Scientific Contributions

Maternal Diastolic Dysfunction and Left Ventricular Geometry in Gestational Hypertension

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Abstract—The objective of this study was to evaluate diastolic parameters and left ventricular geometry in gestational hypertension. Twenty-one consecutive pregnant women with gestational hypertension and 21 normotensive women matched for age and gestational age were enrolled in the third trimester of gestation. Echocardiographic and uterine color Doppler evaluations were performed. Systolic, diastolic, and mean blood pressure, total vascular resistance (TVR), and uterine resistance index were higher in hypertensive women than in control subjects (P<0.01). Left atrial function and cardiac output were significantly lower in gestational hypertension (P<0.01). Patients with gestational hypertension had longer left ventricular isovolumetric relaxation time (IVRT) (P<0.0001); lower velocity-time integral of the A wave (P<0.05) and of the diastolic pulmonary vein flow (P<0.05); and higher velocity-time integral of the reverse pulmonary vein flow (P<0.05). Systolic fraction of the pulmonary vein flow was higher in women with gestational hypertension than in control subjects (P<0.01); the difference in duration of pulmonary vein flow and A wave was closer to 0 in gestational hypertension (P<0.0001). Altered left ventricular geometry was found in 100% of hypertensive patients and in 19.05% of normotensive patients (P<0.001). IVRT, left ventricular end-systolic volume, atrial function, and uterine resistance index were directly related to TVR (P<0.01); deceleration time of the E wave showed a quadratic correlation with TVR (P<0.01). Gestational hypertension is characterized by an altered cardiac geometric pattern of eccentric hypertrophy. The altered geometric pattern assessed during gestational hypertension is associated, in our study, with depressed systolic function, high TVR, altered diastolic function, and left atrial dysfunction. Deceleration time of the E wave, IVRT, and left atrial fractional area change, found in concomitance with the highest TVR, may be useful in the evaluation of cardiac function and hemodynamics present in pregnancy-induced hypertension. (Hypertension. 2001;37: 1209-1215.)

Key Words: hypertension, gestational ■ diastole ■ ventricular function, left

Maternal hemodynamic adaptation begins in the first trimester of pregnancy.1–3 Cardiac output increases and diastolic function is modified according to a rise in preload,4,5 a decreased afterload,4,5 an increased compliance of the conduit vessels,4,5 ventricular remodeling,4,5 and a modification of the renin-angiotensin-aldosterone system.4,5 Cardiac output is increased as the result of enhanced myocardial performance.6

Echocardiographic evaluation provides important information on both systolic and diastolic cardiac function. In particular, the analysis of transmural and pulmonary vein flow patterns allows an evaluation of the diastolic left ventricular filling,5,7 whereas M-mode, 2D, and Doppler echocardiography are used to assess systolic and morphological left ventricular modifications.6,8-11

In the past, it has been reported that cardiac output during normal pregnancy increases until mid gestation. The initial increase appears to be related to an increase in heart rate followed by an increase in stroke volume.1,2 Nevertheless, few data on cardiac diastolic function during physiological pregnancy have been reported,5,12,13 and no data on diastolic function during gestational hypertension exists.

Moreover, although left ventricular geometric pattern based on left ventricular mass and relative wall thickness of the left ventricle has gained interest in hypertensive disease,14-16 no data concerning left ventricular geometric pattern during physiological and pathological pregnancy are available.

For these reasons, this study was designed to evaluate diastolic parameters and left ventricular geometric pattern in a group of women with gestational hypertension. These data were compared with data collected from normotensive pregnant women.
Methods

Patient Selection
A case-control study was performed. Twenty-one consecutive pregnant women with nonproteinuric gestational hypertension, with singleton pregnancy, were enrolled for the study during the third trimester of pregnancy in the period between August 1999 and February 2000. Gestational hypertension was diagnosed according to Deveuze and MacGillivray.17 For each patient with gestational hypertension, a normotensive woman was matched for age and gestational age as a control.

None of these women received medications other than iron supplements and vitamins before their enrollment in the study. Approval of the University Ethics Committee was obtained, and written informed consent was collected from all patients.

Exclusion criteria included the following: undetermined gestational age, tobacco use, history of heart disease, undetermined time of development of hypertensive state, antihypertensive pharmacological treatment, and preexisting chronic medical problems.

Blood pressure was measured from the brachial artery with a manual cuff, and mean arterial pressure (MAP) was calculated as MAP=DBP+(SBP−DBP)/3, where SBP is systolic blood pressure and DBP is diastolic blood pressure.

