Metabolic Responses of Hibernating and Infarcted Myocardium to Revascularization

A Follow-up Study of Regional Perfusion, Function, and Metabolism

Thomas H. Marwick, MBBS; William J. MacIntyre, PhD; Antoine Lafont, MD; James J. Nemec, MD; and Ernesto E. Salcedo, MD

Background. The presence of persistent myocardial uptake of $^{18}$F-deoxyglucose (FDG) within hypoperfused, dysfunctional segments has been shown to predict the recovery of regional contractile function after revascularization. The spectrum of metabolic responses of such hibernating tissue to revascularization is less clear.

Methods and Results. Sixteen patients with previous infarction were studied before and after revascularization by myocardial perfusion imaging using $^{82}$Rb positron emission tomography, digitized twodimensional echocardiography, and imaging of postexercise FDG uptake. Hibernation was identified in 35 of 85 segments showing perfusion and wall motion disturbances before intervention. At follow-up (4.9±2.6 months after revascularization), hibernating segments were characterized by reduction of wall motion score ($p<0.001$), improvement of perfusion ($p<0.001$), and reduction of FDG activity ($p<0.001$). Of the 35 hibernating segments, however, 10 still had abnormal elevation of FDG uptake (>2 SD above normal) without differing from other hibernating segments with respect to postoperative perfusion or wall motion score. Segments with persistently abnormal metabolism were characterized before intervention by more severe malperfusion ($p<0.01$) and greater FDG activity ($p<0.01$).

Conclusions. Although wall motion and perfusion improve with revascularization of hibernating tissue, myocardial metabolism remains abnormal in a significant proportion of segments. These segments are characterized by more extensive perfusion and metabolic changes before revascularization. (Circulation 1992;85:1347-1353)

Key Words • myocardial revascularization • tomography, positron emission

Uptake of the exogenous glucose tracer $^{18}$F-deoxyglucose (FDG) may be imaged by positron emission tomography (PET) and demonstrates the persistence of metabolically active tissue within areas believed by conventional criteria to be infarcted.1-3 Postoperative follow-up has confirmed improvement of regional wall motion in segments predicted by this technique to be viable,4,5 thus confirming them to be “hibernating.”6 The metabolic responses of hibernating tissue to revascularization, however, are less clear,5,7 particularly at late follow-up. This paucity of data may reflect the difficulties inherent in the interpretation of metabolic activity within normally perfused segments by conventional glucose-loaded protocols for imaging FDG uptake. Such studies detect tracer uptake in all viable myocardium, so that hibernation is identified by a “metabolism–perfusion mismatch” within malperfused segments.8 In contrast, use of a fasting postexercise protocol is characterized by low FDG uptake in normal myocardium, so abnormal metabolism (ischemia or hibernation) may be isolated as a “hot spot.”9,10 This ability to assess metabolic activity within normally perfused segments was used in this study to examine the metabolic response of hibernating tissue to revascularization.

Methods

Patient Selection

Between July 1989 and February 1990, 16 patients with previous myocardial infarction who were undergoing coronary revascularization were studied with a protocol of preoperative and postoperative PET. The study protocol was approved by the Institutional Review Board, and all patients gave informed consent. Patients with unstable angina and asthma were excluded because of the use of intravenous dipyridamole stress, as were patients with elevation of fasting blood glucose (>140 mg/dl). No patients with extensive coronary disease (involving all three major epicardial coronary arteries) were entered into the protocol, as the definition of normal FDG uptake required the definition of a site of normal perfusion.
Study Design

After localization and skin marking of the inferior cardiac border at fluoroscopy, patients first underwent myocardial perfusion imaging by dipyridamole stress ⁸²Rb PET. They were then removed from the scanner for treadmill exercise testing. After FDG injection, they resumed the same position in the device, and metabolic imaging was performed. Digitized two-dimensional echocardiography was performed in the resting state on the same day. The entire sequence was repeated at follow-up.

Positron Emission Tomography

All PET imaging was performed with a Positron device (Positron Corporation, Houston, Tex.) with a 256×256 matrix for 21 slices 5 mm thick. A transmission scan of approximately 200 million counts was performed with a ⁶⁷Ga-filled Plexiglas ring. After the patient was repositioned in the scanner according to skin markings, these data were used for attenuation correction for both the perfusion and FDG images. Similarly, both sets of images were processed and reconstructed by the Positron Data Acquisition System and backprojected with a Butterworth filter (order 5, cutoff 0.4). Images were displayed in tomographic (transverse, sagittal, and coronal) views as well as a polar map display with a quantitative color scale. They were read in a segmental fashion over 13 myocardial regions (septal, anteroseptal, anterior, lateral, inferolateral, and inferior at the basal and midventricular level and one apical segment). Use of the same position for both ⁸²Rb and FDG scans and superimposition of images permitted comparison of corresponding segments at each test.

