Increased basal coronary blood flow as a cause of reduced coronary flow reserve in diabetic patients

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Increased basal coronary blood flow as a cause of reduced coronary flow reserve in diabetic patients. Am J Physiol Heart Circ Physiol 301: H2279–H2284, 2011. First published October 7, 2011; doi:10.1152/ajpheart.00615.2011.—A reduced coronary flow reserve (CFR) has been demonstrated in diabetes, but the underlying mechanisms are unknown. We assessed thermodilution-derived CFR after 5-min intravenous adenosine infusion through a pressure-temperature sensor-tipped wire in 30 coronary arteries without significant lumen reduction in 30 patients: 13 with and 17 without a history of diabetes. We determined CFR as the ratio of basal and hyperemic mean transit times (Tm); fractional flow reserve (FFR) as the ratio of distal and proximal pressures at maximal hyperemia to exclude local macrovascular disease; and an index of microvascular resistance (IMR) as the distal coronary pressure at maximal hyperemia divided by the inverse of the hyperemic Tm. We also assessed insulin resistance by the homeostasis model assessment (HOMA) index. FFR was normal in all investigated arteries. CFR was significantly lower in diabetic vs. nondiabetic subjects [median (interquartile range): 0.53 (0.25–0.71) vs. 0.64 (0.50–1.17); P = 0.02]. Basal Tm was lower in diabetic vs. nondiabetic subjects [median (interquartile range): 0.53 (0.25–0.71) vs. 0.64 (0.50–1.17); P = 0.04], while hyperemic Tm and IMR were similar. We found significant correlations at linear regression analysis between logCFR and the HOMA index (r² = 0.35; P = 0.0005) and between basal Tm and the HOMA index (r² = 0.44; P < 0.0001). In conclusion, compared with nondiabetic subjects, CFR is lower in patients with diabetes and epicardial coronary arteries free of severe stenosis, because of increased basal coronary flow, while hyperemic coronary flow is similar. Basal coronary flow relates to insulin resistance, suggesting a key role of cellular metabolism in the regulation of coronary blood flow.

insulin resistance; myocardial blood flow; microcirculation; microcirculatory dysfunction

AN IMPAIRED CORONARY FLOW RESERVE (CFR) has been demonstrated in patients with type 2 diabetes and angiographically normal coronary arteries using coronary Doppler flow wire (34), positron emission tomography (39), and, more recently, intracoronary pressure wire-derived thermodilution (19), suggesting that atherosclerosis of epicardial coronary arteries is not the only mechanism of myocardial ischemia and that a dysfunction of the coronary microcirculation plays a significant role. However, the impairment of CFR in subjects without significant stenosis of epicardial coronary arteries may be driven by two different mechanisms: the first, and most obvious one, is a reduction of hyperemic blood flow due to an impairment of microcirculatory maximum vasodilation; the second one is an increased basal coronary flow, due to an altered cellular metabolism (5, 15). The relative contribution of these two mechanisms to CFR impairment in subjects affected by diabetes is controversial. CFR calculated by Doppler catheter/wire has been previously reported to be reduced but with no information about basal and hyperemic flow (21, 22). Myocardial blood flow reserve, assessed by positron emission tomography, was found reduced in diabetic patients, but this impairment was driven by a lower hyperemic flow in some studies (26) and by a higher basal flow in some others (20).

We therefore undertook the present study to determine the prevailing mechanisms of CFR reduction in diabetic patients. An assessment of thermodilution-derived CFR through a pressure-temperature sensor-tipped wire, the reliability of which has been largely validated in previous studies (8, 12, 19, 25), allows us not only to distinguish between basal and hyperemic coronary flow but also to calculate an index on microvascular resistance (IMR), which directly reflects the vasodilation capacity of the coronary microcirculation. Here we also evaluated insulin resistance with the homeostasis model assessment (HOMA) index and its relationship with CFR and basal and hyperemic coronary flows.

