Maternal Cardiovascular Function in Normal Pregnancy
Evidence of Maladaptation to Chronic Volume Overload

Karen Melchiorre, Rajan Sharma, Asma Khalil, Baskaran Thilaganathan

Abstract—The aim of this study was to investigate cardiac functional status in pregnancy using a comprehensive approach taking into account the simultaneous changes in loading and geometry, as well as maternal age and anthropometric indices. This was a prospective cross-sectional study of 559 nulliparous pregnant women assessed at 4 time points during pregnancy and at 1 year postpartum. All women underwent conventional echocardiography and tissue Doppler velocities and strain rate analysis at multiple cardiac sites. Mean arterial pressure and total vascular resistance index significantly decreased (both \( P<0.001 \)) during the first 2 trimesters of pregnancy and increased thereafter. Stroke volume index and cardiac index showed the opposite trend compared with mean arterial pressure and total vascular resistance index (both \( P<0.05 \)). Myocardial and ventricular function were significantly enhanced in the first 2 trimesters but progressively declined thereafter. By the end of pregnancy, significant chamber diastolic dysfunction and impaired myocardial relaxation was evident in 17.9% and 28.4% of women, respectively, whereas myocardial contractility was preserved. There was full recovery of cardiac function at 1 year postpartum. Cardiovascular changes during pregnancy are thought to represent a physiological adaptation to volume overload. The findings of a drop in stroke volume index, impaired myocardial relaxation with diastolic dysfunction, and a tendency toward eccentric remodeling in a significant proportion of cases at term are suggestive of cardiovascular maladaptation to the volume-overloaded state in some apparently normal pregnancies. These unexpected cardiovascular findings have important implications for the management of both normal and pathological pregnancy states.

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Key Words: diastolic dysfunction ■ echocardiography ■ LV hypertrophy ■ pregnancy ■ remodeling ■ tissue Doppler

Understanding cardiovascular physiological adaptation to pregnancy is particularly important in elucidating the pathophysiology and management of hypertensive disorders of pregnancy—still one of the most common causes of maternal morbidity and mortality worldwide. Functional changes of the heart in pregnancy have been widely investigated during the last few decades with relatively inconsistent results.1-6 Some studies demonstrated an enhancement of cardiac function in pregnancy, whereas others showed depressed cardiac function, and a few, unchanged functional status.1-6 The most likely reason for these conflicting results is that complex data on maternal cardiac function has not been interpreted in the context of heart geometry, loading conditions, and maternal anthropometric factors, which are all modified from as early as the time of conception7 and continue to change continuously throughout pregnancy.3-6,4,5 Furthermore, in the majority of previous studies, cardiac data were usually expressed as single echocardiographic indices compared across gestation without clear delineation between normal and abnormal function.3 Hence, an important limitation of previous work is the lack of distinction between physiological cardiac adaptation to pregnancy and cardiac dysfunction as a consequence of the pregnancy.

Cardiac function is a generic and nonspecific concept that, by necessity, varies depending on the clinical context—alterations in function may simply reflect the effect of hemodynamic changes, altered cardiac geometry or body size on heart function, or indicate true cardiac dysfunction. Cardiac function is conventionally measured by assessing cardiac chamber size, ventricular mass, and function.5-13 However, for systolic or diastolic dysfunction to occur to a clinically relevant degree, there would first have to be impaired myocardial contractility and relaxation. Consequently, only an integrated approach using parallel techniques and multiple indices can provide results that reflect the intrinsic myocardial functional status of the heart.5-13

The aim of this study is to understand maternal cardiac adaptation to pregnancy from myocardium to chamber, using a comprehensive approach taking into account the simultaneous...
changes in maternal loading conditions, cardiac geometry, as well as age and anthropometric indices.

**Methods**

This was a prospective cross-sectional study performed over a 5-year period from June 2008 to February 2013. Healthy nulliparous women with singleton viable pregnancy were recruited consecutively from the routine antenatal clinic at St George’s Hospital, University of London. The local institutional review committee approved the study, and all participants provided written informed consent. Women who subsequently developed adverse maternal complications, such as diabetes mellitus, preeclampsia, peripartum cardiomyopathy, pregnancy complication, or any other medical comorbidity, were excluded from the analysis. Women were recruited at 4 time points during pregnancy (11–14, 20–23, 26–32, and 37–39 weeks’ gestation) and at 1 year postpartum after pregnancy care in our institution. A group of 50 non-pregnant healthy volunteer nulliparous women matched for age was also assessed to derive baseline echocardiographic values. All groups were matched for ethnicity and maternal age. To ensure that we recruited optimally healthy women, we also excluded women with a prepregnancy body mass index ≥30 kg/m² and smokers. The study assessment included a medical and family history, measurement of anthropometric indices, blood pressure profile, conventional echocardiography, tissue Doppler (TD) velocity and deformation analysis, and 12-lead ECG. Maternal symptoms were graded according to standard American Heart Association/New York Heart Association classifications. Maternal blood pressure was measured manually from the brachial artery using a mercury sphygmomanometer according to the guidelines of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy.14

**Echocardiography**

All subjects were studied by 2-dimensional and Doppler transthoracic echocardiography at rest in the left lateral decubitus position and data acquired at end expiration from standard parasternal and apical views using a GE Vivid 9 scanner. The methodology is described here in brief and in more detail in the online-only Data Supplement. Chamber left ventricular (LV) diastolic function, left heart chamber filling pressures, and geometry were assessed and graded using standard diagnostic algorithms with the recommended adjustments reflecting the concomitant systolic function and further adjustments reflecting the pregnant state.5–12,15 Regional longitudinal diastolic function was assessed by measuring color TD early and late diastolic velocity and strain rate. Early/late diastolic myocardial TD index ratio of <1 was taken as an index of altered segmental relaxation as previously proposed.16 The severity of LV dysfunction and remodeling was graded accordingly to the European Association and American Society of Echocardiography (EAE/ASE) guidelines.13 Strain and strain rate indices were investigated as previously described.5,9,16,17 Cardiac functional and geometric status is affected by body size.18 To account for the changing body size in pregnancy and among individuals, conventional echocardiographic indices were normalized for the body surface area (BSA).10,19

