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Reference ranges for tissue Doppler measures of maternal systolic and diastolic left ventricular function

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KEYWORDS: Doppler echocardiography; maternal cardiac function; tissue Doppler imaging

ABSTRACT

Objectives *Tissue Doppler imaging (TDI) is an echocardiographic technique that evaluates longitudinal myocardial tissue velocities during left ventricular systolic and diastolic function, relatively independently of loading conditions. Limited data are available regarding maternal cardiac function using TDI. The aim of this study was to construct reference charts for TDI indices in normal pregnancy.*

Methods *This was a cross-sectional study on 104 pregnant women at 11–38 weeks of gestation and 19 non-pregnant controls. Doppler echocardiography was used to assess transmitral inflow velocities during diastole (peak velocity of early (*E*) and late (*A*) atrial filling), whilst TDI at the septal and lateral margins of the mitral annulus measured diastolic velocities (peak velocity of early (*E′*) and late (*A′*) diastolic filling) and peak systolic velocity (*S′*). The left ventricular filling index (*E : E′ *ratio) was derived. The Tei index (ratio of isovolumetric time to ejection time) was measured.*

Results *Systolic function assessed by TDI S′ velocity was unaltered at the septal and lateral margins, although S′ velocity at the lateral margin was higher (12%, P = 0.028) in the first two trimesters, compared to non-pregnant controls. Diastolic function was modified as demonstrated by an increase in A velocity (P = 0.01). Consequently, E : A decreased with gestation (P = 0.024). Similarly, A′ increased at the septal and lateral margins (P < 0.001 and P = 0.02, respectively), resulting in a decrease in E′ : A′ ratios at the septal and lateral mitral margins (P = 0.001 and P = 0.001, respectively). E : E′ at both mitral margins and Tei index were unaltered.*

Conclusion *This study gives normal ranges for TDI indices in pregnancy. TDI demonstrated modified longitudinal systolic and diastolic function. Future studies will evaluate the potential of this technique in pregnancies complicated by hypertension and cardiac disease.*

INTRODUCTION

Changes during normal pregnancy in invasive hemodynamic measures and transverse systolic function on echocardiography have been comprehensively described. There is a 50% increase in cardiac output, due to an increase in stroke volume and heart rate associated with a fall in vascular tone[1,2]. However, there is uncertainty about diastolic function, since this is usually assessed from the transmitral flow pattern, which is now known to be inadequate on its own. Variation in the early diastolic velocity (*E*), which has been reported to rise[3], fall[4,5], or remain unchanged[6], could be explained by the effects of preload and blood pressure, rather than differences in intrinsic left ventricular (LV) compliance[4,7]. Newer measures, such as the Tei index, which describes both systolic and diastolic function, have not been described in pregnancy. There is also very little information about long-axis shortening or lengthening, despite the fact that these measures are expected to reflect changes in loading or intrinsic LV function more sensitively than ejection fraction[8]. There has been only one prior study, which described an increase in long-axis shortening in the first trimester, followed by a decrease from the mid-second trimester[8].

Tissue Doppler imaging (TDI) is a new technique for assessing long-axis LV function, which is relatively load-independent. Since transmitral velocities are highly flow-dependent, the ratio of the transmitral E wave to the simultaneous TDI wave (*E′*) provides a useful clinical estimate of filling pressure[9,10]. As yet, there are no reference

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data for TDI in a normal pregnant population. The objective of this study was therefore to describe TDI measurements and the Tei index in a normal pregnant population.

METHODS

Patient selection

This was a cross-sectional study of maternal cardiac function in 104 pregnant women with singleton pregnancies and 19 non-pregnant women. The study was approved by the Research Ethics Committee of Kings College Hospital and written informed consent was obtained from all participants. The pregnant women were examined once during their pregnancy and were between 11 and 38 weeks' gestation. Gestation was confirmed by last menstrual period and ultrasound measurement of the fetal crown–rump length in the first trimester. Predetermined exclusion criteria were: fetuses with chromosomal abnormalities, genetic syndromes, infections and maternal cardiovascular disease; and pre-eclampsia, defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy[11].

The women were studied after a rest period of 15 minutes in the left lateral decubitus position. Recordings were made when three consecutive ECG measurements of the heart rate from the R–R interval (i.e. the time period between two consecutive R-waves of the ECG (in ms)) demonstrated a variation below 10%. One examiner (J.B.) performed all measurements, which were averaged over three cardiac cycles.

