Relation Between Left Ventricular Midwall Function and Coronary Vasodilator Capacity in Arterial Hypertension

Michaela Kozáková, Ele Ferrannini, Carlo Palombo

Abstract—In systemic hypertension, depressed left ventricular midwall shortening predicts an adverse outcome and is associated with increased left ventricular relative wall thickness, which has been proposed as an independent predictor of cardiovascular risk and reduced coronary reserve. This study was designed to investigate whether depressed midwall shortening is associated with more critical impairment of coronary function and with exercise-induced myocardial ischemia. Sixty untreated hypertensive patients without coronary artery stenosis and 20 normotensive volunteers underwent exercise ECG testing, standard and transesophageal echocardiography to assess the occurrence of exercise-induced myocardial ischemia, left ventricular mass, geometry, and midwall shortening, and coronary vasodilator capacity. Compared with hypertensive patients with normal midwall shortening, those with depressed function (n = 15) had higher minimum coronary resistance (1.19 ± 0.27 versus 1.39 ± 0.20 mm Hg/cm per second, P < 0.01) and prevalence of exercise-induced myocardial ischemia (36 versus 67%, P < 0.05). Within the hypertensive group, midwall shortening was inversely related to minimum coronary resistance (r = −0.42, P < 0.01). Compared with patients with an exercise ECG test negative for myocardial ischemia, those with a positive test result (n = 26) had higher minimum coronary resistance (1.13 ± 0.21 versus 1.38 ± 0.27 mm Hg/cm per second, P < 0.01) and lower midwall shortening (104 ± 16 versus 93 ± 14%, P < 0.01). We conclude that hypertensive patients with depressed midwall shortening have more severe impairment of coronary function and a higher prevalence of exercise-induced myocardial ischemia as compared with hypertensive patients with normal midwall shortening. These findings suggest that a decrease in myocardial performance may be related, at least in part, to chronic intermittent myocardial ischemia caused by a critical impairment of coronary vasodilator capacity. (Hypertension. 2003;42:528-533.)

Key Words: hypertension, arterial ⋄ echocardiography ⋄ vasodilation ⋄ ventricular function, left ⋄ myocardial contraction ⋄ remodeling

Heart failure is one of the most important contributors to cardiovascular morbidity and mortality,1 and hypertension is the most common cause of heart failure.2,3 Nevertheless, in arterial hypertension, a major cardiovascular risk factor, left ventricular (LV) ejection fraction, is generally normal or even increased and does not have significant prognostic value.4 This paradox may be explained by the fact that in the presence of abnormal LV geometry, as often occurs in hypertensive subjects, ejection fraction does not accurately describe the contractile behavior of myocardium.5 LV midwall fiber shortening in relation to end-systolic wall stress has been proposed as a more accurate index of myocardial performance in systemic hypertension. Depressed midwall shortening has been found in about one sixth of asymptomatic hypertensive patients6 and has been shown to predict morbidity and mortality, mainly caused by coronary and cerebral arterial disease,7,8 independent of age, blood pressure, and LV mass. Reduced midwall shortening is associated with increased LV relative wall thickness9,10 and impaired LV relaxation.10,11 Investigation of coronary function in the hypertensive heart has demonstrated that coronary vasodilator capacity deteriorates with increasing relative wall thickness12,13 and that impaired coronary flow reserve is associated with the occurrence of transient ischemic episodes even in the absence of significant coronary stenosis.14–16 These observations, together with data on the negative prognostic significance of concentric remodeling,17,18 imply that changes in coronary function may represent the link between high relative wall thickness, low midwall shortening, and cardiovascular morbidity. With increasing LV wall thickness, coronary microvascular density decreases,19,20 whereas the extravascular component of coronary resistance and perivascular collagen deposition increase.21–23 Interstitial fibrosis augments LV wall stiffness, which, in turn, impairs ventricular relaxation and interferes with coronary hemodynamics.22 Impaired coronary function prevents an adequate rise in myocardial blood flow when myocardial oxygen demand increases and thus predisposes to episodes of myocardial ischemia.19–16 Repeated ischemic episodes may induce the loss of contractile

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proteins and an additional increase in interstitial fibrosis, hence contributing to the decline of LV contractile performance 24,25 and further impairment of LV relaxation.

