Assessment of thallium-201 redistribution versus glucose uptake as predictors of viability after coronary occlusion and reperfusion

JACQUES A. MELIN, M.D., WILLIAM WUNS, M.D., ANDRÉ KEYEUX, M.D., OLIVIER GURNÉ, M.D., MICHEL COGNEAU, PH.D., CHRISTIAN MICHEL, PH.D., ANNE BOL, PH.D., ANNIE ROBERT, M.S., ANDRÉ CHARLIER, M.D., AND HUBERT POULEUR, M.D.

With the technical assistance of Henri Van Mechelen

ABSTRACT Both $^{201}$Tl redistribution and persistent glucose uptake have been proposed as markers of viability after reperfusion. In the present study, they have been compared in the same open-chest canine preparation of occlusion and reperfusion. Ten fasting dogs were subjected to 2 hr of left anterior descending coronary artery occlusion and 4 hr of reperfusion. Myocardial blood flow was determined by a microsphere technique 100 min after occlusion and 3 hr after reperfusion. $^{201}$Tl was injected intravenously 20 min before reperfusion. Serial biopsy samples were obtained from ischemic and normal areas. $^{18}$F-2-deoxyglucose, a tracer of exogenous glucose uptake, was injected 3 hr after reperfusion. Thirty minutes before the animals were killed, simultaneous blood samples were taken from the femoral artery and the regional coronary veins draining the reperfused and the remote areas. Dogs were killed 4 hr after reperfusion was established. Area at risk was assessed by dye injection in vivo and area of necrosis by triphenyl tetrazolium chloride (TTC) staining, with confirmation by electron microscopy. Immediately after death, endocardial and epicardial samples were taken from regions characterized as risk regions, areas of necrosis, areas of patchy necrosis, and normal areas. These samples were counted in a scintillation well counter. Four hours after reperfusion, in ischemic myocardium (TTC positive) the relative $^{201}$Tl gradient between ischemic and normal regions was 26 ± 13%, whereas in necrotic samples, this gradient was 71 ± 26%. The metabolic rate for glucose measured with $^{18}$F-2-deoxyglucose was low in endocardial and epicardial necrotic samples (1.18 ± 0.74 mg/min/100 g) as compared with that in the ischemic and normal samples (respectively, 3.04 ± 1.92 and 3.85 ± 2.31 mg/min/100 g). Oxygen consumption of the reperfused zone measured by regional arteriovenous oxygen difference was smaller than the oxygen consumption of the normal zone, while glucose consumptions were similar. In summary, delayed redistribution of $^{201}$Tl injected before reperfusion is an indicator of viable myocardium. Depressed glucose uptake indicates irreversible injury, while normal $^{18}$F-2-deoxyglucose uptake is associated with viable tissue; this was observed as early as 4 hr after reperfusion.


ACUTE MYOCARDIAL INFARCTION represents a dynamic event involving progression from reversible ischemic injury to cell death.¹ Autopsy studies have confirmed, as previously shown in animal preparations, the heterogeneity of tissue injury and the coexistence of viable and necrotic tissue in the area of segmental blood flow reduction.² Since the advent of techniques for early restoration of myocardial blood flow after acute myocardial infarction, tests able to differentiate viable from infarcted tissue have become of major clinical value. Previous experimental and human data have shown that both the study of membrane function with use of $^{201}$Tl and the detection of residual metabolic activity could be used as potential indicators of myocardial viability. First, initial $^{201}$Tl uptake imaging was proposed for the early assessment of myocardial salvage.⁴–⁸ However, $^{201}$Tl has been shown to be taken up by reperfused nonsalvaged
myocardium. Thus, it appears that initial myocardial $^{201}$TI uptake can be nearly normal after reperfusion, despite the presence of infarction. The kinetics of myocardial $^{201}$TI uptake and clearance after reperfusion has also been studied after reperfusion in an experimental preparation with use of implanted radiation detectors. In these experiments, $^{201}$TI clearance was faster from reperfused nonsalvaged myocardium. Additionally, a study of Granato et al. has shown that, when $^{201}$TI was given during coronary occlusion, $^{201}$TI gradients between normal and ischemic zones after 2 hr of reperfusion were significantly lower than the gradients measured during coronary occlusion. These two latter experimental studies suggest that delayed redistribution of $^{201}$TI over 2 or 4 hr could be used as a potential indicator of viable myocardium.

