Cardiac Output and Central Distribution of Blood Flow in the Human Fetus

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Background—The objectives of this study were to establish reference ranges for left and right cardiac output and to investigate blood flow distribution through the foramen ovale, ductus arteriosus, and pulmonary bed in human fetuses.

Methods and Results—A prospective study was performed in 222 normal fetuses from 13 to 41 weeks of gestation with high-resolution color Doppler ultrasound. Cardiac output and ductal flow were calculated by use of vessel diameter and the time-velocity integral. Pulmonary blood flow was expressed as the difference between right cardiac output and ductal flow. Foramen ovale flow was established as the difference between pulmonary flow and left cardiac output. Gestational age–specific reference ranges are given for left, right, and biventricular output and volume of ductal blood flow, showing an exponential increase with gestational age. Median ratio of right to left cardiac output was 1.42 and was not associated with gestational age. Right cardiac output was 59% and left cardiac output was 41% of biventricular cardiac output. Median biventricular cardiac output was estimated to be 425 mL · min⁻¹ · kg⁻¹ fetal weight. Ductal blood flow was 46%, estimated pulmonary flow was 11%, and estimated foramen ovale flow was 33% of biventricular output.

Conclusions—The study establishes reference ranges for fetal cardiac output and offers insights into the central blood flow distribution in human fetuses from 13 weeks to term. There is a clear right heart dominance. The estimated ratio of pulmonary blood flow to cardiac output is higher than in fetal lamb studies. (Circulation. 2001;103:1662-1668.)

Key Words: cardiac output ■ ductus arteriosus, patent ■ fetal heart ■ circulation

Cardiac output and the distribution of blood flow have been well studied in animal experiments demonstrating the fetal right heart dominance.¹ Doppler studies in human fetuses have also suggested a right heart dominance. However, the reported ratio of right to left cardiac output ranges from 1.0 to 1.5.²⁻⁷ The very few studies that have focused on blood flow through the ductus arteriosus and through the pulmonary circuit in the human fetus have given conflicting results.⁴⁻⁷ For these reasons, a prospective cross-sectional study that used high-resolution ultrasound equipment, including color Doppler imaging, was performed to establish gestational age–specific reference ranges for left and right cardiac output, combined cardiac output, and volume of blood flow across the ductus arteriosus. Furthermore, the ratio of right to left cardiac output ratio, distribution of right cardiac output (ductus arteriosus to lungs), and foramen ovale blood flow were calculated.

Methods

Population

In this cross-sectional study, 2D and Doppler echocardiography was performed by an experienced examiner (G.M.) in 222 normal singleton fetuses from 13 to 41 weeks (median, 25 weeks) of gestation. Criteria for inclusion in the study were as follows: gestational age confirmed by sonographic biometry in early pregnancy, no malformation, size appropriate for gestational age, normal amniotic fluid volume, fetal rest, fetal apnea, and healthy pregnant women without hypertension, proteinuria, smoking, or use of drugs such as tocolytics, prostaglandin synthetase inhibitors, or glucocorticoids that influence the cardiovascular system. Patients gave informed consent.

Ultrasound Equipment

In all cases, high-resolution color Doppler ultrasound equipment (ATL HDI 3000/ATL UM 9 HDI, Advanced Technology Laboratories) with 4 to 2, 5 to 3, and 7 to 4-MHz broadband transducer and spatial peak temporal average intensities <100 mW/cm² was used.

Echocardiography

The (inner) diameter (trailing to leading edge method) of the aortic valve annulus was determined from the long-axis view of the left heart during systole. The diameters of the pulmonary valve annulus (inner diameter during systole) and of the ductus arteriosus at its middle (inner diameter) were obtained from the transverse scan of the fetal thorax during systole with an insonation perpendicular to the long axis.⁶⁻⁹ Doppler velocity waveforms of the aorta were obtained from the 5-chamber view. Doppler velocity waveforms of the main pulmonary artery and the ductus arteriosus were obtained from the short axis of the fetal heart (sagittal scan of the fetus). All Doppler recordings were obtained at an insonation angle <10° to flow.⁷ Angle correction was not used. Doppler tracings were recorded with the sample volume positioned just distal to the valve in the center of the vessel⁶⁻¹¹; for Doppler recordings in the ductus arteriosus, the.
sample volume was placed in the distal ductal part. The sample volume was set at 1 to 3 mm; the high-pass filter, at 100 to 200 Hz. At least 5 consecutive uniform Doppler velocity waveforms with the highest velocities and a narrow band of frequencies ("clean" signal) were recorded, and 1 cycle was analyzed.