The present study was designed to investigate, in a group of untreated patients with mild to moderate essential hypertension and without significant coronary artery disease, whether (1) depressed LV systolic performance is associated with a more severe impairment of coronary vasodilator capacity, and (2) exercise-induced myocardial ischemia is related to depressed myocardial performance and reduced coronary vasodilator capacity.

Methods

Study Subjects

The study group consisted of 60 untreated patients with essential hypertension (37 men) who completed an exercise ECG test (ETT) with definite diagnostic outcome (positive or negative for exercise-induced myocardial ischemia) and 20 healthy normotensive volunteers (12 men) (Table 1). Hypertension was defined as an office blood pressure of ≥140/90 mm Hg (average of 3 measurements over a period of 1 month). Significant coronary artery disease was excluded on the basis of clinical history, ETT, and evaluation of coronary function, were used in hypertensive patients with a history of chest pain. The institutional review committee approved the study, and each subject provided informed consent to participate.

Study Protocol

All study subjects underwent stepwise, symptom-limited ETT, standard transthoracic, 2-dimensionally targeted M-mode and Doppler echocardiography, and transesophageal echocardiography for the evaluation of coronary flow velocity response to adenosine.

ETT was performed with the subject sitting on the exercise bicycle, according to a modified Bruce protocol (stepwise load increments of 25 W every 2 minutes until reaching 85% of the maximal heart rate predicted for age). The test was considered positive when horizontal or downsloping ST-segment depression ≥0.15 mV developed 80 ms apart from the J point, both in the presence and absence of chest pain. The test was considered negative when completed in the absence of both chest pain and ECG changes.

All transthoracic echocardiograms were performed by the same operator according to standard protocols, and LV mass index, relative wall thickness, endocardial fractional shortening, stroke volume, total peripheral resistance, circumferential end-systolic wall stress, and afterload-adjusted midwall shortening were calculated. 7–8,26–29 LV hypertrophy was defined as an LV mass/height ≥2.7 85% was considered normal. 10 Pulsed Doppler was used to determine transmital flow profile by measurement of early peak E-flow velocity, late peak A-flow velocity, and the E/A ratio. 11 Transesophageal Doppler echocardiography was used to measure coronary flow velocity (CFV) in the proximal left anterior descending artery (SONOS 2500 and 5500, Philips Technologies) at baseline, during intravenous adenosine infusion (700 µg/kg over 5 minutes), and for 5 minutes afterward, as previously described. 12,30 Coronary vasodilator response to adenosine was assessed as coronary flow reserve (CFR) and minimum coronary vascular resistance (MCVR, mm Hg/cm per second), which were calculated according to the standard formulas. 30,31 The accuracy of transesophageal Doppler echocardiography for coronary vasodilator capacity assessment has been previously validated against intracoronary Doppler guide wire, 31 and the reproducibility of the measurements also has been tested. 30

Statistical Analysis

Data are expressed as mean ± SD. ANCOVA was used to compare continuous variables while adjusting for confounders; the χ² test was used to compare categoric variables. Least-squares linear regression was used to assess univariate relations between continuous variables. Stepwise multiple regression analysis was used to study the inde-
Midwall shortening was dependent of association of continuous variables that did not exhibit excessive collinearity with each other. Logistic regression was used to assess the independent association between nominal and continuous variables. Power calculation was performed as recommended. Statistical analysis was performed with commercial software (StatView 5.0, Abacus Concepts Inc).

