Echocardiographic Assessment of Left Ventricular Diastolic Performance in Hypertensive Subjects

Correlation with Changes in Left Ventricular Mass

Vivienne-Elizabeth Smith, William B. White, and Mozafarredin K. Karimeddini

SUMMARY Left ventricular hypertrophy resulting from hypertension is accompanied by significant morbidity and mortality and in advanced stages may be irreversible. Hence, early detection of cardiac changes in hypertensive patients remains an important diagnostic goal. When the hypertrophy is mild or moderate, parameters of left ventricular diastolic function and measurements of left atrial size may facilitate the distinction between normal variation and pathologic increases in left ventricular mass. We measured left ventricular isovolumic relaxation time (IVRT, the time from aortic valve closure to mitral valve opening) and left atrial dimensions and correlated them to left ventricular mass index measured by M-mode echocardiography and rapid left ventricular filling by radionuclide ventriculography. In 20 subjects with untreated mild essential hypertension, IVRT was prolonged compared to a normotensive age-matched control group (91 ± 23 vs 65 ± 13 msec, p < 0.0001). Left atrial dimension index was increased in patients compared to controls (1.9 ± 0.4 vs 1.4 ± 0.5 cm/m², p < 0.001), and this increase was related to prolonged IVRT (r = 0.46, p < 0.001). Abnormal IVRT correlated with both increased left ventricular mass and decreased rapid ventricular filling in the hypertensive subjects. Thus, prolonged IVRT and borderline left atrial dimension may help identify subtle pathologic left ventricular mass increases in hypertensive subjects. (Hypertension 9 [Suppl II]: II-81-II-84, 1987)

KEY WORDS • hypertension • left ventricular relaxation • diastolic function

The presence of left ventricular hypertrophy in hypertension is associated with an unfavorable prognosis. Furthermore, in the presence of established cardiac hypertrophy, the benefits of blood pressure reduction are diminished. Thus, detecting early cardiac changes in hypertensive patients remains an important diagnostic goal. Since modest increases in left ventricular mass may or may not be pathologic, the presence of other echocardiographic correlates of pathologic hypertrophy may help in identifying those changes resulting from hypertension.

Abnormal echocardiographic left ventricular relaxation and filling patterns in hypertensive subjects have been noted previously by a number of investigators. Hanrath et al. demonstrated abnormal relaxation and filling patterns in chronic pressure overload due to aortic valvular stenosis and severe hypertension, and similar results have been reported by Hamada and co-workers in patients with milder forms of hypertension. Neither study specifically related diastolic abnormalities to one another, however, or to changes in left ventricular mass.

Left atrial abnormalities have been well described in patients with hypertension. Tarazi et al. described electrocardiographic P-wave changes in such patients. Subsequently Dreslinski and colleagues reported altered left atrial emptying occurring in the presence of relatively normal left atrial dimensions, although earlier studies of Savage et al. did not demonstrate a difference in atrial size in hypertensive subjects.

We have previously used radionuclide methods to evaluate left ventricular diastolic function in hypertension and have noted abnormalities of left ventricular filling even in the presence of normal left ventricular mass. These abnormalities of diastolic function may be reversed with antihypertensive therapy.

In this study the relationship of left ventricular relaxation to left ventricular filling was examined in hypertensive subjects, and the abnormalities of diastolic function were correlated with left ventricular mass and left atrial dimensional changes.

Methods

Twenty patients (16 men and 4 women) were recruited from the outpatient clinics of the John Dempsey Hospital. Those who were enrolled in the study had a diastolic blood pressure between 90 and 114 mm Hg in the untreated state and had no evidence of coronary artery disease by history, electrocardiography or exercise ventriculography. Previous treatment included a variety of commonly used antihypertensive agents. Age-matched controls (15 men, 5 women) were volunteers from the faculty and staff of the medical school and had no history of hypertension or heart disease. All subjects gave informed consent.

From the Divisions of Cardiology and General Medicine, Department of Medicine, and the Department of Nuclear Medicine, The University of Connecticut, Farmington, Connecticut. Address for reprints: Vivienne-E. Smith, M.D., Division of Cardiology, University of Pittsburgh School of Medicine, 789 Scaife Hall, Pittsburgh, PA 15261.
Medications were withdrawn from patients 1 to 2 weeks prior to the study. At the end of this period, the patients' supine cuff systolic and diastolic blood pressures were recorded (first and fifth Korotkoff sounds). Control subjects' blood pressures were taken at the time of echocardiography.

