

1 **Agreement between anatomical M-mode and tissue Doppler imaging in the assessment of fetal**
2 **atrioventricular annular plane displacement in uncomplicated pregnancies:**
3 **A prospective longitudinal study**
4

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17 **Running Title:** TDI of fetal atrioventricular annular plane displacement
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32 **Abstract**

33 **Aim:** To evaluate the level of agreement between M-mode and pulsed wave-tissue Doppler imaging
34 (PW-TDI) techniques in assessing fetal mitral (MAPSE), tricuspid (TAPSE) and septal (SAPSE)
35 annular plane systolic excursion in a low risk population.

36 **Methods:** This prospective longitudinal study included healthy fetuses assessed from 18 to 40 weeks
37 of gestation. TAPSE, MAPSE and SAPSE were measured using anatomical M-mode and PW-TDI.
38 The agreement between the two diagnostic tests was assessed using Bland-Altman analysis.

39 **Results:** Fifty fetuses were included in the final analysis. Mean values of TAPSE were higher than
40 that of MAPSE. There was a progressive increase of TAPSE, MAPSE and SAPSE values with
41 advancing gestation. For each parameter assessed, there was an overall good agreement between the
42 measurements obtained with M-mode and PW-TDI techniques. However, the measurements made
43 with M-mode were slightly higher than those obtained with PW-TDI (mean differences: 0.03 cm, 0.05
44 cm and 0.03 for TAPSE, MAPSE and SAPSE, respectively). When stratifying the analyses by
45 gestational age, the mean values of TAPSE, MAPSE and SAPSE measured with M-Mode were higher
46 compared to those obtained with PW-TDI, although the mean differences between the two techniques
47 tended to narrow with increasing gestation. TAPSE, MAPSE and SAPSE measurements were all
48 significantly, positively associated with gestational age (all $p < 0.001$).

49 **Conclusions:** Fetal atrioventricular annular plane displacement (AVPD) can be assessed with M-
50 mode technique, or with PW-TDI as the velocity-time integral of the myocardial systolic waveform.
51 AVPD values obtained with M-mode technique are slightly higher than those obtained with PW-TDI.

52

53 **Keywords:** Tissue Doppler Imaging, M-Mode, fetal echocardiography, atrioventricular plane
54 systolic excursion.

55 **Introduction**

56 Fetal echocardiography is the primary tool for prenatal diagnosis of congenital heart disease.
57 Although fetal echocardiography is mainly employed to detect structural anomalies, its use for the
58 evaluation of fetal cardiac function has recently been proposed and is gradually being introduced in
59 clinical practice. Functional assessment of fetal heart has been shown to have the potential to
60 stratify short-term cardiovascular risk of several conditions occurring in fetal life, such as intrauterine
61 growth restriction, twin-to-twin transfusion syndrome or fetal anemia.¹⁻⁷

62 Traditionally, functional assessment of the heart relies on the quantification of ejection fraction as a
63 proxy for systolic function. However, ejection fraction is not commonly used by perinatal
64 cardiologists to assess fetal heart function. Due to its load-dependency, the need for assessing both
65 ventricles separately because of the parallel arrangement of fetal circulation, and the lack of
66 information on longitudinal and circumferential myocardial function, ejection fraction is not
67 considered to represent an objective measure of fetal heart function.

68 Atrio-ventricular annular plane displacement (AVPD) is a reliable measure of longitudinal heart
69 function, and it has been shown to correlate with myocardial performance better than ejection fraction
70 alone in several pediatric and adult conditions such as valvular disease, heart failure and growth
71 restriction. AVPD refers to the distance covered by the atrio-ventricular plane between its positions
72 farthest from the apex at the beginning of ventricular contraction and closest to the apex at the end of
73 contraction. The relevance of AVPD relies on the fact that it can provide information on the
74 longitudinal function of the heart, which can be affected in early stages of cardiac dysfunction.⁸⁻¹²

75 Atrio-ventricular annular plane motion during a cardiac cycle can be evaluated using different
76 ultrasound modalities, such as M-mode, color or pulsed-wave tissue Doppler imaging (PW-TDI) and
77 two-dimensional speckle tracking.¹² However, it still has to be ascertained whether assessment of
78 atrio-ventricular annular plane displacement is affected by the ultrasound technique adopted and
79 whether gestational age at assessment may influence the level of agreement between different

80 imaging modalities. This is fundamental, because the knowledge of the degree of correlation between
81 different diagnostic tools is crucial for their interpretation in clinical practice.