Echocardiographic Evaluation
The M-mode, 2D, and Doppler echocardiographic evaluations were performed with the patient in the left lateral position with a 2.5-MHz transducer interfaced with a commercially available echocardiographic machine (Hewlett Packard Sonos 2500). All data were recorded with patients in the left lateral position during end-expiration apnea and recorded on SVHS videotape. Hypertensive patients were evaluated before the initiation of therapeutic treatment.

M-Mode and 2D Echocardiography
Left atrial and aortic route diameters, left ventricular end-diastolic and end-systolic diameters (LVDd and LVDs, respectively), and interventricular septum and posterior wall diastolic thickness (IVSd and PWd, respectively) were all detected in the parasternal long-axis view during M-mode tracing according to the recommendation of the American Society of Echocardiography.18 The diameter of the left ventricular outflow tract (LVOT) was measured during systole at the base of the aortic leaflets19 during the 2D parasternal long-axis view. Left ventricular mass (LVM) in grams was calculated by the Devereux20 formula.

LVM index (LVMi) was then calculated as follows:

\[
LVMi = \frac{LVM}{m^{2.7}},
\]

where \(m\) was the height of the patient in meters. Relative wall thickness (RWT) was calculated as the ratio (IVSd+PWd)/LVDd. Left ventricular geometric pattern was considered normal if LVMi was ≤50 g/m\(^2\).7 and RWT was <0.44. Concentric remodeling was diagnosed when LVMi was >50 g/m\(^2\) and RWT was >0.44; concentric hypertrophy was defined as LVMi >50 g/m\(^2\) and RWT >0.44; eccentric hypertrophy was diagnosed when LVMi was >50 g/m\(^2\) and RWT was <0.44.4,16 Left ventricular end-diastolic and end-systolic volumes (EDV and ESV, respectively) were calculated according to Teichholz et al.21

Parameters of Systolic Function
Stroke volume was calculated as the difference between EDV and ESV. Cardiac output (CO) was obtained as the product of stroke volume and heart rate (HR) derived from ECG monitoring. Ejection fraction was calculated as EF%=100·(EDV−ESV)/EDV.

Total Vascular Resistance and Uterine Resistance Index
Total vascular resistance (TVR) was calculated in dyne·s·cm\(^{-5}\) according to the formula TVR=([MAP−DBP]/[CO(L/min)]×80. Uterine resistance index (RI) was also assessed. Flow velocity of the right and left uterine arteries were traced with the patient in the semirecumbent position, identifying a longitudinal scan, lateral to the uterus, while visualizing the bifurcation of the common iliac artery. The recording was made where the uterine artery and the external iliac artery crossed as detected by color Doppler. The RI was calculated according to the formula R1=(A−B)/A, where A was the highest and B the lowest waveform systolic velocity. The average of RI of both uterine arteries was calculated.

Doppler Indexes of Diastolic Function
Assessment of diastolic function was obtained by pulsed-wave Doppler of both transmitral and pulmonary venous flow patterns recorded in the apical 4-chamber view.

Mitral flow velocities were detected by placing the sample volume between the tips of the mitral leaflets.22 The following variables were measured: peak flow velocity in early diastole (E wave) and during atrial contraction (A wave); peak E/A ratio; E- and A-wave time-velocity integrals (E-VTI, A-VTI); deceleration time of the E wave (DiE); and duration of the A wave (dA). When atrial contraction occurred before the mitral deceleration had decreased to zero, DiE was calculated as the time between peak E wave and the deceleration slope extrapolated to zero baseline.22 Left ventricular isovolumetric relaxation time (IVRT) was also measured as the interval between the aortic valve closure click and the start of mitral flow.

Pulmonary venous flow velocities were detected by placing a 3- to 5-mm sample volume 1 to 2 cm into the right superior pulmonary vein.23,24 The detected variables were the peak pulmonary venous flow velocity during ventricular systole (PVs) and its time-velocity integral (PVs-VTI); peak pulmonary venous flow velocity during ventricular diastole (PVd) and its time-velocity integral (PVd-VTI); peak pulmonary venous flow velocity at atrial contraction (PVA) and its time-velocity integral (PVA-VTI); and the duration of the PVA pulmonary venous flow (dPVA). When a biphasic PVs was detected, the highest peak velocity was used.24,25 The difference in PVs and A-wave duration (dPVAs−dA) was then calculated. The pulmonary vein systolic fraction used as a marker of ventricular filling pressure was obtained as PVs%=(PVs-VTI)/(PVs-VTI+PVd-VTI).

