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Presurgical identification of hibernating myocardium by combined use of technetium-99m hexakis 2-methoxyisobutylisonitrile single photon emission tomography and fluorine-18 fluoro-2-deoxy-D-glucose positron emission tomography in patients with coronary artery disease

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Abstract. We tested the possibility of identifying areas of hibernating myocardium by the combined assessment of perfusion and metabolism using single photon emission tomography (SPET) with technetium-99m hexakis 2-methoxyisobutylisonitrile (^{99m}Tc-MIBI) and positron emission tomography (PET) with fluorine-18 fluoro-2-deoxy-D-glucose (^{18}F-FDG). Segmental wall motion, perfusion and ^{18}F-FDG uptake were scored in 5 segments in 14 patients with coronary artery disease (CAD), for a total number of 70 segments. Each subject underwent the following studies prior to and following coronary arterybypass grafting (CABG): first-pass radionuclide angiography, electrocardiography gated planar perfusion scintigraphy and SPET perfusion scintigraphy with ^{99m}Tc-MIBI and, after 16 h fasting, ^{18}F-FDG/PET metabolic scintigraphy. Wall motion impairment was either decreased or completely reversed by CABG in 95% of the asynergic segments which exhibited ^{18}F-FDG uptake, whereas it was unmodified in 80% of the asynergic segments with no ^{18}F-FDG uptake. A stepwise multiple logistic analysis was carried out on the asynergic segments to estimate the postoperative probability of wall motion improvement on the basis of the preoperative regional perfusion and metabolic scores. The segments with the highest probability (96%) of functional recovery from preoperative asynergy after revascularization were those with a marked ^{18}F-FDG uptake prior to CABG. High probabilities of functional recovery were also estimated for the segments presenting with moderate and low ^{18}F-FDG uptake (92% and 79%, respectively). A low probability of functional recovery (13%) was estimated in the segments with no ^{18}F-FDG uptake. Despite the potential limitations due to the semiquantitative analysis of the images, the method appears to provide reliable information for the diagnostic and prognostic evaluation of patients with CAD undergoing CABG and confirms that the identification of hibernating myocardium with ^{18}F-FDG is of paramount importance in the diagnosis of patients undergoing CABG.

Key words: Myocardial perfusion – Myocardial metabolism – Radionuclide imaging – Myocardial viability – Coronary artery bypass grafting

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Introduction

Positron emission tomography (PET) permits the differentiation between viable and scar tissue in the heart (Marshall et al. 1983) and the detection of the presence of hibernating myocardium, i.e. ischaemic and asynergic but viable tissue, in patients affected by coronary artery disease (CAD) prior to surgical revascularization (Tillisch et al. 1986; Tamaki et al. 1989). PET is now being widely used for clinical purposes (Schwaiger and Hicks 1991) because of this. The procedure entails the assessment of regional myocardial perfusion by use of either nitrogen-13 ammonia ($^{13}NH_3$) (Schelberg et al. 1979, 1981), rubidium-82 (Goldstein et al. 1983, 1986; Mullani et al. 1983) or oxygen-15 water (Bergmann et al. 1984, 1989) and the evaluation of myocardial metabolism with fluorine-18 fluorodeoxyglucose (^{18}F-FDG; Phelps et al.

1978). Myocardial metabolism is evaluated either following an oral glucose load or under fasting conditions.

Under fasting conditions the normal myocardium derives its energy mainly from the beta-oxidation of fatty acids. An inadequate oxygen supply causes a metabolic shift from fatty acids to glucose utilization in the ischaemic but viable tissue, and energy is produced through anaerobic glycolysis (Bing 1965). Due to this metabolic shift, ischaemic viable myocardium is identifiable due to a markedly higher ^{18}F-FDG uptake compared with necrotic or normal tissue.

While the evaluation of myocardial glucose metabolism can only be pursued via PET and ^{18}F-FDG, regional myocardial perfusion can be assessed using tracers labelled with positron emitting isotopes or single photon emitting radiotracers, including thallium-201 (Strauss et al. 1975) and compounds labelled with technetium-99m, either with planar techniques or single photon emission tomography (SPET) (Maddahi et al. 1986; Kiat et al. 1989; Wackers et al. 1989). For the clinical assessment of myocardial perfusion, the use of single photon techniques is far more common than that of PET.

