Original paper

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Assessment of modified myocardial performance index in foetuses with growth restriction

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Abstract

Aim: To evaluate the modified myocardial performance index (Mod-MPI) in foetuses with growth restriction and compare this index with appropriate for gestational age foetuses. **Material and methods:** A prospective cross-sectional case-control study was conducted involving 76 singleton foetuses between 24 and 34 weeks of gestation divided into three groups (24 appropriate growth foetuses, 30 foetuses with estimated weight between the 3rd and 10th percentiles and 22 foetuses with estimated weight < 3rd percentile, according to the Hadlock table). The Mod-MPI was obtained in the plane of the four chamber view, and the spectral Doppler sample volume was placed in the lateral wall of the aorta, close to the mitral valve. Doppler of umbilical artery was normal in all cases. Analysis of variance (ANOVA) was used to compare the groups and the intra-class correlation coefficient (ICC) was used to assess intra- and inter-observer reproducibility. **Results:** The mean Mod-MPI in the groups of appropriate for gestational age, estimated weight between the 3rd and 10th percentiles, and estimated weight < 3rd percentile was 0.32 ± 0.05, 0.35 ± 0.05 and 0.36 ± 0.06, respectively; there was no statistical difference between the groups ($p = 0.072$). There was good intra- and inter-observer reproducibility (ICC = 0.726 and 0.760, respectively). **Conclusion:** Mod-MPI was not significantly different between foetuses appropriate for gestational age and those with growth restriction. Mod-MPI proved to be a feasible and reproducible technique.

Keywords: foetus, growth restriction, myocardial performance index, umbilical Doppler artery

Introduction

Foetal growth restriction (FGR) can be broadly defined as a pathologic process that modifies the growth potential of the foetus and restricts its intra-uterine development [1]. In clinical practice, the diagnosis of growth restriction is based on an estimated foetal weight <10th percentile, which is obtained by an ultrasound scan. Nowadays, the differentiation between FGR which is associated with foetal-placental deterioration and adverse perinatal outcomes and small for gestational age (SGA) foetuses which is associated with favourable perinatal outcomes is of great importance. This differentiation is easier when it is associated beyond foetal biometry, the estimated foetal weight <3rd percentile for gestational age and pulsatility index (PI) middle cerebral artery / PI umbilical artery Doppler ratio <1. In the last decades, when the SGA was defined with normal PI of umbilical artery Doppler, these foetuses have presented worse perinatal outcomes than foetuses with normal biometric parameters. So, the PI of umbilical artery Doppler cannot be used alone to differentiate FGR and SGA [2].

FGR greatly contributes to perinatal morbidity and mortality compared with foetuses with appropriate growth, with a high risk for sudden intra-uterine death, which is closely associated with FGR severity [3,4]. The

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rate of perinatal mortality is also higher among foetuses with FGR and the mortality risk is two to five times higher than that of normal foetuses [5]. The highest mortality rates are reported for foetuses with umbilical artery Doppler with absent or reversed diastolic flow [6]. However, SGA foetuses with normal PI of umbilical artery Doppler are associated with adverse perinatal outcomes, mainly in foetuses with an estimated weight <3rd percentile for gestational age.

Ductus venosus Doppler is a useful method for monitoring foetal well-being and evaluating the need to interrupt pregnancy, particularly in cases of absent or late signs of foetal impairment, including acidaemia, myocardial necrosis, and perinatal death [7,8]. In addition, this method does not assess the risk of neurological morbidity, which may occur in pre-acidotic stages [9].

The myocardial performance index (MPI) is a Doppler index that combines diastolic and systolic functions. It is increased in foetuses with FGR [10,11] and is linearly correlated with the severity of the haemodynamic status. Previous studies have suggested an increase in MPI in the initial stages of foetal deterioration [12,13]. Others have proposed MPI as a potentially useful method for evaluating foetal adaptive changes in complicated pregnancies [14,15]. However, the results have shown a wide variation between the reference values, probably because of the low reproducibility of the exam when the Tei at al [16] technique was performed [16].

In 2005, Hernandez-Andrade et al [17] proposed the use of a modified MPI (Mod-MPI) in the left ventricle, using the opening and closing clicks of the mitral and aortic valves to clearly define the three periods used to obtain the MPI. This Mod-MPI improved the inter-observer reproducibility associated with the original coefficient [16]. Cruz-Martinez et al [18] indicated that on an average, the MPI values are above the 95th percentile three weeks before the pulsatility index (PI) change in the ductus venosus of foetuses with early-onset FGR.