METHODS

From July 2008 to June 2010, we selected 20 consecutive diabetic patients (referred for elective coronary angiography because of stable angina or inducible myocardial ischemia) and showing an intermediate coronary lesion (36), defined as a lesion with luminal narrowing, assessed by quantitative coronary angiography, ranging from 40 to 50%. Seven out of 20 subjects were ruled out because they met one or more exclusion criteria [serum creatinine >1.5 mg/dl, a recent (≤1 wk) acute coronary syndrome, heart failure, severe valvular disease, or hypertrophic cardiomyopathy].

The diagnosis of diabetes was done according to World Health Organization criteria and to the recent Position Statement of the American Diabetes Association (2).

The remaining 13 patients were asked to sign the consent form after coronary angiography and before performing the pressure wire assessment. All the 13 patients gave written informed consent to the study. Subjects with fractional flow reserve (FFR) values >0.75 were finally included. With an FFR >0.75 in all the coronary lesions under study, all the 13 diabetic patients met the prespecified inclusion criteria and were enrolled.

At the same time, 25 nondiabetic consecutive patients with the same clinical and angiographic features were selected; 8 of them were ruled out because they met 1 or more exclusion criteria. Seventeen subjects gave written consent to the study and underwent pressure wire assessment, confirming, here too, FFR values >0.75 in all lesions under study.

Thirteen diabetic and 17 nondiabetic patients were therefore finally included in the study.
The study was approved by the local Institutional Review Board and registered (ClinicalTrials.gov ID: NCT01014949).

Patients were brought to the cardiac catheterization laboratory in a fasting state without discontinuation of their cardiac medications. After conventional diagnostic coronary angiography, patients were administered 3,000–5,000 IU iv heparin, and a 6-F coronary guiding catheter was advanced in the ostium of the coronary artery of interest. A 0.014-in. coronary pressure wire (Radi Medical Systems, Wilmington, MA) was calibrated, equalized to the guiding catheter pressure with the sensor positioned in the coronary ostium, and then advanced to the distal coronary artery (down to at least two-thirds of the epicardial vessel length). CFR, FFR, and the IMR were then measured as described below.

Coronary circulation physiological measurements. CFR, FFR, and IMR were measured with an intracoronary pressure/temperature sensor-tipped guidewire (Radi pressure wire 4; Radi Medical Systems), with an accuracy of 0.05°C within a temperature range of 15–42°C, to derive thermodilution curves. Previous experimental and human studies (8, 12, 25) have demonstrated that the mean transit time (Tmn) of an intracoronary injection of saline at room temperature, derived from thermodilution curves, is inversely proportional to coronary flow. Therefore, a given percent decrease in Tmn closely reflects a proportional percent increase in coronary flow. Three injections, 3 ml each, of saline at room temperature were performed in the left anterior descending coronary artery, and the resting Tmn was measured. An intravenous infusion of adenosine (Adenoscan; Sanofi Aventis, Milan, Italy) at 140 μg·kg⁻¹·min⁻¹ was then administered to induce a steady-state maximal hyperemia, followed by three further injections of 3 ml each of room-temperature saline to measure hyperemic Tmn.

Simultaneous measurements of mean aortic pressure (through the guiding catheter) and mean distal coronary pressure (by the pressure wire) were also obtained in the resting and maximal hyperemic states. CFR was calculated as the resting Tmn divided by the hyperemic Tmn (8, 25). IMR was calculated as the distal coronary pressure at maximal hyperemia divided by the inverse of the hyperemic Tmn (2, 11). FFR was calculated as the ratio of mean distal coronary pressure to mean aortic pressure at maximal hyperemia (24).

Anthropometric and biochemical measurements. Body weight (kg), height (m), and body mass index (kg/m²) were assessed according to published guidelines. All subjects had blood taken after an overnight fast to assess the lipid profile (total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol). Blood glucose levels were assessed immediately before cardiac catheterization by routine laboratory methods. Plasma insulin was measured with the BI-INSULIN immunoassay (CisBio International, Bagnois/Ceze, France).

