Maternal left ventricular diastolic and systolic long-axis function during normal pregnancy

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KEYWORDS
Maternal cardiac function; Doppler Tissue Imaging; Doppler echocardiography

Abstract Aims: The aim of this study was to evaluate left ventricular (LV) function during normal pregnancy and investigate the effect of maternal factors. Little information about LV diastolic and long-axis systolic function in normal pregnancy exists. Methods and results: Two hundred and twenty eight Doppler echocardiography and DTI studies of the mitral annulus were performed in 63 normal pregnant women longitudinally at 11–14, 20–24, 26–32, 33–38 weeks and 8–12 weeks postpartum. Cardiac output, stroke volume and heart rate increased during pregnancy and total vascular resistance decreased. Long-axis shortening decreased, transmitral A velocity increased (p = 0.003) and the ratio of transmitral E to A velocity decreased (p = 0.001). DTI early diastolic velocity (E0) decreased and late diastolic velocity (A0) remained unaltered. DTI systolic velocity (S0) and the E/E0 ratio did not change significantly during pregnancy. Tei index increased throughout pregnancy (p = 0.03). Maternal age was related to E velocity (p = 0.001) and E/A ratio (p = 0.001) while ethnicity was related to cardiac output (p < 0.001), stroke volume (p < 0.02) and heart rate (p < 0.0001).
Conclusion: This study gives normal ranges for Doppler tissue imaging measurements, but demonstrates that maternal characteristics may affect these and all measures of systolic and diastolic function.

Introduction

In normal pregnancy the maternal left ventricle dilates and develops mild eccentric hypertrophy in response to volume loading and there is an

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increase in stroke volume and heart rate.\textsuperscript{1,2} In pre-eclampsia and fetal growth restriction, deviations from normal left ventricular (LV) transverse systolic function may allow early detection of these conditions\textsuperscript{1,3,4} since the heart starts adapting to the changing hemodynamic state in the prodromal period, but abnormalities of diastolic or long-axis systolic function may be more sensitive.

LV subendocardial fibres are more susceptible than the circumferential fibres to the effects of ischemia or pressure-load.\textsuperscript{5,6} Therefore, in non-pregnant patients, long-axis systolic dysfunction develops before abnormalities of transverse function in patients with cardiomyopathies, hypertensive heart disease, coronary artery disease and aortic stenosis.\textsuperscript{7–9} Similarly, abnormal diastolic function may precede abnormalities of transverse systolic function in disease processes affecting the LV.\textsuperscript{10,11}

However, the few studies of diastolic and long-axis systolic function in normal pregnancies\textsuperscript{1,3,4} give variable results. This variability may partly reflect the small study populations, and differences in population characteristics such as maternal age and race. Differences in methodology are also likely to be important. None used pulsed Tissue Doppler imaging (DTI) at the mitral annulus which is now an established method of assessing diastolic function.\textsuperscript{12} The early diastolic velocity on DTI (E\textsuperscript{′}) is thought to be relatively independent of loading conditions while the transmitral E velocity is highly dependent on left atrial filling pressure. The ratio of transmitral E to DTI E\textsuperscript{′} therefore reflects pulmonary wedge pressure.\textsuperscript{13}

The aim of this longitudinal study was, therefore, to evaluate changes in measures of maternal diastolic and long-axis systolic function in normal pregnancies and to investigate the effect of maternal characteristics on these measures.

Methods

Patients

This was a longitudinal study of maternal cardiac function in 63 healthy pregnant women with normal singleton pregnancies and no history of cardiac disease. The study was approved by the Research Ethics Committee of Kings College Hospital and written informed consent was obtained from all participants. The women were enrolled at their routine first trimester scan. Gestation was confirmed by last menstrual period and ultrasound measurement of the fetal crown-rump-length in the first trimester. The women were examined four times during their pregnancy at 11–14 weeks, 20–24 weeks, 26–32 weeks and 33–38 weeks and once eight weeks to 12 weeks post-partum. Normal fetal anatomy and growth was confirmed by serial ultrasound scans. Pre-determined exclusion criteria were: fetuses with chromosomal abnormalities, genetic syndromes, infections and maternal cardiovascular disease; pre-eclampsia, defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy.\textsuperscript{14} In practice, no exclusions were necessary.

