Relationship Between Left Ventricular Diastolic Relaxation and Systolic Function in Hypertension

The Hypertension Genetic Epidemiology Network (HyperGEN) Study


Abstract—The relation of impaired left ventricular relaxation, as measured by prolonged isovolumic relaxation time, to ventricular systolic function in hypertension remains uncertain in population-based samples. In the Hypertension Genetic Epidemiology Network (HyperGEN) Study, echocardiograms were analyzed in 1457 hypertensive participants without diabetes, ≥2+ valvular regurgitation, or coronary disease. Impaired relaxation (isovolumic relaxation time >100 ms) was present in 219 (15%) of the participants; they were older and had higher arterial pressure than did those with normal relaxation. Ventricular chamber size, wall thicknesses, mass, and relative wall thickness were greater, and stress-corrected midwall shortening and end-systolic stress/end-systolic volume index were lower with impaired relaxation than with normal relaxation time. Fractional shortening and ejection fraction did not differ between the groups. In logistic regression, the likelihood of prolonged isovolumic relaxation time decreased with higher stress-corrected midwall shortening (odds ratio, 0.97%; 95% confidence interval, 0.96 to 0.99), independently of age, heart rate, and ventricular mass. Neither ejection fraction nor the end-systolic stress/end-systolic volume index was independently related to isovolumic relaxation time. In hypertension, impaired left ventricular relaxation parallels ventricular midwall dysfunction but not systolic chamber function. Whether combined diastolic and systolic dysfunction identifies hypertensive patients at especially high risk of cardiovascular events requires further study. (Hypertension. 2001;38:424-428.)

Key Words: hypertension ■ echocardiography ■ ventricular function, left ■ systole ■ diastole

Several studies indicate that in hypertension, diastolic dysfunction precedes reduced left ventricular (LV) ejection fraction or cardiac output.1,2 Recent studies, however, identify a conceptual mismatch in relating LV endocardial shortening to mean end-systolic stress (ESS) across the LV wall,3,4 especially in the presence of abnormal LV geometry,3,4 as often occurs in individuals with hypertension.6 In hypertensive adults with a high prevalence of concentric LV geometry, shifting to an assessment of LV midwall mechanics substantially reduced the number of hypertensive patients with supranormal LV function and identified low LV myocardial performance in approximately one sixth of the patients.7 Low midwall shortening (MWS), in turn, has been shown to predict subsequent cardiovascular morbidity and mortality independent of age, blood pressure, or LV mass.5 Recently, associations of low MWS with abnormal LV diastolic filling have been reported in selected hypertensive patients with normal LV fractional shortening,8–10 but no population-based data have been reported in this regard. Therefore, the present study was undertaken to identify clinical and hemodynamic characteristics associated with impaired diastolic relaxation, as measured by prolonged isovolumic relaxation time (IVRT), and to examine the relation of long IVRT to systolic LV function in a population-based sample of hypertensive participants in the Hypertension Genetic Epidemiology Network (HyperGEN) Study.

Methods

The HyperGEN Study is 1 of 4 components of the Family Blood Pressure Program, funded by the National Heart, Lung, and Blood Institute (NHLBI) to assess the genetic basis of hypertension in population-based samples. As previously described,11,12 HyperGEN primarily relied on a sib-pair design that recruited hypertensive members of sibships in which ≥2 siblings with hypertension onset, without known cause, by age 60 were willing to be studied. Hypertensive individuals were those undergoing antihypertensive treatment or having systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg. Exclusion criteria from the present study were as follows: ≥2+ valvular regurgitation, overt coronary artery disease (by history, previous coronary bypass sur-
were sent to the Reading Center for blinded interpretation by participants from those parent studies previously participated in the NHLBI Family Heart Study, from which a large proportion of hypertensive siblings was sampled for HyperGEN. Many Birmingham, Ala, participants (all African American) were selected from the community. The target population was 100% African American in Birmingham, 50% each African American and white in Winston-Salem, and 100% white in Minnesota and Utah.

The HyperGEN examination obtained standardized measurements of blood pressure at rest and its reactivity to several stimuli. Standardized assessment of body habitus included body mass index, waist/hip ratio, and percent body fat by bioelectric impedance analysis; fasting glucose, insulin, uric acid, lipid, and lipoprotein concentrations were also obtained. Prevalent congestive heart failure was identified by participant reports.