The following features were determined: fetal heart rate (FHR); time velocity integral (TVI); stroke volume (TVI \cdot \pi \cdot d^2/4), where d is the diameter of the vessel; and output per minute (stroke volume \cdot FHR). The ratio of right cardiac output to left cardiac output and the ratios of ductal blood flow to right and combined cardiac output were determined. Pulmonary blood flow was expressed as the difference between right cardiac output and ductus arteriosus blood flow. Foramen ovale blood flow was calculated as the difference between left cardiac output and pulmonary blood flow (right cardiac output per minute minus volume of ductal blood flow per minute). Combined cardiac output per 1 kg fetal weight was estimated with the formulas for fetal weight estimation of Mielke et al (formula 1; 23 to 29 weeks of gestation) and Hansmann et al (30 to 41 weeks). Findings were documented on video prints or videotape. Because of fetal presentation and duration of the examination, not all measurements could be performed in all patients.

Statistical Analyses
Estimation of age-related quantiles followed a proposition of Altman (see also the work by Harris and Boyd). Cubic regression on log scale yielded the median curve $y(t)$. Estimation of age-related SD by quadratic regression of the absolute values of the residuals and multiplying the predicted values by the square root of $\pi/2$ yielded an estimation of age-related SD $s(t)$. With the use of the statistical program GAUSS 3.2.9, quantiles were estimated by $\exp[y(t)+u \cdot s(t)]$, where $u$ is the corresponding quantile of the standardized normal distribution. The influence of gestational age on biventricular output per 1 kg fetal weight and on the ratios of right to left cardiac output and ductal blood flow to right cardiac output was analyzed by means of linear regression after logarithmic transformation of the outcome variables. Significance was set at $\alpha=0.05$.

Results
Cardiac Output and Volume of Blood Flow Through the Ductus Arteriosus
The calculated centiles for right and left ventricular stroke volume (Figures 1 and 2) and output per minute (Figures 3 and 4) increased exponentially with advancing gestational age.

Median fetal heart rate derived from Doppler recordings in the pulmonary trunk, ascending aorta, and ductus arteriosus was 144 bpm (mean, 143.5 bpm; SD, 9.5 bpm; n=216), 148 bpm (mean,147.6 bpm; SD, 8.7 bpm; n=89), and 144 bpm
Figures 5 and 6 demonstrate the increase in calculated centiles for biventricular (combined) cardiac stroke volume and output per minute with advancing gestational age. The calculated 50th centile for biventricular output increased from \( \approx 40 \text{ mL/min} \) at 15 weeks of gestation up to 1470 mL/min at 40 weeks.

Median biventricular output per 1 kg fetal weight was estimated to be 425 mL \( \cdot \min^{-1} \cdot 	ext{kg}^{-1} \) (mean, 429 mL \( \cdot \min^{-1} \cdot 	ext{kg}^{-1} \); SD, 100 mL \( \cdot \min^{-1} \cdot 	ext{kg}^{-1} \); \( n = 37 \); gestational age: range, 23 to 40 weeks; median, 34.9 weeks; mean, 33.1 weeks; SD, 5.2 weeks), which was not associated with gestational age (\( P = 0.47, r = 0.12 \)). Median left cardiac output per 1 kg fetal weight was estimated to be 179 mL \( \cdot \min^{-1} \cdot 	ext{kg}^{-1} \).

In the ductus arteriosus, the calculated centiles for volume of blood flow per cycle (Figure 7) and volume of blood flow per minute (Figure 8) also increased exponentially with advancing gestational age.

**Distribution of Cardiac Output**

The median ratio of right to left cardiac output was 1.42 (mean, 1.50; SD, 0.48; \( n = 87 \)), corresponding to a median ratio of right to combined cardiac output of 0.59 and a median ratio of left to combined cardiac output of 0.41. The ratio of right to left cardiac output was not associated with gestational age (\( P = 0.94 \)). The median ratio of the volume of ductal blood flow per minute to right cardiac output per minute was 0.78 (mean, 0.80; SD, 0.31; \( n = 197 \)). The increase in this ratio with advancing gestational age (factor, 1.002/wk; 95% CI, 0.916 to 1.040) was not significant (\( P = 0.61 \)). The median ratio of the volume of ductal blood flow per minute to combined cardiac output per minute was 0.46 (mean, 0.50; SD, 0.19; \( n = 85 \)). The median ratio of estimated pulmonary blood flow (right cardiac output per minute minus volume of ductal blood flow per minute) to right cardiac output was 0.22 (\( n = 187 \) cases in which right cardiac output per minute and volume of ductal blood flow per minute were determined) and 0.19 (\( n = 85 \) cases in which right cardiac output per minute and volume of ductal blood flow per minute were determined)
minute, ductal blood flow per minute, and left cardiac output per minute were determined). The median ratio of estimated pulmonary blood flow to combined cardiac output was 0.11 (n=85).

