Relation of Left Ventricular Diastolic Properties to Systolic Function in Arterial Hypertension

Giovanni de Simone, MD; Rosanna Greco, MD; GianFrancesco Mureddu, MD; Carmela Romano, MD; Raffaele Guida, MD; Aldo Celentano, MD; Franco Contaldo, MD

**Background**—It is unclear whether impairment of left ventricular (LV) diastolic characteristics is independent of systolic dysfunction.

**Methods and Results**—To address this issue, 159 consecutive hypertensive patients (44±11 years, 78 obese, 96 women) and 165 normotensive subjects (32±11 years, 84 obese, 110 women) were studied with the use of Doppler echocardiography. After adjustment for age, body mass index (BMI), and sex, we found that ejection fraction (EF; M-mode, z-derived) was higher in hypertensive (66.6±5.2%) than in normotensive (63.9±4.4%, P<0.0001) subjects, whereas midwall shortening (MS) was lower (hypertensive patients 16.9±2.0%, normotensive subjects 17.8±2.2%, P<0.02), even after correction for end-systolic wall stress (P<0.05). Isovolumic relaxation time (IVRT) was greater in hypertensive patients (103±14 ms) than in normotensive subjects (78±19 ms), as was deceleration time of E velocity and peak A velocity (all P<0.0001). In multivariate analysis, IVRT was unrelated to EF, but a negative relation was found with MS (P<0.001), independent of age, BMI, presence of arterial hypertension, LV geometry, and load (multiple R²=0.58). For comparable age, sex distribution, BMI, and blood pressure values, hypertensive patients with lower afterload-adjusted MS exhibited longer IVRT than patients with normal MS (P<0.005). However, IVRT remained higher than in normotensive control subjects after control for LV geometry and load.

**Conclusions**—Doppler indices of delayed LV relaxation can be detected in the presence of normal or supranormal EF but are independently related to impaired MS. A less severely abnormal relaxation, however, can be also detected in the presence of normal midwall function, independent of LV geometry and load. Thus, diastolic abnormalities may occur before systolic dysfunction even when it is measured at the midwall. *(Circulation. 2000;101:152-157.)*

**Key Words:** echocardiography ▪ hypertension ▪ ventricles ▪ diastole ▪ systole

There is a substantial body of evidence that abnormalities of left ventricular (LV) diastolic properties may occur in the presence of normal ejection fraction or systolic fractional shortening, often yielding the conclusion that abnormalities in LV diastolic function may precede or be independent of systolic dysfunction.1–9 However, in all studies that address this issue, systolic function has been measured at the level of endocardium, reflecting LV chamber function, which is a physiological result of the interaction between myocardial function and LV geometry.10–12 Recently, measurement of LV systolic function at the level of midwall11 has been shown to be able to identify patients with systolic dysfunction, despite the presence of normal LV chamber function,14,15 an occurrence that has also been shown to have an independent prognostic impact.16 Although many studies have reported relations between LV diastolic properties and measures of chamber function, there are no data on the relation of LV diastolic properties to midwall shortening, information that is potentially important to confirm the relative independence of “diastolic dysfunction” from systolic dysfunction. Accordingly, this study was designed to investigate the relations between LV diastolic properties and midwall function in a group of normotensive and hypertensive patients.

**Subjects**
Three hundred twenty-four participants were included in this analysis. One hundred fifty-nine of them were consecutive hypertensive patients (44±11 years, 79 obese, 96 women) who were seen in the Outpatient Clinic of the Hypertension Unit of the Department of Clinical and Experimental Medicine (DCEM) of the Federico II University Hospital in Naples due to poor control of their blood pressure (systolic >160 mm Hg, diastolic >95 mm Hg) on several clinic measurements. Patients who received medication discontinued treatment for ≥3 weeks after providing formal informed consent. One hundred sixty-five normotensive (32±11 years, 81 obese, 110 women) served as the control group. After providing informed consent, most of the 81 obese normotensive subjects had been enrolled in the Outpatient Clinic of the Nutrition Unit of the DCEM.17 These subjects came to the unit with the sole purpose of losing weight for aesthetic reasons without any signs or symptoms of disease, including diabetes, hypertension, or renal disease. The...
remaining normotensive subjects were volunteers involved in a screening program of the department staff, as previously reported. Obesity was defined as a body mass index of ≥27.8 kg/m² in men and ≥27.3 kg/m² in women. Coronary artery disease was excluded in all participants on the basis of a normal standard 12-lead ECG, a negative family history, the absence of symptoms, and the evidence of normal wall motion at the 2-dimensional echocardiographic examination.