Echocardiographic Methods

Imaging and Doppler echocardiograms were performed by a protocol used in multicenter studies.14,15 Studies were performed with the use of high-quality commercially available echocardiographs equipped with 3.0- to 3.5-MHz and 2.0- to 2.5-MHz transducers with M-mode, 2D, and Doppler (pulsed, continuous, and color-flow) capabilities. The parasternal acoustic window was used to record ≥10 consecutive beats of 2D and M-mode recordings of LV internal diameter and wall thicknesses at or just below the mitral leaflet tips in long- and short-axis views. Additional M-mode, 2D, and Doppler recordings were performed as previously described procedures.16–18 Studies were sent to the Reading Center for blinded interpretation by experienced readers; all measurements were verified by physician investigators.

Echocardiographic Measurements

The correct orientation of planes for imaging and Doppler recordings was verified by standard procedures.16–18 Measurements were made by use of a computerized review station. LV internal dimension and ventricular septal and posterior wall thicknesses were measured at end diastole and end systole by American Society of Echocardiography recommendations17,18 for up to 3 cycles. Pulsed Doppler recordings of transmitral flow velocities at mitral annulus and leaflets tips were traced along the black-white interface to measure peak “E” and “A” wave velocities, acceleration and deceleration times of early diastolic mitral flow, and atrial filling fraction. Pulsed and continuous-wave Doppler LV outflow tract interrogation identified inflow and outflow profiles simultaneously for measurement of IVRT from the aortic closure spike to the onset of mitral inflow.19 In individuals in whom transmitral flow had not been recorded at the mitral annulus, relevant measures were calculated from leaflet tip values by previously reported formulas.5 As previously recommended,20 IVRT >100 ms indicated impaired diastolic relaxation.

Calculation of Derived Variables

End-diastolic LV dimensions were used to calculate LV mass by an anatomically validated formula.21 In 183 hypertensive subjects, we showed high reliability of LV mass estimation by methods similar to those used in HyperGEN.22 LV mass was considered to be an unadjusted variable, and after normalization for height23, partition values of 49.2 g/m2.7 in men and 46.7 g/m2.7 in women identified LV hypertrophy.23 Relative wall thickness (posterior wall thickness/LV radius) was considered elevated if it was >0.43, the 97.5th percentile in a reference population.24 Standard methods were used to calculate endocardial shortening and ejection fraction.16 The Teichholz formula25 was used to estimate LV volumes, which were shown to be accurate in patients with symmetric LV contraction.26 Stroke volume was determined by an invasively validated Doppler echocardiographic method.27

<table>
<thead>
<tr>
<th>Variable</th>
<th>≤100 ms</th>
<th>&gt;100 ms</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, %</td>
<td>65</td>
<td>51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White, %</td>
<td>37</td>
<td>52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, y</td>
<td>53±11</td>
<td>57±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m2</td>
<td>31.7±7.1</td>
<td>30.8±6.8</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>131±21</td>
<td>138±24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>75±11</td>
<td>78±13</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>56±15</td>
<td>60±18</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Measurements are percentages or mean±SD. BP indicates blood pressure.

Diastolic and Systolic Function in Hypertension

Data are presented as mean±SD for continuous variables and as proportions for categorial variables. The χ2 statistic was used to determine differences of categorical variables; unpaired Student’s t tests determined between-group differences of continuous variables. Univariate relations between clinical and echocardiographic variables and IVRT were assessed by Pearson correlation coefficients. Linear regression analysis examined clinical and echocardiographic correlates of IVRT. A value of P<0.05 (2-tailed analysis) indicated statistical significance.

Results

Clinical and Echocardiographic Characteristics

Of 1457 hypertensive HyperGEN participants meeting inclusion criteria for the present study, 219 (15%) had impaired relaxation, as manifested by prolonged IVRT. Participants with long IVRT were more likely to be male and white, were older, and had higher blood pressures than those with normal IVRT (Table 1) but did not differ with regard to body size or use of ACE inhibitors (27% versus 27%, P=NS), β-blockers (23% versus 20%, P=NS), calcium channel blockers (36% versus 36%, P=NS), thiazides (22% versus 21%, P=NS), angiotensin receptor blockers (5% versus 3%, P=NS), or direct vasodilators (both <1%, P=NS).

LV chamber size and wall thicknesses were greater in hypertensive patients with long IVRT than in those with

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Bella et al.
normal IVRT (Table 2). As a result, LV mass and mass indices and relative wall thickness were higher with impaired relaxation. LV hypertrophy was more prevalent with long IVRT than with normal IVRT (30% versus 22%, *P*<0.001). Both concentric and eccentric LV hypertrophy were more prevalent (7% versus 2% and 23% versus 21%, respectively; *P*<0.001) in patients with long IVRT, with a trend toward more concentric remodeling in this group (5% versus 2%).

