Increased uptake of $^{18}$F-fluorodeoxyglucose in postischemic myocardium of patients with exercise-induced angina

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ABSTRACT Regional myocardial perfusion and exogenous glucose uptake were assessed with rubidium-82 ($^{82}$Rb) and $^{18}$F-2-fluoro-2-deoxyglucose (FDG) in 10 normal volunteers and 12 patients with coronary artery disease and stable angina pectoris by means of positron emission tomography. In patients at rest, the myocardial uptake of $^{82}$Rb and FDG did not differ significantly from that measured in normal subjects. The exercise test performed within the positron camera in eight patients produced typical chest pain and ischemic electrocardiographic changes in all. In each of the eight patients a region of reduced cation uptake was demonstrated in the $^{82}$Rb scan recorded at peak exercise, after which uptake of $^{82}$Rb returned to the control value 5 to 14 min after the end of the exercise. In these patients, FDG was injected in the recovery phase when all the variables that were altered during exercise, including regional myocardial $^{82}$Rb uptake, had returned to control values. In all but one patient, FDG accumulation in the regions of reduced $^{82}$Rb uptake during exercise was significantly higher than that in the nonischemic regions, i.e., the ones with a normal increment of $^{82}$Rb uptake on exercise. In the nonischemic areas, FDG uptake was not significantly different from that found in normal subjects after exercise. In conclusion, myocardial glucose transport and phosphorylation seem to be enhanced in the postischemic myocardium of patients with exercise-induced ischemia.

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IT HAS LONG been known that myocardial glucose utilization is enhanced as a consequence of faster anaerobic glycolysis during conditions of reduced oxygen availability, as proved by the greater lactate production.\(^1\) The importance of coronary flow and washout of the interstitial space in maintaining an accelerated glycolytic rate has been emphasized by studies in isolated working rat hearts submitted to anoxia and ischemia.\(^2\)\(^4\) Both anoxia and ischemia produce an initial acceleration of the glycolytic rate caused by rapid activation of glycogen breakdown, which lasts less than 10 min. Thereafter, as tissue glycogen is depleted, the glycolytic rate remains accelerated in the anoxic heart because of a greater utilization of exogenous glucose. In contrast, in the ischemic heart, the accumulation of lactate and the reduction in tissue pH cause a subsequent inhibition of glycolysis in proportion to the degree of restriction of coronary flow.

Myocardial ischemia in man is usually a regional phenomenon. Little is known about the focal changes of myocardial glucose utilization that might be associated with episodes of transient ischemia in patients with coronary artery disease (CAD). The recent availability of positron emission tomography (PET) makes possible the noninvasive evaluation of regional myocardial perfusion and metabolism in man.\(^5\) In the present study, we sought to determine by means of PET whether regional changes in glucose utilization could be demonstrated in the myocardium of patients with CAD and stable angina pectoris after an episode of exercise-induced ischemia.

Regional myocardial perfusion and glucose uptake were assessed with rubidium-82 ($^{82}$Rb) and $^{18}$F-2-fluoro-2-deoxyglucose (FDG), respectively.

Materials and methods

Study population. The study population consisted of 10 normal volunteers (all men, ages 29 to 38 years, with no symp-
toms or signs of myocardial disease and with normal resting electrocardiograms [ECGs] and negative exercise tests] and 12 patients with stable angina pectoris (three women and nine men, ages 41 to 68 years). The patients were selected on the basis of typical electrocardiographic signs of ischemia (flat or downsloping ST depression ≥ 0.1 mV) inducible by exercise and CAD confirmed by coronary arteriography. Five of the patients had signs of prior transmural infarction in the ECG and two had poor progression of the r wave in V1-3, but none entered the study less than 12 weeks after an infarction. None of the patients had diabetes, arterial hypertension, or congestive heart failure. All forms of medical treatment were discontinued 48 to 72 hr before the study. The main clinical and angiographic features of the patient group are reported in table 1. To standardize the dietary state, all subjects (normal and patients) were studied after overnight fasting.

The purpose and nature of the study were approved by the Hammersmith Hospital Research Ethics Committee and the United Kingdom Administration of Radioactive Substances Advisory Committee. Written consent was obtained from all subjects before each entry.