Foramen ovale blood flow was expressed as the difference between left cardiac output and pulmonary blood flow. The median ratio of estimated foramen ovale blood flow to left cardiac output was 0.76, and the median ratio of estimated foramen ovale flow to combined cardiac output was 0.33. A synopsis of the distribution of blood flow is given in the Table.

**Discussion**

Knowledge of fetal cardiac output and its distribution is based predominantly on animal studies. In fetal lambs, biventricular (combined) cardiac output in the second half of pregnancy is 450 mL · min⁻¹ · kg⁻¹ fetal weight.¹ About 60% to 65% of cardiac output is ejected by the right ventricle and 35% to 40% by the left ventricle, corresponding to a ratio of right to left cardiac output of 1.5 to 1.85.¹²⁻²⁴

In fetal lambs, pulmonary blood flow is 6% to 8% of combined cardiac output and ≈10% of right cardiac output; ductus arteriosus blood flow is 54% to 57% of combined cardiac output and ≈90% of right cardiac output.¹₂⁻²⁵ Lamb experiments (n=44) have suggested an increase in pulmonary blood flow from 3.7% of combined cardiac output in 80-g to 450-g fetuses (n=7) to 7% of combined cardiac output in near-term fetuses (n=10). In fetal lambs in the third trimester of pregnancy, pulmonary blood flow did not change relative to lung weight and right ventricular output at the normal low oxygen tension of the fetus despite an increase in pulmonary vessel density.²⁷,²⁸ In near-term fetuses, pulmonary blood flow was 35 to 40 mL · min⁻¹ · kg⁻¹ fetal weight.²⁷

It has been demonstrated in animal experiments that volumetric blood flow through the aortic and pulmonary valves can be accurately determined through sonographic measurements of vessel diameter and the time-velocity integral.⁸ However, previous Doppler studies in human fetuses have resulted in conflicting data concerning fetal cardiac
output and its distribution. Very few studies have focused on fetal cardiac output in the first half of pregnancy.

The present prospective cross-sectional study establishes gestational age–specific reference ranges from 13 to 41 weeks of gestation for left and right cardiac output, biventricular (combined) output, and volume of blood flow across the ductus arteriosus in the human fetus. Furthermore, the data provide insights into the central blood flow distribution.

The calculated centiles for right and left ventricular stroke volume and cardiac output per minute increased exponentially with advancing gestational age. Previous studies based on smaller numbers of examinations show similar results. The calculated 50th centile for biventricular output increased from about 40 mL/min at 15 weeks of gestation up to 1470 mL/min at 40 weeks. Median combined (biventricular) output per 1 kg fetal weight was estimated to be 425 mL · min⁻¹ · kg⁻¹, which was not associated with gestational age. In fetal lambs, reported values of combined cardiac output range from 377 to 549 mL · min⁻¹ · kg⁻¹, unrelated to body weight throughout gestation. In the present study, median left cardiac output per 1 kg fetal weight was estimated to be 179 mL · min⁻¹ · kg⁻¹. During postnatal circulatory changes, left cardiac output increases up to ~240 mL · min⁻¹ · kg⁻¹ within the first 2 hours of birth because of increasing stroke volume. Then left cardiac output falls to ~190 mL · min⁻¹ · kg⁻¹ reflecting an adaption to the decreased demand on the left ventricle as the ductus arteriosus constricts and ductal left-to-right shunt decreases from 62 mL · min⁻¹ · kg⁻¹ at 1 to 2 hours of age to 14 mL · min⁻¹ · kg⁻¹ at 12 hours of age.

In human fetuses, the right heart dominance has been discussed controversially. The reported ratio of right to left cardiac output ranges from 1.0 to 1.5 with advancing gestational age, Rasanen et al found this ratio to be increasing.

In the present study, the median ratio of right to left cardiac output was 1.42 (mean, 1.5; SD, 0.48; n = 87), which was not associated with gestational age, clearly supporting the concept of a right heart dominance in the human fetus.
Because left ventricular output is distributed largely to the upper carcass and brain of the fetus, the reduced ratio of right to left cardiac output in the human fetus compared with the values determined in the fetal lamb (ratio, 1.5 to 1.8) might be explainable by the relatively larger human brain.34

In fetal life, blood shunts continuously right to left across the ductus arteriosus. Doppler velocity waveforms of the ductus arteriosus are characterized by high systolic and low diastolic velocities.35,36 Reproducibility of the velocimetry of peak systolic velocity and the time-velocity integral in the ductus arteriosus has been demonstrated.37,38 In the present study, volume of blood flow across the ductus arteriosus was determined from examinations in 199 fetuses from 13 to 41 weeks of gestation. The calculated centiles show an exponential increase with advancing gestational age. Blood flow across the ductus arteriosus was 78% (median) of right cardiac output and 46% (median) of combined cardiac output.

