Reduced Left Ventricular Functional Reserve in Hypertensive Patients With Preserved Function at Rest

Michaela Kozakova, Alan G. Fraser, Simona Buralli, Armando Magagna, Antonio Salvetti, Ele Ferrannini, Carlo Palombo

Abstract—In many hypertensive patients, left ventricular pump function is normal at rest but abnormal during exercise. Myocardial dysfunction or altered left ventricular loading may be responsible for this finding. To verify the hypothesis of impaired myocardial functional reserve in the hypertensive heart, we assessed the response of stress-adjusted midwall shortening to graded, low-dose dobutamine infusion in hypertensive subjects with normal midwall shortening at rest. Sixty-five subjects (45 never treated hypertensive subjects and 20 normotensive volunteers comparable for age) received dobutamine at 1, 2, 3, 4, and 5 μg·kg⁻¹·min⁻¹ for 5-minute steps; within this range of infusion rates, heart rate and systemic blood pressure were stable. Two-dimensional, M-mode, and Doppler echocardiography were performed at baseline and at the end of each step. In normotensive controls, midwall shortening increased from baseline during 2 μg·kg⁻¹·min⁻¹ dobutamine by an average of 16±4.5% (P<0.01); a value of 2 standard deviations below this mean response was taken as the lower limit of normal. In the hypertensive subjects, 24 had a normal midwall shortening response to dobutamine at this dose (group I) and 21 had a subnormal response (group II). Whereas blood pressure and left ventricular mass were similar in group II and group I, the former had greater relative wall thickness (P<0.01) than the latter. β-adrenergic stimulation by very-low-dose dobutamine unmasks subtle impairment of myocardial functional reserve in hypertensive subjects with normal myocardial performance at rest. This alteration seems to be related mainly to increase in left ventricular relative wall thickness. (Hypertension. 2005;45:1-6.)

Key Words: echocardiography β receptors, adrenergic beta remodeling

A hypertensive heart is the commonest risk factor for heart failure,1 but in hypertensive patients left ventricular (LV) ejection fraction at rest is usually normal or even increased.2 One explanation for this apparent contradiction may be that in many hypertensive patients, heart failure is related to LV diastolic dysfunction;3 alternatively, it is possible that when LV geometry is abnormal, ejection fraction does not accurately describe the contractile behavior of myocardium.4 LV midwall fiber shortening in relation to end-systolic wall stress (MWS) has been proposed as a better index of myocardial performance in systemic hypertension.5 Decreased MWS at rest predicts an adverse outcome in hypertensive patients,2 and it also correlates with a subnormal response of LV ejection fraction to physical exercise.6 Attenuated response of LV pump function to exercise may reflect myocardial dysfunction or altered LV loading.7 8 Previous study7 has proposed altered loading related to LV diastolic dysfunction as a predominant mechanism accounting for a reduced increase in ejection fraction during exercise in hypertensive patients. However, it is difficult to identify early and subtle alterations in myocardial function during exercise because of confounding effects of changes in heart rate and afterload.

Infusion of the β-receptor agonist dobutamine, at low doses that do not influence blood pressure (BP) and heart rate has been shown to increase myocardial contractility in normal subjects.9 Thus, the aim of the present study was to evaluate the response of LV MWS and diastolic filling to graded low-dose dobutamine infusion in never treated hypertensive subjects with systemic hypertension stage 1 and 2 and with normal MWS at rest.

Methods

Study population consists of 65 subjects, including 45 asymptomatic never treated subjects with essential hypertension stage 1 and 2 and normal resting LV systolic performance (defined as stress-adjusted MWS >85% and ejection fraction ≥50%) and 20 healthy normotensive volunteers without LV hypertrophy and with normal LV geometric pattern and systolic performance, comparable for age. Hypertension was defined when office BP was ≥140/90 mm Hg (average of 3 measurements over 1 month). Primary myocardial and heart valve disease, diabetes, and dyslipidemia were exclusion criteria. Significant coronary artery disease was excluded on the basis of noninvasive diagnostic algorithm in normotensive controls and hypertensive subjects. The institutional review committee approved the study, and all participants provided informed consent.

