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ABNORMALITIES IN MYOCARDIAL METABOLISM IN PATIENTS WITH UNSTABLE ANGINA AS ASSESSED BY POSITRON EMISSION TOMOGRAPHY

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SUMMARY. Regional myocardial perfusion and glucose metabolism were assessed in six normal volunteers and 29 patients with coronary heart disease and stable or unstable angina using rubidium-82 (Rb-82) and F-18 fluoro 2-deoxy-D-glucose (FDG) with positron emission tomography.

All normals and patients were studied following overnight fasting, at rest, with no angina or electrocardiographic signs of acute myocardial ischemia or necrosis. Rb-82 myocardial cross-sectional images were obtained employing the continuous infusion technique, while dynamic FDG imaging was employed after intravenous tracer bolus injection. Regional Rb-82 and FDG myocardial concentrations were then calculated by drawing regions of interest over the interventricular septum, anterior and lateral wall of the left ventricle.

The mean Rb-82 uptake for each left ventricular region analyzed was found to be similar between both groups of patients and normal volunteers. The mean myocardial glucose utilization was found to be similar in normal volunteers and patients with stable angina (0.023 ± 0.032 vs. 0.012 ± 0.008 μm ml/min $p<0.42$). However, myocardial glucose utilization was found to be significantly higher in patients with unstable angina compared with both normals and patients with stable angina (0.048 ± 0.047 μM/ml/min $p< 0.001$ for both comparisons). Thus, in patients with severe coronary artery disease and unstable angina, myocardial glucose utilization was enhanced in spite of the absence of clinical, electrocardiographic, or detectable perfusion evidence of acute ischemia.

KEY WORDS. **myocardial metabolism, unstable angina, glucose, deoxyglucose, coronary flow, positron emission tomography**

The impact of several episodes of transient reductions in coronary blood flow on myocardial function and metabolism is not clearly understood yet. Segmental wall motion abnormalities are recognized to persist for long periods of time after the ischemic episode is over in both the clinical setting and experimental models of reperfusion [1, 4].

Sustained regional low concentrations of ATP, impaired free fatty acid utilization, and increased exogenous glucose uptake were found after transient ischemia in several animal models [5, 6]. Evidence of abnormal myocardial metabolism, such as increased glucose uptake and lactate production, was found in patients with coronary artery disease, employing invasive techniques [7, 8]. Regional myocardial metabolism can now be evaluated noninvasively with positron emission tomography (PET). Recently, we reported increased myocardial glucose utilization in the post-ischemic myocardium of patients with exercise-induced ischemia, as evaluated with this technique [9]. In the present study, we assessed noninvasively, regional myocardial perfusion and metabolism in patients with coronary artery disease with stable or unstable angina, using rubidium-82 and F-18 fluoro2-deoxy-D-glucose and PET.

Methods

Study Population

Six normal volunteers with an age ranging from 28 to 39 years and 29 patients with angiographically-proven coronary artery disease were included in this study. Normal volunteers had no history of symptoms, and physical examination, electrocardiogram, and chest x-rays were normal. Of the 29 patients with coronary artery disease seven had chronic stable angina. This group of patients (six men and one woman) aged from 54 to 64 years, had a history of angina ranging from 2 to 15 years, and all had a positive exercise test with ST depression > 0.1 mv. Multiple-vessel disease was present in six and single-vessel disease in one. Global left ventricular function was normal in six and mildly depressed in one.

The remaining 22 patients had unstable angina based on the following criteria:

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1. Clear history of angina with recent crescendo pattern and several episodes of angina at rest associated with transient ST depression
2. No evidence of acute myocardial infarction as assessed by electrocardiogram and serial enzyme determinations

This group of patients (14 men and 8 women) aged from 44 to 72 years and had a history of angina ranging from 1 to 12 years. Multiple-vessel disease was present in 17 patients and single-vessel disease in five. Global left ventricular function was normal in 13, mildly depressed in five, and severely depressed in four patients.

