</th>
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<tbody>
<tr>
<td>Tricuspid valve</td>
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<tr>
<td>(n = 38)</td>
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<tr>
<td>Peak A wave velocity (m/sec)</td>
</tr>
<tr>
<td>Peak E wave velocity (m/sec)</td>
</tr>
<tr>
<td>Flow velocity integral (cm)</td>
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</table>

Discussion

This prospective, quantitative study describes in detail the age-related changes in right and left ventricular stroke volumes and the blood flow velocities across the atrioventricular and semilunar valves and demonstrates that in the normal human fetus, the right ventricle consistently ejects a stroke volume 28% greater than the left ventricle throughout the duration of gestation studied. We did not perform a longitudinal study to obviate any possible deleterious effects on fetal development of repeated nondiagnostic ultrasound examinations. Any vagaries of our study should have been minimized by our examining a large number of fetuses.

![Graph showing relationships between right and left ventricular stroke volumes (ml) and gestational age (weeks).](image-url)
in which great vessel diameters were measured in fetuses of similar gestational age with the use of cross-sectional and M mode echocardiography.\(^1\)\(^,\)\(^5\)\(^,\)\(^6\)

We obtained Doppler flow velocity spectra with an angle of incidence between the Doppler beam and direction of blood flow of less than 25 degrees for both the pulmonary artery and the aorta and were thus able to calculate right or left ventricular stroke volumes for the majority of fetuses. However, in only 44% was it possible to calculate both right ventricular and left ventricular stroke volumes in the same fetus with an angle of 25 degrees between the ultrasound beam and the direction of blood flow. We elected to use angle correction to calculate flow velocity spectra to mini-
mize any possible difference between right and left ventricular stroke volumes due to differences in the angles of incidence between the direction of blood flow and the ultrasound beam. Also, in the fetuses in whom we recorded both pulmonary arterial and aortic velocities, the angle of incidence between the ultrasound beam and blood flow differed, even though the mean values for the angles in the pulmonary artery and aorta in the population as a whole were not significantly different. Right and left ventricular stroke volumes increased by approximately 10-fold from 20 to 40 weeks gestation. For both ventricles there was an exponential relationship between stroke volume and gestational age. This exponential increase in ventricular stroke volumes corresponded with the exponential increase in right and left ventricular weights with gestational age reported in a previous pathoanatomic study.12 The greater variability in right ventricular and left ventricular stroke volumes toward term most probably reflects differences in fetal body size and ventricular volumes.

The peak velocities and flow velocity integrals in the aorta and pulmonary artery tended to increase slightly with gestational age. The almost-constant blood flow velocity integrals and heart rate, which only varied from 150 beats/min at 20 weeks to 140 beats/min at 40 weeks, indicate that the changes in right and left ventricular stroke volumes with gestational age are primarily a function of changes in great vessel size. Although there was considerable individual variation in heart rate, cardiac output had a relationship to gestational age similar to that for stroke volume.

In the 44% of fetuses from whom we obtained Doppler flow spectra in both the aorta and pulmonary artery, there was a close linear correlation between the right and left ventricular stroke volumes. Importantly, however, the right ventricular stroke volume was approximately 28% greater throughout the period of gestation studied, indicating that the right ventricle is functionally dominant in utero. The finding that the right ventricular stroke volume consistently exceeded left ventricular stroke volume is also supported by the plots of individual right and left ventricular stroke volumes with gestational age. This is concordant with results of a recent study in which stroke volumes were determined with the use of atroventricular valve orifice areas.15

Tricuspid diastolic peak blood flow velocities during rapid ventricular filling (E wave) and during atrial systole (A wave) and the integral of the instantaneous flow velocity spectra were greater than those across the mitral valve, which confirms recent findings of greater flow through the tricuspid valve.15 Although we obtained no direct measurements of mitral or tricuspid valve flow volumes, if the mitral and tricuspid valve orifices are approximately equal, as suggested by a number of recent studies, our data on the flow velocity integrals for the mitral and tricuspid valves support a higher volume of flow through the right heart.

Blood flow velocities across both the mitral and tricuspid valves were greater in atrial systole than during rapid filling. This suggests that atrial contraction contributes more to left ventricular filling during prenatal than postnatal life. The E/A blood flow velocity ratios across the mitral valve and tricuspid valve were similar, and both tended to increase from 20 weeks to term. It seems unlikely that this change was related to the small decrease in heart rate over the same period. This ratio, which has been used as an index of diastolic ventricular function, indicates that diastolic myocardial properties of the fetal right and left ventricles are similar.33 This observation is consistent with the equivalent right and left ventricular wall thicknesses and chamber radii with which E/A ratio has recently been shown to correlate.34

There has been controversy concerning the relative dominance of the right versus the left ventricle in utero. This initially emanated from experiments on fetal lambs in which right ventricular output was reported to be from 50% to 100% greater, the same as, or less than that of the left ventricle.35-37 These differences may have reflected variations in experimental conditions and the extent of surgical manipulation. However, these conflicting findings have been perpetuated by autopsy studies in the human fetus, which showed increased right ventricular weights,38,39 and more recently by echocardiographic determinations of right and left ventricular dimensions, which showed increased right ventricular size.1 The differences in echocardiographic dimensions may reflect technical differences in sampling and measurement of the two ventricular diameters. Doppler echocardiography, which enables direct measurement of right and left ventricular stroke volume without changing the fetal physiologic milieu, demonstrates that right ventricular stroke volume is 28% greater than left ventricular stroke volume. This finding may initially appear in conflict with previous echocardiographic and pathoanatomic studies that indicated that right and left ventricular dimensions, mass, and wall thickness were similar.5,6,31 However, the relatively small difference in stroke volume between the two ventricles would be difficult, if not impossible, to detect by the measurement of differences in ventricular dimensions with
two-dimensional echocardiography considering their small sizes, which vary from 0.5 cm at 20 weeks to 2 cm at term. The accuracy of measurements of cardiac output in our study can be confirmed when the combined cardiac output value is compared with expected fetal weight for similar gestational ages in the last trimester. This indicates that combined cardiac output is approximately 450 ml/kg/min, which is similar to values obtained in fetal lambs by microsphere techniques.  

We confirmed that Doppler echocardiography can be used to examine the physiology of intracardiac blood flow and that right and left ventricular stroke volumes can be calculated from measurements of great vessel diameter and flow velocity integrals. This study demonstrates that (1) both right and left ventricular stroke volumes and cardiac outputs increase exponentially, by a factor of 10, with gestational age from 20 weeks to 40 weeks concomitant with the increase in heart weight, (2) the right ventricular stroke volume is consistently greater than that of the left ventricle, (3) the tricuspid peak velocity and flow velocity integrals are greater than the corresponding measurements through the mitral valve, (4) the peak velocities across the mitral and tricuspid valves are greater during atrial systole than during rapid filling, and (5) diastolic left and right ventricular function are similar and tend to change with gestational age.

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