Insulin resistance was measured with the HOMA index [fasting plasma glucose (mmol/l) × fasting plasma insulin (pmol/l)/162], which has been found to correlate with the gold-standard glucose clamp measurement in nondiabetic, diabetic, and hypertensive subjects (14, 18, 27).

Plasma concentrations of IL-6 and TNF-α were measured with the Quantikine HS immunoassays (R&D Systems, Lilly, France).

Statistical analysis. Distributions of continuous variables were tested by the Kolmogorov-Smirnov test. Normally distributed variables were presented as means ± SD, whereas nonnormally distributed variables were presented as median (25th-75th percentile). Comparisons were performed with the Student’s t-test or the Mann-Whitney test for the normally or nonnormally distributed variables, respectively. The χ²-square test was used for categorical binary variables. Regression analysis was performed to assess the correlation between CFR/IMR and the HOMA index, insulin levels, plasma glucose, and Hba1c. The regression fit was tested with increasingly complex regression models (from linear to logarithmic, inverse, quadratic, cubic, or exponential). The use of a model higher than linear was accepted only in the presence of a significant increase in correlation. The GraphPad Prism 4 software (GraphPad, La Jolla, CA) was used for the analyses. Significance threshold was set at P < 0.05 (two-sided).

RESULTS

The demographic and biohumoral and hemodynamic parameters of patients studied are listed in Table 1. The mean age was 63 ± 10 yr; 16 patients (53%) were male. Thirteen patients (43%) were overtly diabetic, but they did not show micro- nor macrovascular complications. Diabetic patients had higher values of plasma glucose, Hba1c, plasma insulin, and HOMA index values compared with nondiabetic patients, but no significant differences were detected as to the lipid profile and inflammatory cytokines.

No patients developed symptoms or signs of ischemia during adenosine infusion.

FFR was similar and within the normal range in diabetic and nondiabetic subjects [median (interquartile range); 0.96 (0.90–1.0) vs. 0.97 (0.93–1.0); P = 0.93]. CFR was lower in diabetic compared with nondiabetic subjects [median (interquartile range); 2.2 (1.4–3.2) vs. 4.1 (2.7–4.4); P = 0.02; Fig. 1]. Basal Tmn was also lower in diabetic patients [median (interquartile range); 0.53 (0.25–0.71) vs. 0.64 (0.50–1.17) s; P = 0.04; Fig. 2], while hyperemic Tmn was comparable in the two groups [median (interquartile range); 0.18 (0.14–0.25) vs. 0.17 (0.13–0.25) s; P = 0.83]. Conversely, IMR was similar in the two groups [median (interquartile range); 16.6 (15.0–23.4) vs. 15.3 (12.1–24.0); P = 0.68].

Linear regression analysis showed a significant correlation between logCFR and the HOMA index (r² = 0.35; P = 0.0005; Fig. 3) and between basal Tmn and the HOMA index (r² = 0.44; P < 0.0001; Fig. 4) but not between the hyperemic Tmn and the HOMA index (r² = 0.02; P = 0.38). After correction for the rate-pressure product, basal Tmn still showed a significant correlation with the HOMA index (r² = 0.27; P = 0.003; Fig. 5). Finally, a trend relating CFR and Tmn to the HOMA index was still present when male and female patients were analyzed separately (data not shown).

Levels of IL-6 and TNF-α were not correlated with any of the hemodynamic parameters investigated (data not shown).

DISCUSSION

In this study, we invasively assessed CFR in patients without significant stenoses of epicardial coronary arteries, with and without a history of diabetes. We here demonstrate that 1) CFR is significantly lower in diabetic vs. nondiabetic patients because of a higher basal coronary flow; 2) the maximum vasodilation of the coronary microcirculation is similar in diabetic and nondiabetic patients; and 3) the increased basal coronary flow relates to insulin resistance.