**Statistical Analysis**

Data were analyzed using SPSS 15 software (SPSS, Chicago, IL). Variables were expressed as median and interquartile range and compared using Mann–Whitney U or \( \chi^2 \) tests, as appropriate. Paired group comparisons were only undertaken if Kruskal–Wallis testing indicated significant differences for multiple group comparisons. A value of \( P<0.05 \) was considered statistically significant, and all tests were 2-sided. A required sample size of 44 in each group was calculated to observe a >15% difference in average septal and lateral mitral valve annulus peak diastolic velocity between cases and controls with 85% power and a 5% type I risk. An over recruitment was planned considering the eventuality of lost to follow-up and a percentage of adverse outcome in \( \approx10\% \) of healthy nulliparous women. Repeatability and reproducibility of both conventional and TD velocity and deformation indices in a subset of patients before study recruitment was previously reported.14

**Results**

Six hundred and twelve pregnant women were recruited, and 559 (91.3%) with a full-term pregnancy with normal maternal pregnancy and neonatal outcomes were finally included into the study analysis. Fifty-three women (8.7%) were excluded because of the development of medical or other complications of pregnancy. Technically adequate echocardiographic assessment enabling analysis of the left and right heart was obtained in 98% and 96% of cases, respectively. The demographic characteristics of the study population are outlined in Table S1 in the online-only Data Supplement.

**Hemodynamic and Geometric Indices**

Significant changes in these indices were noted throughout pregnancy and are summarized in Table 1. The increase in stroke volume (SV) and cardiac output paralleled changes in BSA in the first and second trimesters with SV index and cardiac index being unchanged during the first half of pregnancy (Figure 1). The decrease of total vascular resistance was in excess of what was expected in relation to the BSA, resulting in a significant decrease of total vascular resistance index at term (Figure 2). LV mass (LVM) increased progressively by an average of 40% between the nonpregnant state and term pregnancy (Figure 2). The relative wall thickness was significantly higher compared with the nonpregnant status in the third trimester and at term and returned to baseline value postpartum. Interpreting hemodynamic data in a dichotomized way (physiological versus pathological), using upper threshold indices of 0.42 for relative wall thickness and 95 g/m² for LVM index, cardiac geometry was not significantly abnormally altered by pregnancy (\( P=0.4 \); Table 2).

**Systolic Chamber and Myocardial Functional Indices**

Significant changes in these indices were noted throughout pregnancy and are summarized in Table 3. Interpreting data in a dichotomized way, the proportion of women with radial chamber systolic dysfunction was not significantly higher in pregnancy compared with the nonpregnant state (\( P=0.9 \); Table 2). The proportion of women with longitudinal chamber systolic dysfunction or myocardial systolic dysfunction was not significantly different in pregnancy versus the nonpregnant state (\( P=0.6 \) and \( P=0.7 \), respectively; Table 2).

**Diastolic Chamber and Myocardial Functional Indices**

Significant changes in these indices were noted throughout pregnancy and are summarized in Table 4 and Table S3. Mitral inflow and pulmonary venous velocity and time interval indices, as well as TD velocity indices, changed in pregnancy showing a tendency toward reduced diastolic reserve and impaired chamber diastolic function at term. At 1 year postpartum, there was a tendency toward an improvement of diastolic indices, although they did not return to nonpregnant values (Figure 3). When diastolic indices were interpreted in the context of the simultaneous cardiac remodeling, hemodynamic, and systolic function using validated diagnostic algorithms (Figure S1), chamber diastolic dysfunction was evident.
in late pregnancy (Table 2). A mild degree (stage 1 or 1a) of diastolic dysfunction was seen in a significantly higher proportion of women in the third trimester (13.7%) and at term (17.9%), when compared with the nonpregnant controls and earlier pregnancy (P<0.001; Table 2 and Figure 4). At 1 year postpartum, there was apparent full recovery in diastolic function. Segmental myocardial diastolic dysfunction was seen in 28.4% of women at term, which is a significantly higher proportion than that seen in nonpregnant controls and during the rest of pregnancy (P<0.001; Table 2 and Figure 4).

Right Heart Geometry and Function
Right heart volume was significantly increased in pregnancy and postpartum versus nonpregnant values (Table S2). Tricuspid annular plane systolic excursion declined significantly in the second trimester and at term, returning to normal postpartum. Right ventricular chamber and myocardial diastolic dysfunction were significantly more frequent at term (Table S2; 18% and 29%, respectively; P<0.001), normalizing in the postpartum period. Similarly, they were more frequent than in the nonpregnant state (Table S2; 4% and 13%, respectively).
Clinical Signs and Symptoms

Significant dyspnea at rest (New York Heart Association grade IV) was reported by 7.4% of women at term (7/95), the majority being in the group with chamber diastolic dysfunction (6/17 versus 1/78; \( P < 0.001 \)). All women become asymptomatic postpartum.

Discussion

Healthy pregnancy is universally accepted as a state of physiological adaptation to a protracted volume overloaded state with preserved intrinsic myocardial contractility/relaxation. The current study demonstrates that near term in apparently healthy women with normal pregnancies, there are clear signs...
of early cardiac maladaptation to the volume overload of pregnancy in a small but significant proportion of cases. These findings seem to recover fully by 1 year postpartum.

