CLINICAL INVESTIGATION

Quantitative assessment of growth and function of the cardiac chambers in the normal human fetus: a prospective longitudinal echocardiographic study

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ABSTRACT We assessed the changes in cardiac chamber size, architecture and function in the normal fetus in a prospective, longitudinal, two-dimensional, and two-dimensionally directed M mode echocardiographic study. Serial echocardiograms were recorded in 16 normal fetuses at 4 week intervals from 20 weeks gestation to parturition. Fetal gestational age was assessed by biparietal diameter. Left ventricular, right ventricular, and left atrial chamber sizes and aortic diameter all increased linearly with age. The ratios of right and left ventricular diameter, left atrial to aortic diameters, and relative left ventricular wall thickness that we used as an index of short-axis left ventricular architecture remained constant. Fractional right ventricular and left ventricular cavity shortening did not change significantly throughout the period of study. Right and left ventricular wall thicknesses were similar both on echocardiograms and in postmortem hearts over the same range of gestational ages. In addition, postmortem right ventricular and left ventricular free wall weights were indistinguishable and contributed the same proportion to total heart weight throughout gestation. Left ventricular echocardiographic mass increased linearly from a mean of 0.86 ± 0.09 to 7.47 ± 2.43 g at term and corresponded closely with postmortem left ventricular weight. We conclude that (1) fetal cardiac chamber dimensions, wall thicknesses, and left ventricular mass increased with gestational age, (2) cardiac architecture in terms of the ratios of right ventricular/left ventricular diameters, left atrial/ aortic diameters, and relative wall thickness remained constant, (3) right and left ventricular fractional shortening did not change with age, (4) left ventricular mass assessed echocardiographically corresponded closely with postmortem left ventricular weights in fetal hearts of similar gestational ages, and (5) the similarities between right and left ventricular sizes, wall thicknesses, and free wall weights in this study do not support the theory of right ventricular dominance in the human fetus.


UNTIL RECENTLY the only aspect of human fetal cardiovascular physiology that could be routinely monitored was heart rate. However, the introduction of M mode and two-dimensional echocardiographic imaging of the fetal heart has permitted accurate description of intracardiac anatomy, sequential chamber analysis, and thus early recognition of heart disease in utero. The combination of range-gated Doppler and echocardiographic techniques has also provided measurements of blood flow in the aorta and umbilical vein for assessment of the fetoplacental circulation. Most echocardiographic studies of the human fetus have focused on detection of abnormalities of cardiac anatomy and disorders of cardiac rhythm. There have been few studies directed towards quantitative assessment of cardiac chamber size and these have produced conflicting results with regard to the relative sizes of the right and left ventricles and growth patterns of the various cardiac chambers. Moreover, such studies have not been longitudinal, but cross-sectional studies done at single points in gestation. The cross-sectional and retrospective nature of these studies may
be one cause of these inconsistencies. The purpose of this study, therefore, was to obtain prospective, serial two-dimensional and two-dimensionally directed M mode echocardiograms to quantitate and characterize longitudinal changes in cardiac chamber size, architecture, and function that occur in the normal fetus from 20 weeks gestation to term.

We compared these echocardiographic findings with measurements of left ventricular mass and wall thickness in postmortem hearts from fetuses of a similar range of gestational ages.

Methods and materials

Study population. Our study population consisted of 16 normal mothers selected as consecutive registrants for their first appointment at the routine antenatal clinic. Mothers with diabetes mellitus and other conditions associated with high risk to the fetus were excluded from enrollment in our study. The study protocol was approved by our institution’s Human Studies Committee and informed consent was obtained from each mother. Seventy-eight serial two-dimensional and two-dimensionally directed M mode echocardiograms in 16 normal fetuses were obtained. An initial echocardiogram was obtained in each patient at between 20 and 22 weeks gestation, and others were obtained at approximately 4 week intervals until parturition. All fetuses underwent at least four studies and some as many as six studies. Gestational age was assessed from the first day of the last menstrual period and was corroborated with two-dimensional echocardiographic measurement of biparietal diameter, which has been demonstrated to correlate closely with fetal age.13–15

Gestational age at birth ranged from 34 to 40 weeks (mean 38), and birth weight ranged from 2.8 to 4.8 kg (mean 3.4). All newborns (nine female) were clinically examined at birth and again before discharge from hospital. None had any evidence of congenital heart disease or abnormality of any other organ system.

