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Can abnormal ductus venosus peak velocity index for veins in normal fetuses predict failure of functional closure of the foramen ovale in the postnatal period?

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Abstract

Aim: To investigate whether ductus venosus (DV) wave velocities and/or DV peak velocity index for veins (DV-PVIV) can predict failure of functional closure of the foramen ovale in the postnatal period. **Material and methods**: Fetal echocardiography was performed in 455 healthy women with uneventful pregnancies between the 20-24th gestational weeks. DV blood flow and DV-PVIV data were collected prospectively. Echocardiography was repeated in healthy subjects on the 30th postnatal day. Four hundred patients met the study criteria. Newborns with clearly visible foraminal flaps, interatrial septal defects smaller than 5 mm and right-to-left shunting through the defect were accepted as patent foramen ovale (PFO) (n=91). Newborns without PFO (n=309) comprised the control group. **Results:** A statistically significant difference was detected between the groups with and without PFO in terms of mean DV-PVIV values, DV-D and DV-a wave velocities ($p<0.05$ for all). ROC analysis showed that increased DV-PVIV values were related to and predictive of PFO (AUC=0.75; $p<0.001$) and that a threshold value of 0.62, had a sensitivity of 86.8% (95% CI 78.1-93.0%) and a specificity of 51.7% (95% CI 46.1-57.5%). **Conclusion:** DV-PVIV values above 0.62 at the time of fetal echocardiographic examination can predict failure of functional closure of the foramen ovale in the postnatal period.

Keywords: ductus venosus, foramen ovale, fetal echocardiography, patent foramen ovale

Introduction

In fetal life 30% of the highly oxygenated blood coming from the placenta via the umbilical vein is directed to the left atrium through the ductus venosus (DV) and foramen ovale (FO) to supply the coronary and cerebral circulation. Consequently, the DV blood flow and an open FO are essential for nutrition of the vital organs [1,2]. In the postnatal period, the pressure in the left atrium increases and this difference in pressure cause the foraminal flap to adhere to the septum secundum and close the FO. In the presence of a large FO, however, total closure is not achieved, resulting in left-to-right shunting between the atria, thus forming a patent foramen ovale (PFO) [3]. Incidence of PFO falls gradually from 34% in newborn to 20% in adult [4].

Due to the fact that PFO may lead to various systemic diseases (cryptogenic paralysis, platypnea-orthodeoxia syndrome, decompression syndrome, migraine and vascular type headache, obstructive sleep apnea, peripheral embolism including myocardial and renal infarction), it has been accepted as a congenital heart disease that requires close follow-up and treatment [5,6]. In intrauterine life, however, FO needs to remain open for the existence of the fetus, which is maintained by the flow in DV as well as by the pressure difference between the right and left atria.

The patency of FO is considered to be genetic and multifactorial [7]. Specifically, the defect is an incomplete closure of the atrial septum that results in the creation of

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a flap or a valve-like opening in the atrial septal wall. Recently, examination of the DV flow by pulsed-wave (PW) Doppler at the time of fetal echocardiographic (FE) examination has been suggested, but this method is rather used to check fetal well-being and cardiac functions [8-10]. The **aim** of this study was to assess whether the wave velocities of DV and/or DV peak velocity index for veins (DV-PVIV) can predict the development of PFO.

Materials and methods

This study was performed as a prospective cohort study in the pediatric cardiology unit of Izmir Dr. Behcet Uz Children's Hospital between April 2013 and April 2014. Data were collected prospectively from fetuses of healthy women with uneventful pregnancies referred for FE between the 20-24th gestational weeks. A total of 455 pregnant women with normal FE were enrolled in the study. Exclusion criteria were 1) maternal complications, such as systemic lupus erythematosus, diabetes, hypertension, pre-eclampsia, multiple pregnancy; 2) fetal chromosomal or structural abnormalities, intrauterine growth retardation (abdominal circumference < 5th percentile and umbilical artery pulsatility index >2 standard deviations), and macrosomia (birth weight>90% for gestational age after correcting for neonatal sex and ethnicity 3) neonatal anomalies, cesarean birth, stillbirth, low Apgar score (scores 6 and below), low birth weight (birth weight <2500 g), neonatal infections and stay in neonatal intensive care unit (NICU). Fifty-five subjects were excluded from the study for various reasons (lost to follow-up, perinatal asphyxia, history of postnatal hospitalization, use of antibiotics, diagnosed congenital heart disease). Healthy newborns of the subjects (n=400) were re-examined one month after delivery for presence of PFO. A PFO was diagnosed in 91 newborns (22.7%), which comprised the study group. Newborns without PFO (n=309) comprised the control group. Fetal DV wave velocities and DV-PVIV were compared to each other. The study protocol was approved by the institutional Ethical Committee and each subject gave written informed consent.