For the identification of hibernating myocardium, which requires the assessment of both blood flow and viability, it would be very useful to have a diagnostic procedure that integrates the two major imaging modalities available in nuclear medicine, i.e. PET and SPET, in order to reduce the PET machine time.

The purpose of this study was to evaluate the feasibility of identifying the areas of hibernating myocardium by perfusion studies with ^{99m}Tc-methoxy isobutylisonitrile (MIBI)/SPET and metabolic studies with ^{18}F-FDG/PET under fasting conditions prior to coronary artery bypass grafting (CABG). The postoperative improvement of segmental contractile function was considered to be the proof of the preoperative hibernating status.

Patients and methods

The *study protocol* consisted of physical examination, electrocardiogram (ECG), coronary angiography, first-pass radionuclide angiography, ECG gated planar perfusion scintigraphy, SPET perfusion scintigraphy and PET metabolic scintigraphy at rest. ^{99m}Tc-MIBI was used to perform the first-pass and ECG gated perfusion scintigraphy for the evaluation of wall motion, as well as for the assessment of perfusion (Baillet et al. 1989; Marcassa et al. 1990; Villanueva-Meyer et al. 1990). This approach avoids the use of two different radioactive tracers for the assessment of wall motion and perfusion and reduces the radiation exposure. ^{18}F-FDG was used for the assessment of metabolism. SPET perfusion scintigraphy was also performed after the administration of the tracer under exercise. All the exams were performed over a period of 1 week. The average time elapsed between the completion of the preoperative evaluation of the above variables and the CABG was 9 ± 4 days (mean $\pm$ SD). We examined the above variables in 70 myocardial segments in 14 patients (2 women and 12 men, mean age 61.2 years, range 46–70 years) waiting to undergo CABG. All the patients presented with either stable or unstable angina, chronic multivessel CAD and moderate left ventricular dysfunction (ejection fraction below 50%). In particular, 12 had three-vessel disease, 1 two-vessel disease (left anterior descending artery and right coronary artery), and 1 had one-vessel disease (left anterior descending artery). All the patients underwent diagnostic coronary angiography according to the Judkins technique within 6 months of the nuclear studies. No patient had any acute myocardial infarction in the 7 months preceding the study, nor were any of the patients affected by diabetes mellitus. Each subject underwent the study protocol twice, prior to and after CABG. The average time elapsed between the preoperative and the postoperative study was 179 ± 40 days (mean $\pm$ SD). Patients underwent nuclear studies after cardioactive drug wash-out.

Radiotracers. ^{99m}Tc-Hexakis 2-methoxyisobutylisonitrile was prepared from a commercial kit (Cardiolite) purchased from Du Pont De Nemours (Billerica, Mass.). The tracer was labelled by adding approximately 3000 MBq of ^{99m}Tc to each vial containing 1 mg of MIBI salt. The vial was then placed in boiling water for approximately 10 min. The ^{99m}Tc-MIBI was used, after cooling, within 3 h following its preparation.

The synthesis of ^{18}F-FDG was carried out according to the method previously described (Hamacher et al. 1986) with a compact automated module connected to the cyclotron (CTI/Siemens RDS 112 cyclotron, Siemens/CPS, Knoxville, Tenn.). The ^{18}F-FDG was used within 1 h of its preparation.

Quality control procedures of the tracers was carried out routinely according to methods previously described, and only ^{18}F-FDG and ^{99m}Tc-MIBI samples with a radiochemical purity higher than 95% were used.

First-pass radionuclide angiography was performed at rest as previously described (Baillet et al. 1989) using a rotating gamma-camera (7500 Orbiter, Siemens, Erlangen, Germany) equipped with a general purpose collimator following the i.v. bolus injection of approximately 900 MBq of ^{99m}Tc-MIBI in 0.3–0.5 ml of physiological saline. The patient was supine, positioned for a right anterior oblique (RAO) 30° projection. Data were acquired in list-mode.

