Insulin infusion improves myocardial blood flow (MBF) in healthy subjects. Until now, the effect of insulin on myocardial perfusion in type 2 diabetic subjects with coronary artery disease (CAD) has been unknown. We studied the effects of insulin on MBF in ischemic regions evaluated by single-photon emission–computed tomography and coronary angiography and in nonischemic regions in 43 subjects (ages 63 ± 7 years) with type 2 diabetes (HbA1c 7.1 ± 0.9%). MBF was measured at fasting and during a euglycemic-hyperinsulinemic clamp at rest (n = 43) and during adenosine-induced (140 μg·kg⁻¹·min⁻¹ for 7 min) hyperemia (n = 26) using positron emission tomography and ¹⁵O-labeled water. MBF was significantly attenuated in ischemic regions as compared with in nonischemic regions (P < 0.0001) and was increased by insulin as compared with in the fasting state (P < 0.0001). At rest, insulin infusion increased MBF by 13% in ischemic regions (P = 0.043) and 22% in nonischemic regions (P = 0.003). During adenosine infusion, insulin enhanced MBF by 20% (P = 0.018) in ischemic regions and 18% (P = 0.045) in nonischemic regions. In conclusion, insulin infusion improved MBF similarly in ischemic and nonischemic regions in type 2 diabetic subjects with CAD. Consequently, in addition to its metabolic effects, insulin infusion may improve endothelial function and thus increase the threshold for ischemia and partly contribute to the beneficial effects found in clinical trials in these subjects. Diabetes 55:511–516, 2006

Patients with type 2 diabetes are at high risk for acute cardiovascular events. In type 2 diabetes, endothelial dysfunction is a key step in the development of myocardial ischemia that impairs endothelium-dependent vasodilation in coronary conductions and coronary resistance arteries (1). Insulin is a known vasodilator in the periphery as well as in the myocardium of healthy subjects. It increases blood flow mainly by stimulating nitric oxide synthesis (2). Insulin-induced vasodilation capacity is decreased in several altered metabolic states, specifically in obesity, hypertension, and type 2 diabetes (3–5). In subjects with type 2 diabetes and stable coronary artery disease (CAD), insulin therapy improves peripheral endothelial function (6), and after acute myocardial infarction, aggressive insulin therapy decreases recurrent ischemia (7). We have recently shown that myocardial blood flow can be increased by insulin infusion in healthy subjects and subjects with uncomplicated type 1 diabetes (8–10). Furthermore, it has been suggested that insulin may increase myocardial blood flow at rest in subjects with uncomplicated type 2 diabetes (11). However, although CAD is the leading cause of death in type 2 diabetic subjects, the effect of insulin on myocardial blood flow has not been previously studied in type 2 diabetic subjects with CAD.

The main aim of this study was to determine whether insulin is able to increase myocardial blood flow in the regions of compromised myocardial perfusion in subjects with type 2 diabetes and ischemic CAD. In addition, we also aimed to compare the flow values between ischemic and nonischemic regions. Exercise-rest single-photon emission–computed tomography (SPECT) perfusion imaging, coronary angiography, and echocardiography were performed to locate the ischemic region. Myocardial blood flow at rest and during adenosine-induced hyperemia after an overnight fast and during insulin infusion were measured using positron emission tomography (PET) and [¹⁵O]labeled H₂O. Because other studies have suggested that insulin might cause an increment in the blood flow (8–11), we hypothesized that insulin would also induce vasodilation in these subjects.

RESEARCH DESIGN AND METHODS

We studied 43 type 2 diabetic subjects (28 men and 15 women, ages 62.6 ± 7.4 years) with a history of angina pectoris. Subjects were enrolled from the intervention study with rosiglitazone therapy. Characteristics of the study subjects are given in Table 1. Inclusion criteria were past or present angina pectoris symptoms under stress, type 2 diabetes treated with diet or metformin and/or a sulfonylurea, and good or moderate glycemic control (HbA1c <8.5%). Criteria for exclusion were unstable angina pectoris, symptomatic tachy- or bradycardia, history of percutaneous transluminal coronary angioplasty during the preceding 6 months, asthma, chronic use of insulin, or clinical signs of heart failure. The mean duration of diabetes was 7.6 ± 6.8 years (range 0.4–25.7 years). Of the 43 subjects, 30 had angina pectoris in stress, 13 had silent ischemia, 7 had a history of previous myocardial infarction, 4 had Q-wave, and 4 had microalbuminuria. Medications taken by the subjects are also listed in Table 1. All subjects gave a written informed consent before participating in the study. The study was conducted according to the guidelines of the Declaration of Helsinki, and the protocol was approved by the ethics committee of the Hospital District of Southwest Finland.

