Growth of the Great Vessels in the Normal Human Fetus and in the Fetus With Cardiac Defects

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Background. There is a paucity of quantitative anatomic data regarding human great vessel development that could be useful as a reference for fetal echocardiographers who must distinguish abnormal from normal cardiac development at early stages.

Methods and Results. To determine normal growth patterns, we plotted the diameters of the aortic and pulmonary valves, ductus arteriosus, aortic isthmus, and descending aorta in 274 autopsy specimens from nonselected spontaneous abortuses of normal karyotype. There was a linear increase in the diameters of these structures within the developmental period studied (10–26 weeks). A relative narrowing of the aorta at the isthmus compared with the aortic valve and descending aorta probably indicates that the majority of fetal left heart output goes to the developing heart and brain. In contrast to previous studies of late gestation and neonatal animals, however, we found that the diameter of the aortic isthmus was larger than that of the ductus arteriosus, suggesting substantial isthmic blood flow in these midtrimester fetuses. Among nineteen other hearts with diverse defects, both of two hearts with a narrow isthmus had an enlarged ductus arteriosus and one heart with pulmonary atresia/intact septum had a narrow ductus and increased aortic valve diameter.

Conclusions. During midgestation, the normal heart may have substantial aortic isthmic blood flow that diminishes due to rerouting in late gestation when increased requirements of the fetal brain and other organs prevail. Although fetal shunts may explain some vessel abnormalities, the majority of cardiac defects in this study were not associated with abnormal growth of the great vessels within this developmental age range. (Circulation 1991;84:2028–2033)

Although the development of the aorta and pulmonary artery has been well studied in human embryos as well as in animal models, the rate of growth of these vessels during human gestation has not been determined. The flow-dependence rule\(^1\) states that the size of a vessel is proportional to the amount of blood flow through its lumen. Therefore, cardiovascular malformations that result in obstruction to blood flow or abnormal flow patterns may be expected to have an impact on the development of the great vessels during fetal life. In the current era of high-resolution echocardiography, many cardiac defects are diagnosable in the fetus and therapeutic options may be considered at a relatively early developmental stage. Thus, it is important to define the normal growth patterns for all cardiovascular structures to recognize abnormal development as early as possible.

We studied the growth and development of the great vessels in the fetus by examining cardiovascular structures in autopsied human abortuses. The size of the great vessels in consecutive (nonselected) spontaneous abortuses of normal karyotype without cardiovascular malformations was measured, and growth curves were generated from the collected data. To study the impact of cardiovascular malformations on growth of the fetal great vessels, we also examined a small set of hearts containing cardiac defects and compared the morphological features with those in normal hearts. Our objectives were to generate growth curves for normal development of the great vessels in the human fetus and to examine the relation between heart defects and growth of the great vessels in utero.

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Methods

All of the normal hearts examined in this study were obtained from a large epidemiological, cytogenetic, pathological study of consecutive spontaneous abortions identified at three New York City Hospitals over a 7-year period. Of 4,000 specimens collected, hearts from 412 fetuses at 10–26 weeks of developmental age were identifiable. All were large enough to evaluate anatomically. Of these 412 hearts, 277 were from fetuses of normal karyotype; all except three were normal anatomically, and the 274 hearts served as the basis of this study. The aortic and pulmonary valves were measured in each heart. In addition, 173 of these specimens had the great vessels attached so that the orientation was known and measurements of the ductus arteriosus, aortic isthmus, and descending aorta could be made. Nineteen complete specimens with cardiac defects were analyzed separately as described below. In each of the total 293 cases, a complete autopsy of the fetus and placenta was performed. Developmental age was determined by crown-to-rump length. The hearts were relatively nonmacerated and preserved in 10% neutral buffered formalin (4% formaldehyde) for subsequent study.

