

# Myocardial Velocities, Dynamics of the Septum Primum, and Placental Dysfunction in Fetuses with Growth Restriction

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## ABSTRACT

**Introduction.** Diastolic dysfunction may occur in fetuses with intrauterine growth restriction (IUGR) and may be assessed by myocardial tissue Doppler (MTD). We previously have shown that excursion index of the septum primum (EISP) is reduced in IUGR fetuses over 30 weeks because of a higher left atrial pressure.

**Patients, Setting, and Design.** The sample was made up of 14 fetuses with IUGR. MTD examination was carried out with the sample volume placed at the basal lateral wall of the left ventricle (LV), interventricular septum (IVS), and free wall of the right ventricle (RV) to determine E'/A' ratios. EISP was calculated as the ratio between the maximal excursion of the septum primum into the left atrium during diastole and the maximal diastolic diameter of the left atrium. Mitral and tricuspid flows were assessed by the conventional Doppler method.

**Outcome Measures.** Pearson's correlation test was used to analyze the correlations between the parameters.

**Results.** A positive correlation was observed between UARI and E'/A' ratios for RV ( $r = 0.63$ ,  $P = .02$ ), IVS ( $r = 0.59$ ,  $P = .03$ ), and LV ( $r = 0.41$ ,  $P = .15$ ). There was a negative correlation between EISP and IVS E'/A' ratios ( $r = -0.58$ ,  $P = .03$ ), and a positive correlation for LV ( $r = 0.49$ ,  $P = .08$ ). At the RV position, a weak negative correlation was observed ( $r = -0.32$ ,  $P = .26$ ).

**Conclusions.** A higher left atrial pressure in fetuses with IUGR, indicated by the lower mobility of the septum primum, is accompanied by higher ratios between early and late diastolic myocardial velocities. Placental dysfunction was correlated to septal E'/A' ratios. Fetal MTD can be a useful method to assess severity of placental dysfunction and fetal distress.

**Key Words.** Myocardial Tissue Doppler; Septum Primum; Fetal Heart Function; Diastolic Dysfunction; Intrauterine Growth Restriction; Placental Insufficiency

## Introduction

Placental dysfunction, characterized by increased vascular resistance and decreased placental blood flow, is an important cause of intrauterine growth restriction (IUGR).<sup>1,2</sup> This condition, which involves acidosis and hypoxia, prematurity, and fetal death,<sup>3</sup> affects more than 10% of pregnancies.<sup>4</sup> Early diastolic dysfunction, one of the complex heart abnormalities observed in these cases,<sup>5</sup> can be evaluated by mitral and tricuspid flow,<sup>6–8</sup> excursion index of the septum primum (EISP),<sup>9</sup> and fetal myocardial tissue Doppler (MTD).<sup>10</sup> These methods may be more sensitive in the determination of changes in the

fetal clinical conditions related to hypoxemia than assessment of the fetal biophysical profile and that of flow modifications in the ductus venosus, cerebral arteries, and umbilical vessels.<sup>4–11</sup>

MTD is a technique that allows the measurement of myocardial velocities during systole and diastole with fewer limitations in comparison with conventional Doppler echocardiographic assessment of tricuspid or mitral transvalvular flow, particularly in cases of high heart rate and under preload and afterload conditions.<sup>12,13</sup> Naujorks et al.<sup>10</sup> demonstrated that the E'/A' ratio between myocardial velocity waves is significantly higher in IUGR fetuses, findings confirmed by Comas et al.<sup>14</sup> Hatém et al.<sup>15</sup> reported that MTD shows

evidence of impaired diastolic function in fetuses of diabetic mothers as compared with fetuses of nondiabetic mothers. Similarly, Zielinsky et al.<sup>9</sup> observed a reduction of EISP in fetuses with IUGR over 30 weeks. In these previous studies, MTD<sup>10,15</sup> and EISP<sup>16</sup> were more sensitive than conventional Doppler in assessing atrioventricular flow for the diagnosis of fetal diastolic dysfunction.