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Study Protocol
Each subject was placed in a left decubitus position with an indwelling cannula inserted into the right antecubital vein and a brachial sphygmomanometer cuff placed on the left arm. A very slow infusion of saline was administered while the subject was left to relax for 10 minutes, before resting levels of heart rate and BP were measured, and the resting echocardiographic study was performed (SONOS 3500; Philips Technologies, Andover, Mass) and recorded on S-VHS videotapes for off-line analysis. Echocardiographic study included: (1) 2-dimensionally targeted M-mode echocardiograms of the LV, aortic valve opening, and longitudinal motion of the mitral annulus; (2) apical 4-chamber view of LV; and (3) Doppler interrogation of transmirtal, aortic, and LV outflow tract flow profiles.

After resting recordings, study subjects received an infusion of dobutamine at 1, 2, 3, 4, 5, 10, and 20 µg·kg⁻¹·min⁻¹ for 5-minute intervals at each dosage. During the last 2 minutes of each step, all echo Doppler recordings were repeated. At the end of each step, BP was measured and a 3-lead ECG was recorded.

Echocardiographic Measurements
From the measurements in M-mode echocardiograms, LV mass and mass index, relative wall thickness, endocardial fractional shortening, peak systolic wall stress, circumferential end-systolic wall stress, MWS, and stress-adjusted MWS were calculated using standard formulas. LV hypertrophy was defined as LV mass/height².⁷ In women and >50 g·m⁻² in men. A relative wall thickness of 0.42 was used as a cutoff value for concentric geometry. Mitral annular descent during systole was measured at both septal and lateral margins, and the reported value represents an average of both measurements. In M-mode recordings of mitral annular movement, the time from the QRS complex onset on EKG to the peak of mitral annular excursion was also measured. Ejection fraction was calculated using the Simpson formula. From the transmirtal flow profile obtained at the tips of mitral leaflets, peak early (E-wave) and peak late (A-wave) flow velocities and E-wave deceleration time were measured, and the E/A ratio was calculated. The isovolumic relaxation time was assessed as recommended. Stroke volume and cardiac index were calculated from the aortic velocity–time integral and aortic valve opening. All measurements were taken as the mean of 3 beats.

Statistical Analysis
Data are expressed as mean±SD. ANOVA was used to evaluate the differences between groups and dobutamine steps. Bonferroni-Dunn post-hoc test in 2-way ANOVA for repeated measures was applied to evaluate a significance of trends in each group as well as the differences in trends between the groups. The χ² distribution and Fisher exact test were used for categorical variables. Least-square linear regression analysis was used to assess univariate relations between continuous variables. Statistical analysis was performed by a commonly available software (StatView 5.0; Abacus Concepts Inc, Berkeley, Calif).

Results
Hemodynamic Responses to Low-Dose Dobutamine
In normotensive controls and hypertensive subjects, systolic BP and heart rate did not change at very low doses of dobutamine, but they increased at doses of 10 µg·kg⁻¹·min⁻¹ (Figure). Diastolic and mean BP remained stable at all doses up to 20 µg·kg⁻¹·min⁻¹ in controls, whereas in hypertensive subjects diastolic and mean BP were decreased at infusion rates of 4 and 10 µg·kg⁻¹·min⁻¹, respectively (Figure). Consequently, inotropic response of the heart to stepwise doses of dobutamine was studied during the infusion of 1, 2, 3, 4, and 5 µg·kg⁻¹·min⁻¹, because at these doses dobutamine did not modify heart rate and systolic and mean BP, either in controls or in hypertensive subjects. Chronotropic response to β-adrenergic stimulation was assessed as a percentage of heart rate increase at dobutamine dose of 20 µg·kg⁻¹·min⁻¹.