Procedures. The maternal abdomen was initially scanned with an Advanced Technical Laboratory mark 5 sector scanner with a 3.5 or 5.0 MHz transducer to establish the position of the fetus. The fetal heart was located with the 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 with the more apical disposition of the tricuspid valve, the moderator band in the right ventricle, and the insertion of the inferior vena cava into the right atrium.

A systematic two-dimensional echocardiographic examination of each fetal heart was then performed to exclude any structural abnormality. We established the presence of (1) two normal atrioventricular valves, (2) two normal semilunar valves, and (3) concordant atrioventricular and ventriculoarterial connections in each fetus. The great vessels were identified by their characteristic pattern of major branches.

Two-dimensional echocardiographic images of the fetal heart were obtained in planes similar to the conventional apical and subcostal four-chamber views, the parasternal long- and short-axis views, and the short-axis view of the aorta and left atrium (figures 1 and 2). From these views two-dimensionally directed M mode echograms of the left ventricle, right ventricle, aorta, and left atrium were obtained on a strip-chart recorder at paper speeds of 50 mm/sec (figure 3). The two-dimensional echocardiogram was used to steer the M mode echocardiographic cursor so that it passed directly and perpendicularly through each of the structures studied.

To ensure that maximal left ventricular and right ventricular diameters were obtained, M mode echocardiograms were only recorded from views in which both mitral and tricuspid valve leaflets were visualized concomitantly and continuously. M mode records of the aorta and left atrium were obtained only when the aortic valve leaflets were visualized.

Chamber sizes and wall thicknesses were measured from the M mode echocardiogram to the nearest half millimeter with leading edge "methodology"16 from a minimum of three cardiac cycles of similar cycle length and mean values were calculated. All echocardiographic measurements were made by two experienced observers blinded to gestational age and patient identification number. Values for each of the following echocardiographic variables were obtained:

(1) Heart rate (beats/min).
(2) Dimensions, including (a) maximum diastolic and minimum systolic right and left ventricular diameters (mm), (b) maximum systolic and minimum diastolic septal and left and right ventricular wall thicknesses (mm), and (c) aortic diameter and maximum left atrial diameter (mm).
(3) Intracardiac ratios, including (a) ratio of left atrial and aortic diameters, (b) ratio of maximum right and left ventricular diameters, and (c) diastolic relative wall thickness, which was defined as diastolic left ventricular wall thickness divided by diastolic left ventricular cavity radius.
(4) Left ventricular mass, which was calculated with the cube formula17: 1.055 (septal thickness + mass left ventricular cavity diameter + left ventricular wall thickness)3 – (mass left ventricular cavity diameter)3, where 1.055 is the specific gravity of myocardium.
(5) Systolic function, including (a) percent change in right and left ventricular cavity diameters, and (b) percent change in septal and left ventricular wall thicknesses.

Maximum and minimum cavity diameters and wall thicknesses were measured instead of end-diastolic and end-systolic values because fetal echocardiograms were not monitored.

Bipartrial diameter. After completing each echocardiogram, the biparietal diameter was measured with a Toshiba linear-array ultrasound scanner with a 5 MHz transducer to estimate fetal gestational age.13–15

Postmortem hearts. The heart and lungs were removed from 24 spontaneously aborted normal human fetuses, all of which underwent complete autopsy and none of which had any congenital anomalies of the heart or circulation. Gestational age ranged from 16 to 38 weeks. Hearts were perfused and fixed with formalinized saline via the inferior cava at a perfusion pressure of 15 cm H2O for 24 hr. The lungs were then removed, the cavae and pulmonary veins cut at their insertions into the atria, and the great vessels transected immediately above the semilunar valves. The heart was then carefully dissected as described by Fulton et al.18 to determine atrial and ventricular weights. The right and left atria were detached from the ventricles along the atrioventricular groove (figure 4). The right ventricular free wall was then opened and its free wall detached where it took origin from the posterior interventricular septum16 (figure 4). The left ventricular free wall was then opened and detached where it took origin from the anterior wall of the free left ventricular wall adjacent to the interventricular septum (figure 4).

The atria, right and left ventricular free walls, and the interventricular septum were “blot-dried” with tissue paper and weighed. The percentage weight that each component of the
heart contributed to the total heart weight was then calculated. The right and left ventricular free walls were sectioned coronally 1 mm below the atrioventricular valves so that their respective thicknesses could be determined.

Data analysis

Echocardiographic data. Echocardiographic variables were plotted against gestational age and respective correlation coefficients were determined by linear regression analysis. In addition, we investigated the effects of heart rate, chamber size, and wall thickness on left ventricular systolic function.