Imaging and Doppler echocardiography were performed using a 3.5-MHz transducer (Toshiba Aplio CV, Toshiba Corporation, Tokyo, Japan) according to the guidelines of the American Society of Echocardiography[12]. LV long-axis M-mode was recorded with the cursor at the lateral and septal sides of the mitral annulus, using the apical four-chamber view[8,13]. Transmitral flow was recorded with the sample volume positioned level with the tips of the mitral leaflets in their fully open position in diastole. The peak velocity of early (E) and late (A) diastolic filling were measured, and the E : A ratio calculated[14,15]. The mitral closing to opening time, a, was measured from the end of one mitral inflow waveform to the onset of the succeeding waveform. The LV ejection time, b, was measured from the onset to the end of the pulsed Doppler subaortic waveform. The Tei index was then calculated as $(a - b)/b$[16,17]. Stroke volume was calculated as the product of the cross-sectional area of the LV outflow tract and the velocity time integral of the pulsed Doppler subaortic waveform, recorded in the five-chamber view. Cardiac output was calculated as the product of heart rate and stroke volume[18]. Total vascular resistance (TVR) was calculated as mean arterial pressure $\times 80$/cardiac output. Tissue Doppler was recorded at the septal and lateral sides of the mitral annulus in the four-chamber view, according to the guidelines of the American Society of Echocardiography[19]. The TDI indices peak velocity of early (E') and late (A') diastolic filling and peak systolic velocity (S') were measured at both mitral margins (Figure 1). The $E : E'$ ratio was derived for the septal and lateral margins of the mitral annulus.

Blood pressure was measured using a mercury sphygmomanometer (Accoson Dekamet, AC Cossor & Son (Surgical) Ltd, London, UK) according to the recommendations of the British Hypertension Society[20]. Mean arterial pressure (MAP) was calculated from the equation: ((systolic BP + (2 × diastolic BP))/3).

Transabdominal ultrasound examination was carried out for measurement of the fetal head circumference, abdominal circumference and femur length, to ensure that the women all had normal for gestational age-sized fetuses, and color Doppler was used to measure the pulsatility index in the uterine artery[21].

Statistical analysis

Unpaired t-tests or the χ^2 test, where appropriate, were performed in order to examine the differences in demographic characteristics between the examined populations. The data are expressed as means and standard deviations (SDs). The normality of the distribution was assessed

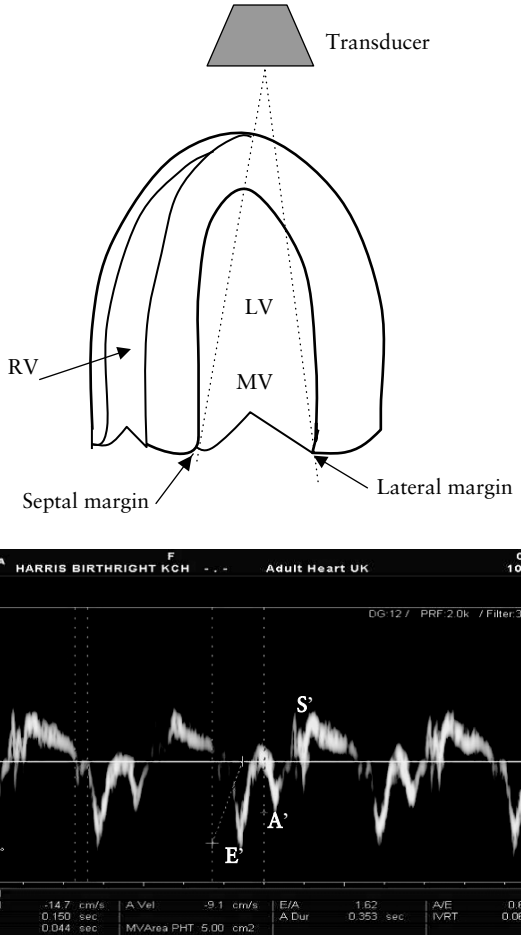

Figure 1 Illustration of cursor placement for measurement of tissue Doppler imaging indices (peak velocity of early (E') and late (A') diastolic filling measured in diastole, and peak systolic velocity (S') measured in systole) at the septal and lateral mitral margins in the apical four-chamber view. LV, left ventricle; MV, mitral valve; RV, right ventricle.