82 The primary aim of this study was to evaluate the level of agreement between anatomical M-mode
83 and PW-TDI in assessing mitral (MAPSE), tricuspid (TAPSE) and septal annular plane systolic
84 excursion (SAPSE) in a low risk population. The secondary aim was to ascertain the role of
85 gestational age at ultrasound in affecting such agreement.

86

87 **Methods**

88 This was a prospective study of healthy fetuses assessed longitudinally from 18 to 40 weeks of
89 gestation at an approximately 4-weekly interval at the University Hospital of North Norway, Tromsø,
90 Norway during 2009-2012. Low risk pregnant women attending antenatal clinic for routine second
91 trimester screening were invited to participate in the study. The study was approved by the Regional
92 Committee for Medical Research Ethics (Ref. REK NORD 105/2008). Written informed consent was
93 signed by each woman involved in the study.

94 Inclusion criteria were: women >18 years of age with uncomplicated singleton pregnancy and normal
95 fetus on second trimester ultrasound, who were willing and able to attend for serial ultrasonographic
96 examinations during the whole pregnancy. Women with a complicated obstetric history or with a
97 medical condition that may have an adverse impact on the current pregnancy were not invited to
98 participate. Exclusion criteria were: multiple pregnancy, fetus with structural or chromosomal
99 anomaly and/or IUGR. Furthermore, fetuses presenting with signs of cardiomegaly or abnormal
100 cardiothoracic ratio were not considered eligible for the inclusion as the assessment of atrio-
101 ventricular annular plane displacement is known to be affected by heart size.^{13,14}

102 Echocardiography was performed using Vivid 7 Dimension ultrasound system (GE Vingmed, Horten,
103 Norway), equipped with a M4S transducer by a single operator. All PW-TDI and 2D recordings were
104 performed from an apical four-chamber view and stored as cine loops of at least 5-10 consecutive
105 cardiac cycles for offline analysis using a dedicated software (EchoPAC PC version 12, GE Medical
106 System). The angle of insonation to the long axis of the heart was kept as small as possible or adjusted
107 manually. The TDI and 2D sector widths were minimized to obtain the highest possible frame rate
108 (201-273 frames/s).^{13,14}

109 Biventricular diameter was measured at the level of the annulus during the systole and at the level of
110 the valves' tip during the diastole. Right and left ventricular length was measured in diastole from the
111 corresponding lateral annulus to the apex. Septal length was measured in diastole from the offset to
112 the apex.

113 TAPSE, MAPSE and SAPSE values were assessed offline using anatomical M-mode in an apical
114 four-chamber view, placing the M-mode cursor on the lateral mitral annulus, lateral tricuspid annulus
115 and the septum just below the offset, respectively. The excursion of mitral, tricuspid and septal
116 annular planes was measured during the same cardiac cycle. Total displacement of the annular planes
117 from the end of diastole until maximal expansion in systole was measured in cm (Figure 1a), avoiding
118 oscillations due to fetal respiration or movements.¹²

119 Myocardial and septal wall motion was assessed with PW-TDI, with a sample size of 1-2 mm, aligned
120 parallel (insonation angle <15 degree) to the myocardial wall at the level of the AV planes and to the
121 interventricular septum at its basal part. The velocity waveforms were obtained during the whole
122 cardiac cycle and three to six cardiac cycles were recorded for offline analysis at a sweep speed of
123 100 mm/s. The velocity-time integral of the systolic waveform (S') that represents the AVPD was
124 measured in cm by tracing the maximum velocity waveform of the annular motion during the ejection
125 phase of the cardiac cycle (Figure 1b)^{12, 23}. All measurements were performed three times and an
126 average value was used for analysis.

