Determinants of Reduction of Coronary Flow Reserve in Patients With Type 2 Diabetes Mellitus or Arterial Hypertension Without Angiographically Determined Epicardial Coronary Stenosis

Maurizio Galderisi, Brunella Capaldo, Milena Sidiropulos, Arcangelo D’Errico, Luigi Ferrara, Annamelia Turco, Pasquale Guarini, Gabriele Riccardi, and Oreste de Divitiis

Background: Coronary flow reserve (CFR) may be reduced even in the absence of coronary artery disease. We investigated the determinants of CFR impairment in Type 2 diabetes mellitus (DM2) and in arterial hypertension (HTN) without epicardial coronary artery stenosis.

Methods: Twenty-eight patients with DM2 and 27 with HTN, both with normal coronary angiography, and 18 healthy controls underwent transthoracic echocardiography, including Doppler recording of the distal left anterior descending artery, at rest as well as after high-dose dipyridamole. Coronary flow reserve was calculated as the hyperemic to resting coronary diastolic peak velocities ratio.

Results: The three groups were comparable for sex, age, and heart rate. Systolic and mean blood pressures were higher in DM2 and HTN patients than in control subjects. Diabetic and hypertensive patients had a higher left-ventricular mass index (LVMi) and relative wall thickness, impaired diastolic indexes, and lower CFR compared with control subjects (P < .005 and P < .03, respectively) because of lower hyperemic coronary velocity (P = .005 and P = .004, respectively). After a multilinear regression analysis (using age, sex, HTN status, DM2 status, smoking, total cholesterol/HDL-cholesterol ratio, and LVMi as potential determinants), the LVMi increase was the main predictor of the reduction of CFR, adjusted for mean BP (P < .0001), in the pooled population, with a minor contribution of age (P = .03), HTN status (P = .02), and DM2 status (P = .03).

Conclusions: In Type 2 DM and HTN without epicardial coronary stenosis, an impairment of CFR is demonstrable. This is partly explained by an increased left-ventricular mass, able to condition the hyperemic stimulation of myocardial blood flow. Am J Hypertens 2007;20:1283–1290 © 2007 American Journal of Hypertension, Ltd.

Key Words: Diabetes mellitus, arterial hypertension, Doppler echocardiography, coronary flow reserve, left-ventricular mass.

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The function of the coronary microcirculation may be clinically evaluated by the quantitation of coronary flow reserve (CFR), ie, the ratio between hyperemic and resting coronary flow. In the absence of significant stenosis of the epicardial coronary arteries, the reduction of CFR represents a reliable marker of coronary microvascular dysfunction. A reduction of CFR was demonstrated by different techniques in diabetic patients without coronary artery stenosis. Although hyperglycemia, insulin resistance, endothelial dysfunction, and increased cardiac sympathetic activity were suggested as possible responsible factors, the mechanisms underlying the reduction of CFR in diabetes mellitus are not fully understood.

Today, CFR may also be determined by noninvasive transthoracic echocardiography (TTE), which allows the measurement of coronary flow velocities in the mid-distal left anterior descending artery. The TTE-derived CFR has excellent concordance with CFR estimated by intracoronary Doppler flow wire, and also offers high feasibility and reproducibility. To the best of our knowledge, no information is available about the determinants of impaired TTE-derived CFR in Type 2 diabetes mellitus (DM2). The aim of the present study was to assess the impact of demographic, metabolic, and Doppler-echocardiographic variables on CFR in patients with DM2. In view of the recognized high prevalence of HTN in DM2, these patients were compared not only with a healthy control group but also with a comparable population of treated hypertensives. The main inclusion criterion for both diabetic and hypertensive patients was the presence of angiographically normal epicardial coronary arteries.