All subjects underwent SPECT imaging to evaluate exercise-induced ischemia of the myocardium and coronary angiography to determine the
TABLE 1  
Characteristics of the study subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (male/female)</td>
<td>43</td>
</tr>
<tr>
<td>Sex</td>
<td>38/15</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.6 ± 7.4</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>87.7 ± 17.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.9 ± 4.6</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>144/77 ± 23/7</td>
</tr>
<tr>
<td>Mean left ventricular ejection fraction (%)</td>
<td>64 ± 7*</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>110 ± 20</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>7.8 ± 1.6</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.4 ± 0.9</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.8 ± 0.9</td>
</tr>
<tr>
<td>Medications [% (n/n)]</td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>79 (34/43)</td>
</tr>
<tr>
<td>Statins</td>
<td>44 (19/43)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>47 (20/43)</td>
</tr>
<tr>
<td>Calcium blockers</td>
<td>16 (7/43)</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>79 (34/43)</td>
</tr>
<tr>
<td>Long-acting nitrates</td>
<td>28 (12/43)</td>
</tr>
</tbody>
</table>

Data are means ± SD. *Measured with echocardiography, range 39–76%.

Stenotic vessel. The PET study was performed to evaluate myocardial blood flow. The studies were performed on 3 separate days.

SPECT perfusion imaging. 99mTc-Myoview-tetrofosmin (Amersham, Little Chalfont, U.K.) was used in the SPECT studies. Subjects refrained from taking β-blockers, calcium blockers, and long-acting nitrates for 48 h before the study. Rest imaging was performed with 250 MBq and exercise imaging with 900 MBq injection, with effective doses of 1.5 and 5.36 mSv, respectively. SPECT acquisition was performed with a VertexPlus EPIC gamma camera (ADAC, Milpitas, CA) 15–30 min after injection. Subjects were placed in the supine position with arms lifted above the head, and the gamma camera was placed at a 90° angle near the thoracic region with the acquisition time on 40 s at rest imaging and 20 s at exercise imaging. Both rest and stress imaging studies were performed on the same day. The exercise test was performed with a bicycle ergometer with 15 W steps. 99mTc-Myoview-tetrofosmin was injected at the level of maximum stress and patient continued pedaling for 2 min.

Coronary angiography. Coronary angiography was performed via the femoral approach using the Judkins technique after an intravenous injection of 3,750 IU of heparin and 0.5 mg of sublingual nitroglycerin. Angiography was performed with 5-Fr catheters (Cordis; Johnson & Johnson, Miami Lakes, FL).

PET study. The positron-emitting tracer, [15O]H2O, was produced as previously described (12). PET studies were performed in subjects after they had fasted for 12 h (Fig. 1). Subjects refrained from caffeine-containing drinks, smoking, and taking all medications with the exception of short-acting nitrates for 12 h before the PET scan. Two catheters were inserted, each in an antecubital vein, one for the insulin, glucose, and [15O]H2O infusions and the other for blood sampling. Insulin (Actrapid; Novo Nordisk, Copenhagen, Denmark) was infused with a primed, continuous infusion at 1 mU · kg⁻¹ · min⁻¹. Normoglycemia was adjusted with 20% glucose infusion. The arm for blood sampling was warmed with a heating pillow to arterialyze the venous blood. The level of plasma glucose was determined every 5–10 min from arterialized venous blood, and levels of insulin and free fatty acids were determined every 30 and 60 min, respectively. The myocardial blood flow was measured at fasting and during insulin infusion at rest and during adenosine infusion (140 μg · kg⁻¹ · min⁻¹ for 7 min). The flow measurements were performed at 60 min of insulin infusion. Whole-body glucose uptake was measured as previously described (13). Electrocardiogram and heart rate were monitored throughout the study. Blood pressure was measured every 3 min during flow studies.