### Results

#### Characteristics of the Study Groups

Forty-five hypertensive patients had normal (>85%) and 15 had depressed (≤85%) afterload-adjusted midwall shortening (Table 1). Hypertensive patients with normal myocardial performance had a mean afterload-adjusted midwall shortening comparable to that of normotensive control subjects. Hypertensive subgroups were comparable for age, body mass index, office diastolic blood pressure, and endocardial fractional shortening. As compared with hypertensive patients with normal myocardial performance, those with depressed midwall shortening had higher office systolic blood pressure, LV mass index, relative wall thickness and prevalence of concentric LV hypertrophy, increased total peripheral resistance, and lower E/A ratio. Heart rate at the time of transmural flow profile recording was comparable between the two subgroups, being 71±7 and 71±8 bpm. In the whole hypertensive group, relative wall thickness was directly related to office systolic blood pressure (r=0.49, P<0.01) and inversely to the E/A ratio (r=−0.32, P<0.05).

#### Baseline Coronary Flow Velocity and Coronary Flow Velocity Response to Adenosine

Compared with normotensive control subjects, baseline CFV was increased only in hypertensive patients with depressed midwall shortening (Table 2). CFV measured at maximal flow response to adenosine was similarly decreased in both hypertensive subgroups. In patients with depressed midwall shortening, however, the measurement was performed under higher perfusion pressure. Consequently, CFR was significantly lower and MCR higher in hypertensive patients with low midwall shortening compared with those with normal midwall shortening (Table 2), even after adjusting for office blood pressure, gender, and previous therapy. To test the adequacy of study group size, power calculation was performed. When a minimum difference in MCR between any patient group and control subjects believed to be important to detect was set at 17% (the percent difference in MCR between hypertensive patients with normal and depressed midwall shortening), power calculation yielded the minimal sample size of 15 individuals for each patient group.

In the hypertensive group as a whole (Figure), afterload-adjusted midwall shortening was directly related to CFR (r=−0.40, P<0.01) and inversely to MCR (r=−0.42, P<0.01). In univariate regression analysis, also the E/A ratio (r=0.31, P<0.05) and office systolic blood pressure (r=−0.41, P<0.01) were related to midwall shortening. In a multivariate model adjusting for gender and previous treatment, only MCR remained independently related to afterload-adjusted midwall shortening (F value=12.3, adjusted r²=0.17, P<0.01).

In addition, in the hypertensive group, the relation of CFV and coronary vasodilator capacity to possible determinants of coronary function—age, systemic hemodynamics, rate-pressure product, LV mass, geometry, inotropism, and diastolic filling—were evaluated (Table 3). Baseline CFV increased with office systolic blood pressure, rate-pressure product, relative wall thickness, and LV mass index, whereas CFV during adenosine decreased with total peripheral resistance and increased with the E/A ratio. CFR decreased with age, office systolic blood pressure, rate-pressure product, relative wall thickness, and LV mass index, and it increased with midwall shortening and the E/A ratio. MCR increased with office systolic blood pressure, relative wall thickness, and total peripheral resistance, and it decreased with midwall shortening and the E/A ratio. In a multivariate model adjusting for gender and therapy, systolic blood pressure, relative wall thickness, and age remained independently related to CFR (F value=9.3, 8.1, and 4.7, adjusted r²=0.41, P<0.001), whereas total peripheral resistance, the E/A ratio, and systolic blood pressure were independently related to MCR (F value=14.4, 6.8, and 6.1, adjusted r²=0.43, P<0.001).

#### Exercise-Induced Myocardial Ischemia

ETT was positive for myocardial ischemia in 26 hypertensive patients. In comparison with the 34 patients with negative test
TABLE 3. Relationships of Coronary Function to Age, Systemic Hemodynamics, RPP, LVM, Geometry, Inotropism, and Diastolic Filling