Methods

Study Population

This study was approved by the Ethics Committee of Federico II University Hospital. All participants gave informed consent to be included in the study and to undergo stress echocardiography. Twenty-eight patients with DM2 (with a diagnosis of DM2 + angiographic evidence of normal epicardial coronary arteries) and 27 pharmacologically treated patients with HTN (with a diagnosis of HTN + angiographic evidence of normal epicardial coronary arteries) were recruited consecutively among subjects fulfilling the criteria for inclusion in the study. Eighteen healthy subjects with a normal resting and maximal treadmill exercise electrocardiogram, randomly selected from our research database, were also included in the study as a healthy control group. Exclusion criteria included diabetic complications such as proliferative retinopathy, autonomic neuropathy, symptoms and signs of heart disease and congestive heart failure, moderate to severe valvular heart disease, a history of major arrhythmias and atrial fibrillation, pericardial disease, and inadequate echocardiographic quality. The diagnosis of diabetes mellitus (DM) was based on American Diabetic Association guidelines. Diabetic patients were treated by diet or oral hypoglycemic agents, and did not use insulin. The diagnosis of HTN was made according to a history of elevated blood pressure (BP) or office BP >140/90 mm Hg (the mean of three measurements on three different visits) or antihypertensive treatment at the time. Diabetic and hypertensive patients underwent coronary angiography because of symptoms suggestive of angina, or an equivocal exercise treadmill test, or an abnormal stress myocardial SPECT, but coronary angiograms did not show any significant stenosis of epicardial coronary arteries in all of them.

Procedures

Laboratory Methods

Twelve-hour fasting blood samples were obtained the same day as standard echocardiographic examination and assessment of CFR. The measurements of lipid and glucose levels were performed by enzymatic methods (Boehringer Mannheim, Mannheim, Germany). The concentration of high-density lipoprotein cholesterol (HDL-C) was obtained after precipitation with dextran sulfate/MgCl2. Low-density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald equation. Microalbuminuria was evaluated by immunoturbidimetry (Randox, Cobas Mira, Mississauga, Ontario, Canada).

Standard Echocardiographic Examination

Echocardiographic examinations were performed by a Vivid Seven ultrasound machine (GE, Northen, Norway) by use of a 2.5-MHz phased-array transducer with harmonic capability. The quantitative analysis of the left ventricle was performed as previously reported. The LV mass index (LVMI) was calculated by normalizing the LV mass for height to the 2.7 power. The LV systolic function was evaluated both as endocardial and midwall fractional shortening. The relative diastolic wall thickness was determined as the ratio of the sum of septal and posterior wall thickness to LV internal end-diastolic diameter. Standard pulsed Doppler imaging of mitral inflow was recorded in apical four-chamber view. Early (E) and atrial (A) peak velocities (m/sec) and their ratio, E velocity deceleration time, and isovolumic relaxation time (both in msec) were measured. The Doppler echocardiographic methods and the reproducibility of results in our laboratory were previously reported.

CFR Evaluation

Doppler assessment of the distal left anterior descending artery was performed using a 5-MHz shallow-focus, phased-array transducer. The methods and reproducibility of results in our laboratory for the assessment of CFR (intraobserver variability, 1.9%; interobserver variability, 4.2%) were previously described. Briefly, the Doppler sample volume was placed on the color signal of the left anterior descending artery, and the spectral pulse wave-Doppler signal was recorded to examine the characteristic biphasic flow pattern with a larger diastolic and smaller systolic component. Coronary
blood flow velocities were recorded in each patient at rest and after administration of high-dose dipyridamole (0.84 mg/kg in a 6-min infusion). Heart rate, BP, and electrocardiogram readings were monitored during the test. In addition, a semi-simultaneous imaging of coronary flow and two-dimensional echocardiographic-derived LV wall motion was performed before and after the dipyridamole infusion, according to a validated protocol. Coronary diastolic peak velocities were measured at rest and after dipyridamole vasodilatation. For each parameter, the highest three spectral Doppler signals were averaged. The CFR was defined as the ratio of hyperemic to resting diastolic peak velocities, and was considered normal when it was >2. The adjusted CFR was calculated, adjusting resting and dipyridamole coronary diastolic peak velocities for the respective mean BP. All images were recorded on magneto-optical disks, and analyzed offline by two observers who were blind to the clinical characteristics of the patients.