Myocardial Perfusion Imaging

Rest and stress ⁸²Rb PET was performed before and after surgery under a previously described protocol. ¹¹ ⁸²Rb derived from a strontium/rubidium generator (Caradigen, Squibb) was injected intravenously as a bolus of 40–60 mCi (this dose depending on generator life). Seventy-five seconds after the conclusion of this injection, resting imaging was performed over 7 minutes. After resting imaging, all patients underwent a dipyridamole handgrip stress under a conventional protocol. ¹² Another injection of 40–60 mCi rubidium was injected 8 minutes after the commencement of this protocol, and stress imaging was performed over 4 minutes, acquiring 20–40 million counts. After image processing and display, segments were categorized by two blinded observers according to the quantitative color scale¹¹ as normal; showing a reversible perfusion defect (identified by a 20% relative reduction of ⁸²Rb activity after stress); or a fixed perfusion defect (defined by regions with >20% fewer than maximum counts). Segments were designated as abnormal only if perfusion defects were identifiable in more than one cut and in more than one plane. In segments showing a mixture of normal, ischemic, or infarcted tissue, categorization was based on the most extensively represented entity within that segment.

Postexercise FDG Imaging

Patients underwent fasting FDG imaging after perfusion imaging according to a previously described protocol. ¹⁰ Four to 10 mCi of tracer were injected 30 minutes after maximum symptom-limited treadmill exercise, and imaging was commenced 40 minutes later to allow for uptake and phosphorylation of deoxyglucose in the heart. Patients were imaged for 20 minutes, with a mean acquisition of 38 million counts per study. Attenuation correction and image reconstruction techniques were the same as those used for ⁸²Rb imaging. Because patients were in the same position for both PET studies, superimposition of FDG over the ⁸²Rb images helped to orient FDG images in situations where the cardiac borders were uncertain because of low FDG activity within normal segments.

Regional FDG activity was assessed by two blinded observers in the same 13 segments as were used for perfusion imaging. In each patient, a “reference normal” segment was determined for metabolic activity by selection of the site of maximum resting flow without significant reduction at stress perfusion imaging and subtended by a normal coronary artery. Sites other than this reference normal segment with resting perfusion within the normal range, supplied by normal coronaries and without stress-induced defects, were then combined to establish a range of normal FDG uptake measured as a percentage below or above the reference level. In each patient, the presence of FDG activity >2 SD (≥30%) above the reference normal segment was classified as abnormal.

Digitized Two-dimensional Echocardiography

Two-dimensional echocardiograms were recorded in the parasternal long- and short-axis and apical four- and two-chamber views at the time of preoperative PET and at least 3 months after revascularization. Images were acquired on standard, commercially available equipment and were digitized on-line (PreVue, Nova Microsonics, Indianapolis, Ind.) into a quad-screen, cine-loop format. For the purpose of interpretation, digitized cine loops before and after surgery were compared in a side-by-side format. Thirteen myocardial segments were scored. From the apical window, the septum and lateral wall were evaluated at basal and midventricular levels in the four-chamber view, and the inferior and anterior walls were scored at the same levels in the apical two-chamber view, with the apex scored once from a composite of both apical views. In the parasternal long-axis view, the posterior (corresponding to the inferolateral by PET) and anteroseptal walls were evaluated at the basal and midventricular levels, and the short-axis view was used to corroborate findings in the midventricular plane of the other views. These regions thus corresponded to the 13 PET segments, although the use of a second imaging modality made this correlation less exact than that between the PET techniques. Wall motion was scored by two blinded observers based on a conventional wall motion score¹³ in which a score of 1 is given for normal wall motion, 2 for hypokinesia, 3 for akinesia, 4 for dyskinesia, 5 for aneurysm, and 6 for akinesia or dyskinesia with thinning of the myocardium. The presence of hibernation was defined by improvement (≥1 point) of the wall motion score within each individual segment.