ECG gated planar perfusion scintigraphy. Some 60 min after the first-pass radionuclide angiography study, the patient was repositioned supine under the same gamma-camera for ECG gated myocardial planar perfusion scintigraphy in the anterior and left anterior oblique (LAO) 45° projections using a procedure similar to the one previously described (Marcassa et al. 1990). The camera was equipped with a high-resolution collimator. Data were acquired from a 24-frame gated study using a 2:1 software zoom, on a 64×64 pixel matrix, collecting up to 3 million counts/view. The accepted interval difference between two consecutive R-R waves was within 10%, and none of the patients presented with arrhythmias.

SPET perfusion studies. SPET scans at rest were carried out 90 min after the first-pass angiography study, with the same gamma-camera, following a standard cholecystokinetic fatty meal at 30 min postinjection. A stress perfusion study was carried out within 72 h following the rest study. The patients were asked to exercise according to the Bruce protocol (Bruce et al. 1963). The tracer was injected when the subjects approached the end point test; the subjects were then encouraged to continue the exercise for at least 1 min. Sixty-four angular projections (64×64 matrix) over 360° were acquired. The acquisition time was between 30 and 40 min (64 steps, 30 s each). Transaxial slices, 6.2 mm thick, were reconstructed using a filtered back-projection algorithm with a Butterworth filter with

a cut-off frequency of 0.4 cycles per pixel. No attenuation correction was performed. Spatial resolution in the transaxial plane was 1.8 cm. Transaxial slices were realigned along the horizontal and vertical long axis and the short axis.

PET metabolic studies. Were performed using an ECAT 931/04-12 tomograph (CPS/Siemens, Knoxville, Tenn.) with a transaxial field-of-view of 55.5 cm and an axial field-of-view of 5.4 cm, equipped with four germanium-68 retractable ring sources for transmission scans. Patients were studied after an overnight fast (at least 16 h). In each patient 2 emission scans, lasting 10 min each, were carried out between 40 and 60 min after the i.v. administration of approximately 250 MBq of ^{18}F-FDG. Two sets of 7 tomographic images of radioactivity distribution, 6.75 mm thick, were reconstructed in the transaxial plane using the Hann filter with a cut-off frequency of 0.5 cycles per pixel. Images were corrected for attenuation using coefficients measured by two 15-min transmission scans carried out prior to the tracer administration. Under these conditions the spatial resolution was 8 mm full width at half-maximum (FWHM). Data were reconstructed on the horizontal and vertical long axis and the short axis.

Coronary artery by-pass grafting. CABG was performed within 2 weeks of the nuclear studies. In 12 patients the surgical procedure was performed using bilateral internal thoracic artery (ITA) and saphenous vein grafts to complete the revascularization. One patient had only one ITA graft while another had 1 ITA graft and 2 additional saphenous vein grafts. All the patients underwent the same myocardial protection protocol according to Buckberg (1987, 1989). To perfuse the coronary bed completely and bypass critical coronary stenoses, antegrade and retrograde delivery of cardioplegic solution were performed after cannulation of the coronary sinus. A "warm cardioplegic induction" was routinely employed in all the patients with an ejection fraction below 40%. In this case the reperfusate solution also contained aspartate and glutamate, two substrates for aerobic metabolism. The techniques employed prevent prolonged myocardial ischaemia, minimize the damage of uncontrolled reperfusion and thus improve myocardial recovery after cardioplegic arrest during cardiopulmonary bypass.

At the time of the CABG the surgeons were unaware of the results of the ^{18}F-FDG/PET study, whereas they were informed of the results of all the other studies.

The *image analysis* was based upon the evaluation of wall motion, perfusion and metabolism in 70 myocardial segments, 5 in each of the 14 patients studied.

Wall motion assessment. Segmental wall motion was assessed on a pixel by pixel basis of the RAO 30° first-pass radionuclide angiography study displayed on a relative colour scale in the anterior, apical and inferior wall (Fig. 1). The analysis of these images was used for the segments in which the wall motion could not be assessed by ECG gated planar perfusion scintigraphy due to the absence of ^{99m}Tc-MIBI uptake. ECG gated perfusion planar scintigraphy was processed by spatial smoothing and displayed in a cinematic mode for observer evaluation. Anterior and LAO 45° projections (Fig. 1) were analysed to assess the wall motion in 5 segments: anterior, apical, inferior, lateral and septum.

