Impaired Myocardial Functional Reserve in Hypertension and Diabetes Mellitus Without Coronary Artery Disease: Searching for the Possible Link With Congestive Heart Failure in the Myocardial Doppler in Diabetes (MYDID) Study II

Satish Govind, Samir Saha, Lars-Åke Brodin, S. S. Ramesh, S. R. Arvind, and Miguel Quintana

Background: Although the impact of type 2 diabetes mellitus (DM) and hypertension (HTN) on myocardial function has recently been studied using tissue Doppler echocardiography (TDE), the independent role of both conditions, and the influence of other risk factors on myocardial function has not been completely defined, particularly in absence of coronary artery disease (CAD). The aim of this study was to assess the myocardial functional reserve in patients with DM or HTN with apparently normal left ventricular (LV) systolic function.

Methods: Standard and dobutamine stress echocardiography using TDE was performed in 128 subjects: 59 had DM, 20 had HTN, 27 had both DM and HTN (HTN/DM), and 22 subjects were controls (C). Subjects with known CAD and depressed LV function were excluded. In addition, standard two-dimensional and Doppler measurements, LV regional peak systolic (PSV), early (E') and late (A') diastolic velocities, strain (S%) and strain rate (SR), were assessed at rest and peak stress.

Results: The LV mass did not differ, although relative wall thickness was significantly higher in subjects with HTN + DM and HTN. The PSV did not differ at rest but was lowest in subjects with HTN + DM at peak stress. The E' wave velocity was significantly lower in subjects with HTN + DM both at rest and during peak stress, as were S% and SR.

Conclusions: The addition of DM to HTN has a negative effect on LV systolic and diastolic functions. A depressed myocardial functional reserve might be postulated as one of the pathophysiologic mechanisms for the excessive occurrence of congestive heart failure in patients with DM or HTN. Am J Hypertens 2006;19:851–857 © 2006 American Journal of Hypertension, Ltd.

Key Words: Type 2 diabetes mellitus, hypertension, congestive heart failure, left ventricular function, tissue Doppler echocardiography.

Type 2 diabetes mellitus (DM) and hypertension (HTN) are independent risk factors for cardiovascular morbidity–mortality, and patients suffering from both illnesses have a progressive increment in risk that is thought to be caused by the high prevalence of coronary artery disease (CAD) observed in those patients. Similarly, HTN and DM are two important epidemiologic risk factors for the development of congestive heart failure (CHF), especially in women and in the elderly population. Although the epidemic of CHF observed in the elderly population may be explained by the high prevalence of CAD, the risk of developing CHF is closely related to the presence of HTN and DM, even when adjusted for coexisting CAD and other risk factors.

Anomalies of myocardial structure and left ventricular (LV) function have been reported among patients with

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HTN or DM.\textsuperscript{6–13} Traditionally, myocardial structure has been evaluated by means of LV absolute and relative wall thickness, fractional shortening, midwall shortening, or myocardial remodeling. The LV function, in particular its diastolic properties, have been studied by means of color and pulsed-wave Doppler echocardiographic techniques.\textsuperscript{13} The abnormalities observed using these techniques have been suggested as the pathophysiologic factors associated with poor exercise tolerance\textsuperscript{14} and the development of CHF in the presence of preserved LV ejection fraction.\textsuperscript{15}

Recently, a new approach to evaluate LV myocardial function in patients with HTN and DM using tissue Doppler echocardiography (TDE) has been used.\textsuperscript{16–21} The results, although concordant in some aspects, still contain differences.\textsuperscript{17–20} Therefore, the present study was designed to investigate the effects of HTN, DM, and its combination on LV systolic and diastolic functional reserve using TDE during dobutamine stress echocardiography (DSE) in patients without CAD.

