Utility of Ductus Venosus Blood Flow in the Study of Cardiac Function in Fetuses with Intracardiac Echogenic Focus

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ABSTRACT: *Purpose.* The purpose of this study was to investigate fetal ductus venosus (DV) wave velocities, DV velocity ratios, and DV diastolic time intervals to derive additional information on fetal cardiac function in the presence of an intracardiac echogenic focus (IEF).

Methods. Seventy fetuses at 19–28 weeks of gestation with an IEF and 63 control fetuses were screened using two-dimensional and power Doppler echocardiography. DV wave velocities, DV velocity ratios, and diastolic time intervals were measured. The aortic peak velocity, pulmonary artery peak velocity, left ventricular shortening fraction, and right ventricular shortening fraction, atrioventricular early-diastolic filling velocity (E), atrial contraction velocity (A), and E/A ratio were also measured.

Results. The study and control groups were similar in terms of maternal age, body mass index, and gestational age in weeks at the time of examination ($p > 0.05$). Significant between-group differences were found in DV v-descent ($p = 0.03$) and a-wave velocities ($p = 0.04$).

Conclusions. Although the presence of an IEF in the fetal heart does not influence conventional measurements (DV velocity ratios and DV diastolic time intervals), it is associated with changes in DV v-descent and a-wave velocities. These changes may be indirectly related to reduced end-systolic relaxation and augmented atrial contraction in the fetal heart. We therefore suggest examination of DV flow velocities in fetuses with IEF. © 2015 Wiley Periodicals, Inc. *J Clin Ultrasound* **44**:170–174, 2016; Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jcu.22308

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INTRODUCTION

The presence of an intracardiac echogenic focus (IEF) is a frequent finding during fetal echocardiography (FE).[1,2] Although IEF is thought to result from microcalcifications in the papillary muscles and is usually considered a benign finding, some reports have described an association between IEF and cardiac dysfunction.[3] In fetal life, 30% of the highly saturated umbilical venous blood is carried to the fetal right atrium via the ductus venosus (DV) without any desaturation and is transmitted directly to the left atrium to be used for the coronary circulation and nutrition of the upper body. The flow pattern of DV is typically antegrade throughout the cardiac cycle, and different wave lengths that occur during the cardiac cycle can be measured quantitatively on pulsed-wave (PW) Doppler scanning. Waveforms obtained from the DV are formed directly by the pressure differences between the atrium and umbilical vein and the volume changes occurring throughout the entire cardiac cycle in the heart. In DV flow, four different waveforms defining the major cardiac events are described: the "S" wave, the "v descent" wave, and the "D" and "a" waves are

associated with ventricle systole, end-systolic ventricular relaxation, and early and rapid ventricular filling of ventricular diastole and atrial contraction, respectively.[4]

Conventional FE is limited in its ability to assess functional cardiac parameters because of the unique anatomy and physiology of the fetal circulation. Tissue Doppler imaging and speckle-tracking imaging have shown higher sensitivity for detecting mild myocardial dysfunction, but such imaging is not possible with the use of standard sonographic machines in everyday practice. In recent years, DV Doppler velocities, DV velocity ratios, and diastolic time intervals have been used to evaluate fetal cardiac function and well-being in complicated pregnancies, such as those involving intrauterine growth retardation, twin-to-twin transfusion syndrome (TTTS), or gestational diabetes.[5–7]

Our aim in this study was to investigate the effects of IEF on DV blood flow, and therefore, cardiac hemodynamics, by comparing the DV wave velocities, DV velocity ratios, and diastolic time intervals in fetuses with and without an IEF detected on FE.

PATIENTS AND METHODS

Seventy fetuses with normal FE examination findings and an IEF in the heart formed the study group, and 63 fetuses with normal FE examination findings and no IEF served as controls during the study period. Fetuses in the study group had an isolated IEF in the left ventricle (n = 48), two IEFs in the left ventricle (n = 4), an isolated IEF in the right ventricle (n = 11), or an IEF in both ventricles (n = 7). The exclusion criteria were maternal complications such as systemic lupus erythematosus, diabetes, hypertension, or pre-eclampsia; fetal chromosomal or structural abnormalities, intrauterine growth retardation, and macrosomia; and neonatal anomalies, low birth weight, high birth weight, and stillbirth.