Therefore, the aim of this study was to compare the Mod-MPI values between foetuses with growth restriction and those appropriate for gestational age and to assess the intra- and inter-observer reproducibility.

Material and methods

A prospective cross-sectional case-control study was conducted between January 2012 and December 2013 using singleton pregnancies between 24 and 34 weeks of gestation. This study was approved by the Research Ethics Committee of the Federal University of São Paulo (UNIFESP) and the pregnant women who voluntarily participated provided consent form.

The pregnant women were selected by the Division of Fetal Growth Restriction of the Department of Obstetrics of UNIFESP. The inclusion criteria were the following: 1) estimated foetal weight <10th percentile with normal umbilical artery Doppler (PI <95th percentile for gestational age) for the study group [20]; 2) estimated foetal weight between the 10th and 90th percentiles for the control group. The estimated foetal weight was assessed using the table proposed by Hadlock et al [19]. The exclusion criterion was the presence of structural malformations or chromosomal abnormalities detected on ultrasound exam. Pregnant women were assessed only once and their perinatal outcomes were not available.

The pregnant women were divided into three groups: 1) estimated foetal weight <10th percentile, 2) estimated foetal weight between the 10th and 3rd percentiles, and 3) controls with estimated foetal weight >10th percentile for gestational age, according to the table proposed by Hadlock et al [19].

The ultrasound examinations were performed using Accuvix A30 (Samsung, Seoul, Korea) apparatus equipped with a multi-frequency convex probe (2–6 MHz) by four examiners specialised in maternal-foetal medicine (CPS, ACRC, ACPZ and ROC). First, a biometric evaluation was performed, including the estimated foetal weight and quantification of the amniotic fluid volume, and a morphological evaluation was performed to exclude any structural malformation or chromosomal abnormalities. Second, a Doppler assessment of the middle cerebral and umbilical arteries was performed.

Subsequently, Mod-MPI was assessed in the absence of foetal movement and, when necessary, with the pregnant woman voluntarily holding her breath. All Mod-MPI evaluations were performed by a single examiner (CPS) with expertise in foetal echocardiography. Three waves were obtained and the mean value was used as the representative value for each foetus. The insonation angle was less than 30° and the filter was set at 70 Hz. The mechanical and thermal indices were kept below 1.0. Mod-MPI was measured using the technique described by Hernandez-Andrade et al [17], which includes measuring the clicks of the mitral and aortic valves as reference points in order to measure the distinct periods necessary to calculate the MPI, with the foetal heart in the plane of the four chamber view and the apex projecting downwards or upwards. The spectral Doppler sample was placed in the medial wall of the ascending aorta, including the aortic and mitral valves, below the aortic valve and slightly above the mitral valve. The spectral Doppler wave showed the opening and closing clicks of the two valves (fig 1). Three MPI consecutive measurements were performed, two by the

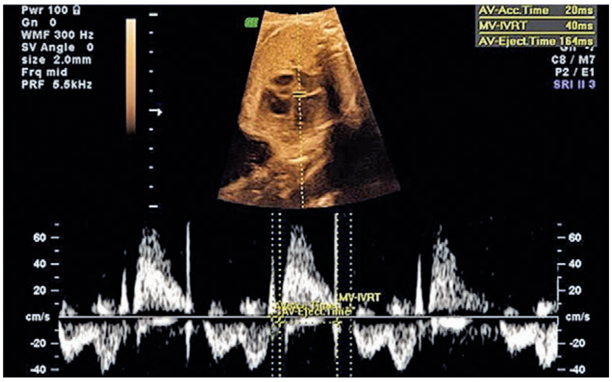

Fig 1. Modified myocardial performance index (Mod-MPI). The sample volume was placed along the lateral wall of the aorta, close to the mitral valve. The references for the time estimations are based on the clicks of the mitral and aortic valve movements. ET: ejection time; ICT: isovolumetric contraction time; IRT: isovolumetric relaxation time.

first examiner (CPS) and one by a second examiner (MMZ).

The images were obtained using a sample volume of 2 to 3 mm, a gain of 60 and a Doppler sweep speed of 150mm/s. The isovolumetric contraction time (ICT), isovolumetric relaxation time (IRT) and ejection time (ET) were calculated using the opening and closing of both the mitral and aortic valves as references. Mod-MPI was calculated using the following equation: Mod-MPI = (ICT + IRT)/ET.