Inotropic Response to Dobutamine
In normotensive controls, stress-adjusted MWS increased by 7±7% at 1 µg·kg⁻¹·min⁻¹ (P<0.05) and by 16±4.5% at 2 µg·kg⁻¹·min⁻¹ (P<0.01). With increasing doses of dobutamine, MWS increased further (Table 1). In the hypertensive
subjects, stress-adjusted MWS was unchanged at 1 μg·kg⁻¹·min⁻¹ but increased by 28±10% at 2 μg·kg⁻¹·min⁻¹ dobutamine (P<0.01). Hypertensive subjects were divided into 2 subgroups according to the response of stress-adjusted MWS to dobutamine infusion at 2 μg·kg⁻¹·min⁻¹. The response to 2 μg·kg⁻¹·min⁻¹ of dobutamine was considered to be normal when the observed percent increase from baseline was within 2 SD below the mean value of normotensive controls, ie, ≥7%. Twenty-four subjects (53%) had a normal response (group I) and 21 subjects (47%) had a subnormal response (group II). In group I, inotropic responses to low-dose dobutamine were comparable to the responses in normotensive controls, whereas in group II the responses were delayed and damped, and a significant increase in stress-adjusted MWS was first observed only at 5 μg·kg⁻¹·min⁻¹ (Table 1). Similar dose–response relationships were observed for unadjusted MWS and endocardial fractional shortening. Bonferroni-Dunn post-hoc test in 2-way ANOVA for repeated measures confirmed an increase in both midwall and endocardial shortening with dobutamine doses in each study group, although the trend of changes was significantly different in group II as compared with group I and normal controls (P<0.001 for midwall shortening and P<0.01 for endocardial shortening). The between-group differences were less significant for the responses in LV ejection fraction and stroke volume (Table 1). The amplitude of mitral annular systolic excursion at baseline did not differ between hypertensive and normotensive subjects (14.3±2.7 versus 14.4±2.0 mm), whereas the time from the QRS onset to the peak of mitral annular excursion was higher in hypertensive subjects (451±59 ms versus 396±28 ms; P<0.05). The increase in mitral annular excursion during dobutamine, first observed at the dose of 3 μg·kg⁻¹·min⁻¹, was comparable in all 3 groups (Table 1).

Responses in Systemic Hemodynamics, Wall Stress, and Diastolic Filling: Comparison Between Groups

The response in BP was comparable between group I and group II hypertensive subjects. The heart rate did not change up to the dose of 5 μg·kg⁻¹·min⁻¹ in any group. At the maximal dose of 20 μg·kg⁻¹·min⁻¹, the percent increase in heart rate was lower in group II (45±15%) than in group I (61±22%, P<0.01) and normotensive controls (57±21%, not significant). LV end-diastolic diameter and peak systolic

### TABLE 1. Responses of Left Ventricular Systolic Performance and Wall Stress to Low-Dose Dobutamine Infusion

<table>
<thead>
<tr>
<th>Indices Measured</th>
<th>Baseline</th>
<th>1 μg</th>
<th>2 μg</th>
<th>3 μg</th>
<th>4 μg</th>
<th>5 μg</th>
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<tbody>
<tr>
<td>MWS-adj, %</td>
<td>Control</td>
<td>111±11</td>
<td>119±14*</td>
<td>128±13</td>
<td>129±11</td>
<td>133±12</td>
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<td></td>
<td>All hypertensive subjects</td>
<td>113±12</td>
<td>116±12</td>
<td>122±15</td>
<td>125±14</td>
<td>127±15</td>
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<td></td>
<td>Group I</td>
<td>111±12</td>
<td>119±10</td>
<td>131±9</td>
<td>133±11</td>
<td>135±10</td>
</tr>
<tr>
<td></td>
<td>Group II</td>
<td>112±14</td>
<td>111±13</td>
<td>112±14</td>
<td>115±14</td>
<td>117±13</td>
</tr>
<tr>
<td>MWS, %</td>
<td>Control</td>
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<td>20.8±2.6*</td>
<td>22.9±2.1</td>
<td>23.5±2.0</td>
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<td>18.6±1.9</td>
<td>20.0±1.7*</td>
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<td>24.1±1.5</td>
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<td>Group II</td>
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<td>18.4±1.8</td>
<td>18.8±2.1</td>
<td>19.9±2.1</td>
<td>20.4±2.4</td>
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<td>EFS, %</td>
<td>Control</td>
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<td>42±6*</td>
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<td>55±6</td>
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<td>Group I</td>
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<td>40±5*</td>
<td>48±5</td>
<td>51±4</td>
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<td>41±5</td>
<td>44±5*</td>
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<td>SV, mL</td>
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<td>94±16</td>
<td>97±17</td>
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<td>Group II</td>
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<td>84±10</td>
<td>88±13</td>
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<td>MAD, mm</td>
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<td>17.4±2.5</td>
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<td>14.2±2.3</td>
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<td>15.8±2.5</td>
<td>16.4±2.8*</td>
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<td>Control</td>
<td>125±22</td>
<td>112±34</td>
<td>95±23</td>
<td>84±24</td>
<td>72±19</td>
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<td>Group I</td>
<td>167±32</td>
<td>145±35*</td>
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<td>102±26</td>
<td>99±29</td>
</tr>
<tr>
<td></td>
<td>Group II</td>
<td>150±35</td>
<td>146±34</td>
<td>135±34</td>
<td>123±28</td>
<td>112±36</td>
</tr>
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</table>

*cESS indicates circumferential end-systolic wall stress; EFS: ejection fraction; EFS: endocardial fractional shortening; MAD: mitral annular descent; MWS: unadjusted midwall shortening; MWS-adj, stress-adjusted midwall shortening (calculated as the ratio between observed MWS and the value predicted from circumferential end-systolic wall stress and expressed as a percentage); SV: stroke volume.

