Left Ventricular Diastolic Function in Normal Human Pregnancy

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Background—Little information is available about changes in left ventricular diastolic function during pregnancy. We used mitral inflow and pulmonary venous flow profiles to evaluate left ventricular diastolic function in 37 healthy pregnant women 26 to 41 years old (mean, 32 years).

Methods and Results—Echocardiographic studies were performed at the end of each trimester. Eight subjects (control group) underwent similar testing 1 to 3.5 months (mean, 1.7 months) postpartum. During pregnancy, the cardiac output increased significantly as a result of an increased heart rate and, to a lesser degree, stroke volume. Significantly decreased systemic vascular resistance and increased left ventricular mass were also noted. Peak mitral flow velocity in early diastole (E) increased 13.3% during the first trimester and remained at the high end of normal throughout pregnancy. Peak A-wave velocity (A) increased maximally in the third trimester. Compared with control subjects, first-trimester subjects had a significantly increased E/A ratio. The ratio subsequently decreased, reflecting the augmented A-wave velocity. Pulmonary venous peak systolic forward flow velocity increased, peaking in the second trimester (nonsignificant), but returned to baseline levels postpartum. The pulmonary venous diastolic time-velocity integral decreased significantly from the first to the third trimester. Peak pulmonary venous reverse flow velocity at atrial contraction increased significantly, without being markedly changed in duration.

Conclusions—Pregnancy, a chronic, natural volume-overload state, has important effects on hemodynamic and echocardiographic variables. Based on pulmonary venous flow and left ventricular inflow velocities, our results provide a standard reference concerning diastolic filling dynamics by trimester. (Circulation. 1999;99:511-517.)

Key Words: pregnancy ■ hemodynamics ■ echocardiography ■ diastole

Pregnancy causes dramatic, usually reversible, changes in a woman’s cardiovascular system. Maternal heart disease (present in 2% of all pregnancies) is the most important nonobstetric cause of death in pregnant women.1 With non-invasive techniques, the patterns of maternal cardiovascular changes can be determined throughout pregnancy. The literature includes studies in which echocardiography was used to evaluate left ventricular (LV) systolic function and cardiac hemodynamics in pregnant patients.2-7 Little information is available, however, about the physiological changes in LV diastolic function that occur during pregnancy.5 Only within the past decade have clinicians and researchers discovered that abnormalities of LV diastolic function are important contributors to the symptoms of a variety of cardiac disorders, including those involving normal or near normal systolic function.8 Therefore, a thorough study of LV diastolic function in normal pregnancy would be useful, not only to assess maternal health in pregnant women with cardiovascular disease but also to predict and possibly treat complicated pregnancies.

LV diastolic function may be assessed by recording the velocity of flow through the mitral valve and pulmonary veins. The mitral inflow profile is affected by a complex interaction of many factors, including myocardial relaxation, ventricular compliance, pericardial restraint, preload and afterload, and myocardial contractility.9 Pregnancy causes a 40% increase in the preload© and an increase in the LV wall thickness and mass.4 Therefore, we hypothesized that LV diastolic filling patterns would be altered during pregnancy. To test this hypothesis, we used diastolic mitral inflow and pulmonary venous flow profiles to prospectively evaluate LV diastolic function in healthy pregnant women.

Methods

Study Participants
The study was performed between July 1996 and August 1997. The participants were 37 healthy pregnant women 26 to 41 years old (mean, 32 years), each of whom carried a single fetus. All the subjects were recruited during the first trimester of pregnancy. Each subject had a normal clinical cardiovascular history and normal...
The pulmonary vein systolic fraction, ie, the sum of the pulmonary venous forward flow fraction and the atrial contraction (A-dur/PVA-dur ratio), Cecconi and coauthors\textsuperscript{13} showed that a value of $\leq0.9$ predicts an LV end-diastolic pressure (LVEDP) of $>20$ mm Hg. Appleton and colleagues\textsuperscript{14} and Rossvoll and Hatle\textsuperscript{12} proved that, if the PVA-dur exceeded the A-dur by $>30$ ms, this finding had an 85% sensitivity and a 79% specificity for predicting an LVEDP of $>15$ mm Hg. We used both formulas to document the LVEDP during pregnancy.

**Statistical Analysis**

Baseline hemodynamic and Doppler variables are expressed as the mean±SD. Differences between mean values for hemodynamic and Doppler variables obtained at each visit were compared by ANOVA. When intergroup differences were found, Scheffe's test was performed to determine which groups were significantly different. In all the statistical tests, a value of $P<0.05$ was considered significant.

