Ultrasound Obstet. Gynecol. 10 (1997) 27–31

Pulmonary venous blood flow in the human fetus

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Key words: PULMONARY VEINS, FETUS, PREGNANCY, ULTRASOUND, DOPPLER ECHOCARDIOGRAPHY

ABSTRACT

The objective of this study was to assess the feasibility of recording pulmonary venous blood flow in the human fetus, and to evaluate its relationship with gestational age.

We studied 152 singleton pregnancies between the 19th and 40th weeks of gestation. One hundred and one cases were studied cross-sectionally to gather data on color flow visualization, and 51 were studied longitudinally. The upper right pulmonary vein was interrogated by pulsed wave Doppler to assess pulmonary venous blood flow.

On color Doppler, the upper right pulmonary vein could be imaged in 89.6% of cases in the peri-atrial tract and in 75% of cases within the lung. The upper left pulmonary vein could only be imaged in 8% of cases close to the atrium and in 41% of cases within the lung. Reliable velocity waveforms were obtained in 91% of cases. The mean systolic peak velocity was 22.19 ± 6.39 cm/s and the mean diastolic peak velocity was 22.1 ± 6.35 cm/s. Both increased significantly with gestational age. Reversed end-diastolic blood flow was present in 18% of cases, regardless of gestational age and fetal heart rate. Expressed as a percentage of the forward flow velocity time integral, its value was 7.65 ± 5.2%.

Our data seem to confirm the presence of pulsatile pulmonary venous blood flow in the second- and third-trimester fetus. Normative data have been established for the second and third trimesters of pregnancy.

INTRODUCTION

In the adult, pulmonary venous blood flow has been extensively studied under physiological and pathological conditions[1–3], and the assessment of pulmonary venous flow has become an integral part in the characterization of left ventricle diastolic function[2]. Generally, the upper right pulmonary vein is sampled at its entrance into the left atrium on an apical four-chamber view of the heart[4], although, with transesophageal echocardiography, inferior pulmonary veins can also be easily studied[5].

Since the introduction of fetal echocardiography in 1980[6], most central and peripheral vascular regions have been investigated in the human fetus[7–10]. In particular, fetal cardiac diastolic and systolic functions have been characterized in fetuses with normal and impaired intrauterine growth. However, virtually all Doppler-derived indices to assess diastolic function were calculated from atrioventricular blood flow velocity waveforms[7,9,10]. For venoatrial connections, inferior vena cava and ductus venosus blood flows have been studied in physiological and pathological conditions[11–14]. Recently, the first cross-sectional Doppler study on pulmonary venous blood flow in the human fetus has been reported[15].

The aim of this investigation was to assess the feasibility of recording pulmonary venous blood flow in the human fetus and to provide normative data for the second and third trimesters of pregnancy.

METHODS

Subjects

The study group consisted of 152 pregnant women followed at our outpatient clinic and referred to our Fetal Cardiology Unit for fetal echocardiography. Since at our institution all pregnant women seen at the outpatient clinic undergo fetal echocardiography, these patients represent an unselected population. All other patients referred to our Cardiology Unit from other institutions due to the presence of risk factors for fetal congenital heart disease were not enrolled in the study. The study design had been previously approved by our ethics committee. For the cross-sectional study, entry criteria were:

(1) Singleton pregnancy;

(2) Gestational age confirmed by an early second-trimester biparietal measurement;

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Received 26–10–95
Revised 28–4–97
Accepted 12–5–97

(3) Fetal abdominal circumference above the 10th centile for gestational age to exclude the presence of intrauterine growth retardation; and

(4) Absence of cardiac and extracardiac malformations on prenatal ultrasound and at birth.

All women gave their informed consent to the study. One hundred and one fetuses were studied cross-sectionally in order to gather the following qualitative data: color imaging rate for the pulmonary veins, feasibility and reproducibility of velocity waveform recording, and waveform analysis. After the cross-sectional study, the first 51 patients from the outpatient clinic who were at 19–20 weeks of gestation and who met the above-mentioned entry criteria and agreed to participate in the study were enrolled into the longitudinal study. These patients were examined at 3-week intervals until delivery.