PET image acquisition, processing, and corrections. Subjects were placed in the supine position in an eight-ring ECAT 931/08-12 tomograph (Siemens/CTI, Knoxville, TN). Photon attenuation was corrected by a transmission scan of 5 min with a removable ring source of 99mTc. Myocardial blood flow was measured by intravenous infusion of [15O]H2O (1.3–1.5 GBq) over 2 min. Dynamic imaging was performed at rest and 60 s after the adenosine infusion (140 μg · kg⁻¹ · min⁻¹) was started with frames of 6 × 5 × 6 × 15, and 8 × 30 × 1. All data were corrected for dead time, decay, and photon attenuation and were reconstructed in a 128 × 128 matrix. The final in-plane resolution in the reconstructed and Hann-filtered (0.3 cycles/s) images was 9.5 mm (full width, half maximum).

Echocardiographic examination. To evaluate the global left ventricular function, all subjects underwent rest echocardiographic examination after the PET imaging during insulin stimulation. All echocardiographic studies were performed using the same ultrasound scanner (Acuson 128XP/10; Acuson, Mountain View, CA). Standard echocardiographic views of the left ventricle were obtained, and resting cardiac dimensions were measured. The left ventricular mass was calculated according to the Penn convention (14), and the left ventricular mass index was defined as the left ventricular mass divided by the body surface area.

Classification of the myocardial regions and calculation of myocardial blood flow. For the PET analysis, the data from the SPECT, coronary angiography, and echocardiography studies were combined, and the ischemic and the nonischemic regions of the myocardium were identified in all subjects. PET analysis used an eight-segment heart phantom map, which is based on the segmental division described by Brunken and colleagues (15,16) dividing the myocardium into anterobasilar, anteroseptal, anterior, lateral, posteroseptal, apical, posterobasilar, and inferior segments. The feasibility of this analysis has been tested in previous studies (17,18).

In the PET analysis, two experienced observers visually scored the rest and stress images; the summed difference score (ischemic score) was calculated based on a 20-segment model as previously described (19). The ischemic region was defined as a completely or partially reversible perfusion deficit (change in segment grade by >1). The nonischemic region had no perfusion deficits. The locations of separate regions were further aligned to the eight-segment heart phantom, and the locations were confirmed from the transaxial slices of the SPECT study. In coronary angiography, coronary anatomy and the location of the stenotic lesions were visually analyzed and the stenotic coronary artery diameters were measured with QCA software (Quantor phantom were included in each region. The ischemic and nonischemic regions were drawn into the PET images. The large regions of interest (ROIs) were placed on the representative transaxial slices in each study to cover the ischemic and nonischemic regions. Each ROI was drawn in the same region for the fasting state and during hyperinsulinemia. The ROIs drawn in the rest images were copied to the

![FIG. 1. PET study design. Myocardial blood flow was first measured in the fasting state at rest and then during adenosine (ADE) infusion (140 μg · kg⁻¹ · min⁻¹). The measurements were repeated during insulin infusion.](image-url)
images obtained during adenosine-induced hyperemia. Myocardial blood flow in the two separate ROIs were calculated using a single-compartment model, as previously described (20). Arterial input function was obtained as previously described (21). Myocardial blood flow was measured at rest in all subjects \((n = 43)\). Adenosine-stimulated blood flow was studied in 26 subjects, and ischemic and nonischemic regions could be analyzed in 25 of those subjects. The rest of the subjects were excluded due to arrhythmias \((n = 6)\), angina \((n = 2)\), consent withdrawal \((n = 5)\), or technical problems \((n = 4)\) during the first adenosine infusion.

**Biochemical analysis.** All laboratory samples were sent by courier to a central laboratory (Quest Diagnostics, Heston, U.K.). Standard methods and quality control for the tests were performed. The LDL cholesterol concentration was calculated with the Friedewald formula.

