Regional myocardial blood flow and glucose utilization during fasting and physiological hyperinsulinemia in humans

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Iozzo, Patricia, Panithaya Chareonthaitaweew, Marco Di Terlizz, D. John Betteridge, Ele Ferrannini, and Paolo G. Camici. Regional myocardial blood flow and glucose utilization during fasting and physiological hyperinsulinemia in humans. Am J Physiol Endocrinol Metab 282:E1163–E1171, 2002.—We investigated the effect of insulin on total and regional myocardial blood flow (MBF) and glucose uptake (MGU) in healthy subjects (50 yr) by means of positron emission tomography (PET) with oxygen-15-labeled water (H215O) and fluorine-18 labeled fluorodeoxyglucose (18FDG) before and during physiological hyperinsulinemia (40 mU·min-1·m-2). Twelve male subjects were included in the study. During hyperinsulinemia, MBF increased from 0.91 ± 0.28 to 1.01 ± 0.31 ml·min-1·g-1 (n = 7 patients, P = 0.05; n = 12 regions, P < 0.005). Intersubject variability ranged from −3.0 to +41%. MGU increased from 0.11 ± 0.08 (n = 5) to 0.56 ± 0.08 µmol·min-1·g-1 (P < 0.0001, n = 7). MBF and insulin-mediated MGU were higher in the septum and anterior and lateral wall along short-axis regions of the heart. During hyperinsulinemia, MBF was also higher in the apex and midventricle compared with the base. MBF and MGU were positively correlated before (r = 0.66, P < 0.0001) and during hyperinsulinemia (r = 0.24, P < 0.05). These results provide evidence that insulin stimulates MBF in normal human hearts and appears to involve mainly those regions of the heart where insulin-mediated MGU is higher. Furthermore, regional distribution of insulin-stimulated MBF and MGU does not appear to be uniform across the left ventricular wall of healthy subjects.

insulin; positron emission tomography; diabetes mellitus

HEMODYNAMIC AND METABOLIC DEFECTS often coexist in heart disease; thus coronary artery disease is characterized by insulin resistance (30, 36) and impaired coronary vascular reserve (10, 49). Several studies (3, 24, 25) have suggested that insulin-induced glucose uptake in target organs may be mediated, at least in part, by an upregulation of tissue perfusion. Most available data (52) focus on skeletal muscle as the predominant glucose consumer in the whole body under insulin-stimulated conditions and indicate that the magnitude of insulin-related stimulation of blood flow in this tissue is both time (24, 50) and dose dependent (5, 53). However, no information on myocardial perfusion can be extrapolated from these studies due to the unique regulation of coronary blood flow (31) and to the distinctive pattern of glucose utilization in this organ (8, 34). Although it is well established that insulin induces a severalfold elevation of glucose consumption by the myocardium (37), its ability to enhance coronary blood flow, as assessed by cardiac catheterization, has yielded conflicting reports (4, 16, 28, 32, 41, 42, 48). Contributing to the controversy are differences in study design, including study population [experimental animals (28, 41) vs. human (16, 32, 42, 48)], insulin dose [physiological (16, 32) vs. pharmacological (42)], route [systemic (16, 48) vs. local (41)], and mode of insulin delivery [bolus (48) vs. infusion (16, 28, 41)] and the different techniques employed for the assessment of blood flow, namely coronary sinus thermodilution (16, 48), intracoronary Doppler (41), and radioactive microspheres (17). Variable circulating substrate concentrations [euglycemia (16) vs. hyperglycemia (48), high vs. low nonesterified fatty acids (NEFA) (41)] and different levels of stress generated by the use of an invasive technique, either alone (4, 16, 28, 48) or in combination with anesthesia (41), represent further confounding factors.

Positron emission tomography (PET) provides the opportunity for noninvasive quantification of regional myocardial blood flow (MBF) and glucose utilization (MGU). Using PET in combination with and [18F]fluoro-2-deoxyglucose (18FDG), Utriainen et al. (51) have shown that, in human skeletal muscle, insulin increases mean blood flow and absolute dispersion of blood flow and redirects flow to areas with high rates of glucose uptake. More importantly, Laine et al. (26) have recently demonstrated that physiological hyperinsulinemia upregulates myocardial perfusion and coronary flow reserve during ad-
enolase-induced hyperemia, as measured with [15O]water (H215O) and PET. In the myocardium, a considerable interregional variability of glucose uptake has been observed with the use of 18FDG and PET after insulin stimulation (21).