Methods

Population

One hundred twenty-eight randomly selected subjects from the myocardial Doppler in diabetes (MYDID) study population,\textsuperscript{22} nonconsecutively evaluated for atypical chest pain, participated in the study. Only subjects with a negative standard DSE were analyzed. Patients with known CAD, other structural heart diseases, depressed LV systolic function (LV ejection fraction <50\%) and with LV regional wall motion abnormalities were excluded from the present analysis. Subjects were grouped as controls (C, \(n = 22\)), patients with HTN alone (\(n = 20\)), DM alone (\(n = 59\)), and both HTN and DM (HTN + DM, \(n = 27\)). Subjects in the control group (without HTN or DM) had a low pretest probability of CAD. The DM subjects were prediagnosed according to World Health Organization criteria. Duration of diabetes was 7.2 ± 5.2 years in DM and 7.4 ± 4.2 years in HTN + DM. Nonfasted samples were used to estimate plasma glucose. Patients were treated for hypertension for 5 ± 2 years and for HTN + DM 2 ± 2 years. Among DM patients, 54 were treated with oral hypoglycemic agents (OHA) and 5 with insulin plus OHA. Two of these patients were also receiving angiotensin-converting enzyme inhibitors (ACEI) for renoprotection. Among patients with HTN, 5 were on \(\beta\)-blockers (BB), 3 on calcium channel blockers (CCB), 3 on diuretics, 2 on ACEI, 2 on angiotensin II receptor blockers (ARB), 2 on combination of BB and CCB, 1 on combination of BB with diuretics, 1 on combination of CCB and diuretics, and 1 on combination of diuretics. Among HTN + DM patients, 18 were treated with an OHA, 4 with insulin, and 5 with the combination of both. In this group, 9 were on BB, 7 on ACEI, 5 on CCB, 2 on diuretics, 2 on ARB, 1 on combination of ACEI with diuretics, and 1 on combination of BB with CCB.

Ethical Clearance

The Ethical Committee of the Karolinska University Hospital at Huddinge, Stockholm, approved the study protocol. All study subjects gave informed consent.

Standard Echocardiography Protocol

Echocardiography was performed with VIVID 5 equipment (General Electric, Vingmed, Horten, Norway) using a 2.5-MHz probe for image acquisition. The images were acquired in parasternal long and short axis, as well as in apical four- and two-chamber projections. The LV dimensions and mass were calculated using standard formula.\textsuperscript{23} In addition to the two-dimensional imaging, pulsed wave Doppler of early (E-wave) and late (A-wave) velocities and E/A ratio were measured along with pulmonary systolic and diastolic flow velocities.

Dobutamine Stress Echocardiography

Dobutamine stress echocardiography was performed using a graded standard 3-min stage protocol (5–40 \(\mu\)g · kg · min\). Patients who failed to achieve the target heart rate were given atropine in increments of 0.3 mg up to a maximum of 1.8 mg. End points of DSE were the achievement of 85\% of maximum heart rate, and the development of severe wall motion abnormalities or subjective intolerance. Standard gray scale images with superimposed color Doppler were acquired in apical four- and two-chamber projections. For visual analysis, the left ventricle was divided into 16 segments. The wall motion of each segment during DSE was scored as follows: hyperkinetic, normal, hypokinetic, akinetic, or dyskinetic. A test was considered normal in the absence of a new-onset wall motion abnormality in at least two consecutive segments. A test was considered eligible for the analysis if at least 12 of 16 segments were interpretable. The echocardiograms were analyzed by one independent, trained echocardiographer (SG) who was blinded to the clinical data. In cases that were uncertain, a second interpretation was done by an independent investigator and a consensus opinion prevailed.

Tissue Doppler Echocardiography

The LV apical images with superimposed color Doppler were obtained at an average frame rate of 130 frames/sec and were digitally stored. Cine loops containing three consecutive cardiac cycles were analyzed off-line at rest and during peak dobutamine stress. A sample volume was placed at the basal segments of each LV wall (septum, lateral, inferior, and anterior). Peak systolic velocity (PSV), early (E') and late (A') diastolic velocities (cm/sec) were computed at rest and during peak stress. Strain (S\%) and strain rate (SR) were calculated from the velocity profiles using a sample volume of 15 mm. Global LV myocardial function was assessed by taking the average of the LV regional measurements.
Table 1. Demographics and laboratory data in the study groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls</th>
<th>HTN</th>
<th>DM</th>
<th>HTN + DM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 22</td>
<td>N = 20</td>
<td>N = 59</td>
<td>N = 27</td>
</tr>
<tr>
<td>Age (y)</td>
<td>53 ± 16</td>
<td>55 ± 7</td>
<td>54 ± 10</td>
<td>56 ± 7</td>
</tr>
<tr>
<td>Male/females</td>
<td>11/11</td>
<td>9/11</td>
<td>41/18</td>
<td>11/16</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161 ± 11</td>
<td>156 ± 7**</td>
<td>164 ± 8</td>
<td>158 ± 9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71 ± 12</td>
<td>71 ± 16</td>
<td>70 ± 13</td>
<td>71 ± 11</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.75 ± 0.16</td>
<td>1.71 ± 0.17</td>
<td>1.75 ± 0.17</td>
<td>1.72 ± 0.14</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 ± 4</td>
<td>29 ± 7</td>
<td>26 ± 5</td>
<td>28 ± 5</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>12.5 ± 1.5†</td>
<td>12.5 ± 1.6**</td>
<td>13.8 ± 1.5††</td>
<td>12.4 ± 0.9</td>
</tr>
<tr>
<td>Plasma glucose (mg/dL)</td>
<td>98 ± 14††</td>
<td>110 ± 8**</td>
<td>172 ± 53</td>
<td>153 ± 27</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.94 ± 0.17‡</td>
<td>1.11 ± 0.41</td>
<td>1.02 ± 0.2‡‡</td>
<td>1.21 ± 0.29</td>
</tr>
<tr>
<td>Serum total-cholesterol (mg/dL)</td>
<td>177 ± 23††</td>
<td>201 ± 35</td>
<td>195 ± 31</td>
<td>185 ± 19</td>
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<tr>
<td>Serum LDL-cholesterol (mg/dL)</td>
<td>118 ± 29</td>
<td>102 ± 24</td>
<td>118 ± 33</td>
<td>97 ± 27</td>
</tr>
<tr>
<td>Serum HDL-cholesterol (mg/dL)</td>
<td>42 ± 4</td>
<td>40 ± 8</td>
<td>42 ± 9</td>
<td>34 ± 3</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dL)</td>
<td>165 ± 31</td>
<td>185 ± 49</td>
<td>192 ± 124</td>
<td>151 ± 30</td>
</tr>
</tbody>
</table>