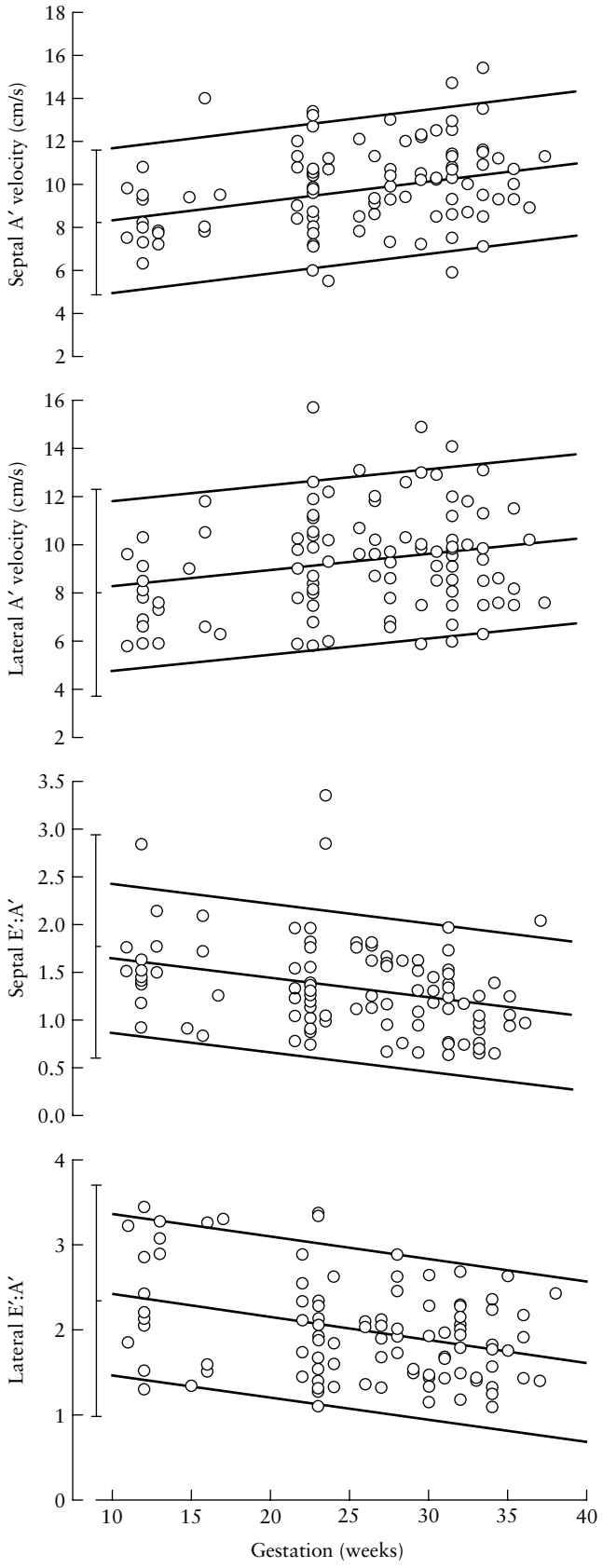

Figure 2 Changes in tissue Doppler imaging late diastolic A' velocity and $E' : A'$ ratio at the septal and lateral margins of the mitral annulus with increasing gestation. Each graph illustrates the regression lines of the normal pregnancies (5^{th}, 50^{th} and 95^{th} centiles). The vertical line at the side illustrates the 5^{th}, 50^{th} and 95^{th} centiles of the non-pregnant controls.

using the Kolmogorov–Smirnov test. Multiple regression analysis was used to evaluate the changes of each parameter with gestation, and 95% reference intervals were created from the formula: centile = mean + 1.96 (SD). In the multiple regression, we investigated the effect of covariates where there has been significant independent contribution in the literature. Comparison between the pregnant women and non-pregnant controls was performed by means of unpaired *t*-tests, using cardiac variables obtained in the first two trimesters of pregnancy, because our previous work has found that this is the stage at which most of the systolic variables reach their maximum values and mean arterial pressure its nadir[4,8].