**Tracers and scanning procedure.** The positron tomograph used (ECAT II, EG and G ORTEC) is a single-slice machine with a spatial resolution of 1.6 cm full-width at half-maximum (FWHM) and a slice thickness of 1.6 cm FWHM. A weekly calibration factor is calculated to relate ECAT pixel counts in the image to counts per milliliter per second in a well counter used for measuring blood samples.

Each subject was positioned within the positron scanner and a mid–left ventricular slice was selected and fixed in relation to the detectors by a low-power laser beam and indelible pen marks on the patient’s skin. A transmission scan of 600 sec was then recorded with an external ring source of germanium-68. This was used to correct all subsequent emission scans for tissue attenuation of the 511 keV annihilation photons.

Directional changes in regional perfusion were assessed by measuring the myocardial uptake of the positron-emitting cation $^{82}$Rb (1/2 78 sec). Although $^{82}$Rb is not a pure flow marker, the tracer has been demonstrated to be suitable for detection of acute transient myocardial ischemia. In addition, the short half-life of the cation allows repeated measurements in the same individual under different clinical conditions. $^{82}$Rb was eluted from a strontium-$^{82}$Rb generator in sterile normal saline and infused into a peripheral arm vein at a rate of 10 ml/min. The infusion was sterilized by terminal filtration (Millipore SLG 02S05, 0.22 μm). Equilibrium scans of 60 sec were recorded when one bank of detectors of the positron tomograph showed constant activity on a linear digital rate meter. Two to 3 min of infusion were needed to reach a constant $^{82}$Rb activity. Washout scans were recorded by stopping the infusion, waiting 30 sec (for the blood pool to clear partially) and then scanning for 120 sec. Fractional uptake of $^{82}$Rb (FURb) in the myocardium was calculated from the ratio of tissue and blood activity of $^{82}$Rb obtained from the washout (decay corrected back to the end of infusion) and equilibrium scan, respectively, according to the following equation:

$$FURb = \frac{\text{regional myocardial activity (washout scan)}}{\text{arterial activity (equilibrium scan)}}$$

where 0.693 is log2, 78 sec is $^{82}$Rb half-life, and the ratio represents the turnover of $^{82}$Rb due to decay. This calculation provides a fraction representing the uptake of $^{82}$Rb in each myocardial region in relation to the delivered arterial activity presented to the heart.

This approach was preferred to a subtraction of the blood pool scan directly from the steady-state scan because with the latter, the errors caused by the unavoidable position changes in the different phases of the study could have been greater than those of the method used, since a single blood pool scan was performed at the end of the study.

The glucose analogue 2-fluoro-2-deoxyglucose labeled with the positron emitter $^{18}$F (FDG, 1/2 110 min) was used to assess regional myocardial uptake of exogenous glucose. FDG competes with glucose for transport sites and phosphorylation by hexokinase in the cell. However, the phosphorylated compound FDG-6-P2 cannot be further metabolized and is trapped within the cell in proportion to the uptake and phosphorylation of exogenous glucose. Myocardial uptake of FDG was measured by scanning for a period of 600 sec, 45 to 60 min after the intravenous injection of 4 to 6 mCi of tracer. In each subject, serial venous blood samples were withdrawn after injection of

**TABLE 1**

**Clinical and angiographic characteristics of patients**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Basal ECG</th>
<th>Coronary angiography</th>
<th>Left ventriculography</th>
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<tbody>
<tr>
<td>3</td>
<td>M</td>
<td>N</td>
<td>LAD 80%, CX 50%, RCA 75%</td>
<td>A + 1 HK</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>A MI</td>
<td>LAD 95%, CX 50%, RCA 50%</td>
<td>A HK</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>I MI</td>
<td>LAD 100%, CX 70%, RCA 100%</td>
<td>A HK</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>I MI</td>
<td>LAD 75%, RCA 100%</td>
<td>I AK + A HK</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>Poor rV1-3</td>
<td>LAD 90%</td>
<td>A HK</td>
</tr>
<tr>
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<td>M</td>
<td>Poor rV1-3</td>
<td>LAD 90%</td>
<td>N</td>
</tr>
<tr>
<td>26</td>
<td>M</td>
<td>I MI</td>
<td>LAD 90%, CX 70%, RCA 90%</td>
<td>A + 1 HK</td>
</tr>
<tr>
<td>30</td>
<td>F</td>
<td>I MI</td>
<td>DIAG. 70%, CX 60%, RCA 75%</td>
<td>I AK</td>
</tr>
<tr>
<td>42</td>
<td>M</td>
<td>N</td>
<td>LAD 75%, RCA 100%</td>
<td>A HK</td>
</tr>
<tr>
<td>50</td>
<td>F</td>
<td>N</td>
<td>LAD 85%, CX 70%, RCA 90%</td>
<td>A HK + 1 AK</td>
</tr>
<tr>
<td>56</td>
<td>M</td>
<td>N</td>
<td>LAD 90%, CX 75%, RCA 90%</td>
<td>A HK</td>
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<tr>
<td>79</td>
<td>F</td>
<td>N</td>
<td>LAD 95%, CX 85%, RCA 100%</td>
<td>A + 1 HK</td>
</tr>
</tbody>
</table>