The sample size was calculated assuming a mean difference between the foetus with growth restriction and the normal foetus of at least one standard deviation (SD) and considering a Mod-MPI variability of 0.03 (SD = 0.03) [17]. A total of 21 foetuses per group (foetuses appropriate for gestational age and with growth restriction) were required to achieve a power of 80% and a confidence interval (CI) of 95%. Because the group with growth restriction was divided into two subgroups, 21 foetuses were used for each subgroup.

Statistical anlysis

The data were transferred in an Excel 2007 (Microsoft Corp., Redmond, WA, USA) spreadsheet and analysed using the SPSS software, version 15.0 (SPSS Int., Chicago, IL, USA). The characteristics of the pregnant women and the gestational age were described using summary statistics (mean, standard deviation, median, minimum and maximum) for the quantitative parameters and absolute and relative frequencies for maternal schooling level. Maternal age and gestational age were compared between the groups using analysis of variance (ANOVA) followed by Bonferroni multiple comparisons when differences were significant, and the association between the groups and maternal schooling level was evaluated using the likelihood ratio test.

To calculate reproducibility, CPS performed a second evaluation of the Mod-MPI in 31 pregnant women who were randomly selected among the three groups, 1 week after the first assessment (intra-observer). A second examiner (MCZ) who specialised in foetal echocardiography performed a third Mod-MPI evaluation in 28 pregnant women, immediately after the second assessment by CPS.

The Mod-MPI values were recorded by both CPS and MMZ using the mean and SD, and intraclass correlation coefficient (ICC) was calculated using the respective 95% CIs to assess the intra- and inter-observer reproducibility of the Mod-MPI measurements and to determine the error between the evaluations (reproducibility). Bland–Altman plots were used to determine any trend between the evaluations [21]. The MPI values were described according to the groups using summary statistics and were compared between the groups using ANOVA. A p-value of <0.05 was considered statistically significant.

Results

The mean age of the pregnant women was 28.6±6.8 years in the estimated foetal weight <3rd percentile group, 29±5.6 years in the estimated foetal weight between the 3rd and 10th percentiles, and 24.7±3.3 years in the control group. No significant difference in maternal age (p=0.011) and gestational age (p=0.314) was observed between the groups (Table I). Therefore, we assumed that the groups were paired.

In all assessed foetuses, the umbilical and middle cerebral artery Doppler were normal, without significant difference between the groups. The amniotic fluid index also did not show significant difference between the groups.

The mean Mod-MPI value was 0.36±0.06 in the group with estimated foetal weight <3rd percentile, 0.35±0.05 in the group with estimated foetal weight between the 3rd and 10th percentiles, and 0.32±0.05 in the control group. The mean Mod-MPI value was not significantly different

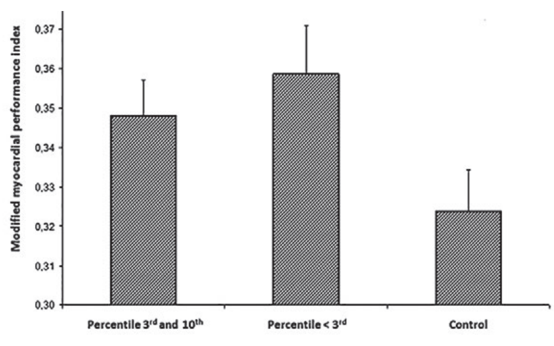

Fig 2. Comparison between the modified myocardial performance index and the three assessed groups (<3rd percentile, between the 3rd and 10th percentiles and control).

Table I. Maternal age, gestational age and schooling level of the three assessed groups.

Variable	Group 3rd to 10th percentile (N = 30)	Percentile < 3rd (N = 22)	Control (N = 24)	Total (N = 76)	p
Maternal age (years)*					0.011
Mean (SD)	29 (5.6)	28.6 (6.8)	24.7 (3.3)	27.5 (5.6)	
Median (min.; max.)	28 (20; 39)	28 (16; 41)	24 (20; 34)	26 (16; 41)	
Gestational age (weeks)*					0.314
Mean (SD)	31.3 (1.9)	30.3 (2.7)	30.9 (2.4)	30.9 (2.3)	
Median (min.; max.)	31.7 (24.9; 33.9)	30.6 (25.1; 34)	31.9 (25.7; 33.9)	31.3 (24.9; 34)	
Maternal schooling level, n (%)					0.569#
Elementary school	11 (36.7)	11 (50)	12 (50)	34 (44.7)	
High school	18 (60)	11 (50)	12 (50)	41 (53.9)	
College	1 (3.3)	0 (0)	0 (0)	1 (1.3)	

Test results using ANOVA; #Results using the likelihood ratio test; *Two samples without data on maternal age and one sample without data on gestational age. N- number of cases

Table II. Values of the modified myocardial performance index in the three assessed groups.