Doppler investigation

Two scanners with color and pulsed wave Doppler 3.5- and 5.0-MHz sector or convex probes (Acuson 128, Acuson Inc., Mountain View, CA, USA; Toshiba 270A, Toshiba Inc., Tokyo, Japan) were used for the study. Fetuses were examined by two authors (D.P. and S.P.). All examinations were carried out with the women lying in a comfortable semi- recumbent position. An apical four-chamber view was sought, and the color flow imaging function superimposed, with settings to optimize the identification of moderate flow. Upper right and left pulmonary veins were sought within the lung and at their entrance into the left atrium (peri-atrial tract, Figure 1). The Doppler recording was considered intra-pulmonary if the sample volume was placed at a distance of > 5 mm from the atrial wall (Figure 2). Since upper right peri-atrial pulmonary blood flow was detectable in most cases, this site was chosen for the longitudinal pulsed wave Doppler study. Velocity waveforms were recorded during periods of fetal apnea and were considered valid for recording angles < 20°. The sample volume width was 2–3 mm, depending on gestational age. Doppler sampling was deemed eligible for the study if more than three similar velocity waveforms were recorded. All measurements were stored on videotape and analyzed on an off-line computer. The following parameters were calculated: systolic maximum velocity (*S* peak), diastolic maximum velocity (*D* peak), the *S/D* ratio, forward flow velocity time integral and reversed flow velocity time integral.

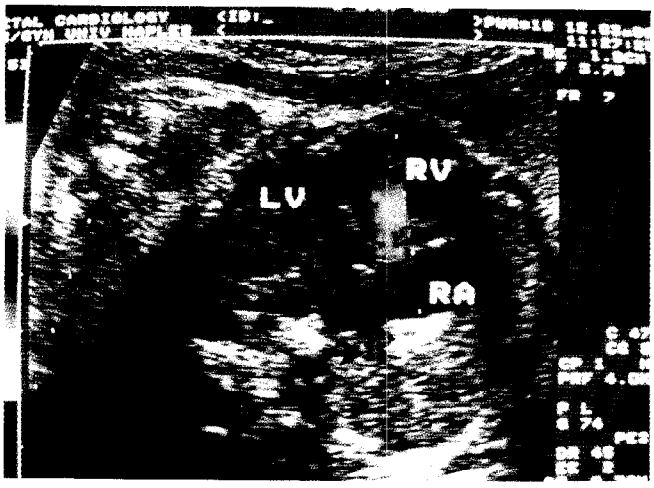

Figure 1 Four-chamber view of the heart in a 29-week fetus. Color flow imaging shows the right upper pulmonary vein draining into the left atrium. The arrow points to the site of the peri-atrial flow recording. LV, left ventricle; RV, right ventricle; RA, right atrium

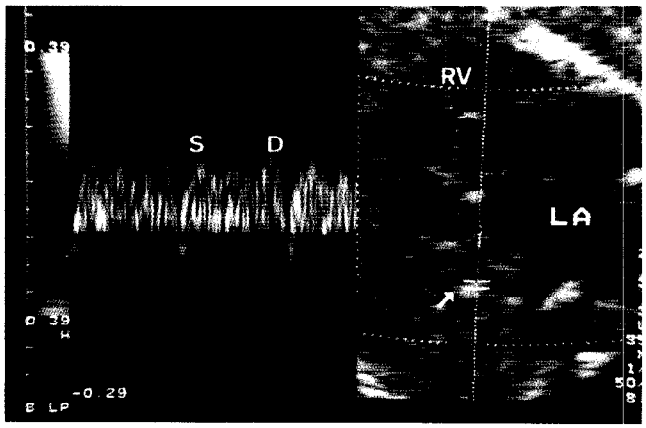

Figure 2 Pulmonary venous Doppler velocity waveform. The arrow indicates the site of intrapulmonary flow recordings (> 5 mm from the atrial wall). In some instances, as in this 26-week fetus, reversed flow at the time of the atrial contraction can be recorded. S, systolic peak velocity; D, diastolic peak velocity; LA, left atrium; RV, right ventricle

Intra- and interobserver variabilities were calculated for the first 20 fetuses: the first examiner recorded the pulmonary blood flow twice and measured the above-mentioned parameters on each recording; successively, the fetus was re-examined by the other operator, who re-recorded the pulmonary vein blood flow, re-calculating the same parameters. To evaluate interobserver and intraobserver variabilities, limits of agreement were calculated according to the method of Bland and Altman[16].

During the longitudinal study, if the fetal position was unsuitable for the Doppler analysis, the woman was asked to walk about and return in 15–30 min to complete the examination.

Statistics

All calculations were performed with the statistical SPSS software[17]. Systolic and diastolic peak velocities were regressed on gestational age as predictor variable, and regression curve best fit was performed. Confidence intervals for the regression curve were also calculated.

RESULTS

Cross-sectional study (n = 101)

The mean gestational age was 27 weeks (range 18–37 years). With the color mode set to detect low–medium

range velocities (20–40 cm/s) on a four-chamber view of the heart, the upper right pulmonary vein was readily imaged at the right atrium entrance in 90/101 cases (89.6%) (Figure 1), while the main venous conduit could be traced within the lung in 76 cases (75%). For the upper left pulmonary venous flow, the detection rate was very low for the peri-atrial tract (8%), in agreement with postnatal studies[18]. In 41% of cases (41/101), a large intrapulmonary venous conduit could be seen paralleling the left ventricular wall.

