Characterization of Left Ventricular Diastolic Function in Hypertension by Use of Doppler Tissue Imaging and Color M-Mode Techniques

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Background: Abnormalities in left ventricular (LV) relaxation and/or increased filling pressures are indicators of LV diastolic dysfunction in patients with hypertension (HTN). The purpose of this study was to assess clinical use of pulsed wave Doppler, Doppler tissue imaging (DTI), and color M-mode (CMM) indices for determination of diastolic function in patients with HTN.

Methods: In all, 278 ambulatory patients with normal LV systolic function were grouped according to the presence of HTN with and without LV hypertrophy (LVH) (determined by the 2-dimensional area-length method) as follows: healthy control subjects (NC, n = 122), HTN without LVH (HTN, n = 70), and HTN with LVH (HTN+LVH, n = 86). Pulsed wave Doppler-derived measurements included transmural E- and A-wave velocities, E/A ratio, and deceleration and isovolumic relaxation time intervals; DTI-derived early diastolic (Em) velocities were obtained at 4 LV annular sites. CMM-derived flow propagation velocity and the intraventricular pressure gradient were also calculated. Analysis of covariance adjusted for age and sex of diastolic indices was performed to compare the differences among groups.

Results: Only DTI-derived filling pressures demonstrated progressive statistically significant differences among all 3 groups (ie, HTN vs NC, HTN+LVH vs NC, and HTN vs HTN+LVH). However, CMM-derived flow propagation velocity and intraventricular pressure gradient indices were similar among the groups.

Conclusion: DTI is a robust method compared with pulsed wave Doppler- and CMM-derived indices for the quantitative assessment of LV relaxation and filling pressures in patients with HTN. (J Am Soc Echocardiogr 2006;19:872-879.)

Hypertension (HTN) affects over 65 million people in the United States. Approximately 25% to 50% of affected individuals have evidence of left ventricular (LV) hypertrophy (LVH). HTN with LVH is a known risk factor for the development of asymptomatic LV dysfunction and congestive heart failure. Pulsed wave Doppler (PWD)-derived indices of LV diastolic dysfunction (LVDD) have been well described in patients with HTN. LVH and LVDD are markers of end-organ damage; the presence of either constitutes evidence of hypertensive heart disease. Early detection of LVDD in HTN, before development of LVH, may represent a clinical finding that would justify aggressive treatment aimed at reducing cardiovascular morbidity and mortality.

Noninvasive evaluation of diastolic function by PWD-derived indices of transmural inflow is confounded by strong correlations with variables such as filling pressures, age, and heart rate. Doppler tissue imaging (DTI) of early diastolic mitral annular velocity (Em) and color M-mode (CMM)-derived flow propagation velocity (Vp) are reported to be relatively load-independent measures of relaxation and correlate with measurements of the time constant of relaxation (Tau) and peak dP/dt, and have been used to estimate LV filling pressures. The spatial-temporal CMM-derived velocity has been used to determine the intraventricular pressure gradient (IVPG)—the pressure difference between the...
LV base and the LV apex in early diastole— that is independent of preload and correlates well with the invasive measurements of diastolic function. The PWD-, DTI-, and CMM-derived methods to assess LV diastolic function have not been compared in the same cohort of patients with HTN. This study was designed to test the hypothesis that in patients with normal systolic function and HTN, with and without LVH, DTI- and CMM-derived indices discriminate abnormalities of LV diastolic function.

**METHODS**

**Patient Population**

The study population consisted of 278 consecutive, stable ambulatory patients with normal LV systolic function who participated in a cardiovascular genetics study at our institution. Inclusion criteria were: (1) normal LV systolic function by 2-dimensional (2D) echocardiography (ie, LV ejection fraction [LVEF] ≥ 55%); and (2) cardiovascular examination without signs or symptoms of heart failure. Exclusion criteria were: (1) atrial fibrillation; (2) history of myocardial infarction; and (3) type 2 diabetes mellitus. Patients were grouped according to presence of HTN, with or without LVH. HTN was determined by antihypertensive drug therapy and/or blood pressures of systolic greater than 140 mm Hg and/or diastolic greater than 90 mm Hg after 10 minutes of rest at the time of evaluation. LVH was defined by 2D echocardiography as outlined below. The resultant study groups were as follows: healthy control group without HTN and/or LVH (NC, n = 122), HTN without LVH group (HTN, n = 70), and HTN with LVH group (HTN+LVH, n = 86). The study was reviewed and approved by the Human Studies Committee at Washington University; all patients provided written informed consent.