To determine interobserver and intraobserver variability of Doppler echocardiographic measurements, variables for 10 randomly selected patients were analyzed by 2 independent observers (interobserver variability) and by 1 observer on 2 different occasions (intraobserver variability).\textsuperscript{15}

**Results**

One of the 37 subjects was excluded after she underwent a first-trimester miscarriage; another subject missed her second-trimester visit. The control group underwent postpartum studies 1 to 3.5 months (mean, 1.7 months) after delivery.

**Hemodynamic Variables**

Table 1 and Figures 2 through 4 show the hemodynamic variables observed during and after normal pregnancy. The systolic blood pressure was unchanged throughout pregnancy. The diastolic blood pressure decreased slightly, reaching its nadir in midpregnancy; this difference was nonsignificant ($P=NS$), and the pressure returned to nonpregnant levels near term.\textsuperscript{2,4,6}

The mean arterial pressure decreased maximally in the second trimester and returned to baseline postpartum ($P=NS$).\textsuperscript{16}

SVR, based on the ratio between the cardiac output and the mean arterial pressure, decreased by 350 dynes s cm$^{-5}$ (23%) ($P<0.05$) in the second and third trimesters, remaining at baseline levels in the first trimester and postpartum\textsuperscript{15} (Figure 2). Because the cardiac output remained elevated until term, SVR was decreased until term postpartum ($P=NS$).

At 34±2 weeks' gestation, the heart rate increased by 21.8%, from 68±6 to 87±10 bpm. This change was significant when the second- and third-trimester results were compared with the postpartum results ($P<0.05$) (Figure 3). The heart rate increased early and peaked at term (maximum increase, 19 bpm).

Throughout gestation, the stroke volume increased by 13%, from 62±8 to 71±14 mL ($P=NS$).
The mean cardiac output, as determined by the pulsed-wave Doppler method, increased throughout pregnancy, from 4.6 ± 0.8 L/min in the control subjects to 6.0 ± 1.3 L/min at 34 ± 1 weeks’ gestation. The cardiac output underwent a significant increase throughout gestation (Figure 4).

From the first to the third trimester, the mean cardiac index increased by 20.6%, from 2.7 ± 0.5 to 3.4 ± 0.6 L·min⁻¹·m⁻². The increased cardiac output was due to both a significant increase in the heart rate and a slight increase in the stroke volume.

The aortic valve cross-sectional area did not change significantly during or after pregnancy. Compared with the first-trimester findings, the third-trimester results showed a slight trend toward an increasing aortic valve diameter (mean extent of increase, 6.17%).

**Echocardiographic Variables**

Table 2 and Figure 5 show the 2D echocardiographic variables observed during and after normal pregnancy. The LV end-diastolic and end-systolic dimensions did not change significantly during or after pregnancy. Compared with control values, the LV ejection fraction and LV fractional shortening did not change during pregnancy. From the first to the third trimesters, the left atrial size increased by 9.1%, from 3.0 ± 0.4 to 3.3 ± 0.4 cm, but this change was not significant. LV mass was 15.6% greater in the third trimester than in the first trimester (P<0.05) (Figure 5).

**LV Inflow Velocities**

Table 3 and Figure 6 show the peak mitral flow velocity in early diastole (E) and at atrial contraction (A), as well as the E/A ratio, mitral deceleration time (DT), and IVRT in each trimester and postpartum. Compared with postpartum (control) subjects, women in the first trimester had a higher E value, which increased by 13.3%, from 78 ± 13 to 90 ± 17 cm/s. This value remained at the high end of normal throughout pregnancy. The peak A-wave velocity increased maximally in the third trimester, by 17.6%, but no significant...
change was seen between trimesters. The E/A ratio decreased during pregnancy, reflecting the rise in the A-wave velocity. Compared with control subjects, first-trimester subjects had a significantly increased E/A ratio. No significant change was seen in the IVRT or DT. In the postpartum period, the DT was significantly prolonged, probably because of slower heart rates.

**Pulmonary Venous Flow Velocities**

Table 3 and Figure 6 show pulmonary venous flow throughout pregnancy. Transthoracic pulmonary venous flow Doppler recordings were obtained in 94.5% of the subjects.