Reproducibility for a single examiner (J.B.) and between J.B. and a second examiner was analyzed in 10 non-pregnant women. Intraobserver variabilities of Doppler and tissue Doppler imaging measurements were in the range 3–5% and interobserver variabilities 3–7%. For power calculation, using the standard deviation of the non-pregnant controls, recruitment of 18 non-pregnant and 90 pregnant women was calculated to allow detection of 1.3 L in cardiac output as a marker of overall cardiac function, with a 90% power at the 5% level. All statistics were performed using the statistical package SPSS 11.5 (SPSS for Windows, Rel. 11.5.0. 2002, Chicago: SPSS Inc) and MedCalc for Windows, version 8.1.1.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

General

The demographic characteristics of the population are shown in Table 1. The characteristics are expressed as means, SDs, and percentages. There was no difference in the maternal race, age, height, body surface area, and parity between the pregnant and non-pregnant women. Table 2 shows the multiple regression equations for the changes in the cardiac variables assessed by two-dimensional M mode and Doppler echocardiography. Cardiac index, cardiac output, stroke volume, and heart rate increased, while ejection time decreased, linearly with gestation. MAP increased and TVR decreased

Table 1 Demographic characteristics of the study populations

Parameter	*Non-pregnant women* (n = *19*)	*Pregnant women* (n = *104*)	P
Age (years, mean (SD))	30.38 (5.6)	29.58 (4.17)	0.55
Height (m, mean (SD))	1.64 (0.69)	1.67 (0.81)	0.09
BSA (m^2, mean (SD))	1.69 (0.16)	1.69 (0.14)	0.87
Ethnicity (*n* (%))			
Caucasian	15 (78.9)	70 (67.3)	
Afro-Caribbean	2 (10.5)	26 (25)	0.37
Asian	2 (10.5)	8 (7.7)	
Nulliparity (%, mean (SD))	16 (13.1)	62 (27.4)	0.44

BSA, body surface area = (weight$^{0.425}$ × height$^{0.725}$) × 0.007184 (DuBois and DuBois)[34].

significantly in early gestation, but TVR slowly increased after mid-second trimester up to term. The Tei index did not change during gestation. There was a statistically significant decrease in uterine artery PI during gestation. Cardiac index was negatively correlated with age, while stroke volume was positively correlated with height. Ethnicity was related to cardiac output, heart rate and TVR.

Long-axis systole

Long-axis shortening decreased significantly at the septal margin and non-significantly at the lateral margin with increasing gestation (Table 2). Table 3 shows the multiple regression equations for the changes in the TDI cardiac indices. S' velocity did not change significantly during pregnancy at the septal or lateral margin.

Diastole

There was a statistically non-significant decrease in transmitral E velocity, while A velocity significantly increased, resulting in a significant decline in $E:A$ ratio (Table 2). There was a statistically non-significant decrease in E' velocity at the septal and lateral margins, while A' velocity significantly increased with gestation at both margins. $E':A'$ decreased at the septal and lateral margins (Figure 2). $E:E'$ at the septal and lateral margins remained unaltered. $E:A$ (Table 2) and $E':A'$ ratios (Table 3) at the septal and lateral margin related negatively to age, and A' at both margins related positively to age.

Comparison with non-pregnant controls

Cardiac index, cardiac output, stroke volume, and heart rate (Table 4) were higher in the pregnant women compared with the non-pregnant controls. The S' velocity was non-significantly higher at the septal margin (Table 5) and significantly higher at the lateral margin, while TVR, E velocity and $E:A$ ratio (Table 4), the $E':A'$ ratio at the septal margin, and the $E:E'$ ratio using the lateral E' velocity (Table 5) were all significantly lower in the pregnant women than in the non-pregnant controls.

Table 2 Multiple regression equations for Doppler echocardiography in normal pregnancy ($n = 104$)

	Regression			*Covariate*
Parameter	*Equation*	R^2	P	P
Cardiac output	$5.84 + 0.079$ GA $- 0.60$ Et	0.30	< 0.01	(Et) < 0.01
Cardiac index	$3.67 + 0.05$ GA $- 0.031$ Age	0.29	< 0.01	(Age) < 0.01
Stroke volume	$13.26 + 0.3$ GA $+ 37.01$ Ht	0.07	0.02	(Ht) 0.04
Heart rate	$71.62 + 0.69$ GA $- 4.08$ Et	0.24	< 0.01	(Et) 0.02
Ejection time	$298.1864 - 0.6965$ GA	0.05	0.03	
Total vascular resistance	$1378.46 - 37.35$ GA $+ 0.60$ GA$^2 + 61.30$ Et	0.21	< 0.01	(Et) 0.04
Mean arterial pressure	$68.81692 + 0.36$ GA	0.09	< 0.01	
Long-axis shortening (septal)	$9.71 + 0.37$ GA $- 0.01$ GA^2	0.06	0.04	
Long-axis shortening (lateral)	$16.37 - 0.03$ GA	0.01	0.29	
Transmitral E velocity (E)	$85.08 - 0.38$ GA	0.37	0.05	
Transmitral A velocity (A)	$44.35 + 0.38$ GA	0.06	0.01	
$E:A$ ratio	$2.46 - 0.02$ GA $- 0.02$ Age	0.27	< 0.01	(Age) < 0.01
Tei index	$0.35 - 0.0001$ GA	< 0.01	0.94	
Mean uterine artery pulsatility index (PI)	Log(PI) $= 0.2152 - 0.0134$ GA	0.43	< 0.01	

Et, ethnic group; GA, gestational age; Ht, height.