127 For each recorded variable, the agreement between the two diagnostic tests (M-mode and PW-TDI)
128 was assessed using Bland-Altman analysis, which was performed in the overall sample, and in four
129 subgroups stratified by gestational age (20⁺⁰-23⁺⁶, 24⁺⁰-27⁺⁶, 29⁺⁰-33⁺⁶ and 34⁺⁰-39⁺⁶ weeks).¹⁵⁻¹⁷ In
130 all analyses, the level of agreement was expressed as the mean difference between observations made
131 using the two methods (M-mode minus PW-TDI), with 95% limits of agreement, which provide an
132 interval within which 95% of differences are expected to lie. In the analysis of the overall sample, we
133 used the Bland-Altman method for repeated observations, as more than one measurement was
134 available for each fetus.¹⁵⁻¹⁷ To further explore the relationship between gestational age and test
135 agreement, we fitted a random-effect linear regression with individual test difference (i.e. value
136 obtained by TDI minus value obtained by M-mode) as the dependent variable, and each fetus as the
137 cluster variable.

138 Finally, a random-effect linear regression (with each fetus as the cluster variable) was performed to
139 explore the associations between AVPD parameters (TAPSE, MAPSE, and SAPSE) and cardiac
140 dimensions (biventricular diameter, and the right ventricular, left ventricular and septal length,
141 respectively). For each AVPD parameter, three separate models were fit considering as dependent
142 variable: (1) the value obtained with M-mode technique (b) the value obtained by PW-TDI
143 technique, and (c) the difference between the two techniques (PW-TDI minus M-mode).

144 Statistical significance was defined as a two-sided p-value<0.05 for all analyses. Bland-Altman plots
145 were performed using MedCalc for Windows 15.2 (MedCalc Software, Ostend, Belgium, 2015);
146 linear regression analysis was made using Stata 13.1 (Stata Corp., College Station, Texas, USA,
147 2013).

148 **Results**

149 Fifty uncomplicated singleton pregnancies studied longitudinally (a total of 174 examinations) were
150 included in the final analysis. The baseline characteristics and outcome of these pregnancies are
151 presented in Table 1. Median gestational age at scan was 26 weeks (interquartile range, IQR: 17.6-
152 34.1). A total of 15.5% (95% CI 10.5-21.8; 27/174) of examinations were performed at 20⁺⁰-23⁺⁶,
153 35.6% (95% CI 28.5-43.2; 62/174) at 24⁺⁰-27⁺⁶, 29.3% (95% CI 22.7-36.8; 51/174) at 29⁺⁰-33⁺⁶and
154 19.5% (95% CI 13.9-26.2; 34/174) at 34⁺⁰-39⁺⁶ weeks of gestation. Median number of examination
155 per patient was 3 (IQR 3-5). Pregnancy outcome was uneventful for all the included cases.

156 Mean values of TAPSE were higher than that of MAPSE (Table 2). There was a progressive increase
157 of TAPSE, MAPSE and SAPSE values with advancing gestation (Table 3). On random effect linear
158 regression analysis, TAPSE (regression coefficient: 0.09, 95% CI 0.02; 0.16 for 1 cm increase; p=
159 0.02) and SAPSE (regression coefficient: 0.10, 95% CI 0.05-0.16 for 1 cm increase; p< 0.001), but
160 not MAPSE (p= 0.6) were positively associated with bi-ventricular diameter (Table 4). Likewise,
161 TAPSE (regression coefficient: 0.07, 95% CI 0.00-0.14; p= 0.045), but not MAPSE (p= 0.18) was
162 positively associated with ventricular length, while the positive association was observed only
163 between septal length and SAPSE measured with M-Mode (regression coefficient: 0.05, 95% CI
164 0.01; 0.09; p= 0.012) but not with TDI (p= 0.9).

165
166 For each excursion parameter, the overall agreement between the measurements obtained with M-
167 mode and with TDI are shown in Figures 2-4. Each Figure reports the Bland-Altman plot performed
168 separately for TAPSE, MASPE and SAPSE, respectively, and the results of each plot are summarized
169 in Table 2. For all parameters, the measurements made with M-mode were slightly higher than those
170 obtained with PW-TDI (mean differences between the two techniques: 0.03 cm, 0.05 cm and 0.03 for
171 TAPSE, MAPSE and SAPSE, respectively). In all cases, however, the 95% limits of agreement were
172 wide and not consistent, with the differences between the two techniques lying between -0.23 cm and

173 0.28 cm for tricuspid; -0.20 cm and 0.31 cm for mitral; -0.17 cm and 0.24 cm for septal annular plane
174 systolic excursion.