Postmortem data. Left ventricular weight (free wall and septum) was plotted against gestational age, and the correlation coefficient and slope of this relationship was determined by linear regression analysis. A comparison was made between postmortem left ventricular weight and echocardiographic estimates of left ventricular mass vs gestational age.

Measurements of wall thickness were expressed as the ratio of right to left ventricular wall thickness.

Results

Heart rate. Resting heart rate varied from 135 to 160 beats/min, but did not change significantly from 20 weeks gestation to term.

Dimensions. Maximum diastolic and minimum sys-

tolic right and left ventricular diameters were similar throughout, with both more than doubling in magnitude over the period of study. Maximum diastolic and minimum systolic right ventricular diameters increased linearly and in parallel from 0.70 ± 0.10 and 0.45 ± 0.10 cm at 20 weeks to 1.45 ± 0.20 and 1.00 ± 0.20 cm prior to term (r = .89, r = .85; figure 5). Maximum diastolic and minimum systolic left ventricu-
lar diameters also increased linearly with gestational age from 0.70 ± 0.10 and 0.50 ± 0.10 cm at 20 weeks to 1.55 ± 0.15 and 1.05 ± 0.10 cm at term (r = .92, r = 0.87; figure 5).

Maximum systolic and minimum diastolic left ven-
tricular wall thicknesses were 0.30 ± 0.05 and 0.20 ± 0.05 cm at 20 weeks and did not differ significantly from the corresponding values for septal thicknesses (0.25 ± 0.05 and 0.20 ± 0.05 cm) and right ventricular wall thicknesses (0.30 ± 0.05 and 0.20 ± 0.05 cm). All increased linearly and in parallel with the progressive increase in fetal age such that they were not significantly different at any time during the period.

![FIGURE 1. Two-dimensional echocardiograms of the fetal heart similar to the conventional apical and subcostal four-chamber views (A and B), and parasternal long- and short-axis views (C and D). M mode echocardiographic records for measurement of right ventricular (RV) and left ventricular (LV) cavity diameters were selected from the subcostal four-chamber views, with both tricuspid and mitral valves (tv and mv) visualized simultaneously. RA = right atrium; LA = left atrium; AO = aorta; FO = foramen ovale.](http://circ.ahajournals.org/lookup/fig/1)
of gestation studied (figure 6). At term, mean values for maximum systolic left ventricular, septal, and right ventricular wall thicknesses were all 0.45 ± 0.05 cm, while minimum diastolic thicknesses were 0.35 ± 0.03, 0.35 ± 0.05, and 0.30 ± 0.05 cm, respectively. The individual regression lines with gestational age are demonstrated in figure 6.

Aortic diameter almost doubled from 0.50 ± 0.05 cm at 20 weeks to 0.90 ± 0.10 cm at term, increasing linearly throughout (r = .91; figure 5). Left atrial dimension increased progressively with age from 0.65 ± 0.10 to 1.00 ± 0.10 cm at term (r = .84; figure 5).

Intracardiac ratios. The left atrial/aortic ratio, which has proved useful postnatally as an index of left-to-right shunting,19 was continuously greater than 1.2, and the gradual decrease as gestation progressed towards parturition was not significant (r = .23; figure 7).

The ratio of maximum right to left ventricular diameter remained virtually constant at approximately .96 throughout the period of study (r = .17; figure 7).

The ratio for diastolic left ventricular relative wall thickness varied over a range of from .31 to .54, but did not change significantly with gestational age (r = −.21; figure 7) or with absolute left ventricular cavity size.

Left ventricular mass calculated with the cube formula increased linearly by approximately 10-fold from a mean value of 0.86 ± 0.09 g at 20 weeks to 7.47 ± 2.43 g at term (figure 7).

Systolic function. Percent change in right ventricular chamber diameter changed very little with age, varying from 36 ± 8% at 20 weeks to 35 ± 4% at term (r = −.31). Similarly, fractional left ventricular shortening decreased slightly, but not significantly, from 36 ± 6% at 20 weeks to 32 ± 5% before term (r = −.07).

Percent systolic thickening of the right and left ventricular walls and septum all varied over similarly wide ranges throughout gestation. Mean values for right and left ventricular and septal systolic thickening were 49 ± 16%, 62 ± 22%, and 39 ± 9% at 20 weeks. These did not change significantly from their respective mean values of 52 ± 20%, 46 ± 15%, and 43 ± 12% prior to term.