M-mode phonoechocardiography was performed using a Irex System II by standard techniques. All patients were imaged in the modified left lateral decubitus position. Left ventricular mass was calculated by the method of Reichek and Devereux using the Penn measurement conventions; left ventricular mass index resulted from division of mass by body surface area. Isovolumic relaxation time (IVRT) was taken as the interval from the aortic second sound identified from the aortic valve echo (Figure 1, left panel) to mitral valve opening (Figure 1, right panel). IVRT was recorded at a paper speed of 100 cm/sec, the optimum recording speed for identification of mitral valve opening. Values for six consecutive cardiac cycles were averaged, and the result formed the basis for analysis. For the purposes of this study, left atrial size was taken as the maximum internal dimension (leading edge of the posterior aortic root to leading edge of the posterior atrial wall; see Figure 1).

Average rapid left ventricular filling rate (the division of rapid filling volume by rapid filling time) was determined from the $^{99m}$Tc-labeled left ventricular blood pool in 14 of the hypertensive subjects using a computerized nuclear probe with methods we have detailed previously.

**Results**

**Blood Pressure and Heart Rate**

Systolic and diastolic blood pressure were significantly higher in patients than in controls, but heart rate did not differ between the groups (Table 1).

**Isovolumic Relaxation Time**

**Left Ventricular Mass**

Left ventricular mass index was higher in hypertensive patients than in controls. Although there was a moderate correlation of systolic blood pressure and left ventricular mass index in patients and control subjects as a group ($r = 0.52$, $p<0.001$), blood pressure and mass did not correlate for controls or patients when considered separately. IVRT was significantly longer in patients than in controls (Figure 2). Of the 20 hypertensive patients, 10 patients (50%) had abnormal relaxation times (failure to fall within two standard deviations of the mean for control subjects).

IVRT did not correlate with left ventricular mass index in controls but correlated significantly with mass in the hypertensive patients ($r = 0.59$, $p<0.01$). Among the 14 hypertensive patients with normal left ventricular mass, 4 (28%) had increased IVRT, and all 6 hypertensive patients who had an increased left ventricular mass index had abnormal IVRT (Figure 3).

**Blood Pressure**

When hypertensive patients and controls were analyzed separately, IVRT did not correlate with either systolic or diastolic blood pressure. For the pooled group of patients and controls, however, there was a moderate but significant correlation of systolic blood pressure and IVRT ($r = 0.37$, $p<0.001$, data not shown).

**Age**

In this small group of subjects, no correlation was found between IVRT and age in either the patient or control group ($r = 0.36$, NS; $r = 0.15$, NS, respectively).

---

**Table 1. Hemodynamics, Left Ventricular Mass, Isovolumic Relaxation, and Left Atrial Dimensions in Hypertensive and Control Subjects**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Patients</th>
<th>Controls</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>$48 \pm 11$</td>
<td>$48 \pm 12$</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>$68 \pm 11$</td>
<td>$65 \pm 10$</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>$153 \pm 10$</td>
<td>$124 \pm 12$</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>$99 \pm 10$</td>
<td>$82 \pm 8$</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>$123 \pm 33$</td>
<td>$84 \pm 19$</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>Isovolumic relaxation time (msec)</td>
<td>$91 \pm 23$</td>
<td>$64 \pm 13$</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>Left atrial dimension (cm)</td>
<td>$3.5 \pm 0.4$</td>
<td>$2.5 \pm 0.4$</td>
<td>$p &lt; 0.0001$</td>
</tr>
</tbody>
</table>

Values are means ± SD.

**Filling**

For the 14 hypertensive patients who had both phonoechocardiography and radionuclide filling studies, the left ventricular filling rate was $1.88 \pm 0.42$ end-diastolic counts per second (EDC/sec; normal = $>2.00$ EDC/sec in our laboratory), and IVRT was $94 \pm 26$ msec. There was a significant negative relationship between the echocardiographic isovolumic relaxation period and the radionuclide average left ventricular filling rate ($r = -0.68$, $p<0.01$; Figure 4).

**Left Atrial Dimensions**

The mean left atrial dimension was not above normal limits in 18 of 20 hypertensive patients, but the mean value for patients was significantly different from that of normal controls ($3.5 \pm 0.4$ cm vs $2.5 \pm 0.5$ cm, $p<0.0001$; Figure 5). This difference persisted when indexed values were compared (1.8 ± 0.4 vs 1.4 ± 0.5 cm/m², $p<0.001$). In addition, when patients and controls were treated as separate groups, a significant difference persisted ($p<0.001$) for mean left atrial length (Table 1).

**Figure 1.** M-mode echocardiography. Left panel: Identification of aortic valve closure and phonocardiogram of the aortic second sound (A2) at the onset of isovolumic relaxation. The left atrial (LA) dimension is measured in this view (American Society of Echocardiography convention). Right panel: Determination of isovolumic relaxation time (IVRT), the interval from aortic valve closure (A2) to mitral valve opening (MVO).
Figure 2. Isovolumic relaxation time (IVRT) in 20 hypertensive patients and 20 age-matched controls (p<0.01).

