Effects of heart rate on ventricular size, stroke volume, and output in the normal human fetus: a prospective Doppler echocardiographic study

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ABSTRACT The effect of heart rate on cardiac output in the fetal heart is controversial. We used Doppler echocardiography to investigate the effects of increasing heart rate on stroke volume and ventricular output in the normal human fetal heart. Heart rate was increased in 25 human fetuses (mean age 36 weeks) by auditory stimulation with a sound emitter placed on the mother's abdomen. Aortic or pulmonary diameters were measured at valve level from two-dimensional echocardiographic images and cross-sectional areas were calculated. Blood flow velocity spectra from the pulmonary artery or aorta were digitized to obtain flow velocity integrals before and after auditory stimulation. Stroke volume was calculated as the product of the flow velocity integral and the area of the great vessel. Pre-stimulation mean heart rate was 132 ± 8 beats/min and increased after auditory stimulation to 158 ± 9 beats/min (p < .001). Stroke volume decreased with the increase in heart rate from 3.7 ± 1.4 ml before stimulation to 3.0 ± 1.1 ml after stimulation (p < .001), but ventricular output calculated as the product of stroke volume and heart rate remained unchanged (0.48 ± 0.18 liter/min before vs 0.48 ± 0.17 liter/min after stimulation). The decrease in stroke volume was accompanied by a decrease in ventricular end-diastolic area, although there was no change either in end-systolic area or fractional change in area. This study demonstrates that increases in heart rate within the physiologic range in the normal human fetus result in a decrease in ventricular size and stroke volume but no change in ventricular output or ventricular shortening.


THE FORCE-VELOCITY RELATIONSHIP and biochemical composition of the contractile proteins in isolated fetal mammalian myocardium differ from those in adult myocardium in all species that have been studied, including man.1–4 Studies of cardiac function in the intact heart in utero have been performed mostly in the fetal lamb, and little is known of cardiac function in the human fetus. One area of controversy regarding fetal cardiovascular physiology is the role of heart rate and the Frank-Starling mechanism in regulating cardiac output. Some investigators have demonstrated that change in heart rate is the major determinant of cardiac output and not the Frank-Starling mechanism, since increases in preload result in only limited increases in stroke volume and cardiac output.5 By contrast others have shown that the major regulator of cardiac output is the Frank-Starling mechanism and that changes in heart rate have little if any effect on cardiac output.6,7 Recently a number of laboratories have demonstrated that Doppler echocardiography can be used to quantify right ventricular and left ventricular stroke volumes and cardiac output in the human fetus from 20 weeks gestation to term.8–10

We used Doppler echocardiography to measure stroke volume and ventricular output in the normal human fetus at rest and after increases in heart rate induced by auditory stimulation. Our purpose was to examine the relationship between heart rate and stroke volume in the normal fetus in an attempt to resolve the controversy regarding the regulatory effect of heart rate on cardiac output. This may have direct clinical relevance in predicting the effects of drugs with chronotropic activity currently used in the treatment of heart failure and arrhythmias in the human fetus.
Study population. The study population consisted of 25 normal mothers who were recruited from patients referred for obstetric ultrasound examination. Indications for ultrasound examination included estimation of gestational age and fetal weight and determination of placental location. Mothers with diabetes mellitus, hypertension, preeclampsia, rhesus incompatibility, multiple gestations, or infants with congenital malformations were excluded from this study. Doppler echocardiograms were obtained from fetuses with gestational ages ranging from 26 weeks to term, with a mean age of 36 weeks. Gestational age was assessed from the first day of the last menstrual period and corroborated with ultrasound measurements of the biparietal diameter. We selected fetuses in the third trimester so that measurements of great vessels and ventricular dimensions would not be limited by the resolution of our equipment.

The study was approved by the Brigham and Women’s Hospital Human Subjects Committee and written informed consent was obtained from each mother.

Methods

Data acquisition. Studies were performed with a Hewlett Packard 77020 AC/AR ultrasound system with 3.5 or 5.0 MHz transducers. The fetal heart was located using 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 following data were obtained from each fetus at rest and serially after auditory stimulation until heart rate returned to control: (1) High-quality two-dimensional echocardiographic images of the aorta and main pulmonary artery were recorded from the short-axis view or the five-chamber apical view oriented as orthogonally as possible to the axial plane of the ultrasound beam to determine vessel diameters. (2) High-quality two-dimensional echocardiographic images of the apical four-chamber view were recorded to determine maximum diastolic and minimum systolic left ventricular areas. (3) Blood flow velocity spectra from the aorta or pulmonary artery were recorded by means of two-dimensional echocardiographic images to position the Doppler sample volume in the great vessels immediately distal to the semilunar valves with the ultrasound beam parallel to the direction of blood flow. The rationale for recording blood flow velocity spectra from either the aorta or the pulmonary artery was that it was not possible to sample both vessels simultaneously at the same heart rates and calculate combined cardiac output because fetal heart rate returned to baseline within 2 to 3 min. We therefore assessed the flow velocity integrals in the pulmonary artery and in the aorta individually to determine whether the effects of increases in heart rate were similar in the left and right ventricles. Two-dimensional images and Doppler flow velocity spectra were recorded on standard 1/2 inch videotape for subsequent analysis.