In most pregnant women, the peak pulmonary venous flow velocities in early ventricular systole (PVs1) and in later ventricular systole (PVs2) were fused, and the pulmonary systolic component was calculated as a unit. Interestingly, the peak systolic forward flow velocity (PVs) increased during pregnancy, peaking in the second trimester, but this increase was not significant, and the PVs returned to baseline levels in the postpartum period. The pulmonary venous diastolic forward flow (PVd) velocity increased in the first trimester, maintaining the normal diastolic predominance for this age group, as seen in our postpartum (control) subjects. In the second trimester, the relationship between PVd and PVs changed. In the second and third trimesters, a nonsignificant trend toward systolic dominance was documented. The increase in PVd velocities in the first trimester correlated with the slight increase in the mitral E value. The PVdTVI decreased during pregnancy by 23%, from 11.0 to 8.5 cm; this change became significant in the third trimester ($P<0.05$). The peak pulmonary venous reverse flow velocity at atrial contraction (PVa) increased significantly ($P<0.05$) during pregnancy, by 22%, from 23.0 (control value) to 29.5 cm/s, without showing a significant change in duration. This finding correlated with the increase in the velocity of the mitral A wave during pregnancy. The PVs and peak pulmonary venous diastolic flow velocity (PVd) ratio tended to increase during pregnancy.

**Mean LAP and LVEDP**

Indirectly, we observed no increase in the mean LAP or the LVEDP during pregnancy.

**Reproducibility of Measurements**

For pulmonary venous flow velocities, the interobserver and intraobserver variability values were $0.84\pm4.2\%$ ($r=0.98$) and $0.2\pm1.7\%$ ($r=0.99$), respectively, for the PVs; $0.15\pm5.8\%$ ($r=0.97$) and $0.1\pm1\%$ ($r=0.99$), respectively, for

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**Table 2. 2D Echocardiographic Variables During and After Normal Pregnancy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>T1 (10±1 wk)</th>
<th>T2 (24±2 wk)</th>
<th>T3 (34±1 wk)</th>
<th>Postpartum* (1.7±1 mo)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV diastolic diameter, cm</td>
<td>4.3±0.4</td>
<td>4.4±0.4</td>
<td>4.3±0.4</td>
<td>4.3±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>LV systolic diameter, cm</td>
<td>2.8±0.3</td>
<td>2.8±0.3</td>
<td>2.8±0.3</td>
<td>2.8±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Left atrial size, cm</td>
<td>3.0±0.4</td>
<td>3.2±0.4</td>
<td>3.3±0.4</td>
<td>3.1±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Septal wall thickness, cm</td>
<td>0.8±0.1</td>
<td>0.8±0.1</td>
<td>0.9±0.1</td>
<td>0.9±0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Posterior wall thickness, cm</td>
<td>0.8±0.1</td>
<td>0.8±0.1</td>
<td>0.9±0.1</td>
<td>0.9±0.1</td>
<td>NS</td>
</tr>
<tr>
<td>LV fractional shortening, %</td>
<td>35.4±4</td>
<td>35.0±5</td>
<td>34.5±3</td>
<td>35.0±3</td>
<td>NS</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>61±4.5</td>
<td>61±4.5</td>
<td>60±3</td>
<td>60±3</td>
<td>NS</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>108±14</td>
<td>115±16</td>
<td>128±18</td>
<td>116±15</td>
<td>T3 vs T1†</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>63±8</td>
<td>65±8</td>
<td>72±10</td>
<td>69±7</td>
<td>T3 vs T1†</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

*Control group.

†$P<0.05$. 
the peak PVd; 0.54±7.4% (r=0.94) and 1±6.2% (r=0.99), respectively, for the PVa; and 1.2±4.8% (r=0.98) and 0.6±1.4% (r=0.99), respectively, for the PVa-dur.

**Discussion**

This study characterized the LV response to a chronic volume overload state (pregnancy) in healthy women, paying particular attention to changes in the diastolic filling patterns of the left ventricle (Figure 7). Our data confirmed observations previously made with invasive and noninvasive methods. As expected, we noted a significant increase in the heart rate, cardiac output, cardiac index, and LV mass and index, as well as a significant decrease in SVR, during pregnancy. We also noted an increase in stroke volume and LV end-diastolic septal and posterior wall thickness, but these increases were not significant. Compared with control values, the LV ejection fraction and LV fractional shortening did not change during pregnancy; this finding is supported by the findings of Katz and associates but not others.

The LV end-diastolic and end-systolic dimensions did not change significantly during or after pregnancy; this finding agrees with the results of Mabie and coworkers but differs from those of other investigators.