Cardiac Adaptation From the First to Early Third Trimester of Pregnancy

From the first to third trimester of pregnancy, preload is higher because of increased venous return as reflected in the larger left atrial volumes, whereas afterload is reduced as demonstrated by decreased total vascular resistance, mean arterial pressure, and end-systolic wall stress. The left atrium is moderately dilated in the first trimester as may be seen in patients with anemia and other high-output states in the absence of diastolic dysfunction.20–22 Likewise, it is often present in elite athletes on an intensive training schedule for a year.20 This increase in volume load triggers a remodeling response, which consists mainly of LV geometric changes and spherical dilatation along the LV short axis. This remodeling response increases myocardial contractility, as demonstrated by an increase in SV, heart rate, and cardiac output. The increase in myocardial contractility is also evident in the observed increase in myocardial deformation indices, which reach peak values in the second trimester of pregnancy.

Myocardial deformation is determined by the size of the ventricle, the loading, and the intrinsic myocardial contractility.9 During the first to third trimester of pregnancy, we observed an increase in deformation indices that are likely to represent a true enhancement in myocardial contractility. Over this period, radial systolic chamber function, as expressed by ejection fraction, is maintained, whereas longitudinal systolic function, as expressed by TD velocity and displacement indices, is decreased. The reduction in TD systolic indices is likely to be because of the geometric changes related to the observed ventricular dilatation and increased stroke work. Myocardial deformation indices in diastole—an indirect sign of normal myocardial relaxation—are unchanged during the first to third trimester of pregnancy. Chamber diastolic function is also preserved, and filling pressures are normal.

Cardiac Adaptation in Pregnancy at Term and Postpartum

At term, afterload increases compared with the first half of pregnancy as demonstrated by the increase in end-systolic wall stress—partially compensated by an increase in relative wall thickness. This is likely to be a consequence of the persistent overload of volume, compensated by an enlarged ventricle to maintain SV at the expense of end-systolic wall stress. The magnitude and potential consequences of the observed changes only become evident when pregnancy is compared with other scenarios—for example, elite athletes. In this study, the LVM increased by 35% over the course of pregnancy compared with ≈25% reported in elite athletes on an intensive training schedule for a year.20 This considerable increase in LVM at term is associated with the additional hemodynamic findings of an increase in total vascular resistance index and decrease in cardiac index. These findings at term seem disadvantageous for the ventricle, which shows signs of deterioration in chamber and myocardial function. Indeed, at term, deformation indices are reduced notwithstanding the increased SV. This reduction in systolic deformation indices can be explained by the increase in chamber size and by the increased afterload more than by intrinsic impaired myocardial contractility. Diastolic deformation indices reach their lowest point at term and are an indirect sign of impaired myocardial relaxation, which is evident in almost one third of normal term pregnancies.

When global chamber function is considered, almost one fifth of pregnancies at term meet the EAE/ASE diagnostic criteria for diastolic dysfunction. Diastolic dysfunction was severe enough in this group to cause significant dyspnea at rest (New York Heart Association grade IV) in a third of the women compared with in <2% of women with normal chamber diastolic dysfunction. Impaired myocardial relaxation in the presence of apparently preserved contractility may be explained by the high-energy dependency of this process,
making it more vulnerable to reduced oxygen availability. The constellation of findings at term—reduced SV index, diastolic dysfunction, and eccentric remodeling—have been described in other volume overload states as maladaptation occurs, such as mitral regurgitation.\(^1\) One year was chosen as the appropriate postpregnancy time point for assessment given the previous finding of persistent postpartum cardiac findings in preeclampsia.\(^2\) At 1 year postpartum in the study participants, all geometric and hemodynamic indices returned to baseline.

### Table 3. Left Ventricular Systolic Chamber and Myocardial Functional Indices

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NPC</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>Term</th>
<th>PP</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF, %</td>
<td>65 (55–69)</td>
<td>61 (56–66)</td>
<td>63 (55–67)</td>
<td>60 (54–65)†</td>
<td>60 (55–64)†</td>
<td>63 (51–66)</td>
<td>0.024</td>
</tr>
<tr>
<td>Septal Sm, cm/s</td>
<td>7.0 (6.4–7.4)</td>
<td>6.8 (6.3–7.6)</td>
<td>7.0 (6.0–7.7)</td>
<td>7.3 (6.0–7.9)</td>
<td>6.3 (5.6–7.0)†‡§</td>
<td>6.0 (5.9–7.0)</td>
<td></td>
</tr>
<tr>
<td>Septal Sm/LAX</td>
<td>0.94 (0.87–0.97)</td>
<td>0.85 (0.75–0.97)</td>
<td>0.85 (0.77–0.97)</td>
<td>0.94 (0.90–1.0)</td>
<td>0.81 (0.70–0.89)†‡§</td>
<td>0.80 (0.71–0.89)†‡§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lateral Sm, cm/s</td>
<td>7.1 (6.9–9.3)</td>
<td>7.5 (6.0–9.0)</td>
<td>7.0 (6.0–9.0)</td>
<td>8.0 (7.0–9.2)</td>
<td>7.4 (5.7–8.3)§</td>
<td>7.0 (6.0–8.0)</td>
<td></td>
</tr>
<tr>
<td>Lateral Sm/LAX</td>
<td>0.96 (0.87–1.3)</td>
<td>0.94 (0.77–1.2)</td>
<td>0.91 (0.78–1.0)</td>
<td>0.99 (0.84–1.1)†</td>
<td>0.91 (0.77–1.1)§</td>
<td>0.83 (0.72–0.97)†‡§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAPSE, mm</td>
<td>14 (13–16)</td>
<td>14 (12–15)</td>
<td>13 (12–15)</td>
<td>14 (12–15)*†</td>
<td>12 (10–13)*†‡§</td>
<td>13 (12–15)*</td>
<td></td>
</tr>
<tr>
<td>Long axis shortening lateral</td>
<td>1.9 (1.7–2.2)</td>
<td>1.8 (1.6–2.0)*</td>
<td>1.6 (1.5–1.8)‡</td>
<td>1.6 (1.5–1.9)*</td>
<td>1.5 (1.3–1.7)†‡§</td>
<td>1.6 (1.5–1.9)‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAPSE, mm</td>
<td>14 (13–15)</td>
<td>14 (12–15)</td>
<td>14 (11–15)</td>
<td>14 (13–15)</td>
<td>12 (11–14)*†‡§</td>
<td>14 (12–15)</td>
<td></td>
</tr>
<tr>
<td>Long axis shortening septal</td>
<td>2.0 (1.7–2.1)</td>
<td>1.8 (1.6–1.9)*</td>
<td>1.6 (1.5–1.8)‡</td>
<td>1.6 (1.6–2.0)*†</td>
<td>1.6 (1.4–1.8)*‡</td>
<td>1.8 (1.6–1.9)‡</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as median (interquartile range). EF indicates ejection fraction; LAX, end-diastolic left ventricular long axis length; long axis shortening, MAPSE normalized for LAX (expressed in mm); NPC, nonpregnant controls; PP, postpartum; Sm, color tissue Doppler peak systolic velocity; and Sm/LAX, color tissue Doppler peak systolic velocity normalized for LAX (expressed in cm).