Another attractive approach that may allow distinction between reversibly and irreversibly injured ischemic myocardium is the detection of residual metabolic activity by means of labeled carbohydrates or fatty acids. Previous animal experiments have demonstrated that metabolic imaging with positron-emission tomography can differentiate reversible from irreversible tissue injury after transient ischemia. Reversible tissue injury revealed enhanced glucose utilization relative to blood flow, whereas blood flow and glucose utilization were decreased concordantly in the presence of irreversible tissue injury. In reperfused canine myocardium studied 24 hr after reperfusion, regional increases in glucose utilization identified myocardium with little histologic evidence of necrosis and delayed recovery of contractile function. Also, in patients with acute myocardial infarction studied within 72 hr of onset of symptoms, positron-emission tomography revealed a high incidence of residual viable tissue in ventricular segments with reduced flow and impaired function.

The purpose of this study was thus to compare $^{201}$TI redistribution and $^{18}$F-2-deoxyglucose (FDG) uptake in canine myocardium as early as 4 hr after reperfusion to examine the respective values of these tracers as markers of viability. To avoid ambiguous interpretation, results have been referred to direct measurements under comparable conditions and validated by in vitro and histochemical techniques.

**Methods**

**Animal preparation.** Ten adult mongrel dogs weighing 19 to 27 kg were studied after a 12 hr overnight fast. The dogs were anesthetized with sodium pentobarbital (30 mg/kg), intubated, and ventilated with room air (Harvard respirator). Morphine sulfate (1 mg/kg im) was given at induction and throughout the remainder of the experiment to maintain adequate anesthesia. The heart was exposed through a left thoracotomy and suspended in a pericardial cradle. Catheters were inserted into the left atrium and descending aorta. One pair of crystals, used to measure segmental shortening, was inserted through small scalpel incisions into the midmyocardium in the area to become ischemic. These crystals were positioned perpendicular to the major axis of the heart, at a separation of 10 mm. All dogs were subjected to an occlusion of the left anterior descending coronary artery with an atrumatic vascular clamp. In five dogs, before the complete occlusion, coronary artery constriction was produced distal to the clamp location; this was performed by encircling the coronary vessel by a 4 to 5 mm long plastic cylinder that was split so that the coronary artery could be slipped into its lumen. The area of the lumen of the cylinder was then progressively reduced by tying sutures inserted on both sides of the split. This ligature was progressively tightened until an alteration in segmental shortening was observed; the ligature was then slightly released until control shortening was restored. This degree of stenosis was maintained to provoke a slow reflow at the time of reperfusion. In these five dogs, the partial stenosis was maintained throughout the entire experiment.

**Experimental protocol.** A summary of the experimental protocol is outlined in figure 1. All dogs were pretreated with lidocaine. The left anterior descending coronary artery was occluded for 2 hr. Two dogs fibrillated and were defibrillated during occlusion, before injection of any tracers. These dogs had the largest infarcts (infarct region/risk region: 100% and 45%). Microspheres were injected into the left atrium at 100 min after occlusion, and immediately after the withdrawal of the reference.

![FIGURE 1](http://circ.ahajournals.org/DownloadedFrom/figure1.jpg) Experimental protocol. Biopsies were performed at 115 min after occlusion (10 min after $^{201}$TI injection), and at 2 hr and 4 hr after reperfusion. Bx = biopsy; LAD = left anterior descending coronary artery; EM = electron microscopy.
blood sample, 500 μCi ²⁰¹Tl was injected intravenously. Ten minutes later, transmural biopsy samples were taken from both ischemic and normal myocardium in vivo with a Travenol Trucut needle. Five minutes later, the occlusive vascular clamp was suddenly released; five dogs underwent rapid reperfusion, while five others underwent slow reperfusion through a persistent stenosis. No dogs fibrillated after reperfusion. Biopsy samples were obtained at 2 hr after reperfusion. Myocardial blood flow was determined 180 min after reperfusion. Thereafter, 6 to 8 mCi of FDG was injected intravenously and an arterial input function was obtained by rapid arterial sampling. Thirty minutes before the animals were killed, arterial and regional coronary venous samples were taken for the measurement of oxygen content, glucose, lactate, and free fatty acids. A third set of biopsy samples was taken 4 hr after reperfusion, just before death. Immediately thereafter, the left anterior descending artery was occluded with a snare, blue dye was injected into the left atrium, and the heart was arrested with concentrated KCl solution.