Correlations between MTD in IUGR fetuses and other indices of diastolic function, such as EISP, and between MTD and the level of placental resistance have not been previously studied. This study was designed to obtain this information.

## Methods

In this cross-sectional study, the sample was composed of 14 fetuses with weights below the 10th percentile for gestational age. Gestational age was previously determined by routine obstetrical ultrasound before the 16th week. Fetuses with congenital malformations or arrhythmias, as well as fetuses of mothers presenting drug addiction, smoking habits, and systemic diseases other than hypertension, were excluded.

Measurements taken from the 25th week of pregnancy onward included abdominal circumference; femur length; estimated weight (Hadlock formula<sup>17</sup>); placenta thickness; amniotic fluid volume; and flow velocity of umbilical artery, middle cerebral artery and uterine arteries.<sup>2</sup> Umbilical artery flow curves were assessed using the ratio of maximum (systolic) and minimum (diastolic) velocities in a free loop of the umbilical cord. The umbilical artery resistance index (UARI) was calculated from this ratio.

Fetal echocardiographic examinations were performed with ultrasonographic equipment models Vivid 3 Expert and Vivid 7 (GE Medical Systems, General Electric Company, Fairfield, CT, USA) with electronic transducers, obtaining second harmonic images with frequencies of 1.7–5 MHz. Flow analysis was performed with pulsed Doppler and color flow mapping. Flow velocity waveforms at the atrioventricular valves were assessed from the 4-chamber apical view. The mean of 3 measurements of peak E and A flow velocities was recorded. The E/A ratio was calculated from the mean value of each variable. MTD examination was carried out by pulsed Doppler with the sample placed in the basal myocardial segments in three positions: lateral wall of the left ventricle (LV), interventricular septum (IVS), and free wall of the right ventricle (RV).<sup>10,14,18</sup> Mean

values of early diastolic waves (E') and late diastolic or atriogenic waves (A') were recorded. The ratio between mean E' and A' velocities in each position, as well as the ratio between E waves of mitral and tricuspid inflow and tissue E' waves of the LV lateral wall and RV free wall (E/E' ratios), were established. All measurements were performed during periods of fetal apnea.

EISP was calculated as the ratio between the maximal excursion of the septum primum into the left atrium during diastole (A) and the maximal diastolic diameter of the left atrium (B).<sup>19</sup> The AB ratio (linear EISP) was determined considering the mean value of three consecutive measurements in apnea.

All the pregnant women signed a term of informed consent, and the study was approved by the Medical Research Ethics Committee of the Instituto de Cardiologia do Rio Grande do Sul/Fundação Universitária de Cardiologia.

Data were analyzed using the statistical software SPSS version 15.0 (IBM Corporation, Armonk, NY, USA). The quantitative variables were described as mean and standard deviation. Pearson's correlation test was used for correlation studies, and the significance level was  $P < .05$ . Chi-square tests for normal distribution were applied and showed all data to be normally distributed.