**Statistical analysis.** Data are reported as means ± SD. The overall effect of insulin on blood flow and the overall comparison between the ischemic and nonischemic regions were analyzed with a mixed model taking into account the repeated measurements and separate regions in each subject. In addition, a paired \(t\) test was used to compare the flow values between the fasting state and hyperinsulinemia and between the ischemic and nonischemic regions at rest and during adenosine infusion. The tests were performed for 43 ischemic and nonischemic regions at rest and for 25 ischemic and nonischemic regions during adenosine infusion, \(P < 0.05\) was considered statistically significant. All statistical analyses were performed with SAS (Version 8.2; SAS, Cary, NC).

**RESULTS Coronary angiography and localization of ischemia.** Coronary angiography revealed one-vessel disease in 53% (23 of 43), two-vessel disease in 33% (14 of 43), and three-vessel disease in 14% (6 of 43) of subjects. The location of main stenosis was the left anterior descending artery in 67% (29 of 43), the left circumflex artery in 5% (2 of 43), and the right coronary artery in 28% (12 of 43) of subjects. The median of the degree of stenosis was 70% (range 9–100%). Collateral circulation was found in seven subjects. In the SPECT analysis, the average ischemic score was 8.4 ± 4.3 and the average number of segments presenting ischemic deficits was 8.3 ± 2.9. After matching the data from the SPECT, the coronary angiogram, and the echocardiogram, 27 subjects had ischemic region in the anterior wall; 2, in the lateral wall; 2, in the apical region; and 12, in the infero-posterior region. Nonischemic regions were located in the inferior region in 4 subjects, in the lateral wall in 33 subjects, and in the anterior wall in 6 subjects.

**Hemodynamic, metabolic, and echocardiographic findings.** Heart rate was higher during hyperinsulinemia at rest \((n = 43)\) and adenosine infusion \((n = 26)\) \((P < 0.0001\) and \(P = 0.03\), respectively) (Table 2). The rate-pressure product \((\text{systolic blood pressure} \times \text{heart rate})\) was increased by insulin infusion at rest \((P = 0.0003)\) but not significantly during adenosine infusion \((P = 0.11)\). The serum insulin level was significantly elevated during hyperinsulinemia \((P < 0.0001)\) (Table 3). Insulin infusion significantly decreased blood glucose levels from 7.8 ± 1.6 to 5.4 ± 0.7 mmol/l \((P < 0.0001)\). The mean left ventricular ejection fraction was 64 ± 7% (range 39–76%) and the mean left ventricular mass index was 118.6 ± 24.6 g/m².

**Myocardial perfusion.** Insulin had an improving effect on the overall myocardial blood flow \((P < 0.0001)\). At rest, insulin infusion increased myocardial blood flow by 13% \((\text{from} 0.98 ± 0.30 \text{ to} 1.07 ± 0.35 \text{ ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}; P = 0.043)\) and 22% \((\text{from} 1.09 ± 0.36 \text{ ml} \text{ to} 1.28 ± 0.39 \text{ ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}; P = 0.003)\) in ischemic and nonischemic regions, respectively (Fig. 2). Accordingly, insulin increased adenosine-induced hyperemia by 20% \((\text{from} 3.34 ± 0.93 \text{ to} 3.83 ± 1.06 \text{ ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}; P = 0.018)\) in ischemic regions and 18% \((\text{from} 3.82 ± 0.90 \text{ to} 4.30 ± 1.07 \text{ ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}; P = 0.045)\) in nonischemic regions. The response to the insulin infusion was similar in the ischemic and nonischemic regions (NS).

In general, the myocardial blood flow was significantly attenuated in the ischemic regions as compared with in the nonischemic regions \((P < 0.0001)\). In separate analyses, in the fasting state myocardial blood flow was significantly lower in ischemic regions as compared with in nonischemic regions at rest \((P = 0.000)\) and during adenosine infusion \((P = 0.006)\). Concordantly, during insulin infusion, myocardial blood flow was significantly lower in ischemic regions at rest \((P = 0.0005)\) and during adenosine-induced hyperemia \((P = 0.017)\). The difference between ischemic and nonischemic regions remained significant when blood flow values were corrected with the rate-pressure product at rest in the fasting state \((0.97 ± 0.30 \text{ vs} 1.10 ± 0.28 \text{ ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}; P = 0.0016)\) and during insulin infusion \((1.02 ± 0.32 \text{ vs} 1.22 ± 0.36 \text{ ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}; P = 0.0009)\). The severity of coronary stenosis did not correlate with the response to insulin at rest or during hyperemia.