**Echocardiography**

Transthoracic echocardiography was performed using a commercially available imaging ultrasound system (Acuson-Sequoia, Siemens Medical Systems, Mountain View, Calif) with harmonic imaging. Image acquisition and analysis was performed according to American Society of Echocardiography guidelines. Real-time images were digitally stored for offline analysis using an analysis station (ProSolv, Problem Solving Concepts, Indianapolis, Ind); CMM-derived IVPG was determined by newly developed software (Siemens Medical Systems). The 2D, PWD, and DTI data represent the average of 3 cardiac cycles; CMM data were the average of two cardiac cycles.

The 2D-derived measurements included LV volumes at end diastole and end systole from the apical 4- and 2-chamber views (method of disks). The LVEF was calculated using the biplane method; LV systolic dysfunction was defined as an LVEF less than 55%. LV mass was determined by the area-length method. The LV volumes and mass were indexed by body surface area. LVH was defined as 2SD above normal (LV mass index > 88 g/m² for women and 105 g/m² for men). Left atrial (LA) size was determined at end systole from the parasternal long-axis view.

PWD-derived transmitral indices were obtained at the mitral leaflet tips to determine early diastolic (E-wave) and atrial (A-wave) wave inflow velocities, the E/A ratio, and the E-wave deceleration time (DT) (Figure 1). The isovolumic relaxation time was measured by continuous wave Doppler as the time from the closing click of the aortic valve to the onset of transmitral inflow. DTI was performed in the apical 4- and 2-chamber views. Measurements of early diastolic (Em) velocities were made at the 4 LV basal sites: septal (Emseptal), lateral (Emlateral), anterior (Emanterior), and inferior (Eminferior) (Figure 1). The Emglobal Em was calculated as the average of the 4 sites. The mitral E-wave/Em ratio was calculated to estimate the LV filling pressure.

The CMM velocity profile was obtained from the apical 4-chamber view (Figure 1). CMM-derived Vp was measured as described in previous studies. Briefly, the slope of the first aliasing velocity of the CMM flow profile was measured from the base of the mitral valve annulus to 4 cm into the LV cavity. The mitral E wave/Vp ratio was calculated as an additional index of LV filling pressure. Abnormal LV diastolic relaxation was defined by PWD-derived indices as an E/A ratio less than 1 and DT greater than 260 milliseconds and by DTI-derived indices as Emseptal less than 8 cm/s.

The theoretic basis for noninvasive determination of the IVPG has been previously described. Briefly, the Navier-Stokes coupled differential equations describe the conservation of energy and momentum of flow in the 3-dimensional space. Assuming negligible blood viscosity, lack of turbulence, and 1-dimensional blood flow along the mitral inflow scan line, and solving for the pressure, the Euler equation is obtained:

\[
\frac{\partial P}{\partial s} = -\rho \left( \frac{\partial v}{\partial t} + \frac{v}{s} \right)
\]

where \(\partial P/\partial s\) is a partial derivative of pressure with respect to space, \(\rho\) is the density of blood, \(\partial v/\partial t\) is a partial derivative of blood velocity with respect to time (representing the inertial acceleration component), and \(v/\partial s\) is the blood velocity multiplied by the partial derivative of blood velocity with respect to space (representing the convective acceleration component).

Integrating the Euler equation along the mitral valve inflow from the base of the left ventricle (LV base) to the apex of the left ventricle (LV apex) yields the unsteady-state Bernoulli equation for incompressible fluids:

\[
\Delta P = \frac{1}{2} \rho \left( v_{\text{apex}}^2 - v_{\text{base}}^2 \right) + \rho \int_{\text{base}}^{\text{apex}} \frac{\partial v}{\partial t} ds
\]

where \(\rho\) is the density of blood, \(v_{\text{apex}}^2\) is the blood velocity at the LV apex, \(v_{\text{base}}^2\) is the blood velocity at the LV base,
and \( \int_{\text{base}}^{\text{apex}} \frac{\partial v}{\partial t} \, dt \) is the integral of the partial derivative of blood velocity with respect to time over the span of the LV (from the LV base to the LV apex) representing the inertial acceleration component.

Interrogation of the CMM-derived spectral image was used to obtain the IVPG (Figure 2). The color pixels were converted into true velocities with a de-aliasing algorithm that incorporated the Nyquist limit; subsequent computational steps determined the IVPG. All velocities from the CMM profile are used to calculate the IVPG; therefore, the measurement of Vp slope does not influence the IVPG calculation.

