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Temporal Changes in Function and Regional Glucose Uptake within Stunned Porcine Myocardium

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This study compared the effects of porcine myocardial stunning on the uptake of [^{18}F]-fluorodeoxyglucose (FDG) at 24 hr and 7 days after reperfusion. Prior studies in animals subjected to severe myocardial ischemia have shown a sustained increase in FDG uptake relative to perfusion (FDG/MBF). The time course of recovery of FDG/MBF relative to function poststunning, however, has not been well characterized. **Methods:** Stunning was induced in eight swine by partially occluding the LAD artery for 20 min. At 1 and 7 days postreperfusion, function was assessed by two-dimensional echocardiography and PET studies were obtained with FDG and either ^{15}O-water or ^{13}N-ammonia. Blood flow by microspheres was determined at baseline, during ischemia and after stunning. Myocardial uptake of FDG relative to blood flow on matching images (FDG/MBF) was calculated for all ROIs and expressed as a ratio of LAD to non-LAD areas. **Results:** After stunning, left ventricular ejection fraction (LVEF) increased from 42% ± 10% on Day 1 to 52% ± 6% on Day 7 ($p < 0.05$). At Day 1, myocardial blood flow was 0.60 ± 0.10 ml/min/g in LAD and 0.67 ± 0.16 in non-LAD regions and neither differed at Day 7. The magnitude of FDG/MBF in the LAD region when normalized to the non-LAD region was 1.29 ± 0.16 on Day 1 and 1.09 ± 0.08 on Day 7 ($p < 0.05$) and was inversely proportional to global measures of LVEF ($r^2=0.61$; $p < 0.005$). **Conclusion:** The severity of postischemic LV dysfunction at 1 and 7 days after stunning correlates with the degree of enhanced regional glucose uptake as estimated by PET. Both normalize within 7 days, suggesting that metabolic and functional abnormalities within completely reperfused myocardium recover in parallel.

Key Words: PET; myocardial stunning; myocardial ischemia; reperfusion injury; glucose uptake; fluorine-18-FDG

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Imaging of the heart with PET can detect underperfused but metabolically active myocardium. Enhanced uptake of the glucose analog [^{18}F]fluorodeoxyglucose (FDG) within hypoperfused regions has been termed a flow-metabolism mismatch and is 70%–80% predictive of the return of regional function after coronary artery revascularization (*1,2*). In patients who have had a recent myocardial infarction, FDG uptake may also be increased within stunned regions, but the return of function occurs primarily within normally perfused segments (*3,4*). Although normalization of blood flow is the primary determinant of functional recovery after stunning, knowledge of the time course of metabolic recovery within reperfused myocardium allows the clinician to assess whether patients with a recent myocardial infarction can tolerate subsequent demands on the heart.

PET studies in animals have identified important temporal changes in myocardial blood flow, glucose uptake and oxygen consumption after severe ischemia and reperfusion. Within stunned myocardium, enhanced glucose uptake relative to blood flow may not be evident immediately after reperfusion but can be detected 24 hr and longer after the ischemic event (*5–7*). Oxygen consumption, as measured by the decay of ^{11}C-acetate and fatty acid utilization using ^{11}C-palmitate, may also be abnormal after ischemia (*8–10*), but, along with function, recovers within 2 wk (*10*). Although there is some evidence that FDG uptake normalizes by 4 wk of reperfusion, the relationship between glucose uptake and function within stunned myocardium has not been well characterized.

Accordingly, the aim of this study was to relate postischemic changes in function with FDG uptake relative to perfusion (FDG/MBF) after 20 min of ischemia. This degree of ischemia is too brief to induce inflammation that could confound the interpretation of enhanced FDG uptake in postischemic regions (*11*). We postulated that the ratio of FDG uptake to perfusion

when normalized to remote areas correlates with the return of function after reperfusion.

MATERIALS AND METHODS

This study was performed under the guidance of the animal care committee at the VA Medical Center and in accordance with the policies adopted by the American Heart Association on research animal use.