Biparietal diameter. Biparietal diameter increased from a mean of 4.5 to 9.0 cm over the period of study.

Failures. In two of 78 echocardiographic examinations (2.6%) we were unable to record the standard two-dimensionally directed M mode echocardiograms. Both of these failures occurred in the third trimester. One was due to excessive fetal mobility, and the other to a combination of fetal mobility and maternal obesity and discomfort. Both mothers were examined 1 week later at which time all fetal echocardiographic data were obtained.

Interobserver variability. We assessed interobserver variability in the measurements of ventricular chamber diameter and wall thicknesses by pooling left and right ventricular wall thicknesses for each observer and comparing one observer with the other by linear regression analysis. The correlation coefficient between the two observers for measurement of right and left ventricular diameters was .94 and the intercept of the regression line was 0.03 with a slope of 0.94, i.e., close to the line of identity. For measurements of right and left ventricular wall thicknesses the correlation coefficient between the two observers was also .94, with an intercept of 0.01 and a slope of 1.07.

Postmortem hearts. Right and left ventricular free
wall weights in each heart were similar, increased linearly with age (figure 8), and contributed the same percent proportion to total heart weight (29 ± 3% vs 30 ± 3%). Total postmortem left ventricular weight (free left ventricular wall + septum) corresponded closely to the echocardiographic estimates of left ventricular mass in vivo. Statistical testing for parallelism of slopes and comparison of intercepts of the regression lines for postmortem left ventricular weight vs age and echocardiographic left ventricular mass vs age.

FIGURE 3. A, M mode echocardiographic strip-chart recording of right (RV) and left ventricles (LV) showing both tricuspid and mitral valves. B, M mode echocardiogram of aorta (AO) and left atrium (LA).
echocardiography alone for two reasons: first, because the greater sampling frequency of M mode echocardiography provided better definition of epicardial and endocardial boundaries and second, because we used two-dimensional echocardiograms to steer the M mode beam to be sure that it passed perpendicularly through the same location in each of the cardiac structures imaged in serial examinations. We sought to optimize the accuracy of our measurements by using high-frequency transducers and minimum gain settings so that lines of the echograms were as thin as possible. To obviate ambiguity in measurements of chamber dimension and wall thickness, we always obtained M mode records from the same two-dimensional echocardiographic planes in each fetus.

We selected the period of gestation from 20 weeks to term because it included a period of very rapid fetal growth during which total body weight increases from approximately 300 to 3500 g. Although fetal hearts of less than 20 weeks could be imaged, we had difficulty in being certain we were obtaining maximum diameters, and thereby encountered a higher incidence of incomplete studies. In addition, wall thicknesses in fetal hearts that are very much less than 20 weeks gestation were at the limit of the resolution of our instrumentation. Since we did not monitor the fetal electrocardiogram, we measured maximum and minimum chamber sizes and wall thicknesses, which were similar to the electrocardiographically gated end-diastolic values reported in previous studies.

Maximum and minimum right and left ventricular diameters more than doubled in size, increasing linearly throughout the period of gestation studied. This linear growth pattern of both ventricles is in contrast with the exponential pattern of cardiac chamber growth reported recently. Furthermore, right and left ventricular diameters were similar, increasing in parallel so that the ratio of maximum right ventricular to left ventricular diameters constantly approximated unity. These findings are consistent with those of Allen et al., who measured right ventricular and left ventricular diameters from the orthogonal short-axis view of the left ventricle at the mitral valve level, but differ from those of Sahn et al., who found the right ventricle consistently slightly larger than the left ventricle.

Our echocardiographic findings stimulated us to investigate these discrepancies in ventricular sizes in a series of postmortem hearts of the same gestational age. Since heart muscle undergoes postmortem contracture, ventricular cavity sizes may vary widely. For this reason, we did not attempt to measure ventricular volumes or diameters, but elected instead to assess

Discussion

We quantitated the longitudinal changes in cardiac chamber size and architecture in the normal human fetus from 20 weeks to term and assessed the effects of increasing chamber size and muscle mass on cardiac function. We chose two-dimensionally directed M mode echocardiography rather than two-dimensional
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FIGURE 5. Maximum right ventricular diameter (top left), maximum left ventricular diameter (top middle), and maximum left atrial diameter (top right) all increased linearly with age, as did minimum right ventricular diameter (bottom left), minimum left ventricular diameter (bottom middle), and aortic diameter (bottom right).

septal, right ventricular, and left ventricular free wall weights, which were equal and consistently contributed similar proportions to total heart weight from 16 to 40 weeks gestation.