Figure 4. Average left ventricular filling rate (LVFRav) in end-diastolic counts (EDC) per second in relation to isovolumic relaxation time (IVRT) in 14 hypertensive patients.

 controls were considered as a continuous group, the left atrial dimension (indexed) correlated moderately but significantly with IVRT (r = 0.46, p < 0.001) and modestly with left ventricular mass index (r = 0.39, p < 0.05; data not shown).

Discussion
Principal Findings
These investigations confirm that isovolumic relaxation is prolonged in many patients with mild to moderate essential hypertension. Furthermore, this abnormality of diastolic function is related to decreased rapid left ventricular filling rate and increased left ventricular mass and left atrial size.

Methods
While IVRT may be affected by heart rate, this value was not different between patients and controls; hence it is unlikely that the abnormality in hypertensive subjects is due to the effects of slower heart rates. Intraobserver variation might also affect values obtained, but such variability would presumably affect patients and control subjects equally. We chose to study relaxation time by echocardiography because this is a simple interval to derive without need for complex analysis systems.

Previous Investigations
The values for IVRT in the normal and hypertensive subjects reported here are remarkably similar to those obtained in the investigations of Hamada et al., who used similar methods. Our study confirms and extends their results by relating IVRT to changes in left ventricular mass and filling. Our finding of normal but comparatively increased left atrial dimensions in hypertensive patients agrees with the data of Dreslinski and colleagues but is at odds with the earlier studies of Savage et al. Moreover, this upward shift in atrial dimension occurs in relation to prolongation of IVRT. It appears, then, that the left atrial dimension does correlate with changes in left ventricular structure and diastolic function in hypertensive individuals.

Brutsaert et al. have pointed out that ventricular relaxation is influenced not only by hemodynamic load but by "diminished load dependence" as well. Diminished load dependence might occur, for example, with persistent systolic interaction of the contractile proteins. Prolonged IVRT could result from changes in lusitropic calcium uptake across the sarcoplasmic reticulum in a hypertensive ventricle. These fluxes are dependent on adenosine 5'-triphosphate (ATP) and ATP content is reduced by...
chronic pressure overload. This mechanism may account in part for the abnormal relaxation in hypertensive patients even with normal or minimally increased left ventricular mass. Once frank hypertrophy has supervened, relaxation may be further impaired by reduced oxygen supply and altered myocardial elastic element content.

Although we found a correlation between systolic blood pressure and IVRT when considered over a wide range of blood pressure, the physiologic significance of this observation is unclear. In animal studies, Weisfeldt and colleagues found that increased mean arterial pressure was associated with increased peak negative rate of change of pressure but that increased mean arterial pressure did not affect the duration of isovolumic diastole. Furthermore, Hirota could not demonstrate differences in the time constant of left ventricular relaxation in hypertensive subjects compared to normal controls. These discrepancies are likely due to the fact that the relaxation function of the heart represents not only the effect of energy supply-demand mismatch but the complex interaction of regional mechanics and hemodynamic load as well.

Clinical Significance of the Findings

Hypertensive patients with modest hypertrophy of the left ventricle may manifest impaired isovolumic relaxation and tend to have atrial dimensions at the upper limits of normal. Furthermore, the prolonged IVRT correlates with impaired ventricular filling and may therefore distinguish such hypertrophy as pathologic, since ventricular relaxation and filling in physiologic hypertrophy are normal. Left ventricular relaxation time can be easily assessed by m-mode phonoechocardiography without need for complex analysis systems. The constellation of modestly increased mass, greater left atrial dimension, and prolonged ventricular relaxation time in an individual with borderline hypertension may indicate the need for antihypertensive therapy or at least more frequent observation. However, the precise therapeutic implications of such findings should be determined from the results of large prospective trials.

References

10. Smith V-E, White WB, Karimeddini MK, Meeran M, Schulman P. Improved left ventricular filling accompanies reduced left ventricular mass during therapy of essential hypertension [Abstract]. Circulation 1984;70(suppl II):1507
15. Katz AM, Smith V-E. Regulation of myocardial function in the normal and diseased heart: modification by inotropic drugs. Eur Heart J 1982;3(suppl D):11-18
Echocardiographic assessment of left ventricular diastolic performance in hypertensive subjects. Correlation with changes in left ventricular mass.
V E Smith, W B White and M K Karimeddini

Hypertension. 1987;9:II81
doi: 10.1161/01.HYP.9.2_Pt_2.II81

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/9/2_Pt_2/II81

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/