**Statistical Analysis**

Data were analyzed using SPSS 12.0 software (SPSS, Chicago, IL). Data are expressed as mean value ± standard deviation. Differences between groups of participants were assessed by analysis of variance followed by the Scheffé post hoc test. Least-squares linear regression was used to evaluate univariate and multivariate correlates of CFR. For multiple linear regression modeling, multicollinearity was also examined by computation of in-model tolerance. Collinearity was considered acceptable, and the regression model stable, for a tolerance >0.70. The null hypothesis was rejected for \( P < .05 \).

**Results**

**Characteristics of the Study Population**

The characteristics of the study population are reported in Table 1. Patients with DM2 had a higher body mass index and both systolic and mean BP in comparison with the healthy controls, but no difference in body mass index, in systolic, diastolic, and mean BP, and in heart rate was found between diabetic and hypertensive patients. Total cholesterol and triglycerides were not significantly different among the three groups, but HDL-C was lower, and the total cholesterol/HDL-C ratio (TC/HDL-C) was higher, in patients with DM2 and HTN. In diabetic patients, the fasting blood glucose level was 169.4 ± 35.2 mg/dL, and glycosilated hemoglobin (HbA1c) was 7.7%. The mean duration of DM was 10.5 years. The prevalence of cigarette smoking and significant microalbuminuria was similar in DM2 and HTN patients. Ten of twenty-eight diabetic patients (35.7%) also had HTN, whereas no hypertensive patient was diabetic. Antihypertensive drugs used in both diabetic (\( n = 11/28 \)) and hypertensive (\( n = 27/27 \)) patients included diuretics, angiotension-converting enzyme-inhibitors, beta-blockers, calcium channel blockers, and angiotensin 2-receptors blockers. Cholesterol-lowering medications used in patients with dyslipidemia (13 with diabetes, and 12 with hypertension) included statins and gemfibrozil (data not in Table 1).

**Doppler Echocardiographic Analysis**

Table 2 reports the results of Doppler echocardiographic analysis. The LVMi and relative wall thickness were significantly higher in patients with DM2 and HTN than in patients with controls.

**Table 1.** Characteristics of study population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls (( n = 18 ))</th>
<th>( P ) value, controls versus HTN</th>
<th>HTN (( n = 27 ))</th>
<th>( P ) value, HTN versus DM2</th>
<th>DM2 (( n = 28 ))</th>
<th>( P ) value, controls versus DM2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>13/5</td>
<td>.892</td>
<td>20/7</td>
<td>.827</td>
<td>20/8</td>
<td>.953</td>
</tr>
<tr>
<td>Age (y)</td>
<td>48.9 ± 7.2</td>
<td>.460</td>
<td>50.9 ± 5.6</td>
<td>.943</td>
<td>50.3 ± 7.0</td>
<td>.636</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>25.6 ± 2.1</td>
<td>.274</td>
<td>27.3 ± 3.8</td>
<td>.655</td>
<td>28.1 ± 3.5</td>
<td>.05</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>128 ± 12</td>
<td>&lt;.001</td>
<td>140 ± 5</td>
<td>.551</td>
<td>137 ± 13</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>79 ± 6</td>
<td>&lt;.005</td>
<td>85 ± 5</td>
<td>.280</td>
<td>83 ± 8</td>
<td>.152</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>95 ± 6</td>
<td>&lt;.0001</td>
<td>104 ± 3</td>
<td>.252</td>
<td>101 ± 8</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>72.8 ± 12.0</td>
<td>.952</td>
<td>73.7 ± 6.7</td>
<td>.948</td>
<td>72.9 ± 9.3</td>
<td>1.000</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>92.7 ± 9.0</td>
<td>.986</td>
<td>91.7 ± 7.7</td>
<td>&lt;.0001</td>
<td>169.4 ± 35.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>195.7 ± 22.8</td>
<td>.456</td>
<td>210.9 ± 38.7</td>
<td>.853</td>
<td>215.9 ± 48.1</td>
<td>.216</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>52.4 ± 8.0</td>
<td>.04</td>
<td>46.2 ± 7.6</td>
<td>.714</td>
<td>44.5 ± 8.1</td>
<td>.006</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>3.8 ± 0.5</td>
<td>.02</td>
<td>4.7 ± 1.4</td>
<td>.715</td>
<td>4.9 ± 1.0</td>
<td>.003</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>117.4 ± 18.8</td>
<td>.426</td>
<td>133.1 ± 42.4</td>
<td>.798</td>
<td>140.4 ± 44.7</td>
<td>.165</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>128.9 ± 22.8</td>
<td>.190</td>
<td>158.0 ± 54.0</td>
<td>.969</td>
<td>161.6 ± 62.1</td>
<td>.122</td>
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<tr>
<td>Smoking</td>
<td>9/18</td>
<td>.830</td>
<td>12/27</td>
<td>.899</td>
<td>13/28</td>
<td>.815</td>
</tr>
<tr>
<td>Microalbuminuria*</td>
<td>0/18</td>
<td>.009</td>
<td>6/27</td>
<td>.808</td>
<td>7/28</td>
<td>.005</td>
</tr>
</tbody>
</table>