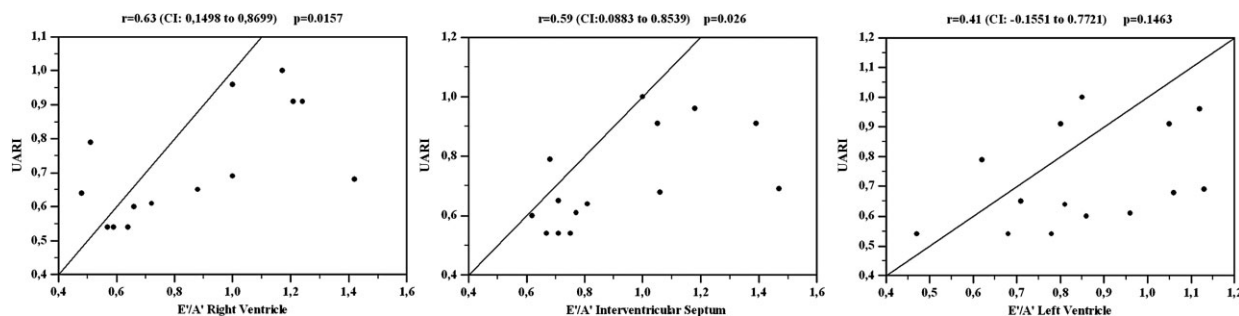
## Results

Correlation analyses were performed between the variables. Between UARI and E'/A' ratio (Figure 1), strong positive correlation was observed at the RV ( $r = 0.63$ ,  $P = .02$ ) and IVS ( $r = 0.59$ ,  $P = .03$ ) positions, but only a weak and non-significant correlation at the LV position ( $r = 0.41$ ,  $P = .15$ ).

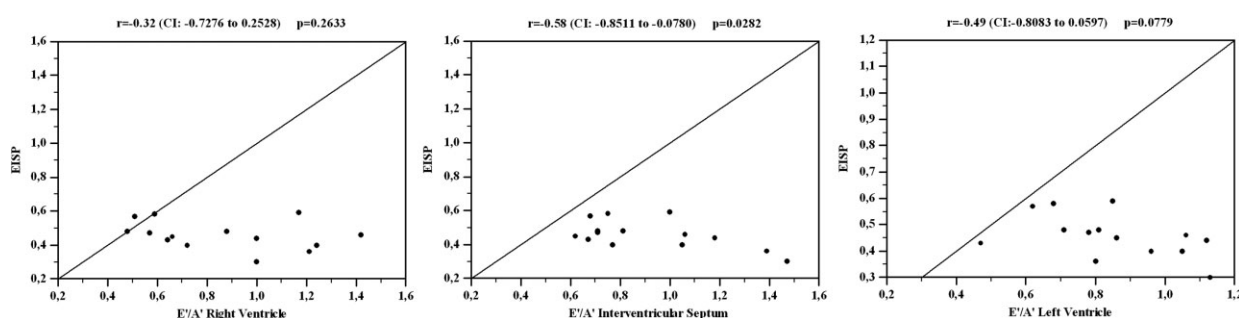
Analyzing the correlation between EISP and E'/A' (Figure 2), a statistically significant negative correlation was observed at IVS ( $r = 0.58$ ,  $P = .03$ ) and a lack of correlation at LV ( $r = 0.49$ ,  $P = .08$ ). A weak correlation was observed for the RV position ( $r = 0.32$ ,  $P = .26$ ).

No correlation was observed between EISP and UARI ( $r = 0.03$ ,  $P = .9$ ). Even when IUGR cases with gestational age above 30 weeks ( $n = 11$ ) were analyzed separately, there was no correlation between these parameters ( $r = 0.06$ ,  $P = .8$ ).

Weak and nonsignificant correlations were observed between the E wave of mitral and tricuspid ventricular filling and the E' wave obtained by MTD at the LV and RV walls ( $r = 0.44$ ,  $P = .17$  between E/E' and E'/A' in the RV;  $r = 0.03$ ,  $P = .93$



**Figure 1.** Correlations between UARI and E'/A' ratios at the right ventricular free wall, interventricular septum, and lateral wall of the left ventricle. LV, left ventricle; RV, right ventricle; UARI, umbilical artery resistance index.



**Figure 2.** Correlations between EISP and E'/A' ratios at the right ventricular free wall, interventricular septum, and lateral wall of the left ventricle. LV, left ventricle; RV, right ventricle; EISP, excursion index of the septum primum.

between E/E' and E'/A' in the LV). Similarly, the results showed no significant correlation between E/E' ratios and EISP ( $r = 0.23$ ,  $P = .49$  in the RV;  $r = 0.47$ ,  $P = .09$  in the LV), and a weak correlation between E/E' ratios and UARI ( $r = 0.22$ ,  $P = .44$  between UARI and E/E' in the RV;  $r = 0.29$ ,  $P = .32$  between UARI and E/E' in the LV).