The right ventricle has generally been considered dominant and larger than the left ventricle during intrauterine life because of the supposedly greater right ventricular blood flow. These data have been based largely on studies in the fetal lamb.22,23 However, there has been debate as to whether right ventricular output is actually greater, the same as, or less than that of the left ventricle whenever right and left ventricular minute volumes have been measured in experimental animals.22-26 Unfortunately, this conundrum could not be resolved with our data from the normal human fetus since we did not determine right or left ventricular stroke volumes.

The remarkable similarities we observed between results of echocardiographic and postmortem examinations with respect to right and left ventricular sizes,
wall thicknesses, and free wall weights do not support the theory of right ventricular dominance in the human fetus, and are more consistent with equal right and left ventricular outputs. Evaluation of pulmonary and aortic blood flow with range-gated Doppler echocardiography may prove helpful in resolving the issue of whether there are quantifiable differences between right and left ventricular outputs.

Septal and left ventricular wall thicknesses increased linearly and at the same rate, and there were no significant differences between them at any point in time from 20 weeks to term. We did not observe asymmetric septal hypertrophy, which has been described as a normal phenomenon during fetal cardiac growth.  

If we had used M mode echocardiography alone, we could have missed the presence of asymmetric septal hypertrophy had it been confined to the posterior or midseptum. However, we examined the septum with two-dimensional echocardiography in the left ventricular long-axis and multiple short-axis views and its thickness appeared to be similar to that of free left ventricular wall from base to apex.

In most fetuses it was also possible to measure right ventricular wall thickness, which did not differ from septal or left ventricular wall thickness at any point in gestation, increasing linearly from 20 weeks to term. This is consistent with the finding of equal right ventricular and left ventricular wall thicknesses reported in normal newborns. Since we could not be sure which part of the cardiac cycle wall thickness at autopsy represented, we did not directly compare postmortem measurements of wall thickness with echocardiographic data. However, the ratio of anatomic right to left ventricular wall thickness was close to unity irrespective of gestational age, a finding that corroborated our echocardiographic data.

We were interested in obtaining an estimate of left ventricular muscle mass in the human fetus, for which we used the cube formula, and to follow its course through the period of gestation studied. Echocardiographic left ventricular mass increased by almost 10-fold from 20 weeks to term, which is similar to the expected increase in total body weight, and corresponded very closely to postmortem left ventricular weights; even the slopes of their respective regressions with gestational age were similar.

The patterns of intrauterine growth of the septum and right and left ventricular wall thicknesses, echocardiographic left ventricular mass, and postmortem left ventricular weight were linear and not exponential over the period of gestation studied and were similar to those of ventricular chamber diameters. However, regardless of the increasing left ventricular chamber size and muscle mass, the relationship between cavity radius and relative wall thickness did not change with age, and varied over the same range as observed in adults and children.  

Similarly, left ventricular function assessed by fractional shortening remained unchanged with age, and was independent of chamber size or heart rate. This unchanging function of the left ventric-
ular pump may relate to the maintenance of the constant relative wall thickness, which emphasizes the importance of wall thickness in normalizing left ventricular afterload during gestation.

Left atrial and aortic diameters also increased linearly, so that the left atrial/aortic ratio, which is used postnatally as an indicator of ductal shunting,19 varied between 1.35 and 1.15 throughout gestation.

We conclude from this prospective longitudinal study of the human fetal heart that (1) chamber dimensions, wall thickness, and ventricular muscle mass increase linearly and not exponentially with gestational age, (2) the ratios of right ventricular to left ventricular diameters, left atrial/aortic diameters, and relative wall thickness maintain fixed relationships with gestational age, (3) left ventricular cavity fractional shortening remains constant throughout gestation, (4) left ventricular mass can be assessed echocardiographically, and corresponds closely with postmortem anatomic left ventricular weights, and (5) the similarities between right and left ventricular size, wall thicknesses, and free-wall weights may warrant reexamination of the theory of right ventricular dominance in the human fetus.

We acknowledge Eileen Slattery of the Johnson Foundation for preparing the medical illustrations.

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Quantitative assessment of growth and function of the cardiac chambers in the normal human fetus: a prospective longitudinal echocardiographic study.
M G St John Sutton, M H Gewitz, B Shah, A Cohen, N Reichek, S Gabbe and D S Huff

Circulation. 1984;69:645-654
doi: 10.1161/01.CIR.69.4.645

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/69/4/645