Study Protocol

Medical treatment of all patients with chronic stable angina was discontinued 48 to 72 hours before the study. Patients with unstable angina were admitted to the coronary care unit and maintained on aspirin and sublingual nitrates as required, but chronic administration of nitrates or calcium antagonists were discontinued 12 to 18 hours before the study. No patients were on beta blockers.

During that period, a 24-hour Holter monitoring was recorded immediately before the PET study. All normal volunteers and patients underwent the PET study following 12 to 15 hours fasting. None of the patients with unstable angina had symptoms or electrocardiographic signs of acute ischemia at the time of the PET study. Regional myocardial perfusion was assessed in all normals, all patients with chronic stable angina, and in 10 patients with unstable angina, and regional myocardial exogenous glucose utilization was studied in all subjects.

This study was approved by the Hammersmith Hospital Research Ethics Committee and the United Kingdom Administration of Radioactive Substances Advisory Committee. Written consent was obtained from all patients involved in this study.

Tracers and Procedures

PET was performed using a single slice scanner (ECAT II, CTI) with a spatial resolution of 17 mm (full width at half maximum) in the image plane and an axial resolution of 16 mm. The tomograph was cross-calibrated against a well counter used for measuring blood tracer concentrations. A mid-left ventricular slice was selected for each patient and then a 600-second transmission scan was recorded in order to correct all subsequent emission scans for tissue attenuation.

Myocardial Blood Flow

Regional myocardial perfusion was assessed by measuring myocardial uptake of the positron emitting potassium analogue rubidium-82(Rb-82; half-life 76 seconds), according to the procedure previously described [9, 10]. Briefly, Rb-82 was eluted from a strontium-82/rubidium-82 generator in normal saline and then infused into a peripheral vein at a constant rate of 10 ml/min. Once dynamic equilibrium was achieved (3 to 4 minutes into the continuous infusion), a 120-second scan was recorded (equlibrium scan). Then, the tracer infusion was turned off, and after 30 seconds, when Rb-82 partially had cleared from the blood pool, a second scan (myocardial scan) was obtained for a period of 120 seconds.

Regional Rb-82 fractional uptake was calculated after the myocardial scan had been corrected for decay and normalized to the "arterial input" taken from the equilibrium scan. This measurement is proportional to the product of myocardial blood flow and the tracer extraction fraction. Although Rb extraction may vary with flow, in particular, it decreases with high flow, the method chosen in the present study was proven to be useful to detect transient ischemia in patients [9-11].

Myocardial Glucose Utilization

The glucose analogue F-18 2-fluoro, 2-deoxy-D-glucose (FDG) was used to assess regional myocardial glucose uptake. FDG competes with glucose for transport and phosphorylation by hexokinase in the cell. However, the phosphorylated compound FDG-6-P is not significantly further metabolized and is trapped within the cell in proportion to the rate of transport and phosphorylation of exogenous glucose [12]. Three minutes after injection of 5 to 10 mCi of the tracer, consecutive serial 5-minute scans were recorded over a period of 60 to 70 minutes. Venous blood samples were withdrawn while scanning, and the blood tracer concentration was measured in a well counter in order to obtain the input function.

At the end of FDG scanning, a blood pool scan was recorded after the in vivo labeling of red blood cells by inhalation of C-11 carbon monoxide (CO) [13].

An index of glucose utilization was obtained from the determination of the rate of increase of myocardial tracer concentrations over time. After subtracting

^{11}CO blood pool from each FDG scan (scaled to the corresponding FDG plasma activity), the extravascular myocardial tracer concentration was measured by drawing regions of interest on the interventricular septum, the anterior wall, and the free wall. A plot of myocardial extravascular FDG activity divided by the plasma activity at mid-scan time against the normalized input function, the integral of plasma activity from injection time to mid-scan time divided by the plasma activity at mid-scan time, results in a straight line. The slope *(k)* of this line is proportional to the metabolic rate for glucose (MRG) [14].