**Echocardiography**

Doppler echocardiography was performed in a dimly light room with patients in the partial left decubitus position with the use of commercially available machines (SIM7000/Challenge or AU3; ESAOTE) equipped with 2.5- to 3.5-MHz annular-array transducers. M-mode tracings and Doppler signals were recorded and the measurements performed as previously reported in detail. LV mass was measured according to Penn convention and normalized for height to the power of 2.7 and LV diastolic dimension for the first power of height. LV hypertrophy was defined as values of LV mass index of ≥47 g/m² to the power of 2.7 in women or ≥49 g/m² to the power of 2.7 in men.

LV systolic function was evaluated as midwall shortening as both an absolute value and a percent of the value predicted from the corresponding circumferential end-systolic wall stress (afterload-adjusted midwall shortening). Ejection fraction was calculated from time of E velocity, as previously reported. The reliability of Doppler measurements was assessed by calculating between-observer (GdS and GFM) interval of agreements of main direct measures used in this study in a different group of 20 subjects (10 hypertensive).

**Statistical Analysis**

Two-factor ANOVA was used to compare normal-weight or obese normotensive control subjects with body size–matched hypertensive patients generated on the basis of values of normal or low afterload-adjusted midwall shortening. A full factorial model was used, and multiple simple contrasts were obtained after adjustment of the multiple comparison error. Ejection fraction was identical to that of the normotensive control subjects (96.36 ± 11.56%) (Table 2). These patients were compared with the 42 hypertensive patients who had values of afterload-adjusted midwall shortening of ≤85% (78.76 ± 4.70%).

Normotensive control subjects were significantly younger than both hypertensive subgroups but had a comparable sex distribution and body mass index (Table 2). After adjustment for age and sex and in consideration of the differences related to the presence or absence of obesity, patients with low afterload-adjusted LV midwall shortening exhibited higher relative wall thickness (P<0.0001) but a similar increased LV mass index compared with patients with normal LV midwall performance. Their ejection fraction was identical to that of the normotensive group and lower than that of patients with normal afterload-adjusted midwall shortening (P<0.0001), who indeed exhibited supranormal ejection fraction values (P<0.0001). Patients with low afterload-adjusted LV mid-
Obese hypertensive patients with low afterload-adjusted midwall shortening (n=24) exhibited similar blood pressure and LV mass index but higher relative wall thickness and ejection fraction (0.47% and 64.8%) than normal-weight patients in the same midwall function subgroup (n=18; 0.42% and 61.1%, P<0.007 and <0.002, respectively). For comparable clusters of LV midwall function, isovolumic relaxation time was longer in obese (88 ms in normotensives, 102 and 111 ms in patients with normal [n=55] or low afterload-adjusted midwall shortening, respectively) than in normal-weight subjects (68, 100, and 104 ms; P<0.0001), a difference that did not achieve statistical significance for deceleration time of E velocity, peak E or A flow velocities, and the ratio of E to A velocity. The differences in isovolumic relaxation time between obese and normal-weight individuals remained unchanged even after the addition of relative wall thickness, end-systolic stress, and LV diastolic dimension in the model of ANCOVA (P<0.0001).

The univariate correlation of LV diastolic parameters to ejection fraction was evaluated in separate normal-weight (80 hypertensive, or 49%) or obese (79 hypertensive, or 49%, P=NS) individuals. Late peak A flow velocity and isovolumic relaxation time were positively related to ejection fraction in both normal-weight and obese individuals (all P<0.01), whereas no relations were found with early peak E flow velocity and time of deceleration of E velocity (Table 3).