Table 3 Multiple regression equations for tissue Doppler imaging indices in normal pregnancy ($n = 104$)

	Regression			*Covariate*
Parameter	*Equation*	R^2	P	P
Septal E' velocity	$13.75 - 0.06$ GA	0.02	0.13	
Septal A' velocity	$3.14 + 0.10$ GA $+ 0.13$ Age	0.22	< 0.01	(Age) < 0.01
Septal $E':A'$	$2.78 - 0.02$ GA $- 0.028$ Age	0.09	0.001	(Age) < 0.01
Septal systolic velocity (S')	$9.81 + 0.03$ GA	0.01	0.26	
Lateral E' velocity	$19.55 - 0.07$ GA	0.03	0.07	
Lateral A' velocity	$2.99 + 0.08$ GA $+ 0.14$ Age	0.18	< 0.01	(Age) < 0.01
Lateral E' : A' ratio	$4.0 - 0.03$ GA $- 0.04$ Age	0.26	0.001	(Age) < 0.01
Lateral systolic velocity (S')	$13.4 - 0.01$ GA	0.002	0.67	
Transmitral E : septal E' (E/E's)	$6.04 + 0.02$ GA	0.004	0.5	
Transmitral E : lateral E' (E/E'l)	$4.45 - 0.0043$ GA	0.001	0.74	

GA, gestational age.

Table 4 Comparison of maternal cardiac variables assessed by conventional echocardiography between pregnant women and non-pregnant controls

Parameter	*Non-pregnant controls* (n = *19*)	*Pregnant women* (n = *104*)	P
Cardiac output (L/min)	4.35 (0.84)	6.34 (1.21)	< 0.001
Cardiac index (L/min/m^2)	2.58 (0.45)	3.74 (0.75)	< 0.001
Stroke volume (mL)	64.79 (11.4)	79.60 (12.6)	< 0.001
Heart rate (beats/min)	67.74 (10.87)	79.87 (10.41)	< 0.001
Ejection time (ms)	296.32 (26.85)	283.43 (23.37)	0.05
Septal long-axis shortening (mm)	13.27 (2.036)	13.34 (2.05)	0.89
Lateral long-axis shortening (mm)	15.50 (2.89)	15.60 (2.58)	0.86
Total vascular resistance (dynes/s/cm^5)	1478.25 (324.70)	995.39 (188.64)	< 0.001
Mean arterial pressure (mmHg)	77.72 (10.04)	76.47 (7.68)	0.57
E velocity (cm/s)	85.67 (10.96)	77.88 (13.58)	0.03
A velocity (cm/s)	52.08 (9.9)	53.01 (9.85)	0.70
E : *A* ratio	1.68 (0.27)	1.49 (0.31)	0.02
Tei index	0.32 (0.05)	0.34 (0.11)	0.37

Values are mean (SD).

Table 5 Comparison of tissue Doppler imaging variables between pregnant women and non-pregnant controls

Parameter	*Non-pregnant controls* (n = *19*)	*Pregnant women* (n = *104*)	P
Septal *E*′ velocity (cm/s)	13.98 (2.99)	12.68 (2.58)	0.07
Septal *A*′ velocity (cm/s)	8.23 (1.67)	9.21 (1.97)	0.05
Septal *E* : *A* ratio	1.77 (0.59)	1.45 (0.51)	0.03
Septal systolic velocity (cm/s)	9.82 (1.23)	10.38 (1.86)	0.22
Lateral *E* velocity (cm/s)	17.76 (2.85)	18.28 (2.82)	0.48
Lateral *A* velocity (cm/s)	8.01 (2.15)	9.07 (2.11)	0.62
Lateral *E* : *A* ratio	2.34 (0.68)	2.13 (0.63)	0.22
Lateral systolic velocity (cm/s)	12 (2.2)	13.38 (2.42)	0.03
Transmitral *E* : septal *E* (cm/s)	6.35 (1.37)	6.34 (1.44)	0.97
Transmitral *E* : lateral *E* (cm/s)	4.90 (0.81)	4.32 (0.85)	0.01

Values are mean (SD).

