Transmural distribution of FDG uptake in stunned myocardium

JAMES A. FALLAVOLLITA, CHRISTOPHER TROJAN, AND JOHN M. CANTY, JR.
Department of Veterans Affairs Western New York Health Care System, Buffalo 14215; and the Departments of Medicine and Physiology at the State University of New York at Buffalo School of Medicine and Biomedical Sciences, Buffalo, New York 14214

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Fallavollita, James A., Christopher Trojan, and John M. Canty, Jr. Transmural distribution of FDG uptake in stunned myocardium. Am J Physiol Heart Circ Physiol 279: H102–H109, 2000.—Fasting [18F]fluoro-2-deoxyglucose (FDG) uptake is increased in viable, chronically dysfunctional myocardium, but the relationship to acute episodes of ischemia remains undefined. To investigate FDG uptake in acute stunning, chronically instrumented pigs (n = 9) and sham controls (n = 8) were studied while in a fasted, closed-chest, anesthetized state. One-hour partial occlusion reduced subendocardial flow from 1.24 ± 0.14 to 0.35 ± 0.06 ml · min⁻¹ · g⁻¹ and wall thickening from 16.8 ± 2.1 to 3.7 ± 0.7%. Regional function remained depressed during reperfusion (8.3 ± 1.4%) despite the return of flow to resting levels. Triphenyl tetrazolium chloride staining showed no irreversible injury. FDG uptake in stunned myocardium was variably increased and averaged 1.5-fold higher than that of normal regions, with no consistent transmural variation. Subgroup analysis showed that variability in FDG uptake was related to alterations in insulin levels that varied directly with ischemic risk region.

glycolysis; ischemia; regional blood flow; reperfusion; [18F] fluoro-2-deoxyglucose

CHRONIC ALTERATIONS in fasting [18F]fluoro-2-deoxyglucose (FDG) uptake have been demonstrated in viable, chronically dysfunctional myocardium in humans (8, 14, 18) and pigs (6, 7). These changes are associated with severe coronary artery disease and regional reductions in coronary flow reserve, but their relationship to episodes of acute ischemia is undefined. Although glycolytic flux increases during acute ischemia (16), absolute FDG uptake remains either unchanged or decreases due to reduced delivery (10). Myocardial FDG uptake after resolution of acute ischemia has been measured in isolated hearts (4) and open-chest anesthetized animal preparations (12, 15) with discordant findings. This may be related to differences among animal species, isolated heart versus intact animal preparations, baseline substrate utilization, or background stimulation of glucose uptake. This variation makes the results difficult to compare with hibernating myocardium in human and animal studies.

In support of a potential relation between chronic increases in FDG uptake and acute ischemia is the finding that FDG uptake in individual myocardial samples varies inversely with local coronary flow reserve (7). In addition, FDG uptake in hibernating myocardium varies across the myocardial wall and is threefold higher in the subendocardial layers that are most vulnerable to myocardial ischemia (7). Nevertheless, these observations contrast with studies examining 2-deoxyglucose uptake following acute ischemia produced by brief total coronary occlusions where uptake is relatively uniform in all myocardial layers (20). This difference in transmural distribution between chronic and acute experiments supports the possibility that chronic alterations in FDG uptake may not simply reflect preceding episodes of ischemia. Alternatively, the disparate findings may be secondary to severe levels of flow reduction in all myocardial layers during a total coronary occlusion or from differences between the tracer concentrations used with the FDG technique versus nontracer amounts of deoxyglucose required for nuclear magnetic resonance spectroscopy (which could irreversibly block glycolysis and independently alter uptake).