Instrumentation and Induction of Ischemia

Following a 12-hr fast, domestic swine of both sexes (31–39 kg) were sedated with intramuscular ketamine (20 mg/kg) and intravenous thiopental (10 mg/kg). They were intubated and mechanically ventilated with a mixture of room air and halothane (0.75%–1.30%). The left neck and thorax were prepped and draped and an incision made to expose the internal jugular vein and carotid artery. 7-Fr. catheters were secured into each vessel and tunneled subcutaneously out the back. The incision was closed in layers and a dressing was applied. A left thoracotomy was performed in the fifth intercostal space and the heart was exposed within a pericardial cradle. A 7-Fr. catheter was placed and secured into the left atrium and tunneled out subcutaneously. The LAD artery was dissected free from its adventitia just distal to the major septal branch and instrumented with an hydraulic occluder and Pulsed Doppler flow probe (20 MHz, 2.5 mm; Instrumentation Development Laboratories, Houston, TX).

By using the hydraulic occluder and the mean Doppler flow recordings, coronary blood flow was reduced by > 80% for a total of 20 min. Transmural myocardial blood flow was determined before and during ischemia by injecting 1–2 million microspheres (15 μ) labeled with ^{141}Ce, ^{113}Sn, ^{103}Ru or ^{95}Nb into the left atrial catheter. Reference arterial blood samples were withdrawn from the arterial catheter at a fixed rate of 10 ml/min, beginning 5 sec before and for 2 min after microsphere injection. After 15 min of reperfusion, when the animal was stabilized, the incisions were closed in layers and sterile dressings applied. Cephazoline (1 g intravenously) was given before and 12 hr following the procedure and repeated daily for 3 days. Gentamicin (80 mg q12 hr intravenously) was added if the pig developed a fever. Pain prophylaxis was provided during the first 3 postoperative days with buprenex (0.5 mg q12 hr; im). Animals were maintained on an ordinary diet of standard chow.

Microsphere blood flows were reinjected 24 hr and 7 days postischemia. At the conclusion of each experiment, the distribution of the postischemic myocardium was identified by injecting methylene blue dye into the left atrium during LAD occlusion and the animal was killed. Hearts were fixed in 10% formalin for at least 48 hr and separated into LAD and non-LAD regions. Each was then divided into three layers of equal thickness (inner, mid and outer) and placed in 1–2-g samples. Myocardial and reference blood samples were counted in a multichannel analyzer and regional blood flows were determined. Plasma for glucose, lactate and free fatty acids were obtained midway through the FDG scan. Glucose and lactate levels were assayed by enzymatic techniques and free fatty acids levels were determined by standard RIA kits.

PET Protocol

Animals were scanned 24 hr and 7 days after ischemia under general anesthesia. PET scans were obtained on a high-resolution scanner, capable of rapid dynamic imaging. The camera consists of 16 contiguous rings of bismuth germanate detectors allowing 31 cross-sectional images of the heart simultaneously recorded in a 10.8-cm axial field of view. Images were reconstructed using a Hanning filter with a cutoff frequency of 0.4 of maximum (0–0.5 scale).

Animals were positioned on the table so that the heart was in the center of the field of view. A 20-min transmission scan was done that provided attenuation of tissue density for the subsequent PET images. Images of myocardial blood flow were obtained with either ^{15}O-water or ^{13}N-ammonia. Oxygen-15-water (40 mCi) was infused intravenously over 20 sec and data were acquired with the following scanning schedule: twelve 5-min, six 20-min, three 40-min frames and one 60-min frame. Myocardial blood flow images were then obtained by summing all 22 frames and subtracting the scaled blood volume image. The latter was determined by summing the initial 9 frames over 45 sec, which was the time that the tracer by time-activity curves existed primarily in the blood pool (*6*). In those animals receiving ^{13}N-ammonia, a 15-min emission scan was obtained 6 min after an intravenous infusion of 10 mCi.