\(^*P<0.05\) vs NPC.

\(†P<0.05\) vs T2.

\(‡P<0.05\) vs T1.

\(§P<0.05\) vs T3.

\(||P<0.05\) vs term.

### Table 4. Left Ventricular Diastolic Chamber and Myocardial Functional Indices

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NPC</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>Term</th>
<th>PP</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/A ratio</td>
<td>1.80 (1.66–2.13)</td>
<td>1.88 (1.55–2.24)</td>
<td>1.63 (1.31–2.01)†</td>
<td>1.61 (1.29–1.71)‡</td>
<td></td>
<td>1.22 (1.03–1.48)</td>
<td></td>
</tr>
<tr>
<td>DT, ms</td>
<td>184 (172–207)</td>
<td>166 (138–201)*</td>
<td>163 (133–183)*</td>
<td>179 (150–207)</td>
<td>167 (155–202)†</td>
<td>166 (139–199)†</td>
<td>0.001</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>74 (68–80)</td>
<td>74 (68–81)</td>
<td>77 (73–83)*†</td>
<td>77 (72–84)*†</td>
<td>81 (75–94)*‡§</td>
<td>81 (77–90)*‡§</td>
<td>0.001</td>
</tr>
<tr>
<td>S/D ratio</td>
<td>1.0 (0.78–1.44)</td>
<td>1.0 (0.85–1.17)</td>
<td>0.98 (0.85–1.20)</td>
<td>1.15 (0.83–1.35)</td>
<td>1.13 (0.93–1.30)</td>
<td>1.0 (0.80–1.20)</td>
<td>0.4</td>
</tr>
<tr>
<td>AR, cm/s</td>
<td>0.26 (0.24–0.28)</td>
<td>0.25 (0.24–0.31)</td>
<td>0.25 (0.23–0.28)</td>
<td>0.25 (0.23–0.31)</td>
<td>0.29 (0.25–0.32)§∥</td>
<td>0.23 (0.19–0.30)§∥</td>
<td>0.01</td>
</tr>
<tr>
<td>AR dur–A dur</td>
<td>−11 (−13 to 0)</td>
<td>−5 (−42 to 24)</td>
<td>0 (−14 to 18)*</td>
<td>−1 (−17 to 4)*‡§</td>
<td>4 (−18 to 28)*‡§</td>
<td>3.5 (−9 to 18)*‡§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tissue Doppler velocity indices</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Septal E'/A'</td>
<td>1.9 (1.8–2.1)</td>
<td>1.5 (1.1–1.9)†</td>
<td>1.6 (1.3–1.8)†</td>
<td>1.1 (1.0–1.4)§</td>
<td>1.2 (1.0–1.4)§</td>
<td>1.6 (1.3–1.8)∥</td>
<td></td>
</tr>
<tr>
<td>Lateral E'/A'</td>
<td>3.2 (2.1–3.8)</td>
<td>2.3 (1.5–3.0)</td>
<td>2.4 (1.6–2.7)</td>
<td>1.9 (1.4–2.1)†§</td>
<td>1.5 (1.3–1.8)†§</td>
<td>2.3 (1.8–2.7)∥</td>
<td></td>
</tr>
<tr>
<td>Septal Em/Am</td>
<td>2.1 (1.8–2.8)</td>
<td>2.1 (1.6–2.8)</td>
<td>2.1 (1.6–2.8)</td>
<td>1.6 (1.2–2.0)†‡§</td>
<td>1.3 (1.1–1.9)†§</td>
<td>2.1 (1.6–3.0)∥</td>
<td></td>
</tr>
<tr>
<td>Lateral Em/Am</td>
<td>3.1 (2.0–3.9)</td>
<td>2.4 (1.6–2.9)</td>
<td>2.5 (1.6–3.1)</td>
<td>1.9 (1.4–2.3)†§</td>
<td>1.6 (1.5–2.8)*§</td>
<td>2.3 (1.8–3.1)∥</td>
<td></td>
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<tr>
<td>Chamber filling pressure indices</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average E/E'</td>
<td>5.6 (5.0–6.2)</td>
<td>5.6 (4.3–6.5)</td>
<td>5.4 (4.7–5.8)</td>
<td>6.0 (4.3–6.4)</td>
<td>6.3 (5.4–6.6)§</td>
<td>5.6 (4.9–6.8)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