The women were studied after a rest period of 15 min in the left lateral decubitus position. Recordings were made when three consecutive ECG measurements of the heart rate from the R-R interval demonstrated a variation below 10%. One examiner (JB) performed all measurements and in all parameters three cardiac cycles were averaged.

Echocardiography

Imaging and Doppler echocardiography were performed using a 3.5-MHz transducer (Toshiba Apio CV; Toshiba Corporation: Tokyo, Japan) according to the guidelines of the American Society of Echocardiography.\textsuperscript{15} 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.\textsuperscript{6,16} 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 atrial filling (A) were measured and the E to A ratio calculated.\textsuperscript{3,17} The mitral closing to opening time: (a) was measured at the interval from the end to the onset of the mitral inflow velocity pattern. The left ventricular ejection time: (b) was measured from the onset to the end of the Doppler subaortic waveform pattern. The Tei index was calculated as (a–b)/b.\textsuperscript{18} Stroke volume was calculated as the product of the cross-sectional area of the left ventricular (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.\textsuperscript{19} Total vascular resistance (TVR) was calculated as TVR = Mean arterial pressure \times 80/cardiac output. Tissue Doppler imaging recordings were made using a 3.5 mm sample volume for the septal side and a 5 mm sample volume at the lateral sides of the mitral annulus in the 4-chamber view according to the guidelines of the American Society of Echocardiography.\textsuperscript{12} The peak velocity of early (E\textsuperscript{′}) and late (A\textsuperscript{′}) diastolic filling and the peak
systolic velocity ($S'$) were measured and the E/E' ratio was derived for the septal and lateral margins of the mitral annulus.

**Blood pressure**

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.\(^\text{20}\) Mean arterial pressure was calculated from the equation: Mean arterial pressure = (B/P systolic + (2 * B/P diastolic))/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 size fetuses and colour Doppler was used to measure the pulsatility index in the uterine artery.\(^\text{21}\)

**Statistical analysis**

Summary demographic characteristics were obtained for the examined populations. Data were expressed as mean and standard deviation (SD). The normality of the distribution was assessed using the Kolmogorov–Smirnov test. A repeated-measures analysis using mixed models was done.\(^\text{22,23}\) For each measure (response), a model was first fitted to represent the dependence on gestational age, if any. This was either linear or quadratic. In addition to the overall average effect (the "fixed" part), the slope and intercept were allowed to vary from patient to patient (i.e. a "random" effect). Only significant coefficients were retained. Using the resulting model as baseline, the effects of background (demographic) covariates were then estimated.

Reproducibility for a single examiner (JB) and between JB and a second examiner was analysed in 10 non-pregnant women. Intraobserver variabilities of Doppler and tissue Doppler imaging measurements ranged from 3% to 5% and interobserver variabilities from 3% to 7%. A sample size of 34 women would be required to detect a difference of 2 cm/s in $E'$ velocity at the septal and lateral edge of the metal annulus, and 1 L in cardiac output at $P < 0.05$ and 90% power. We tried to recruit a sample size double this in order to allow for patient dropout. Statistical computing was done using the statistical package SPSS 11.5 (SPSS for Windows, Rel. 11.5.0. 2002, Chicago: SPSS Inc) and R system (R Development Core Team, 2005). Mixed models were fitted using the R package nlme.

**Results**

**General**

The demographic characteristics of the population are shown in Table 1. All women had uncomplicated pregnancies. All 63 were examined at 11–14, 62 at 20–24, 59 at 26–32, and 44 at 33–38. 17 women returned for post natal studies. Total vascular resistance decreased significantly with gestation although the mean arterial pressure did not change. Cardiac output, stroke volume and heart rate increased with gestation peaking in the late third trimester (Fig. 1). The uterine artery PI decreased progressively with gestation. Significant covariates on uterine artery PI were parity ($p = 0.037$) and ethnic group ($p = 0.038$).

**Long-axis systole**

In contrast to measures of global systolic function, long axis shortening decreased significantly at the septal ($p = 0.02$), but not the lateral margin of the mitral annulus. Doppler tissue peak systolic velocity did not change with gestation (Fig. 2).