175 When stratifying the analyses by gestational age, the mean values of TAPSE, MAPSE and SAPSE
176 measured with M-mode were higher compared to those obtained with PW-TDI, although the mean
177 differences between the two techniques tended to narrow with the increase of gestational age. In
178 fetuses ≥ 34 weeks, the mean values obtained with PW-TDI were higher than those measured with M-
179 mode. For all parameters, however, the limits of agreement remained wide in all age classes (Table
180 3). Random-effect linear regression showed a positive association between test differences and
181 gestational age (regression coefficient: 0.008, 0.011, 0.008 for TAPSE; MAPSE and SAPSE,
182 respectively, for each 1-week increase; all $p < 0.001$) (Table 5).

183 **Discussion**

184 Applicability PW-TDI to assess AVPD as the velocity-time integral of myocardial systolic waveform
185 has not been explored. In the absence of an electrocardiogram, compared to M-mode, PW-TDI has
186 the advantage of more clearly identifying isovolumic events of the fetal cardiac cycle,¹² which should
187 be excluded in the measurement of AVPD²⁵. The findings from our study indicate that AVPD could
188 be assessed by both techniques, but values obtained with M-mode were higher than those obtained
189 with PW-TDI. However, when stratifying the analyses by gestational age the mean differences
190 between the two techniques tended to narrow with the increasing gestational age. It remains unclear
191 whether this is a physiological phenomenon or related to the fact that recording M-mode and PW-
192 TDI waveforms from the fetuses as well as defining the cardiac cycle events becomes easier with
193 advancing gestation. Mean values of TAPSE were higher than that of MAPSE, and there was a
194 progressive increase in AVPD values with advancing gestation which is in line with previous reports.
195 Functional assessment of fetal heart may help to prenatally stratify the short-term cardiovascular risk
196 of several fetal conditions.¹⁻⁷ Early detection of fetuses at high risk of post-natal cardiovascular
197 compromise would allow early monitoring and intervention, thus potentially being able to change the
198 natural history of the disease and improve children's cardiovascular health. AVPD is a major
199 contributor to ventricular pumping, accounting for 80% of right ventricular systolic performance and
200 60% of left ventricular one in adults and has been recognized to differentiate myocardial disorders
201 better than ejection fraction alone.^{11,12,18-20}

202 Fetal AVPD may be affected in several relevant in utero conditions, but whether it can help in
203 stratifying these fetuses to predict the short and long-term prognosis depends on how reliably it can
204 be measured during pregnancy. Different ultrasound modalities such as M-mode, color-TDI, PW-
205 TDI and speckle tracking echocardiography can be employed to measure AVPD in the fetus. It is
206 therefore important that clinicians are provided with an up-to date estimation on the degree of
207 concordance between different modalities in assessing this parameter.

208 M-mode is a relatively easy and accessible technique. Assessment of AVPD with M-mode is
209 commonly performed by measuring the maximum systolic excursion as a distance between the nadir
210 and the zenith of the annular motion profile. Measurement of AVPD using M-mode was introduced
211 in 2001 and the gestational age-specific reference ranges have been recently provided.^{21,22} One of the
212 major advantages of using M-mode when assessing AVPD is its high sampling rate (>1000/s) and
213 excellent interface definition. However, pre- and post-ejection phases of the cardiac cycle may be
214 difficult to identify accurately in the absence of a fetal electrocardiogram¹².

215 Pulsed-wave TDI is a relatively recent ultrasound modality in fetal cardiovascular imaging and uses
216 frequency shifts of ultrasound waves to calculate myocardial velocities that are displayed as the
217 maximum velocity waveform envelope representing all phases of the cardiac cycle.²³ TDI requires
218 operator expertise and a dedicated ultrasound equipment and it is not commonly performed in clinical
219 practice. However, it allows better definition of the events of the cardiac cycle in the absence of an
220 electrocardiogram and myocardial velocities can be simultaneously assessed.