The DV Doppler measurements were done in a midsagittal or transverse abdominal plane using the smallest possible insonation angle (<30°) and filtering at 100Hz, at a time the fetus did not have breathing movements [11-13]. DV flow, which is normally antegrade throughout the cardiac cycle, was evaluated with PW Doppler and the peak velocities of the waves were measured quantitatively in cm/sec.

Four wave tracings (S-wave, v-descent, D-wave and a-wave) were recorded from DV flow in a single cardiac cycle, as described by Baschat et al [12] (fig 1). The venous Doppler indices were determined automatically by using a practical and reliable index- peak velocity index

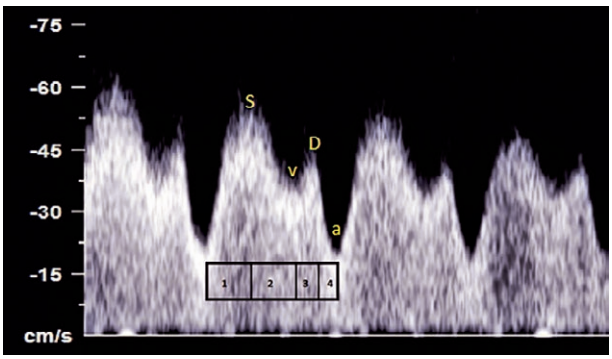

Fig 1. Measurement of the ductus venosus flow velocities. S-wave: ventricular systolic contraction, v-descent: End-systolic ventricular relaxation, D-wave: early passive diastolic ventricular filling, a-wave: atrial contraction, 1: ventricular systolic contraction, 2: end-systolic ventricular relaxation, 3: early passive diastolic ventricular filling, 4: atrial contraction

for veins (PVIV) (S-a/D) [13]. The diameter of the FO of the fetus was measured with two-dimensional echocardiography with the heart in a four-chamber view when the flap of FO was distinctly seen and the diameter was the largest. The diameter of FO was measured three times for each fetus, and average of three measurements was calculated. Newborns with clearly visible foraminal flaps, interatrial septal defects smaller than 5 mm and right-to-left shunting through the defect were accepted as patent foramen ovale (PFO).

All echocardiographic studies were performed using a 3S-RS 1.5-4 MHz transducer for FE and a 6S transducer for postnatal echocardiography, on a Vivid-6S 256 model device (GE-Vingmed Ultrasound AS, Horten, Norway).

Statistical analysis

Windows SPSS 18 software was used for statistical analysis (PASW Statistics for Windows, Version 18.0. Chicago, IL, USA). The distributions of the groups were evaluated with the Kolmogorov-Smirnov test in addition to graphical methods. The difference between mean of the parameters that meet the normal distribution was evaluated with the Student's t test and the results were given as mean ± standard deviation (SD). A p value of less than 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were used to determine the cut-off value for the DV-PVIV that predicted failure of the FO to close in the postnatal period with maximum sensitivity and specificity.

Results

Demographic and fetal echocardiographic data of study and control groups are detailed in Table I. Characteristics of the study population are shown in Table II

Table I. Demographic and fetal echocardiographic data of study and control groups.