Wall motion scores were given by three independent observers in each segment from 0 to 4 (0 = dyskinesis, 1 = akinesis, 2 = severe hypokinesis, 3 = hypokinesis, 4 = normal kinesis).

In those segments presenting with severe perfusion defects (n = 11) in which the evaluation of wall motion by analysis of the ECG gated planar perfusion study was inadequate, the score was given using the first-pass radionuclide angiography study. By combining

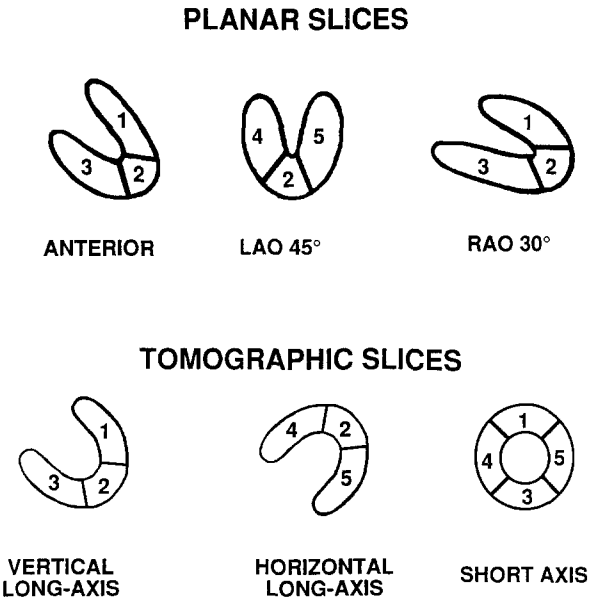

Fig. 1. Diagrammatic left ventricle segmentation of the right anterior oblique (RAO) 30° first-pass radionuclide angiography, of the anterior and left anterior oblique (LAO) 45° electrocardiogram (ECG) gated perfusion planar scintigraphy used for the analysis of regional wall motion and of the single photon emission tomography (SPET) and positron emission tomography (PET) images used for the analysis of regional perfusion and metabolism (for details, see text) *1* anterior wall, *2* apex, *3* inferior wall, *4* septum, *5* lateral wall

the use of these two methods, in only one septal and three lateral segments was the assessment of wall motion impossible prior to surgery; these segments were considered akinetic, whereas a score could be attributed after CABG following an improvement of perfusion.

Wall motion was considered to be improved when the score increased by 1 or more after the CABG.

First-pass radionuclide angiography was used also to evaluate the left ventricular ejection fraction (LVEF) computed from the end-diastolic (ED) and end-systolic (ES) ventricular edges as follows:

$$\text{LVEF} = (\text{ED counts} - \text{ES counts})/\text{ED counts}$$

SPET and PET assessment. A semi-quantitative visual analysis was carried out on the tomographic images of perfusion and metabolism by dividing the left ventricle image into 5 segments comparable with those selected for the wall motion analysis (Fig. 1). The SPET perfusion studies at rest and during exercise were evaluated concurrently and visually scored by three independent observers, who were unaware of the results of the PET study. The score ranged from 0 to 3 (0 = markedly reduced or absent perfusion at rest, 1 = rest hypoperfusion worsening after stress, 2 = hyperfusion only under stress, 3 = normal perfusion). The PET studies of metabolism were evaluated and visually scored by three other independent observers who were unaware of the results of the SPET study. The score ranged from 0 to 3 (0 = no ^{18}F-FDG uptake, 1 = low uptake, 2 = moderate uptake, 3 = high uptake).