*P<0.05 and †P<0.01 vs baseline. 2-way ANOVA for repeated measures with Bonferroni-Dunn post-hoc test was used to evaluate trends in LV function during dobutamine.
wall stress did not change up to the dose of $5 \mu g \cdot kg^{-1} \cdot min^{-1}$ in any group. Decrease in end-systolic wall stress was slightly delayed in group II as compared with normotensive controls and group I (Table 1). The responses in the indices of LV diastolic filling were comparable between study groups: isovolumic relaxation time decreased ($P<0.01$) at $5 \mu g \cdot kg^{-1} \cdot min^{-1}$ in all groups, whereas E-wave deceleration time did not change in any group. E-wave flow velocity slightly increased at the dose of $5 \mu g \cdot kg^{-1} \cdot min^{-1}$ in both hypertensive groups; however, the E/A ratio did not change up to the dose of $5 \mu g \cdot kg^{-1} \cdot min^{-1}$ in any group.

### Possible Determinants of Reduced Inotropic Response: Comparison Between Groups I and II

Hypertensive subjects with a reduced inotropic response to low-dose dobutamine (group II) had a similar mean age and body mass index as the hypertensive subjects with a normal response (group I) (Table 2). There were no differences in resting BP, heart rate, LV mass index, and prevalence of LV hypertrophy, which was present in two-thirds of the subjects in either group. Resting LV systolic function, wall stress, and indices of global diastolic filling did not discriminate between groups I and II (Table 2).

Subjects in group II differed from those in group I in LV geometry. Group II subjects had more concentric LV geometry ($33\%$ versus $4\%; P<0.01$), with slightly smaller end-diastolic dimension ($-5\%; P<0.05$), greater LV wall thickness ($+13\%; P<0.01$), and relative wall thickness ($+18\%; P<0.01$) (Table 2). In the entire hypertensive population (ie, groups I and II combined), LV relative wall thickness was inversely related to the increment of stress-adjusted MWS at dobutamine steps of 2, 3, 4, and $5 \mu g \cdot kg^{-1} \cdot min^{-1}$ ($r=-0.46,-0.39,-0.39,$ and $-0.38; P<0.01$ for all).

### Discussion

The main findings of the present study are: (1) the response of LV MWS to inotropic stimulation by very low doses of the $\beta_1$-adrenergic agonist dobutamine is attenuated in almost half of subjects with systemic hypertension stage 1 and 2 and normal myocardial performance at rest; (2) hypertensive subjects with a reduced inotropic response to dobutamine had a similar mean age and body mass index as the hypertensive subjects with a normal response (group I) (Table 2). There were no differences in resting BP, heart rate, LV mass index, and prevalence of LV hypertrophy, which was present in two-thirds of the subjects in either group. Resting LV systolic function, wall stress, and indices of global diastolic filling did not discriminate between groups I and II (Table 2).
subjects with normal or attenuated inotropic responses to dobutamine differ in LV geometry; and (3) lusitropic response to dobutamine is not altered in hypertensive patients with an attenuated inotropic response.

Data of recent studies indicate that concentric LV geometry represents an unfavorable LV adaptation to pressure overload.\textsuperscript{17–20} Our observation, suggesting that an increase in LV wall thickness relative to chamber diameter is associated with decreased response of midwall circumferential fibers to β-adrenergic stimulation, adds another piece of information to this evidence. An objection can be raised that calculated MWS may be determined by relative wall thickness, because LV end-diastolic diameter and wall thicknesses are the variables represented in the formula of both indices. However, in this study the baseline MWS was normal and comparable between the groups, despite differences in relative wall thickness. The differences between hypertensive groups emerged only during inotropic stimulation by low doses of dobutamine that did not modify systemic hemodynamics, so that LV end-diastolic diameter and wall thicknesses remained unchanged. Thus, an attenuated response of MWS to dobutamine observed in hypertensive subjects with higher relative wall thickness could be interpreted as blunted myocardial functional reserve.