BMI = body mass index; BSA = body surface area.  
The P value in the last column is for trends with ANOVA. The other P values represent the post-hoc analysis with Tukey test.
* P < .05 C v HTN; † P < .05 C v DM; ‡ P < .05 C v HTN + DM.
** P < .05 HTN v DM; †† P < .05 HTN v HTN + DM; ‡‡ P < .05 DM v HTN + DM.

Statistical Methods

Data are expressed as mean ± SD. One-way ANOVA followed by post hoc Tukey honest test was performed to compare the differences between groups. To study the possible determinants of LV global myocardial systolic function expressed as PSV at peak stress, a linear regression analysis was performed introducing all the variables described in Tables 1 and 2. Only the variables showing a correlation with a P value of ≤ .1 were entered in a multiple forward stepwise regression analysis. As a previous large study24 has shown a significant correlation between heart rate and plasma cholesterol levels with PSV, and as female gender has been related to concentric remodeling of the LV and diabetes,25 these variables were introduced in a second multiple forward stepwise regression analysis. A PC-based version of Statistica version 6.0 (Statsoft, Tulsa, OK) was used for data analysis. A P value of < .05 was considered significant.

Results

Age, body weight, body surface area, and body mass index were not significantly different among the groups (Table 1). Patients with DM were, however, taller than those in the other groups. The plasma creatinine level was higher in subjects with HTN and HTN + DM compared with the

Table 2. Two-dimensional and Doppler echocardiographic findings in all groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>HTN</th>
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<td>N = 22</td>
<td>N = 20</td>
<td>N = 59</td>
<td>N = 27</td>
</tr>
<tr>
<td>SWTd (mm)</td>
<td>9.7 ± 1.4††</td>
<td>10.5 ± 2.5</td>
<td>10.9 ± 1.7</td>
<td>11.4 ± 2.1</td>
</tr>
<tr>
<td>PWTd (mm)</td>
<td>9.6 ± 1.8</td>
<td>10.1 ± 2.2</td>
<td>10.4 ± 1.8</td>
<td>10.8 ± 1.3</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>145 ± 43</td>
<td>146 ± 47</td>
<td>165 ± 49</td>
<td>163 ± 49</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>81 ± 19</td>
<td>85 ± 27</td>
<td>93 ± 27</td>
<td>88 ± 23</td>
</tr>
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<td>RWT</td>
<td>0.44 ± 0.06‡</td>
<td>0.51 ± 0.15</td>
<td>0.49 ± 0.09</td>
<td>0.54 ± 0.15</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>44 ± 4</td>
<td>42 ± 6</td>
<td>44 ± 6</td>
<td>42 ± 6</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>69 ± 5*††</td>
<td>65 ± 5</td>
<td>63 ± 4‡‡</td>
<td>65 ± 7</td>
</tr>
<tr>
<td>E-wave (cm/sec)</td>
<td>90 ± 13*††</td>
<td>71 ± 14</td>
<td>79 ± 20</td>
<td>74 ± 20</td>
</tr>
<tr>
<td>A-wave (cm/sec)</td>
<td>83 ± 20‡</td>
<td>87 ± 13</td>
<td>81 ± 16‡‡</td>
<td>93 ± 20</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.09 ± 0.28*‡</td>
<td>0.83 ± 0.18</td>
<td>0.98 ± 0.31</td>
<td>0.82 ± 0.27</td>
</tr>
<tr>
<td>Pulm vein S (cm/sec)</td>
<td>65 ± 13</td>
<td>65 ± 13</td>
<td>58 ± 16</td>
<td>59 ± 9</td>
</tr>
<tr>
<td>Pulm vein D (cm/sec)</td>
<td>46 ± 11</td>
<td>42 ± 8</td>
<td>38 ± 14</td>
<td>41 ± 10</td>
</tr>
<tr>
<td>Pulm vein S/D</td>
<td>1.46 ± 0.34</td>
<td>1.55 ± 0.26</td>
<td>1.53 ± 0.28</td>
<td>1.50 ± 0.33</td>
</tr>
</tbody>
</table>