The *statistical analysis* was carried out on the scores of perfusion, metabolism and wall motion from the 70 myocardial segments considered. One-way ANOVA was used to test interobserver variability. A stepwise multiple logistic analysis was carried out on

the segments that exhibited an impaired wall motion prior to the intervention to estimate the independent contribution of the preoperative perfusion and metabolism scores on wall motion improvement. For this purpose we used the BMDP statistical package. The maximum likelihood method was used to assess the significance of each term in selecting the one to be removed or entered in each step (Engelman 1985). The only statistical test carried out on the 14 patients as a set of data was a two-tailed Student's *t*-test to compare the mean values of the ejection fraction before and after the CABG.

Results

The interobserver score variability of wall motion, perfusion and metabolism was not statistically significant; therefore, scores from the observers of each of the above three functions were averaged for the analysis.

Perfusion studies

The ^{99m}Tc-MIBI/SPET study identified 67/70 segments (96%) with different degrees of perfusion abnormalities in the 14 subjects examined. Perfusion was absent at rest in 11/70 segments (16%), it was impaired at rest and worsened after stress in 31/70 segments (44%), it was impaired only after stress in 25/70 additional segments (36%), and 28/70 segments appeared normally perfused at rest. Perfusion improved in 53/67 segments (79%) after the CABG, while it remained unchanged in 14/67 (21%). An improvement of perfusion occurred in 91% of the segments with preoperative markedly reduced or absent perfusion at rest, in 77% of those with preoperative rest hypoperfusion worsening under stress, and in 76% of the segments with preoperative hypoperfusion only under stress.

Metabolic studies

The PET study identified 47/70 segments (67%) with ^{18}F-FDG uptake. At least 1 segment with abnormal ^{18}F-FDG uptake was present in all 14 subjects examined. Low uptake was observed in 16/70 segments (23%), moderate uptake in 19/70 (27%) and high uptake in 12/70 (17%) segments. The postoperative study identified 30/70 segments (43%) with ^{18}F-FDG uptake. The uptake of ^{18}F-FDG was absent after the CABG in 17 of the 47 segments (36%) in which it was observed prior to surgery; it was decreased in 14/47 segments (30%), persisted at the preoperative level in 12/47 segments (26%) and increased in 4/47 segments (9%). ^{18}F-FDG uptake was present in 4/23 segments (17%) in which there was no uptake prior to the CABG.

Perfusion and metabolism

The preoperative ^{18}F-FDG/PET study identified 2 segments with ^{18}F-FDG uptake among the 3 that appeared normally perfused both under stress and at rest. Within the hypoperfused segments, 45 of 67 (67%) evidenced ^{18}F-FDG uptake. After the CABG, the perfusion improved in 38/45 segments (84%) and remained unchanged in 7/45 segments (16%). Perfusion improved in 15/22 segments (68%) in which a perfusion defect was present and ^{18}F-FDG uptake was not observed prior to the CABG.

Wall motion

The evaluation of the first-pass radionuclide angiography and of the ECG gated perfusion planar scintigraphy performed prior to surgery showed 54/70 segments (77%) with abnormal wall motion in 14 patients (Fig. 2). Wall motion improved in 40/54 segments (74%) after the CABG, while it remained unchanged in 14/54 (26%).

The ^{18}F-FDG/PET study showed within the segments with abnormal wall motion 39 of 54 (72%) with ^{18}F-FDG uptake (Fig. 2) and 15 without ^{18}F-FDG uptake. Wall motion improved in 37/39 (95%) of the segments with ^{18}F-FDG uptake and remained unchanged in 2 (5%). Wall motion improved in 3/15 (20%) of the segments in which ^{18}F-FDG uptake was not observed prior to the CABG and remained unchanged in 12 (80%).