We designed the present study to determine whether the distribution of FDG uptake during early reperfusion varies in relation to the severity of antecedent ischemia. Studies were conducted using a protocol similar to that used to assess regional variations in FDG uptake in chronically instrumented, closed-chest pigs with chronic hibernating myocardium (7). To circumvent early alterations in FDG uptake that could be secondary to transient changes in FDG delivery during reactive hyperemia or the repletion of glycogen during early reperfusion, we injected FDG after flow returned to baseline levels. A transmural gradient in perfusion during ischemia was produced by a partial coronary occlusion that allowed us to examine the relationship between the level of flow reduction and the subsequent magnitude of FDG uptake in subendocardial and sub-

Address for reprint requests and other correspondence: J. A. Fallavollita, Biomedical Research Bldg., Rm. 347, Division of Cardiology, Dept. of Medicine, University at Buffalo, 3435 Main St., Buffalo, NY 14214 (E-mail: jaf7@buffalo.edu).

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epicardial layers. The results indicate that FDG uptake is increased in stunned myocardium, but the magnitude is less than that found in hibernating myocardium and poorly related to the severity of ischemia.

**METHODS**

All experimental procedures and protocols conformed to institutional guidelines for the care and use of animals in research.

**Chronic instrumentation.** Seventeen farm-bred pigs [47.7 ± 1.8 (means ± SE) kg] were fasted overnight. On the morning of surgery they were premedicated with a mixture of Telazol and xylazine (tiletamine (50 mg/ml), zolazepam (50 mg/ml), and xylazine (100 mg/ml); 0.022 ml/kg im) and given prophylactic antibiotics (cephalothin 50 mg/kg iv and gentamicin 5 mg/kg im). After endotracheal intubation, they were mechanically ventilated, and a surgical plane of anesthesia was maintained with a halothane (1–2%) and oxygen (balance) mixture. A thoracotomy was performed in the fourth left intercostal space. The proximal left anterior descending coronary artery (LAD) was dissected and instrumented with a flow probe and hydraulic occluder. A high-fidelity micromanometer (Konigsberg P6.5 transducer) was secured in the left ventricular apex. Epicardial piezoelectric crystals (Crystal Biotech) were placed on the left ventricular free wall for wall thickening measurements in the LAD perfusion territory and on the posterolateral wall supplied by the circumflex or right coronary artery. Saline-filled catheters were placed in the left atrium and the descending aorta for pressure monitoring and microsphere flow determinations. The chest incision was closed in layers, the intercostal nerves were infiltrated with 2% lidocaine for analgesia, and the pneumothorax was evacuated. A single postoperative dose of antibiotics was repeated after the chest was closed. Intramuscular analgesics (butorphanol 0.025 mg/kg) were given postoperatively and repeated as required to alleviate pain.

**Experimental protocol.** After the animals were fasted overnight, (~16 h), experimental studies were conducted with the animals in a closed-cage, anesthetized state 11 ± 2 days after initial instrumentation. Regional ischemia was induced in nine animals (ischemic); eight animals that were not subjected to ischemia served as sham-operated controls. The animals were sedated with Telazol-xylazine (0.022 ml/kg im), endotracheally intubated, and mechanically ventilated. Anesthesia was maintained with 1–2% isoflurane or halothane and oxygen (balance). In two animals (one ischemic and one sham), anesthesia was maintained with α-chloralose (80 mg/kg loading dose then 30 mg · kg⁻¹ · h⁻¹). A jugular catheter was placed for administration of fluids and FDG. In the event that the left atrial and/or aortic catheters were nonfunctional, an introducer was placed in a carotid artery, and a 7-French catheter was advanced to the aorta or left atrium. Heparin (100 U/kg iv) was given after the completion of instrumentation.

After a 30-min stabilization period, moderate ischemia was produced by partially inflating the LAD occluder to approach regional akinesis (~0% wall thickening) without producing dyskinesia. Regional ischemia was maintained at this level for 60 min, followed by complete release of the occluder. Regional myocardial blood flow was determined using colored microspheres (15 μm diameter, Dye-Trak, Tri-ton) immediately before ischemia, 5 min before reperfusion, and at 15 and ~65 min after reperfusion, using previously published techniques (11). Briefly, microspheres suspended in saline with thimerosal (0.01%) and Tween 80 (0.01%) were sonicated and vortex agitated before injection. Approximately 3 million microspheres labeled with one of up to four different colored dyes (yellow, red, white, and blue) were administered through the left atrial catheter. FDG was administered as a bolus (1–2 mCi iv) ~20 min after reperfusion. FDG was allowed to accumulate for 45 min at which time the final microsphere measurement was performed. In one animal FDG was not administered. Animals were subsequently euthanized by KCl injection, and the heart was rapidly excised for tissue sampling.