Statistical Analysis

Variables are expressed as mean ± SD. Student t test was used to compare continuous variables among the groups. The Mann-Whitney and \( \chi^2 \) tests were used to compare nonparametric and categorical variables, respectively. Pearson and Spearman correlations were used as appropriate. Because PWD, DTI, and CMM-derived variables exhibited a significant correlation with age and sex, analysis of variance with covariate adjustment for these two variables and Tukey adjustment for multiple comparisons was performed. Contrast matrix analysis within the analysis of variance with covariate adjustment algorithm was used to determine the statistical significance of the data. To determine the intraobserver and interobserver reproducibility of the measurements of Vp and IVPG, 50 studies were randomly selected and the data were analyzed using the intraclass correlation coefficient (ICC) and Bland-Altman analysis to determine the measurement accuracy. A \( P \) value less than .05 was considered statistically significant. The analyses were performed using software (SPSS, Version 11.0, SPSS, Chicago, Ill).

RESULTS

Patient Demographics

The demographic and 2D echocardiographic characteristics of the study population are shown in Table 1. Blood pressures were similar in the HTN and HTN+LVH groups. LV volumes and LA size were larger in the HTN+LVH group. According to study design, the LV mass index was higher in the HTN+LVH group compared with the NC and HTN groups. There were no significant differences in use of anti-hypertensive medications in the HTN groups.
Correlation Among CMM-, PWD-, and DTI-derived Indices

Pearson correlations were performed to determine the linear associations among PWD-, DTI-, and CMM-derived diastolic indices. Emglobal and Emseptal velocities were correlated with E velocity and E/A ratio ($r = 0.41$ and $r = 0.34$, respectively, $P < .001$ for both); inverse correlation with DT was shown as well ($r = -0.38, P < .001$). IVPG and Vp were inversely related to age ($r = -0.30$ and $r = -0.28$, respectively, $P < .01$ for both). Vp and IVPG were correlated ($r = 0.49, P < .001$). IVPG correlated with E velocity ($r = 0.40, P < .001$) and E/A ratio ($r = 0.42, P < .001$); Emglobal and Emseptal velocity ($r = 0.45$ and $r = 0.39$, respectively, $P < .001$ for both); and inverse correlation with DT was shown ($r = -0.35, P < .001$). Vp demonstrated correlation with E velocity ($r = 0.30, P < .001$) and E/A ratio ($r =
Table 1 Demographic, hemodynamic, and 2-dimensional echocardiographic variables compared among the patient groups

<table>
<thead>
<tr>
<th></th>
<th>NC (n = 122)</th>
<th>HTN (n = 70)</th>
<th>HTN+LVH (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57 ± 9</td>
<td>55 ± 14</td>
<td>56 ± 12</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>46 (38%)</td>
<td>34 (49%)</td>
<td>32 (37%)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>66 ± 11</td>
<td>67 ± 11</td>
<td>65 ± 11</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>122 ± 11</td>
<td>144 ± 13*</td>
<td>150 ± 13*</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>75 ± 9</td>
<td>88 ± 8*</td>
<td>87 ± 9*</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.9 ± 0.2</td>
<td>1.9 ± 0.2</td>
<td>1.9 ± 0.3</td>
</tr>
<tr>
<td>LV EDVI, cm³/m²</td>
<td>52 ± 16</td>
<td>50 ± 13</td>
<td>61 ± 22*</td>
</tr>
<tr>
<td>LV ESVI, cm³/m²</td>
<td>17 ± 7</td>
<td>17 ± 5</td>
<td>21 ± 9*†</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>67 ± 6</td>
<td>66 ± 6</td>
<td>66 ± 6</td>
</tr>
<tr>
<td>LVMI, gm/m²</td>
<td>86 ± 16</td>
<td>82 ± 9</td>
<td>114 ± 21*</td>
</tr>
<tr>
<td>LA, cm</td>
<td>3.8 ± 0.5</td>
<td>3.9 ± 0.5</td>
<td>4.1 ± 0.5*</td>
</tr>
</tbody>
</table>

BSA, Body surface area; DBP, diastolic blood pressure; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; HTN, hypertension alone; HTN+LVH, hypertension and left ventricular hypertrophy; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NC, healthy control subjects; SBP, systolic blood pressure.

*P < .001 compared with NC group.
†P < .001 compared with HTN group.

0.35, P < .001). The E/Vp ratio correlated with E/Em_global ratio (r = 0.61, P < .001).

