DOI: 10.1002/pd.4529

ORIGINAL ARTICLE

Dynamics of pulmonary venous flow in fetuses with intrauterine growth restriction

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ABSTRACT

Objective To test the hypothesis that the pulmonary vein pulsatility index (PVPI) is higher in fetuses with growth restriction (IUGR) than in normal fetuses.

Methods Twenty-two fetuses with IUGR and twenty-one (21) fetuses with appropriate growth for gestational age from healthy mothers were studied. PVPI was calculated by Doppler echocardiography [maximal velocity (systolic or diastolic peak) – pre-systolic peak / mean velocity]. Obstetric ultrasound was used to assess fetal biometry and Doppler to assess the uterine, umbilical and middle cerebral arteries PI. Statistical analysis used *t* test and Pearson's correlation.

Results Mean gestational age was 31.5 +/− 2.1 weeks in the control group and 31.4 +/− 3.1 weeks in IUGR ($P = 0.91$). The PI of uterine and umbilical arteries were higher in IUGR than in controls ($P < 0.001$). Mean PVPI in IUGR fetuses was 1.31 +/− 0.41, and in controls it was 0.83 +/− 0.11 ($P < 0.001$).

Conclusion The pulsatility index of pulmonary venous flow in fetuses with growth restriction is higher than in normal fetuses, probably as a result of left atrial dynamics alteration secondary or not to fetal left ventricular diastolic dysfunction. © 2014 John Wiley & Sons, Ltd.

Funding sources: This study was supported in part by grants of CAPES Foundation (Coordination of Improvement of Higher Education Personnel), CNPq (National Council of Technological and Scientific Development), FAPERGS (State of Rio Grande do Sul Agency for Research Support) and FAPICC (Institute of Cardiology Fund for Research and Culture Support), Brazil.
Conflicts of interest: None declared

INTRODUCTION

Intra-uterine growth restriction (IUGR) is associated with high rates of perinatal and childhood morbidity and mortality.[1] Low birth weight has been associated with increased risk of cardiovascular disease and type II diabetes in adulthood. IUGR prevalence is variable (8 to 17% of pregnancies), according to the population studied, the criteria used to confirm gestational age and the growth curve applied.[2,3] The most common cause of IUGR (30 to 40%) is maternal systemic arterial hypertension caused by changes in placental vascular bed and subsequent reduction of its functional area in both hypertensive disorders of pregnancy (HDP) and chronic arterial hypertension (CH).[4]

Assessment of fetal–placental hemodynamics by Doppler ultrasound has been widely reported. Several studies have shown that changes in systemic venous blood flow waveforms occur after umbilical arterial alterations and are significantly correlated with severe complications and increased mortality. Therefore, systemic venous Doppler investigation is more important than arterial Doppler in predicting neonatal adverse effects.[5] Absent end-diastolic or reversed flow in the ductus venosus and pulsations in the umbilical vein are associated with fetal acidemia and may be a reason to optimize the delivery time.[6,7]

The Doppler pattern of pulmonary venous flow is similar to that of ductus venosus (Figure 1-A). In situations of reduced compliance of the left ventricle (LV), the presystolic component (A wave) of the pulmonary vein will be decreased, absent or reversed, with consequent increase in PI, representing the increased impedance to left atrial inflow[8] (Figure 1-B). It has already been shown that the pulmonary vein PI can be a Doppler-echocardiographic useful parameter to assess diastolic function of the fetal left heart, since it reflects left atrial dynamics.[8,9] However, its usefulness in assessing LV diastolic dysfunction in IUGR has not been established.[10,11] The aim of this study was to test the hypothesis that the PVPI in fetuses with IUGR is higher than in fetuses with adequate growth.