We observed a slight but not significant increase in left atrial size. This has been shown to be an indirect indicator of LV filling status. The increase in atrial diameter during pregnancy, as documented by ourselves and others, supports the findings of Katz and associates but not others.

Pregnancy causes an increase in LV wall thickness and mass that is demonstrable in the second trimester and is most marked at the end of pregnancy. Our findings confirm that LV hypertrophy occurs during pregnancy because of increased blood volume and cardiac output; these changes

<table>
<thead>
<tr>
<th>Variable</th>
<th>T1 (10±1 wk)</th>
<th>T2 (24±2 wk)</th>
<th>T3 (34±1 wk)</th>
<th>Postpartum* (1.7±1 mo)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVRT, ms</td>
<td>74±12</td>
<td>80±12</td>
<td>82±12</td>
<td>84±8</td>
<td>NS</td>
</tr>
<tr>
<td>E, cm/s</td>
<td>90.0±17</td>
<td>91.5±19</td>
<td>84.0±19</td>
<td>78.5±13</td>
<td>NS</td>
</tr>
<tr>
<td>A, cm/s</td>
<td>58.5±13.5</td>
<td>66.0±12</td>
<td>68.0±14</td>
<td>56.0±5</td>
<td>NS</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.6±0.4</td>
<td>1.4±0.3</td>
<td>1.3±0.2</td>
<td>1.4±0.2</td>
<td>T1 vs PP†</td>
</tr>
<tr>
<td>DT, ms</td>
<td>181±13</td>
<td>179±12</td>
<td>180±13</td>
<td>206±59</td>
<td>PP vs T1, T2, and T3†</td>
</tr>
<tr>
<td>A-dur, ms</td>
<td>116±18</td>
<td>117±21</td>
<td>115±19</td>
<td>131±41</td>
<td>NS</td>
</tr>
<tr>
<td>PVs, cm/s</td>
<td>50.5±12</td>
<td>54.0±12</td>
<td>48.5±10</td>
<td>44.0±12</td>
<td>NS</td>
</tr>
<tr>
<td>PVd, cm/s</td>
<td>54±9.5</td>
<td>48±6.6</td>
<td>47±12</td>
<td>50±11</td>
<td>NS</td>
</tr>
<tr>
<td>Pva, cm/s</td>
<td>24.0±6.7</td>
<td>29.5±7</td>
<td>29.0±7</td>
<td>23.0±7</td>
<td>PP vs T2 and T3†</td>
</tr>
<tr>
<td>PVo/PVd ratio</td>
<td>0.95±0.2</td>
<td>1.17±0.3</td>
<td>1.08±0.3</td>
<td>0.93±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>PVsTVI, cm</td>
<td>11±3</td>
<td>12±3</td>
<td>11±3</td>
<td>10±4</td>
<td>NS</td>
</tr>
<tr>
<td>PVDVTI, cm</td>
<td>11±2</td>
<td>10±2</td>
<td>8.5±2</td>
<td>9.4±2</td>
<td>T1 vs T3†</td>
</tr>
<tr>
<td>PVaTVI, cm</td>
<td>1.3±0.5</td>
<td>1.7±0.6</td>
<td>1.5±0.6</td>
<td>1.4±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>LAP (pulmonary systolic fraction), cm‡</td>
<td>0.498±0.10</td>
<td>0.542±0.08</td>
<td>0.549±0.07</td>
<td>0.507±0.10</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDP (A-dur−PVo-dur), ms</td>
<td>15.03±18.6</td>
<td>16.88±22.9</td>
<td>16.72±21.7</td>
<td>35.13±36</td>
<td>NS</td>
</tr>
<tr>
<td>A-dur/PVa-dur ratio</td>
<td>1.17±0.2</td>
<td>1.19±0.2</td>
<td>1.19±0.2</td>
<td>1.36±0.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations as in text and Table 1.
*Control group.
†P<0.05.
‡(PVsTVI+PVdTVI)/(PVsTVI).

![Figure 6](Image) Schematic of the expected normal mitral inflow (top) and pulmonary venous (bottom) flow velocity pattern in the first, second, and third trimesters of pregnancy. Control values were obtained a mean of 1.7 months postpartum.
LV Diastolic Function in Normal Human Pregnancy

Figure 7. Doppler tracing of (top) mitral inflow in a third-trimester subject, showing peak E and A velocities and DT, and (bottom) pulmonary venous flow in the same patient, showing PVs and PVD forward flow and TVIs and PVa.

resemble those seen in long-distance runners, as suggested by Robson and coworkers.6 In pregnant women, Katz and colleagues3 demonstrated progressive eccentric LV enlargement related to the decrease in the ratio between the posterior wall thickness and the LV end-diastolic radius.