Coronary microcirculatory function was here assessed by a thermodilution technique, the feasibility and accuracy of which have been extensively assessed in previous studies. De Bruyne et al. (8) first demonstrated the validity of the thermodilution principle to assess CFR in an in vitro model; then showed that a simultaneous measurement of FFR (by estimating coronary pressure) and CFR (by estimating coronary flow by thermodilution) is possible also in humans by a single pressure/temperature sensor-tipped guidewire; and finally found that a good correlation exists between thermodilution- and Doppler-measured CFR (8). The simultaneous measurements of FFR and
CFR provide reliable information on the coronary microcirculatory function. Indeed, in patients without a significant pressure drop along the epicardial artery, a low CFR in the presence of a normal (nonischemic) FFR strongly suggests a microvascular involvement (7).

Our data show lower values of CFR in diabetic compared with nondiabetic patients, in agreement with previous studies documenting a significantly reduced CFR in diabetic patients by using the coronary Doppler flow wire (34) and positron emission tomography (39). The thermodilution technique used in our study has been recently used by Melikian et al. (19) to assess coronary microvascular vasodilation in humans. In agreement with our results, microvascular vasodilation, estimated by the CFR after adenosine infusion, tended to be reduced in the subgroup of diabetic patients.

### Table 1. Clinical and hemodynamic parameters in the overall population and in patients distinguished in diabetic and nondiabetic