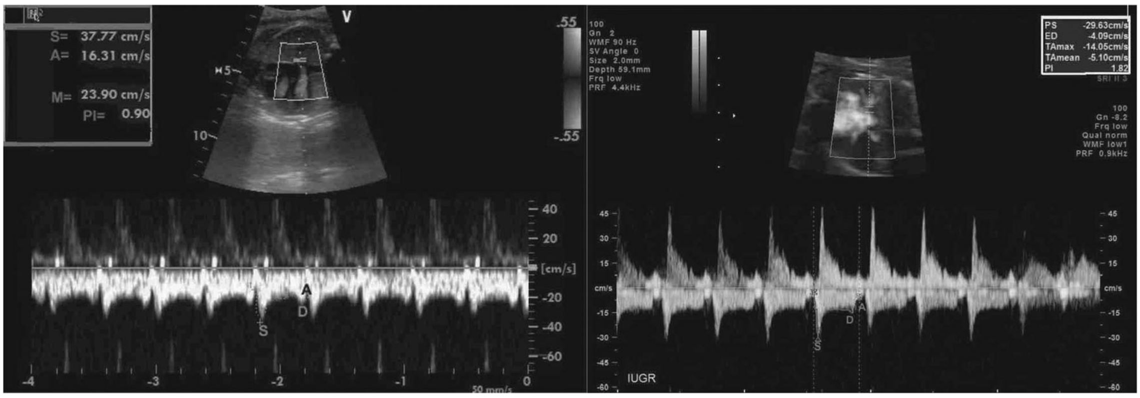

Figure 1 (A) Doppler tracing of a typical normal pulmonary vein flow (3-flow waves): S, systolic; D, diastolic and A, presystolic. Pulsatility index (PI) is 0.9. (B) Pulmonary vein pulsatility index (PVPI) obtained in a fetus with IUGR. Velocities were electronically calculated after manual tracing of waveforms. S, systolic peak; D, diastolic peak; A, presystolic velocity (a wave); M, mean velocity; PI, pulsatility index. PVPI is 1.82

METHODS

This is a prospective, observational cross-sectional study assessing 45 fetuses with gestational age from 25 weeks to term followed at three tertiary centers of Fetal Cardiology.

A power analysis was performed to calculate the effect size, based on previous publication on fetal pulmonary veins pulsatility index in fetuses of diabetic mothers, and the results suggested a necessary sample size of 15 fetuses for each group, for an alpha of 5% and a power of 20%.[12] The mothers were divided into two groups. The first group included 24 pregnant women whose fetuses were diagnosed as IUGR with fetal Doppler abnormalities. The control group was made up by 21 pregnant women without systemic diseases and whose fetuses had normal development. Gestational age (GA) was confirmed by the date of the last menstruation or early first trimester ultrasound. Fetuses were included in this study when the ultrasound images obtained were of adequate quality. After delivery, 2 newborns were excluded from the IUGR group, because their weights were higher than the 10^{th} percentile for gestational age, differently than the weights estimated at fetal examination, leaving the study group with 22 fetuses. All the other cases showed concordance between fetal and neonatal weights.

Twin fetuses, fetuses with a gestational age below 25 weeks, or with any other structural or functional abnormalities and those whose mothers had diseases not related to IUGR, were excluded.

All women included in this study were examined only once using ultrasound and echocardiography equipments with 3.0–5.0 MHz convex transducers, and presets for obstetrics and fetal cardiology, 2D/3D/4D images, M-mode and Doppler modes (pulsed, continuous, power and color mapping). Obstetric ultrasound was performed in all pregnant women to assess fetal morphology, amniotic fluid (AF) and fetal biometry. Biparietal diameter (BD), femur length (FL), head circumference (HC) and abdominal circumference (AC) were obtained, according to Hadlock *et al.*[13] The AF index was calculated by the sum of amniotic fluid depths at the four quadrants of the maternal abdomen.[14] Doppler velocimetry ultrasound was performed in all patients at the same time as fetal echocardiography. Fetoplacental flow analysis was performed with color mapping and pulsed Doppler using standardized techniques to analyze flow of the umbilical cord vessels, middle cerebral vessels and uterine arteries.[15] The average of three measures obtained in fetuses in apnea and without body movements were used. Venous and arterial flows were studied, and the pulsatility (PI) indexes of the arterial vessels (umbilical, cerebral medium and uterine) were obtained.

Diagnosis of IUGR was considered when the fetal weight was below the 10^{th} percentile for gestational age, using Lubchenco *et al.* fetal growth curves and classified as severe in those with body weight below the third percentile.[16,17] Only fetuses with altered umbilical Doppler velocimetry were included. Criteria for altered obstetric Doppler were (i) increased umbilical artery systole/diastole ratio and, (ii) either uterine or umbilical artery PI at least two standard deviations above normal values for gestational age.[18] Fetal echocardiography was performed in all pregnant women according to sequential segmental approach. To analyze the pulmonary venous flow, the Doppler sample volume was placed at the right superior pulmonary vein adjacent to the venoatrial junction ("distal position") guided by color-flow mapping or power-angio Doppler. Scales of 0–20 cm/s and filters of 50–100 Hz were used, and three measurements were obtained in apnea. In all fetuses, the pulmonary vein pulsatility index [peak velocity (systolic or diastolic) minus pre-systolic velocity/mean velocity] was calculated by the equipment after manual tracing of the pulmonary venous flow waveform. All records were stored in CD, DVD and USB drive for calculation of the inter- and intra-observer variability in 10 samples of each group.[19] Informed consent was obtained in all cases. The Institutional Ethical Committee of both participating centers approved this study.