Explicitly

$$K = \frac{\text{MRG}}{C_{wb}} \times \frac{E_{FDG}}{E_G}$$

where C_{wb} represents blood glucose concentration and E_{FDG} and E_G are the extraction fractions for FDG and glucose, respectively. The ratio E_{FDG}/E_G is equal to the "lumped constant" (LC), which specifically relates the rate of transmembrane transport and phosphorization of FDG and glucose. In the absence of an absolute value of LC in humans, an estimation of the metabolic rate of glucose (MGR) was expressed in relative terms as MRG × LC = $K \times C_{wb}$. The resulting units are micromoles of glucose per milliliter of myocardium per minute.

Plasma glucose and insulin levels were measured to ensure that all patients were studied under identical dietary conditions [15]. In addition, the MRG in the chest wall muscle was measured from the same tomogram using the same procedure as for the myocardium. This was based on the observation that chest wall muscle responds similarly to the myocardium to fasting-fed conditions [16].

Results

Holter Monitoring

None of the patients with chronic stable angina had pain or electrocardiographic signs of acute myocardial ischemia. Eight of the patients with unstable angina had no pain or ST changes during the recording period. Six patients had angina but no ST changes, and eight had both angina and ST depression. Five of these patients with symptoms and ECG changes had the episode within 2 hours before the PET study.

Myocardial Perfusion

Mean Rb-82 uptake (mean value for the whole scan) was found to be similar in all three groups (0.43 ± 0.09; 0.44 ± 0.06; 0.45 ± 0.07 min^{-1}; mean ± SD for normals and patients with stable and unstable angina, respectively). The regional Rb-82 uptake was also comparable. (Figure 1).

Myocardial Glucose Utilization

The mean MRG (mean for all six regions analyzed) was not different between patients with stable angina and normals (0.023 ± .032 vs. .012 ± .008 μM/ml/min; $p < 0.42$).

Conversely, the mean MRG was significantly higher in patients with unstable angina compared with both normals and patients with stable angina (mean MRG for the unstable group .084 ± .047 μM/ml/min $p < .001$ and $p < 0.01$, respectively).

Regional myocardial MRG also showed no differences between normals and patients with stable angina but was significantly higher for all regions in patients with unstable angina (Figure 2). In these patients, only 6 out of 66 left ventricular regions had a metabolic rate within two standard deviations of the normal mean.

When regional measurements were performed in patients with unstable angina and single-vessel disease, no differences were found between those regions supplied by stenotic arteries and those supplied by nonstenotic arteries (the ratio of MRG of nonstenotic to stenotic was from 0.92 to 1.09).

Myocardial MRG was found to be similar in those patients who had an episode of chest pain or ST changes within 2 hours before the PET study and those with no episodes (0.085 ± 0.05 vs. 0.078 ± 0.06 μM/ml/min p = NS). (Figure 3). Plasma glucose and insulin levels in patients with unstable angina were similar to those values in patients with stable angina and normal volunteers (4.66 ± 0.56, 4.67 ± 0.36, 4.65 ± 0.32 μM/100 ml and 9.04 ± 0.12, 8.41 ± 0.2, 8.9 ± 0.18 μM/ml, respectively).

Discussion

In this study, the age, onset of angina, and angiographic severity of coronary atherosclerotic obstructions were similar between patients with stable and unstable angina. Furthermore, no significant differences in myocardial blood flow were shown by Rb-82. Despite these similarities, myocardial glucose utilization was found to be about four times greater in patients with unstable angina. This increase in glucose utilization seems to be confined to the myocardium,