221 AVPD can be assessed either by pulsed-wave or color TDI.²⁴ Assessment of AVPD by TDI is
222 different from that performed on M-mode, where the measurements are expressed as the distance
223 (cm) between the nadir and the zenith of the annular motion profile. Using TDI, AVPD measurements
224 are derived by tracing the velocity-time integral (cm) of annular velocity waveform during the
225 ejection phase of cardiac cycle, which essentially represents the systolic annular displacement. Both
226 techniques are, however, angle dependent.

227 In adults, M-mode and TDI-derived AVPD have been demonstrated to have an overall good level of
228 agreement.²⁵ However, there is still paucity of data in fetal period. In our study, although the 95%
229 limits of agreement were wide and not consistent between two techniques, mean excursion values
230 measured by anatomical M-mode were slightly higher than those measured by PW-TDI. The
231 difference between two techniques could be due to the fact that the M-mode assess the global motion
232 along of the whole length of the ventricular wall/septum, whereas the PW-TDI derives the regional
233 motion of the ventricular /septal basal areas. Difficulty associated with accurately identifying and

234 excluding the components of excursion occurring during isovolumic phases of the cardiac cycle in
235 the fetus when using the M-mode technique could be another explanation.

236 Only few studies have assessed the degree of correlation between different prenatal ultrasound
237 modalities in evaluating AVPD. In the study by Cruz-Lemini et al., 69 fetuses affected by intra-
238 uterine growth restriction requiring delivery before 34 weeks of gestation were compared with 46
239 normal pregnancies.³ The authors reported that MAPSE and TAPSE were significantly lower in
240 fetuses affected by intra-uterine growth restriction compared to controls; furthermore, M-mode
241 measurements showed a similar performance to TDI in assessing AVPD. However, the authors did
242 not explore the level of agreement between these two different techniques according to the gestational
243 age at scan and the included fetuses were delivered at a relatively large gestational age window, i.e.
244 between 26 and 34 weeks of gestation. Furthermore, the authors compared M-mode with TDI
245 velocities rather than TDI-derived AVPD. Messing et al. explored the correlation between MAPSE,
246 gestational age and fetal weight.²⁴ They compared values obtained by M-mode with spatiotemporal
247 image correlation between 20 and 38 weeks of gestation and provided gestational age specific
248 reference ranges.²⁴ These investigators reported that MAPSE had a linear correlation with gestational
249 age and fetal weight, and that the two different ultrasound modalities were comparable.²⁴ Our study
250 shows similar results although different techniques (M-mode and pulsed-wave TDI) were compared.
251 Mean values of TAPSE, MAPSE and SAPSE increased through pregnancy as previously reported;
252 this finding might be related to the increase in heart size and body surface area rather than to an actual
253 improvement of fetal systolic function which has been reported to be relatively constant throughout
254 pregnancy.²⁶⁻²⁸

255 The major strength of our study is its prospective longitudinal design, which allowed us to assess the
256 effect of gestational age on the agreement between two techniques of AVPD measurement. Its
257 limitations are a relatively small sample size and lack of a concurrent electrocardiographic evaluation.
258 Furthermore, AVPD was assessed using anatomical rather than real time M-mode. Although the two
259 techniques have been shown to have an overall good agreement between, mean excursion values were

260 higher when anatomical M-mode was used, and this should be considered when comparing with
261 TDI.²⁹

262

263 Mean AVPD values are slightly higher when measured by anatomical M-mode compared to PW-TDI.
264 These differences should be considered when evaluating longitudinal fetal heart function. TAPSE,
265 MAPSE and SAPSE showed a linear correlation with gestational age. Further large studies aimed at
266 assessing the degree of correlation between M-mode and PW-TDI in different pathological conditions
267 and at different gestational age windows are needed to ascertain whether routine assessment of AVPD
268 may help in identifying fetuses at risk of cardiovascular dysfunction during pregnancy.