**Diastole**

There was a statistically non-significant fall in transmitral E wave velocity with gestation, but the A wave velocity increased leading to a significant decrease in the E/A ratio (Fig. 3). There was a statistically significant fall in Doppler tissue E' velocity at the septal and lateral margins, and A'

| Table 1 Demographic characteristics of the study populations, mean and standard deviation or number (n) and percentage |
|---|---|
| Age (yr) | 30 (6) |
| Height (m) | 1.64 (0.06) |
| Pre-pregnancy weight (Kg) | 65.20 (16.18) |
| Ethnicity |  |
| Caucasian | 48 (76.2%) |
| Afro-Caribbean | 15 (23.8%) |
| Parity n (%) |  |
| 0 | 39 (61.9%) |
| 1 | 16 (25.4%) |
| 2 | 7 (11.1%) |
| 3 | 1 (1.6%) |
| Non-smoker | 63 (100%) |
| Gestation at delivery (wk) | 39 (2) |
| Birthweight (gm) | 3409 (452) |
did not change significantly either at the septal or lateral margin (Fig. 4). The E'/A' ratio decreased at the septal, but not the lateral margin. There was a non-statistically significant trend to an increase in the E/E₀ ratio at the septal margin, but the ratio remained constant at the lateral margin (Fig. 5).

Maternal characteristics

Height was positively related to cardiac output (p < 0.001) and stroke volume (p < 0.001). Age was associated with S' at the septum and lateral margin (p = 0.02 and p = 0.001, respectively), TVR (p < 0.04), E velocity (p = 0.001), A velocity (p = 0.006), and Doppler tissue A' at both margins (p = 0.001 and 0.001, respectively). The E/A ratio (p = 0.001) and E'/A' ratio at both margins (p = 0.001 and p = 0.001, respectively) were inversely associated with age as was E/E₀ at the lateral margin (p = 0.01).

The adjusted means for cardiac output, stroke volume and heart rate were higher in black compared to white women (7.05 (0.20) vs. 6.33 (0.14) L/min, (p < 0.001), 83.66 (2.45) vs. 77.71 (1.68) mL/min (p < 0.020), and 89.70 (1.56) vs. 80.20 (1.05) bpm (p < 0.001)) respectively.

Post-partum subgroup

Table 2 shows the comparison of Doppler echocardiography and DTI parameters in the subgroup of women evaluated both in the late third trimester and postpartum. Cardiac output, stroke volume, heart rate and S' at the septal margin of the mitral annulus fell significantly compared to the late
third trimester measurement. TVR increased significantly between the late last third trimester visit and post-partum. There was a slight increase in Tei index (Fig. 5, Table 2), although this was not significant.

Discussion

This study showed a 20% increase in stroke volume and a 15% increase in heart rate leading to a 30% increase in cardiac output during pregnancy. This
confirms previous work and is consistent with the expected effects of increased circulating volume and decreased vascular resistance. However, the response to normal pregnancy is not uniform and cardiac output may also remain constant or even fall in the last trimester.

This variation could be related partly to differences in systemic vascular resistance. Blood pressure in an individual can increase despite remaining within the population normal range so that relative change may be more important than the absolute level of blood pressure. However there may also be variability in intrinsic contractile function. We showed a decrease in long axis shortening during gestation in confirmation of a previous cross-sectional study. Long-axis function is more sensitive to changes in both loading and intrinsic contractility than transverse function. However the Doppler tissue S velocity, which did not change significantly during pregnancy, decreased in the post natal period despite normalisation of total vascular resistance, falling below the accepted normal range of 8 cm/s in five of 17 (29%) women. Furthermore, the Tei index which is a combined measure of both systolic and diastolic function rose progressively during pregnancy and increased further after birth. These observations are consistent with an intrinsic abnormality of contractility associated with pregnancy.

Others also showed a fall in systolic function not explicable by changes in vascular resistance. Mone et al., studied the relationship between mean velocity of circumferential fiber shortening and end systolic meridian wall stress as an afterload-adjusted, preload-independent index of contractility. Both this measure and fractional shortening fell by term, decreased further 2–4 weeks post-partum and then returned to baseline by 8–10 weeks. Geva et al. reported a similar decrease in the afterload-adjusted velocity during pregnancy with normalisation post-partum. However, as before, the response to pregnancy is not uniform. In contrast to these studies, Poppas et al. found no change in fractional shortening or velocity of circumferential shortening. Gilson et al. found no change in ejection fraction or fractional shortening, but showed a non-significant increase in the velocity of circumferential fiber shortening and a 12% decrease in left ventricular wall stress, implying an increase in contractility.