Postmortem tissue preparation. After death of the animals, the heart of each was excised and the ventricles were sectioned parallel to the atrioventricular groove, forming five slices 1 to 1.5 cm thick. Tissue specimens were immediately excised, with a scalpel, from the center and the lateral portion of the area at risk and from the nonischemic (blue-stained) region for examination by electron microscopy. One endocardial sample and one epicardial sample were taken from each of the three regions, making a total of six samples per heart. Thereafter, the basal surfaces of the heart slices and margins of the areas at risk were traced onto acetate sheets. Biopsy sites were identified on the sheets. In nine dogs, the biopsy samples obtained in vivo from the area at risk were identified as not necrotic on the postmortem slice. The slices were weighed and then placed in a solution of triphenyl tetrazolium chloride (TTC) at 37° C for 30 min. After TTC staining, sampling sites previously taken for electron microscopy within the area at risk were identified as being necrotic (TTC−) or ischemic (TTC+). Endocardial and epicardial sampling for regional myocardial blood flow and for ²⁰¹Tl and ¹⁸F activity was made in the center of the infarct (TTC−), in ischemic but noninfarcted tissue (area unstained by blue but TTC+), and in the nonischemic muscle. Ischemic samples were cut to avoid contamination by the nonischemic tissue and by the necrotic area. Necrotic samples were subdivided into homogenous, confluent areas of necrosis and patchy necrosis. Samples were weighed and counted in a scintillation well counter at appropriate energy windows.

The size of myocardial infarcts and areas at risk were measured planimetrically. The fractions of total left ventricular area representing the area at risk and the infarcted tissue were multiplied by the weight of each left ventricular slice to obtain the percentage, by weight, of total left ventricle that was infarcted and at risk. Microspheres (15 ± 1 μm) were labeled with ⁸⁵Sr, ⁶⁹Nb, or ¹³¹Sn. Myocardial blood flow was calculated with the equation: Qm = (Cm × R)/Cr, where Qm = myocardial blood flow (ml/min); Cm = tissue counts (counts/min); R = reference arterial blood flow (ml/min); Cr = counts in reference blood sample. Flow per gram of myocardium was calculated by dividing blood flow by the sample weight. To account for the different scatter fractions and half times, all samples were counted three times: on the day of the experiment, and 24 hr and 3 weeks later. A multichannel analyzer was used with the following windows: ¹³¹Sn, 60 to 1079 keV; ²⁰¹Tl, 40 to 100 keV; ⁸⁵Sr, 500 to 580 keV; ⁹⁵Nb, 735 to 835 keV; ¹³¹Sn, 375 to 425 keV. A computer program was used to correct for activity overlap between the energy windows. The rate of exogenous glucose utilization was calculated applying the FDG model described by Sokoloff et al. ¹⁸ Fixed values for the four rate constants and a lumped constant of 0.67 were used to calculate the glucose metabolic rate in myocardial tissue (expressed in mg/min/100 g).¹⁹, ²⁰ Samples obtained for electron microscopic examination were classified as showing cell death or cell injury without definite evidence of cell death. The criteria for injured cells were sub-sarcolemmal blebs, separation and disruption of sarcomeres, and mitochondrial swelling. Criteria for cell death included amorphous matrix densities in mitochondria, disruption of the mitochondria, and marked clumping of nuclear chromatin along the nuclear membrane.¹

Data analysis. Myocardial ²⁰¹Tl time activity curves were calculated with results of the serial biopsies. ²⁰¹Tl activity was expressed as percent of the initial normal ²⁰¹Tl activity as measured in the initial biopsy sample obtained in the normal region, supplied by the circumflex artery. Myocardial blood flows and tracer activities in ischemic and infarcted samples were normalized by dividing these values by the nonischemic zone activity in the corresponding left ventricular ring.

Percent segment shortening was calculated from the formula:

\[
\text{% segmental shortening} = \left( \frac{\text{end-diastolic length} - \text{end-systolic length}}{\text{end-diastolic length}} \right) \times 100
\]

End-diastolic length was defined as segmental length at the peak of the R wave, and end-systole was taken at the dicrotic notch of the aortic pressure tracings.