In the present study, resting MBF and MGU were measured by PET in normal volunteers before and during physiological hyperinsulinemia. The objective was to establish whether insulin affects global and regional MBF in healthy humans and, if so, whether a relationship exists between insulin-stimulated glucose uptake and blood flow in the myocardium.

METHODS

Subjects. The study population comprised 12 healthy male volunteers (aged 45–59 yr, mean±SD: 50±5 yr; body mass index: 26.80±1.96 kg/m²). None had a personal or family history of cardiovascular disease or diabetes. Inclusion criteria included normal heart rate, blood pressure (130±11/74±6 mmHg), normal resting electrocardiogram and echocardiogram, and serum total cholesterol concentrations <6.0 mmol/l (234 mg/dl). Subjects participating in intense physical training programs were excluded. All subjects were asked to consume a diet containing 200 g of carbohydrate for 3 days before the study. None of them was taking any medication at the time of the study.

The study was approved by the Research Ethics Committee of Hammersmith Hospital and by the United Kingdom Administration of Radioactive Substances Advisory Committee. Each subject gave written informed consent before participating in the study.

Study design. All subjects underwent a baseline measurement of MBF. In seven subjects, a euglycemic-hyperinsulinemic clamp study was subsequently performed for quantification of insulin-stimulated MBF and MGU. In the remaining five subjects, a baseline assessment of MGU was carried out.

PET scan. All scans were performed in a two-dimensional imaging mode using an ECAT 931–08/12 scanner (CTI, Knoxville, TN) with a 10.5-cm axial field of view and a resolution of 8.4×8.3×6.6 mm³ full width at half-maximum (22, 45). All studies were conducted after a 10- to 12-h fast.

Insulin, glucose, and radioactive tracers were administered through a right forearm vein catheter. All blood samples were collected from a second catheter, which had been inserted peripherally into a vein of the left hand. A heating pad was placed around the left hand to achieve arterIALIZATION of venous blood for the entire duration of each study.

After optimization of patient position, a 20-min transmission scan was performed after exposure of a retractable 68Ge ring source to correct all subsequent emission data for tissue attenuation and reconstructed through standard reconstruction algorithms. Image manipulation and data handling were performed on a SUN SPARC 2 and Ultra 10 workstations (Sun Microsystems, Mountain View, CA) as previously described (12, 30, 36).

Fig. 1. [18F]fluoro-2-deoxyglucose ([18F]FDG, kBq/ml) image during the clamp in one of the study subjects. The left ventricular wall was divided into 3 portions along the long axis (A). Regions of interest (ROIs) were defined on each short-axis plane as shown in B. Ant, anterior; Lat, lateral; Post, posterior; Inf, inferior; Sept, septum; Sept ant, anteroseptal; Sept post, posteroseptal. Data were corrected for partial volume to generate myocardial glucose uptake values (MGU; μmol·min−1·g−1).

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The arterial input for [15O]water was obtained from the left discrete plasma samples. Delay correction was performed.

\( \text{Input function for FDG was derived from continuous monitoring of arterialized blood radioactivity. Whole blood was converted into plasma input by using a limited number of Matlab (The MathWorks, Natick, MA) software package.} \)

Input function for PDG was derived from continuous monitoring of arterIALIZED blood radioactivity. Whole blood was converted into plasma input by using a limited number of discrete plasma samples. Delay correction was performed. The arterial input for [15O]water was obtained from the left atrium time activity curve.

**Regions of interest.** All images were resliced along the short axis, and the free wall of the left ventricle was divided according to the 16-segment model recommended by the American Society of Echocardiography (29, 43). Along the long axis, the left ventricle was divided into three portions, as shown in Fig. 1A. First, the most proximal and the most apical left ventricular short-axis planes were identified. The plane adjacent to the one where the membranous septum was seen was considered to be the most basal plane. The plane toward the left ventricular apex that was proximal to the one with no evident ventricular cavity was considered to be the most apical plane. The number of short-axis images included between the most basal and the most apical plane was counted and grouped into three equal left ventricular portions: basal, mid, and apical. If the number of planes identified did not allow for division by three, the planes where the papillary muscles were clearly identified were assigned to the midleft ventricular portion. Regions of interest (ROIs) were drawn on the short-axis images, as shown in Fig. 1B, on a plane-by-plane basis. Six ROIs, corresponding to anteroseptal, anterior, lateral, inferior, posterior, and posteroseptal walls, were traced on each plane that comprised the basal and midsections of the left ventricle. Four ROIs, corresponding to the anterior, lateral, inferior, and posterior walls, were traced on each plane comprising the apical section of the left ventricle. MGU and MBF were quantitated as previously described (19, 30, 36) in corresponding ROIs. A lumped constant of 1.0 was used to derive MGU (6, 38). MGU was divided by tissue fraction (30, 36) to correct for partial volume effects. Myocardial [15O]water images were corrected for spillover of radioactivity from the right and the left ventricular chamber.