The left ventricle was weighed and cut into concentric rings with a midventricular ring used for flow and FDG measurements. Thin rings on either side were stained with triphenyl tetrazolium chloride (1 g in 100 ml of phosphate buffer) to exclude myocardial infarction. The ring used for flow and FDG was divided into 12 circumferential wedges of approximately equal size (4 septal and 8 freewall), and each wedge was subdivided into subendocardial, midmyocardial, and subepicardial samples.

**Analysis of regional perfusion and FDG uptake.** Myocardial samples were placed into tared vials, and FDG activity was quantified by direct measurement of annihilation gamma radiation at 511 keV in a gamma counter (model 1470, EG&G Wallac). Myocardial activity was expressed as counts per minute per gram wet weight of tissue, and all samples were decay corrected to the time of FDG administration. After tissue activity had been quantified, the myocardial samples were frozen at ~20°C for ~48 h to allow the 18F to decay to background. Subsequently, the myocardial tissue samples were thawed, digested in 4 M KOH with 2% Tween 20, and processed using previously published techniques (11). The color dyes were eluted from the microspheres using a measured volume of dimethylformamide, and aliquots were placed in a multiple wavelength spectrophotometer (model U-2000, Hitachi, Tokyo, Japan). Absorbance was measured at the principal absorbance peak of each pure color dye. Corrections for the absorbance from overlapping spectra were performed using a matrix inversion technique (9, 11). Using the absorbance and flow rate of the arterial reference sample and myocardial microsphere absorbance per unit sample weight, we calculated regional myocardial perfusion as follows (9, 11): $Q_{\text{sample}} = \frac{\text{Abs}_{\text{sample}} \cdot Q_{\text{ref}}}{\text{Abs}_{\text{ref}}}$, where $Q_{\text{sample}}$ is the flow (ml · min⁻¹ · g⁻¹) in the tissue sample, $\text{Abs}_{\text{sample}}$ is the absorbance of a given dye eluted from the tissue sample, $Q_{\text{ref}}$ is the reference blood sample withdrawal rate (ml/min), and $\text{Abs}_{\text{ref}}$ is the absorbance of a given dye eluted from the blood reference.

Average values for flow and FDG uptake in the LAD and normal regions were obtained by determining the weighted means for all of the samples within a given region after the perfusion boundaries were determined by analyzing the circumferential distribution of perfusion during ischemia. Border samples between the LAD and the normally perfused regions were excluded. The LAD perfusion territory usually supplied approximately half of the tissue samples. In the sham animals, the weighted average of two samples each from the left ventricular freewall adjacent to the LAD (LAD region) and the posterior descending artery (normal region) were used.

The percentage of the left ventricle subjected to ischemia was estimated in animals with a functional flow probe. Baseline coronary flow (in ml/min) was divided by the baseline full-thickness microsphere flow in the LAD region (in ml · min⁻¹ · g⁻¹) to yield the mass of myocardium at risk for ischemia. This mass was divided by the weight of the left
ventricle to determine the percentage of the left ventricle subjected to ischemia. The mass of myocardium at risk as a percentage of the left ventricle was the same in ischemic versus sham animals (29 ± 4% vs. 28 ± 5%, respectively, P = not significant).

Metabolic substrate and insulin levels. Blood samples for glucose, lactate, free fatty acid, and insulin levels were obtained immediately before the administration of FDG. Enzymatic colorimetric assays were used to quantitate nonesterified fatty acids (NEFA C, Wako Chemicals) and plasma glucose and lactate levels (Sigma Diagnostics). Insulin levels were determined by radioimmunoassay (Biotrak, Amersham International).