Regional substrate consumption was determined with use of the Fick principle. The chemical substrate concentrations were measured in the regional coronary veins corresponding to the nonischemic myocardium and to the reperfused myocardium. The chemical extraction ratio (percent) for a given substrate was calculated from the arteriovenous difference divided by the arterial concentration. The substrate consumption was determined as the product of the arteriovenous difference and the microsphere-determined regional flow. The regional ratio of oxygen supply to consumption was determined as the ratio SaO₂/(SaO₂ − SvO₂), where SaO₂ and SvO₂ are the arterial and venous oxygen saturations. ²² Oxygen contents were determined using a Læ-O₂-VCON analyzer. Lactate, glucose, and fatty acids were measured by enzymatic methods. ²²

All results are expressed as the mean ± SD. The mean values of flow and tracer activities for each animal within each group were used as individual data points in the analysis of variance for all animals, despite the fact that a different number of samples was obtained in each animal. Statistical analysis of changes in the studied variables were computed by analysis of variance for repeated measures (BMDP statistical package).

Results

Hemodynamic data, By 100 min after occlusion, at the time of the first microsphere injection, mean heart rate was 131 ± 27 beats/min, not different than the control values (139 ± 25 beats/min), and mean aortic pressure was slightly decreased (114 ± 32 mm Hg) compared with the preocclusion pressure (124 ± 20 mm Hg; p < .05). Mean segmental shortening was −1 ± 5% during occlusion, while control shortening was 20 ± 8% (p < .001).

Three hours after reperfusion, a small decrease in heart rate (119 ± 29 beats/min) was observed and mean aortic pressure was similar to that before occlusion (123 ± 37 mm Hg). Segmental shortening improved but remained severely depressed (4 ± 4%).

Infarct size and myocardial blood flow. Despite a similar risk region size, the two groups of dogs, those under-
TABLE 1
Infarct size and myocardial blood flow

<table>
<thead>
<tr>
<th></th>
<th>Abrupt reflow (n = 5)</th>
<th>Slow reflow (n = 5)</th>
<th>All dogs (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk region/left ventricle (%)</td>
<td>21 ± 5</td>
<td>22 ± 6</td>
<td>22 ± 5</td>
</tr>
<tr>
<td>Necrotic region/risk region (%)</td>
<td>49 ± 30</td>
<td>11 ± 11^a</td>
<td>30 ± 29</td>
</tr>
<tr>
<td>Necrotic region/left ventricle (%)</td>
<td>10 ± 7</td>
<td>3 ± 3^a</td>
<td>7 ± 6</td>
</tr>
<tr>
<td>Myocardial blood flow during occlusion (%)</td>
<td>Ischemic area (TTC +) 36 ± 24</td>
<td>43 ± 19</td>
<td>41 ± 20</td>
</tr>
<tr>
<td></td>
<td>Patchy necrosis       8 ± 5</td>
<td>23 ± 7^a</td>
<td>18 ± 10</td>
</tr>
<tr>
<td></td>
<td>Necrosis (TTC −)       4 ± 4</td>
<td>10 ± 1^a</td>
<td>5 ± 4</td>
</tr>
<tr>
<td>After reperfusion (%)</td>
<td>Ischemic area (TTC +) 77 ± 16</td>
<td>88 ± 17</td>
<td>84 ± 17</td>
</tr>
<tr>
<td></td>
<td>Patchy necrosis       98 ± 25</td>
<td>92 ± 36</td>
<td>94 ± 38</td>
</tr>
<tr>
<td></td>
<td>Necrosis (TTC −)       66 ± 45</td>
<td>83 ± 20</td>
<td>73 ± 65</td>
</tr>
</tbody>
</table>

^a p < .05 vs abrupt reflow.

going abrupt and slow reflow, appeared to have different infarct sizes (table 1). However, this difference in ultimate infarct size can be explained by less residual myocardial blood flow during occlusion in the ischemic and necrotic areas of the group undergoing abrupt reflow. Three hours after reperfusion, the degree of restoration of flow was comparable in the two groups of dogs. Heart rate, mean aortic pressure, and mean segmental shortening were similar in the two groups of dogs, both during occlusion and after reflow (table 2). In the subsequent presentation of results, the data on the two groups of dogs have been pooled together because no differences in terms of tracer concentrations and metabolic rates for glucose were observed in the two groups of dogs.

The range of the infarct region/risk region ratios was large (table 1). Two dogs had no infarcts at all, and one dog had a 100% infarct.