## Discussion

The use of MTD for assessment of basal myocardial velocities in fetuses with IUGR showed the existence of a negative correlation between the ratio of early and late velocities (E'/A' ratio) and EISP in the IVS position and of a positive correlation between E'/A' and UARI in the RV and IVS positions.

Previous investigations of fetal diastolic function have analyzed primarily mitral and tricuspid flows, showing that the normal ratio of influx E and A waves is maintained below 1 during fetal life.<sup>8,20</sup> However, Hatém and colleagues<sup>15</sup> observed that, in fetuses of diabetic mothers, the E/A ratio for atrioventricular blood flow may not change in many cases of diastolic dysfunction detected by MTD. The present study also showed that mitral

and tricuspid E/A ratios were normal in fetuses with IUGR, but the mean E'/A' ratio was greater than 0.8 in all positions evaluated. Another study of the same group showed that this parameter was statistically higher in IUGR fetuses than in fetuses with normal growth from both hypertensive and normotensive mothers.<sup>10</sup>

Studies that analyzed the mobility of the septum primum in the developing of human fetus<sup>19</sup> led to the determination of the EISP, defined as the ratio between the maximal excursion of the valve into the left atrium during diastole and the maximal diameter of the left atrium. The EISP seems to depend on the volume of blood from the venous duct and the right atrium (preload) and on the left atrial pressure, which can be increased in the presence of left ventricular diastolic dysfunction.<sup>21</sup> Lower EISP has been reported in fetuses at over 30 weeks of gestation with IUGR due to placental insufficiency,<sup>9</sup> and similar results have been reported in a study that assessed this index in fetuses of diabetic mothers.<sup>15</sup> In accordance with previous reports, the present study showed that flow velocities through the mitral and tricuspid valves were not significantly altered in IUGR, despite the reduction in mobility of the septum primum. These data

strengthen the idea that EISP is a more sensitive parameter for assessment of diastolic function in these fetuses than atrioventricular flows. Its specificity, however, deserves future attention in further studies. In our study, analysis of variability to EISP measurements was limited by the small sample. A previous study<sup>22</sup> including a larger sample of normal fetuses showed good intraobserver reproducibility (5.5% intraobserver variability) for EISP measures.

MTD is a Doppler echocardiographic technique that allows the measurement of myocardial velocities in systole and diastole with fewer limitations in cases of high heart rate and under preload and afterload conditions.<sup>13</sup> In a previous study,<sup>10</sup> good reproducibility for intra- and interobserver MTD E'/A' ratios in IUGR fetuses was demonstrated. In the fetus, where the analysis of diastolic function requires the examination of the two ventricles, tissue Doppler is a potential non-invasive method for analysis of left and right diastolic function. Harada et al.<sup>18</sup> have described the normal values and the changes related to gestational age. Gardiner et al.<sup>23</sup> found an almost linear correlation of MTD parameters and myocardial longitudinal excursion velocities with the advancement of gestational age and fetal myocardial maturation in both ventricles, regardless of load conditions. Our results showed a strong positive correlation between UARI and the E'/A' ratio in RV free wall and basal interventricular septum. On the lateral wall of the LV, the correlation was not significant, an issue that could be attributable to the small sample size. These findings support the idea that more severe placental dysfunctions, as determined by UARI, correlate with higher E'/A' ratios. This variable can therefore indicate a greater degree of fetal hypoxia and be an additional tool for the ultrasound follow-up of fetal functional status in cases of IUGR.