Acoustic Quantification of the Left Atrium
Because M-mode measurement of the left atrium is considered inaccurate and not sensitive enough to detect left atrial dimension modifications,27 2D-derived measurements of this cavity were detected. In the past,37,28,29 left atrial areas were used as a sensitive index of the real left atrial dimensions. Left atrial maximal and minimal areas were therefore used to obtain an accurate measure of the left atrium and its function.

During a 2D standard apical 4-chamber view, the automatic boundary detection (ABD) was activated and the left atrium was chosen as the area of interest; left atrial maximal and minimal areas were derived. Planimetry of both maximal and minimal left atrial areas (LAmax and LAmin, respectively) were also obtained through the integrated software of the machine to compare the value obtained with ABD.

Left atrial fractional area change (LA FAC%), calculated either by ABD methods (Acoustic Quantification) or by planimetric tracing of the left atrial border, has been reported as a fairly reliable index of left atrial function.29,30 Assessment of left atrial function was therefore obtained through LA FAC%, calculated as LA FAC%=(LAmax−LAmin)/LAmax.

Statistical Analysis
Data are expressed as mean±SD. Comparison between normal and hypertensive patients was performed with a Student’s t test for paired data according to gestational age. Linear and quadratic regression analyses were performed.

To test intraobserver and interobserver variability, 2 independent observers measured data on videotape recordings from 10 randomly selected patients. The same data were then remeasured on tape after 1 month by one of the two observers.
Results

General Characteristics of the Studied Groups
Gestational age at the time of examination was 32±3 weeks (range, 27 to 36) (Table 1). Age, height, and HR were similar in the two groups, although HR was slightly but not significantly lower in the hypertensive group. SBP, DBP, and MAP were significantly higher in the hypertensive group than in the control subjects. RI in hypertensive patients was significantly lower than in the control subjects. ESV was significantly lower in the hypertensive group than in the control subjects (P<0.0001). CO was significantly lower in the women with gestational hypertension than in the control subjects (P<0.01).

M-Mode and 2D-Derived Parameters
Aortic route diameter was significantly larger in hypertensive patients compared with the control subjects (P<0.0001); LVOT, left atrial diameter, LVDD, and EDV did not differ in the two groups (Table 2). Left atrial maximal area was not statistically different in the two groups, whereas women with gestational hypertension showed left atrial minimal area and LA FAC% significantly lower than that in the control subjects (P<0.001).

Correlations
Correlations were found between TVR and left atrial function, TVR and systolic function parameters, and TVR and ejection fraction in the hypertensive patients than in the control subjects. ESV was larger and EF% was lower than that in control subjects.

Diastolic Function
Patients with gestational hypertension have diastolic function parameters with significantly longer IVRT (P<0.0001), lower values of VTI of the A wave (P<0.05) and PVd-VTI (P<0.05), higher PVa-VTI (P<0.05), shorter dA (P<0.01), and longer dPVa (P<0.001) than that in control subjects (Table 3). PVs% was higher in women with gestational hypertension than in control subjects (P<0.01); dPVa-da values close to 0 were less negative during pregnancy-induced hypertension than in physiological pregnancy (P<0.0001). No difference was found for the other parameters of diastolic function.

Geometric Pattern of the Left Ventricle
In the normotensive group, 80.95% (17 of 21) subjects showed a normal geometric pattern; 19.05% (4 of 21) subjects showed an altered geometric pattern: 2 with concentric remodeling and 2 with eccentric hypertrophy. In the hypertensive group, 100% of the patients showed an altered geometric pattern: 28.57% (6 of 21) with concentric remodeling, 38.10% (8 of 21) with eccentric hypertrophy, and 33.33% (7 of 21) with concentric hypertrophy. In the hypertensive group, the percentage of subjects with left ventricular geometric alterations was significantly higher than in the control subjects (100% versus 19.05% P<0.001).
diastolic function parameters. In particular, IVRT was directly related to TVR ($P<0.001$), whereas DdE showed a quadratic correlation with TVR ($P<0.01$) (Figure); ESV and LA FAC% showed significant correlations with TVR ($r=0.48$ and $r=-0.76$, respectively; $P<0.01$). Uterine RI and TVR were significantly and directly related ($r=0.59$, $P<0.001$) (Table 4).