**Statistical analysis.** Differences in paired data were evaluated using the Student’s paired t-test for single repeated measurements. One-way ANOVA was used for unpaired group comparisons. Regression analyses were carried out according to standard techniques. All data are presented as means ± SD. The SD across all myocardial segments was used as a measure of absolute dispersion (14). The coefficient of variation (CV), calculated as the ratio of the SD to the average value for each of 16 segments in every subject, was used as a measure of relative dispersion (14). Distribution changes in the whole myocardium were interpreted by visual inspection (51).

**RESULTS**

The characteristics of the study group are given in Table 1. Euglycemia was maintained throughout the clamp, with a CV of <5%. Whole body glucose uptake calculated during the last 40 min of the insulin clamp was 23 ± 7 μmol·min⁻¹·kg⁻¹.

Fasting vs. clamp MBF and MGU are described in the whole myocardium. In addition, because the cardiac walls are not supposed to contract in a uniform fashion (27, 47), we evaluated whether MBF and MGU changes would show regional differences (Table 2).

During the clamp, a significant increase in mean blood flow was documented by a rightward shift of the distribution curve (from 0.91 ± 0.28 to 1.01 ± 0.31 ml·min⁻¹·g⁻¹, \( P < 0.005, n = 112 \) myocardial regions; \( P = 0.05, n = 7 \) patients) (Fig. 2). The SD of MBF was slightly but not significantly increased during the clamp (from 0.27 ± 0.04 to 0.29 ± 0.04 ml·min⁻¹·g⁻¹), whereas the corresponding CV was unaffected (fasting vs. clamp: 30 ± 5 vs. 29 ± 4%, respectively, \( P = 0.05 \) or less).

On the basis of visual inspection and absolute regional mean values (Fig. 3), MBF increased in five of seven subjects during the clamp. For statistical computation, a Student’s paired t-test was carried out on each 16 segments of single patients. The increment

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**Table 1. Characteristics of the study population**

<table>
<thead>
<tr>
<th></th>
<th>Fasting (n = 12)</th>
<th>Clamp (n = 7)</th>
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<tbody>
<tr>
<td><strong>Plasma glucose, mmol/l</strong></td>
<td>4.70 ± 0.52</td>
<td>4.76 ± 0.46</td>
</tr>
<tr>
<td><strong>Plasma insulin, μU/ml</strong></td>
<td>3.8 ± 1.3</td>
<td>63 ± 6*</td>
</tr>
<tr>
<td><strong>RPP, mmHg x beats/min</strong></td>
<td>8,195 ± 1,213</td>
<td>8,339 ± 844</td>
</tr>
<tr>
<td><strong>NEFA, μEq/l (60 min)</strong></td>
<td>0.41 ± 0.15*</td>
<td>0.34 ± 0.27*</td>
</tr>
<tr>
<td><strong>NEFA (150 min), μEq/l</strong></td>
<td>0.34 ± 0.27*</td>
<td>0.34 ± 0.27*</td>
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</tbody>
</table>

Data are shown as means ± SD; *P < 0.0005 vs. fasting; †P < 0.01 vs. fasting. RPP, rate-pressure product; NEFA, nonesterified fatty acids.