**LV Function and Systemic Hemodynamics**

Endocardial shortening and ejection fraction were statistically similar in hypertensive subgroups, but indices of myocardial and chamber function were lower in participants with impaired relaxation than in those with normal IVRT (Table 3). There was no difference between subgroups in regard to paired relaxation. LV hypertrophy was more prevalent with long IVRT than with normal IVRT (30% versus 22%, *P*<0.001). Both concentric and eccentric LV hypertrophy were more prevalent in patients with long IVRT, with a trend toward more concentric remodeling in this group (5% versus 2%).

**TABLE 2. LV Geometry in Hypertensive HyperGEN Participants Grouped by Duration of IVRT**

<table>
<thead>
<tr>
<th>Variable</th>
<th>IVRT</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤100 ms</td>
<td>&gt;100 ms</td>
</tr>
<tr>
<td>ST, cm</td>
<td>0.94±0.12</td>
<td>1.00±0.15</td>
</tr>
<tr>
<td>LVID, cm</td>
<td>5.1±0.47</td>
<td>5.2±0.52</td>
</tr>
<tr>
<td>PWT, cm</td>
<td>0.88±0.11</td>
<td>0.94±0.12</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>169±64</td>
<td>191±47</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>86±18</td>
<td>96±21</td>
</tr>
<tr>
<td>LV mass/height², g/m²²</td>
<td>42.4±10.1</td>
<td>45.9±10.9</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.35±0.05</td>
<td>0.36±0.06</td>
</tr>
</tbody>
</table>

Values are mean±SD. ST indicates septal thickness; LVID, LV internal diameter; and PWT, posterior wall thickness.

In patients with prolonged IVRT compared with those with normal IVRT, stroke volume was slightly higher (80±17 versus 77±15 ms, respectively) and heart rate was lower (64 versus 69 bpm, respectively; *P*<0.01). Cardiac output (5.1±1.1 versus 5.3±1.2 L/min) and index (2.58±0.55 versus 2.70±0.56, both *P*<0.05) were slightly lower, whereas total peripheral resistance (1.71±452 versus 1.646±410) and the resistance index (3382±913 versus 3195±739, both *P*<0.05) were elevated in hypertensive patients with impaired relaxation.

As expected, the mean mitral E/A ratio was lower (0.94 versus 1.05, *P*<0.001), mitral deceleration time was longer (228 versus 214 ms, *P*<0.009), and the atrial filling fraction was higher (0.41 versus 0.38, *P*<0.002) in hypertensive patients with long IVRT than in patients with normal IVRT.

**Clinical and Echocardiographic Correlates of IVRT**

In univariate analyses, IVRT was most closely related to higher LV mass (r=0.21), followed by lower heart rate (r=−0.19), older age (r=0.16), higher peripheral resistance (r=0.15, all *P*<0.001), higher systolic and diastolic pressures (r=0.14 and 0.15), higher relative wall thickness (r=0.14), lower MWS (r=−0.14, all *P*<0.01), lower stress-corrected MWS (r=−0.11), and lower body mass index (r=−0.05, both *P*<0.05). IVRT was not significantly related to either ejection fraction or the circumferential ESS/end-systolic volume index.

**Regression Analyses**

The likelihood of IVRT prolongation increased with lower stress-corrected MWS, independent of older age, lower heart rate, and higher LV mass (Table 4). Mean blood pressure, male gender, and use of antihypertensive medications had no independent relationship with IVRT. When ejection fraction or circumferential ESS/end-systolic volume index were substituted for stress-corrected MWS, neither measure of chamber function had an independent relationship with IVRT (both *P*>0.08).

**Diastolic Parameters with Normal or Decreased Systolic Function**

Measures of diastolic function were not statistically different between HyperGEN participants with normal or subnormal LV ejection fraction by gender-specific partition values (Table 5). However, when participants were grouped by gender-specific partition values for stress-corrected MWS (Table 6), IVRT was longer, the atrial filling fraction was higher, and the mitral E/A ratio was lower in patients with subnormal stress-corrected MWS. IVRT was prolonged more commonly in participants with low stress-corrected MWS (odds ratio, 2.4; 95% CI, 1.3 to 4.3).