Twenty-five grams of dextrose were infused intravenously approximately 1 hr before the FDG scan. After decay of the blood flow tracer (~5 half-lives), [^{18}F]FDG (5 mCi) was infused over 20 sec and dynamic scanning acquired with the following protocol: twelve 10-min, six 30-min, four 60-min, three 120-min, three 300-min frames and one 600-min frame. At the conclusion of the dynamic FDG images, a 20-min gating image was acquired with eight separate intervals.

Data Analysis

ROIs from the myocardium were selected from eight to ten planes of the final frame of the FDG scan (primarily myocardial image). Based on the initial visual inspection of the LAD artery and its branches and the gated FDG image 24 hr later, 10–15 circular-tissue ROIs (~2-mm diameter) were drawn within each of the LAD and non-LAD regions. Placement of the ROIs remained in the same relative positions for the 24-hr and 7-day scans.

A flow-metabolism ratio was determined for the LAD and non-LAD regions. For each ROI, the amount of tracer uptake (counts/pixel) within the last frame of the FDG image was divided by the amount of tracer uptake (counts/pixel) from the matching myocardial blood flow image. By using the same ROIs for the two images, errors due to differences in partial volume effects between myocardial regions were minimized. The average ratio of FDG/MBF in the LAD region was then divided by the average ratio of FDG/MBF in the non-LAD region and expressed as a ratio. This value represents the amount of FDG retention normalized to perfusion in the anterior wall compared with remote areas.

Myocardial Function

Two-dimensional echocardiograms were performed 24 hr and 7 days after ischemia. Data were recorded on tape from the right parasternal and apical views. Regional wall thickening was determined at the mid portion of the parasternal short axis view and analyses performed in the anterior (LAD) and posterior walls (non-LAD). Wall thickening was computed as the differences in wall thickness between end-systole and end-diastole and expressed as a percent of end-diastolic thickness. Ejection fraction was computed from differences in LV size between end-diastole and end-systole and expressed as a percentage of end-diastole. The end-diastolic and end-systolic frames were defined as the onset of the qrs and the frame with the smallest chamber size, respectively (Fig. 1).

Statistical Analyses

Results are expressed as arithmetic means ± s.d. Differences in myocardial blood flows and regional function between LAD and non-LAD regions at the two reperfusion times were tested with Student's t-test and Bonferroni correction ($p < 0.025$ was considered significant). Differences in ejection fraction and flow-metabolism ratio at 24 hr and 7 days postischemia were compared with

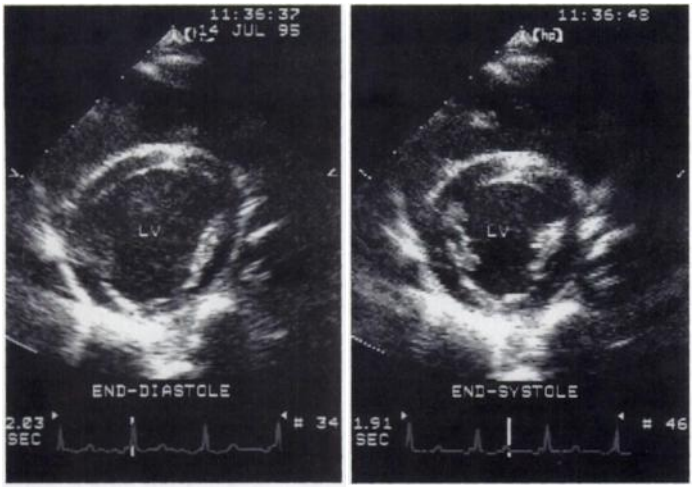

FIGURE 1. These two-dimensional echocardiographic images from one pig were obtained from the right parasternal short-axis view at end-diastole and end-systole. Measures of regional and global LV function were obtained below the mitral valve at mid ventricle.