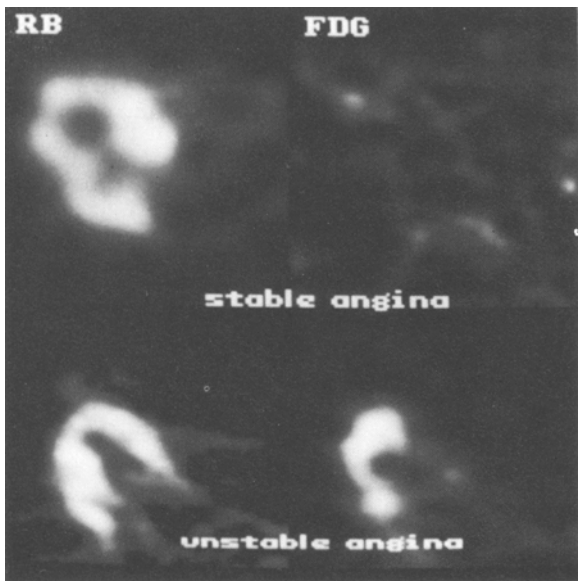

Fig. 1. Rb-82 images are shown on the left side of this figure. No clear regional myocardial perfusion abnormalities are seen in either patient. FDG images (right side of this figure) show very low tracer uptake in the patient with stable angina and increased uptake, particularly in the anterolateral wall of the patient with unstable angina.

since the same measurement performed in the chest wall muscle showed no differences between normals and both groups of patients.

The low exogenous glucose utilization found in normal volunteers and patients with chronic stable angina is in agreement with the fact that the non-ischemic myocardium utilizes free fatty acids preferentially as a source of energy under resting and fasting conditions [15].

The reason for increased glucose utilization in this group of patients with severe unstable angina remains unclear. At the time these patients were studied, there was no evidence of transient myocardial ischemia. In addition, the lack of correlation between the level of myocardial glucose uptake and the proximity of the PET study of the occurrence of transient ischemic episodes (detected by Holter monitoring) suggest that we were observing prolonged metabolic abnormalities in connection with this acute syndrome.

Recent studies with PET have been focused on the restoration of the biochemical process after reperfusion. Thus, Schwaiger and coworkers [6] reported decreased regional myocardial fatty acid oxidation and increased exogenous glucose utilization in a canine model of myocardial reperfusion. These regional abnormalities were clearly present 24 hours after perfu-