	Study	Control	p
Maternal age (years)	27.94±5.2	28.13±4.89	0.743
Gestational age (weeks)	22.14±1.32	22.39±1.47	0.221
BMI	25.49±4.6	26.12±4.5	0.154
FO diameter (mm)	3.98±0.70	3.82±0.65	0.564
S-wave (cm/sec)	62.30±11.63	60.53±12.11	0.207
v-descent (cm/sec)	46.07±8.61	44.88±8.93	0.342
D-wave (cm/sec)	52.14±10.70	48.23±11.40	**0.003**
a-wave (cm/sec)	30.55±6.72	25.09±6.93	**<0.001**
PVIV	0.61±0.12	0.73±0.13	**<0.001**

S-wave: ventricular systolic contraction, v-descent: end-systolic ventricular relaxation, D-wave: early passive diastolic ventricular filling, a-wave: atrial contraction, DV-PVIV: ductus venosus peak velocity index for veins.
BMI: body mass index

Table 2. Characteristics of the study population (n=91)

Maternal age (years)	28 [19-38]
Parity	0 [0-3]
Gestational age at delivery (week)	38 [36-39]
Vaginal delivery	91 (100)
Birth weight (g)	3200 [2800-3450]
No neonatal complications	91 (100)

Data are presented as numbers with percentages in parentheses and medians with ranges in brackets.

ROC analysis showed that elevated values of PVIV were related to PFO and could be used as a predictor of occurrence of PFO (AUC=0.75, p<0.001). When a DV-PVIV value of 0.62 is taken as threshold, as it has the highest Youden index, PFO can be predicted with a sensitivity of 86.8% (95% CI=78.1-93%) and a specificity of 51.7% (95% CI=46.1-57.5%).

All fetal and postnatal echocardiographic examinations were made by a single experienced pediatric cardiologist (YY) with a calculated intra-class correlation coefficient of 0.824, demonstrating high reproducibility (p=0.018) for measurement of DV-PVIV.

Discussions

In the recent years, it has been suggested to use venous Doppler velocities and indices of the cardinal veins carrying blood to the heart (DV, vena cava, hepatic veins and pulmonary veins) for evaluating the fetal hemodynamics. The venous Doppler findings are useful indicators of cardiac preload, as presence of increased atrial and central venous pressure causes elevation of venous indices and pulsatile flow in the cardinal veins [14,15]. In recent years, two of the DV Doppler indices, DV-PVIV and pulsatility index (DV-PI), are being increasingly used in the evaluation of fetal well-being and cardiac hemodynamics. It has been reported that DV indices may be utilized in the assessment of fetal cardiac hemodynamics, as well as in the follow-up of complicated pregnancies (fetal growth restriction, fetal acidemia, twin-to-twin transfusion syndrome, fetal anemia, congenital heart disease, and fetal myocardial hypertrophy) [16-22].

Sanopa et al have reported that the use of PI, the most frequently used DV Doppler index, is limited in evaluating cardiac functions because it does not fully reflect the changes in DV-v and D waveforms [8]. Smrcek et al have reported that, in tricuspid insufficiency, the DV S/D ratio is a better indicator than DV-PI index [23]. In our study, we preferred the DV-PVIV for its practicality and reliability. We found significantly higher values of fetal DV-PVIV in subjects who later developed PFO as compared to those who did not. Baschat et al have related DV-S wave to the systolic ejection of the ventricle, v-descent to the end-systolic relaxation of the ventricle, D wave to the early and rapid filling of the ventricular diastole, and a wave to atrial contraction [12]. In our study, the DV-a and DV-D velocities were significantly increased in the study group as compared to controls (p<0.001 and p=0.003; respectively), whereas S and V wave velocities were not statistically different between the two groups (p=0.207 and p=0.342; respectively). We speculate that the increase in DV-D wave velocity can be attributed to the early and rapid diastolic filling of the ventricle caused by increased FO flow, and the increase in DV-a wave velocity to the reduced atrial contraction caused by resultant increased ventricular volume load.