Student's t-test. Differences were considered statistically significant at the $p < 0.05$ level.

RESULTS

Eight animals underwent the ischemia-reperfusion protocol without ventricular fibrillation and comprise the study group. One animal demonstrated minimal FDG uptake on Day 1 but good quality images on Day 7. Another animal died on Day 3 and did not receive a late scan. Therefore, seven FDG studies were performed on Days 1 and 7 poststunning.

Induction of Ischemia

Before ischemia, mean arterial blood pressure was 70 ± 6 mmHg and decreased to 58 ± 11 mmHg during ischemia ($p < 0.05$). Over the same period, heart rate increased slightly from 81 ± 13 bpm to 83 ± 17 bpm (ns). Before ischemia, myocardial blood flow by radiolabeled microspheres was 0.81 ± 0.33 ml/min/g and 0.77 ± 0.27 ml/min/g in the LAD and non-LAD regions, respectively. During ischemia, myocardial blood flow was reduced to 0.09 ± 0.08 in the LAD region ($p < 0.05$ compared with pre-ischemia) and 0.51 ± 0.17 ml/min/g in the non-LAD region ($p < 0.05$ compared with pre-ischemia). The decreased blood flow in remote regions was a result of the decreased blood pressure during ischemia.

Myocardial Blood Flow and FDG Uptake Postreperfusion

Twenty-four hours following ischemia, mean arterial blood pressure was 79 ± 7 mmHg and heart rate was 107 ± 32 bpm; and neither differed from values obtained 7 days later. Plasma substrates and myocardial blood flows are shown in Table 1 and demonstrate no differences between the two reperfusion days.

TABLE 1
Plasma Substrate and Regional Myocardial Blood Flow 1 and 7 Days Poststunning

	Plasma substrate			Myocardial blood flow	
Day	Glucose (μmole/ml)	Lactate (μmole/ml)	FFA (ng/μl)	LAD (ml/min/g)	Non-LAD (ml/min/g)
1	4.2 ± 2.4	0.99 ± 0.28	67 ± 65	0.60 ± 0.10	0.67 ± 0.16
7	5.5 ± 4.2	0.96 ± 0.21	55 ± 15	0.74 ± 0.15	0.78 ± 0.15

n = 7; mean ± s.d.; myocardial blood flow by radiolabeled μ spheres; FFA = free fatty acids.

The ratio of FDG uptake to blood flow on matching images was obtained for the LAD region and expressed as a ratio of the non-LAD region at the two time points. Figure 2 shows matching images of myocardial blood flow (MBF) and FDG from one pig after stunning. In this animal, FDG uptake in the LAD distribution was higher than perfusion, at a time that a severe wall motion abnormality was observed. The extent of enhanced FDG/MBF in the LAD region when normalized to remote areas is shown for all animals at 1 and 7 days postreperfusion (Fig. 3). Although seven measurements were available at both time points, only six animals had paired measurements. The ratios at Days 1 and 7 were 1.29 ± 0.16 and 1.09 ± 0.08, respectively, which, by paired Student's t-test, was significant ($p = 0.07$). When independent Student's t-test was used, however, the differences with all measurements were $p < 0.01$.

Myocardial Function Postreperfusion

Table 2 summarizes the effects of ischemia and reperfusion on global and regional measures of left ventricular function. Regional wall thickening in the LAD region remained lower than remote regions at 24 hr postischemia and normalized by 7 days. LVEF was also depressed at 24 hr following ischemia compared with 7 days (Fig. 4).

To relate changes in glucose uptake with function poststunning, the ratio of FDG/MBF in the LAD region (normalized to non-LAD region) was compared with LV ejection fraction at 24 hr and 7 days after ischemia. Combining all data from each time point, a significant inverse relationship was observed between relative FDG uptake and LV function ($r^2=0.61$; $p < 0.005$) (Fig. 5).