BM1 = body mass index; BP = blood pressure; DM2 = diabetes mellitus; HDL-C = high-density lipoprotein-cholesterol; HTN = hypertension; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol.

* Significant microalbuminuria for values >30 mg/mL.

Prevalence of sex, smoking, and significant microalbuminuria were determined by chi-square analysis.
IVRT (msec) 79.2

Peak velocity E (cm/sec) 0.71

Midwall FS (%) 17.9

Peak velocity A (cm/sec) 0.60

Peak velocity E/A ratio 1.20

PWTd (cm) 8.3

LVIDs (cm) 31.8

Endocardial FS (%) 36.7

IVSTd (mm) 8.9

LVMi (g/m^2.7) 35.4

Peak velocity A (cm/sec) 0.60

SBP at high Dip (mm Hg) 94.9 ± 13.4

HR at high Dip (mm Hg) 14.7 .001 24.2 ± 45.1 .04

SBP at rest (mm Hg) 127 ± 13

DBP at rest (mm Hg) 81 ± 7

HR at rest (bpm) 74.1 ± 11.4

CPPF at rest (cm/sec) 22.1 ± 5.6

SBP at high Dip (mm Hg) 124 ± 14

DBP at high Dip (mm Hg) 77 ± 9

HR at high Dip (mm Hg) 94.9 ± 13.4

CPPF at high Dip (cm/sec) 71.0 ± 14.5

CVR

Adjusted CVR

A – transmitral atrial diastolic velocity; DT – deceleration time; E – transmitral early diastolic velocity; FS – fractional shortening; IVRT – isovolumic relaxation time; IVSTd – interventricular septal wall thickness in diastole; LVIDd – LV internal end-diastolic diameter; LVIDs – LV internal end-systolic diameter; LVMi – LV mass index; PWTd – posterior wall thickness in diastole; RWTd – relative diastolic wall thickness. Other abbreviations as in Table 1.

control subjects. Midwall fractional shortening and peak velocity E/A ratio were significantly lower, and both deceleration time and isovolumic relaxation time were longer, in diabetic and in hypertensive patients than in control subjects. No significant difference in the various Doppler echocardiographic measurements was found between diabetic and hypertensive patients. The prevalence of LV hypertrophy (LVMi ≥50 g/m^2.7)22 was 42.9% (12/28) in patients with DM2, and 40.7% (11/27) in those with HTN (data not in Table 2).