Myocardial 201TI activity. 201TI redistribution was assessed both by the 201TI activity curves of normal and ischemic tissue obtained by biopsy, and by the relative 201TI gradient between normal, ischemic, and necrotic regions after death (at 4 hr after injection).

The myocardial 201TI time-activity curves from the tissue obtained in the ischemic and normal myocardial regions are shown in figure 2. 201TI count rates for the biopsy samples were between 80 and 300 counts/ mg/min. The weight of each sample was between 10 and 22 mg. Ten minutes after intravenous injection and before reperfusion, 201TI activity in the ischemic zone was 28 ± 20% of normal. Two hours after reperfusion, 201TI activity in the ischemic zone rose to 46 ± 25% of initial normal, while in the normal zone, 201TI activity decreased to 84 ± 8% of initial normal. Four hours after injection, 201TI activity in the normal zone was 59 ± 16% of the initial normal activity and in the ischemic zone, it was 47 ± 16% of initial normal (p < .01 vs normal activity at 4 hr; p < .001 vs ischemic activity at 10 min). The relative gradient in 201TI activity between nonischemic and ischemic zones (nonischemic minus ischemic activity) decreased from 72 ± 26% at 10 min after injection to 12 ± 16% at 4 hr. The results shown in figure 2 are from nine of the 10 studied dogs because one of the 10 dogs had a 100% infarct. In this particular dog, the kinetic curve was flat: 201TI activity in the necrotic zone started at 15% of normal at 10 min after injection, and remained at 16% at 4 hr.

Table 3 compares mean normalized 201TI activity in postmortem myocardial samples and at 4 hr after injection and microsphere activity during occlusion and after reperfusion. The comparison is made for endocardial and epicardial samples obtained from necrotic regions (TTC −) and ischemic but noninfarcted regions (TTC +). In ischemic samples, mean normalized 201TI activity was 74 ± 11% (n = 39 samples; 13 endocardial and 26 epicardial), whereas the normalized

![FIGURE 2](http://circ.ahajournals.org/)

**FIGURE 2.** Time course of myocardial 201TI activity, determined from myocardial biopsies in nine dogs. The upper curve is derived from the biopsies taken in the left circumflex artery territory. The lower curve is derived from the biopsies taken in the left anterior descending artery territory before and after reperfusion (REPER). **p < .01 vs normal activity at 4 hr.
TABLE 3

| Normalized microsphere, $^{201}$Tl, and $^{18}$F activity after reperfusion |
|-----------------|-----------------|-----------------|
|                  | Ischemic area (TTC +) | Patchy necrosis | Necrosis (TTC -) |
| Myocardial blood flow (%) |
| During occlusion | Endocardium: 41 ± 25 | 17 ± 6 | 5 ± 4 |
|                  | Epicardium: 41 ± 17 | 18 ± 20 | 5 ± 7 |
|                  | All: 41 ± 20 | 18 ± 10$^b$ | 5 ± 4$^c$ |
| After reperfusion | Endocardium: 87 ± 13 | 98 ± 40 | 91 ± 64 |
|                  | Epicardium: 81 ± 20 | 85 ± 44 | 70 ± 12 |
|                  | All: 84 ± 17 | 94 ± 38 | 73 ± 65 |
| $^{201}$Tl (4 hr) activity (%) |
| Endocardium: 74 ± 13 | 47 ± 15 | 26 ± 15 |
| Epicardium: 73 ± 11 | 61 ± 7 | 42 ± 50 |
| All: 74 ± 11 | 52 ± 14$^a$ | 29 ± 24$^b$ |
| $^{18}$F activity (%) |
| Endocardium: 100 ± 34 | 82 ± 25 | 45 ± 28 |
| Epicardium: 106 ± 41 | 120 ± 15 | 36 ± 23 |
| All: 103 ± 37 | 97 ± 50 | 43 ± 26$^c$ |

$^a$p < .05; $^b$p < .01; $^c$p < .001 vs ischemic area (TTC +).