Little previous work on diastolic function is available. The first echocardiogram in this study was recorded around the end of the first trimester at 11–14 weeks when increased preload as a result of increased blood volume causes an increased E velocity and a relatively low A velocity.

We then showed a statistically non-significant fall in E velocity and an increase in transmitral A velocity. This confirms longitudinal observations by Valensise et al., and cross-sectional data by Kometas et al. However, several studies show discrepancies with these results. Mabie et al. found no change in E velocity, whilst Mesa et al. reported a progressive increase in E velocity throughout pregnancy. Technical limitations or population characteristics including blood pressure might account for these differences or, as with
measures of systolic function there might be a normal variation in the response of diastolic function to pregnancy. Consistent with this is our observation of a broadening of the $E/E'$ range at the septum and lateral edge in the late third trimester, with some women encroaching on the upper limit of normality. However, although there was a trend to a higher $E/E'$ ratio towards the end of pregnancy, values remained within the normal range. This confirms the work of Mesa et al. who indirectly estimated mean left atrial pressure and found that it did not change during pregnancy, which further suggests that left atrial pressure is normal in healthy pregnancy.

Maternal characteristics

In addition to the temporal pattern in cardiac function, we sought to investigate the effect of maternal characteristics on maternal cardiac function where there has been significant independent contribution in the literature. Height is an important determinant of aortic annulus diameter, and therefore stroke volume and cardiac output, so this finding was expected.

We performed a repeated-measures analysis using mixed models. These models certainly produce $p$-values so that our hypothesis that maternal cardiac variables might be influenced by maternal characteristics is tested, but this technique does not test conventional correlations. However, some trends were observed. We confirmed previous observations in non-pregnant subjects of an increased contribution of atrial activity with increasing age shown by an age-related increase in transmitral peak $A$ and DTI peak $A'$ velocity and a fall in the $E/A$ and $E'/A'$ ratios. By contrast $E/E'$ decreased with age at the lateral margin rather than increased as previously reported and DTI peak $S$ velocity increased with age rather than decreased as previously reported. These discrepancies are likely to be explained by the narrow age range of our pregnant population compared with the data in non-pregnant people which are based on ages ranging from 20 to 80 years.

We observed no racial difference in cardiac index although non-pregnant black subjects are reported to have a lower cardiac output and higher resting systemic vascular resistance than white subjects even after adjusting for body surface area. We showed a lower heart rate in white compared to black women although others showed the reverse. However, our results might be influenced by our small population, and future larger studies may resolve these inconsistencies.

Clinical implications

Changes in measures of diastolic and long-axis systolic function can occur as a result of