Turan et al investigated the relationship between DV, umbilical vein, middle cerebral artery and umbilical artery Doppler findings with vasodepressor necessity in postnatal second day, presence of PDA and/or PFO, blood flow pattern and myocardial contractility in fetuses with FGR by using DV pulsatility index (DV-PVI, peak systolic velocity-end diastolic velocity/time averaged velocity). As a result, they found a relationship between abnormal prenatal DV Doppler findings with long time vasodepressor need in postnatal period, presence of PFO and/or PDA, continuity of right to left shunt, cardiac instability and mortality [24]. We found a relationship between prenatal high DV wave velocity findings with the presence of PFO in the postnatal period as in the study of Turan et al. On the other hand we conducted a study with normal fetuses and we used DV-PVIV which is more reliable and easily usable with all echocardiography machines contrary to the pulsatility index which requires time averaged velocity calculation not found in all echo machines so that did not seem to be usable in daily practise.

Phillipos et al have followed the FO in fetuses between 20 and 38 weeks of gestation and reported that the increase in the diameter of FO is directly proportional to the number of gestational weeks [25]. According to some studies, fetuses with subnormal FO diameters may experience altered fetal hemodynamics (blood flow in umbilical vein, DV and vena cava inferior) leading to hemodynamic disorders ranging from mild right-sided cardiac failure to severe hydrops fetalis [26-28]. On the other hand, increased FO diameter has been associated with *atrial septal defect* (ASD) in postnatal life. Li et al, using ROC analysis, have reported that large FO diameters and FO/Aorta ratios can be used to predict development of secundum ASD in the postnatal period [29]. Although there was no significant difference between the FO diameters in the two groups in our study, the DV-D and DV-a velocities were significantly increased in the study group, which is interpreted as an increased preload. Thus, the FO is capable of accommodating increased blood flow despite its relatively fixed diameter and tunnel-like structure.

A limitation of our study was that, due to technical insufficiency, we could not quantitatively measure the blood passing through FO. Further studies with larger patient populations and advanced imaging techniques for the quantitative assessment of flow through the FO are required.

As a conclusion, in this study, ROC analysis has shown that an elevated DV-PVIV value observed in fetal echocardiography is associated with PFO in the postnatal period and thus may be used as a predictor of PFO. We conclude that cases with DV-PVIV values above 0.62 in fetal echocardiography should be scheduled for follow-up controls in the postnatal period. Larger patient populations and advanced imaging techniques for quantitative assessment of flow through the FO are required.