Statistical analysis

The distribution of variables was expressed as mean and standard deviation. Student's *t*-test and Pearson's correlation were used to compare the two groups. Inter- and intra-observer variabilities were evaluated in 10 samples from each group using the Bland–Altman test, and plots were created to show the mean differences between the measurements. A critical alpha of 0.05 was used. Statistical analysis was performed using SPSS version 21.0.

RESULTS

Mean maternal age in group 1 (IUGR) was 30.5 +/− 4.7 years (18 to 43 years) and in group 2 (healthy pregnancies) was 26.8 +/− 6.9 years (25 to 36 years) ($P = 0.08$). Mean gestational age was, respectively, 31.4 +/− 3.1 weeks in cases with IUGR, and 31.5 +/− 2.1 weeks in the control group ($P = 0.91$). Among the risk factors associated with fetal growth restriction, the most frequent was maternal hypertension (64%), followed by environmental factors (drug addition, smoking) and placental disease. Mean right uterine, left uterine and umbilical arteries PI in the group with IUGR were higher than in the control group ($P < 0.01$, $P = 0.01$ and $P < 0.01$, respectively). Mean value of cerebral artery PI in group 1 were lower than in the healthy group ($P = 0.013$). P values and mean values of PVPI and PI of arterial vessels are shown in Table 1. The PVPI in fetuses with IUGR was higher (1.30 +/− 0.40) than in normal fetuses (0.83 +/− 0.11) with a significant difference between the groups ($P < 0.001$) (Figure 2). Prospectively, in group 1 a moderate correlation was demonstrated between PVPI and PI of umbilical artery ($r = 0.326$), but not with middle cerebral artery ($r = 0.1$) (Figure 3). Mean differences between for intra- and interobserver measurements were 0.04 and −0.045, with coefficients of 0.96 and 0.95 (Figures 4 and 5).

DISCUSSION

The classical approach to fetal diastolic function utilizes the analysis of mitral and tricuspid flows, both by conventional Doppler and tissue Doppler, or else by the analysis of isovolumetric relaxation time.[20,21] However, since in the fetal circulation the ventricles are interdependent, other parameters which reflect left atrium (LA) dynamics, such as pulmonary veins pulsatility index, should be added.[22,23]

This study shows that fetuses with IUGR have an increased PVPI, when compared to fetuses with adequate growth from healthy mothers. The increase in LA pressure with consequent reduction of the "a" wave velocity in the pulmonary vein could explain the elevation of PVPI. This phenomenon may be

Table 1 Maternal, fetal and placentary Doppler parameters (PI) in IUGR and control groups

PI	Group 1	Group 2	P value
L Ut	1.41 +/− 0.55	0.72 +/− 0.2	<0.01
R Ut	1.29 +/− 0.64	0.72 +/− 0.13	0.01
UA	1.31 +/− 0.39	0.89 +/− 0.16	<0.01
MCA	1.51 +/− 0.42	1.8 +/− 0.25	0.013
PV	1.30 +/− 0.40	0.8 +/− 0.11	<0.01

PI values of arteries and pulmonary veins in fetuses with IUGR (group 1) and in fetuses from healthy mothers with weight appropriate for gestational age (group 2). Values are mean +/− SD. Mean values indicated by the same letter differed significantly by *t*-test ($\alpha = 5\%$). L Ut, left uterine artery. R Ut, right uterine artery. UA, umbilical artery. PV, pulmonar vein. PI, pulsatility index.