The ^{99m}Tc-MIBI/SPET study identified within the segments with abnormal wall motion 53/54 hypoperfused segments (98%); 11/53 with a perfusion score of 0 (21%), 22 with a perfusion score of 1 (41%) and 20 with a perfusion score of 2 (38%). Wall motion improved in 38/53 hypoperfused segments (72%) and remained unchanged in 15 (28%) despite the fact that there was an improvement in perfusion in 10/15 segments and despite the fact that ^{18}F-FDG uptake was present in 2/10 segments. Wall motion improved in 72% of the segments with a preoperative perfusion score of 0, in 77% of the

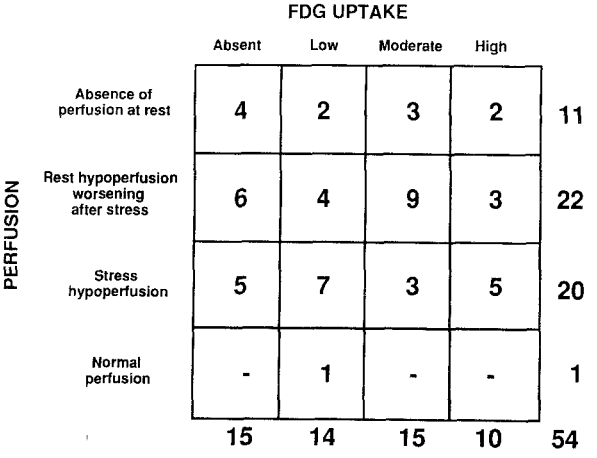

Fig. 2. Number of segments with wall motion abnormalities. Data in each cell indicate the number of segments with abnormal wall motion in relation to the different combinations of metabolic and perfusion scores

segments with a perfusion score of 1 and in 75% of the segments with a perfusion score of 2.

Of the 16 segments presenting with normal wall motion, 8 exhibited ^{18}F-FDG uptake, and 7 of them were hypoperfused.

LVEF improved in 13/14 patients and remained unchanged in 1. The preoperative LVEF (%) was 37.5 ± 4.9 (mean $\pm$ SD), whereas the postoperative LVEF was 47.9 ± 4.1 ($P < 0.001$).

The mean wall motion score of the segments presenting with abnormal kinesis was 2.02 ± 0.9 before CABG and 3.02 ± 0.9 after CABG.

Multiple logistic analysis

Two multiple logistic analyses were performed on the scores of metabolism and perfusion. The first was to predict wall motion improvement, taking into account both perfusion and metabolic data. The results, which provide the estimates of wall motion recovery as a function of the preoperative scores of perfusion and metabolism, are shown in Fig. 3. This analysis demonstrated that different probabilities of functional recovery are associated with different degrees of perfusion and metabolism. The highest probability of wall motion recovery is associated with the presence of a high ^{18}F-FDG uptake and severe hypoperfusion.

PERFUSION	FDG UPTAKE: Absent	Low	Moderate	High
Absence of perfusion at rest	25	94	96	99
Rest hypoperfusion worsening after stress	14	89	92	97
Stress hypoperfusion	7	78	84	94
Normal perfusion	-	4	-	-

Fig. 3. Estimated probability of wall motion improvement. Values in each cell indicate the estimated percentage probabilities of wall motion improvement in relation to different combinations of preoperative metabolic and perfusion scores

FDG UPTAKE			
Absent	Low	Moderate	High
13	79	92	96

Fig. 4. Estimated probability of wall motion improvement. Values indicate the estimated percentage probabilities of wall motion improvement in relation to different preoperative metabolic scores, independent of the perfusion score

The second analysis was performed on the ^{18}F-FDG uptake data. This analysis estimated the probability of wall motion improvement at 13% for the segments with no ^{18}F-FDG uptake and at 79%, 92% and 96% for segments with ^{18}F-FDG uptake score of 1, 2 and 3, respectively (Fig. 4).

Discussion

Although an improvement of ventricular function is almost always the rule after a CABG, the detection of hibernating myocardium, i.e. ischaemic asynergic viable myocardial tissue, is a key issue in patients presenting with CAD and left ventricular dysfunction waiting to undergo CABG (Schwaiger and Hicks 1991).

The identification of hibernating myocardium can be pursued by the use of tracers labelled with single photon or positron emitting isotopes that permit the assessment of cell membrane integrity or cellular metabolic activity (Gould 1991a).

This study had two main objectives. The first was to identify the areas of hibernating myocardium, prior to CABG, by the combined use of ^{18}F-FDG/PET and ^{99m}Tc-MIBI/SPET, in patients with CAD. The reversibility of segmental myocardial wall motion dysfunction after CABG was taken as the reference standard of a preoperative hibernating status.