1 = inferior left ventricular wall; A = anterior left ventricular wall; N = normal; LAD = left anterior descending coronary artery; CX = left circumflex coronary artery; RCA = right coronary artery; MI = ECG signs of prior myocardial infarction; HK = hypokinesia; AK = akinesia.

*The severity of stenoses is expressed as percent lumen reduction.
FDG (i.e., 30, 60, 90, and 120 sec after the injection and then every minute up to 10 min and every 5 min up to 60 to 80 min) and the plasma concentrations of the tracer were measured in the calibrated well counter. At the end of each study, a blood pool scan was acquired for 300 sec by means of the \(^{11}\)C-carboxyhemoglobin (CO) technique. This is based on labeling of red blood cells in vivo by inhalation of tracers amounts of \(^{11}\)C-labeled carbon monoxide. Venous blood samples were taken during the CO scan to measure the \(^{11}\)C activity in the blood.

**Study protocol.** The regional myocardial uptake of \(^{82}\)Rb and FDG was assessed at rest in six patients (group A). In eight patients (group B), regional myocardial uptake of \(^{82}\)Rb was assessed at rest, at peak exercise, and in the recovery phase. In this group, regional myocardial FDG uptake was measured after exercise. In two patients, myocardial FDG uptake was assessed both at rest and on exercise in two different sessions.

Regional myocardial uptake of FDG was also assessed in five normal volunteers at rest and in five after exercise.

**Exercise.** A bicycle ergometer test was performed in the supine position within the positron camera. The workload was started at 25 W and increased by the same amount every 2 min until the ECG showed significant ST segment depression (≥ 0.1 mV). At this stage the workload was kept constant and exercise continued for a further 3 to 9 min depending on the patient's compliance. Lead V\textsubscript{5} of the ECG was monitored continuously throughout the exercise. A complete 12-lead ECG and arterial blood pressure were recorded every minute during the test and in the first 10 min of the recovery.

Regional myocardial \(^{82}\)Rb uptake was assessed during basal conditions, at peak exercise, and in the recovery phase. In all patients \(^{82}\)Rb uptake in the recovery phase was measured after the ECG had normalized. If ejection fraction in the first recovery scan was still visually abnormal, one or more additional measurements were performed, as soon as the previous \(^{82}\)Rb activity had completely decayed, until the uptake defects that had developed during the stress test were no longer detectable. One equilibrium and one washout scan were recorded for each measurement.

FDG was injected intravenously 6 to 15 min after the end of the exercise when heart rate, blood pressure, ECG, and myocardial uptake of \(^{82}\)Rb had returned to basal values. In five normal subjects, FDG was injected intravenously 5 to 18 min after the end of the exercise test when values had returned to basal levels. A fixed exercise level (8 min, 100 W) in the normal group was chosen arbitrarily to demonstrate the effect of an increased cardiac workload on subsequent myocardial glucose utilization. It was beyond the scope of our study to investigate the correlation between cardiac workload and myocardial glucose utilization.

Venous blood samples for plasma glucose and insulin assay were obtained during basal conditions in all patients and normal volunteers to exclude the possibility of nonfasting conditions (i.e., postabsorptive state) increasing myocardial glucose utilization.