We used auditory stimulation to induce increases in heart rate in the fetus. Auditory stimulation was performed with an artificial larynx (Western Electric model 5C), which produces a mixed sound and vibratory output as previously described.11 The fetal head was located by two-dimensional echocardiographic imaging; the sound emitter was then placed on the mother’s abdomen over the fetal ear and a single 3 sec pulse was delivered.

Data analysis. Echocardiographic images and Doppler flow velocity spectra were transferred from video tape to the digital disc of a Franklin Quantic 1200 ultrasound analysis system and digitized with the electronic cursor. Measurements of the aortic or pulmonary diameters were made at the level of the valve anulus from the systolic frame showing maximum diameter and rounded off to the nearest millimeter. A minimum of five separate cycles were measured and mean values were calculated. Measurements of left ventricular maximum diastolic and minimum systolic areas from three consecutive cardiac cycles were digitized from the two-dimensional apical four-chamber views and mean values were calculated before stimulation and at maximum heart rate after stimulation. We used minimum area to represent end-systole and maximum area to represent end-diastole.

The blood flow velocity spectra obtained in the aorta or in the pulmonary artery from a minimum of three consecutive cardiac cycles were digitized through the middle of the densest portion of the flow velocity spectral envelope to obtain mean flow velocity integrals. Doppler flow velocity spectra were not analyzed when the angle between the direction of blood flow and the ultrasound beam was greater than 25 degrees because of the risk of underestimating flow velocity. In addition, velocity spectra that were not clearly defined or in which there was considerable variation in amplitude were not analyzed.

The following measurements were made at rest and serially after auditory stimulation: Heart rate (beats/min), pulmonary arterial or aortic diameters (cm) (rounded off to the nearest mm) from which cross-sectional area (CSA) was calculated assuming a circular orifice; pulmonary or aortic flow velocity integrals (FVI)(cm), right or left ventricular stroke volumes (SV)(ml) calculated as the product of flow velocity integral (FVI) and cross-sectional area of the great vessel (CSA): SV = FVI × CSA, right or left ventricular outputs (VO) (liters/min) calculated as VO = HR × SV, left ventricular end-systolic (ESA) and end-diastolic areas (EDA) (cm²), left ventricular stroke areas (SA) (cm²) where SA = EDA-ESA, and fractional area shortening (%) calculated as (SA × 100)/EDA.

Statistics. In each fetus, stroke volume was plotted against heart rate, and the correlation coefficient, slope, and intercept were determined by linear regression analysis. The stroke volumes and ventricular outputs at minimum heart rates were compared with stroke volumes and ventricular outputs at maximum heart rates by Student’s paired t test. Similarly, ventricular areas were compared at minimum and maximum heart rate by Student’s paired t test.

Results

Of the 25 fetuses studied, blood flow velocity spectra were recorded from the aorta in 20 and from pulmonary artery in five (figure 1). The resting or mean minimum heart rate before stimulation was 132 ± 8 beats/min and increased to a mean maximum of 158 ± 9 beats/min after stimulation (p < .001). In all patients, right or left ventricular stroke volume decreased with increase in heart rate after stimulation. There was a smaller close inverse relationship between heart rate and stroke volume in both the right and left ventricles.
FIGURE 1. Two-dimensional echocardiogram showing the aorta from the apical five-chamber view (left) and a representative Doppler blood flow velocity profile (right) obtained from the aorta immediately distal to the aortic valve. The distance between the white calibration marks represents a velocity of 20 cm/sec.

as illustrated in figure 2 (r = −.93, p < .001). A mean of 8 ± 2 data points were used for regression analysis in each fetus. The regression lines of the heart rate–stroke volume relationship were calculated for each of the 25 fetuses (figure 3) and showed a consistent inverse proportionality. Mean stroke volume was 3.7 ± 1.4 ml at minimum heart rate before stimulation and decreased to 3.0 ± 1.1 ml at maximum heart rate after auditory stimulation (p < .001). The 20% increase in heart rate resulted in a 23% decrease in stroke volume.