Microsphere activity during occlusion was 41 ± 20%; the relative $^{201}$Tl gradient between ischemic and normal regions at 4 hr after injection was 26 ± 13%. In necrotic samples, the relative $^{201}$Tl gradient was 48 ± 13% in the samples with patchy necrosis (n = 11 samples; eight endocardial and three epicardial) and it was 71 ± 26% in the samples with homogenous necrosis (n = 22 samples; 18 endocardial and four epicardial). Even though the values for $^{201}$Tl activity at 10 min after injection were not available for these samples obtained only after death, some degree of $^{201}$Tl redistribution had to be present because the normalized $^{201}$Tl activity was 29 ± 24% in the necrotic samples, with a normalized microsphere activity during occlusion of 5 ± 4%.

Glucose metabolism. Table 3 shows the normalized $^{18}$F activity in the different tissue samples. In the necrotic samples, the normalized $^{18}$F activity was significantly smaller than in ischemic samples (43 ± 26% vs 103 ± 37%; p < .001). In samples with patchy necrosis, the normalized $^{18}$F activity was 97 ± 50%.

Figure 3 and table 4 show the metabolic rate for glucose (mg/min/100 g) in normal, ischemic, and necrotic myocardium. The values in homogeneously necrotic samples (1.18 ± 0.74) were smaller than in samples with patchy necrosis (1.82 ± 1.02; p < .05) or in ischemic (3.04 ± 1.92; p < .05) or normal samples (3.85 ± 2.31; p < .001). The metabolic rates in ischemic samples (TCC+) and in normal samples were not significantly different. No difference was noted between endocardial and epicardial samples.

Normalized values of glucose utilization rates, shown in table 4, were different from 100% only in the necrotic tissue. The normalization of metabolic rate was obtained by dividing the values in ischemic and infarcted samples by the nonischemic zone value in the corresponding left ventricular ring. The large SDs noted in the ischemic tissue and in patchy necrosis reflect the fact that three of the nine dogs with ischemic tissue (TTC+) had a normalized transmural glucose metabolic rate of more than 150%. When individual samples were correlated, no correlation was found between glucose metabolism and occlusion flow rate (r = .25; NS).

The arteriovenous differences and extraction ratios of glucose, free fatty acids, and lactate are given in table 5. These values are derived from venous blood of the reperfused zone that drains both ischemic and necrotic tissue. The arterial levels of glucose, free fatty acids, and lactate were, respectively, 366 ± 54, 35 ± 12, and 143 ± 74 µmol/100 ml. Both free fatty acids and lactate net uptake were significantly reduced in the reperfused zone. Glucose consumption was similar (6.29 ± 3.83 vs 6.08 ± 6.4 µmol/min/100 g), while oxygen consumption of the reperfused zone was smaller than that of the normal zone (3.28 ± 2.26 vs 7.31 ± 2.23 ml/min/100 g; p < .001). Thus, these data show a shift in substrate utilization in the reperfused zone. The oxygen supply/oxygen consumption ratio was significantly higher in the reperfused area (5.41 ± 4.69) than in the normal zone (1.78 ± 0.38; p < .001).

Electron microscopy of reperfused samples. All the samples in TTC− regions showed features of myocardial cell death, although the same electron micrographs showed inhomogeneous signs of necrosis in four dogs. The samples from TTC+ areas showed features of reversible ischemic damage except in one dog that had signs of cell death on two electron micrographs.

![Figure 3](http://circ.ahajournals.org/)

**FIGURE 3.** Transmural myocardial glucose metabolic rates (MR-Glc) in normal, ischemic, and necrotic tissues. **p < .01; ***p < .001.
TABLE 4
Absolute and normalized metabolic rates for glucose after reperfusion

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Ischemic area (TTC +)</th>
<th>Patchy necrosis</th>
<th>Necrosis (TTC −)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute metabolic rates (mg/min/100 g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocardium</td>
<td>4.43 ± 2.65</td>
<td>3.19 ± 1.01</td>
<td>1.70 ± 1.28</td>
<td>1.21 ± 0.7</td>
</tr>
<tr>
<td>Epicardium</td>
<td>3.27 ± 1.87</td>
<td>2.93 ± 2.03</td>
<td>2.06 ± 0.34</td>
<td>1.07 ± 1.14</td>
</tr>
<tr>
<td>All</td>
<td>3.85 ± 2.31</td>
<td>3.04 ± 1.92</td>
<td>1.82 ± 1.02</td>
<td>1.18 ± 0.74b</td>
</tr>
<tr>
<td>Normalized metabolic rates (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocardium</td>
<td>112 ± 69</td>
<td>85 ± 74</td>
<td>36 ± 27</td>
<td></td>
</tr>
<tr>
<td>Epicardium</td>
<td>121 ± 70</td>
<td>167 ± 25</td>
<td>25 ± 25</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>117 ± 68</td>
<td>113 ± 72</td>
<td>33 ± 25c</td>
<td></td>
</tr>
</tbody>
</table>

*p < .01; **p < .001, vs normal.
*p < .05 vs 100%.