**Data analysis.** The FDG scans were corrected for decay and for the intravascular activity of FDG present at the time of scanning. For the latter correction, the CO scan was subtracted pixel by pixel from the FDG scan in proportion to the ratio of the respective blood levels according to the following formula:

\[ \text{FDG scan} - \text{CO scan} \times \frac{\text{FDGbl}}{\text{CObl}} \]

where FDGbl and CObl are the respective whole-blood specific activities of FDG and CO measured in whole blood samples obtained at the time of scanning with the calibrated well counter. The ratio of FDGbl and CObl obtained from regions of interest in the right atrium (minimizing the partial volume and spillover effect) gave the same results as those obtained with the well counter. In each patient, the percent fractional uptake of FDG in the myocardium was calculated according to the following formula:

\[ \text{FDG fractional uptake} \% = \frac{C_{\text{FDG}}}{\text{o}^{1/2} \text{Cpdt}} \times 10^2 \]

where \(C_{\text{FDG}}\) is the activity (counts per pixel) of FDG in the myocardium obtained from the FDG scan not corrected for partial volume effect, and \(o^{1/2} \text{Cpdt}\) is the integral of the FDG plasma values from the time of injection to the end of scanning (T). This calculation provides a fraction that represents the uptake of FDG in each myocardial region in relation to the delivered dose presented to the heart. Definition of the actual input function, as obtained by arterial sampling, would be required for a more accurate measurement of myocardial FDG uptake. However, in this study, any error caused by either venous sampling or its low temporal resolution would affect all patients equally. In fact, the main aim of this normalization procedure was to compare FDG uptake in different subjects.

Six circular regions of interest, 2.3 cm\(^2\) × 1.6 cm each (113 voxels), were selected in the resting \(^{82}\)Rb scan: two in the septum, two in the anterior wall, and two in the free wall of the left ventricle. These regions of interest were reproduced on all the subsequent \(^{82}\)Rb and FDG scans of the same patient. In the normal subjects, the six regions of interest were selected directly in the FDG scans recorded at rest or after exercise.

The following measurements were computed from each \(^{82}\)Rb tomogram for each patient: (1) the average value of \(^{82}\)Rb uptake (mean ± SD) in each scan (at rest, at peak exercise, and during recovery), (2) range of uptake within each tomogram (i.e., the difference between the maximal and minimal value of uptake in the six regions of interest) and the change in range of uptake during exercise and recovery (as a measurement of homogeneity of uptake in each scan), and (3) change of uptake, between the resting and exercise scans, in the region with the largest and the smallest increase in uptake (to identify the regions responsible for the inhomogeneity).

Regional \(^{82}\)Rb uptake at rest and during exercise was considered abnormal (ischemic myocardium) if it was more than 2 SDs below the mean of a previously studied group of normal subjects.

Paired t tests were used to compare differences within patients and unpaired t tests to compare differences between different patients and between patients and normal subjects.

**Results**

**Myocardial \(^{82}\)Rb uptake.** Average \(^{82}\)Rb uptake (FURB) was similar in normal subjects and patients at rest (0.47 ± 0.07 vs 0.44 ± 0.06). In contrast, the range of uptake within scans, an index of the degree of nonhomogeneity, was significantly greater in patients than in normal subjects (0.14 ± 0.04 vs 0.06 ± 0.03; \(p < .005\)). Despite this greater nonhomogeneity, in only one patient (No. 7) was a region of significantly reduced \(^{82}\)Rb uptake (i.e., 2 SDs below normal) detected in the resting \(^{82}\)Rb scan.

The exercise test performed within the positron
scanner produced typical electrocardiographic changes and chest pain in all the patients of group B (table 2). Average $^{82}$Rb uptake at peak exercise was significantly lower than that in normal subjects ($0.52 \pm 0.08$ vs $0.65 \pm 0.09$; $p < .005$). In all patients the range of uptake within the six regions of each exercise $^{82}$Rb scan was increased (figure 1) relative to rest and was significantly greater than that in exercising normal subjects ($0.27 \pm 0.09$ vs $0.09 \pm 0.03$; $p < .001$). Also, in all patients $^{82}$Rb uptake in the region with the smallest increase (or largest decrease) recorded during exercise was more than 2 SDs below the mean value for the normal volunteers (table 2, figures 2 and 3). A region of absolute reduction of cation uptake was found in five patients (table 2). $^{82}$Rb uptake in the nonischemic areas (i.e., those with the largest increase during exercise) rose to $0.63 \pm 0.07$ and fell to within the range of values observed in normal subjects during exercise ($0.65 \pm 0.09$).