A-wave = A-wave velocity of the mitral valve inflow; E-wave = E-wave velocity of the mitral valve inflow; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; Pulm vein D = pulmonary vein flow diastolic velocity; Pulm vein S = pulmonary vein flow systolic velocity; PWTd = posterior wall thickness in diastole; RWT = relative wall thickness; SWTd = septum wall thickness in diastole. Statistical analysis: see Table 1.
* P < .05 C v HTN; † P < .05 C v DM; ‡ P < .05 C v HTN + DM.
** P < .05 HTN v DM; †† P < .05 HTN v HTN + DM; ‡‡ P < .05 DM v HTN + DM.
other groups. The blood hemoglobin level was higher in DM than in the other groups. Men and women were similarly represented among groups; however, men represented almost 70% of the DM group.

Table 2 shows the two-dimensional and Doppler echocardiographic findings. Statistically significant differences were found in LV septum thickness, LV ejection fraction, mitral E- and A-wave velocities, and in the E/A ratio. All other two-dimensional echocardiographic parameters were identical.

Table 3 shows the DSE findings. Although the patients with HTN + DM had a somewhat higher heart rate at rest than the other groups, the peak heart rate was lower compared with the other groups. The resting and peak systolic blood pressures (BP) were higher in patients with HTN and HTN + DM than those in the other groups. The diastolic BP was higher in the HTN group than in the other groups, including the HTN + DM group. The rate pressure product (RPP) at rest was higher in the HTN + DM group compared with the other groups; at peak DSE the RPP was higher in the HTN group compared with the other groups.

The PSV at rest was similar among groups, but at peak stress there were statistically significant differences among the groups, and a possible additive effect could be observed (Fig. 1). The E’ wave velocity at rest was lower in patients with HTN + DM compared with the other groups. This difference was more pronounced at peak stress. Almost similar results were observed in the A’ wave at peak stress. Strain rate (SR) at rest and at peak stress was lowest in patients with HTN + DM compared with other groups. Similar results were observed in strain (S%).

The determinants of global LV myocardial systolic reserve, expressed as PSV at peak stress, were calculated. Among all the parameters listed in Tables 1 and 2, along with the presence of DM and HTN, the following variables showed a linear correlation with a $P$ value of $\leq .1$: age, HTN, DM, plasma glucose, plasma creatinine levels, LV mass index, posterior wall thickness (PWT), relative wall thickness (RWT), and A-wave velocity, and E/A velocity ratio. To avoid variables containing redundant information, PWT, RWT, and E/A velocity ratio were not