Right and left ventricular minute outputs did not change significantly with increases in heart rate after auditory stimulation, as illustrated by the relationship between heart rate and ventricular output in a typical fetus (figure 4). The individual regression lines relating ventricular output to heart rate for the 25 fetuses (figure 5) had a mean correlation coefficient of −.05 ± .45, a mean slope of −0.0006 ± 0.0015, and a mean intercept of 0.556 ± 0.309. The slopes of the individual regression lines were not significantly different from 0 (p > .1), indicating that right and left ventricular outputs were not significantly altered by changes in heart rate. The mean ventricular output at a mean minimum heart rate of 132 beats/min before stimulation was unchanged at a mean maximum heart rate of 158 beats/min after stimulation (0.48 ± 0.18 vs 0.48 ± 0.17 liter/min). Thus, although stroke volumes decreased significantly, ventricular outputs remained unchanged as a result of the proportional increase in heart rate.

We were able to measure end-diastolic and endsystolic left ventricular areas from two-dimensional echocardiograms in 11 fetuses before and after auditory stimulation (figure 6). There was a mean reduction in end-diastolic area of 11% (p < .02) at maximum heart rate but no concomitant significant change in either end-systolic area or fractional area shortening (figure 7). The mean changes in ventricular area in these 11 fetuses corresponded to a decrease in mean Doppler-determined stroke volume of 19% (3.6 ± 1.2 vs 3.0 ± 1.7 ml; p < .005), whereas cardiac output in these fetuses did not change (0.47 ± 0.15 liter/min before vs 0.48 ± 0.12 liter/min after stimulation). These results indicate that the decline in stroke volume with increasing heart rate was related to a decrease in end-diastolic chamber size.

The interobserver variability in measurements of pulmonary arterial and aortic diameters and pulmonary artery and aortic Doppler blood flow velocity integrals from our laboratory have been reported previously.9

Discussion

This study of the normal human fetus describes the changes in ventricular dimensions (areas), stroke volumes, and ventricular outputs that occur with increases in heart rate induced by auditory stimulation. We used echocardiography to measure the dimensions of the
cardiac chambers and great vessels and assessed right and left ventricular stroke volumes and outputs per minute with Doppler echocardiography. Right and left ventricular stroke volumes have been quantified previously in the human fetus, derived as the product of the Doppler blood flow velocity integrals across either the semilunar or atrioventricular valves and the cross-sectional area of the blood flow.\textsuperscript{6-10} We chose to calculate right and left ventricular stroke volumes from the blood flow velocity spectra across the semilunar valves rather than the atrioventricular valves for two reasons. First, because of controversy regarding the shape and constancy of the cross-sectional area of the atrioventricular valve orifice, and second because validation studies of Doppler estimates of volume flow in adults through the semilunar valves have correlated best with roller pump volume flow studies.\textsuperscript{12, 13} We studied fetuses only in the latter part of the third trimester of pregnancy so that measurements of great vessel dimensions, ventricular areas, and volume flow would not be limited by the resolution of our equipment.

We used auditory stimulation as a method of increasing heart rate from resting values. Auditory stimulation results in a startle response in the fetus, which is associated with a rapid rise in heart rate that returns to baseline over a period of minutes. This technique is not known to result in any harmful effects to the fetus and is routinely used in obstetrics as an indicator of fetal well-being, as a predictor of perinatal mortality, to assess fetal hearing, and to determine fetal neurologic status.\textsuperscript{11, 14-17}

Our study demonstrated a similar inverse relationship between stroke volume and heart rate in the right and left ventricles, although the two ventricles were assessed individually and nonsimultaneously. In addition there were no concomitant changes in either right

\textbf{FIGURE 2.} Regression line derived from the heart rate–stroke volume relationship for a typical fetus, illustrating the decrease in stroke volume with the increase in heart rate.

\textbf{FIGURE 3.} Individual regression lines for each of the 25 fetuses, illustrating the inverse relationship between heart rate and stroke volume. The changes in right ventricular stroke volumes with heart rate are indicated by interrupted lines and the changes in left ventricular stroke volume with heart rate are indicated by continuous lines.