\(A\) indicates peak late diastole transmitral wave velocity; \(A'\), peak late diastolic velocity at the mitral valve annulus; \(Am\), peak late diastolic myocardial velocity; \(AR\), peak retrograde late diastolic pulmonary venous flow velocity; ARdur, AR duration; (ARdur–Adur), the time difference between pulmonary AR duration and mitral A-wave duration; \(Average E/E'\), \(E\) to average lateral and septal \(E'\) ratio; \(D\), peak anterograde early diastolic pulmonary venous flow velocity; DT, deceleration time of \(E\) wave; \(E\), peak early diastole transmitral wave velocity; \(Em\), peak early diastolic myocardial velocity; IVRT, isovolumetric relaxation time; NPC, nonpregnant controls; PP, postpartum; and \(S\), peak systolic pulmonary venous flow velocity.

\(^*P<0.05\) vs T1.

\(†P<0.05\) vs NPC.

\(‡P<0.05\) vs term.

\(§P<0.05\) vs T2.

\(||P<0.05\) vs T3.
Comparison With Previous Studies

Our findings confirm those of previous studies, which also showed that pregnancy is a hyperdynamic, high volume, and low resistance state with eccentric remodeling and increased LVM.1 The findings on cardiac function are in agreement with those of Mone et al who also showed a preservation of contractile function throughout pregnancy with a decrease in function near term.3 Our results are aligned in some aspects to those of Savu et al, but in the latter study, echocardiographic changes in the last 8 weeks of pregnancy—where we found cardiac findings to be most pronounced—were not investigated.8 Furthermore, the authors did not formally assess diastolic function, which was the most significant finding in our study. Both previous studies also did not normalize echocardiographic indices for changing BSA and geometry in pregnancy—with demographic data on ethnicity, height, BSA, and body mass index remaining unreported, despite these factors being known to significantly influence cardiac structure and function.18,23

Limitations of the Study

Corroborative evidence for the finding of diastolic dysfunction at term is assumed from the deterioration of indexed hemodynamic parameters, such as SV index, cardiac index, and total vascular resistance index. The latter is based on extensive evidence that cardiovascular structure and function scale with body size—such as it occurs in childhood or different physiological body stature in adults.18,35 Allometric scaling and adjustment of Doppler-derived indices are also important to differentiate the contribution of loading and remodeling versus the effect of intrinsic myocardial contractility/relaxation on the changes of functional indices.18,35 We acknowledge that the increase in BSA because of increased body weight during pregnancy is likely to underestimate the observed cardiac functional changes observed in this study—because the increase in fat-free mass is greater in pregnancy than in nonpregnant women with a similar weight gain. We would argue that using BSA in the metabolically active state of pregnancy may be an underestimate of the tissue oxygen demands, and this is partly supported by

Figure 3. Changes in mitral ratio of peak early to late diastolic filling velocity (mitral E/A ratio) throughout pregnancy. 1st indicates first trimester; 2nd, second trimester; 3rd, third trimester; NP, nonpregnant control; PP, 1-year postpartum; and Term, term of pregnancy. Thick line, box, and whiskers stand for median, interquartile range, 5th and 95th percentiles, respectively. *P<0.05 vs nonpregnant control; †P<0.05 vs T1; ‡P<0.05 vs T2; ||P<0.05 vs term.

Figure 4. Summary of significant left-sided cardiac findings in pregnancy presented in a dichotomized analysis with indices rated as normal or dysfunctional. Myocardial diastolic dysfunction (white column) was diagnosed with average early to late strain rate ratio of <1 and chamber diastolic dysfunction (black columns) according to the American Society of Echocardiography/European Association of Echocardiography diagnostic algorithms. 1st indicates first trimester; 2nd, second trimester; 3rd, third trimester; NP, nonpregnant control; PP, 1-year postpartum; and Term, term of pregnancy. *P<0.05 vs nonpregnant control; †P<0.05 vs T1; ‡P<0.05 vs T2.
the persistent significance of changes in echocardiographic indices seen in this study, even after their normalization for BSA. Second, it could be argued that the modified algorithm of Nagueh et al, which was used to diagnose diastolic dysfunction, was suboptimal because it did not include left atrium volume index or the peak velocity of the tricuspid regurgitation. The opposing argument was that, in this study, specific importance was given to indices that reflect diastolic function at the time of assessment (transmitral, pulmonary, and TD velocities, time intervals, and regional deformations) rather than indices of left atrial remodeling, which commonly reflect the cumulative effect of chronic conditions of volume or pressure load. Hence, it is likely that the use of the modified algorithm under-represents the effects of pregnancy cardiac adaptation. Finally, the study could be criticized for reliance on TD index rather than speckle tracking imaging. However, the use of TD index was deliberate on the basis of the improved reproducibility and reliability of the technique, as well as its accuracy—both in our studies and others.\textsuperscript{15,27,36}

Conclusions
In this prospective study, we have demonstrated that cardiovascular changes in pregnancy follow the typical pathway expected for adaptation of the heart to a protracted increase in volume load. The first response is remodeling to maintain an adequate volume of circulating blood. However, because persistent remodeling is an abnormal situation with inherent mechanical disadvantages, it leads to subtle chamber and myocardial dysfunction by the end of pregnancy in a small but significant number of women labeled as having a normal pregnancy. This cardiac impairment is mainly seen during the relaxation phase, and it is transient because there is full recovery by 1 year postpartum when the heart is unloaded. The relevance of maternal cardiovascular dysfunction to the development of cardiovascular pregnancy complications, such as preeclampsia, deserves further investigation.