In contrast, in both normal-weight and obese subjects, isovolumic relaxation time was negatively related to midwall shortening either as an absolute value or as a percent of predicted from end-systolic stress (afterload adjusted), whereas a positive relation was found with peak E velocity and E/A velocity ratio (all P<0.01, Table 3). In normal-weight individuals, midwall shortening was also negatively related to the time of deceleration of E velocity (P<0.005).

### TABLE 2. General Characteristics and Diastolic Parameters in Normotensive Control Subjects and Hypertensive Patients With Normal or Reduced Afterload-Adjusted Midwall Shortening

<table>
<thead>
<tr>
<th></th>
<th>Normotensive Control Subjects (n=165)</th>
<th>Normal LV Midwall Function (n=117)</th>
<th>Lower LV Midwall Function (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>31.86±10.84</td>
<td>42.94±10.90*</td>
<td>45.60±8.15*</td>
</tr>
<tr>
<td>Sex, % women</td>
<td>110 (67)</td>
<td>69 (64)</td>
<td>27 (59)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.40±5.22</td>
<td>28.22±5.42</td>
<td>28.91±4.70</td>
</tr>
<tr>
<td>Overweight-obesity, %</td>
<td>56 (34)</td>
<td>31 (26)</td>
<td>15 (36)</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>118/75±11/8</td>
<td>154/98±17/8*</td>
<td>156/100±17/7*</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>73.52±11.58</td>
<td>75.47±10.99†</td>
<td>75.16±12.72</td>
</tr>
<tr>
<td>LV mass index, g/m²⁷</td>
<td>32.82±10.74</td>
<td>47.63±14.00*</td>
<td>48.82±10.30*</td>
</tr>
<tr>
<td>LV diastolic dimension, cm</td>
<td>4.84±0.47</td>
<td>5.00±0.45</td>
<td>4.74±0.34</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.33±0.05</td>
<td>0.36±0.05‡§</td>
<td>0.44±0.10*</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>63.89±4.37</td>
<td>67.77±4.67†</td>
<td>63.23±5.28</td>
</tr>
<tr>
<td>Isovolumic relaxation time, ms</td>
<td>77.83±19.09</td>
<td>101.33±13.85*</td>
<td>107.81±12.07*</td>
</tr>
<tr>
<td>E-velocity deceleration time, ms</td>
<td>150.24±31.09</td>
<td>175.49±32.27†</td>
<td>181.09±26.95†</td>
</tr>
<tr>
<td>Early peak E flow velocity, cm · s</td>
<td>71.98±15.86</td>
<td>63.68±10.70</td>
<td>57.48±7.11†</td>
</tr>
<tr>
<td>Late peak A flow velocity, cm · s</td>
<td>54.83±13.33</td>
<td>65.25±12.11*</td>
<td>67.84±10.93†</td>
</tr>
<tr>
<td>E/A velocity ratio</td>
<td>1.38±0.42</td>
<td>0.98±0.25*</td>
<td>0.86±0.17*</td>
</tr>
</tbody>
</table>

Values are adjusted for age and sex; 2-way ANOVA, with obesity as the second factor, full-factorial, hierarchical design.

*P<0.0001, †P<0.03, ‡P<0.01; ¶P<0.005, vs normotensive control subjects.

§P<0.01, ||P<0.0001 vs hypertensive patients with reduced LV midwall function.
Effect of LV Hypertrophy on Relation Between LV Systolic and Diastolic Performance

After control for systolic and diastolic blood pressure, no significant associations were detected between ejection fraction and relative wall thickness, LV mass, or LV mass index in normal-weight individuals, whereas in obese individuals, ejection fraction was directly related to relative wall thickness (partial $r=0.25$, $P<0.001$). In contrast, midwall shortening was more closely and negatively related to relative wall thickness in both normal-weight (partial $r=-0.50$, $P<0.0001$) and obese (partial $r=-0.55$, $P<0.0001$) individuals. In the presence of obesity, midwall shortening was also weakly and negatively related to LV mass (partial $r=-0.19$, $P<0.02$) or LV mass index (partial $r=-0.17$, $P<0.03$). Thus, LV diastolic properties were also evaluated in the subgroups of hypertensive patients without LV hypertrophy.