On the basis of the color flow imaging study, we decided to evaluate only upper right venous pulmonary blood flow.

Feasibility and reproducibility

Reliable velocity waveforms from the peri-atrial or intraparenchymatous tract were obtained in 92 cases (91%). In the last weeks of pregnancy, failure to obtain a reliable Doppler recording was related to prolonged fetal breathing or gulping, fetal trunk movements and maternal respiratory diaphragmatic excursions. The mean difference between two repeated observations by the same observer was 0.0 ± 0.4 cm/s; the mean difference between two observations by the two operators was 0.25 ± 0.23 cm/s. The low standard error values indicate the absence of significant differences between repeated observations.

Waveform analysis

As in the adult, the pulmonary venous velocity waveform presents two peaks (Figure 2). The first (*S* peak) corresponds to ventricular systole, and is monophasic. The second (*D* peak) follows the early diastolic ventricular filling phase and precedes the atrial contraction. Reversed blood flow during atrial contraction was not a systematic finding, occurring in only 18% (18/101) of cases, regardless of gestational age (Figure 2). Expressed as a percentage of the forward flow velocity time integral, its mean value was 7.65 ± 5.2%. In 22 cases, the upper right pulmonary vein was sampled both intraparenchymally and at the left atrium entrance, to detect possible variations in peak velocities and direction of flow. Systolic peak velocity was higher close to the atrium than within the lung (22.3 cm/s vs. 16.5 cm/s, $p < 0.05$). For the diastolic peak velocity, figures were higher at the atrium entrance than within the lung, but the difference did not reach statistical significance ($p = 0.59$). No statistically significant relationship was found between the occurrence of reversed end-diastolic blood flow and sampling site (peri-atrial or intrapulmonary).

Longitudinal study ($n = 51$)

The mean peak velocity was 22.19 ± 6.39 cm/s and 22.11 ± 6.35 cm/s for the *S* peak and *D* peaks, respectively. Both *S* and *D* peak velocities showed a positive correlation with gestational age (Figures 3 and 4). The best assessment of the relationship between peak velocity and gestational age was achieved with a quadratic regression model: the correlation coefficients (r^2) were 0.719 (intercept 0.45, slope b_1 0.45, b_2 0.01) for systolic peak velocity and 0.694 (intercept −3.53, slope b_1 0.86, b_2 0.00) for diastolic peak velocity. Confidence intervals for the regression curves are shown in Figures 3 and 4. The *S/D* ratio did not change significantly with gestational age.

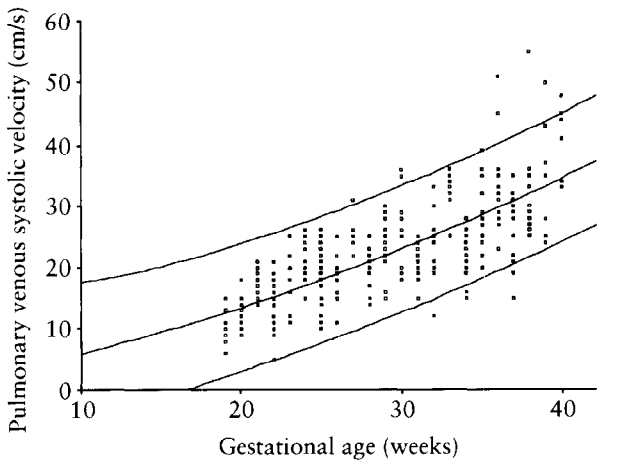

Figure 3 Pulmonary venous blood flow. Systolic peak velocity versus gestational age (scatterplot with mean regression line and 95% confidence intervals). The regression equation parameters are: intercept = 0.45, slope $b_1 = 0.45$, $b_2 = 0.01$

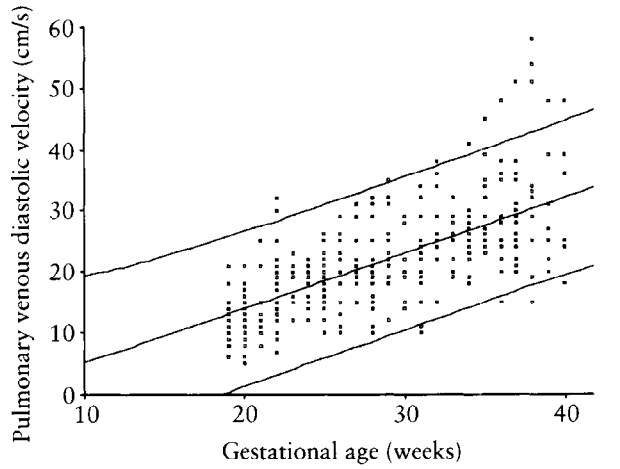

Figure 4 Pulmonary venous blood flow. Diastolic peak velocity versus gestational age (scatterplot with mean regression line and 95% confidence intervals). The regression equation parameters are intercept = −3.53, slope $b_1 = 0.86$, $b_2 = 0.00$

DISCUSSION

The cross-sectional part of this study was undertaken to assess the visualization rate of pulmonary veins on color Doppler, and the feasibility of pulsed wave Doppler recording of pulmonary venous blood flow in the human fetus during the second and third trimesters of pregnancy. The 89.6% (90/101 fetuses) color Doppler visualization rate obtained in this study in 101 second- and third-trimester fetuses is in close agreement with the 84–97% reported by

Anteby and colleagues[19], who evaluated the visualization rate of pulmonary veins in 734 second-trimester fetuses (weeks 14–21).