CFR Test

After dipyridamole infusion, neither major adverse reactions nor angina symptoms occurred in any participant, and no patient showed significant electrocardiogram modifications or LV wall-motion abnormalities. The data of the CFR test are summarized in Table 3. The CFR was similar in DM2 and HTN patients, but significantly lower compared with healthy control subjects (P = .02). This was because of the lower values of high dipyridamole-induced coronary flow peak velocity (P = .005), whereas the velocity at rest was not significantly different among the three groups. Abnormal CFR (ie, <2) was found in four diabetic patients and three hypertensive patients. The CFR remained significantly lower in Type 2 DM and in HTN, even after adjusting for either resting or dipyridamole coronary peak flow velocity for the respective mean BP (ie, adjusted CFR). Figure 1 shows the CFR in a

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>P value, controls versus HTN</th>
<th>HTN</th>
<th>P value, HTN versus DM2</th>
<th>P value, controls versus DM2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP at rest (mm Hg)</td>
<td>127 ± 13</td>
<td>&lt;.0001</td>
<td>140 ± 5</td>
<td>.998</td>
<td>140 ± 12</td>
</tr>
<tr>
<td>DBP at rest (mm Hg)</td>
<td>81 ± 7</td>
<td>.05</td>
<td>86 ± 5</td>
<td>.194</td>
<td>83 ± 7</td>
</tr>
<tr>
<td>HR at rest (bpm)</td>
<td>74.1 ± 11.4</td>
<td>.992</td>
<td>73.8 ± 6.6</td>
<td>.927</td>
<td>73.7 ± 9.2</td>
</tr>
<tr>
<td>CPPF at rest (cm/sec)</td>
<td>22.1 ± 5.6</td>
<td>.982</td>
<td>21.8 ± 5.0</td>
<td>.919</td>
<td>22.3 ± 4.6</td>
</tr>
<tr>
<td>SBP at high Dip (mm Hg)</td>
<td>124 ± 14</td>
<td>&lt;.0001</td>
<td>139 ± 4</td>
<td>.543</td>
<td>135 ± 15</td>
</tr>
<tr>
<td>DBP at high Dip (mm Hg)</td>
<td>77 ± 9</td>
<td>.05</td>
<td>84 ± 6</td>
<td>.120</td>
<td>79 ± 12</td>
</tr>
<tr>
<td>HR at high Dip (mm Hg)</td>
<td>94.9 ± 13.4</td>
<td>.509</td>
<td>90.6 ± 10.0</td>
<td>.702</td>
<td>93.8 ± 16.1</td>
</tr>
<tr>
<td>CPPF at high Dip (cm/sec)</td>
<td>71.0 ± 14.5</td>
<td>.004</td>
<td>57.1 ± 11.5</td>
<td>.998</td>
<td>56.6 ± 13.9</td>
</tr>
<tr>
<td>CVR</td>
<td>3.3 ± 0.8</td>
<td>.03</td>
<td>2.8 ± 0.7</td>
<td>.973</td>
<td>2.7 ± 0.8</td>
</tr>
<tr>
<td>Adjusted CVR</td>
<td>3.5 ± 1.1</td>
<td>.03</td>
<td>2.7 ± 0.7</td>
<td>.944</td>
<td>2.8 ± 1.0</td>
</tr>
</tbody>
</table>

CFR – coronary flow reserve; CPPF – coronary peak flow velocity; DBP – diastolic blood pressure; Dip – dipyridamole; HR – Heart rate; SBP – systolic blood pressure. Other abbreviations as in Table 1.

Adjusted CVR was determined by correcting resting and high-dose dipyridamole coronary flow velocities for the respective mean BP.
A patient with DM2 of our population. The CFR is reduced, despite the evidence of normal coronary artery tree on coronary angiography.