<table>
<thead>
<tr>
<th>Variables</th>
<th>Stage</th>
<th>Controls</th>
<th>HTN</th>
<th>DM</th>
<th>HTN + DM</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>Rest</td>
<td>75 ± 14</td>
<td>76 ± 14</td>
<td>82 ± 14</td>
<td>84 ± 14</td>
<td>.061</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>Rest</td>
<td>126 ± 10††</td>
<td>150 ± 12††</td>
<td>149 ± 10††</td>
<td>140 ± 13</td>
<td>.012</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>Rest</td>
<td>76 ± 7†</td>
<td>92 ± 8**††</td>
<td>79 ± 7†</td>
<td>87 ± 8</td>
<td>.002</td>
</tr>
<tr>
<td>RPP</td>
<td>Rest</td>
<td>9459 ± 2080†</td>
<td>11324 ± 2432</td>
<td>10630 ± 1998</td>
<td>12082 ± 2761</td>
<td>.01</td>
</tr>
<tr>
<td>PSV (cm/sec)</td>
<td>Rest</td>
<td>5.66 ± 1.74</td>
<td>5.30 ± 1.35</td>
<td>5.61 ± 1.19</td>
<td>5.47 ± 1.08</td>
<td>.761</td>
</tr>
<tr>
<td>A’ wave (cm/sec)</td>
<td>Rest</td>
<td>6.42 ± 2.19†</td>
<td>5.55 ± 1.90**</td>
<td>6.60 ± 1.97††</td>
<td>5.27 ± 1.55</td>
<td>.011</td>
</tr>
<tr>
<td>SR$^{-1}$</td>
<td>Rest</td>
<td>12.17 ± 1.87†</td>
<td>11.26 ± 1.82</td>
<td>12.05 ± 1.64†</td>
<td>10.61 ± 1.83</td>
<td>.002</td>
</tr>
<tr>
<td>S%</td>
<td>Rest</td>
<td>0.66 ± 0.14††</td>
<td>0.37 ± 0.20**††</td>
<td>0.55 ± 0.16†</td>
<td>0.46 ± 0.17</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

A’-wave – myocardial velocity during the atrial contraction period; E’-wave – myocardial velocity during the rapid filling period; HR = heart rate; PSV = peak systolic velocity; RPP = rate pressure product; S% = strain; SR = strain rate. Statistical analysis: see Table 1.

* $P < .05$ C v HTN; † $P < .05$ C v DM; †† $P < .05$ C v HTN + DM.

** $P < .05$ HTN v DM; ††† $P < .05$ HTN v HTN + DM; ‡‡‡ $P < .05$ DM v HTN + DM.

Table 3. Findings during dobutamine stress echocardiography (DSE) in all groups

FIG. 1. Peak systolic velocity (PSV), early E’ and late A’ diastolic velocities obtained as the average of the four basal left ventricular segments at peak dobutamine stress echocardiography. *$P < .05$ HTN + DM versus Controls or HTN versus Controls. DM = type 2 diabetes mellitus; HTN = hypertension.
introduced in the multiple forward stepwise regression analysis. In this analysis only the following variables remained statistically significant: age (F = 7.9, P ≤ 0.001), LV mass index (F = 8.4, P ≤ 0.005), the presence of HTN (F = 5.9, P = 0.01), and plasma glucose levels (F = 4.8, \( P = 0.03 \)). When female gender, plasma cholesterol levels, and heart rate at peak stress were introduced in the model, only the following variables remained statistically significant: age (F = 8.6, \( P = 0.004 \)), LV mass index (F = 11.8, \( P = 0.001 \)), and HTN (F = 4.9, \( P = 0.03 \)).

**Discussion**

In the present study, global LV myocardial systolic reserve assessed by TDE during DSE was depressed in patients with HTN and those with DM compared with the controls. The coexistence of both diseases seems to have an additive harmful effect. The clinical implication of the present study lies in the fact that early detection of “subclinical” LV systolic dysfunction is possible by means of TDE, at stages where parameters of LV systolic function are still normal (ie, LV ejection fraction or fractional shortening) when assessed by conventional techniques. This subclinical LV systolic dysfunction may play an important role in the pathogenesis of CHF with preserved LV ejection fraction observed in the elderly population and in women, groups with extremely high prevalence of DM and HTN.12,25,26

Previous studies have shown contradictory results regarding the LV longitudinal function (assessed by quantification of the movement of the LV from base to apex17,19) when assessed by means of TDE during DSE.17,20 Although one study17 showed that the LV longitudinal function was depressed both at rest and at peak DSE, another20 has shown that patients with DM and/or HTN showed a depressed longitudinal function at rest but a normal response at peak DSE. In addition, differing with other studies,16,18 we found a normal LV longitudinal function at rest in patients with DM or HTN assessed by means of TDE. In the light of the results of the previous and the present study, the existence of different stages of myocardial systolic dysfunction among patients with HTN or DM may be hypothesized. In its mildest form, the disease may be characterized by a declined systolic functional reserve at peak stress, a moderate form showing depressed function already at rest but normal functional reserve at peak stress, whereas a more severe form of the illness may cause depressed systolic function both at rest and during peak stress. However, differences among the studied populations may explain the apparently contradictory results of the mentioned studies; therefore, larger studies involving several hundred patients are necessary to elucidate the natural history of LV systolic and diastolic dysfunction in subjects with DM or HTN.