269 **Disclosure**

270 No conflict of interest to declare from any of the authors

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355 **Table 1.** General characteristics of the study population analyzed.

| Variables | Overall sample (n=50) |
|---------------------------------------|-----------------------|
| Maternal age (year)* | 30.4±3.9 |
| Maternal height (m)* | 1.7±0.04 |
| Body mass index (Kg/m ²)* | 23.2±3.1 |
| Gestational age at birth (weeks)§ | 40 (39-40) |
| Caesarean section | 10% (5/50) |
| Birthweight (g)* | 3378±0.5 |
| Livebirth | 100% (50/50) |
| Apgar score <7 at 5 min | 4% (2/50) |
| pH* | 7.25±0.1 |
| Base excess (mmol/L) | -4.29±3.7 |

356 *: Values expressed as mean (±standard deviation).

357 §: Values expressed as median (interquartile range).

358 **Table 2.** Overall agreement between the tests (M-mode vs pulsed wave tissue Doppler
 359 imaging (PW-TDI) techniques in assessing systolic atrioventricular annular plane
 360 displacement (AVPD) in fetus.

361

| Variables | M-mode | PW-TDI | Mean difference* |
|-------------------|------------------|------------------|-------------------------|
| AVPD | Mean (SD) | Mean (SD) | (95% LoA) |
| TAPSE (cm) | 0.58 (0.12) | 0.56 (0.16) | 0.03 (-0.23; 0.28) |
| MAPSE (cm) | 0.47 (0.10) | 0.42 (0.14) | 0.05 (-0.20; 0.31) |
| SAPSE (cm) | 0.36 (0.06) | 0.33 (0.10) | 0.03 (-0.17; 0.24) |

362

363 TAPSE = Tricuspid anular plane systolic excursion; MAPSE = Mitral anular plane
 364 systolic excursion; SAPSE = Septal annular plane systolic excursion. SD = Standard
 365 deviation. LoA = Limits of agreement. M-mode vs TDI.

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367

368

369 **Table 3.** Overall agreement between M-mode vs pulsed wave tissue Doppler imaging (PW-TDI)
 370 techniques in assessing systolic atrioventricular annular plane displacement (AVPD) in fetus for each
 371 selected variable, stratified by gestational age.
 372

| Variables | M-mode Technique | Tissue Doppler | Mean difference* |
|--|---------------------|-------------------|---------------------|
| AVPD | Mean (SD) | Mean (SD) | (95% LoA) |
| TAPSE (cm) | | | |
| 20 ⁺⁰ -23 ⁺⁶ weeks | 0.42 (0.08) | 0.48 (0.09) | -0.06 (-0.14; 0.26) |
| 24 ⁺⁰ -27 ⁺⁶ weeks | 0.55 (0.10) | 0.49 (0.09) | 0.06 (-0.10; 0.22) |
| 29 ⁺⁰ -33 ⁺⁶ weeks | 0.63 (0.10) | 0.61 (0.12) | 0.02 (-0.22; 0.27) |
| 34 ⁺⁰ -39 ⁺⁶ weeks | 0.65 (0.10) | 0.73 (0.14) | -0.08 (-0.41; 0.26) |
| MAPSE (cm) | | | |
| 20 ⁺⁰ -23 ⁺⁶ weeks | 0.40 (0.07) | 0.28 (0.07) | 0.11 (-0.06; 0.29) |
| 24 ⁺⁰ -27 ⁺⁶ weeks | 0.46 (0.09) | 0.36 (0.07) | 0.10 (-0.12; 0.32) |
| 29 ⁺⁰ -33 ⁺⁶ weeks | 0.50 (0.10) | 0.45 (0.11) | 0.05 (-0.21; 0.30) |
| 34 ⁺⁰ -39 ⁺⁶ weeks | 0.51 (0.08) | 0.57 (0.12) | -0.06 (-0.29; 0.18) |
| SAPSE (cm) | | | |
| 20 ⁺⁰ -23 ⁺⁶ weeks | 0.33 (0.06) | 0.23 (0.05) | 0.10 (-0.05; 0.24) |
| 24 ⁺⁰ -27 ⁺⁶ weeks | 0.35 (0.04) | 0.29 (0.06) | 0.06 (-0.07; 0.19) |
| 29 ⁺⁰ -33 ⁺⁶ weeks | 0.37 (0.06) | 0.36 (0.08) | 0.01 (-0.18; 0.20) |
| 34 ⁺⁰ -39 ⁺⁶ weeks | 0.39 (0.06) | 0.42 (0.10) | -0.03 (-0.26; 0.20) |