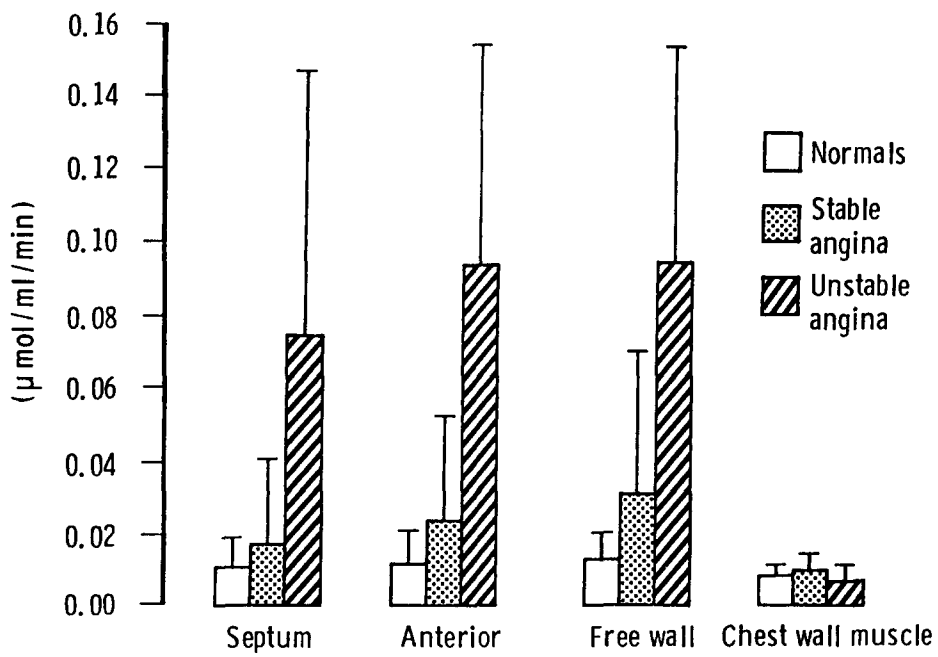

Fig. 2. This graph shows the results of regional myocardial and chest wall muscle metabolic rate for glucose in normals and patients with coronary artery disease. Glucose utilization was found to be increased in patients with unstable angina as compared to both normals and patients with stable angina ($p < 0.001$ and $p < 0.01$, respectively). It should be noted that this increase in glucose utilization was confined to the myocardial, as the chest wall muscle was similar in all three groups.

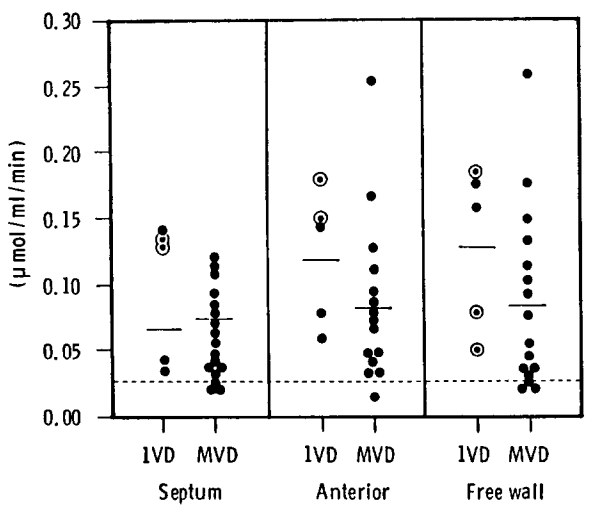

Fig. 3. This graph shows the metabolic rate for glucose in patients with unstable angina with single-vessel disease (1VD) and multivessel disease (MVD). The dotted line indicates the upper limit of the normal range, short lines indicated mean values, dots with open circles indicate areas perfused by stenosed arteries. Note that the level of glucose utilization was similar in both groups.

sion and lasted for up to 1 week. In a clinical setting, Camici and coworkers [9] showed enhanced glucose uptake in the post-ischemic myocardium of patients with exercise-induced ischemia, and Tillish and coworkers described the same finding in patients with coronary artery disease and regional wall motion abnormalities [17]. Thus, we postulate that our findings in this group of patients with unstable angina may be explained as a prolonged metabolic derangement after recurrent transient episodes of ischemia, whereby a shift from free fatty acid metabolism towards glucose utilization may occur to meet the energy demands in the injured myocardium. Since FDG traces only transport and phosphorylation of exogenous glucose, its subsequent fate remains unknown. The increase anaerobic in FDG uptake might be caused by either glycogen resynthesis, increased glycolysis, or a combination of both [18, 19].

The increased glucose utilization found in regions supplied by nonstenotic arteries raises the possibility that a normal increase in glucose uptake may occur in normal areas as a consequence of greater stress imposed on these regions. Such a phenomenon has been demonstrated in the adjacent aerobic myocardium remote to the ischemic area in an experimental model of coronary occlusion [20]. Although a quantitative approach was preferred in this study, several technical limitations should be considered. These include incomplete recovery of counts due to the spatial resolution of the tomograph and the effect of cardiac motion [21]. Both effects lead to an underestimation of the tracer uptake. Since all subjects were studied under the same technical conditions and assumptions, the results obtained are considered to be comparable between different groups.

In conclusion, our study shows that myocardial metabolic changes can be noninvasively demonstrated in patients with unstable angina, even in the absence of detectable acute myocardial ischemia. This observation may be relevant in further studies to elucidate pathophysiological aspects of this syndrome and may become an objective tool for further evaluation of the effect of medical treatment.

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