<table>
<thead>
<tr>
<th>Coronary Function</th>
<th>Related Variables</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CFV</td>
<td>Systolic blood pressure</td>
<td>0.32</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Rate-pressure product</td>
<td>0.39</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Relative wall thickness</td>
<td>0.28</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Adenosine CFV</td>
<td>Total peripheral resistance</td>
<td>-0.43</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>E/A ratio</td>
<td>0.26</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CFR</td>
<td>Age</td>
<td>-0.33</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Systolic blood pressure</td>
<td>-0.57</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Rate-pressure product</td>
<td>-0.28</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Relative wall thickness</td>
<td>-0.53</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>LV mass index</td>
<td>-0.29</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Afterload-adjusted MWS</td>
<td>0.40</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>E/A ratio</td>
<td>0.39</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MCR</td>
<td>Systolic blood pressure</td>
<td>0.49</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Relative wall thickness</td>
<td>0.41</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Total peripheral resistance</td>
<td>0.48</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Afterload-adjusted MWS</td>
<td>-0.42</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>E/A ratio</td>
<td>-0.45</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Results, those with a positive test had, after adjusting for gender and therapy, higher office systolic blood pressure, relative wall thickness, total peripheral resistance, and MCR and lower midwall shortening, E/A ratio, CFR, and CFV during adenosine infusion (Table 4). Heart rate at the time of transmural flow profile recording was comparable between the two subgroups, being 71 ± 8 and 72 ± 7 bpm. The difference in systolic blood pressure at peak exercise was at the limit of statistical significance (P = 0.06) (Table 4). In logistic regression, MCR and the E/A ratio were independently related to a positive ETT (r² = 0.26, P < 0.05 for both). The prevalence of LV hypertrophy was comparable between patients with positive and negative test results; however, those with a positive test result had a slightly higher prevalence of concentric hypertrophy. The prevalence of exercise-induced myocardial ischemia was higher in patients with reduced midwall shortening (Table 2). Patients with reduced midwall shortening had also higher systolic blood pressure at peak exercise compared with those with normal myocardial performance (231 ± 14 versus 220 ± 14 mm Hg, P < 0.05), whereas diastolic blood pressure at peak exercise was comparable between the two subgroups (125 ± 10 versus 121 ± 12 mm Hg, NS).

TABLE 4. Clinical Profile, LV Geometry, Function, and Coronary Vasodilator Capacity in Hypertensive Patients Stratified by ECG Response to Exercise (ETT)

<table>
<thead>
<tr>
<th></th>
<th>Hypertensive Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Profile, LV Geometry, Function, Coronary Function</td>
<td>ETT Negative</td>
</tr>
<tr>
<td>n</td>
<td>34</td>
</tr>
<tr>
<td>Age, y</td>
<td>52±8</td>
</tr>
<tr>
<td>Office systolic BP, mm Hg</td>
<td>163±12</td>
</tr>
<tr>
<td>Office diastolic BP, mm Hg</td>
<td>99±9</td>
</tr>
<tr>
<td>Systolic BP at peak exercise, mm Hg</td>
<td>219±17</td>
</tr>
<tr>
<td>Diastolic BP at peak exercise, mm Hg</td>
<td>121±12</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>61±18</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.42±0.09</td>
</tr>
<tr>
<td>Prevalence of LVH, %</td>
<td>74</td>
</tr>
<tr>
<td>Prevalence of concentric LVH, %</td>
<td>24</td>
</tr>
<tr>
<td>Endocardial fractional shortening, %</td>
<td>39.3±5.1</td>
</tr>
<tr>
<td>Afterload-adjusted MWS, %</td>
<td>104±16</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.96±0.19</td>
</tr>
<tr>
<td>TPR, dynes·s·cm⁻²·m⁻²</td>
<td>3123±791</td>
</tr>
<tr>
<td>Baseline CFV, cm/s</td>
<td>32.6±8.2</td>
</tr>
<tr>
<td>Adenosine CFV, cm/s</td>
<td>87.7±19.7</td>
</tr>
<tr>
<td>CFR</td>
<td>2.80±0.45</td>
</tr>
<tr>
<td>MCR, mm Hg·s·cm⁻¹</td>
<td>1.13±0.21</td>
</tr>
</tbody>
</table>

*P < 0.05 vs ETT negative; †P < 0.01 vs ETT negative.
Discussion

The main findings of the present study are (1) hypertensive patients with depressed midwall shortening have lower CFR and higher MCR as compared with hypertensive patients with normal midwall shortening, (2) exercise-induced myocardial ischemia in hypertensive patients without significant coronary stenosis is associated with a more severe impairment of systolic myocardial performance, LV diastolic filling, and coronary vasodilator capacity irrespective of LV mass, and (3) in the hypertensive heart, the increase in LV relative wall thickness arises as an important structural abnormality mediating the relations between reduced LV performance, impaired coronary function, and myocardial ischemia.