Group	Mean	SD	Median	Minimum	Maximum	N	p
Percentile 3rd to 10th	0.35	0.05	0.35	0.25	0.46	30	0.072
Percentile < 3rd	0.36	0.06	0.36	0.26	0.48	22	
Control	0.32	0.05	0.32	0.22	0.43	24	
Total	0.34	0.05	0.34	0.22	0.48	76	

Table III. Evaluation of the intra- and inter-observer reproducibility of the measurement of the modified myocardial performance index.

Agreement	Examiner	Mean	SD	N	ICC	CI (95%) Inferior	CI (95%) Superior	Repeatability
Inter-observer	Examiner 1	0.36	0.06	28	0.760	0.527	0.883	0.02
	Examiner 2	0.35	0.05	28				
Intra-observer	Examiner 1	0.36	0.06	31	0.726	0.508	0.857	0.03
	Examiner 2	0.37	0.06	31				

ICC: intra-class correlation coefficient; CI: confidence interval.

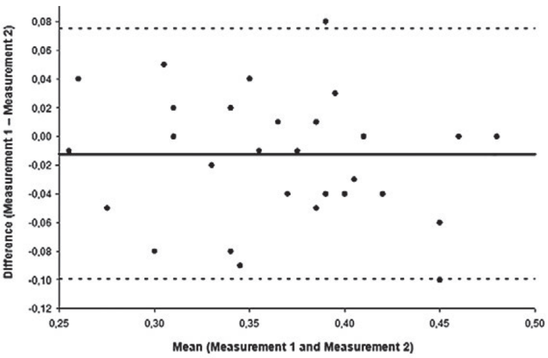

Fig 3. Bland–Altman plot showing the mean relative difference between the two measurements performed by one examiner (intra-observer) plotted against the difference between the means of the modified myocardial performance index.

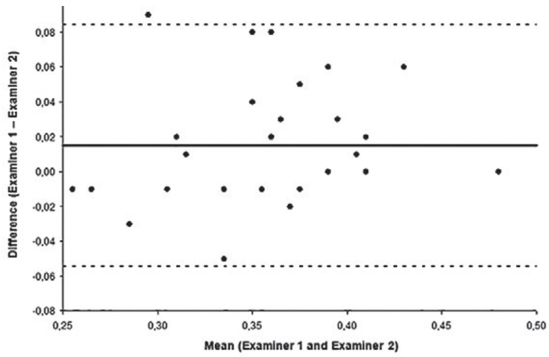

Fig 4. Bland–Altman plot showing the mean relative difference between the two measurements performed by two examiners (inter-observer) plotted against the difference between the means of the modified myocardial performance index.

between the three assessed groups (p=0.072) (Table II), although a lower Mod-MPI value was observed in appropriate growth foetuses (fig 2).

The mean±SD of PI umbilical artery Doppler was 0.92±0.19 (percentile <3rd), 0.90±0.17 (3rd and 10th percentile) and 0.87±0.16 (control) without statistical difference between them (p=0.10).

There was good intra-observer reproducibility (ICC = 0.726; 95% CI, 0.508–0.857) and inter-observer reproducibility (ICC = 0.760; 95% CI, 0.527–0.883) (Table II, fig 3-4).

Discussions

No significant differences were observed between the appropriate growth foetuses with those with growth restriction (estimated foetal weight <10th percentile and between the 3rd and 10th percentiles for gestational age, respectively) despite the slightly higher values among those with appropriate growth.

Perinatal mortality prediction is essential for the management of foetuses with FGR. Many techniques are used to monitor these foetuses, such as arterial and venous Doppler, cardiotocography during pregnancy and the evaluation of the biophysical profile. Although ductus venosus Doppler is considered the gold standard for monitoring of pregnancy and to assess the need for its interruption, when there is evidence that this parameter is abnormal, the foetal health may already be compromised. Moreover, ductus venosus Doppler does not predict the risk of neurological morbidity [9].