In the adult the Doppler velocity waveform of pulmonary veins is biphasic, with absent or reversed flow during atrial contraction. This aspect of the velocity waveform has been directly related to systolic and diastolic factors[1]; the systolic displacement of the mitral annulus, the atrial contraction, relaxation and compliance have all been claimed to determine a suction mechanism, draining blood from pulmonary veins into the left atrium and ventricle[1,2,4,18]. In the fetus, several factors might interfere or interact with the systolic and diastolic phenomena responsible for the suctioning effect in the adult. First, the patency of the two shunts, represented by the ductus arteriosus and the foramen ovale, might interfere with the atrial pressure, due to the high amount of blood passing through the foramen ovale into the left atrium. Second, the relative stiffness of the fetal myocardium, due to the presence of immature isotypes of the contracting proteins[20], greatly affects cardiac function in the fetus, as shown by several authors[7,21]. Third, the fact that less than 30% of the right cardiac output reaches the pulmonary circulation in the fetus[22] must affect the pressure gradient between pulmonary veins and the left atrium. Finally, as cardiac output increases with gestational age, the changing ventricular loading conditions, which have been shown to modify ventricular filling patterns[11], and, hence, interact with the factors responsible for the suctioning effect, might also interfere with pulmonary venous blood flow.

However, Laudy and colleagues[15] have recently demonstrated in a cross-sectional study of 123 fetuses that fetal pulmonary venous velocity waveforms resemble those recorded in the adult and that there is a significant increase in systolic and diastolic peak velocities with advancing gestational age. In their study, the only difference was the presence of significant forward flow during atrial contraction, which is absent or reversed in the adult[23,24].

Our longitudinal study seems to confirm the presence of pulsatile pulmonary venous blood flow in the second- and third-trimester fetus. Also, the reference curves for systolic and diastolic peak velocities are in fair agreement with those reported by Laudy and colleagues[15]. Another point to consider regards maximum peak velocities: our figures of 22.19 ± 6.39 cm/s and 22.11 ± 6.35 cm/s for *S* and *D* peak peri-atrial velocities are much lower than the average 48 ± 9 cm/s and 50 ± 10 cm/s reported in postnatal studies[4,18]. However, taking into consideration only third-trimester values (31 cm/s, Figures 3 and 4), these are relatively closer to figures reported in neonatal series[3]. The significant postnatal increase in peak velocities is directly related to the switch of the pulmonary circulation from the fetal to the neonatal type; in fact, with the closure of the shunts, the entire right cardiac output, and not a small part of it as during prenatal life, reaches the lungs and the pulmonary veins. Furthermore, the closure of the foramen ovale allows atrial contraction to create the pressure gradient responsible for the reverse flow wave.

Continuous forward flow during atrial contraction was found in 82% of fetuses, whereas in the remaining 18% a reversed flow component concomitant with atrial contraction was recorded (Figure 2). This event, which has been reported in 72–88% of normal adults[23,24], did not show any significant relationship with gestational age or heart rate. A possible explanation is that, despite the elevated fetal heart rate (140–160 bpm), which should increase the negative wave, the presence of an alternative outlet represented by the foramen ovale might dampen the pressure wave determined by the atrial contraction and cancel the consequent reversed flow wave in most cases. Another hypothesis involves the relative stiffness of the fetal myocardium[20]. In the adult, it has been shown that, in older individuals in which the isovolumic relaxation time is prolonged (i.e. the myocardium is stiffer), the reversal with atrial contraction is increased in comparison with younger patients[4]. Similarly, it can be speculated that those fetuses showing a reversal during atrial contraction may represent a subset of normal fetuses with a transient minor delay in myocardial maturation. However, given the dimensions of fetal pulmonary veins, the possibility of a sampling artifact cannot be completely ruled out.

In conclusion, we have confirmed that Doppler recording of pulmonary venous blood flow in the human fetus is feasible. In addition, normative data have been established for Doppler-derived indices in the second and third trimesters of pregnancy. Further studies are needed to evaluate pulmonary venous blood flow modifications in fetal congenital heart disease and in intrauterine growth retardation.

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