Both the overall uptake of $^{82}$Rb and the range of uptake within scans measured in the recovery scan ($0.45 \pm 0.08$ and $0.16 \pm 0.08$, respectively) were not statistically different from the values obtained in the same patients before the exercise (table 2, figure 1).

In the two patients of group B with single-vessel disease, the area of reduced $^{82}$Rb uptake during exercise was in the territory of distribution of the diseased artery. In the others, with two- or three-vessel disease, the area of reduced cation uptake during exercise was always located in the territory of the most severely diseased vessel (tables 1 and 2).

**Myocardial FDG uptake.** FDG fractional uptake at rest in patients of group A was not statistically different from that in normals ($0.11 \pm 0.03$ vs $0.07 \pm 0.04$).

In all patients of group B and in the normal subjects, who were injected after exercise, myocardial FDG uptake was significantly higher relative to the values measured in patients and normal subjects at rest (figure 4). FDG uptake in the nonischemic regions (i.e., the regions that showed a normal increment of $^{82}$Rb uptake during exercise) was not significantly different from that in normal subjects ($0.33 \pm 0.18$ vs $0.35 \pm 0.21$), whereas it was significantly lower than the uptake in the ischemic regions ($0.47 \pm 0.18$, $p < .05$) (figure 4).

In group B the region of reduced $^{82}$Rb uptake during exercise was characterized by a greater FDG uptake during the recovery phase than in the nonischemic myocardium of the same patient, with the exception of patient 25, who showed a greater FDG uptake in the nonischemic myocardium (figures 2, 3, and 5). In patient 7, the highest FDG uptake was observed in the region in which $^{82}$Rb uptake was already significantly reduced at rest (figure 3).

Plasma glucose and insulin levels in the patients were not significantly different from those in normal subjects ($4.8 \pm 0.6$ vs $4.7 \pm 0.5$ mmol/liter and $7 \pm 0.4$ vs $10 \pm 1.5$ mU/liter, respectively). In none of the normal subjects or patients were the values of glucose and insulin in the blood outside the limits for fasting individuals.

**Discussion**

The results of the present study show that transient regional defects of $^{82}$Rb uptake can be demonstrated

### Table 2

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Watts (x 10³)</th>
<th>RPP</th>
<th>Ex. duration (min)</th>
<th>ST (mV)</th>
<th>Leads</th>
<th>Rest</th>
<th>Exercise</th>
<th>Recovery</th>
<th>Ischemic region</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>75</td>
<td>19.2</td>
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<td>0.45</td>
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<tr>
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<tr>
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<td>0.44</td>
<td>0.57</td>
<td>0.36</td>
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<td>0.42</td>
<td>0.67</td>
<td>0.46</td>
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<td>0.39</td>
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<tr>
<td>56</td>
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<td>0.43</td>
<td>0.42</td>
<td>0.56</td>
<td>0.38</td>
</tr>
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</table>

See Materials and methods for further details regarding the definition of ischemic and nonischemic myocardium.

RPP = rate pressure product; ST = maximal ST segment depression; N.IS. = nonischemic myocardium; IS. = ischemic myocardium; ischemic region = region of reduced rubidium uptake during exercise; A = anterior left ventricular wall; S = interventricular septum; FW = free wall of left ventricle.
the fact that, in some patients, these were in the territory of a severely stenosed vessel. In all cases, $^{82}$Rb uptake returned to control values within 5 to 14 min after the end of the exercise. Thus, in agreement with previous results from our group, the findings of this study indicate that, although $^{82}$Rb is not a pure flow marker and several factors may modify its extraction by the myocardium, the tracer is suitable for the detection of acute transient myocardial ischemia. Previous experiments have demonstrated the inverse relationship between myocardial flow and $^{82}$Rb extraction. Although the initial distribution of the tracer occurs through flow, the positron camera measures the mass of intramyocardial tracer. Therefore several factors, including flow, residence time, extracted fraction, fractional escape, and metabolism, affect the data. However, when a reduction in regional perfusion is accompanied by evidence of ischemia, myocardial $^{82}$Rb uptake is severely and absolutely decreased below the control level.