**Univariate Relationships of CFR**

In the pooled population, the adjusted CFR had significant inverse relations with age ($r = -0.31$, $P = .008$), body mass index ($r = -0.29$, $P < .01$), fasting blood glucose ($r = -0.23$, $P < .05$), systolic and mean BP ($r = -0.39$, $P < .001$, and $r = -0.29$, $P < .01$, respectively), LVMi ($r = -0.51$, $P < .0001$) (Fig. 2), relative wall thickness ($r = -0.25$, $P = .03$), and E velocity deceleration time ($r = -0.22$, $P = .05$). In the patients with DM, the adjusted CFR was related to age ($r = -0.42$, $P = .05$), fasting blood glucose ($r = -0.40$, $P = .05$), HbA1c ($r = -0.43$, $P = .02$), LVMi ($r = -0.53$, $P = .005$), relative wall thickness ($r = -0.41$, $P = .05$), E velocity deceleration time ($r = -0.38$, $P = .05$), and total cholesterol/HDL-C ratio ($r = -0.36$, $P = .05$).

**Multivariate Associations of CFR**

Table 4 summarizes the results of a multiple linear regression analysis performed in the pooled population to identify the independent associations of adjusted CFR. Variables directly related to diabetes, such as fasting blood glucose or HbA1c, which could result in colinearity, were not included in the model, whereas the possible confounding effects of age, sex, smoking, HTN status, DM2 status, total cholesterol/HDL-C ratio, and LVMi were taken into account. By this analysis, the increase in LVMi was the main independent determinant in reduction of CFR, with an additional contribution of age, HTN, and DM2 status. When LVMi was replaced by relative wall thickness, this variable was not independently associated with adjusted CFR (standardized beta coefficient $= -0.019$, $P = .895$).

**Discussion**

Diabetes mellitus induces functional and structural abnormalities of the coronary microvascular circulation, which can play a role in the development of diabetic cardiomyopathy. Coronary microvascular function may be evaluated noninvasively by the assessment of TTE-de-
induced by coexisting elevated BP. Notably, the presence of cardiovascular risk factors can also be involved in this impairment. However, the impact of concomitant cardiovascular risk factors, and particularly of elevated BP, should also be taken into account.23 Notably, because the degree of CFR restriction in DM is associated with the magnitude of retinopathy24 and of renal insufficiency,25 a common microvascular impairment occurring in multiple microvascular beds may be hypothesized in the natural history of diabetic patients. To the best of our knowledge, the present study is the first to explore the impact of structural cardiac changes on CFR impairment in DM2 by comparing data not only with healthy control subjects but also with hypertensive patients. Importantly, patients with either DM2 or HTN all had angiographically normal coronary arteries.

Left-ventricular hypertrophy is an independent hallmark of cardiovascular risk in the general population.26 It develops frequently in diabetic patients, independent of the effect of concomitant risk factors,27 but can also be induced by coexisting elevated BP.26 Notably, the presence of LV hypertrophy is associated with LV diastolic dysfunction28 and the impairment of midwall mechanics29 in both diabetic and hypertensive patients. In accordance with previous experiences,12–15,23,24 CFR was lower in patients with DM2 than in healthy control subjects. Conversely, CFR of diabetics was similar to CFR of hypertensive patients. In addition, the reduction of CFR adjusted for mean BP showed a strong, inverse, univariate relation with LV mass increase in the pooled population, whereas the association with increased relative wall thickness was marginal. The adjusted CFR in the present study confirmed a previously observed association with LV diastolic function;15 CFR being mildly but significantly related to E velocity deceleration time (inverse relation). Also, the association of CFR with metabolic indexes (fasting blood glucose and HbA1c), although marginal, was confirmatory of other reports.12 The inverse association with age appears to be a likely expression of the long exposure to DM2 needed to determine clinically relevant microvascular damage.