DISCUSSION

The findings from this study are compatible with the results of others, who have shown that FDG uptake is persistently increased relative to perfusion within postischemic myocardium (*6–8,12*). The principal new finding is that a significant inverse relationship exists between the extent of the glucose abnormalities and left ventricular function. Because the design of this study used only 20 min of ischemia, estimates of glucose uptake, perfusion and function could be assessed within purely stunned myocardium. Previous studies in dogs showed that the

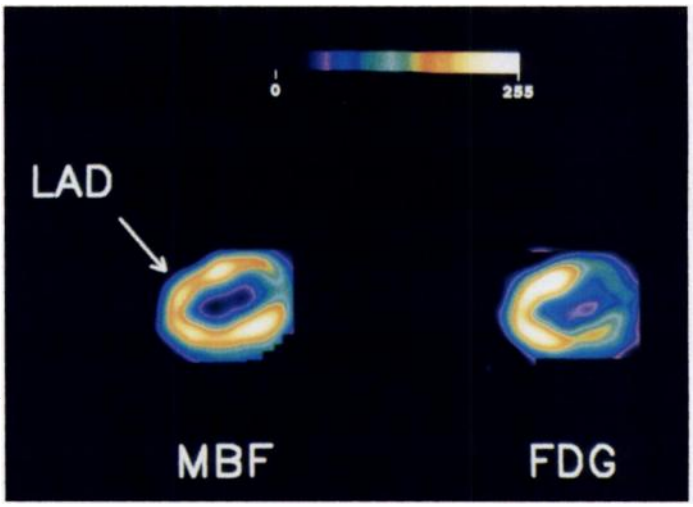

FIGURE 2. These matching images of myocardial blood flow (MBF, ^{13}N-ammonia) and FDG were obtained in one of the pigs after severe stunning. The animal is lying on its right side and the projections are directed cephalad. A sustained increase in FDG uptake relative to perfusion was observed in the postischemic LAD region. The appearance of decreased perfusion most likely represents some partial volume effects in the thinner stunned regions.

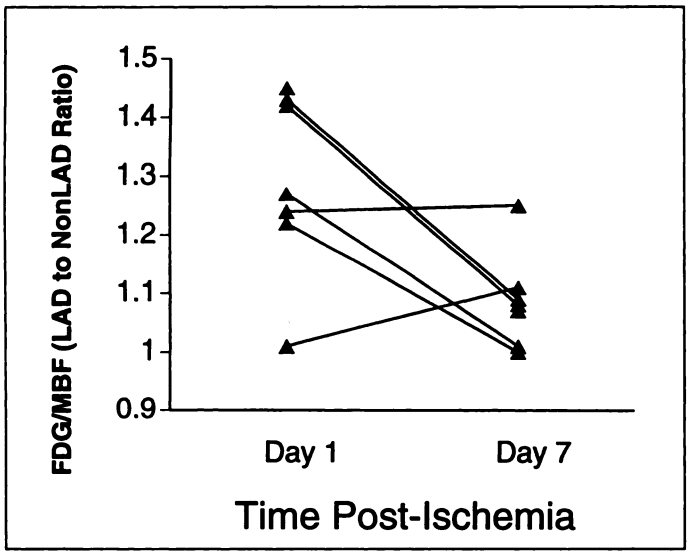

FIGURE 3. Relative estimates of glucose uptake were obtained from the average values of FDG/MBF in the LAD region and expressed as a ratio of the average values from the non-LAD territory. The ratios at Days 1 and 7 after ischemia were 1.29 ± 0.16 and 1.09 ± 0.08, respectively. (n = 8; one animal died before Day 7 and another had no FDG uptake on Day 1; thus, paired values were available in six pigs).