Hemodynamic and statistical data analysis. Tracings of all hemodynamic parameters and wall thickness measurements were recorded on a Gould model 2800W recorder and simultaneously displayed on a Gateway 2000 computer (sampling rate, 200 Hz) using the Dataflow Analysis System (Crystal Biotech). Regional myocardial function was assessed as systolic thickening fraction using a single crystal pulsed Doppler probe (Crystal Biotech) as previously described (22). End diastole was determined from the onset of the rapid upstroke of the first derivative of left ventricular (LV) pressure (LV + dp/dt), and end systole was defined as 20 ms before peak LV –dp/dt. Percent systolic thickening was calculated as the ratio of systolic excursion to sample volume depth, multiplied by 100. When both crystals in the LAD region were functional, the more apical crystal was used for measurements. Wall thickening crystals were nonfunctional in the normally perfused region in three animals (2 from the ischemia group and 1 sham) and in the LAD region of one sham animal. Measurements averaged over 15 s were obtained from the digitized data.

All data are expressed as means ± SE. An analysis of variance was used to evaluate changes in hemodynamics, flow, and function over the course of the study, and significant differences were confirmed by paired t-test with Bonferroni correction. An analysis of variance was also used to determine whether there were differences in FDG uptake across the myocardial wall. Differences between the LAD and control region means were determined using a paired t-test. Comparison to sham animals used unpaired t-tests. Statistical significance was defined as P < 0.05.

RESULTS

All animals were in good health at the time of study and had gained weight since the surgical instrumentation. Blood gases averaged values of pH 7.41 ± 0.00, Pco₂ 45.1 ± 1.5 Torr, and Po₂ 495 ± 19 Torr, with an average hematocrit of 0.29 ± 0.01. There were no differences among groups. Control hemodynamics are shown in Table 1. There were no significant differences between the sham and ischemic groups nor were there significant changes in hemodynamics during the experiment in either group.

Table 1. Control hemodynamics and full-thickness perfusion

<table>
<thead>
<tr>
<th></th>
<th>HR, beats/min</th>
<th>SBP, mmHg</th>
<th>MBP, mmHg</th>
<th>LAP, mmHg</th>
<th>RPP, beats min⁻¹ mmHg</th>
<th>Flow, ml min⁻¹ g⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic</td>
<td>94 ± 6</td>
<td>118 ± 5</td>
<td>97 ± 3</td>
<td>13 ± 1</td>
<td>11,100 ± 1,000</td>
<td>1.20 ± 0.13</td>
</tr>
<tr>
<td>Sham</td>
<td>96 ± 7</td>
<td>117 ± 5</td>
<td>93 ± 5</td>
<td>12 ± 2</td>
<td>11,300 ± 1,200</td>
<td>1.09 ± 0.12</td>
</tr>
</tbody>
</table>

Values are means ± SE. HR, heart rate; SBP, systolic blood pressure; MBP, mean blood pressure; LAP, mean left atrial pressure; RPP, rate pressure product (HR × SBP); LAD, left anterior descending coronary artery.

Regional function and transmural flow. Microsphere measurements of full-thickness perfusion under control conditions for the ischemic and sham-instrumented animals are shown in Table 1. There were no significant changes in perfusion over the course of the experiment in sham-instrumented controls or in the normally perfused region of the ischemic animals. Subendocardial flow and wall thickening in the LAD region of ischemic and sham animals are illustrated in Fig. 1. Under control conditions, LAD subendocardial perfusion (Fig. 1A) and wall thickening (Fig. 1B) were similar between ischemic and sham animals. Partially

![Fig. 1](http://alphah.fphysiology.org/10.2307.331.1)
occluding the LAD caused subendocardial flow to decrease to \(0.35 \pm 0.06 \text{ ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}\) and was accompanied by a reduction in wall thickening to \(3.7 \pm 0.7\%\) (20% of initial baseline measurements). Flow returned to control levels 15 min after release of the occlusion and was not different from shams, yet LAD wall thickening remained depressed. There were no significant differences between the perfusion and function measurements obtained during reperfusion (\(\sim 15\) and 65 min after reperfusion); therefore, for clarity only the values acquired 15 min after reperfusion were included in the subsequent results. Staining with triphenyl tetrazolium chloride showed no evidence of myocardial necrosis.