Pulmonary blood flow was 11% (median) of combined cardiac output. This fraction was not significantly associated with gestational age. The volume of pulmonary blood flow was estimated to be 47 mL · min⁻¹ · kg⁻¹ fetal weight (11% of combined cardiac output). Thus, in this study of human fetuses, pulmonary blood flow was a greater fraction of right cardiac output and combined cardiac output than in fetal lamb studies (6% to 8% of combined cardiac output).

Few other Doppler studies have been performed in human fetuses to calculate the volume of blood flow across the ductus arteriosus and through the pulmonary vascular bed. In a study of 38 fetuses between 18 and 37 weeks of gestation, the calculated pulmonary blood flow was 22% of combined cardiac output and 48% of right ventricular output.4 There was no association with gestational age. In a study of 39 fetuses (gestational age not mentioned), the calculated pulmonary blood flow was 6.4% of combined cardiac output and ≈11% of right ventricular output.39 In a recent study of 63 fetuses, the calculated proportion of pulmonary blood flow increased from 13% of combined cardiac output at 20 weeks to 25% of combined cardiac output at 30 weeks; from 30 to 39 weeks of gestation, its proportion remained unchanged.7

Because foramen ovale blood flow is calculated as the difference between left cardiac output and pulmonary blood flow, Rasangan et al7 found that foramen ovale blood flow decreased from 34% of combined cardiac output at 20 weeks to 18% at 30 weeks, whereas from 30 to 38 weeks, the proportions of foramen ovale blood flow and pulmonary blood flow remained unchanged. In the present study, median estimated foramen ovale blood flow was 76% of left cardiac output and 33% of combined cardiac output. In fetal lamb studies, foramen ovale flow was 34% of combined cardiac output.24

Although animal experiments have demonstrated that the echocardiographic Doppler method can accurately quantify volumetric flow through the aortic and pulmonary valve,4 methodological problems have to be considered. Errors in volumetric measurements arise from inaccuracies in vessel diameter and Doppler recordings. In the present study, volume of blood flow was calculated from the Doppler-derived time-velocity integral and the inner diameter of the vessel (aortic and pulmonary valve annulus, lumen of the ductus arteriosus at its middle) with the trailing to leading edge method (from the inner, or trailing, edge of the anterior vessel wall to the inner, or leading, edge of the posterior wall). The accuracy of this noninvasive method has been demonstrated in invasive animal experiments.8 However, others have used the leading edge method (from the external surface of the anterior wall to the internal surface of the posterior wall), which overestimates the diameter and therefore the volume of blood flow by including 1 vessel wall thickness. Vessel areas represent the most important source of error in flow calculation. This error will be substantial especially in vessels with a small diameter such as the ductus arteriosus or the left and right pulmonary arteries. As modern high-resolution ultrasound equipment makes accurate measurement of the inner vessel diameter possible, the trailing to leading edge method may be more appropriate.

The use of color Doppler imaging optimizes positioning of the pulsed-wave Doppler sample volume in the middle of the vessel just distal to the valvular annulus, which is the flow-limiting point in the outflow tract. Animal studies have shown that the volumetric flow calculation is far more accurate when the diameter of the aortic valve annulus is used, as in the present study, than when the sino-tubular junction diameter is used.8 Moreover, in the present study, the pulsed-wave Doppler beam was aligned as parallel as possible to the direction of blood flow at an angle <10° to flow to avoid errors resulting from angle correction.9

In addition, the population of the study group is of great importance. Fetal cardiac output and the distribution of blood flow are influenced by maternal drug intake.36,40 Intrauterine growth retardation is associated with reduced cardiac output and a redistribution of blood flow with a reduced ratio of right to left cardiac output.41 Therefore, only healthy women with

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<td>Left cardiac output, %</td>
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<td>Ductus arteriosus blood flow, %</td>
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<td>32–40</td>
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<td>Pulmonary blood flow, %</td>
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<td>22</td>
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<td>Foramen ovale blood flow, %</td>
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<td>34–18</td>
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<td>Biventricular output, mL · min⁻¹ · kg⁻¹</td>
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<td>425</td>
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normal singleton pregnancies and gestational age confirmed by sonographic imaging in early pregnancy were included into the present study. For these reasons, we believe that the results of this study represent the optimal data that can be obtained.

Conclusions

Doppler investigations offer insights into fetal cardiovascular physiology. The present study establishes reference ranges for fetal cardiac output and ductus arteriosus blood flow and describes the central blood flow distribution in the second and third trimesters of pregnancy, confirming the conception of a right heart dominance in the human fetus. The estimated pulmonary blood flow is a greater fraction of right cardiac output and of combined cardiac output than in fetal lamb studies.

References

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