Data Analysis

This study observed the behavior of segments having a resting wall motion abnormality and perfusion defect before revascularization. In the first instance, these
were divided into hibernating and nonhibernating groups on the basis of the presence or absence of improvement of regional wall motion after revascularization. Segments were then subdivided according to their metabolic response to revascularization. Groups were compared with regard to continuous and noncontinuous variables by the t test or χ² or Fisher's exact test, respectively (the latter depending on sample sizes). Values were expressed as mean±SD.

Results

Study Population

The study group (n=16) ranged from 42 to 76 years of age; 14 were men. All patients had previous myocardial infarction (5±11 months before the preintervention studies). Nine had one-vessel and seven had multivessel disease, but none had disease in all three major coronary arteries. Revascularization was accomplished in nine by coronary angioplasty and in seven by coronary bypass surgery. In all patients, segments identified as potentially hibernating were adequately revascularized. Six patients had angina before revascularization, and none had ongoing angina at the time of follow-up.

Distinction of Hibernation and Infarction

A total of 85 regions showing fixed perfusion defects and resting wall motion disturbances were identified at the prerevascularization studies. At least 2 months (4.9±2.6 months) after intervention, 35 (41%) of these segments (in 12 patients) demonstrated improved function by two-dimensional echocardiography and were classified as hibernating. Fifty segments failed to improve at follow-up and were considered nonhibernating. The preoperative FDG activity was significantly higher in hibernating than in nonhibernating segments (29±11% versus 15±15% above reference normal, p<0.001), but preoperative perfusion and wall motion results did not distinguish between the groups. Of the 35 hibernating segments, 25 were correctly predicted to be viable, and of the 50 nonhibernating segments, 38 were correctly predicted to be nonviable by FDG criteria. Thus, with this 13-segment analysis, the sensitivity of this FDG protocol for the identification of hibernation was 71%, the specificity was 76%, and the positive and negative predictive values were 68% and 79%, respectively.

In the hibernating segments (Table 1), the mean wall motion score improved from 2.8±0.7 to 1.4±0.5 (p<0.001), including 24 segments that improved regional function by one point on the wall motion score and 11 that improved by more than one point (Figure 1). Twenty-one segments returned to normal function, and 14 were left with hypokinesis. By definition, there was no improvement of regional function in the nonhibernating group.

In parallel with the improvement of regional wall motion, myocardial perfusion improved significantly in the group with hibernation (57±11% to 69±13% of maximum counts, p=0.001) but did not improve significantly in the group without hibernation (Table 1). Ischemia, evidenced by a stress-induced ⁸²Rb perfusion defect, was apparent in six patients before surgery. Of the segments with hibernation, adjacent areas of ischemia subtended by the same coronary artery were present in three. At postoperative follow-up, dipyridam-

| Table 1. Prerevascularization and Postrevascularization Measurements of Wall Motion, Perfusion, and ¹⁸F-Deoxyglucose Activity in Myocardial Segments Without and With Hibernation |
|---------------------------------|-----------------|-----------------|----------|
|                                 | Before RVS      | After RVS       | p        |
| Wall motion*                    |                 |                 |          |
| Nonhibernating (n=50)           | 3.0±1.0         | 3.0±0.9         | NS       |
| Hibernating (n=35)              | 2.8±0.7         | 1.4±0.5         | <0.001   |
| Perfusion†                      |                 |                 |          |
| Nonhibernating (n=50)           | 55±13           | 58±13           | NS       |
| Hibernating (n=35)              | 57±11           | 69±13           | <0.001   |
| ¹⁸F-Deoxyglucose activity‡      |                 |                 |          |
| Nonhibernating (n=50)           | 15±15           | 7±19            | <0.001   |
| Hibernating (n=35)              | 29±11           | 16±17           | <0.001   |

*Mean segmental wall motion score.
†Regional ⁸²Rb activity expressed as percentage of maximum activity.
‡Percent above normal.

FIGURE 1. Graph of regional wall motion (WM) scores in each of the 35 hibernating segments before and after revascularization (revasc). n, number of segments showing each wall motion score.

ole stress ⁸²Rb PET imaging showed that all areas of ischemia surrounding hibernating segments demonstrated resolution, with no new evidence of ischemia in any patient.

In the 35 hibernating segments, regional FDG activity fell from 29±11% to 16±17% above the reference normal segment (p<0.001) after revascularization (Table 1). In the 50 nonhibernating segments, a reduction of FDG activity from 15±15% to 7±19% above the reference normal segment also occurred, despite failure of regional wall motion and regional perfusion to improve after revascularization.