Figure 2 summarizes the transmural distribution of LAD blood flow in ischemic and sham animals under control conditions, during ischemia, and after reperfusion immediately before the FDG injection. Flow in ischemic and sham animals was similar under resting conditions (Fig. 2A) and 15 min after reperfusion (Fig. 2C). However, with partial inflation of the occluder (Fig. 2B), there was a 60% reduction in full-thickness LAD flow during the 1-h period of ischemia. This resulted in a steep transmural gradient in LAD perfusion and a reversal of the normal endocardial-to-epicardial (Endo/Epi) flow ratio from \(1.12 \pm 0.06\) to \(0.48 \pm 0.06\) (\(P < 0.001\)). Flow was reduced below sham values in each myocardial layer.

Transmural FDG uptake in stunned myocardium. The transmural distribution of FDG in excised tissue samples is summarized in Fig. 3. On average, the ischemic LAD region preferentially retained FDG administered following prolonged moderate ischemia. On a full-thickness basis, FDG uptake in the stunned LAD territory relative to the normally perfused region (LAD/normal) averaged \(1.5 \pm 0.2\) in ischemic animals versus \(0.9 \pm 0.1\) in the shams (\(P < 0.05\)). Metabolic substrate levels were similar in stunned and sham animals (Table 2). In individual layers, the relative uptake of FDG varied from 1.6 in the subendocardium to 1.3 in the subepicardium and was significantly increased above shams in each layer. There was a significant correlation between relative FDG uptake and the severity of antecedent ischemia in individual samples [relative FDG uptake = \((-0.69 \times \text{relative flow during ischemia}) + 1.76\), \(P = 0.01\) (\(n = 48\))]. Nevertheless, this relation explained only a small portion of the variability in FDG uptake (\(r^2 = 0.12\)).

Analysis of transmural FDG uptake in individual animals was variable and, as illustrated in Fig. 4, showed two responses. One group demonstrated an approximate twofold increase in FDG uptake in stunned compared with normal myocardium, whereas the other group had uniform FDG uptake that was similar to shams. Ischemic animals with regionally increased FDG uptake had a greater LAD Endo/Epi ratio of FDG activity (\(1.5 \pm 0.2\)) than animals with homogeneous FDG uptake (\(0.9 \pm 0.2\), \(P = 0.07\)), but neither subgroup was significantly different from the LAD Endo/Epi ratio in sham animals (\(1.3 \pm 0.1\)).

We analyzed a number of factors in an attempt to explain the variability of FDG uptake in individual animals. There were no differences in hemodynamics between the two subgroups at any point in the protocol. Metabolic substrate levels were the same with the exception of insulin levels, which were modestly increased among the subgroup of animals with no regional difference in FDG uptake after ischemia (\(0.61 \pm 0.01\) vs. \(0.40 \pm 0.03\) \(\mu\text{g/l}\), \(P < 0.05\)). An explanation for the difference in insulin levels was not readily appar-
ent, but because they were obtained after ischemia and immediately before FDG administration, we examined whether they could have been related to the severity of ischemia or stunning. Although neither the reduction in flow nor wall thickening could explain the variability, the percentage of the left ventricle at risk of ischemia was higher in animals with elevated insulin levels (36 ± 6 vs. 21 ± 4%, *P* < 0.057), and there was a strong correlation between the amount of myocardium subjected to ischemia and insulin levels in individual animals (Fig. 5). When the divergent effects of ischemia on circulating insulin levels were taken into consideration, the relation between relative FDG uptake in individual samples and the severity of antecedent ischemia showed two responses (Fig. 6). In animals with normal fasting insulin levels, there was an inverse relation between flow and FDG uptake [relative FDG uptake = (−1.97 × relative flow during ischemia) + 3.04, *r*² = 0.58, *P* < 0.01]. In contrast, animals with moderately elevated insulin levels after ischemia demonstrated a relatively flat relation between flow and regional FDG uptake [relative FDG uptake = (0.26 × relative flow during ischemia) + 0.81, *r*² = 0.19, *P* < 0.05].