Age- and Sex-adjusted Doppler Indices

The age- and sex-adjusted comparisons among PWD-, DTI-, and CMM-derived variables are shown in Table 2. When abnormal LV relaxation was defined using PWD-derived indices (ie, E/A < 1 and DTI > 260 milliseconds), 24% of the NC group had abnormal relaxation compared with 35% of the HTN group without LVH group (P < .5 vs NC), and 37% of the HTN+LVH group (P < .05 vs NC and P < .05 vs HTN). However, among the PWD-derived indices, only isovolumic relaxation time differed among groups and was longer in the HTN+LVH compared with the HTN-only group (Table 2).

When abnormal LV relaxation was defined according to DTI-derived indices (ie, Em_septal < 8 cm/s), 16% of the NC group had abnormal diastolic function compared with 21% in HTN without LVH group (P < .01 vs NC) and 38% in HTN+LVH group (P < .05 vs HTN). Em_global velocities demonstrated a stepwise decrease from NC to HTN and to HTN+LVH groups; a similar but opposite stepwise increase was shown by E/Em_global ratio. Furthermore, the E/Em_global ratio was statistically different in pairwise comparisons among all 3 groups (Table 2). Similar data were obtained when Em_septal and E/Em_septal indices were compared instead of the respective global measures (Table 2). When Em_lateral and E/Em_lateral indices were used, the discrimination between NC and HTN groups was lost (Table 2). There were no significant pairwise comparisons in the CMM-derived indices (ie, Vp or IVPG) among groups (Table 2).

Table 2 Age- and sex-adjusted echocardiographic indices of left ventricular diastolic function

<table>
<thead>
<tr>
<th></th>
<th>NC (n = 122)</th>
<th>HTN (n = 70)</th>
<th>HTN+LVH (n = 86)</th>
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</thead>
<tbody>
<tr>
<td>PWD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E-wave, cm/s</td>
<td>66 ± 15</td>
<td>71 ± 17</td>
<td>75 ± 21*</td>
</tr>
<tr>
<td>A-wave, cm/s</td>
<td>62 ± 16</td>
<td>63 ± 20</td>
<td>69 ± 20†</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.2 ± 0.3</td>
<td>1.2 ± 0.5</td>
<td>1.1 ± 0.5</td>
</tr>
<tr>
<td>DTI, ms</td>
<td>210 ± 38</td>
<td>206 ± 37</td>
<td>218 ± 50</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>105 ± 19</td>
<td>101 ± 18</td>
<td>112 ± 29†</td>
</tr>
<tr>
<td>E/Em_global</td>
<td>6.3 ± 1.8</td>
<td>7.0 ± 2.2†</td>
<td>8.5 ± 2.2‡</td>
</tr>
<tr>
<td>Em_septal/cm/s</td>
<td>9.6 ± 1.8</td>
<td>9.3 ± 2.6</td>
<td>8.5 ± 2.2‡</td>
</tr>
<tr>
<td>Em_lateral/cm/s</td>
<td>7.0 ± 2.0</td>
<td>8.2 ± 3.6†</td>
<td>9.3 ± 3.2‡</td>
</tr>
<tr>
<td>E/Em_lateral</td>
<td>5.7 ± 1.7</td>
<td>6.1 ± 2.1</td>
<td>7.9 ± 6.1‡</td>
</tr>
<tr>
<td>CMM</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Vp, cm/s</td>
<td>59 ± 15</td>
<td>63 ± 16</td>
<td>58 ± 15</td>
</tr>
<tr>
<td>E/Vp ratio</td>
<td>1.2 ± 0.3</td>
<td>1.2 ± 0.3</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>IVPG, mm Hg</td>
<td>1.7 ± 0.6</td>
<td>1.9 ± 0.6</td>
<td>1.8 ± 0.6</td>
</tr>
</tbody>
</table>

A-wave, transmitral A wave; CMM, color M-mode; DTI, deceleration time; DTI, Doppler tissue imaging; E-wave, transmitral E wave; Em_global, global Doppler tissue early diastolic mitral annular velocity; Em_septal, lateral Doppler tissue early diastolic mitral annular velocity; Em_lateral, septal Doppler tissue early diastolic mitral annular velocity; HTN, hypertension alone; HTN+LVH, hypertension and left ventricular hypertrophy; IVPG, intraventricular pressure gradient; IVRT, isovolumic relaxation time; NC, healthy control subjects; PWD, pulsed wave Doppler; Vp, flow propagation velocity.

A* P < .05 compared with NC group.
†P < .001 compared with NC group.
‡P < .001 compared with HTN group.

Reproducibility of the CMM-derived Measurements

The agreement in the interobserver variability of the IVPG measurements was 0.94 and for intraobserver variability was 0.98 as determined by the intraclass correlation coefficient (ICC). The Bland-Altman plots for IVPG are shown in Figure 3, A and B. The interobserver variability for CMM-derived Vp measurements was good (ICC = 0.69, P < .001) and the intraobserver variability was excellent (ICC = 0.91, P < .001). The Bland-Altman plots for Vp are shown in Figure 3, C and D.