Our results demonstrate that the presence of hibernating myocardium can be detected by the combined assessment of perfusion and metabolism using SPET with ^{99m}Tc-MIBI and PET with ^{18}F-FDG, respectively, and under fasting conditions even with PET and ^{18}F-FDG alone. We observed that, among the asynergic segments, wall motion impairment was reversible in 95% of the segments with ^{18}F-FDG uptake and that it was irreversible in 80% of the segments with no ^{18}F-FDG uptake.

The information obtained with this method is consistent with that obtained previously with PET studies of perfusion and metabolism (Tillisch et al. 1986; Tamaki et al. 1989). The reversibility of the asynergy was observed by Tillisch et al. in 85% of the regions with ^{18}F-FDG uptake. Irreversible asynergy was observed in 92% of the segments which presented PET criteria for infarction. Similarly, Tamaki et al. observed reversible asynergy in 78% of the ischaemic segments presenting with ^{18}F-FDG uptake and irreversible asynergy in 78% of the ischaemic segments presenting with no uptake. The differences among the three studies, i.e. Tillisch et al., Tamaki et al. and the current study, can be reasonable attributed to the use of different methodologies for the evaluation of wall motion and to the different patient population, and perhaps to myocardial protection protocols during the CABG.

In a very limited number of segments, the myocardium remained asynergic despite an improvement of per-

fusion and the presence of ^{18}F-FDG after the CABG. These segments could be still hibernating 6 months after the CABG. The period of time during which the hibernating myocardium may recover its function may extend, in fact, beyond the 6 months of our observation. In our study we may have overlooked the delayed recovery of some segments.

The estimated probability of recovery 6 months after the CABG varied depending on the degree of preoperative ^{18}F-FDG uptake, and it was lower for segments with a low ^{18}F-FDG uptake than for segments with a high uptake. However, at this time it is difficult to speculate whether this difference is due to prolonged hibernation in the segments with lower ^{18}F-FDG uptake or whether the asynergy is irreversible for these segments and a low ^{18}F-FDG uptake is predictive of an evolution towards fibrosis. The uptake of ^{18}F-FDG observed postoperatively in some segments can be interpreted as indicating the presence of viable tissue; however, it is impossible to conclude whether or not it has the same significance as the preoperative uptake, since very little is known on this variable after a CABG.

The second objective of the study was the development of a statistical analysis to estimate the probability of regional wall motion recovery on the basis of the preoperative perfusion and metabolic score. The possibility of estimating the probability of the recovery of wall motion with ^{18}F-FDG/PET studies alone under fasting conditions was also postulated based on the fact that the concentration of ^{18}F-FDG in the heart at the time defined for the conventional imaging procedures is mostly a function of metabolism (Krivokapich et al. 1982). Due to the differing metabolic patterns in the ischaemic, necrotic and normal myocardium, the uptake of tracer under fasting conditions was considered the most sensitive signal for the differentiation of hibernating tissue from normal as well as necrotic tissue. To determine whether this assumption was correct was one of the goals of the study. Although it appears possible to predict the reversibility of asynergy based solely on the presence of ^{18}F-FDG uptake, the estimated probabilities are more accurate when both perfusion and metabolism scores are taken into account in the analysis.

Some considerations must be given to the criteria used in this study for the selection of the population sample and segmental analysis, on the use of ^{18}F-FDG under fasting conditions and the use of ^{99m}Tc-MIBI for the assessment of perfusion.

Since the uptake of ^{18}F-FDG has been reported to be inconsistent in diabetic subjects and in the setting of acutely evolving myocardial infarction (Gould 1991 b), these two conditions were excluded in our patient population. Therefore, our results cannot be extrapolated to patients with diabetes and acute myocardial infarction. All the patients were affected by severe CAD, and in these patients the recovery of ventricular function after CABG is expected. However, the study was aimed at the evaluation of each segment's perfusion, metabolism and wall motion and at the estimation of the probability of segmental wall motion recovery.