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients (n = 30)</th>
<th>Diabetic (n = 13)</th>
<th>Nondiabetic (n = 17)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>63 ± 10</td>
<td>63 ± 10</td>
<td>63 ± 10</td>
<td>0.96</td>
</tr>
<tr>
<td>Females</td>
<td>14 (47%)</td>
<td>7 (54%)</td>
<td>7 (41%)</td>
<td>0.49</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29 ± 5</td>
<td>31 ± 6</td>
<td>28 ± 4</td>
<td>0.13</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>100 (93–112)</td>
<td>101 (94–117)</td>
<td>100 (92–103)</td>
<td>0.23</td>
</tr>
<tr>
<td>Cardiovascular risk factors, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (70%)</td>
<td>10 (77%)</td>
<td>11 (65%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Current smoking</td>
<td>3 (10%)</td>
<td>2 (15%)</td>
<td>1 (6%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Family history</td>
<td>11 (36%)</td>
<td>6 (46%)</td>
<td>5 (29%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Glucose metabolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/l</td>
<td>5.9 (5.3–7.3)</td>
<td>7.4 (6.0–8.6)</td>
<td>5.4 (5.1–6.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dl</td>
<td>107 (96–132)</td>
<td>133 (108–154)</td>
<td>98 (92–109)</td>
<td>0.002</td>
</tr>
<tr>
<td>Fasting plasma insulin, pmol/l</td>
<td>6.4 ± 3.5</td>
<td>8.0 ± 4.0</td>
<td>5.1 ± 2.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Hemoglobin A₁C, %</td>
<td>5.6 ± 1.0</td>
<td>6.4 ± 0.9</td>
<td>5.1 ± 0.6</td>
<td>0.003</td>
</tr>
<tr>
<td>HOMA index</td>
<td>1.8 ± 1.0</td>
<td>2.5 ± 1.0</td>
<td>1.3 ± 0.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Lipid parameters, mg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>184 ± 40.1</td>
<td>177.8 ± 34.9</td>
<td>190.3 ± 45.5</td>
<td>0.34</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>41 (38–55)</td>
<td>40 (33–51)</td>
<td>43 (38–60)</td>
<td>0.48</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>110.5 ± 34.9</td>
<td>103.4 ± 28.8</td>
<td>115.8 ± 38.9</td>
<td>0.31</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>121 (91–169)</td>
<td>126 (93–176)</td>
<td>117 (89–162)</td>
<td>0.98</td>
</tr>
<tr>
<td>Inflammatory cytokines, pg/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td>1.2 (0.5–1.95)</td>
<td>1.4 (0.5–1.7)</td>
<td>0.8 (0.4–2.3)</td>
<td>0.67</td>
</tr>
<tr>
<td>IL-6</td>
<td>1.55 (0.75–2.5)</td>
<td>1.5 (0.9–2.4)</td>
<td>1.6 (0.6–2.7)</td>
<td>0.90</td>
</tr>
<tr>
<td>Hemodynamic parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>21</td>
<td>10 (77%)</td>
<td>11 (65%)</td>
<td>NS</td>
</tr>
<tr>
<td>CCX</td>
<td>9</td>
<td>3 (23%)</td>
<td>6 (35%)</td>
<td>NS</td>
</tr>
<tr>
<td>RCA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Basal MAP, mmHg</td>
<td>110 (104–119)</td>
<td>115 (105–120)</td>
<td>105 (101–113)</td>
<td>0.21</td>
</tr>
<tr>
<td>Basal HR, beats/min</td>
<td>80 (74–90)</td>
<td>84 (73–91)</td>
<td>80 (74–88)</td>
<td>0.54</td>
</tr>
<tr>
<td>Rate-pressure product</td>
<td>8,840 (8,233–9,445)</td>
<td>9,240 (8,570–9,445)</td>
<td>8,688 (8,055–9,350)</td>
<td>0.21</td>
</tr>
<tr>
<td>Resting Tmn, s</td>
<td>0.57 (0.4–0.91)</td>
<td>0.53 (0.25–0.71)</td>
<td>0.64 (0.50–1.17)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hyperemic Tmn, s</td>
<td>0.17 (0.13–0.25)</td>
<td>0.18 (0.14–0.25)</td>
<td>0.17 (0.13–0.25)</td>
<td>0.83</td>
</tr>
<tr>
<td>CFR</td>
<td>3 (1.85–4.3)</td>
<td>2.2 (1.4–3.2)</td>
<td>4.1 (2.7–4.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>IMR</td>
<td>15.9 (12.5–24)</td>
<td>16.6 (15.0–23.4)</td>
<td>15.3 (12.1–24.0)</td>
<td>0.68</td>
</tr>
<tr>
<td>FFR</td>
<td>0.96 (0.92–1)</td>
<td>0.96 (0.90–1.0)</td>
<td>0.97 (0.93–1.0)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Quantitative data are given as means ± SD for the normally distributed variables and median (25th–75th percentile) for the nonnormally distributed variables. BMI, body mass index; HOMA, homeostasis model assessment; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TNF, tumor necrosis factor; IL, interleukin; LAD, left anterior descending; CCX, circumflex coronary artery; RCA, right coronary artery; MAP, mean arterial pressure; HR, heart rate; Tmn, mean transit time; CFR, coronary flow reserve; IMR, index of microvascular resistance; FFR, fractional flow reserve.

Fig. 1. Coronary flow reserve in diabetic and nondiabetic patients. ■, Diabetic patients; ▲, nondiabetic patients. Bars represent the median.

Fig. 2. Basal mean transit times in diabetic and nondiabetic patients. ■, Diabetic patients; ▲, nondiabetic patients. Bars represent the median.

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However, CFR impairment in patients without significant stenoses of epicardial coronary arteries may be driven either by a lower hyperemic flow or by a higher basal flow; in the former case, CFR reduction may be attributed to a dysfunction of coronary microcirculation that fails to reach maximal vasodilation; in the latter case, a defective cellular metabolism may be responsible for an increased basal coronary flow (5, 15).

The contribution of these two mechanisms to CFR reduction in diabetes is controversial. In diabetic lambs, resting coronary blood flow was reduced over a wide range of aortic pressures compared with controls (16). Nasher et al. (21), using Doppler catheter/wire in humans, reported a lower CFR in diabetic subjects, which was driven by a reduced maximal coronary vasodilation. However, the Doppler technique is not capable of measuring absolute myocardial perfusion; thus, it is uncertain whether the impairment in vasodilation in diabetic subjects is due to an elevation of resting myocardial perfusion, a reduction in perfusion during the pharmacologic and metabolic stimuli, or both.