Conflict of interest: none

References

1. Kiserud T, Rasmussen S, Skulstad S. Blood flow and the degree of shunting through the ductus venosus in the human fetus. Am J Obstet Gynecol 2000; 182: 147-153.
2. Kiserud T, Acharya G. The fetal circulation. Prenat Diagn 2004; 24: 1049-1059.
3. Gardiner HM. Fetal echocardiography: 20 years of progress. Heart 2001; 86: 12-22.
4. Hagen PT, Scholz, DG, Edwards, WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc 1984; 59: 17-20.
5. Cabanes L, Mas JL, Cohen A, et al. Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age. A study using transesophageal echocardiography. Stroke 1993; 24: 1865-1873.
6. Wilmshurst PT, Ellis BG, Jenkins BS. Paradoxical gas embolism in a scuba diver with an atrial septal defect. Br Med J (Clin Res Ed) 1986; 293: 1277.
7. Clark EB. Pathogenic mechanisms of congenital cardiovascular malformations revisited. Semin Perinatol 1996; 20: 465-472.
8. Sanapo L, Turan OM, Turan S, Ton J, Atlas M, Baschat AA. Correlation analysis of ductus venosus velocity indices and fetal cardiac function. Ultrasound Obstet Gynecol 2014; 43: 515-519.
9. Raboisson MJ, Fouron JC, Lamoureux J, et al. Early intertwin differences in myocardial performance during twin-twin transfusion syndrome. Circulation 2004; 110: 3043-3048.
10. Turan OM, Turan S, Sanapo L, Rosenbloom JI, Baschat AA. Semiquantitative classification of ductus venosus blood flow patterns. Ultrasound Obstet Gynecol 2014; 43: 508-514.
11. Kiserud I, Eik-Nes SH, Blaas HG, Hellevik LR. Ultrasonographic velocimetry of the fetal ductus venosus. Lancet 1991; 338: 1412-1414.
12. Baschat AA, Turan OM, Turan S. Ductus venosus blood-flow patterns: more than meets the eye? Ultrasound Obstet Gynecol 2012; 39: 598-599.
13. Hecher K, Campbell S, Snijders R, Nicolaides K. Reference ranges for fetal venous and atrioventricular blood flow parameters Ultrasound Obstet Gynecol 1994; 4: 381-390.
14. Hecker K, Campbell S, Doyle P, Harrington K, Nicoloides K. Assessment of fetal compromise by Doppler ultrasound investigation of the fetal circulation. Arterial, intracardiac and venous blood flow velocity studies. Circulation 1995; 91: 129-138.
15. Rizzo G, Arduini D, Romanni C: Doppler echocardiographic assessment of fetal cardiac function. Ultrasound Obstet Gynecol 1992; 2:434-45
16. Hecher K, Snijders R, Campbell S, Nicolaides K. Fetal venous, intracardiac and arterial blood flow measurements in intrauterine growth restriction: relationship with fetal blood gases. Am J Obstet Gynecol 1995; 173: 10-15.
17. Hecher K, Ville Y, Snijders R, Nicolaides K. Doppler studies of the fetal circulation in twin-twin transfusion syndrome. Ultrasound Obstet Gynecol 1995; 5: 318–324.
18. Kiserud T, Hellevik LR, Eik-Nes SH, Angelsen BA, Blaas HG. Estimation of the pressure gradient across the fetal ductus venosus based on Doppler velocimetry. Ultrasound Med Biol 1994; 20: 225-232.
19. Zielinsky P, Marcantonio S, Nicoloso LH, et al. Ductus venosus flow and myocardial hypertrophy in fetuses of diabetic mothers. Arq Bras Cardiol 2004; 83: 51-56.
20. Wong SF, Chan FY, Cincotta RB, McIntyre HD, Oats JJ. Cardiac function in fetuses of poorly-controlled pre-gesta-

tional diabetic pregnancies – a pilot study. Gynecol Obstet Invest 2003; 56: 113-116.
21. Kiserud T, Eiknes SH, Hellevik LR, Blaas HG. Ductus venosus blood velocity changes in fetal cardiac diseases. J Matern Fetal Invest 1993; 3: 15-20.
22. Turan OM, Turan S, Sanapo L, et al. Reference ranges for ductus venosus velocity ratios in pregnancies with normal outcomes. J Ultrasound Med 2014; 33: 329-336.
23. Smrcek JM, Krapp M, Axt-Fliedner R, et al. Atypical ductus venosus blood flow pattern in fetuses with severe tricuspid valve regurgitation. Ultrasound Obstet Gynecol 2005; 26: 180-182.
24. Turan S, Turan OM, Salim M, et al. Cardiovascular transition to extrauterine life in growth-restricted neonates: relationship with prenatal Doppler findings. Fetal Diagn Ther 2013; 33: 103-109.
25. Phillipos EZ, Robertson MA, Still KD. The echocardiographic assessment of the human fetal foramen ovale. J Am Soc Echocardiogr 1994; 7: 257-263.
26. Donofrio MT, Bremer YA, Moskowitz WB. Diagnosis and management of restricted or closed foramen ovale in fetuses with congenital heart disease. Am J Cardiol 2004; 94: 1348-1351.
27. Hagen A, Albig M, Schmitz L, et al. Antepartum diagnosis of isolated foramen ovale obstruction. A report of two cases. Fetal Diagn Ther 2005; 20: 70-73.
28. Chobot V, Hornberger LK, Hagen-Ansert S, Sahn DJ. Prenatal detection of restrictive foramen ovale. J Am Soc Echocardiogr 1990; 3: 15-19.
29. Liu L, He YH, Li ZA, et al. Diagnostic value of an ROC curve of the size of the antepartum foramen ovale in the prediction of puerperal atrial septal defect. Exp Ther Med 2013; 5: 1501-1505.