Clinical Perspective
The data provided are of value in differentiating physiological from maternal cardiovascular maladaptation in pregnancy. Our assertion that there is cardiac maladaptation in a proportion of pregnant women near term is also supported by data from cardiac biomarkers showing elevated levels of cardiac biomarkers in normal pregnancy and not just with preeclampsia. We and others have previously identified compromised cardiac function in pregnancy complicated by preeclampsia both at the time of diagnosis and in the early preclinical phase at midgestation.\textsuperscript{1,5,26–28} The cardiovascular findings of diastolic dysfunction and myocardial impairment seen in normal pregnancy at term in this study are strikingly similar to those previously observed in preeclampsia.\textsuperscript{15,26–29} It is possible that if these normal pregnancies had not been truncated by term birth, they may have gone on to develop preeclampsia—a time-dependent disorder that is eliminated by such intervention bias. Preeclampsia is conventionally thought to be the consequence of poor placental development, but the latter hypothesis does not explain the similarities between cardiovascular disorders and preeclampsia for predisposing factors, the predominantly cardiovascular clinical features, or the well-recognized long-term cardiovascular legacy of preeclampsia. The latter observations all suggest that preeclampsia has features which are more consistent with a primary cardiovascular disorder rather than that having a placental origin.\textsuperscript{30–34} Although preterm preeclampsia is predominantly of placental origin, we speculate that term preeclampsia—also called maternal preeclampsia—may well be a primary cardiovascular disorder. Parallels can be drawn to gestational diabetes mellitus—a metabolic disorder that is similarly caused by the inability of the maternal pancreas to deal with the metabolic load of the pregnancy is cured by birth and leaves a long-term maternal diabetic legacy.

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Disclosures
None.

References


Maternal Cardiovascular Function in Normal Pregnancy: Evidence of Maladaptation to Chronic Volume Overload
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MATERNAL CARDIOVASCULAR FUNCTION IN NORMAL PREGNANCY: EVIDENCE OF MALADAPTATION TO CHRONIC VOLUME OVERLOAD AT TERM

Short title: Cardiac function and geometry in pregnancy

SUPPLEMENTARY MATERIAL

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METHODS

Echocardiography
All subjects were studied by two-dimensional and Doppler trans-thoracic echocardiography at rest in the left lateral decubitus position and data acquired at end expiration from standard parasternal and apical views using a GE Vivid 9 scanner. For each acquisition, three cardiac cycles of non-compressed data were stored in cine-loop format and analyzed off-line by one investigator (KM) on a dedicated workstation (GE Echopac system) to derive conventional and tissue Doppler indices. The investigator who performed the off-line analysis was blinded for patient group derivation.

Cardiovascular system assessment
Chamber left ventricular (LV) diastolic function, left heart chamber filling pressures and geometry were assessed and graded using standard diagnostic algorithms with the recommended adjustments reflecting the concomitant systolic function and further adjustments reflecting the pregnant state. As diastolic indices are strongly affected by age, in order to properly interpret cardiac findings age-adjusted cut-off for diastolic indices were used differentiating the 20-39 year age group. Indices were only considered as abnormal for the categorical analysis if they were >2 SDs from the expected mean for the age group. Pregnancy is a state of changing loading, in order to limit the effects of preload and after-load on the measurement of chamber function emphasis was given to those cardiac indices which are least affected by loading conditions (left lateral more than septal tissue Doppler indices). Finally, in view of the acute nature of PE on the cardiovascular system, specific importance was given to indices that reflect diastolic function at the time of assessment (transmitral, pulmonary and TD velocities, time inter intervals, and regional deformations) rather than indices of left atrial remodeling, which commonly reflect the cumulative effect of filling pressure in chronic conditions such as longstanding essential hypertension.

Regional longitudinal diastolic function was assessed by measuring color TD early and late diastolic velocity and strain rate indices positioning the sample at the level of the basal and midsegments of the inferoseptal and anterolateral LV walls in 4-chamber view. Early/late diastolic myocardial TD index ratio of <1 was taken as an index of altered segmental relaxation (segmental diastolic dysfunction) as previously proposed.

The following diastolic indices were measured: mitral inflow and pulmonary flow velocity and time interval indices; septal and lateral mitral annular pulsed tissue Doppler velocity indices in 4 chamber view; Color TDI velocity indices at the basal and mid segments of the inferoseptal and anterolateral LV walls. Other clinically validated indices were derived from the previous ones using standardized formulae.

LV chamber radial systolic function was derived by measuring ejection fraction (EF) from Simpson's modified biplane method from apical four-chamber and two chamber views. LV chamber radial systolic dysfunction was defined as EF less than 55%. LV longitudinal systolic function was derived by measuring color tissue Doppler velocity and displacement indices at the level of the basal and mid segments of the inferoseptal and anterolateral LV walls. Longitudinal systolic dysfunction was defined as average peak systolic color tissue Doppler velocity at the basal level of the anterolateral and septal LV wall index (Av Sm divided by LV long axis length) two SDs below the expected mean for age. LV cavity dimensions, wall thickness,
volumes and mass were calculated using linear measurements as previously described. LV geometry was defined as normal if relative wall thickness was below or equal to 0.42 and left ventricular mass index was below or equal to 95 g/m² and altered in all the other circumstances. Hemodynamic indices were calculated by Doppler methods using standardized formulae. The severity of LV dysfunction and remodeling was diagnosed and graded accordingly to the European Association and American Society of Echocardiography (EAE/ASE) guidelines.  