DISCUSSION

This study compared PWD-derived mitral inflow indices, DTI-derived Em velocities, and CMM-derived Vp in patients with HTN, with and without LVH, and normotensive control subjects. All participants had a normal LVEF. The results demonstrated that PWD-derived E/A ratio and DT intervals were not significantly different among the 3 groups. The DTI-derived Em velocities were lower in HTN+LVH group; however, only the ratios of E/Em_global and

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Figure 3 Bland-Altman graphs of reproducibility data. Interobserver (A) and intraobserver (B) analysis of intraventricular pressure gradient. Interobserver (C) and intraobserver (D) analysis of flow propagation velocity. Horizontal lines, Mean ± 1.96 · SD of difference.
E/Em$_{septal}$ had significant differences in pairwise comparisons among all the 3 groups. CMM-derived Vp and IVPG were statistically similar in all 3 groups. The HTN+LVH group had increased LV volumes and LA size compared with patients with HTN only and the normotensive group, likely a reflection of early LV remodeling. The results of this study, therefore, suggest that elevation of LV filling pressures is an early abnormality in the progression of hypertensive heart disease, and that development of LVH is not only associated with abnormal relaxation but is accompanied by further increases in LV filling pressures.

Measurements of LV inflow parameters (ie, PWD-derived E- and A-wave velocities) are influenced by instantaneous LA-LV pressure gradients and were higher in the HTN+LVH group and likely explain why the E/A ratios were similar among groups. DTI-derived Em and CMM-derived Vp have both been described as relatively load-independent methods to assess LV relaxation. $^6,^7$ DTI-derived Em velocity indices reflect myocardial displacement during early diastole whereas PWD- and CMM-derived methods assess LV diastolic function by measurements of blood flow velocities. The findings that Em velocities were lower in the HTN+LVH group, compared with the other groups, is consistent with prior studies. $^7$ However, this study failed to identify CMM-derived indices as useful in discriminating among groups with mild (HTN without LVH) compared with more extensive hypertensive heart disease (ie, HTN+LVH group). This finding is consistent with previous reports describing that the Vp is determined by several factors, including the rate of pressure decline from LV base to apex, LA pressure, LV minimal pressure at the time of mitral valve opening, the LV “suction effect,” and LV elastic recoil (ie, end-systolic volume). $^{15}$ Similarly, IVPG is also likely influenced by LV elastic recoil and LA-LV pressure differences during early diastolic filling. In the HTN+LVH group, end-systolic volumes and LV filling pressures (ie, E/Em$_{global}$, E/Em$_{septal}$) were significantly greater when compared with those with HTN without LVH and with the normotensive group. This complex relationship between changes in LA pressure and LV diastolic pressure likely influences the early diastolic gradient and/or the pressure decline both at the LV base and at the apex, possibly contributing to the lack of differences in Vp and IVPG among groups. This hypothesis is supported by recent studies that suggest that Vp has greater load dependence than previously thought and, thus, is likely influenced by the same factors that contribute to the variance in PWD-derived indices. $^{16,17}$ Furthermore, a recent study reported that Vp is influenced by LVEF in patients with abnormal LV systolic function. $^{18}$ The results of this study also demonstrated that IVPG was similar among groups and suggests that LV systolic function may also have a significant role in determining the LV base-apex gradient.

**Limitations**

This study did not include direct comparison of echocardiographic data with invasive catheter-derived measurements. All patients included in the study were clinically stable and invasive measurements were not clinically warranted. The hypothesis of the study also relies on an assumption that LV diastolic function progressively worsens from patients who are normotensive to HTN to patients with HTN and LVH. There is sufficient evidence that PWD-derived mitral E/A ratio, DT, and isovolumic relaxation time correlate with the invasive determinants of diastolic function including tau and LV end diastolic pressure, $^{19}$ as do DTI-derived indices.$^{20,21}$ CMM indices have also been correlated with invasive determinants of LV elasticity and relaxation.$^{14}$ In addition, CMM-derived IVPG correlates with the invasive data.$^{8,10,14}$

**Conclusions**

This study demonstrates that in an ambulatory patient population with HTN and normal LVEF, DTI-derived Em velocity, particularly in combination with the E/Em$_{global}$ ratio, is a robust technique for the assessment of LV relaxation and filling pressures in hypertensive heart disease.

**REFERENCES**