**DISCUSSION**

This study demonstrated a novel finding that insulin infusion improves myocardial blood flow in the ischemic and nonischemic regions in subjects with type 2 diabetes.

**TABLE 3 Metabolic characteristics of study subjects**

<table>
<thead>
<tr>
<th></th>
<th>At fasting</th>
<th>During insulin infusion</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose ((\text{mmol/l}))</td>
<td>7.8 ± 1.6</td>
<td>5.4 ± 0.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum insulin ((\text{pmol/l}))</td>
<td>56 ± 32</td>
<td>435 ± 87</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum free fatty acids ((\text{mmol/l}))</td>
<td>0.79 ± 0.3</td>
<td>0.19 ± 0.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Whole-body glucose uptake ((\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}))</td>
<td>—</td>
<td>11.7 ± 5.2</td>
<td>—</td>
</tr>
</tbody>
</table>

Data are means ± SD.
and CAD. Blood flow is lower in the ischemic regions as compared with the nonischemic regions at rest and during adenosine infusion in these subjects.

Intensive insulin therapy has been extensively studied since the 1960s. However, controversial results have been observed in clinical trials. In the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study in type 2 diabetic subjects, long-term survival was improved and mortality was significantly reduced with intensive insulin therapy after myocardial infarction (22). Furthermore, a large meta-analysis of earlier studies showed that glucose-insulin-potassium (GIK) infusion reduces in-hospital mortality after myocardial infarction, even in nondiabetic subjects (23). In contrast, a neutral effect on mortality and morbidity was found in the DIGAMI-2 and Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation-Estudios Clinicos Latino America (CREATE-ECLA) studies (7,24). However, the GIK infusion was carried out in a manner that produced significant hyperglycemia in the two latter studies. High blood glucose levels alone were found to be an independent predictor of mortality (24); thus, the presence of hyperglycemia may have blunted the possible beneficial effects of insulin on prognosis. On the other hand, the CREATE-ECLA study demonstrated a significant reduction of recurrent ischemia in the GIK infusion group, suggesting that insulin therapy may have a beneficial effect on endothelial function presented as an increased threshold for ischemia. In addition, it was recently determined that insulin has protective effects on the endothelium at the cellular level (25).

In animal studies, insulin has been shown to improve cardiac function (26) and contractile dysfunction in ischemic myocardium (27). In subjects with uncomplicated type 2 diabetes, insulin improves myocardial blood flow at rest (11). We have recently shown that intravenous insulin infusion increases myocardial blood flow during adenosine-induced hyperemia by 20% in healthy subjects and 23% in young subjects with type 1 diabetes (9,10). In the present study, we have shown that insulin is able to induce an increase of similar degree in the blood flow in both ischemic and nonischemic regions in type 2 diabetic subjects with CAD. The degree of increase in the myocardial blood flow at rest is relatively small and may not be equally clinically significant as the increase in hyperemic blood flow. However, the present study has demonstrated that insulin may cause vasodilation at rest and, more importantly, during adenosine-induced hyperemia; thus, in addition to the effect on substrate metabolism, the vasodilatory effects of insulin may partly contribute to the improvement in endothelial function and, consequently, insulin may increase the threshold for ischemia in type 2 diabetic subjects with stable CAD.

Insulin causes vasodilation through a nitric oxide–mediated pathway. In type 2 diabetic subjects with CAD, insulin improves peripheral endothelial function (6). In the current study, coronary vasodilatory function was examined during adenosine-induced hyperemia. A significant part of the adenosine-induced vasodilation was endothelium dependent (28); therefore, adenosine-induced vasodilation is an integrating measure of endothelial function and vascular smooth muscle relaxation. In contrast to resting conditions where flow and myocardial work (oxygen consumption) are tightly coupled, during adenosine stimulation, metabolic control of myocardial blood flow is lost but endothelial and neurogenic controls are still functional (29). In addition, a significant correlation exists between the vasodilation capacity of the epicardial artery and the coronary blood flow velocity (30). It has also been suggested that an abnormal endothelium-dependent vaso-reactivity exists in the corresponding regions in which subjects have regional myocardial perfusion defects, even though these subjects have a normal angiogram (31).