M-mode, B-mode, and PW Doppler interrogation of DV blood flow, in addition to other measurements, were used in each study. Right and left ventricular diastolic function was evaluated using the ratio between the early and atrial peak velocities (early-diastolic filling velocity [E], atrial contraction velocity [A]; E/A ratio) across the atrioventricular (AV) valves. For this measurement, the Doppler sample volume was placed immediately distal to the respective AV valve in the four-chamber view.

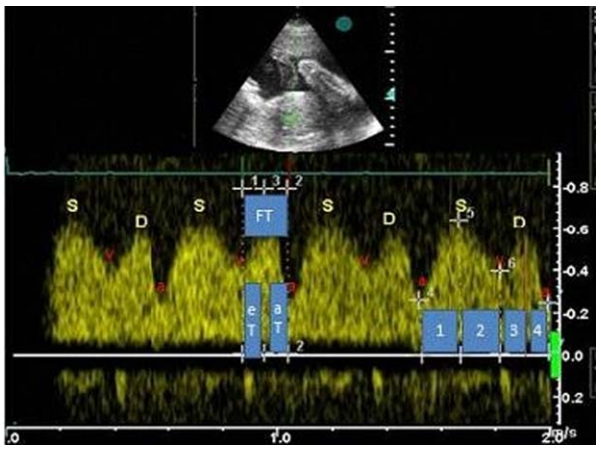

FIGURE 1. Measurements of the ductus venosus flow velocities and diastolic time intervals recorded in a single cardiac cycle. S, systole; D, diastole; FT, ventricular filling time; eT, early diastolic filling time; aT, late diastolic filling time; 1, ventricular systolic contraction; 2, end-systolic ventricular relaxation; 3, early passive diastolic ventricular filling; 4, atrial contraction.

The DV Doppler measurements were obtained with the fetus in the midsagittal or transverse abdominal plane. The umbilical vein and DV were visualized in the region nearest to their connection with the inferior vena cava after color Doppler imaging; the insonation angle was maintained at 0 degrees (angle correction was used), and filtering was maintained at 100 Hz. Measurements were performed while the fetus was not exhibiting breathing movements.[8] The DV flow, which is antegrade throughout the cardiac cycle, was evaluated with PW Doppler imaging, and the peak velocities of the waves were measured quantitatively in centimeters per second (Figure 1).

The following four wave tracings were recorded from the DV flow in a single cardiac cycle, as described by Baschat et al[4]:

1. First rising wave tracing: ventricular systolic contraction (S-wave),
2. First decrease after occurrence of the S-wave in the second half of systole: end-systolic ventricular relaxation (v-descent),
3. Second rising wave after v-descent: early passive diastolic ventricular filling (D-wave), and
4. Final sharp decline: atrial contraction (a-wave).

Simultaneously, the following three diastolic time intervals were obtained from the DV flow in diastole in one cardiac cycle and measured in milliseconds[9]:

1. Total diastolic filling time (FT): from the lowest point of v-descent to the lowest point of the

a-wave, representing the entire ventricular diastolic period,
2. Early diastolic filling time (eT): from the lowest point of v-descent to the peak of the D-wave, indicating the early passive ventricular FT, and
3. Late diastolic filling time (aT): from the peak of the D-wave to the lowest point of the a-wave, showing the atrial contraction time.

All FE studies were performed by using a Vivid-6S 256 model device (GE-Vingmed Ultrasound AS, Horten, Norway) equipped with a 3S-RS 1.5–4-MHz transducer. The study was approved by the institutional ethics committee, and all patients gave written informed consent.

For statistical analyses, we used Windows SPSS 18 software (PASW Statistics for Windows, Version 18.0; SPSS, Inc., Chicago, IL). The distributions of the groups were evaluated with the Kolmogorov–Smirnov test in addition to graphical methods. Differences between the means of the normally distributed parameters were evaluated with Student's *t* testing, and the results are given as means ± SD. Differences between the medians of the nonnormally distributed parameters were evaluated with the Mann–Whitney *U* test, and the results are given as the median. A *p* value less than 0.05 was considered statistically significant.