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 374 TAPSE = Tricuspid annular plane systolic excursion; MAPSE = Mitral annular plane
 375 systolic excursion; SAPSE = Septal annular plane systolic excursion. SD = Standard
 376 deviation. LoA = Limits of agreement. * M-mode vs PW-TDI.
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379 **Table 4.** Associations of the atrio-ventricular annular plane displacement (AVPD) parameters (TAPSE,
380 MAPSE, and SAPSE) with cardiac dimensions (biventricular diameter, and the right ventricular, left
381 ventricular and septal length, respectively). For each excursion parameter, the analyses were repeated three
382 times, considering: (a) the result of the M-mode assessment (b) the results of the Pulsed-wave Tissue
383 doppler imaging (PW-TDI) assessment, and (c) the difference between the two techniques (PW-TDI minus
384 M-mode).

| | M-mode | | | PW-TDI | | | Difference ^ψ | |
|--|-------------------------------|--------|--|-------------------------------|-------|--|-------------------------------|--------|
| | Reg. coefficient (95% CI)* | p | | Reg. coefficient (95% CI)* | p | | Reg. coefficient (95% CI)* | p |
| <i>Bi-ventricular diameter, 1-cm increase</i> | | | | | | | | |
| TAPSE (cm) | 0.1 (0.11; 0.23) | <0.001 | | 0.09 (0.03; 0.15) | 0.004 | | 0.09 (0.02; 0.16) | 0.02 |
| MAPSE (cm) | 0.04 (-0.02; 0.10) | 0.17 | | 0.03 (-0.03; 0.00) | 0.3 | | 0.02 (-0.05; 0.09) | 0.6 |
| SAPSE (cm) | 0.07 (0.03; 0.12) | 0.001 | | -0.03 (-0.06; 0.00) | 0.09 | | 0.10 (0.05; 0.16) | <0.001 |
| <i>Right ventricular length, 1-cm increase</i> | | | | | | | | |
| TAPSE (cm) | 0.14 (0.08; 0.20) | <0.001 | | 0.08 (0.03; 0.14) | 0.004 | | 0.07 (0.00; 0.14) | 0.045 |
| <i>Left ventricular length, 1-cm increase</i> | | | | | | | | |
| MAPSE (cm) | 0.04 (-0.01; 0.10) | 0.11 | | 0.00 (-0.05; 0.05) | 0.9 | | 0.04 (-0.02; 0.11) | 0.18 |
| <i>Septal length, 1-cm increase</i> | | | | | | | | |
| SAPSE (cm) | 0.05 (0.01; 0.09) | 0.012 | | 0.00 (-0.03; 0.03) | 0.9 | | 0.05 (-0.00; 0.10) | 0.06 |

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386 * All models were adjusted for gestational age (1-week increase). ^ψ PW-TDI minus M-mode.

387 AVPD = Atrio-ventricular annular plane displacement; TAPSE = Tricuspid annular plane systolic
388 excursion; MAPSE = Mitral annular plane systolic excursion; SAPSE = Septal annular plane systolic
389 excursion; Reg. = regression.

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392 **Table 5.** Random-effect linear regression exploring the relationship between test difference (PW-
393 TDI minus M-mode) and gestational age.

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| Test differences | Regression coefficient for 1 week increase (95% CI) | p |
|-------------------------|--|----------|
| TAPSE (cm) | 0.008 (0.005; 0.012) | <0.001 |
| MAPSE (cm) | 0.011 (0.008; 0.014) | <0.001 |
| SAPSE (cm) | 0.008 (0.006; 0.010) | <0.001 |

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396 PW-TDI = Pulsed-wave tissue Doppler imaging; TAPSE = Tricuspid
397 annular plane systolic excursion; MAPSE = Mitral annular plane
398 systolic excursion; SAPSE = Septal annular plane systolic excursion.