**Strain and strain rate assessment**

Strain and strain rate indices were investigated as previously described. Segmental peak systolic strain rate was considered abnormal if it was two SDs below the expected mean for age. If at least one myocardial segment was affected, it was termed segmental myocardial systolic dysfunction. Early to late diastolic strain rate ratio was considered abnormal if it was two SDs below the expected mean for age. If at least one myocardial segment was affected, it was termed segmental myocardial diastolic dysfunction. If the average of the investigated segments was below the cut-off value was termed systolic or diastolic myocardial dysfunction, respectively. Color TDI and color TDI-encoded strain and strain rate analysis are detailed in the expanded method in supplementary material.

**Correction of indices and cut-off values**

Cardiac functional and geometric status is affected by body size. In order to account for the changing body size in pregnancy and among individuals, conventional echocardiographic indices were normalized for the body surface area using the DuBois and DuBois formula (BSA = (W^{0.425} x H^{0.725}) x 0.007184 where the weight is in kilograms and the height is in centimeters). Tissue Doppler velocity and displacement indices have recently been shown to require scaling for LV length in healthy humans. In order to account for the hypothetical change in LV geometry in pregnancy and among individuals, tissue Doppler velocity and displacement indices were adjusted for the actual end-diastolic left ventricle long axis length. The average peak systolic color tissue Doppler velocity at the basal level of the anterolateral and inferoseptal LV wall index (Av Sm/LV long axis length) two SDs below the expected mean for age was calculated to be 0.5 for an age ranging between 20 and 40 years, corresponding to a cut off value of 4 cm/sec when the velocity is not normalized for LV geometry as previously described. Average peak systolic strain rate and average early to late diastolic strain rate ratio two SDs below the expected mean for an age ranging between 20 and 40 years was calculated to be 0.90 and 1, respectively.

**Repeatability and reproducibility**

In brief, to test inter-observer and intra-observer reproducibility, two independent operators undertook off-line analyses on the cine-loops from 10 randomly selected women and repeated this after one month. The 95% limits of agreement, coefficients of variation, within-subjects standard deviations and repeatability coefficients were calculated and previously published in extent. The intra-observer and inter-observer coefficients of variation ranged between 1.7% and 12% for all conventional, tissue Doppler, strain and strain rate indices. The intra- and inter-observer 95% limits of agreements were good for all indices. Furthermore, in this study all deformation indices were derived and analyzed by a single operator (KM) using a single ultrasound platform, thereby minimizing errors due to reproducibility and different equipment manufacturers.
Calculation of echocardiographic indices

Stroke volume (SV) was calculated as the product of aortic Doppler flow velocity time integral and cross-sectional area of the left ventricle outflow tract. SV index (SVI) was calculated as SV divided by body surface area (BSA).

Cardiac output (CO) was obtained as the product of stroke volume and heart rate derived from ECG monitoring. Cardiac index (CI) was calculated as CO divided by BSA.

Mean arterial pressure was calculated as \([\text{systolic blood pressure}+(2\times\text{diastolic blood pressure})]/3\).

Total vascular resistance (TVR) was calculated in dynes x sec x cm\(^5\) according to the formula: \(\text{TVR} = (\text{Mean arterial pressure in mmHg}/\text{CO in L/min}) \times 80\). TVR index (TVRI) was calculated as TVR multiplied by BSA.

Cardiac work (CW) was calculated using the formula: \(\text{CW}=\text{CO} \times \text{MAP}\).

Relative wall thickness (RWT) was calculated as following: \(\text{RWT}=2\times\text{LV posterior wall thickness in diastole}/\text{LV end diastolic dimension}\).

Left ventricle meridian end-systolic stress (ESS) was calculated using cuff systolic blood pressure (SBP) taken at the end of the echocardiographic examination. ESS meridian = \(1.35\times\text{SBP}\times\text{LVESD}]/[(4\times\text{LVPWs}) \times(1+{\text{LVPWs}/\text{LVESD}})]\), where LVESD is left ventricle end-systolic dimension and LVPWs is left ventricle posterior wall thickness in systole.

Left ventricular mass (LVM) was calculated from LV linear dimensions based on modeling the LV as a prolate ellipse of revolution: \(\text{LVM}=0.8\times(1.04[(\text{LVEDD}+\text{LVPWd}+\text{LVPWs})3-(\text{LVEDD})3]+0.6 \text{ g.} \) Where LVPWs is LV posterior wall thickness in systole. LVM index (LVMI) was calculated as LVM divided by BSA.

Cardiac geometry was defined accordingly to the following 4 mutually exclusive categories:

- Normal geometry: normal LVMI (< 95 g/m\(^2\)) and RWT (< 0.42).
- Concentric remodeling: normal LVMI with increased RWT (> 0.42).
- Eccentric remodeling: increased LVMI (> 95 g/m\(^2\)) with normal RWT.
- Concentric hypertrophy: increased LVMI (> 95 g/m\(^2\)) and RWT (> 0.42).

Right-sided cardiovascular system assessment

Right heart function and remodeling were assessed integrating conventional echocardiographic indices and tissue Doppler velocity and deformation indices following recently published guidelines. Right ventricle (RV) hypertrophy, RV enlargement, right atrial (RA) enlargement, RV longitudinal systolic dysfunction, RV global diastolic dysfunction were defined as present according to the European Association and American Society of Echocardiography 2010 guidelines.\(^3\)

Technical details for color tissue Doppler and color tissue Doppler-encoded strain and strain rate analysis are provide in the supplementary material.