**Correlations were found between LVMi and left atrial function, LVMi and systolic function parameters, and LVMi and diastolic function parameters.**

**Table 3. Diastolic Function Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal (n=21)</th>
<th>Hypertensive (n=21)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>E wave, cm/s</td>
<td>93±13</td>
<td>83±18</td>
<td>NS</td>
</tr>
<tr>
<td>E-wave velocity-time integral, s</td>
<td>15±3</td>
<td>14±3</td>
<td>NS</td>
</tr>
<tr>
<td>Deceleration time of E wave, ms</td>
<td>203±24</td>
<td>199±33</td>
<td>NS</td>
</tr>
<tr>
<td>Isovolumetric relaxation time of left ventricle, ms</td>
<td>72±5</td>
<td>98±13</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>A wave, cm/s</td>
<td>69±10</td>
<td>63±13</td>
<td>NS</td>
</tr>
<tr>
<td>A-wave velocity-time integral, s</td>
<td>8.4±0.7</td>
<td>6.7±1.0</td>
<td>$&lt;0.05$</td>
</tr>
<tr>
<td>Duration of A wave, ms</td>
<td>150±8</td>
<td>128±23</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>Peak E/peak A ratio</td>
<td>1.35±0.10</td>
<td>1.34±0.36</td>
<td>NS</td>
</tr>
<tr>
<td>Peak pulmonary venous systolic flow, cm/s</td>
<td>57±10</td>
<td>59±12</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary venous systolic-time integral, s</td>
<td>14±3</td>
<td>15±3</td>
<td>NS</td>
</tr>
<tr>
<td>Peak pulmonary venous diastolic flow, cm/s</td>
<td>51±8</td>
<td>49±11</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary venous diastolic velocity-time integral, s</td>
<td>12±3</td>
<td>9±2</td>
<td>$&lt;0.05$</td>
</tr>
<tr>
<td>Peak pulmonary venous flow at atrial contraction, cm/s</td>
<td>24±6</td>
<td>28±6</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary venous velocity time integral at atrial contraction, s</td>
<td>1.8±0.7</td>
<td>3.1±1.0</td>
<td>$&lt;0.05$</td>
</tr>
<tr>
<td>Duration of pulmonary venous flow at atrial contraction, ms</td>
<td>96±17</td>
<td>125±26</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Difference in duration between pulmonary venous flow at atrial contraction and A wave, ms</td>
<td>$-54±15$</td>
<td>$-3±21$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Systolic fraction of the pulmonary vein flow, %</td>
<td>54.8±6.9</td>
<td>61.5±3.5</td>
<td>$&lt;0.01$</td>
</tr>
</tbody>
</table>

**Interobserver and Intraobserver Variability**

For pulmonary vein flow velocity, interobserver and intraobserver variability values were $0.85±3.5\%$ ($r=0.97$) and

**Total Vascular Resistance and Deceleration Time of the E wave**

![Graph showing the relationship between TVR and DdE](image)

DdE in milliseconds and TVR in dyne·s·cm$^{-5}$, showing $r^2=0.236$ ($P<0.01$).
These measurements allowed for differentiating between hypertensive and normotensive pregnant women.

In our results, diastolic dysfunction described in the hypertensive patients through the Doppler analysis of transmitral and pulmonary vein flow pattern appears to be the more relevant difference. Diastolic dysfunction is evidenced through a prolongation of the IVRT and a high systolic fraction of the pulmonary vein flow.

Poppas et al. have reported a reduction of LV end-systolic pressure in normotensive pregnant women. In normal pregnancy, an increased preload and a decreased afterload favor an improved emptying of the left ventricle during systole and a reduction of the end-systolic pressure. This reduces the gradient between the left atrium and the left ventricle and reduces the interval of time necessary for the left ventricular pressure to fall below the atrial pressure. As a consequence, left ventricular filling during diastole is realized under the best conditions.

In patients with gestational hypertension, we found that the elevated afterload (high TVR) is linked with a reduced emptying of the left ventricle, as demonstrated by the higher end-systolic volume found compared with the normal subjects and by the correlation existing between end-systolic volume and TVR. The elevated end-systolic volume is most probably related to the elevated end-systolic pressure generated by the increased afterload, thus explaining the IVRT prolongation; for example, in hypertensive patients, a longer time is therefore needed for the left ventricular pressure to fall below the atrial pressure compared with normotensive control subjects. A delayed mitral valve opening and an altered ventricular compliance reduce the diastolic filling of the left ventricle. The modified intraventricular pressure regimen has
an effect on the left atrial filling. We found a reduced left atrial filling during diastole through the low TVI of pulmonary vein flow (PVd-VTI), resulting in a high systolic fraction (PVs%). Similar results were described in nonpregnant subjects with essential hypertension.\textsuperscript{31}

Additional supporting evidence suggesting that diastolic function is deeply modified comes from the DtE. In patients with gestational hypertension, there is evidence of significant changes, for example, a slight prolongation in hypertensive disease as TVR increases, whereas in the worst cases, with the highest TVR, DtE shows a progressive reduction. This is probably due to the initial compensation mechanism generated by hypertrophy that leads to an increase of the DtE value. Subsequently, the increase in TVR and the increase in IVRT results in a shortening of the DtE value for the reduction of the length of the whole diastolic filling of the left ventricle. For these reasons, the DtE value mimics a bimodal distribution, although this finding could be influenced by one or two extreme observations in our study population and should be confirmed on larger numbers.