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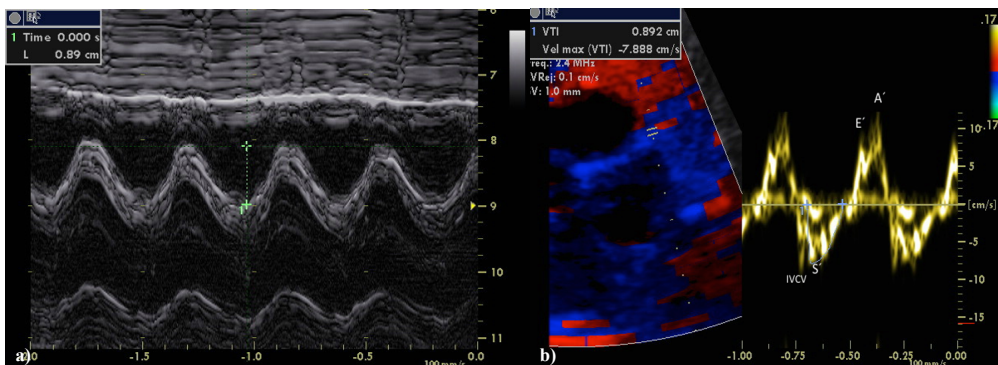
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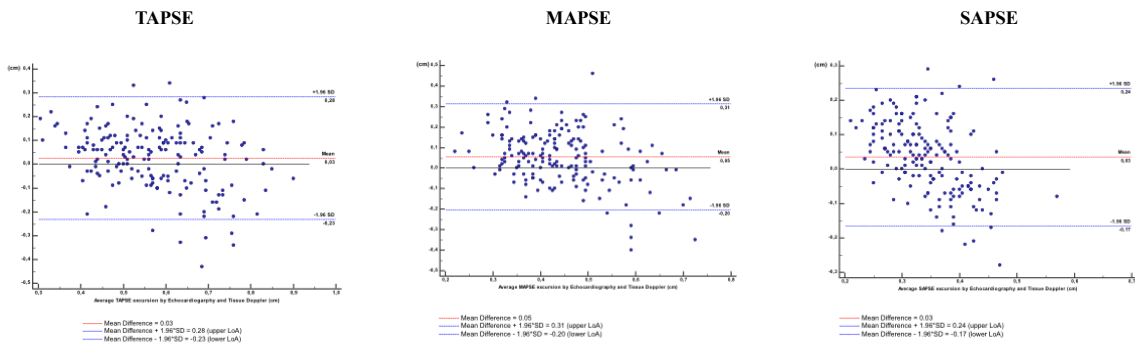
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415 **Figure 1 (a-,b).** Measurement of atrioventricular annular plane displacement (AVPD) in a fetus at 36
416 weeks of gestation: Figure 1a. Tricuspid annular plane systolic excursion (TAPSE) measured as the
417 distance between nadir and zenith (between the calipers) of its motion recorded at a horizontal sweep
418 speed of 100 mm/s with M-mode technique. Figure 1b. Tricuspid annular plane systolic excursion
419 (TAPSE) measured as the velocity time integral (VTI) of the myocardial systolic waveform (S')
420 recorded at a horizontal sweep speed of 100 mm/s with pulsed wave tissue Doppler imaging (PW-
421 TDI) technique using a 1 mm Doppler gate. Note that the isovolumic contraction velocity (IVCV)
422 component is not included in the measurement. E' represents the myocardial velocity during early
423 filling and A' represents the myocardial velocity during the atrial contraction phase of the cardiac
424 cycle.



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427 **Figure 2 (a-c).** Bland-Altman plot of the difference in TAPSE, MAPSE and SAPSE measurement
 428 between M-mode and tissue Doppler. The central red line represents the mean difference between the
 429 two measurements; the two blue lines represent the upper and the lower Limits of Agreement (LoA).
 430 (TAPSE = Tricuspid annular plane systolic excursion; MAPSE = Mitral annular plane systolic
 431 excursion; SAPSE = Septal annular plane systolic excursion; SD = Standard Deviation).
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