The multiple linear regression model provided further important information. By this analysis, the reduction of adjusted CFR appeared to be associated with LV mass increase, independent of the impact of cardiovascular risk factors. The LVMi was the main independent predictor of CFR in the pooled population, with an additional, minor contribution of HTN status, DM2 status, and age. Although caution should be exercised regarding an interpretation of the lack of significant associations for smoking and lipid ratios with CFR (regression models cannot distinguish confounding from a mechanistic pathway), this finding points out that the coronary microvessel impairment of DM2 and HTN patients could be, at least in part, mediated by changes in LV structure associated with LV hypertrophy. Extravascular compressive forces and a concomitant hypertrophy of the coronary microvascular walls might be mechanisms underlying the abnormalities of CFR observed in the diabetic and hypertensive heart.23 Because of differences either in general characteristics (see Table 1) or in the multiple regression analysis (Table 3) between the DM2 and HTN groups, the possibility should be taken into account that CFR could be influenced by other covariates (measured or not measured in the present study) shared by diabetic and hypertensive patients.

### Table 4. Multiple independent correlates of CFR in the pooled population

<table>
<thead>
<tr>
<th>Unstandardized coefficients</th>
<th>Standardized coefficients (Beta)</th>
<th>P</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>7.329</td>
<td>.0001</td>
<td>0.923</td>
</tr>
<tr>
<td>Age</td>
<td>-0.032</td>
<td>.03</td>
<td>0.901</td>
</tr>
<tr>
<td>Male sex</td>
<td>-0.139</td>
<td>.540</td>
<td>0.798</td>
</tr>
<tr>
<td>HTN status</td>
<td>-0.556</td>
<td>.02</td>
<td>0.829</td>
</tr>
<tr>
<td>DM2 status</td>
<td>-0.318</td>
<td>.03</td>
<td>0.815</td>
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<tr>
<td>Smoking</td>
<td>-0.038</td>
<td>.848</td>
<td>0.827</td>
</tr>
<tr>
<td>TC-HDL-C ratio</td>
<td>-0.017</td>
<td>.845</td>
<td>0.790</td>
</tr>
<tr>
<td>LVMi</td>
<td>-0.033</td>
<td>.0001</td>
<td>0.790</td>
</tr>
</tbody>
</table>

Abbreviations as in preceding tables.

Multiple linear regression analysis included age, sex, HTN status, DM2 status, smoking, TC/HDL-C ratio and LVMi as potential determinants.

The multiple linear regression analysis included age, sex, HTN status, DM2 status, smoking, TC/HDL-C ratio and LVMi as potential determinants.
with higher levels of LV mass and a high prevalence of both LV hypertrophy and concomitant risk factors. However, the evidence of normal coronary angiography was a pivotal selection criterion, to exclude the presence of significant epicardial coronary artery stenosis.

The definition of “normal” epicardial coronary arteries by using pure angiographic criteria can be considered a further limitation. Because of arterial remodeling, extensive atherosclerosis within the artery wall may be present despite the absence of angiographic stenosis, particularly in diabetic patients who have diffuse vascular disease. Accordingly, intravascular ultrasound (IVUS) would have been more useful for demonstrating “real” normal epicardial coronary arteries in the study population. Unfortunately, IVUS was not part of the study design. Nevertheless, the diabetic and hypertensive patients in the present study were completely asymptomatic, and had normal resting and stress electrocardiograms. No wall-motion abnormalities were detected after high-dose dipyridamole. On these grounds, the presence of clinically relevant coronary artery disease can be reasonably excluded in our study population.

One could consider the lack of measurement of insulin sensitivity as a limitation. Insulin resistance is a recognized determinant of CFR impairment, and its relationship with CFR might have blunted the extent of the association with LV mass in the present study. The hyperinsulinemic glucose clamp, as a way to measure the degree of insulin resistance in the clinical setting, was not part of the protocol of the present study. However, DM2 corresponds to a condition of insulin resistance, and is associated with concomitant risk factors which, together, comprise the typical picture of metabolic syndrome.

In conclusion, transthoracic Doppler echocardiographic assessment confirmed the reduction of CFR in DM2, already demonstrated by other techniques, but also showed for the first time that this reduction is substantially similar to that detectable in arterial hypertension, and that it can be partly explained by LV mass increase. Further studies will be needed to evaluate the effect of pharmacologic treatment over time on the association of LV myocardial structure and the coronary microvascular bed in DM2, with and without arterial hypertension.

References