Cardiac dysfunction was assessed as a precise indicator of FGR progression. It occurs in the initial stages of growth restriction, and deterioration progresses with the worsening of fetal impairment. Crispi et al [13] evaluated cardiac dysfunction according to Mod-MPI, the E/A ratio (ratio between two flow velocity peaks observed through the atrioventricular valves during diastole), the cardiac output, and natriuretic peptide type B level in the umbilical cord blood and in cells from the myocardial tissue of foetuses with FGR. They found that Mod-MPI was significantly higher in the initial stage and it increased throughout the deterioration stages. Moreover, Mod-MPI was significantly higher in foetuses that died than in those that survived.

The results found in the present study were similar to those obtained by Nassr et al [22], who demonstrated that the cardiac function of foetuses with FGR and normal umbilical artery PI was similar to that of foetuses with appropriate growth and the same perinatal outcomes; this suggests that most of these foetuses were small and healthy. In addition, these studies revealed that foetuses with growth restriction and abnormal Mod-MPI had worse perinatal outcomes and increased morbidity compared with foetuses with growth restriction and normal Mod-MPI and appropriate growth foetuses.

According to the results of this study, we suggest that a finding of normal Mod-MPI in FGR and normal umbilical artery Doppler indicates that these foetuses still exhibit adequate cardiac function, even among those with growth restriction <3rd percentile that are at a higher risk of adverse perinatal outcomes. However, we cannot prove our results, because the perinatal outcomes were not obtained. New studies with a higher number of cases and the assessment of perinatal outcomes are necessary to prove our assumption.

In the present study, the mean Mod-MPI values in appropriate growth foetuses are in agreement with those obtained by Hernandez-Andrade et al [17], who established a reference range between 19 and 39 weeks of gestation, with a small increase in values at more advanced gestational ages. This increase results from the combination of increased IRT and decreased ET. A manifestation of foetal cardiac maturation is the gradual increase in the ventricular wall compliance, expressed as an increased relaxation capacity and the E component of the E/A wave at more advanced gestational ages. As a result, the cardiac diastolic performance improves and the ejection time is reduced. Van Mieghem et al [23] found mean values of 0.34 for healthy foetuses, whereas Raboisson et al [24] reported a mean value of 0.37 and without variation according to gestational age. However, these values differed from those obtained in other studies that used the methodology described by Tei et al [25].

With regard to the methods used to assess MPI, we chose the technique modified by Hernandez-Andrade et al [17] because it can identify the click echoes of the mitral and aortic valves on the spectral Doppler, thereby exhibiting lower intra- and inter-observer variability compared with the technique described by Friedman et al [16].

In the present study, good intra- and inter-observer reproducibility was observed, indicating that the Mod-MPI method is feasible for foetuses with growth restriction. However, it requires training to achieve the necessary competence to perform the exam. In the study conducted by Cruz-Martinez et al [18], the learning curve to achieve competence in the Mod-MPI measurement was evaluated; the maximum disagreement between examiners was 10% and 65 measurements on an average were required to attain significant competence. Meriki et al [26] propose refinement adjustments in the apparatus where the MPI measurements will be performed, because these adjustments can influence the inter-observer repeatability as well as the opening and closing clicks valve.

Recently, two reference ranges for the MPI were established. Luewan et al [27] established reference values for the Mod-MPI in 562 Thai singleton pregnant women between 12 and 20 weeks of gestation. 50th percentile ranged from 0.45 at 12 to 0.57 at 40 weeks of gestation, respectively. Meriki et al [28] determined a reference range for Mod-MPI in 235 Australian singleton pregnant women between 18 and 37 weeks of gestation. 50th percentile ranged from 0.48 at 18 to 0.57 at 37 weeks of gestation, respectively. The 50th percentiles of Mod-MPI of both reference ranges in ethnically different populations were similar.

Regarding limitations of this study, we can refer to the absence of perinatal outcomes, because it was a cross-sectional study. Therefore, we cannot guarantee that all fetuses with estimated weight <10th percentile were really restricted. However, the determination of a new group with an estimated foetal weight <3rd percentile could increase the probability of real FGR. Furthermore, we did not assess the ductus venosus Doppler which is other parameter that can assist in the identification of the real FGR cases. On the other hand, all Doppler examinations were performed by only two experienced examiners which were proved by the good intra- and inter-observer reproducibility. Experienced examiners are essential to obtain adequate MPI measurements, because of apparatus settings.

Conclusion

In summary, we demonstrated that Mod-MPI was not significantly different between appropriate and growth restriction foetuses. Mod-MPI proved to be a feasible and reproducible technique that can be applied in different obstetrical clinical pathologies. However, it is necessary to discuss a better setting of apparatus as well as the obtaining of the waveform to better the inter-observer repeatability of the method.

Conflict of interest: none

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