Midwall Shortening, Coronary Vasodilator Capacity, and Exercise-Induced Myocardial Ischemia

LV midwall fiber shortening related to circumferential end-systolic wall stress has been proposed as a better index of LV myocardial performance in patients with systemic hypertension, in whom LV geometry is often abnormal. Depressed midwall shortening has been found in a considerable proportion of asymptomatic hypertensive patients, has been shown to be associated with impaired LV relaxation, and to mark cardiovascular risk. The present study provides the first evidence that hypertensive patients with a low midwall shortening also have a more severe impairment of coronary function and a higher prevalence of exercise-induced myocardial ischemia. The association between depressed myocardial performance and more critically reduced coronary vasodilator capacity may be, at least in part, a consequence of chronic intermittent myocardial ischemia. Recurrent periods of myocardial ischemia may provoke loss of contractile proteins and reparative fibrosis, thus leading to the decline of LV systolic contractile function and impairment of diastolic relaxation. In our group of untreated hypertensive patients without significant coronary artery disease, those with an exercise ECG test positive for myocardial ischemia had higher relative wall thickness, systolic blood pressure, total peripheral resistance, and MCR and lower E/A ratio compared with those with negative test results. On the whole, this pattern of relations suggests that a high afterload promotes an increase in LV wall thickness, which then initiates a cascade of structural alterations leading to impairment of coronary vasodilator capacity, episodes of effort myocardial ischemia, and, eventually, decreased myocardial performance.

Study Limitations

By design, our study group had a high prevalence of exercise-induced myocardial ischemia and is therefore not representative of an asymptomatic general hypertensive population, in which depressed midwall shortening behaves as an independent predictor of cardiovascular risk. The main goal of the study was to assess the possible relation between coronary vasodilator capacity and LV systolic performance. However, coronary function and LV midwall shortening are closely related to LV diastolic relaxation. In the present study, LV diastolic filling was roughly estimated by E/A ratio of transmural flow. More sensitive indexes, such as LV isovolumic relaxation time or those derived from tissue Doppler imaging, should be used to analyze the relations between LV diastolic properties, LV systolic performance, and coronary function. On the other hand, in a previous study, increase in E/A ratio has been shown to parallel LV hypertrophy regression and CFR improvement during antihypertensive therapy. The possible limitations of transesophageal echocardiography for the assessment of coronary vasodilator capacity in hypertensive patients have been previously discussed.

Conclusions

The current evidence, obtained in untreated patients with mild to moderate essential hypertension and without significant coronary artery disease, suggests that a decreased LV performance can be, at least in part, a result of recurrent episodes of intermittent myocardial ischemia related to a critical impairment of coronary vasodilator capacity. The increase in LV wall thickness related to chamber diameter appears to play a prominent role in the association between systolic performance, coronary function, and myocardial ischemia.

Perspectives

Depressed midwall shortening represents an independent determinant of cardiovascular risk in hypertensive patients. Impairment of coronary function that in hypertensive heart is often associated with myocardial fibrosis and diastolic dysfunction may contribute to this risk. Nowadays, with the use of new ultrasound modalities such as transthoracic or transesophageal coronary Doppler, tissue Doppler imag-
ing,36,37 and acoustic tissue characterization,39 the above-mentioned alterations can be studied noninvasively. Thus, an integrated ultrasound approach can represent a useful tool for risk stratification and the assessment of therapeutic interventions in hypertensive patients.

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