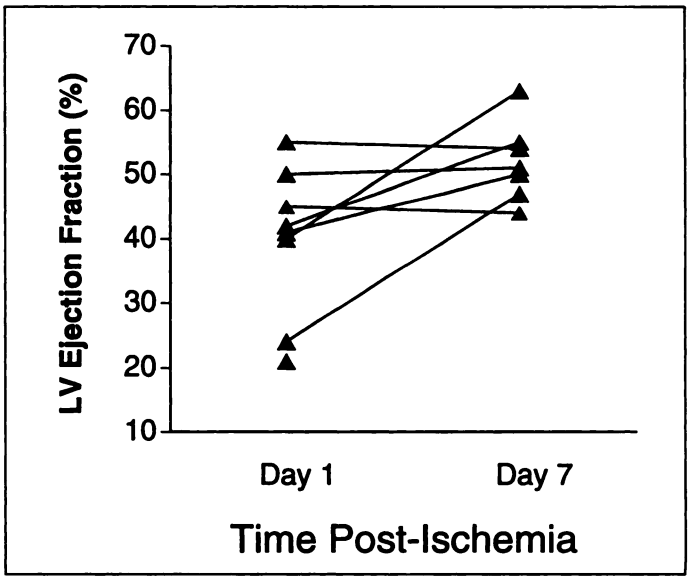

FIGURE 4. Two-dimensional echocardiography measurements of LV function were obtained from the right parasternal short axis view in the mid ventricle. Ejection fraction was 42% ± 10% on Day 1 and increased to 52% ± 6% on Day 7 ($p < 0.05$). (n = 8; one animal died before Day 7; thus, paired values were available in seven pigs).

ratio of FDG uptake to blood flow within viable reperfused myocardium normalized within 4 wk, although fractional shortening in the postischemic region remained depressed (*8*). It is likely that the prolonged period of ischemia in that study (3 hr) resulted in incomplete recovery of regional function in the perinfarct zones, making it difficult to correlate return of function with glucose metabolism.

Clinical Significance of Increased FDG Relative to Flow

In patients with severe obstructive coronary artery disease, the presence of a flow-metabolism mismatch (i.e., enhanced FDG uptake within hypoperfused myocardium) has important implications for therapy. In patients who have undergone successful coronary artery revascularization, it not only predicts recovery of regional function (*1,2*) but also correlates well with improved functional status (*13*). Of equal significance, the presence of such a flow-metabolism mismatch portends a poor prognosis on long-term follow-up in medically treated patients (*14,15*). This suggests that persistently increased FDG uptake within hypoperfused myocardium signals the presence of viable myocardium at risk for subsequent ischemia.

Within stunned but viable myocardium, glucose uptake may be increased relative to blood flow but the latter should normalize after ischemia. Accordingly, PET imaging with tracers of glucose and perfusion may be an important way of risk-stratifying individuals with a recent myocardial infarction. In one study of 17 patients treated with thrombolytics, five demonstrated normal perfusion within the infarct zone and all had improved function on late follow-up (*3*). Of six patients with decreased perfusion and enhanced FDG uptake in this study, only one was found to have functional recovery. These data suggest that individuals with a flow-metabolism mismatch after a myocardial infarction have not only stunned myocardium but also have chronic ischemia with a high probability of future cardiac events. The results of the present study are compatible with previous work in that the return of blood flow within reperfused myocardium prognosticates recovery of function on follow-up. The enhanced FDG uptake relative to perfusion in the present study is a marker of the extent of the prior ischemic burden and is most likely a result of glycogen repletion and lactate production (*12*). On the basis of our results, abnormalities in glucose uptake within stunned myocardium correlate with the severity of the wall motion abnormality after reperfusion and both recover in parallel.

TABLE 2
Global and Regional Myocardial Function 1 and 7 Days Poststunning

Day	Ejection fraction (%)	Wall thickening-LAD (%)	Wall thickening-non-LAD (%)
1	42 ± 10*	15 ± 8*	29 ± 12
7	52 ± 6	24 ± 4	29 ± 6

*$p < 0.05$ versus Day 7.
n = 7; mean ± s.d.