Positron emission tomography is considered a more accurate technique to measure myocardial flow reserve, since it allows to distinguish between resting and hyperemic myocardial blood flow; nevertheless literature data with this technique are inconsistent. Meyer and Schweiger (20) found an impairment in flow reserve in diabetic patients compared with a control group, and this was primarily due to a significantly higher resting myocardial blood flow. On the contrary, two similar studies (26, 38) attributed the lower CRF in diabetic subjects to a lower myocardial blood flow during hyperemia, while baseline myocardial blood flow was similar in patients with diabetes and in control subjects. Our data clearly show that CFR reduction in our diabetic patients is due to a higher basal coronary flow, as demonstrated by the lower Tmn [median (interquartile range): 0.53 (0.25–0.71) vs. 0.64 (0.50–1.17) s; $P = 0.04$; Fig. 2].

Biochemical data in the literature provide mechanistic explanations for the observed increased basal coronary flow in diabetic patients. In the diabetic heart, glucose and lactate oxidation are decreased (6, 31) and fatty acid oxidation is increased (33), which results in increased free fatty acid uptake and oxidation in the mitochondria (33, 35, 40), as well as increased expression of mitochondrial uncoupling proteins (4), both of which decrease the amount of ATP produced per molecule of oxygen consumed in the mitochondrial electron transport chain (4, 35). Therefore, the diabetic heart has increased baseline oxygen requirements (37), which are physiologically coupled with a higher resting blood flow. Furthermore, patients with diabetes have a lower energy metabolism, as demonstrated by a significantly lower phosphocreatine-to-ATP ratio, despite apparently normal cardiac morphology and function (29). Previous studies (41, 42) have also demonstrated that the release of purines from isolated working rat hearts is higher in hypoxic conditions. Therefore, a working hypothesis to explain our findings is that adenosine release may occur in the diabetic heart to raise basal coronary flow and match the increased oxygen requirement. Furthermore, linear regression analysis here showed that basal, but not hyperemic, coronary flow relates to insulin resistance ($r^2 = 0.44$; $P < 0.0001$; Fig. 4), suggesting that the compensatory increase of basal coronary flow rises in parallel with the reduction of insulin sensitivity and glucose uptake. This hypothesis would now be worth testing.

Our data also show that hyperemic flow is not different between diabetic and nondiabetic subjects [median (interquartile range): $T_{mn} = 0.18$ (0.14–0.25) vs. 0.17 (0.13–0.25) s; $P = 0.83$], thereby demonstrating that the maximal vasodilation of coronary microcirculation is not altered in our diabetic patients. This finding is supported by the IMR calculated during maximal hyperemia, which specifically assesses microcirculation function (11) and shows similar values in the two
groups of patients [median (interquartile range): 16.6 (15.0–23.4) vs. 15.3 (12.1–24.0); \( P = 0.68 \)]. This result is not unexpected, since maximal hyperemia was here obtained by adenosine, the mechanism of which in inducing coronary arteriolar vasodilation, although not yet fully understood, apparently involves the stimulation of both A1 and A2 receptors and the opening of K-ATP channels on smooth muscle cells (10, 32) and is considered mainly endothelium-independent. In agreement with our results, previous animal studies (3, 23) have shown that endothelium-dependent vasodilation of coronary arterioles is impaired since the early stage of diabetes, while endothelium-independent vasodilation seems to be preserved up to the latest disease stages.

One might argue that both CFR and IMR should be reduced in diabetic subjects, as both indexes express coronary microcirculatory function in the absence of critical stenoses of epicardial vessels. In contrast, our results show that CFR, but not IMR, is reduced in diabetic patients, and the explanation for this apparent paradox is that baseline coronary flow, but not hyperemic coronary flow, is different in diabetic vs. nondiabetic subjects. IMR takes into account hyperemic, but not basal coronary flow, while CFR value, being calculated as the resting flow divided by the hyperemic flow, is affected by both.