This analysis was carried out in 78 of 117 patients with normal (67%; 38 women, 32 obese, age $40.3±10.4$ years) and 21 of 42 patients with low afterload-adjusted midwall shortening (50%; 10 women, 8 obese, age $43.4±7.7$ years) who did not have clear-cut LV hypertrophy. Average body mass index was similar in the 2 hypertensive subgroups (27.6 and 27.9 kg/m$^2$, respectively), as were heart rate (both 75 bpm), blood pressure (150/97 and 150/99 mm Hg), and LV mass index (40 and 41 g/m$^2$). In contrast, after control for age, sex, and body mass index, relative wall thickness was substantially higher (0.43±0.07) and ejection fraction was lower (62±4%) in patients with low than in patients with normal afterload-adjusted midwall shortening (0.35±0.05% and 67±5%) or normotensive control subjects (all $P<0.001$). Similarly, isovolumic relaxation time was higher in the subgroup of patients with low (105±11 ms) than in patients with normal afterload-adjusted midwall shortening (98±14 ms) or in normotensive control subjects (both $P<0.0001$). However, even patients with normal midwall function and normal LV geometry exhibited substantially prolonged isovolumic relaxation times compared with control subjects ($P<0.0001$). These differences remained unchanged even after further control for relative wall thickness, end-systolic stress, LV end-diastolic dimension, and LV mass, in addition to demographic covariates (age, sex, and body mass index). The adjusted mean values were 80 ms for normal control subjects, 96 ms for hypertensive patients with normal afterload-adjusted midwall shortening, and 99 ms for hypertensive patients with low afterload-adjusted midwall shortening (all $P<0.0001$).

The differences among groups reported for isovolumic relaxation time were also confirmed for the time of deceleration of E velocity (all $P<0.02$).

### Independent Correlates of Isovolumic Relaxation Time

Models of multiple linear regression analysis were generated to highlight independent correlates of isovolumic relaxation time with the use of significant univariate correlates (age, sex, body mass index, end-systolic stress, end-diastolic dimension, relative wall thickness, presence of hypertension) and, alternatively, ejection fraction or midwall shortening as measures of LV systolic function. Isovolumic relaxation time increased in the presence of arterial hypertension, with increasing age, body mass index, relative wall thickness, and LV chamber dimension and with decreasing end-systolic stress (multiple $r^2=0.57$, $P<0.0001$), whereas no significant effect was detected for ejection fraction (partial $r=-0.10$, $P=0.06$). In contrast, when midwall shortening was used instead of ejection fraction, a negative relation with isovolumic relaxation time was detected (partial $r=-0.16$, $P=0.004$), independent of the significant effect of the other covariates (multiple $r^2=0.58$, $P<0.0001$).

### Discussion

In addition to the common opinion that abnormalities of the diastolic properties of the LV can be detected when systolic function is normal, there is much evidence that congestive heart failure can occur in the presence of normal ejection fraction, reinforcing the notion of a relative independence of LV diastole from systolic mechanics. Despite this broad clinical evidence, however, the process of producing “external” work during systole is energetically balanced by an “internal” work during diastole, which is able to restore the energy spent during systole to pump blood into the arterial tree. Accordingly, when some impairment occurs during diastole, it should also be reflected during systole, and vice versa, making it difficult to separate diastolic and systolic abnormalities from either mechanical or energetic stand-
Results of this study show that when measurements of LV systolic function are taken at the level of endocardium (LV chamber function), a number of diastolic abnormalities can be demonstrated in hypertensive patients in the presence of normal or supranormal systolic function. In this relatively large population, delayed relaxation (ie, prolongation of both isovolumic relaxation time and E deceleration time) was associated with normal-to-high ejection fraction. In addition, ejection fraction was positively related to peak A velocity, a measure of late LV filling. Thus, the pattern emerging from those findings is an association between abnormal LV diastolic properties with normal or supranormal LV systolic function.