Left atrial function is affected by the altered loading conditions of the left ventricle: Left atrial filling is reduced during the diastolic phase. The differences in the mean left atrial areas were found mostly in the minimal area. The hypertensive patients showed a minimal area value higher than that in the control subjects, which is probably due to the increased diastolic ventricular pressures that affect atrial voiding. This is in part demonstrated by the lower TVI of the A wave and the value of dR-dA difference of the hypertensive patients compared with control subjects.

LA FAC\% is therefore one of the more reliable parameters that shows the variation of the atrial filling and function independent from the absolute values of maximal and minimal areas obtained.

We were surprised to find structural modifications of the heart in patients with gestational hypertension, particularly because the duration of the disease could be thought to be too brief to induce structural cardiac changes. Assessing left ventricular geometry has allowed us to evaluate the modifications evidenced in normal pregnancy and those produced by severely altered hemodynamics. Nevertheless, in pregnancy-induced hypertension, we observed patients with concentric remodeling, eccentric hypertrophy, and concentric hypertrophy. Concentric hypertrophy was not found in normotensive subjects, although 9.5% had concentric remodeling and 9.5% had eccentric hypertrophy. In the past, a progressive eccentric left ventricular enlargement with a decreased ratio between posterior wall thickness and left ventricular end-diastolic diameter was reported in normal pregnancy.\textsuperscript{32} The prolonged cardiac adaptation to the pregnancy state could lead to an eccentric hypertrophy as the final step of the adaptive process in response to a plasma volume expansion. Previous data have described an increase of LVM during physiological expansions without a clear hypertrophic state when LVM was related to the body surface area.\textsuperscript{33} Our data showing eccentric hypertrophy during normotensive pregnancy may be explained through the different method of calculation. We indexed LVM for height because it was reported to be more sensitive in identifying cardiac hypertrophy.\textsuperscript{14,20,34}

The hypertrophic response in hypertensive patients is more common and probably developed during the latent phase of the disease. In our results, concentric hypertrophy appears to be the more frequent cardiac pattern found in pregnancies complicated by gestational hypertension and may be the result of a lack of increase of left ventricular end-diastolic dimensions, whereas wall thickness increases under the stimulus of the elevated TVR. A reduced maternal plasma volume expansion is often associated with fetal growth restriction and/or pregnancy-induced hypertension\textsuperscript{35,36} and may help to explain the lack of increase of left ventricular end-diastolic dimensions.

The altered geometric pattern is associated in our study with a depressed systolic function, high TVR, altered diastolic function, and left atrial dysfunction.

High TVR may be a possible cause of depressed systolic function. The elevated afterload found in patients with gestational hypertension may explain the lower CO and EF compared with normotensive subjects. A recent report\textsuperscript{37} has shown that gestational hypertension is characterized by high cardiac output and low vascular resistance. These different findings might be due to the clinical features of our population that had hypertension with evidence of abnormal placental implantation process (high uterine RI). The correlation existing between RI and TVR is a confirmation of a model of gestational hypertension as a disease with high TVR. Although pregnancy-induced hypertension is a multifactorial disease, the linkage between abnormal placental implantation, increased peripheral resistance, and elevated blood pressure has been documented with histological evidence.\textsuperscript{38} The clinical relevance of the increased RI in the uterine circulation has been extensively described,\textsuperscript{39} confirming the possibility that gestational hypertension is a disease with elevated peripheral resistance.

Conclusions

Left atrial and diastolic function evaluation with the analysis of DtE and IVRT might be useful in the evaluation of patients with gestational hypertension with altered TVR. Moreover, the findings of an increased uterine Doppler RI during the second trimester, used in clinical practice as a sign of increased risk for further development of hypertensive disease in pregnancy,\textsuperscript{40} could induce the request for a cardiac maternal evaluation to gain more information on the effects that the peripheral condition exerts on cardiac function.

References


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