Dissection of the fixed hearts and great vessels was performed according to standard autopsy techniques. Each heart was opened along the path of blood flow. All observations and measurements were made on the preserved specimen under 10-fold magnification by one person (P.C.U.) using a dissecting microscope. Previous studies have shown that there is no discernible difference in measurements of great vessel diameters after fixation in 4% formaldehyde compared with the fresh specimen. Measurements of the internal circumferences of the aortic and pulmonic valve annuli, aortic isthmus, ductus arteriosus at its midpoint, and descending aorta one-half centimeter distal to the ductus were made with a small, flexible ruler or with a piece of thread and the ruler. For the purpose of graphic presentation, the diameter was calculated from the circumference, assuming that the structures were approximately circular in situ. For each parameter, the regression of that heart measurement on developmental age was obtained. Confidence intervals (68% and 95%) were calculated.

To investigate the effect of various congenital heart defects on the size of the arterial valves and the great vessels including the ductus arteriosus, we compared 19 malformed hearts (12 from induced and four from spontaneous abortuses of known abnormal karyotype as well as three from spontaneous abortuses of normal karyotype) with corresponding normal hearts from spontaneous abortuses of normal karyotype. This set of malformed hearts of known developmental age had been collected during the same 7-year period. These hearts had been preserved in formalin and dissected exactly as those in the larger set had been. The above-described measurements were made in each heart. The morphological characteristics of these fetal hearts were described according to the scheme of Tynan et al. In addition to clear-cut abnormalities such as septal defects, more subtle changes caused by relative stenoses or dilatations were considered to be abnormal if measurements were outside the 95% confidence intervals of those of the normal hearts in the corresponding developmental age range. For example, aortic isthmus narrowing was defined as those cases in which the isthmus was smaller than the lower 95% confidence interval. Similarly, the ductus arteriosus was considered to be enlarged or dilated if it had a diameter greater than the 95% confidence interval. The values for each parameter in the abnormal hearts were plotted on the graphs generated from the data obtained from the normal hearts.

Karyotypes were determined by tissue culture of fetal tissue and subsequent staining by the G-banding method.

Results

Normal Hearts

Among the 274 normal hearts from spontaneous abortuses of normal karyotype, there was a linear increase in the diameters of the aortic and pulmonary valve annuli, ductus arteriosus, aortic isthmus, and descending aorta with advancing developmental age (Figures 1–5). At each developmental age, the diameter of the aortic isthmus was greater than that of the ductus arteriosus (Figures 3 and 4). Diagrams showing the 50th centile measurement at the above locations for each of four representative developmental ages are presented in Figure 6. Ratios of ductus arteriosus diameter to pulmonary valve diameter and
aortic isthmus diameter to both aortic valve and descending aorta diameters (Table 1) remained constant to the end of the second trimester.

Hearts With Cardiovascular Defects

There were 12 hearts with perimembranous ventricular septal defects, four with atrioventricular septal defects, two with a narrow aortic isthmus and no other defect, and one with pulmonary atresia and intact septum. The size of the ventricular septal defect was smaller than the aortic root in all but two cases; in these two hearts, the greatest diameter of the defect was similar to the aortic valve diameter. The measurements of the aortic and pulmonic valves,

Figure 2. Plot showing aortic valve diameter as a function of developmental age. Normal hearts show linear increase in aortic valve diameter with advancing developmental age. One fetus with narrow aortic isthmus at 18 weeks had significantly smaller aortic valve diameter. Fetus with pulmonary atresia and intact ventricular septum (23 weeks) had enlarged aortic valve diameter. CI, confidence limit; △, heart with ventricular septal defect; ●, heart with atrioventricular septal defect; ×, heart with narrow aortic isthmus; ○, heart with pulmonary atresia and intact ventricular septum.

Figure 4. Plot showing diameter of ductus arteriosus as a function of developmental age. Linear increase in diameter of the ductus arteriosus occurs throughout the second trimester of normal fetal life. Both specimens with narrow aortic isthmus had significantly enlarged ductus arteriosus, whereas specimen with pulmonary atresia and intact ventricular septum had a very narrow ductus. CI, confidence limit; △, heart with ventricular septal defect; ●, heart with atrioventricular septal defect; ×, heart with narrow aortic isthmus; ○, heart with pulmonary atresia and intact ventricular septum.

Figure 3. Plot showing diameter of aortic isthmus as a function of developmental age. With advancing development, normal hearts show linear increase in diameter of the aortic isthmus. There were two specimens with significantly smaller isthmuses and no other defect. CI, confidence limit; △, heart with ventricular septal defect; ●, heart with atrioventricular septal defect; ×, heart with narrow aortic isthmus; ○, heart with pulmonary atresia and intact ventricular septum.