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**Table 2. MGU and MBF during fasting and clamp in short-axis regions (perimeter) and long-axis segments of the heart**

<table>
<thead>
<tr>
<th></th>
<th>Anterior</th>
<th>Lateral</th>
<th>Inferior</th>
<th>Posterior</th>
<th>Septum</th>
<th>Base</th>
<th>Midventricle</th>
<th>Apex</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline MBF, ml-min⁻¹·g⁻¹</strong></td>
<td>1.00 ± 0.29</td>
<td>0.94 ± 0.20</td>
<td>0.89 ± 0.29</td>
<td>0.73 ± 0.26*</td>
<td>0.94 ± 0.28</td>
<td>0.88 ± 0.28</td>
<td>0.92 ± 0.30</td>
<td>0.96 ± 0.22</td>
</tr>
<tr>
<td><strong>Clamp MBF, ml-min⁻¹·g⁻¹</strong></td>
<td>1.23 ± 0.31**</td>
<td>1.03 ± 0.20*</td>
<td>0.86 ± 0.28*</td>
<td>0.80 ± 0.26*</td>
<td>1.04 ± 0.32*</td>
<td>0.92 ± 0.29*</td>
<td>1.06 ± 0.31*</td>
<td>1.07 ± 0.33</td>
</tr>
<tr>
<td><strong>Baseline MGU, μmol-min⁻¹·g⁻¹</strong></td>
<td>0.12 ± 0.08</td>
<td>0.12 ± 0.08</td>
<td>0.11 ± 0.09</td>
<td>0.11 ± 0.09</td>
<td>0.11 ± 0.08</td>
<td>0.12 ± 0.08</td>
<td>0.11 ± 0.08</td>
<td>0.11 ± 0.08</td>
</tr>
<tr>
<td><strong>Clamp MGU, μmol-min⁻¹·g⁻¹</strong></td>
<td>0.58 ± 0.08*</td>
<td>0.59 ± 0.07*</td>
<td>0.51 ± 0.06**</td>
<td>0.48 ± 0.07**</td>
<td>0.58 ± 0.08*</td>
<td>0.58 ± 0.09*</td>
<td>0.55 ± 0.08*</td>
<td>0.54 ± 0.08*</td>
</tr>
</tbody>
</table>

Values are means ± SD. MBF, myocardial blood flow; MGU, myocardial glucose uptake. *P < 0.05 or less vs. fasting; †P = 0.09 (lateral wall) and P = 0.14 (septum) vs. fasting; ‡P < 0.05 or less vs. septum and anterior and lateral wall (short axis) or vs. midventricle and apex (long axis); ‡‡P < 0.05 or less vs. septum and anterior wall; *P < 0.05 or less vs. septum and lateral wall.

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was significant \((P < 0.02)\) in three and nonsignificant in two patients; no change or a slight decline \((\sim 3\%)\) was observed in the remaining two subjects, respectively (Fig. 3). Along the short axis, the change in MBF was nonsignificant in the regions with a lower basal blood flow. Among the segments with a higher basal blood flow, the increase was significant in the anterior wall \((1.00 \pm 0.29 \text{ vs. } 1.23 \pm 0.31 \text{ ml/min}^{-1} \cdot \text{g}^{-1}, P = 0.02)\) and borderline in the septum and lateral wall \((0.94 \pm 0.28 \text{ vs. } 1.04 \pm 0.32 \text{ ml/min}^{-1} \cdot \text{g}^{-1}, P = 0.14; 0.94 \pm 0.20 \text{ vs. } 1.03 \pm 0.20 \text{ ml/min}^{-1} \cdot \text{g}^{-1}, P = 0.09, \text{ respectively})\). Among long-axis regions, the increase in MBF during the clamp was significant in the midventricular wall \((0.92 \pm 0.30 \text{ vs. } 1.06 \pm 0.31 \text{ ml/min}^{-1} \cdot \text{g}^{-1}, P < 0.05)\) (Fig. 3 and Table 2).

During both fasting and insulin infusion, MBF was significantly lower in the posterior wall (fasting \(0.73 \pm 0.26\), clamp \(0.80 \pm 0.26 \text{ ml/min}^{-1} \cdot \text{g}^{-1}\)) than in the septum \((P < 0.05)\), the anterior \((P < 0.005 \text{ and } P < 0.0001, \text{ fasting and clamp, respectively})\), and the lateral wall \((P < 0.05)\). During the clamp, MBF was also lower in the inferior wall (fasting \(0.89 \pm 0.29\), clamp \(0.86 \pm 0.28 \text{ ml/min}^{-1} \cdot \text{g}^{-1}\)) compared with the septum and anterior wall \((P < 0.05 \text{ and } P < 0.0001, \text{ respectively})\), higher in the anterior wall than in the septum and lateral wall \((P < 0.05)\), and higher in the apex.