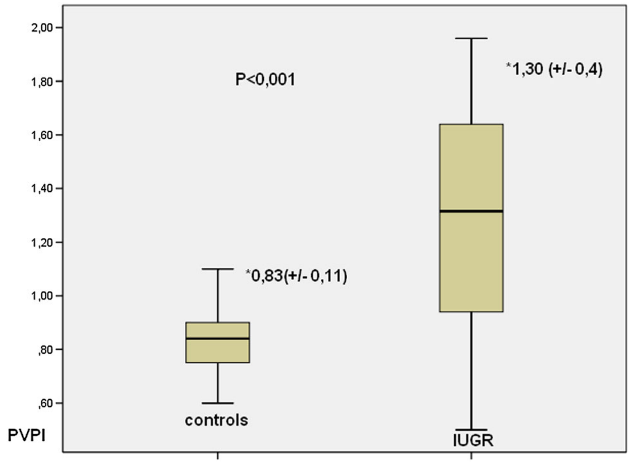

Figure 2 Comparison of pulmonary vein pulsatility index (PVPI) between fetuses with normal growth (group2) and IUGR fetuses (group 1). Horizontal bars above and below median boxes represent maximal and minimal values of PVPI. (*) PVPI mean values

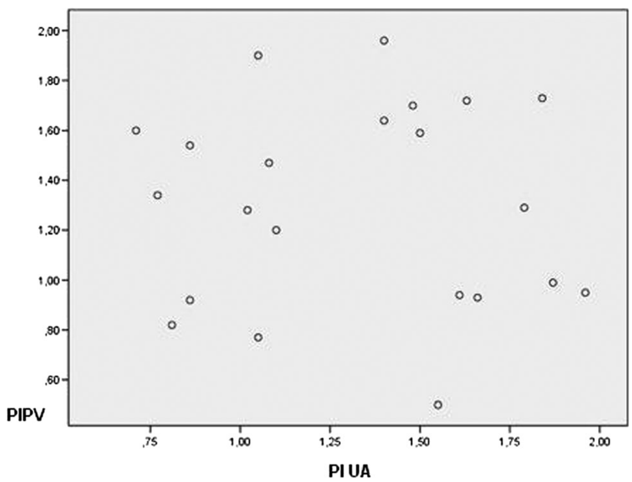

Figure 3 Diagram depicting moderate correlation with umbilical artery PI (UA PI) and PVPI

secondary to decreased LV compliance, as already demonstrated in other studies.[8,24] Alternatively, left atrial dynamics could be abnormal in IUGR due to redistribution of flow.

In IUGR there are changes in fetal cardiac dynamics, as a result of alterations in preload and afterload, ventricular compliance and myocardial contractility. The increase in uteroplacental vascular impedance and right ventricular preload contribute to a preferential flow to the LV, associated with decreased LV compliance and increased left atrial pressure. LV function assessment in the fetus is difficult due to the large amount of functional reserve of the fetal myocardium. One question is: why does the LV manifest filling abnormalities that reflect diastolic dysfunction while the RV does not. We speculate that this could be explained by differences in atrial filling dynamics between the RV and LV. It is known that the arterial diastolic pressure of fetuses with IUGR is higher and therefore the wall stress is increased in both ventricles. The LV findings in IUGR including those in this

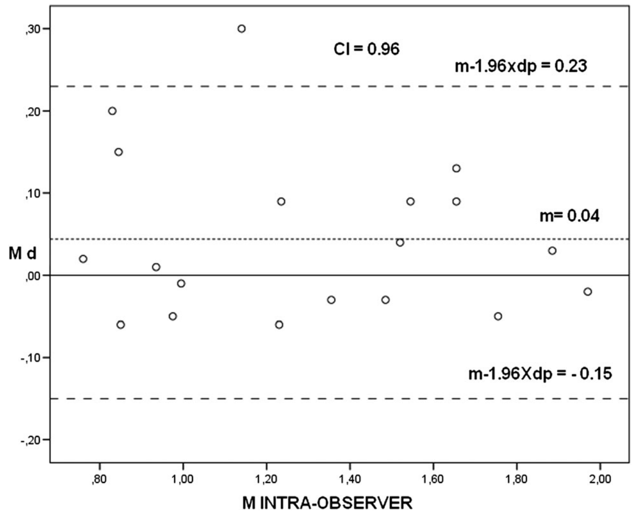

Figure 4 Bland–Altman plots showing intra-observer variation in measurements of PIPV. PIPV, pulsatility index of pulmonay vein. M, mean. Md, mean difference between the measurements made by the same observer in. CI, confidence interval