In addition to other traditional risk factors such as hypertension and dyslipidemia, poor glycemic control seems to contribute to the poor coronary vasodilatory function in type 2 diabetic subjects. The prevalence of abnormal glucose metabolism is high in subjects with acute myocardial infarction (32). In sustained hyperglycemia, the vasodilatory action of insulin may be impaired (33). In the current study, the subjects were highly insulin resistant, which is typical for type 2 diabetic subjects. It has been previously shown that insulin resistance may impair endothelial function (34). Endothelial dysfunction may be more prominent in type 2 than in type 1 diabetic subjects despite comparable glucose homeostasis, which would suggest a significant role for other factors (35). In our study, subjects had good or moderate glycemic con-

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FIG. 2. Myocardial blood flow in ischemic and nonischemic regions in the fasting state and during insulin infusion at rest and during adenosine infusion. *P = 0.043; †P = 0.018; ‡P = 0.003; §§P = 0.045.
control. Therefore, it is unlikely that the improvement in myocardial blood flow was due only to the modest improvement in blood glucose levels.

The relation of myocardial blood flow and the degree of stenosis of a coronary artery is controversial. Results from several studies in nondiabetic subjects suggest that myocardial blood flow is decreased in regions of significant stenosis (36,37). On the other hand, myocardial blood flow remains unchanged in regions of significant stenosis at rest, but it is significantly lower in stenotic regions during adenosine-induced hyperemia (38,39). Another study has shown that in nondiabetic subjects with CAD, myocardial blood flow is lower as compared with in healthy control subjects in both the stenotic and the nonstenotic regions (40). In the current study, we found that myocardial blood flow was significantly reduced in regions of coronary stenosis both at rest and during hyperemia in type 2 diabetic subjects with CAD.

Data from many previous studies have suggested reduced coronary vasodilatation is present in diabetic subjects (41,42). The level of myocardial blood flow during pharmacologically applied stress conditions is significantly decreased in subjects with uncomplicated type 2 diabetes and in type 2 diabetic subjects with CAD (43,44). However, in type 2 diabetic subjects, myocardial blood flow at rest does not significantly differ from that in healthy control subjects or from that in type 2 diabetic subjects with CAD (45). In another study, resting myocardial blood flow was higher in type 2 diabetic subjects as compared with in healthy volunteers (46). In many studies, comparisons of the flow values are made between healthy control subjects and patient groups. In the present study, we measured myocardial blood flow in the same region in the fasting state and during hyperinsulinemia; thus we were able to compare the values within each patient and exclude between-subject variability.

In the present study, the subjects were on several medications, which is typical for this patient population. To avoid the confounding effects of other medications, the subjects refrained from all their medications for 12 h before the PET study, but otherwise the subjects were on stable medical therapy throughout the study. It is known that some medications may affect absolute myocardial blood flow. For example, the statin and ACE inhibitor therapies improve myocardial blood flow in subjects with CAD (47,48). In addition, β-adrenergic blockade has been shown to reduce myocardial blood flow at rest but either increase or decrease the hyperemic blood flow (49,50). However, the results of our study indicate that insulin has additive effects over the concomitant medication on the absolute myocardial blood flow.

In conclusion, insulin improves myocardial blood flow similarly in ischemic and nonischemic regions both at rest and during adenosine-induced hyperemia in subjects with type 2 diabetes and CAD. According to these results, we suggest that insulin-induced vasodilation, in addition to its metabolic effect, improves endothelial function and thus increases the threshold for ischemia in these subjects. This may contribute to the positive effects found in clinical trials with intensive insulin therapy.

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R. LAUTAMÄKI AND ASSOCIATES
INSULIN IMPROVES MYOCARDIAL BLOOD FLOW