TABLE 1
Comparison of Demographic and Fetal Echocardiographic Data of Patients with and Without Intracardiac Echogenic Focus*

Characteristic	Study Group (IEF) (n = 70)	Control Group (No IEF) (n = 63)	*p* Value
Maternal age, years	27.2 ± 4.6	27.5 ± 5.3	0.79
Gestational age, weeks	22 (19–28)	23 (20–28)	0.22
Body mass index, kg/m^2	26.2 ± 2.8	25.9 ± 2.3	0.53
IEF diameter, mm	2.6 ± 0.7	NA	NA
LVSF, %	0.39 ± 0.04	0.38 ± 0.05	0.52
RVSF, %	0.37 ± 0.04	0.36 ± 0.06	0,47
PPV, cm/s	0.7 ± 0.1	0.7 ± 0.1	0.75
APV, cm/s	0.7 ± 0.1	0.7 ± 0.1	0.54
Diastolic function indices, E/A ratio			
Tricuspid valve	0.6 ± 0.08	0.6 ± 0.06	0.67
Mitral valve	0.6 ± 0.1	0.6 ± 0.09	0.58
DV flow velocities (waveforms), cm/s			
S-wave	64.4 ± 12.2	61.1 ± 11.3	0.21
v-descent	39.7 ± 7.5	43.1 ± 7.8	0.03
D-wave	54.6 ± 10.6	47.6 ± 8.7	0.07
a-wave	29.4 ± 7.6	32.8 ± 6.9	0.04
DV velocity ratios			
S/v	1.6 ± 0.1	1.5 ± 0.2	0.17
S/D	1.2 ± 0.1	1.2 ± 0.1	0.31
v/D	0.8 ± 0.07	0.8 ± 0.09	0.55
S/a	2.3 ± 0.7	2.1 ± 0.4	0.6
v/a	1.4 ± 0.4	1.4 ± 0.2	0.6
D/a	1.8 ± 0.6	1.8 ± 0.3	0.77
Diastolic FT, ms			
FT	132.4 ± 24.3	133.5 ± 19.4	0.56
aT	34.5 ± 21.2	35.9 ± 17.7	0.62
eT	97.5 ± 12.3	96.9 ± 14.5	0.73

Abbreviations: IEF, intracardiac echogenic focus; NA, not applicable; LVSF, left ventricular shortening fraction; RVSF, right ventricular shortening fraction; PPV, pulmonary peak velocity; APV, aortic peak velocity; E, atrioventricular early-diastolic filling velocity; A, atrial contraction velocity; DV, ductus venosus; S-wave, ventricular systolic contraction; v-descent, end-systolic ventricular relaxation; D-wave, early passive diastolic ventricular filling; a-wave, atrial contraction; FT, total diastolic filling time; aT, late diastolic filling time; eT, early diastolic filling time.
*Data are given as means ± SD.

RESULTS

The comparisons between the study and control groups are presented in Table 1. We found no statistically significant differences between the groups in terms of maternal age ($p = 0.79$), gestational age in weeks ($p = 0.22$), or body mass index ($p = 0.53$). The mean IEF size was 2.6 ± 0.7 mm (range, 1.9–5.1 mm; median, 3.2 mm). There were also no statistically significant differences between the two groups in the left ventricular shortening fraction (LVSF; $p = 0.52$) and right ventricular shortening fraction (RVSF; $p = 0.47$); in the Doppler systolic indices, namely the pulmonary peak velocity ($p = 0.75$) and aortic peak velocity ($p = 0.54$); or in the diastolic function indices, namely the E/A ratio for each AV valve (tricuspid, $p = 0.67$; mitral, $p = 0.58$).

The study and control groups were also compared with respect to the DV flow velocities. Although there were no significant between-group differences in the S-wave ($p = 0.21$) and D-wave ($p = 0.07$) velocities, statistically significant differences between the groups were observed in the v-descent ($p = 0.03$) and a-wave ($p = 0.04$) velocities. No significant between-group differences were observed in the S/v ($p = 0.17$), S/D ($p = 0.31$), v/D ($p = 0.55$), S/a ($p = 0.60$), v/a ($p = 0.6$), and D/a ($p = 0.77$) ratios or in the DV diastolic time intervals: FT ($p = 0.56$), aT ($p = 0.62$), and eT ($p = 0.73$).

DISCUSSION

IEF is a common finding during FE examinations in the second trimester of pregnancy. Although usually perceived as a benign entity, its clinical significance is not yet clearly understood.

Investigators in studies conducted with conventional echocardiography or tissue Doppler imaging have concluded that IEF does not disrupt fetal cardiac function.[10–12] Only Degani et al[3] reported the occurrence of diastolic dysfunction in fetuses with IEF. Likewise, conventional echocardiographic measurements in our study failed to show any association between IEF and systolic or diastolic dysfunction of the fetal heart.