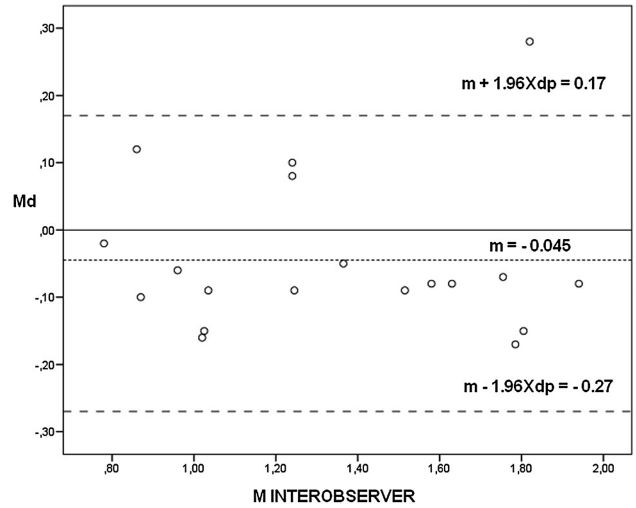

Figure 5 Bland–Altman plots showing interobserver variation in measurements of PIPV. PIPV, pulsatility index of pulmonay vein. M, mean. Md, mean difference between the measurements made by two observers in. CI, confidence interval.

study may be present related to the differences in LA function and loading. Therefore, the filling abnormalities noted at the mitral valve may not reflect intrinsic LV myocardial changes.

Several studies on myocardial motion and cardiac deformation in IUGR have been reported. Traditionally, M-mode is a very sensitive tool for cardiac measurements and it has been shown that it can be used in both mitral and tricuspid annuli (TAPSE and MAPSE) with good correlation with tissue Doppler to detect subclinical cardiac dysfunction in IUGR.[21] In fetuses with IUGR, E/A ratio obtained by the pulsed Doppler is lower, and tissue Doppler imaging has demonstrated lower systolic and diastolic myocardial velocities in mitral and tricuspid annulus with higher E′/A′ ratios[22] The myocardial performance index (MPI) is an earlier marker of cardiac dysfunction in chronic hypoxia with predictive value for perinatal death in preterm IUGR fetuses, and left MPI provides information on systolic and diastolic LV function.

Recent studies have demonstrated that children who had been exposed to IUGR show more globular cardiac shaped and increased carotid wall and LV thickness, reflecting remodeled and less efficient hearts in childhood.[25] The cardiac irregularity shape can be assessed by echocardiographic sphericity index, calculated by the base-to-apex ventricular length/basal diameter. Another technique is the speckle tracking (2D strain), which can evaluate myocardium deformation. In a postmortem study, it was shown that the cardiac dysfunction in IUGR is associated with ultrastructural cardiomyocyte changes in the form of shorter sarcomere length.[26] These findings could explain the Baker hypothesis of fetal developmental origins of cardiovascular disease in adulthood. Additionally, since diastolic function depends on ventricular shape it could be another explanation as to why the elevated PVPI in IUGR fetuses demonstrated in our study could be secondary to LV dysfunction.

In this study, the increased impedance to LA filling was assessed by the PVPI, evaluating the effects of flow redistribution to the left heart in IUGR. The elevated impedances in umbilical and uterine arteries in fetuses of the group IUGR, when compared to controls, were expected. We also found a moderate correlation between PVPI and umbilical artery PI but not with MCA PI, since many of these fetuses were not centralized.

The PVPI was easy to obtain and had a high reproducibility as shown in the present study.[9,12] Since diastolic dysfunction precedes systolic dysfunction and fetal deterioration, PVPI could be used as a cardiac monitoring parameter in IUGR.

In conclusion, the present study demonstrated that fetuses with IUGR show an increased PVPI when compared to normal fetuses, reflecting altered left atrial dynamics and/or left ventricular diastolic dysfunction. This Doppler parameter is easy to obtain, reproducible and may be utilized as a good parameter to assess cardiac dynamics in IUGR.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- In IUGR fetuses, the hemodynamic changes in the left heart due to the preferential flow to the LV are associated with a decrease in LV compliance and an increase in LA pressure.
- The pulmonary veins flow pulsatility index is a good Doppler parameter to assess left atrial events. However, its applicability in IUGR has not yet been demonstrated.

WHAT DOES THIS STUDY ADD?

- It was shown that the pulmonary vein pulsatility index (PVPI) is higher in fetuses with IUGR.
- We propose the use of the fetal PVPI as a reproducible echocardiographic parameter to assess LV diastolic function and/or LA dynamics in IUGR.

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