Figure 5. Plot showing diameter of distal aorta as a function of developmental age. Among normal fetuses, diameter of the distal aorta increases linearly with advancing developmental age. CI, confidence limit; △, heart with ventricular septal defect; ●, heart with atrioventricular septal defect; ×, heart with narrow aortic isthmus; ○, heart with pulmonary atresia and intact ventricular septum.
aortic isthmus was small. One heart with pulmonary atresia and intact ventricular septum had a significantly smaller ductus diameter; the same specimen had a large aortic valve. One of the four hearts with atrioventricular septal defect had a significantly small pulmonary valve.

**Discussion**

Our data show that in hearts from normal second-trimester fetuses, there is a linear increase in the diameters of the arterial valves and great vessels from 10 to 26 weeks. At any single developmental age, pulmonary valve diameter was slightly larger than aortic valve diameter. By the flow-dependence rule,\(^1\) this is consistent with at least equivalent blood flow across the pulmonary valve compared with the aortic valve during this stage of fetal development. Moreover, the diameter of the aortic isthmus was smaller than that of either the aortic valve or the descending aorta. Rudolph and colleagues\(^8\)–\(^11\) noted this relative isthmic narrowing in normal late gestational animals as well as in human neonates. These investigators attributed this finding to large cranial blood flow from the ascending portion of the aorta, resulting in less flow through the isthmus into the descending aorta. They reported that the diameter of the ductus arteriosus was greater than that of the aortic isthmus. The data from the present study, however, were obtained from hearts at an earlier developmental stage. During midtrimester human fetal development, we found that the ratio of isthmus to descending aortic diameter was 71–78%, similar to the 75% figure cited for normal human fetuses\(^6\) and neonates.\(^11\) However, in contrast to studies performed in late gestation,\(^9\)–\(^11\) the mean diameter of the aortic isthmus was larger than that of the ductus arteriosus. A previous investigation using direct measurement of fixed specimens also documented a larger isthmus compared with ductus arteriosus in midtrimester human fetuses.\(^6\) This observation, which argues against the concept of large fetal blood flow through the ductus arteriosus and relatively little through the isthmus during midgestation, may have several explanations. First, the effect of cranial blood flow on vessel size may not be reflected until a later gestational age. Indeed, it is during the last part of gestation that blood flow to the brain and other organs increases dramatically.\(^10\) During this latter period, the growth of the ascending aorta and ductus arteriosus may outstrip that of the isthmus, thus accentuating the narrowing. Second, it could be said that the ductus arteriosus in specimens from our study and the previous investigation\(^6\) may be artificially constricted due to fixation. In this regard, freeze-fixation of the vessel may be preferable, as has been demonstrated in neonatal rats.\(^12\) We presume, however, that the lesser amount of smooth muscle and its relative immaturity would make the ductus arteriosus from the midtrimester human fetus less susceptible to the astringent formaldehyde used in our study. This absence of constriction artifact during midtrimester development is suggested by the con-

![Figure 6](http://circ.ahajournals.org/)

**FIGURE 6.** Fiftieth centile vessel diameters (in millimeters) at four developmental stages are shown diagrammatically. At each age, pulmonary valve diameter is greater than that of the aortic valve. There is relative narrowing of the aorta at the isthmus, and diameter of the isthmus is larger than that of the ductus arteriosus.

| Table 1. Ratios of Mean Vessel Diameters at Four Developmental Stages |
|--------------------------|---------------------|---------------------|---------------------|---------------------|
| Developmental age (in weeks) | <12 | 16 | 20 | >23 |
| Ductus diameter/pulmonary valve diameter | 36% | 35% | 36% | 40% |
| Isthmus diameter/aortic valve diameter | 55% | 61% | 65% | 58% |
| Isthmus diameter/descending aorta diameter | 71% | 73% | 71% | 78% |
stant ratio of ductus arteriosus diameter to pulmonary valve diameter shown in Table 1. Third, our results are supported by echocardiographic data from living fetuses at 23–27 weeks of gestational age that suggest at least equivalent size of the ductus arteriosus and isthmus in vivo. Thus, the animal models from which the concept of high ductal–low isthmic blood flow in the fetus was formulated may not translate accurately to the human situation.