In only one of five patients with signs of prior transmural infarction on the ECG was $^{82}$Rb uptake in the infarcted area significantly reduced at rest. However, in all five, the range of uptake in the resting scan was significantly broader than that in normal subjects. All

![Figure 1](http://circ.ahajournals.org/)

**FIGURE 1.** Frequencies of distribution of $^{82}$Rb uptake in the myocardium of a patient (No. 3) measured at rest (*top panel*), during exercise-induced ischemia (*middle panel*), and in the recovery phase (*bottom panel*). The Y axis represents the number of pixels per unit range of $^{82}$Rb uptake and the X axis represents $^{82}$Rb uptake. During resting conditions myocardial $^{82}$Rb uptake shows a gaussian distribution. By contrast, during exercise $^{82}$Rb uptake is clearly characterized by a bimodal distribution. This is because of the different behavior between the nonischemic myocardium, which increases $^{82}$Rb uptake during exercise, and the ischemic myocardium, where $^{52}$Rb uptake during exercise remains unchanged relative to control. $^{52}$Rb distribution in the recovery phase is superimposable on that measured during control conditions.

during exercise in the myocardium of patients with CAD and stable angina pectoris. The region of reduced $^{82}$Rb uptake during exercise was always located in the territory of distribution of the most severely narrowed artery. The location of the area of reduced cation uptake was not predictable from electrocardiographic changes observed during exercise. Those regions with the greatest increase of cation uptake during exercise had absolute values of $^{82}$Rb uptake well within the range measured in normal subjects on exercise despite

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

**FIGURE 2.** Positron computed tomographic images of $^{82}$Rb and FDG uptake in the left ventricle of patient 3. Each image is a transaxial slice of the heart (1.6 cm thick). In each image the left ventricular free wall is in the 6 to 10 o’clock position, the anterior wall and septum are in the 10 to 3 o’clock, and the remaining open area is the plane of the mitral valve. The $^{82}$Rb scan at rest (*top left*) shows a homogeneous cation uptake in all myocardial walls. The $^{52}$Rb scan recorded during exercise (*top right*) shows a severely reduced cation uptake in the anterior left ventricle wall. The $^{52}$Rb scan recorded 6 min after the end of exercise (*bottom left*) is comparable to the preexercise scan. FDG was injected 8 min after the end of exercise. The FDG scan, recorded 60 min after tracer injection, shows a greater FDG uptake in the previously ischemic area (*bottom right*). FDG uptake in the anterior wall is 1.55 times higher than that in the nonischemic muscle.
$^{82}$Rb uptake during exercise were characterized by an FDG uptake, in the recovery phase, that was significantly higher than that in the nonischemic regions (i.e., those with a normal increment of cation uptake on exercise). This was observed for a wide range of exercise levels, demonstrating that the phenomenon is probably independent of the anginal threshold. However, FDG uptake in the nonischemic regions was not statistically different from that found in normal subjects after exercise.

Based on the small number of patients studied and on the practical difficulties of having each patient as his or her control for the rest and exercise FDG studies, one has to limit the inferences that can be made from these results. In patient 25, the exercise test was performed twice, and similar workloads and electrocardiographic changes were achieved. On both occasions cation uptake was reduced in the septum during exercise and FDG uptake during recovery was consistently higher in the nonischemic myocardium (free wall) compared with the septum.

A possible explanation for the findings in this patient might be the degree of partial volume effect in the different cardiac walls. Because the spatial resolution of the ECAT II is 1.6 cm FWHM, the recovery of counts from the different myocardial walls, which are thin relative to the spatial resolution of the tomograph, is affected by their relative thickness. In a mid-ventricular section, the free wall of the left ventricle is thicker than the anterior and septal walls, compounded by the presence of the posterior papillary muscle in this region. This was responsible for a consistently higher