**Discussion**

To our knowledge, the present study is the first to provide information on clinical and LV structural and functional

**TABLE 3. Systolic Function in Hypertensive HyperGEN Participants Grouped by Duration of IVRT**

<table>
<thead>
<tr>
<th>Variable</th>
<th>IVRT</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤100 ms</td>
<td>&gt;100 ms</td>
</tr>
<tr>
<td>Fractional shortening, %</td>
<td>34.5±4.6</td>
<td>33.3±5.4</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>63.0±7.4</td>
<td>62.1±7.7</td>
</tr>
<tr>
<td>MWS, %</td>
<td>17.6±1.8</td>
<td>16.9±2.1</td>
</tr>
<tr>
<td>Stress-corrected MWS, %</td>
<td>106±11</td>
<td>103±12</td>
</tr>
<tr>
<td>Low stress-corrected MWS, %</td>
<td>3.7</td>
<td>8.5</td>
</tr>
<tr>
<td>ESS, kdyne</td>
<td>158±35</td>
<td>162±41</td>
</tr>
<tr>
<td>ESS/end-systolic volume index, ×10⁴</td>
<td>6.90±1.44</td>
<td>6.63±1.63</td>
</tr>
</tbody>
</table>

Values are mean±SD.
characteristics of hypertensive individuals with impaired diastolic relaxation in a large population-based sample of hypertensive adults. The present study provides the first population-based evidence that hypertensive adults with long IVRT have lower LV myocardial function (as measured by stress-corrected MWS) and lower LV chamber contractility (as assessed by circumferential ESS/end-systolic volume index) than do hypertensive patients with normal IVRT. This finding extends previous evidence in selected clinical populations of associations between lower LV myocardial function and reduced early diastolic LV filling.8–10 Schussheim et al9 found low MWS to be associated with a reduced mitral E/A ratio in a small group of asymptomatic mildly hypertensive patients with normal LV fractional shortening. Furthermore, among untreated hypertensive patients with echocardiographic LV hypertrophy, the atrial filling fraction was higher in patients with reduced compared with normal stress-corrected MWS.9

Contrary to previous studies suggesting that diastolic dysfunction precedes systolic dysfunction in hypertension,1,2 the present study identifies subnormal myocardial function in hypertensive individuals with impaired diastolic relaxation. It is well known that the LV myocardium consists of circumferential fibers in the midwall and longitudinal fibers in the subepicardial and subendocardial walls,30 with circumferential shortening contributing most to LV ejection.31 MWS exceeds that of the outer or subepicardial layers3,4; as a result, an end-diastolic midwall circumferential fiber shows a relative migration toward the epicardium during contraction, and the fiber must then move inward toward the endocardium during LV filling.32 The effect of nonuniform wall thickening is greatest with increased relative wall thickness and thus leads to overestimation of myocardial performance when endocardial fiber shortening is compared between individuals with higher versus lower relative wall thicknesses.4

In addition to evidence of an association between abnormal LV diastolic filling and systolic myocardial dysfunction in a population-based sample of hypertensive adults, we found that LV mass and relative wall thickness were higher with prolonged IVRT. As a result, concentric and eccentric LV hypertrophy were more prevalent in hypertensive adults with prolonged IVRT. These results extend previous evidence of a relationship between diastolic LV filling, assessed as the peak LV filling rate and LV mass.1

The present study also provides the first assessment of systemic hemodynamics in relation to evidence of normal or impaired early diastolic relaxation. Cardiac output and cardiac index were lower, and peripheral resistance and its index were higher in this subgroup of hypertensive patients. Of note, antihypertensive medication use and the level of myocardial afterload were similar in subgroups defined by IVRT. Results of our primary analyses were confirmed by logistic regression models, in which IVRT prolongation was independently related to older age, lower heart rate, greater LV mass, and lower stress-corrected MWS. In alternative analyses, neither the LV ejection fraction nor the circumferential ESS/end-systolic volume index ratio had an independent relationship with IVRT.

Study Limitations
In the present study, noninvasive measurement of IVRT precluded assessment of whether high left atrial pressures may have shortened the IVRT in some participants with slow relaxation rates. Furthermore, the partition value of 100 ms that was used to identify long IVRT is an arbitrary one. However, stress-corrected MWS was also lower in patients with long IVRT as opposed to normal IVRT when an alternative partition value of <105 ms was used (103±12% versus 106±10%, respectively; P=0.003).

Conclusions
In hypertension, impaired LV relaxation, as measured by IVRT, parallels LV midwall dysfunction but not LV systolic chamber function. The parallelism between diastolic and systolic function may aid in the identification of hypertensive patients at high risk of future congestive heart failure.

Acknowledgments
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