Normalization of Metabolism After Revascularization

In 25 of the 35 hibernating segments (in eight of the 12 patients with hibernation), regional FDG activity was within the normal range after revascularization (Figure 2). Despite the significant overall reduction of FDG uptake in the hibernating group, however, in 10 segments (29%) the FDG level was still >2 SD above the reference normal site (Figure 3). This pattern was seen in four patients who were studied 5.0±2.4 months after
intervention. Six of these hot spots were located in the anterior, anteroseptal, and apical regions, and four were in the inferior or inferolateral regions. In eight of the 10 segments, the preoperative FDG had been abnormally elevated. Evidence of abnormal metabolism was also present in nine of the 50 nonhibernating segments after intervention; six of these had shown elevated regional FDG activity before intervention.

Table 2 compares the metabolic, perfusion, and functional characteristics of hibernating segments showing normalization of FDG uptake with those showing persistently abnormal metabolism. Hibernating myocardium with normal FDG uptake after surgery was characterized by less prominent preoperative FDG hot spots than myocardium displaying persistently abnormal metabolism (26±9% versus 37±11% above the reference...
normal segment, \( p < 0.01 \). This correlation of persistent FDG activity with higher preoperative FDG levels in hibernating and nonhibernating segments is illustrated in Figure 4. Likewise, the severity of the preintervention perfusion defect was less in those with postoperative recovery of abnormal metabolism, but the groups did not differ significantly with respect to the preintervention wall motion disturbance.

Despite the division of hibernating segments into two groups on the basis of differences in regional FDG activity, after revascularization there were no significant differences in regional systolic function and perfusion between these groups (Table 2).

**Discussion**

**Revascularization of Hibernating Myocardium**

It is now well accepted that chronically ischemic myocardium may “hibernate,” becoming dysfunctional without being infarcted. Conventional indexes of myocardial viability have proved inaccurate for the prediction of functional recovery in this hibernating tissue after revascularization.\(^1\)\(^4\)\(^5\) The demonstration of preoperative FDG uptake within malperfused segments, however, has been shown to correlate with functional improvement with the restoration of perfusion,\(^4\)\(^5\) a finding supported by our data.

Previous studies have pointed toward the persistence of abnormal metabolism in some hibernating segments. Tamaki et al\(^5\) identified persistent FDG activity at 5–7 weeks after revascularization. Using a dog model involving a 3-hour episode of ischemia with subsequent stunning, Schwaiger et al\(^1\)\(^8\) showed a slow functional recovery over 4 weeks matched by continuing metabolic abnormalities, including increased FDG uptake. In humans, longitudinal follow-ups 2 days and 2 months after angioplasty were performed by Nienaber et al,\(^7\) demonstrating early resolution of perfusion disturbances but delay in functional and metabolic improvement until the later study. A longer delay in functional recovery was documented in a recent case report,\(^1\) although a correlation of metabolic with contractile function was not performed at late follow-up, and there was a possible toxic contribution to left ventricular dysfunction. The improvement of hibernating tissue after revascularization might have been considered to be gradual, with functional recovery following metabolic recovery.\(^2\)

The data obtained in this selected series of patients confirm the presence of these persistently FDG-positive segments at late follow-up, despite the improvement of perfusion and contractile function. Examination of the correlates of this pattern indicates that such tissue is characterized before surgery by more severe hypoperfusion and a more severe metabolic disturbance.

**Significance of Increased FDG Uptake**

The metabolic response to ischemia is characterized by an acceleration of glucose uptake and glycolysis.\(^2\)
During exercise, normal myocardium also increases glucose usage, but when FDG injection is delayed until the postischemic state, malperfused areas can be seen to show greater FDG activity than the surrounding myocardium. This phenomenon may reflect the repletion of glycogen used during the ischemic period. The same metabolic responses appear to occur in chronically ischemic (hibernating) myocardium, as evidenced by functional improvement in areas of resting malperfusion and contractile dysfunction in the presence of increased FDG activity. Thus, both acutely and chronically ischemic myocardium share the hallmark of increased regional fasting FDG activity; their distinction is based on the respective presence or absence of a reversible perfusion defect by 82Rb PET. Persistence of this FDG hot spot in the postvascularization state in the absence of other evidence of ischemia (e.g., stress-induced 82Rb defects) implies that the continuing abnormal FDG activity is an index of residual metabolic disturbance rather than ischemia alone.