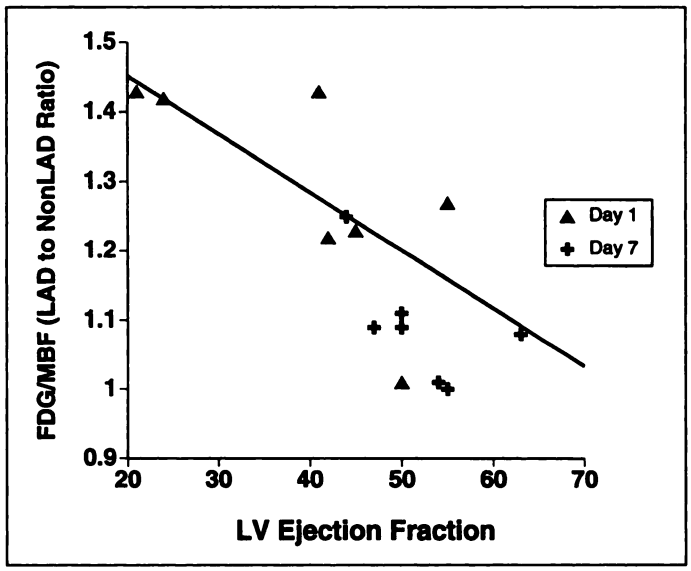

FIGURE 5. These data show the relationship between regional FDG uptake and LV function at 1 and 7 days after reperfusion. The extent of the relative increase in glucose uptake in the postischemic region was inversely proportional to left ventricular ejection fraction ($r^2=0.61$; $p < 0.005$).

Oxidative Metabolism within Reperfused Myocardium

Within postischemic but viable myocardium, oxygen consumption may be reduced but disproportionately less than the degree of myocardial dysfunction (*16–18*). Both return to normal within 2 wk of severe ischemia, which suggests that postischemic recovery of function and metabolism occur simultaneously (*10*). In patients with a recent myocardial infarction, oxidative metabolism as measured by the clearance of ^{11}C-acetate correlates with the increase in FDG uptake and is predictive of the recovery of regional function. It also identifies those patients with significant coronary artery disease and reduced function who show improved function with revascularization (*19,20*). The enhanced glucose uptake relative to oxygen consumption after ischemia does not necessarily indicate that reperfused myocardium is more dependent upon glucose for its energy supply. On the contrary, fatty acid utilization remains the preferred substrate for ATP production after reperfusion (*21*) while the enhanced glucose metabolism is primarily nonoxidative (*12*).

Methodological Considerations

In this study, relative measurements of myocardial glucose uptake in the postischemic area are presented rather than absolute measurements based on Patlak analysis. Because of differences in partial volume effects between stunned and remote regions, a greater underestimation of glucose uptake in the stunned regions would be expected when using tracer kinetic models. By using matching images of perfusion and FDG, we can minimize the effects of differences in wall thickness. In this study, FDG/MBF ratios from the LAD region were normalized to values obtained from remote regions, which should approximate the relative increment in glucose uptake within stunned regions. Although two-dimensional echocardiography measurements from the midventricle could theoretically approximate mean differences in wall thickness, any derived correction factor would likely underestimate differences in partial volume from the distal LAD region including the apex.

A potential limitation of FDG studies with PET is based on the assumption that ischemia and reperfusion does not alter the factor relating transport and phosphorylation of glucose and deoxyglucose (lumped-constant). It is clear that variable levels of substrate can alter this constant which would confound the interpretation of absolute estimates of glucose metabolism (*22*). Although it is unknown in vivo whether regional myocardial differences in the lumped-constant can be induced after ischemia, evidence from isolated rat hearts suggests that it does not occur (*23*).

CONCLUSION

Within severely stunned myocardium, a sustained increase in FDG uptake relative to perfusion is observed 24 hr following ischemia and is inversely proportional to the severity of left ventricular dysfunction. Both abnormalities recover in parallel by 7 days, which suggest that the return of function after complete reperfusion correlates with recovery of glucose uptake.

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