Because of myocardial relaxation and compliance changes with aging, different age groups would be expected to have different diastolic filling patterns.21,22 Mitral flow, pulmonary venous flow velocity, and other Doppler diastolic variables in our postpartum (control) subjects were similar to values encountered in healthy nonpregnant 21- to 40-year-old women.23 In healthy young women, LV elastic recoil is vigorous, and myocardial relaxation is swift, so filling is almost completed during early diastole, and only a small amount of filling occurs at atrial contraction. We observed some changes in diastolic mitral inflow during each trimester of pregnancy. A significant increase in the E value was seen in first-trimester subjects compared with control subjects. In the first and second trimesters, the volume load occurred during the early diastolic phase, reflecting an increase in the E value; with the onset of the second trimester, and even more so the third trimester, atrial contraction became more important to LV filling. This change caused a gradual increase in the A value with each trimester, and the E/A ratio declined in late pregnancy. Mabie and coauthors5 postulated that the mean LAP and/or LVEDP increases within the upper limits of normal in the second and third trimesters, necessitating that the atrial contractile force be increased to complete ventricular filling; alternatively, the increment in LV mass (wall thickness) may reduce ventricular compliance, necessitating more powerful atrial contraction. Both of these hypotheses may be true. As shown in our control subjects, the findings in question return to baseline in the postpartum period.

During pregnancy, both the PVd and the PVdTVI decreased as more LV filling occurred, particularly with the aid of atrial contraction. When we compared the first trimester with the third trimester with respect to the PVdTVI, the difference was significant (P<0.05). These changes were influenced by the increase in heart rate34 that occurs during pregnancy and reaches its peak in the third trimester.

The PVa increases throughout pregnancy without changing in duration. In lightly sedated normal dogs undergoing volume loading, Appleton24 showed that this increase results from a heightened mean LAP. Similarly, Nishimura et al25,26 and others27 showed that in the presence of a heightened atrial preload, as occurs with fluid loading, atrial contractility increases, and both mitral forward flow and the PVa increase at atrial contraction. We clearly documented an increased PVa during chronic volume overloading (pregnancy) in the normal heart.

With each trimester, the pulmonary systolic fraction related to volume loading tends to increase, as shown in animal studies.24,28,29 In contrast, patients with cardiac disease have a reduced pulmonary systolic fraction as the filling pressures increase.11–13,30 This apparent paradox most likely results from the fact that the normal atria and ventricles exhibit a preload reserve and increased contractility in response to volume loading but that abnormal hearts often fail under these conditions.24 Increased left atrial contractility enhances atrial relaxation, which augments the PVs1. At the same time, increased LV contractility augments left atrial compliance and the PVs2 by increasing the left atrial long-axis dimension. In contrast, increased pressures in diseased hearts often cause left atrial and LV systolic failure, reduced left atrial compliance, phasic LAP changes, a lower PVs1 and PVs2, and a lower pulmonary systolic fraction.

Study Limitations
LV mass increased during pregnancy and decreased postpartum but had not returned to baseline levels at a mean of 1.7 months after delivery. This indicates that this value takes several more months to reach baseline. Robson and colleagues7 demonstrated that LV mass continues to decrease for 24 weeks after delivery, although most of this decrease occurs by 12 weeks postpartum. Clapp and Capeless16 showed that LV volume, cardiac output, and SVR gradually return toward baseline but remain significantly different from prepregnancy values 1 year after delivery. In our study, the postpartum follow-up time may have been too short to reflect baseline status. Nevertheless, in our postpartum (control) subjects, the mitral flow, pulmonary venous velocity, and other Doppler diastolic values were similar to those observed by Oh and associates23 in nonpregnant women whose age range was similar to that of our control subjects.
Conclusions
Pregnancy has important effects on pulmonary venous flow and LV inflow velocities in healthy subjects during each trimester. Our results provide a standard reference concerning these filling variables by trimester. Because a chronic, natural volume-overload state strongly influences diastolic filling dynamics, future Doppler studies of LV diastolic function in pregnant women should include comparisons with trimester-matched control subjects.

References