Several pathophysiological mechanisms may account for a blunted myocardial functional reserve: myocardial ischemia,\textsuperscript{21} cardiac β-adrenergic dysfunction,\textsuperscript{22,23} and structural changes within myocardium\textsuperscript{24–25} might all be considered from a theoretical point of view. In our clinical model, myocardial ischemia related to reduced vasodilator capacity of coronary microcirculation\textsuperscript{21} could not diminish MWS response to dobutamine because heart rate and peak systolic wall stress, ie, the main determinants of myocardial oxygen consumption,\textsuperscript{26} did not increase during the very low-dose dobutamine infusion. By contrast, the reduced chronotropic response to higher doses of dobutamine (20 μg·kg\textsuperscript{-1}·min\textsuperscript{-1}) observed in hypertensive subjects with a blunted inotropic response is in keeping with the hypothesis of β-adrenergic receptors downregulation.\textsuperscript{20,22–23}

Structural changes within myocardium related to neurohumoral factors of hypertension, above all the accumulation of fibrillar collagen,\textsuperscript{24–25} are supposed to contribute to the impairment of myocardial performance.\textsuperscript{27} Decrease in myocardial contractility may be partly compensated by increase in LV wall thickness, aimed to preserve the pump function.\textsuperscript{20,28}

Cardiac contractility may be partly compensated by increase in myocardial functional reserve: myocardial ischemia,\textsuperscript{21} cardiac downregulation.\textsuperscript{20,22–23} A blunted response of midwall fibers to inotropic stimulation observed in hypertensive subjects with more concentric LV geometry might therefore reflect the presence of structural changes within myocardium. The dose-dependent increase in the effective pump performance, estimated as LV ejection fraction and Doppler-derived stroke volume, was rather preserved in hypertensive subjects with blunted myocardial response, probably because of the fact that the dose-dependent increase in long-axis shortening was not decreased.\textsuperscript{29} Actually, the amplitude of mitral annular descent was comparable between normotensive and hypertensive subjects, whereas time-to-peak of annular descent was longer in the hypertensive population. This finding indicates that in the hypertensive heart with normal baseline LV function, long-axis systolic velocities may be decreased, as previously described,\textsuperscript{30} but the effectiveness of long-axis shortening is preserved.

The finding that hypertensive subjects with reduced inotropic response to dobutamine showed normal response of LV diastolic relaxation is not surprising. The lusitropic response to dobutamine has been shown to be well-preserved even in the failing heart with a significantly attenuated positive inotropic response.\textsuperscript{31}

Study Limitations

Our study cohort is not representative of a general hypertensive population because, by study design, all hypertensive subjects had normal MWS. As a result of this criterion our hypertensive population has a low prevalence of concentric LV geometry.\textsuperscript{5} Myocardial functional reserve has been evaluated by M-mode quantitative echocardiography as the response of stress-adjusted MWS to graded dobutamine infusion. Myocardial tissue Doppler and strain-rate imaging, which can quantify the amount and the rate of local myocardial deformation, might be more sensitive for the appraisal of subtle changes in LV circumferential and longitudinal function.\textsuperscript{9,23,29–30} Nonetheless, we used stress-adjusted MWS as an index of myocardial performance, because it represents a recognized predictor of adverse outcome in subjects with essential hypertension.\textsuperscript{5}

Conclusion

In our selected hypertensive population with normal resting myocardial performance, β-adrenergic stimulation by dobutamine at very low doses that do not modify systemic hemodynamics was able to unmask blunted myocardial functional reserve. This functional alteration was mainly related to an increase in LV wall thickness.

Perspectives

Our study presents the use of low-dose dobutamine infusion combined with the echocardiographic assessment of LV performance as a possible test for estimating myocardial functional reserve in the clinical setting, without confounding effects of changes in heart rate, blood pressure, and LV wall stress. The sensitivity and diagnostic accuracy of the test may be expected to improve by using more advanced ultrasound techniques, such as tissue Doppler imaging. More extensive and prospective clinical studies are necessary to understand the actual clinical usefulness of this approach in identification of hypertensive subjects with subclinical cardiac involvement prone to have heart failure develop over the years.

References


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