![Fig. 2. Myocardial blood flow (MBF) \((A\) and \(C)\) and MGU \((B\) and \(D)\) distribution frequencies in 80 myocardial regions during the fasting state \((A\) and \(B)\) and during the insulin clamp \((C\) and \(D)\). Insulin stimulation of MGU and MBF is documented by rightward shift of the distribution curves. Reshaping of the MBF curve suggests that redistribution of blood flow occurred during the clamp.](http://ajpendo.physiology.org/)

![Fig. 3. A: average measures of MBF from 16 segments per subject before and during the insulin clamp. The increase was significant in 3 of 7 subjects. B: average measures of MBF in the anterior \((\circ, n = 21)\), lateral \((\triangle, n = 21)\), inferior \((*, n = 19)\), posterior wall \((+, n = 14)\), and septum \((\square, n = 35 \text{ segments})\). C: average measures of MBF in the apical \((\circ, n = 27)\), midventricular \((\odot, n = 42)\), and basal wall \((\circ, n = 41 \text{ segments})\)．](http://ajpendo.physiology.org/)
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MGU (Fig. 2) was significantly higher during the clamp (0.56 ± 0.08 μmol·min⁻¹·g⁻¹) than in fasting conditions (0.11 ± 0.08 μmol·min⁻¹·g⁻¹, P < 0.0001). The SD of MGU was similar during both conditions, whereas the CV was strikingly lower during clamp (14 ± 1%) compared with fasting studies (72 ± 7%, P < 0.0001).

MGU was consistently higher in each cardiac segment (P < 0.001) during the clamp compared with baseline. Across regions, insulin stimulation uncovered a pattern of distribution characterized by significantly higher values in the septum (0.58 ± 0.08 μmol·min⁻¹·g⁻¹) and the anterior (0.58 ± 0.08 μmol·min⁻¹·g⁻¹) compared with the inferior (0.51 ± 0.06 μmol·min⁻¹·g⁻¹, P < 0.0005, and P = 0.0005, respectively) and posterior wall (0.48 ± 0.07 μmol·min⁻¹·g⁻¹, P < 0.0001, and P < 0.0001, respectively).

In synthesis, insulin-mediated redistribution of MBF and MGU was anatomically related phenomena, suggesting that insulin improved the co-localization of these functions around the circumferential perimeter of the heart.

Regression analysis was carried out to investigate the extent to which MBF changes might be responsible for MGU changes and vice versa. In the whole myocardium, MGU and MBF were strongly intercorrelated variables in the fasting state (Fig. 4). There was a single measurement of 112, in which both MBF and MGU were lower than normally expected. The correlation between MGU and MBF did not change after this value was excluded from the analysis (r = 0.65, P < 0.0001). This relationship was still present, but weaker, during the clamp. Obviously, these segments include those in which a correlation became stronger and those in which it became weaker or disappeared completely. The results indicate that MBF and MGU changes occurred independently of each other during the clamp.

This does not at all exclude that, in those segments of the heart in which insulin acted to increase blood flow, it also stimulated MGU the most. This phenomenon would not be reflected by the overall correlation analysis that includes counteracting phenomena. To overcome this problem, values of MBF and MGU in each region of the left ventricular perimeter were averaged (n = 5); the correlation between MGU and MBF across these areas was strong (r = 0.87), although its statistical significance was borderline due to small sample size (P = 0.058). After correction for changes in MBF with a multiple regression model, a correlation was observed in the whole myocardium between the degree of NEFA release suppression during the clamp (calculated as the difference between fasting and clamp circulating levels) and MGU values.

DISCUSSION

The current findings indicate that an increase in plasma insulin levels, closely mimicking in magnitude and duration the levels observed during daily life, increases MBF by ~11%. Considering the time dependency of the phenomenon (52), it is of note that 1 h of insulin stimulation was sufficient to elicit a significant, albeit small, response. Our results are very similar to those observed in dogs within the same time frame with the use of the microsphere technique during infusion of glucose, insulin, and potassium and in some human studies (42). Rocchini et al. (41) reported a higher degree of insulin-induced blood flow increase in dogs (30%); a similar figure (25%) was recently found by McNulty et al. (32) in humans after a 60-min insulin stimulation at plasma concentrations of 134 μU/ml. Conversely, we (16) and others (4, 48) have been previously unable to detect any change. To partly reconcile the discrepancies, our results document a marked interindividual variability of response of insulin-stimulated blood flow in the myocardium. In our population, insulin-related changes in mean blood flow ranged from −3.0 to +41% in different individuals, a result