Methodological Considerations

The methodology of metabolic imaging used in this study differs from the majority of previous FDG imaging studies in humans. By the conventional resting glucose-loaded methodology, FDG uptake in normal myocardium is enhanced, so the tracer is seen in all viable tissue, and the glucose avidity of postischemic viable myocardium may be hidden. In contrast, with fasting protocols, increased FDG uptake is associated with postischemic or hibernating myocardium, whereas normal tissue is characterized by very low FDG uptake. Thus, use of the fasting methodology in this study permitted analysis of the level of FDG activity within areas where perfusion had been restored after revascularization. Despite this benefit, however, this approach has some disadvantages; it is technically more difficult, especially with respect to image orientation, and may be complicated by false-positive FDG hot spots, particularly in the posterolateral wall. Finally, the variability in FDG activity in normal fasting subjects prevents the application of a “normal range” between patients. The alternative relative approach used in this study involves the use of a reference normal region in each patient, which has the disadvantage of restricting the methodology to patients with known coronary anatomy and without extensive coronary disease.

Myocardial Responses to Ischemia

The effects of ischemia on the myocardium occur in a spectrum reflecting the duration and severity of the ischemic insult. Although cell death may take some hours to occur after an ischemic event, the onset of morphological changes occurs at an earlier stage and is characterized initially by membrane damage. Cellular degeneration, involving the replacement of myofibrils by mitochondria, sarcoplasmic reticulum, and glycogen granules, occurs with chronic ischemia. Thus, significant morphological changes short of cellular death occur in postischemic cells.

Little is known of the progression of metabolic disturbances that may parallel this sublethal cellular damage. Our data suggest that after chronic ischemia, several groups of metabolically abnormal (FDG-positive) cells remain. Some of these may be minimally damaged and improve contractile and metabolic function with revascularization. At the other extreme, despite increased preoperative FDG activity, other segments are presumably too severely injured to improve contractile function (even at late follow-up) and constitute false-positives at the preoperative FDG study. An intermediate group characterized by more severe ischemia and disordered metabolism before surgery improves contractile function (thereby falling into the category of hibernation) but does not revert to normal oxidative activity. The latter group may constitute a heterogeneous population of cells with various degrees of viability. This spectrum of ischemic injury has been anticipated by Bashour and Mason in a recent editorial.

Limitations

This study involved the use of PET for observations of perfusion and metabolism in patients before and after revascularization. It represents a selected group as a result of the exclusion of those with three-vessel disease because of technical constraints imposed by the FDG technique. For reasons of timing in a busy clinical laboratory, only static imaging was performed, precluding the accurate quantification of myocardial blood flow or metabolic rate. No assessment of oxidative metabolism (e.g., with 13C-acetate) was possible because of the absence of an on-site cyclotron. Therefore, the study reflects the persistence of abnormal glycolytic metabolism, which in view of the selection process may not have the same prevalence in other groups.

Despite the use of a fasting FDG protocol, we believe, for two reasons, that the hot spots reflect persistent abnormal metabolism rather than heterogeneity of the metabolic response. First, the locations of these sites are dispersed through all regions of the myocardium, in contrast to the usual posterolateral site of false-positive findings. Second, the prevalence of false-positives with fasting, postexercise FDG imaging is lower than that reported for resting imaging.

Finally, the nature of the myocardium producing the persisting elevated uptake of FDG may be debated. We have used the presence of a stress-induced perfusion defect to define ischemia. In the absence of this defect after surgery and in the presence of adequate revascularization in all patients, we have concluded that the tissue causing this signal suffered persistent metabolic upset rather than ongoing ischemia. It is true, however, that postexercise FDG imaging is exquisitely sensitive to ischemia, and ongoing subendocardial ischemia occurring in the absence of ischemia by 82Rb PET cannot be excluded.

Conclusions

The long-term persistence of abnormal glycolytic metabolism after revascularization suggests that complete reversibility of ischemic damage may not necessarily be achieved. These data support the existence of subpopulations of myocytes with differing degrees of functional and metabolic disturbances within ischemic myocardial segments. The clinical implications of these groups of cells, with reference to both their effect on functional recovery and their clinical significance, warrant further study.
Acknowledgments

The superb technical assistance of Janet King, RN, Gopal Saha, PhD, and Annette Beachler, CNMT, and the support of Raymundo T. Go, MD, are gratefully acknowledged.

References

Metabolic responses of hibernating and infarcted myocardium to revascularization. A follow-up study of regional perfusion, function, and metabolism.
T H Marwick, W J MacIntyre, A Lafont, J J Nemec and E E Salcedo

Circulation. 1992;85:1347-1353
doi: 10.1161/01.CIR.85.4.1347

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/85/4/1347