<table>
<thead>
<tr>
<th>Parameter</th>
<th>33–38 subgroup</th>
<th>Post-partum</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output L/min)</td>
<td>7.31 (1.20)</td>
<td>4.96 (1.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>89.78 (16.74)</td>
<td>72.76 (13.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>82.64 (12.05)</td>
<td>68.76 (9.46)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ejection time (ms)</td>
<td>273.80 (24.5)</td>
<td>294.50 (17.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Septal long axis shortening (mm)</td>
<td>12.61 (1.64)</td>
<td>12.88 (1.89)</td>
<td>0.64</td>
</tr>
<tr>
<td>Lateral long axis shortening (mm)</td>
<td>15.01 (2.20)</td>
<td>14.29 (2.33)</td>
<td>0.36</td>
</tr>
<tr>
<td>Transmitral $E$ velocity (cm/s)</td>
<td>71.84 (11.35)</td>
<td>76.24 (14.97)</td>
<td>0.38</td>
</tr>
<tr>
<td>Transmitral $A$ velocity (cm/s)</td>
<td>55.17 (8.83)</td>
<td>51.99 (8.25)</td>
<td>0.35</td>
</tr>
<tr>
<td>$E/A$</td>
<td>1.38 (0.30)</td>
<td>1.49 (0.31)</td>
<td>0.29</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>82.09 (6.59)</td>
<td>79.25 (10.13)</td>
<td>0.19</td>
</tr>
<tr>
<td>Total vascular resistance (dynes.s.cm$^{-5}$)</td>
<td>932.63 (172.97)</td>
<td>1320.26 (287.50)</td>
<td>0.001</td>
</tr>
<tr>
<td>Tei Index</td>
<td>0.37 (1.11)</td>
<td>0.44 (0.11)</td>
<td>0.06</td>
</tr>
<tr>
<td>Septal $E'$ velocity (cm/s)</td>
<td>12.44 (3.18)</td>
<td>12.51 (2.04)</td>
<td>0.93</td>
</tr>
<tr>
<td>Septal $A'$ velocity (cm/s)</td>
<td>10.04 (2.05)</td>
<td>8.85 (1.68)</td>
<td>0.08</td>
</tr>
<tr>
<td>Septal $E'/A'$ ratio</td>
<td>1.30 (0.50)</td>
<td>1.47 (0.39)</td>
<td>0.29</td>
</tr>
<tr>
<td>Septal peak systolic velocity (cm/s)</td>
<td>10.58 (1.27)</td>
<td>9.18 (1.18)</td>
<td>0.02</td>
</tr>
<tr>
<td>Lateral $E'$ velocity (cm/s)</td>
<td>16.45 (3.51)</td>
<td>16.14 (2.68)</td>
<td>0.78</td>
</tr>
<tr>
<td>Lateral $A'$ velocity (cm/s)</td>
<td>8.43 (2.25)</td>
<td>7.78 (2.13)</td>
<td>0.36</td>
</tr>
<tr>
<td>Lateral $E'/A'$ ratio</td>
<td>2.13 (0.94)</td>
<td>2.18 (0.64)</td>
<td>0.87</td>
</tr>
<tr>
<td>Lateral peak systolic velocity (cm/s)</td>
<td>12.24 (1.81)</td>
<td>11.05 (2.68)</td>
<td>0.14</td>
</tr>
<tr>
<td>Transmitral $E$/septal $E'$</td>
<td>5.96 (1.61)</td>
<td>6.10 (0.77)</td>
<td>0.76</td>
</tr>
<tr>
<td>Transmitral $E$/lateral $E'$</td>
<td>4.36 (1.10)</td>
<td>4.78 (0.98)</td>
<td>0.25</td>
</tr>
</tbody>
</table>
physiological changes or pathology. These may be surprisingly hard to differentiate since the changes in normal pregnancy are sometimes inconsistent with the expected effects of increased preload or changes in vascular resistance.\textsuperscript{37}

A pathological state is suggested by a rise in LV filling pressure. In our study, the $E'/E$ ratio remained within normal limits throughout gestation, but there was a broadening of the values with a number of subjects almost reaching a ratio of 10. Furthermore the Doppler tissue systolic velocity was abnormal in 29\% of women. We speculate that there is a spectrum of LV response to pregnancy rather than a clear-cut division between normal and pathological making some women more vulnerable to the effects of intercurrent illnesses including anaemia, a sustained relative elevation of blood pressure or sudden intermittent episodes of mild hypertension not requiring treatment.\textsuperscript{38}

Reduced intrinsic function could occur as a result of subendocardial fibrosis consequent on high wall stress or possibly the effect of high catecholamine levels. Idiopathic fibrosis was found in 2 of 39 and 1 of 44 women who died from cardiac causes in recent confidentiality enquiries into maternal deaths in the United Kingdom (1994–1996 and 2000–2002).\textsuperscript{39,40}

Limitations

The population size is small although as large or larger than most published studies. Furthermore, follow-up was incomplete, but this is unfortunately common in such studies because of early delivery and drop out and the study participants arose from a mobile inner city population. However it is conceivable that the women attending post partum evaluations may have been more aware of their general health than those not returning.

Conclusion

Changes in long-axis systolic function and diastolic function occur in the presence of normal transverse systolic function in normal pregnancy and are partly dependent on maternal height, age and ethnicity. The changes do not resolve fully in the early post-partum period suggesting the possibility of intrinsic abnormalities of LV function.

Acknowledgement

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References