\textbf{FIGURE 4.} Regression line derived from the heart rate–ventricular output relationship for the same fetus as in figure 1, illustrating that ventricular output did not change significantly with the increase in heart rate.
or left ventricular outputs with increases in heart rate, suggesting that the response of the combined right and left ventricular outputs, i.e., total cardiac output, would not change with increasing heart rate and would parallel that of either ventricle. The relationship between heart rate and stroke volume in the human fetus is similar to that observed in the recumbent adult heart during atrial pacing and more recently in the atrially paced fetal lamb; in both, stroke volume decreases with increasing heart rate and cardiac output remains unchanged. In contrast, stroke volume and cardiac output both increase with the increasing heart rate during submaximal musculoskeletal exercise as a result of substantial alterations both in ventricular loading conditions and in myocardial contractile state. The decrease in stroke volume during atrial pacing-induced tachycardia results from reduction in the duration of the diastolic filling period and therefore in ventricular preload. Increases in heart rate with atrial pacing produced decreases in end-systolic, end-diastolic, and stroke volumes, with no change in cardiac output or ejection fraction. We were unable to compute left ventricular volumes in our fetuses but instead assessed ventricular areas and demonstrated a decrease in end-diastolic area with increasing heart rate.

Our findings are consistent with those of Kirkpatrick et al. and Anderson et al., who showed that left ventricular output in chronically instrumented fetal lambs determined by indicator dilution techniques remained unchanged over a wide range of spontaneous heart rates. Left ventricular stroke volumes changed only with perturbations in end-diastolic ventricular dimensions or pressure. In contrast, Rudolph and Heymann, using the same animal preparation, reported that right ventricular output measured by electromagnetic flow meters applied around the pulmonary artery increased with increases in heart rate and decreased when heart rate decreased. They suggested that the

**FIGURE 5.** Individual regression lines for each of the 25 fetuses, illustrating that neither right ventricular output (interrupted lines) nor left ventricular output (solid lines) varied with increases in heart rate.

**FIGURE 6.** Changes and mean values for left ventricular diastolic areas (left) and systolic areas (right) from minimum resting to maximum heart rate after auditory stimulation in 11 fetuses.

**FIGURE 7.** Changes and mean values for left ventricular stroke areas (left) and percent left ventricular area shortening (right) from minimum resting to maximum heart rate after auditory stimulation in 11 fetuses.
major determinant of fetal cardiac output was heart rate and not the Frank-Starling mechanism. All the studies of the fetal lamb involved varying degrees of surgical manipulation of the fetus in utero, whereas our study was performed in the undisturbed intact human fetus in its normal physiologic milieu.

Potential limitations of our study deserve consideration. The circulatory changes resulting from auditory stimulation in the human fetus may have been contributed to in part by alterations in ventricular afterload mediated by activation of the peripheral autonomic nervous system. Theoretically, short-term stimulation of the sympathetic nervous system would increase afterload, which in turn would increase end-diastolic dimension and volume and decrease stroke volume, ejection fraction, and cardiac output. In our study end-diastolic dimension decreased while fractional shortening and cardiac output were unchanged with the increase in heart rate, indicating that if there were reflex changes in ventricular loading they were minimal. Moreover, studies in fetal and newborn mammals, including man, have demonstrated that although the peripheral sympathetic nervous system is operative, it is functionally immature.

Our study of the undisturbed human fetus indicates that increases in fetal heart rate alone do not result in any significant change in cardiac output, similar to that recently reported in the lamb. These findings are contrary to conventional teaching, which suggests that cardiac output increases with positive chronotropic interventions. Thus reduction in afterload or increase in preload may be more successful in increasing cardiac output than increasing heart rate in the human fetus, although the response to increases in preload may be blunted. We assessed only the effects of increasing heart rate on stroke volume and ventricular output per minute over the normal physiologic range of heart rates. Thus it is not possible to predict the changes in cardiac output with heart rates above or below the normal physiologic range from this study, but it is known that sustained tachycardia and bradycardia in utero may result in congestive heart failure with development of hydrops fetalis if heart rate is not corrected.

This study of the normal human fetus in the third trimester of pregnancy demonstrates that increases in heart rate induced by auditory stimulation result in a parallel decrease in right and left ventricular stroke volumes and no change in right and left ventricular outputs. Increase in heart rate results in reduction of the ventricular diastolic filling period and end-diastolic volume, which in turn is accompanied by a decrease in stroke volume as predicted by the Frank-Starling mechanism. The inverse proportionality between heart rate and stroke volume is such that there is no change in either right or left ventricular minute output, indicating that the major regulator of cardiac output in the human fetus is the Frank-Starling mechanism and not heart rate, similar to that in the adult heart. Clarification of this normal physiologic relationship in the human fetus may have clinical importance in predicting how chronotropic drugs modulate cardiac output and therefore may prove useful in the selection of optimal therapy for the treatment of heart failure and arrhythmias in utero.

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