**DISCUSSION**

Our data indicate that on a group basis, acutely stunned myocardium was associated with regionally increased FDG uptake in the fasting state, which is consistent with studies of exercise-induced ischemia in patients with coronary artery disease (2, 13). Acutely stunned myocardium was not associated with a transmural gradient in FDG uptake as we have previously shown in viable, chronically dysfunctional myocardium (6, 7), but increased insulin levels in a subgroup of animals may have confounded this result.

Although FDG uptake was increased in stunned myocardium, the results in individual animals were variable. Subgroup analysis revealed two distinct responses that correlated with the mass of myocardium at risk of ischemia. Animals with a relatively limited volume of ischemic myocardium maintained normal insulin levels and demonstrated regionally increased FDG uptake. In these animals, FDG uptake was inversely correlated with the degree of antecedent ischemia (*r*² = 0.58). In contrast, animals with a greater volume of ischemic myocardium had modestly elevated insulin levels following ischemia thereby stimulating glucose-FDG uptake in the normally perfused remote myocardium.

**Table 2. Metabolic substrate and insulin levels**

<table>
<thead>
<tr>
<th></th>
<th>Glucose, mmol/l</th>
<th>Lactate, mmol/l</th>
<th>Free Fatty Acids, meq/l</th>
<th>Insulin, µg/l</th>
</tr>
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<tbody>
<tr>
<td>Ischemic</td>
<td>6.3 ± 1.2</td>
<td>1.73 ± 0.26</td>
<td>0.28 ± 0.06</td>
<td>0.50 ± 0.04</td>
</tr>
<tr>
<td>Sham</td>
<td>5.4 ± 1.6</td>
<td>1.70 ± 0.35</td>
<td>0.26 ± 0.06</td>
<td>0.44 ± 0.04</td>
</tr>
</tbody>
</table>

Values are means ± SE.
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Relative Ischemic Flow (LAD/Normal)

Fig. 6. Relative FDG uptake (LAD/Normal) in individual samples from the LAD region as a function of relative flow in that sample (LAD/Normal) during partial coronary occlusion. Samples from the four ischemic animals with normal insulin levels and regionally increased FDG uptake were regressed separately from ischemic animals with elevated insulin levels and homogeneous FDG uptake. Samples from sham animals were similarly divided into two groups based on median insulin level. Three LAD samples from each animal (subendocardial, midmyocardial, and subepicardial) are included. Samples from animals with normal insulin levels demonstrated a close, inverse correlation between the level of antecedent ischemia and regionally increased FDG uptake. More severe ischemia resulted in a greater regional increase in FDG uptake. In contrast, samples from animals with elevated insulin levels were more loosely correlated, with more severe episodes of ischemia resulting in modest reductions in regional FDG uptake.

This resulted in a homogeneous distribution of FDG throughout the left ventricle and poor correlation with the degree of antecedent ischemia ($r^2 = 0.19$). These disparate individual responses are consistent with the variability seen in previous animal studies of FDG uptake in stunned myocardium (4, 12, 15).

Relation to previous studies examining FDG uptake after acute ischemia. In fasting humans with coronary artery disease, FDG uptake assessed by positron emission tomography (PET) was increased after exercise-induced ischemia (2, 13). FDG was administered 10 (2) to 30 min (13) after exercise, when perfusion had returned to baseline levels and electrocardiographic S-T segment changes had resolved. Both of these studies demonstrated a 1.4-fold increase in FDG uptake in previously ischemic versus normally perfused remote regions. FDG uptake in the present study reflected a similar time point after resolution of ischemia (~20 min), and ex vivo counting resulted in a similar relative increase in FDG uptake (1.5-fold greater than the remote normal region). Thus the full-thickness results of the present study in closed-chest, anesthetized pigs subjected to moderate ischemia by acute reduction in coronary flow are similar to studies in humans with demand-induced myocardial ischemia.