Discussion

The results of this study indicate that, in reperfused myocardium, delayed redistribution of 201Tl injected before reperfusion is an indicator of viable myocardium and that depressed glucose utilization indicates irreversible injury while normal FDG uptake is associated with viable tissue.

Some details of the experimental preparation were designed to parallel the clinical situation. The assessment of viable and necrotic tissue was made as early as 4 hr after reperfusion. The effects of slow reperfusion through a residual stenosis were compared with rapid reflow through a patent vessel. No difference between these two groups of dogs was observed in terms of the distribution of tracers.

Both time-activity curves and postmortem samples showed near normalization of the relative 201Tl activity in the ischemic zone, while the necrotic samples contained a low level of 201Tl activity. At 4 hr after injection of isotope, 201Tl activity in the ischemic zone was 80% of that in the nonischemic zone, as shown by the results of biopsy, and in the postmortem samples it was 74%, giving a gradient of 26% between the normal and the ischemic zones. Conversely, in the necrotic samples, 201Tl activity was 29% of that in the nonischemic zone after death, giving a 201Tl gradient of 71% between the normal and necrotic zones at 4 hr after injection. This latter value suggests that a small degree of redistribution might exist, taking into account the low-flow microsphere values (5% of control) during occlusion, at the time of 201Tl injection, in these necrotic samples. The 5% normalized microsphere value might be lower than the normalized 201Tl value at the same time, because 201Tl slightly overestimates flow measured with microspheres in this low range of values. Accordingly, the redistribution in the necrotic regions could have been slightly overestimated.

Thus, our data confirm and extend those reported by Granato et al.13, 23 After 3 hr of coronary occlusion and 2 hr of reflow, these authors showed little delayed 201Tl redistribution, as seen by a 201Tl gradient of 51 ± 9%, which was not different from the 201Tl gradient seen in dogs undergoing a sustained 3 hr occlusion (55 ± 5%). In contrast, for dogs undergoing 1 hr of occlusion and reperfusion, the same authors reported a gradient between normal and ischemic regions of only 26 ± 5% after reflow.

On the other hand, FDG was used for evaluating exogenous glucose utilization. In necrotic samples, a significant decrease in metabolic activity was observed, whereas preserved glucose utilization was demonstrated in ischemic tissue. In three of the nine dogs with ischemic samples inside the risk region, we noted an increased uptake of FDG in reperfused relative to control myocardium. The large interanimal variability in glucose metabolic rates calculated from FDG uptake both for normal and ischemic tissue samples is not surprising. FDG traces transmembranous transport and phosphorylation of exogenous glucose. These steps in glucose metabolism are influenced by hormones (insulin, growth hormone, epinephrine, cortisol), extracellular glucose concentration, cardiac work, and the availability of alternative substrates. In addition,

TABLE 5
Arteriovenous differences and extraction ratios of glucose, free fatty acids, and lactate

<table>
<thead>
<tr>
<th></th>
<th>Arteriovenous differences (µmol/100 ml)</th>
<th>Chemical extraction ratios (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reperfused zone</td>
<td>Normal zone</td>
</tr>
<tr>
<td>Glucose</td>
<td>16.2 ± 22.7</td>
<td>12.3 ± 29.3</td>
</tr>
<tr>
<td>Free fatty acids</td>
<td>6.8 ± 5.9</td>
<td>14.1 ± 7.9</td>
</tr>
<tr>
<td>Lactate</td>
<td>14.0 ± 23.6</td>
<td>42.2 ± 27.6</td>
</tr>
</tbody>
</table>

*p < .05; **p < .01; ***p < .001.
the glycolytic pathway will be inhibited to varying degrees during ischemia, depending on the rate of accumulation and washout of toxic metabolites. None of all the above-cited factors can be controlled in a preparation of reperfused myocardial infarction in vivo.