Finally, it is worth noticing that the group of diabetic patients enrolled in this study showed no clinical signs of micro- or macro-angiopathy, that insulin resistance and blood glucose values were both quite low, and that inflammatory cytokines were also low and similar to nondiabetic patients. Thus, by all aspects, our patients should be considered as affected by early stage diabetes, in whom CFR is reduced because of an increased basal coronary flow. We may also speculate that at a later stage of disease an impairment of the hyperemic flow may also occur and that both mechanisms at that point may contribute to the CFR reduction. This hypothesis, able to reconcile the disparate findings in the literature, would need now to be confirmed in further studies.

In summary, in patients with diabetes with early vascular disease and without angiographically significant atherosclerosis in the epicardial coronary arteries, CFR is reduced due to an increased basal coronary flow, while hyperemic flow is not different between diabetic and nondiabetic subjects. Basal coronary flow relates to insulin resistance, suggesting a compensatory underlying mechanism to meet the increased oxygen demands of the diabetic myocardium.

**Study limitations.** The main limitation of this study is the relatively small number of patients enrolled.

CFR values may be affected by hemodynamic conditions and cardiac function (15, 28). Although normalization of resting flow for heart rate and blood pressure did not significantly affect the results, we recognize that this correction remains incomplete. Others factors, such as age, sex, endothelial dysfunction, drugs, anemia, and the presence of myocardial fibrosis, may affect resting blood flow (5).

In the presence of an obstructive coronary lesion, collateral flow becomes increasingly important with increasing stenosis severity (1). In this study, we did not take collateral flow into account since pressure wire assessment was performed in coronary vessels free of severe stenoses, with FFR values >0.80 in all subjects: here the influence of collateral flow on CFR values is expected to be quite low.

The reproducibility of the thermodilution technique may represent a further limitation. The position of the guiding catheter is a potential source of errors. The guiding catheter needs to be sufficiently engaged in the coronary artery to guarantee adequate delivery of the indicator into the vessel. Two of our thermodilution CFR values were very high (CFR values of 8.7 and 9.8). In a small proportion of cases, thermodilution-derived CFR has been shown to overestimate the true value of CFR especially in the case of large side branches (25). This may be an explanation for occasionally high CFR values in our series. Although we do not have a definitive explanation for this, such artefacts, which have been previously described with intracoronary thermodilution techniques (12, 17), would occur at random and are therefore not likely to affect our inference.

Positron emission tomography, an alternative method for the noninvasive study of the coronary microcirculation, permits the absolute quantification of perfusion and also enables us to detect regional dishomogeneties. Furthermore, positron emission tomography allows measurement of perfusion and resistance, while distinguishing between the subendocardial and subepicardial layers, which may provide important information as ischemia mainly occurs in the subendocardium (13, 15). A positron emission tomography validation study of the present findings will therefore be desirable.

The diagnosis and characterization of diabetes may represent a final limitation. We have used the World Health Organization criteria, commonly used in clinical practice and largely used in similar studies (9, 29, 30) for the diagnosis of diabetes, and the HOMA index to characterize the degree of insulin resistance, which is a correlate, and the alleged underlying promoter, of the deranged values of basal coronary blood flow in diabetic subjects. The use of other criteria for the diagnosis of diabetes, or of the hyperinsulinemic, euglycemic clamp, currently considered the gold standard for the measurement of insulin resistance, might have provided more accurate assessment and characterization of the diabetic status of our patients.

**Conclusions.** In diabetic patients with early vascular disease, coronary flow reserve is significantly reduced compared with nondiabetic patients because of a higher basal coronary flow, while the maximum vasodilation of the coronary microcirculation is similar in diabetic and nondiabetic patients. The increased basal coronary flow relates to insulin resistance. Further studies on the mechanisms for the early occurring increase in coronary blood flow in diabetes are warranted.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**


**REFERENCES**