In contrast, when LV systolic function was measured at the midwall level, abnormalities of LV diastolic properties paralleled abnormalities of LV systolic performance, a correspondence suggested many years ago in a pioneering work by Shimizu et al.\(^3\) This discrepancy was fundamentally due to the influence of relative wall thickness, which amplified LV chamber function, while matching a depressed midwall function.\(^1\) Abnormalities of the diastolic properties of the LV are indeed more pronounced in patients with clear-cut midwall systolic abnormalities. This relation indicates that there is a continuum in the progressive appearance of these abnormalities, suggesting that changes in systolic and diastolic function may occur concomitantly. However, some degree of diastolic abnormalities could also be detected in the absence of systolic dysfunction even if measured at the midwall level, suggesting that abnormalities of LV diastolic properties might precede the appearance of LV systolic dysfunction.

The reasons for the early appearance of impairment of active relaxation in hypertensive patients with supranormal LV chamber function and normal LV midwall performance were not directly appreciable in our analysis but could be related to the changes in LV geometry, with midwall shortening negatively related to LV mass and relative wall thickness. To address this issue, an analysis of the subgroup of patients with normal LV mass index, which confirmed that LV concentric geometry is associated to depressed midwall performance, also showed that active relaxation was prolonged in the group of hypertensive patients with normal LV midwall performance and normal LV geometry. Thus, no geometric or hemodynamic reasons could be found in a number of multivariate procedures to explain the abnormally prolonged isovolumic relaxation time in patients with normal LV midwall performance and geometry, which might be due at least in part to metabolic abnormalities that directly affect the mechanism of inactivation, as recently reported.\(^3\)

The multiple regression analysis allowed us to generate a summary model that included all the measurable variables. Thus, isovolumic relaxation time was confirmed to increase in the presence of arterial hypertension, with aging, and with increasing body mass index. Isovolumic relaxation time was also found to be prolonged by increasing LV concentric geometry and LV cavity dimension, used as a raw measure of LV preload. Moreover, as already shown,\(^7\) end-systolic stress, a load applied at the beginning of relaxation (relaxation load), reduced isovolumic relaxation time.

**Potential Study Limitations**

The presence of a large proportion of obese individuals, which was useful to expand the variability of many parameters analyzed in this study, could represent a limitation for the purpose of the study because of the abnormalities of LV diastolic properties found in obese patients, even in the absence of arterial hypertension.\(^17,19\) To reduce the possibility of a bias, normotensive and hypertensive subjects were examined with the use of a statistical procedure that allowed separation of the effect of obesity from that of LV systolic function measured at the midwall and, moreover, the detection of the interactive influence of obesity and LV systolic function on the different variables examined. This procedure highlighted that the relation between diastolic characteristics and midwall systolic function was substantially independent of body size, information of potential importance given the high prevalence of obesity in clinical populations of hypertensive patients.

Although in this study isovolumic relaxation time was considered to be the key feature of diastolic function, there are limitations in the measurement of this index that should be taken into account when producing physiological inferences. Isovolumic relaxation time is indeed a rough index of LV active relaxation (which actually begins before the closure of aortic valve), sensitive to changes in load,\(^19\) and potentially influenced by technical variability. To partially overcome these limitations, in the present study, an analysis of isovolumic relaxation time was carried out that also took into account both wall stress (myocardial afterload) and LV internal dimension (as a crude measure of myocardial preload). In addition, reliability analysis performed with interobserver interval of agreement shows that the error is reasonably small to allow the use of this measure in epidemiological studies.

**Conclusions**

LV diastolic properties are abnormal in arterial hypertension and are characterized by delayed active relaxation. This abnormality is independent of LV chamber systolic function but is associated with the extent of systolic performance as measured by LV midwall shortening, a more precise measure of wall mechanics. For comparable LV midwall performance, obesity is associated with more severely prolonged relaxation. This study demonstrated that abnormalities of the diastolic properties of the LV are related to and progress with systolic midwall dysfunction but might also precede abnormalities of myocardial contraction. Metabolic abnormalities, which directly influence the mechanism of inactivation, might play a role in this primary diastolic abnormality.

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**References**


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