![image](https://www.ajpendo.org)

**Fig. 4.** Simple regression analysis showed a correlation between MBF and MGU during fasting (A). A weak correlation was still evident during the clamp (B).
comparable to that observed in skeletal muscle, in which this functional relationship has been more extensively investigated (52). Two considerations merit attention. First, aside from its vasodilatory properties, insulin is a recognized sympathetic neural activator (1), which, under certain circumstances, may behave as a vasoconstricting agent. Second, cardiac catheterization is an invasive procedure; as such, it is inevitably associated with a degree of sympathetic activation. In fact, the occurrence of this event was evident in our previous study (16), in which values of whole body glucose uptake in response to insulin (17 ± 1 μmol·min⁻¹·g⁻¹) were lower than expected and lower (by ~30%) than the values observed in the present study (at similar plasma insulin concentrations and in a population with comparable characteristics). Although we cannot completely exclude the occurrence of mild stress, induced by the duration of the procedure in the present study, it is very unlikely that this amount of stress would equal that induced by cardiac catheterization. The work published by Laine et al. (26) provides some interesting insight concerning the interaction between myocardial perfusion, insulin, and sympathetic activation. These authors showed that insulin-related sympathetic activation and norepinephrine release did not prevent insulin stimulation of myocardial hyperemic flow and coronary flow reserve in healthy subjects. This would rule out minimal stress as a confounding variable. It is still reasonable that a stronger sympathetic activation, comparable to that occurring during invasive studies, would partly counteract vasodilatation. Furthermore, whether sympathetic activation might interfere and amplify interindividual variability of response remains unclear.

Altogether, the aforementioned considerations suggest that variation in methodology and study design can explain some of the disagreement among studies, especially when small changes are to be detected, as in the case of short-term insulin stimulation of MBF. The current method has the advantage of being relatively stress free, and it has been recently shown to yield reproducible measures of blood flow in the myocardium (23). Indeed, our estimates of relative dispersion of blood flow (30%) are within the same range as those described in animals (27%) with the use of labeled microspheres (17).

The relationship between whole MBF and MGU in the basal state is consistent with the fact that, when no stimuli are applied to a specific intracellular metabolic pathway, energy production in the normal human heart depends on substrate delivery (8, 18), i.e., blood substrate concentrations and blood flow rates. Conversely, under insulin-stimulated conditions, the intrinsic ability of single myocytes to augment glucose uptake in response to the hormone, i.e., glucose extraction from the blood pool, becomes rate limiting for myocardial glucose consumption. As such, it should be relatively independent of blood flow in healthy individuals. In other words, the increase in blood flow occurring concomitantly with that of glucose uptake is not caused by an augmented demand for glucose by the heart. Alternatively, an increase in blood flow, whatever the underlying mechanism, has been proposed to promote glucose uptake (3, 24, 25), thus playing an active role in glucose metabolism. Such an effect remains yet to be proved, and studies on skeletal muscle using adenosine (33) or bradykinin (35) have failed to show any major effect of vasodilation on glucose uptake in this tissue during acute physiological hyperinsulinemia. With regard to our study, the observed increase of blood flow was very small and would not by itself justify the strong enhancement of glucose uptake.

Taken together, the aforementioned considerations seem to point in the direction of separate effects of insulin on cardiac blood flow and glucose handling in our study.

Insulin has been suggested to induce vasodilation in an endothelium-dependent fashion, as it appears to enhance the synthesis of nitric oxide (NO), this effect being prevented by the concomitant administration of N⁵-monomethyl-L-arginine (a competitive inhibitor of NO synthase) (44, 46). In their work, Laine et al. (26) showed that physiological hyperinsulinemia increases adenosine-mediated myocardial perfusion and coronary flow reserve in healthy subjects and suggested NO-dependent mechanisms as the most reasonable explanation for their findings. A trend toward an increment in cardiac workload, as reflected by the rate-pressure product, was observed in our subjects and might constitute an alternative mechanism for insulin stimulation of MBF. Insulin is recognized to promote MGU both indirectly, by reducing the availability of competing substrates (39), and directly, by enhancing glucose transport across the plasma membrane (13). In line with the former mechanism, we found a relationship between insulin-mediated changes in circulating NEFA and MGU. Most intriguingly, NO has also been implicated in the regulation of glucose metabolism (7, 54), raising the possibility that this compound might represent a common link between insulin-regulated blood flow and metabolism. In fact, inhibition of NO synthesis has been shown to reduce exercise-related skeletal muscle glucose uptake in humans (7). During exercise, glucose uptake is mostly dependent on glucose transporter translocation to the plasma membrane (40), and this appears to be the mechanism by which NO mediates exercise-induced glucose uptake in skeletal muscle (2, 54). Interestingly, glucose transporter translocation is also recognized to be rate limiting for myocardial glucose utilization.