FIGURE 3. Positron computed tomographic images of $^{82}$Rb and FDG uptake in the left ventricle of patient 7. The $^{82}$Rb scan at rest (top left) shows a reduced cation uptake in the anterior wall of the left ventricle, corresponding to an old infarction. The same region becomes acutely ischemic during exercise, as shown by the $^{82}$Rb scan recorded during the exercise test (top right). The $^{82}$Rb scan recorded 6 min after the end of the exercise (bottom left) is comparable to the control. FDG was injected 9 min after the end of the exercise when all the signs of ischemia had reversed. The FDG scan (bottom right), recorded 60 min after tracer injection, outlines the previously ischemic area; FDG uptake in the anterior wall is 1.6 times higher than that in nonischemic tissue. For figure orientation see legend to figure 2.

four patients in whom regional $^{82}$Rb defects could not be identified had signs of inferior infarction on their ECGs. The difficulty of evaluating the inferior left ventricular wall with transaxial tomography, particularly with a single-slice tomograph and in the absence of cardiac gating, could partly explain the inability to detect $^{82}$Rb defects in these four patients. The same limitation could have affected the detection of other possible ischemic regions during exercise.

Under resting conditions, the patients could not be differentiated from the normal subjects in terms of myocardial FDG uptake. In the patients and the normal subjects receiving tracer after exercise, myocardial FDG uptake was significantly higher in comparison with that measured at rest. In the patients, however, myocardial FDG uptake after exercise had a regional distribution opposite to that of $^{82}$Rb during exercise. In fact, in seven of eight patients, the regions of reduced

FIGURE 4. Histograms representing the mean values of myocardial fractional uptake of FDG in the normal subjects and in the patients at rest and after exercise. Both in normal subjects and patients, myocardial FDG uptake measured after exercise is significantly higher than that at rest (p < .025 and p < .02, respectively). In addition, in the patient group FDG uptake in the ischemic regions (IS) is significantly higher than that in the nonischemic regions (NON IS; p < .05).
FDG uptake in this wall in normal subjects injected after exercise, which is in agreement with the findings of Marshall et al.\textsuperscript{14} In particular, in patient 25 the occurrence of ischemia in the relatively thinner septum, probably also affected by an old infarction (which would further reduce the mass of viable tissue), could explain the detection of an absolutely lower FDG uptake in this region as compared with the thicker free wall. In fact, the ratio of FDG to \textsuperscript{82}Rb uptake, which should cancel the partial volume effect, was higher in ischemic than in nonischemic myocardium also in this patient.

In patients with an old infarction who show a region of reduced \textsuperscript{82}Rb uptake at rest (e.g., patient 7), the suggested presence of transient ischemia, indicated by a further reduction of cation uptake during exercise (which might otherwise be interpreted as a consequence of motion artifacts and thinning during exercise-induced ischemia\textsuperscript{15}), is supported by the finding of increased FDG uptake in the same area, indicating the presence of metabolically active tissue.

It is known that glycogen breakdown in the myocardium is enhanced during ischemia as well as during conditions of increased cardiac work.\textsuperscript{4, 16} This seems to be largely caused by the conversion of phosphorylase from the b to the a form, which could be mediated by epinephrine through an increased production of cyclic AMP.\textsuperscript{16}

Increased glycogen synthesis in the myocardium has been reported in experimental animals after exercise.\textsuperscript{17, 18} Moreover, as reported by Fell et al.,\textsuperscript{19} the degree of glycogen depletion in an isolated perfused skeletal muscle preparation after strenuous exercise seems to regulate the degree of exogenous glucose uptake in the recovery phase.

Preliminary results in the isolated perfused working rat heart, in which the rate of incorporation of exogenous glucose into the glycogen pool was measured after 15 min of global ischemia, indicate that the rate of glycogen synthesis in the recovery from ischemia is significantly higher than that during control conditions.\textsuperscript{20}

The increased FDG uptake observed in the myocardium after exercise indicates only an increased transport and phosphorylation of exogenous glucose. In fact, because of the early metabolic trapping of the tracer as FDG-6-PO\textsubscript{4}, it is not possible to obtain direct information on its later fate. Nevertheless, it may be hypothesized that the higher FDG uptake in the postischemic muscle might be caused by increased glycogen resynthesis as well as by an increased flux through glycolysis. The former could be the result of more severe glycogen depletion in postischemic myocardium resulting from the combined effect of increased work and ischemia. The latter could be the result of a preferential use of glycolytic substrates for energy production in the postischemic phase.\textsuperscript{21}

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