A particular strength of our study is the large number of normal specimens used to generate the growth curves. For the purpose of presentation, we chose to use confidence intervals to define normal versus abnormal measurements. We recognize, however, that some points close to but outside of the 95% confidence interval may be at the end of a spectrum of normal. For example, two fetuses had a narrow aortic isthmus and nor other defect. One examined at a developmental age of 18 weeks had an aortic isthmus diameter barely smaller than the 95% confidence interval. In this case, the small aortic valve diameter and enlarged ductus arteriosus suggest a significant albeit mild abnormality compared with the other specimen at 21 weeks, which had an extremely narrow isthmus consistent with severe coarctation. Neither specimen had the juxtauductal ridge in the aorta similar to the obstructing shelflike projection found in neonates with coarctation. We presume that this “shelf” is an acquired lesion related to contraction of smooth muscle in the wall of the ductus arteriosus after birth. Our definition of aortic isthmus narrowing is similar to if not more stringent than that of others who have defined abnormal as being an isthmic diameter no more than 40% of that of the ascending aorta.13,14

Cardiovascular hemodynamics during embryogenesis has long been considered important in determining aortic arch selection (preservation of some arch segments and involution of others) as well as normal or abnormal cardiac morphogenesis. For example, Rychter15 has shown experimentally that mechanical obstruction of certain of the aortic arches in avian embryos causes reproducible malformations of the great vessels. Similar principles may be applied to explain known cardiovascular malformations in humans. Rudolph and colleagues6 postulated anatomic effects of a variety of defects on cardiovascular structure and analyzed clinical data including angiograms from human neonates and young infants to confirm that in cardiac lesions with reduced pulmonary arterial blood flow (e.g., pulmonary or tricuspid atresia), the diameter of the aortic isthmus is increased, and that in cardiac defects with left ventricular outflow tract obstruction, the diameter of the aortic isthmus is abnormally decreased. An example of this concept is the hypothesis that leftward malalignment of the interventricular septum leads to the development of hypoplasia of the aortic arch or coarctation.13,16 Because none of our specimens contained a malalignment type of ventricular septal defect, we could not examine the effect of this defect in the midtrimester fetus. Our study did include one heart with pulmonary atresia and intact septum that had a significantly enlarged aortic isthmus; it also included two specimens with aortic isthmus narrowing, both of which had an enlarged ductus arteriosus suggestive of larger-than-normal flow across this vessel. These observations from a limited number of specimens support the concept of an important hemodynamic influence on the structure of the developing human cardiovascular system. To our knowledge, this study is the first to show that hemodynamic effects may be apparent in the human fetus as early as 18 weeks of developmental age. It is important to emphasize, however, that in the majority of specimens with cardiac defects, we found normal great vessel dimensions. Thus, although the sample of abnormal hearts was small, it is clear that not all intracardiac defects are associated with abnormalities in the growth of great vessels in the human fetus within this developmental age range.

The flow-dependence rule1 may reflect only one of a number of elements associated with abnormal growth of the great vessels. Cardiac dysgenesis may also be an important factor. It has been shown that complete removal of the cardiac neural crest in chick embryos results in persistent truncus arteriosus; partial ablation of these tissues leads to a variety of defects characterized by a malposed aorta (e.g., double-outlet right ventricle, tetralogy of Fallot).17 There is circumstantial evidence that similar pathogenetic mechanisms apply to human cardiac maldevelopment.17

In this study, we characterized the growth pattern of the great vessels in fetuses from 10 to 26 weeks of developmental age. This period of human development follows completion of cardiogenesis and precedes the exponential phase of growth that occurs during the last trimester. Although fetal heart size at 15 weeks is at the limit of resolution of current echocardiographic techniques, in the future this and other clinical tools will be developed to have the capability of investigating smaller-size organs. Until now, there has been a paucity of quantitative anatomic data regarding the early developmental stages addressed by our study. The growth curves generated from our data should be useful as a reference for fetal echocardiographers who must distinguish normal from normal cardiac development at early fetal ages.

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References


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