The relationship between ^{18}F-FDG uptake in the heart and dietary state as well as the use of a procedure based on glucose load or on fasting for the evaluation of myocardial viability is the subject of much debate (Gropler et al. 1990; Berry et al. 1991). Metabolic heterogeneity in the heart has been reported by Gropler et al. (1990) after 5 h fasting. Berry et al. (1991) described a mean tissue/blood pool ratio of ^{18}F-FDG below 1.5 in normal subjects fasted for 12 h and above 3 in the glucose-loaded state. Under both conditions some degree of heterogeneity was also present. However, since an inverse correlation between fasting time and myocardial ^{18}F-FDG uptake exists (Yamada et al. 1985), the tissue/blood pool ratio of ^{18}F-FDG is likely to be even lower after at least 16 h fasting in the normal myocardium, thus reducing the effect of heterogeneity. Indeed, in a separate group of normal subjects ($n=10$) examined by us following the fasting protocol used in this study, the tissue/blood pool ratio was approximately 1.2 (unpublished observation), while it was always above this value in the segments in which the ^{18}F-FDG uptake was considered at least mild in the present series of patients. Thus, in this study performed under fasting conditions in non-diabetic patients with chronic CAD, it was assumed that any uptake of ^{18}F-FDG visually detectable above that of the blood pool would indicate a metabolic shift in hibernating tissue that could be scored as described above. With this criterion, only 2 segments with normal perfusion, 1 of which had abnormal wall motion as well, were classified among those with ^{18}F-FDG uptake. These could be either false-positive observations or true metabolic abnormalities due to the presence of a coronary stenosis demonstrated by coronary angiography. However, since the analysis was aimed at the identification of hibernating myocardium, and not at the detection of metabolic abnormalities in segments with normal kinesis, no hypothesis was tested in relation to the ^{18}F-FDG uptake in the segments that appeared normally perfused and/or with normal motion.

The use of ^{99m}Tc-MIBI/SPET for the assessment of perfusion has been validated (Kiat et al. 1989) and is accepted worldwide; therefore, there is no reason in principle to reject its use in combination with ^{18}F-FDG/PET metabolism studies. The use of a PET tracer of perfusion, such as $^{13}NH_3$ or $H_2^{15}O$, was excluded in this study because one of the aims of the project was the validation of a procedure for the identification of hibernating tissue with a SPET tracer of perfusion and a PET tracer of viability. The use of ^{99m}Tc-MIBI allows the saving of a substantial amount of PET time and, in the case of patients who undergo a ^{18}F-FDG/PET study of viability having already had elsewhere a ^{99m}Tc-MIBI/SPET study, avoids an unnecessary repetition of the perfusion exam. The results of the perfusion studies with ^{99m}Tc-MIBI/SPET have been examined along with the results of the ^{18}F-FDG/PET studies for the multiple

logistic analysis. However, they were not analysed in relation to the reversibility of asynergy since it has not been shown consistently that this tracer is adequate to provide satisfactory information on the presence of hibernating tissue, although tissue viability might be one of the requirements for the uptake of ^{99m}Tc-MIBI. An examination of the ^{99m}Tc-MIBI distribution pattern with respect to viability was beyond the goals of this report.

Conclusions

The results of this study demonstrate that there is a clearcut difference in the wall motion improvement between segments with no ^{18}F-FDG uptake and those in which there is at least some uptake. Although the outcome may vary slightly depending upon the degree of ^{99m}Tc-MIBI and ^{18}F-FDG uptake, the observation of ^{18}F-FDG uptake, even in the presence of a marked depression of perfusion and asynergy, is highly predictive of the existence of hibernating myocardium.

Based on the results obtained in this study, as well as on those given in Tamaki et al. (1989), there is no reason at the moment to reject a protocol based on prolonged fasting for the identification of hibernating tissue in non-diabetic patients.

The procedure tested in this study, based solely upon visual inspection of stress/rest perfusion studies using SPET with ^{99m}Tc-MIBI and metabolism using PET with ^{18}F-FDG after overnight fasting, is tailored to the clinical evaluation of segmental myocardial viability. Despite potential limitations due to its semi-quantitative nature, the method appears to provide reliable information on the presence of hibernating myocardial tissue.

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