Despite significant differences in methodology, the average results of the present study are similar to those reported using nontracer levels of 2-deoxyglucose and nuclear magnetic resonance spectroscopy in acutely instrumented open-chest dogs (20). Under control conditions 2-deoxyglucose uptake was increased in the subendocardium with an Endo/Epi ratio of 1.7 ± 0.2. In a separate group of animals, the effects of severe ischemia were assessed with four 5-min repetitive occlusions. This protocol reduced blood flow to levels that have been associated with reduced FDG uptake during acute ischemia (0.05 ml · min$^{-1}$ · g$^{-1}$ in the subendocardium and 0.14 ml · min$^{-1}$ · g$^{-1}$ in the subepicardium) (10). Nevertheless, 2-deoxyglucose uptake assessed after 30 min of reperfusion was increased approximately twofold over control conditions in each myocardial layer. Because of the uniform increase in uptake, there was no significant change in the Endo/Epi ratio (1.59 ± 0.11).

The finding of increased FDG uptake in stunned myocardium has not been uniformly observed, and other animal studies have found FDG uptake following an episode of reversible ischemia to be either unchanged (12) or even reduced (4, 15). Using arterial-venous sampling and open-chest anesthetized pigs, Liedtke et al. (12) demonstrated an increase in glucose oxidation within the first 40 min of reperfusion but no change in the uptake of tracer-labeled 2-deoxyglucose. McFalls et al. (15) found that FDG uptake assessed from PET Patlak analysis was depressed in previously ischemic versus normal remote regions ~60 min after the resolution of ischemia and returned to normal 24 h later. Recently, Doenst and Taegtmeyer (4) compared the uptake of tracer glucose and FDG in isolated, buffer-perfused rat hearts subjected to low-flow ischemia. When substrate availability was limited to glucose or glucose and oleate, ischemia had no effect on glucose oxidation but systematically decreased FDG uptake during the initial phase of reperfusion. Although the time of 2-deoxyglucose administration varied in these studies, they are similar to the range in clinical and experimental studies in which FDG uptake was increased. Interspecies differences are unlikely to be an explanation because increased (present study), unchanged (12), and reduced (15) 2-deoxyglucose uptake have been demonstrated after reversible ischemia in pigs.

An explanation for the variability of FDG uptake in previous studies may be variation in the background stimulation of glucose-FDG uptake in normally perfused reference regions. Despite the conduct of studies in “fasted” animals, studies in which 2-deoxyglucose uptake was unchanged or reduced following ischemia were conducted in acutely instrumented animals and may have been associated with a stimulated state of glucose uptake in the control regions. Before low-flow ischemia, Liedtke et al. (12) found the FDG uptake rate to average ~0.23 μmol · min$^{-1}$ · g$^{-1}$ (corresponding to a reported value of 68 μmol · h$^{-1}$ · g dry wt$^{-1}$). Doenst and Taegtmeyer (4) reported an FDG uptake rate of ~0.40 μmol · min$^{-1}$ · g$^{-1}$ before the onset of low-flow ischemia in rat hearts from fasted animals perfused with glucose and oleate (2.02 μmol · min$^{-1}$ · g dry wt$^{-1}$) (4). McFalls et al. (15) found the rate of FDG uptake to average 0.27 μmol · min$^{-1}$ · g$^{-1}$ in normal myocardium (0.41 μmol · min$^{-1}$ · g$^{-1}$ × lumped constant). These values are all significantly higher than those for fast-
ing FDG uptake in normal myocardium, which has been reported to average 0.05–0.07 μmol · min⁻¹ · g⁻¹ in humans (8, 14) and 0.07 μmol · min⁻¹ · g⁻¹ in pigs (7). Thus, although these previous studies examined fasting animals, the conclusions regarding regional differences in FDG uptake may have resulted from background stimulation of glucose transport in normally perfused regions.