Investigations of methods capable of early detection of fetal cardiac dysfunction have become popular in recent years. One suggested method is the use of venous Doppler indices of the cardinal veins (the DV and the caval, hepatic, and pulmonary veins), which bring blood to the fetal heart, most commonly the DV peak velocity index of the veins (PVIV) and the pulsatility index (PI).[7,13] Baschat et al[4] described four consecutive wave tracings recorded from the DV flow in a single cardiac cycle and associated the S-wave with ventricular systolic ejection, the v-descent with ventricular end-systolic relaxation, the D-wave with ventricular early passive diastolic filling, and the a-wave with atrial contraction. Changes in DV flow have been seen in both experimental animal fetuses and human fetuses with hypovolemia and hypoxia.[14,15]

Two of the DV Doppler indices, the DV-PVIV and DV-PI, are being used with increasing frequency in the evaluation of fetal well-being and cardiac hemodynamics. Sanapo et al[6] reported that the use of the PI is restricted because it does not closely reflect changes in the v-descent and D-wave. Smrcek et al[16] reported that the DV S/D ratio was a better indicator than the DV-PI index was in cases of tricuspid regurgitation. Turan et al[5] advocated the use of DV wave velocities and ratios (S/v, S/D, v/D, S/a, v/a, and D/a) rather than the classic Doppler index (PI) in the assessment of fetal well-being and cardiac function. In this study, we found statistically significant increases in the depth of the a-wave and the v-descent in fetuses with IEF, which translate as velocity reductions in the v-descent and a-wave.

We speculate that this change in the velocity of the v-descent and a-wave may be related to decreased end-systolic relaxation and increased atrial contraction. We relate these changes in cardiac function to (1) restriction of AV valve motion owing to microcalcifications in the papillary muscles, leading to delayed atrial passive emptying, augmented atrial contraction, and a-wave depression; and (2) restricted ventricular end-systolic relaxation owing to increased calcium deposition in the myocardium (v-descent depression). Although we found that both the ventricular systolic and the diastolic functions were normal, the detection of changes in the DV a-wave and v-descent in fetuses with IEF demonstrates that PW Doppler examination of DV waves may be superior to conventional echocardiographic measurements in the assessment of fetal cardiac hemodynamics.

DV wave velocities and ratios can be used in the assessment of ventricular systolic and diastolic functions, and this approach has led to the recent demonstration that ventricular diastolic intervals obtained from DV flow measurements can also be used to assess ventricular diastolic function. Bensouda et al[9] used DV blood flow and diastolic time intervals to demonstrate myocardial dysfunction in patients with TTTS, using the modified myocardial performance index (mod-MPI) as a reference. They compared diastolic time intervals and mod-MPI values in donor and recipient twins in the early phase of TTTS and found that the FT and eT were significantly shortened in fetuses with myocardial dysfunction, as demonstrated by prolonged mod-MPI values. The authors related their finding of shortened eT to a prolonged isovolumetric relaxation time. Thus, they were able to demonstrate diastolic myocardial dysfunction in the early phase of TTTS in the recipient by using DV diastolic time intervals. Similarly, in another study on TTTS, Hecker et al[7] reported that prolonged isovolumetric relaxation time is an early marker of subclinical diastolic dysfunction. However, our findings differ from those previously reported: we observed no significant differences between the study and control groups in the diastolic time intervals obtained from DV flow studies in this study.

Thus, in this study, IEF did not influence conventional echocardiographic measurements in fetuses at 19–28 weeks of gestation. However, significant changes in the velocity of the DV v-descent and a-wave and, consequently, in the DV diastolic time intervals, may reflect possible changes in ventricular relaxation. Such changes may be related to decreased end-systolic relaxation and increased atrial contraction.

Although the right ventricle is the dominant ventricle in fetal life, we evaluated global ventricular functions by means of DV wave velocities in our study; however, we do not consider this a limitation of our study because the study group included fetuses with right and/or left ventricular IEFs.

In summary, although the presence of an IEF in the fetal heart does not influence conventional measurements (DV velocity ratios and

DV diastolic time intervals), it is associated with changes in DV v-descent and a-wave velocities. These changes may be indirectly related to reduced end-systolic relaxation and augmented atrial contraction in the fetal heart. Measurement of DV flow is an easy and rapid technique for assessing fetal cardiac function in everyday practice, and we conclude that when the cardiac function of fetuses with IEF is to be assessed, DV flow studies should be included in the diagnostic workup.

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