The strength of the present and other studies17,20 lies in the fact that the investigators of these studies have demonstrated that HTN and DM, even in the absence of significant CAD, induces deterioration of the LV systolic and diastolic functions that can be assessed by clinically meaningful variables. Using TDE, a technique that allows the study of LV myocardial functions relatively independent of loading conditions of the heart, it has been demonstrated that patients with DM or HTN have a depressed LV longitudinal myocardial function,17,19 whereas the radial LV myocardial function is increased.17,21 This increment in the radial LV myocardial function has been proposed as a compensatory mechanism to maintain LV hemodynamics in the presence of depressed longitudinal functions, which are presumably caused by ischemic and fibrotic processes of the subendocardial longitudinal fibers.8,27 This situation resembles that of the normal heart during exercise. At the beginning of exercise most of the increment of the LV myocardial function occurs due to an increase in longitudinal function, whereas at the later stages of exercise, most of the augmented LV dynamics is explained by a continuous increment of the radial function.28

Epidemiologic studies have shown some degree of impairment in myocardial structure and LV function among patients with DM or HTN. Those studies have dealt mostly with LV mass, geometry, and diastolic function.4,11,12,25,29 However, the modest changes observed in some of the studied variables preclude its use in clinical practice. In addition, the most widely used parameters in clinical practice, namely the LV ejection fraction, did not differ between patients and controls, although in the present clinical study we could demonstrate some form of LV myocardial geometric remodeling, as shown by the increased RWT in patients with HTN + DM compared with the other groups.

In the present study, age, LV mass index, the presence of HTN, and plasma glucose levels were independent determinants of LV systolic myocardial function. However, when gender, plasma cholesterol levels, and heart rate at peak stress were introduced in the model, plasma glucose level was no longer an independent predictor. These statistical associations do not establish any causal relationship that needs to be tested in larger and prospective studies. In the study by Fang et al30 only glycosylated hemoglobin (HbA1c) and treatment with ACEIs independently predicted LV systolic myocardial function. However, the exclusion of LV hypertrophy, a common finding in diabetics even in the absence of hypertension,11 and inclusion of as many as 25 covariates in the model, makes the results of the multivariate analysis less accurate. We did not include in our model any treatment because the patients were not randomized to any therapy and because the treatment options for both DM and HTN were diverse with multiple combinations as presented in the Methods section.

Separating the relative importance of each risk factor in clinical practice is, however, almost impossible, because up to 40% of patients with DM are on antihypertensive medication25 and up to 73% of patients have a BP ≥ 130/80.
random plasma blood glucose samples, which is probably
accuracy. The grade of metabolic control was assessed by
out the presence of CAD with approximately 90% ac-

Limitations of the Study
Although coronary angiography was not used to rule out
significant CAD, the use of a negative DSE enabled to rule
out the presence of CAD with approximately 90% ac-
curacy. The grade of metabolic control was assessed by
random plasma blood glucose samples, which is probably
not as effective as HbA1c as a marker of metabolic control.
We did not assess LV radial contraction and, therefore, we
could not confirm the results of previous studies. Because
we did not measure plasma insulin level or do a homeo-
static model assessment (HOMA), we do not know how
many of the studied patients had insulin resistance syn-
drome, which might have contributed to depressed myo-
cardial systolic and diastolic functions. The higher number
of men in the DM group may have influenced the results
introducing a higher than expected value for PSV at peak
stress. These finding needs to be confirmed in future
studies.

Future Perspectives
The findings of the present study may help to modify
future strategies for the classification and treatment of
CHF with preserved LV ejection fraction, because, as
known, a substantial percentage of patients with CHF and
preserved LV ejection fraction have LV systolic dysfunc-
tion, which is usually not identified by standard Doppler
methods or other techniques. An early selection of those
patients for conventional treatment of CHF may result in
an improved prognosis, a promise not yet fulfilled by
current clinical trials, in which patient selection was based
on the presence of a “normal” or “near-normal” LV ejec-
tion fraction.

Conclusions
A reduction of both systolic and diastolic LV functions is
observed in patients with HTN and DM when assessed by
means of TDE during DSE. The coexistence of DM and
HTN seems to have an additive negative effect on both
systolic and diastolic functions and may be considered as
one of the pathophysiologic mechanisms that might ex-
plain the development of CHF with preserved LV ejection
fraction commonly seen in elderly subjects and in women,
groups in whom the coexistence of DM and HTN is
extremely high.

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