Color Tissue Doppler study and derived myocardial deformation analysis was performed at the level of the inferoseptal, anterolateral and right ventricle walls in 4-chamber view with samples positioned at the level of the base and mid myocardial segments. Frame-by-frame manual tracking was performed during post-processing to maintain the computational area within the myocardial region of interest throughout the cardiac cycle. Aortic valve opening and closure were defined using pulsed wave Doppler tracings acquired during the same examination and with a similar R–R interval in order to determine the duration of ejection. A frame rate of 200–300 frames per second was used to acquire data. An image sector angle of 15° and an optimal
depth of imaging were used to increase temporal resolution. Special attention was paid to the color Doppler velocity range setting in order to avoid any aliasing within the image. For this purpose and to simultaneously optimize velocity resolution, pulsed repetition frequency (PRF) values were set as low as possible, just avoiding aliasing. A computation area of 10 mm and with a width of 1 mm (to avoid averaging different ultrasound beams) was used. Color tissue Doppler encoded strain and strain rate indices were measured from the same myocardial regions. All parameters were averaged over 3 cardiac cycles. Tissue Doppler, strain and strain rate indices are given as absolute values.
REFERENCES


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<td>62* (55-61)</td>
<td>65† (60-73)</td>
<td>70*†† (64-80)</td>
<td>75†† (67-85)</td>
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<td>BMI (kg/m²) at echocardiogram</td>
<td>21 (19-24)</td>
<td>23* (20-25)</td>
<td>24†* (22-27)</td>
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<td>1.39*</td>
<td>1.51†</td>
<td>1.62*††</td>
<td>1.72*†† §</td>
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<td>12 (11-14)</td>
<td>22 (20-23)</td>
<td>28 (27-30)</td>
<td>36 (35-38)</td>
<td>12 (12-14)</td>
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<td>40.1</td>
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<td>Birth-weight (centile)</td>
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<td>51 (36-79)</td>
<td>48 (31-74)</td>
<td>46 (31-69)</td>
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Data are expressed as median (interquartile range) or number of patients (percentage). NPC=non-pregnant controls, PP=post-partum, BMI=body mass index; BSA=body surface area; GA=gestational age; BW=birth weight. All the anthropometric measurements were taken at the moment of the echocardiographic assessment. S=significant; NS=not significant; *P<0.05 versus NPC; †P<0.05 versus T1; ‡P<0.05 versus T2; §P<0.05 versus T3; || P<0.05 versus term.
### Table S2. Right heart geometric and functional indices

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<th>Parameter</th>
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<td>Right atrial volume (ml)</td>
<td>37 (32-43)</td>
<td>57* (44-68)</td>
<td>45*† (38-52)</td>
<td>52* (42-56)</td>
<td>41†§ (37-54)</td>
<td>43*†§</td>
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<tr>
<td>Sm (cm/sec)</td>
<td>10.5 (9.0-11.3)</td>
<td>10.0 (9.1-11.2)</td>
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<td>TAPSE</td>
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<td>21* (19-23)</td>
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<td>Basal peak systolic strain rate (1/sec)</td>
<td>2.0 (1.7-2.7)</td>
<td>1.95 (1.7-2.7)</td>
<td>2.3 (1.7-3.0)</td>
<td>2.0 (1.7-3.4)</td>
<td>1.8 (1.4-3.0)</td>
<td>1.5 (1.5-3.4)</td>
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<td>Basal end systolic strain (%)</td>
<td>28 (24-47)</td>
<td>32 (25-41)</td>
<td>34 (27-42)</td>
<td>34 (31-48)</td>
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<td>Em/Am</td>
<td>1.25 (0.81-1.72)</td>
<td>1.70* (1.25-2.33)</td>
<td>1.50* (1.1-2.2)</td>
<td>1.39†‡ (0.94-1.60)</td>
<td>0.97*†‡§ (0.84-1.42)</td>
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<td>Basal early to late diastolic strain ratio</td>
<td>1.29 (0.67-1.67)</td>
<td>1.79* (1.14-2.72)</td>
<td>1.55* (1.12-2.31)</td>
<td>1.39† (0.89-1.74)</td>
<td>1.0†‡ (0.85-1.25)</td>
<td>1.46†</td>
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NS=not significant; *P<0.05 versus NPC; †P<0.05 versus T1; ‡P<0.05 versus T2; §P<0.05 versus T3; || P<0.05 versus term.
Sm=Colour tissue Doppler peak systolic velocity; TAPSE= tricuspid annular plane systolic excursion; Em: Colour tissue Doppler peak early diastolic velocity; Am: Colour tissue Doppler peak late diastolic velocity.
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<td>Early to late diastolic strain rate ratio</td>
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</tbody>
</table>

NS=not significant; *P<0.05 versus NPC; †P<0.05 versus T1; ‡P<0.05 versus T2; §P<0.05 versus T3; || P<0.05 versus term.
Figure S1. Diagnostic algorithm for the classification of diastolic dysfunction

- **EF>50%**
  - Lateral $E'>=14$ cm/sec
    - Normal diastolic function
    - $E/A<0.73$
      - $DT>194$ ms
      - IVRT$>83$ ms
      - $Val\Delta E/A<0.5$
      - $\pm Av\ E/E'<=8$
    - $E/A>2.33$
      - $DT<138$ ms
      - IVRT$<51$ ms
      - $\pm AR-A>=30$ ms
      - $\pm Val\Delta E/A>0.5$
      - $\pm Av\ E/E'>=13$
  - Lateral $E'<14$ cm/sec
    - ARdur-Adur
      - Impaired myocardial relaxation with normal left ventricular end diastolic pressure (GRADE I)
      - Impaired myocardial relaxation with increased left ventricular end diastolic pressure (GRADE Ia)
    - Pseudonormal filling pattern (GRADE II)
    - Restrictive pattern (GRADE III)