DISCUSSION

In recent years, evaluation of systolic and diastolic function using tissue Doppler imaging (TDI) has gained clinical prominence. However, this technology has not been explored in the evaluation of maternal cardiac function and this is the first study to describe normal ranges.

LV systolic function

We found an early non-sustained increase in longitudinal shortening velocities in the first and second trimesters of pregnancy, compared to non-pregnant controls. There was also a 45% higher cardiac output in the first two trimesters, as a result of a higher stroke volume (23%) and heart rate (18%), compared to non-pregnant controls, and this difference increased further towards term. Previous studies have found similar increases in cardiac output[1,8]. Robson *et al.*[2] found that ejection fraction was increased as early as 8 weeks post-conception, remaining constant between 12 and 28–32 weeks of gestation, then declining towards term. Similarly, Kametas *et al.*[8] demonstrated a 4.5% first-trimester enhancement in ejection fraction, compared to non-pregnant controls, with a plateau until 30 weeks of gestation, thereafter decreasing to term[8]. Other studies report either non-significant increases[22] or no change in ejection fraction during pregnancy[23–25]. These studies calculated ejection fraction using the Teicholz formula, which assumes that the LV approximates to an ellipsoid, which is inappropriate for pregnancy, due to changes in LV geometry[2,4,26,27].

Assessment of long-axis function avoids these geometric assumptions. LV fibers are arranged predominantly longitudinally or obliquely in the subendocardium and subepicardium, but circumferentially in the intermediate layers. During early systole, the longitudinal and oblique fibers contract first, causing the cavity to become more spherical. The circumferential fibers then contract and are responsible for ejection. A correlation is reported between the peak velocity of long-axis shortening (*S*′) and ejection fraction in non-pregnant individuals[28–31], and the matched first-trimester rise in *S*′ velocity and ejection fraction are in agreement with longitudinal series which report that most cardiovascular changes begin early and are complete by the first half of pregnancy[2,24].

One recent study reported a correlation of long-axis shortening with stroke volume in the first trimester, and MAP in the mid-second and third trimesters[8]. It is likely that that the decline in long-axis shortening observed in our study population is a reflection of the observed increase in MAP, despite the fact that this remained within normal limits.

LV diastolic function

The increase in *A*′ velocity and decrease in *E*′ : *A*′ ratio are consistent with enhanced left atrial contraction in the face

of the gestational increases in LV mass and afterload previously reported[7]. The transmitral flow patterns showed similar changes and we found a significant correlation between between the $E:A$ and $E':A'$ ratios at both mitral margins ($r = 0.5$).

The transmitral E:TDI E' ratio is a validated, non-invasive index of pulmonary capillary wedge pressure in non-pregnant people[32]. We showed that the $E:E'$ ratio remained within normal limits, which is in agreement with Mesa *et al*., who found normal LV filling pressures during pregnancy[3]. An unexpected result was the observation that $E:E'$ at the lateral margin was 12% lower in the first two trimesters, compared to non-pregnant controls. This dissimilarity in the trend for $E:E'$ at the septal and lateral margins of the mitral annulus (also seen in S' velocity and long-axis shortening) may be a reflection of changes in LV geometry or, more likely, in right ventricular geometry and systolic pressure. These are expected to affect the septum more than the lateral wall of the LV.

Global function

The Tei index is a measure of both LV systolic and diastolic function, with a normal cut-off value of < 0.4 in non-pregnant subjects[16]. We found a wider range of 0.10–0.64 in our pregnant population, compared to 0.2–0.38 in the non-pregnant controls. This result is consistent with the effects of increased afterload and increased mass[33], or of reduced contractility, and is similar to the effect of essential hypertension on the Tei index[33]. It is therefore consistent with the changes shown on transmitral flow and TDI.

Limitations

Our comparison was with non-pregnant control subjects rather than with pre-conception measurements in the study group, and this might have introduced uncontrolled variables. We did not measure ejection fraction or LV mass, as these have been extensively assessed in the literature.

CONCLUSIONS

In conclusion, we have described changes in indices of TDI during normal pregnancy for the first time. Our data demonstrate an increase in measures of LV systolic function and the atrial contribution to diastole, without evidence of a rise in filling pressure.

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