Although the tissue measurements of glucose uptake with FDG cannot be directly compared with arteriovenous differences in the substrate glucose, the glucose metabolic rates obtained with FDG in the normal and ischemic zones were corroborated by the glucose consumption calculated in the normal and reperfused areas by the regional arteriovenous differences. Because decreased oxygen consumption was noted in the reperfused area, an increase of glucose uptake relative to oxygen consumption was observed, indicating a shift in substrate utilization. This is further illustrated by the decreased free fatty acids and lactate arteriovenous differences in this reperfused zone. A recent study of Myeare et al. indicated that canine myocardium reperfused after 1 hr of ischemia exhibits enhanced uptake of glucose and impaired utilization of palmitate, as shown by arteriovenous differences. However, the pattern of substrate utilization did not predict the relative contribution of an individual substrate to overall oxidative metabolism.

Comparison with the study by Schwaiger et al. reveals that the gradient in glucose uptake between ischemic and normal samples was more pronounced 24 hr after reperfusion in a dog preparation of 3 hr coronary occlusion than under our experimental conditions. In their study, the ratio of FDG uptake in reperfused over normal tissue was 1.49 ± 0.62 as measured with positron-emission tomography. However, such a ratio can be affected by changes in the reperfused tissue, the normal tissue, or both. Although we did not measure contractile function in the normal zone directly, an increase in the metabolic demand in the circumflex territory is likely to occur during the first hours after occlusion of the left anterior descending artery due to hypercontraction or mechanical disadvantage secondary to the acute loss of active myocardium. If present, such a mechanism would increase the absolute glucose uptake of the normal zone, thereby reducing the gradient with ischemic tissue, as we observed. Another hypothesis is that enhanced glucose uptake by reperfused tissue is a delayed phenomenon. In dogs, Schwaiger et al. showed that regional FDG concentration in reperfused myocardium was significantly higher than in control myocardium at 24 hr, while one hour after reperfusion, FDG uptake in reperfused territory was only 79% of control.

Finally, it should be noted that some degree of redistribution and some low residual glucose metabolic activity (1.18 ± 0.74 mg/min/100 g) were observed in the necrotic samples. Most likely, the infarcted tissue samples still contained some ischemic cells. Although TTC is an accepted indicator of irreversible damage after reperfusion and the gross inspection revealed no staining by TTC, some electron micrographs showed inhomogeneity of cell injury. Also, the small persistent metabolic activity could partially reflect the metabolic activity of the blood cells present in these grossly hemorrhagic infarcts.

In conclusion, these results, along with others, provide a rationale for the use of myocardial 201Tl redistribution as an index of myocardial viability after reperfusion. However, practical limitations should be stressed: the determination of directional changes in ischemic zone necessitates a 201Tl injection performed before reperfusion and two sequential acquisitions (the first one early after intravenous injection and the other 3 to 4 hr later). Also, when imaging is performed in vivo in patients, the interpretation of 201Tl scintigrams has to take into account the fact that a smaller 201Tl defect after reperfusion could be caused by enhanced collateral blood flow or alterations in left ventricular volume. Alternatively, impaired thickening of the stunned myocardium consequent to ischemia in the absence of necrosis might result in an underestimation of the true concentration of tracer in tissue, whether it be 201Tl or FDG, because of the partial volume effect.

On the other hand, preservation of myocardial metabolic activity, as determined by the uptake of FDG, also correlated well with the presence of viable tissue as early as 4 hr after reperfusion. In contrast, regions of infarction were characterized by a reduction in glucose uptake. These differences could probably be depicted with the quantitative capabilities of positron-emission tomography, especially with the advent of instrumentation with improved resolution. Additional experimental studies with positron imaging in vivo are necessary for the confirmation of these observations in vitro and for further quantitative characterization of the time course of the metabolic abnormalities after reperfusion both in ischemic and normal tissue.

Electron micrographs were prepared and analyzed with great care by M. Stevens and J. Rahier, M.D., from the Department of Pathology. The authors appreciate the expert technical assistance provided by D. Ockrromovicz-Bemelmans and E. Willems. The manuscript was typed with great care by D. Vangebergen. The authors appreciate the generous support of the DAMMAN Foundation.

References

2. Lee JT, Ideker RE, Reimer KA: Myocardial infarct size and location
Assessment of thallium-201 redistribution versus glucose uptake as predictors of viability after coronary occlusion and reperfusion.

Circulation. 1988;77:927-934
doi: 10.1161/01.CIR.77.4.927

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/77/4/927

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/