Regional distribution of MBF and MGU. To our knowledge, the present study provides the first combined evidence that insulin-stimulated glucose uptake and blood flow are nonuniformly distributed through myocardial regions. Our results extend those of previous studies in that the increase in blood flow was shown to involve the entire circumferential wall of the heart, with a clear predominance of the septum, anterior and lateral territories, and midventricular wall compared with the other long-axis sections. Consistent with other studies (17), the absolute rise in coronary flow was proportionally related to the perfusion gradi-
ent observed throughout the myocardium under fasting conditions, being higher in highly perfused regions and lower in low-flow regions. The degree of heterogeneity of MBF was ~30%, a value that is very similar to that reported (27%) in animal studies (17) and in human skeletal muscle (31%) with the use of PET in combination with H_2^{15}O (51). In agreement with this work, insulin had no impact on this parameter. During hyperinsulinemia, glucose uptake was significantly lower in the inferior and posterior compared with the anterior and lateral wall and the septum in our study. It is of note that, both in the basal state and after insulinization, coronary blood flow was higher in those regions in which glucose uptake was preferentially stimulated. Accordingly, the increase of MBF over basal values appeared to be higher in those same areas (~20% vs. 9%). These findings closely resemble those described in skeletal muscle and suggest that insulin operates to metabolically favor discrete territories of the myocardium in coincidence with their relative hemodynamic dominance. It needs to be mentioned that a lumped constant of 1.0 was used to calculate MGU in the present study. Though it seems very unlikely, the possibility of lumped constant interregional differences cannot be excluded on the basis of the available data.

Physiological and clinical implications. A considerable body of evidence indicates that, on the basis of its architecture and differential patterns of preload and afterload distribution on myocardial walls, the cardiac chamber does not contract in a uniform manner (27, 47). In addition, data supporting variable rates of oxygen consumption and NEFA fluxes across myocardial regions, both basally and after insulin stimulation, have been provided by PET studies of [11C]acetate uptake and clearance within the normal human heart (18, 21). In the present study, plasma insulin concentrations closely resembling those encountered under physiological circumstances induced a significant, albeit small, increment in cardiac blood flow, a marked increment in myocardial glucose consumption, and realignment of blood flow and glucose uptake in such a way that the cardiac areas with higher rates of glucose uptake would be preferentially perfused. The importance of these findings stems from three considerations. First, in defining cut-off guidelines for therapeutic interventions in cardiovascular disease using metabolic parameters (15), interregional differences cannot be discounted. Second, elevations of plasma insulin levels occur repeatedly during the day and coincide with an augmented oxygen demand by peripheral tissues and an increased cardiac workload. Under these circumstances, an absolute upregulation of blood flow would impose further stress on the heart, whereas an optimized regional redistribution of fuel and oxygen in keeping with relative contractile efforts would represent a more efficient adjustment. Third, all states of insulin resistance are typically associated with a high cardiovascular risk. The impairment of insulin action is recognized primarily to affect glucose and lipid metabolism (11), often involving the myocardium (30, 36). Endothelial dysfunction often coexists (38a) and might involve the ability of insulin to regulate blood flow increase and/or distribution. In the heart, the effect of insulin to promote coronary blood flow has been shown to be lost in obese compared with lean dogs (41) and to be absent in patients with type 2 diabetes compared with healthy individuals (32). Studies addressing regional distribution of either function in these populations are lacking. The findings of the present study raise the intriguing hypothesis that an impaired ability of insulin to couple MBF and MGU might impose recurrent efforts on the heart of insulin-resistant individuals throughout everyday life.

In conclusion, the present study documents that insulin increases myocardial blood flow in healthy subjects under noninvasive experimental conditions, the magnitude of response being remarkably variable among individuals. In addition, insulin appears to redistribute glucose uptake and blood flow across different territories of the heart.

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REFERENCES


49. Uren NG, Melin JA, De BB, Wijns W, Baudhun T, and Camici PG. Relation between myocardial blood flow and the