A confounding role related to background glucose stimulation is also supported by the variability that we noted in FDG uptake among individual pigs with stunned myocardium. One subgroup of animals demonstrated an approximate twofold regional increase in FDG uptake. Insulin levels in these animals (0.40 ± 0.03 μg/l) were similar to those in fasted, chronically instrumented animals with hibernating myocardium and regionally increased FDG uptake (0.36 ± 0.02 μg/l) (5). Despite being studied under identical conditions (i.e., the fasted, closed-chest anesthetized state), the other subgroup had higher insulin levels (0.61 ± 0.01 μg/l, P < 0.05 vs. animals with increased FDG uptake) and homogeneous FDG accumulation. An increase in insulin level could not be explained by differences in hemodynamics, regional flow, or regional function. However, regression analysis revealed that the percentage of the left ventricle at risk for ischemia was directly correlated with increased insulin levels. Whereas the increase in insulin levels was modest, it occurred on the steep portion of the myocardial glucose uptake-insulin relation (1) and could increase baseline glucose-FDG uptake in the remote, normal region. Whether differences in insulin levels or the size of the ischemic risk region are the explanation for the disparate results in the literature is uncertain, because these parameters have not been routinely quantified in previous studies.

A similar effect of insulin on the spatial distribution of FDG is seen in hibernating myocardium. Glucose loading (3, 19) increases insulin levels and minimizes the regional increase in FDG uptake observed in fasting humans with hibernating myocardium (8, 14). Maximal stimulation of FDG uptake with insulin clamp techniques (to 0.31–0.53 μmol · g⁻¹ · min⁻¹ in normal regions) actually reverses the fasting differences and results in mildly reduced FDG uptake in hibernating versus normal regions (8, 14). Like the human studies, we recently observed a shift from regionally increased to homogeneous FDG uptake during insulin stimulation in pigs with viable, chronically dysfunctional myocardium (5). Thus, in a situation remarkably similar to the effects following acute ischemia (2, 4, 12, 13, 15), hibernating myocardium can be associated with increased, unchanged, or even reduced FDG uptake compared with normal regions with the pattern depending on the degree of baseline glucose stimulation.

**Methodological limitations.** Although FDG is a clinically useful analog of glucose and an alteration in uptake in reversibly dysfunctional myocardium is clinically relevant, kinetics of FDG uptake are not identical to those of glucose. Importantly, alterations in the relative kinetics of FDG and glucose (lumped constant) may be responsible for regional differences in FDG uptake. Therefore, altered FDG uptake may not reflect changes in glucose uptake or utilization.

Our results did not demonstrate a transmural gradient in FDG uptake in stunned myocardium, which is probably related to ischemia-induced alterations in insulin levels. Our subgroup regression analysis supports the possibility that there is a fairly strong gradient when insulin levels remain at fasting levels (Fig. 6). Further studies will be required to evaluate these relations in detail.

This study does not address the molecular basis for the altered glucose uptake following short-term ischemia. Previous studies have shown that the insulin-sensitive glucose transporter, GLUT4 (and to a lesser extent GLUT1) was translocated to the cell surface during acute ischemia (17, 21). The time course for normalizing GLUT translocation after regional myocardial ischemia is unknown, and persistence of ischemically mediated changes after the resolution of reactive hyperemia may explain the regional increase in FDG uptake. Unfortunately, the use of chronically instrumented animals precluded the rapid tissue sampling required to confirm this hypothesis with localization studies of glucose transporter proteins and glycogen repletion.

In conclusion, FDG uptake was regionally increased in fasted pigs with stunned myocardium, but the response among individual animals was variable. This variability appeared to be the result of modestly increased circulating insulin levels that varied directly with the size of ischemic risk region. Thus a greater mass of ischemic myocardium was associated with increased insulin release, stimulation of glucose-FDG uptake in normally perfused remote regions, and minimization of the relative difference between stunned and normal myocardium. Future study of FDG uptake in stunned myocardium should evaluate catecholamine and insulin levels before and after ischemia and their relation to the size of the ischemic risk region.

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**REFERENCES**

3. **Conversano A, Walsh JF, Geltman EM, Perez JE, Bergmann SR, and Gropler RJ.** Delineation of myocardial stunned...