The correlation between E waves of atrioventricular flow and E' recorded by MTD at the lateral walls of the LV or RV (E/E') is significantly lower in fetuses of diabetic mothers, regardless of the presence of ventricular hypertrophy.<sup>15</sup> Our study found no correlation of E/E' ratios with UARI or EISP. However, E/E' ratios are lower when compared with normal control fetuses investigated in previous studies by our group.<sup>10,15</sup> Future studies with larger samples can corroborate the hypothesis that higher E' velocities of basal myocardium, along with unaltered velocities of mitral and tricuspid E waves, occur in situations of lower ventricular compliance at early diastole and that E/E' ratios could

also be sensitive parameters for the investigation of IUGR and fetal myocardial dysfunction.

The main limitation of our study is the small sample size. Gestational age was determined by first-trimester ultrasound, since this method is considered more accurate than the date of the last menstruation.<sup>24</sup> Another factor that contributed to limit the sample size was the exclusion of cases where other maternal or fetal abnormalities were present that could be related to the diagnosis of IUGR. However, we chose to study a more specific sample in relation to the diagnosis of IUGR due to placental insufficiency (Table 1). The 10th percentile is widely used for diagnosing IUGR.<sup>4</sup> Data were not adjusted for gestational age, although all subjects were in the third trimester, with small variation of gestational age. Because of the small number of IUGR fetuses below 30 weeks of gestational age (4 cases in 14), a stratified analysis by gestational age was not performed and, in our study, the correlation between EISP and UARI was not confirmed. A previous study by our group showed good reproducibility of measurements of myocardial velocities in normal and IUGR fetuses.<sup>10</sup> Despite these limitations, our data may help to reinforce that fetal myocardial tissue Doppler can be a useful method in early assessment of the severity of placental dysfunction and fetal distress. Other studies, with larger sample number and stratification by gestational

**Table 1.** Maternal and Fetal Characteristics and Doppler-velocimetric Evaluation in 14 Fetuses with IUGR

| Variable                             | (n = 14)    |
|--------------------------------------|-------------|
| <b>Maternal</b>                      |             |
| Maternal age (y)                     | 26.2 ± 6.0  |
| Pregnancy age (wk)                   | 32.2 ± 2.6  |
| Initial weight (kg)                  | 56.2 ± 8.8  |
| Initial body mass index              | 21.1 ± 2.4  |
| Primiparity (%)                      | 7 (50.0)    |
| Hematocrit (%)                       | 31.2 ± 1.5  |
| Previous abortions (%)               | 1 (7.1)     |
| <b>Fetal Doppler</b>                 |             |
| MCA resistance index                 | 0.71 ± 0.10 |
| UA resistance index                  | 0.72 ± 0.16 |
| MCA/UA ratio                         | 1.02 ± 0.21 |
| <b>Transvalvar Doppler</b>           |             |
| Mitral E/A relationship              | 0.79 ± 0.16 |
| Tricuspid E/A relationship           | 0.77 ± 0.1  |
| <b>Myocardial tissue Doppler</b>     |             |
| E'/A'—LV side wall                   | 0.85 ± 0.19 |
| E'/A'—Interventricular septum        | 0.92 ± 0.28 |
| E'/A'—RV side wall                   | 0.86 ± 0.31 |
| LV E/E'                              | 5.5 ± 1.5   |
| RV E/E'                              | 6.5 ± 1.5   |
| Excursion index of the septum primum | 0.46 ± 0.08 |

LV, left ventricle; MCA, middle cerebral arteries; RV, right ventricle; UA, umbilical arteries.



age and by the degree of placental dysfunction, should be conducted in the future.

In conclusion, higher interventricular septal E'/A' ratios as determined by MTD are correlated to lower mobility of the septum primum. Also, we find correlation between UARI and E'/A' ratios in the RV and interventricular septum. E'/A' ratios may be a parameter even more sensitive than EISP in detection of fetal diastolic dysfunction in situations of placental dysfunction.

### Author Contributions

AAN and PZ participated in study design and coordination and drafted the manuscript. EB, LHN, ALP, and RF participated in data acquisition and data analysis and interpretation. CB, SB, ML, and CK performed bibliographic research. All authors read and approved the final manuscript.

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