

Feasibility of Planar Fluorine-18-FDG Imaging after Recent Myocardial Infarction to Assess Myocardial Viability

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The aim of this study was to define the clinical feasibility of planar myocardial ^{18}F -fluorodeoxyglucose (FDG) imaging and to assess the relation between ^{201}Tl , FDG and left ventricular function early after myocardial infarction. **Methods:** Fifty-one patients were studied 5 ± 2 days after infarction. Scintigraphic images were visually and quantitatively analyzed using a circumferential profiles technique. FDG uptake was normalized to the area with maximal ^{201}Tl uptake. Scintigraphic data were compared with left ventricular wall motion as assessed by ventriculography in 22 patients. Relative regional ^{201}Tl uptake was categorized as normal ($\geq 75\%$ of peak activity), moderately reduced (50%–75%) or severely reduced ($< 50\%$). These tracer defects were considered viable if FDG uptake exceeded ^{201}Tl uptake by $\geq 20\%$ and/or if FDG uptake was normal ($\geq 75\%$). All regions with FDG uptake 20% less than ^{201}Tl uptake were considered nonviable. **Results:** Four hundred forty-one myocardial regions were analyzed; 200 showed normal ^{201}Tl uptake, 241 had reduced uptake, 191 had moderately reduced ^{201}Tl uptake and 50 regions had severely reduced uptake. Viability for moderately and severely reduced regions was observed in 62% and 48%, respectively. A concordance between flow and metabolism was observed in 38% and 52%, respectively. **Conclusion:** Myocardial FDG imaging is feasible with standard gamma camera systems and enables the identification of regions with preserved glucose metabolism in patients shortly after infarction.

Key Words: planar myocardial imaging; fluorine-18-fluorodeoxyglucose; myocardial infarction; myocardial viability

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Under normal physiologic conditions, and particularly in the fasting state, fatty acids are the preferred substrates for myocardial energy production (1). Only a minority of the energy is obtained from glucose and lactate. Both animal and clinical studies have shown that glucose utilization

is enhanced in ischemic but viable myocardium. This increased myocardial glucose utilization can be traced non-invasively by PET using ^{18}F -fluorodeoxyglucose (FDG) (2,3). Tillisch et al. and Tamaki et al. (4,5) showed recovery of wall motion abnormalities in patients undergoing coronary bypass surgery could be predicted by normal or enhanced myocardial FDG uptake before revascularization. These studies have validated FDG as a valuable tracer of myocardial viability.

It is possible to visualize myocardial FDG uptake with a standard gamma camera and a 511-keV collimator (6–8). Because gamma camera systems are more readily available than PET systems, development of planar FDG scintigraphy to assess myocardial viability may enable the application of FDG in routine clinical practice. We performed a study in patients shortly after myocardial infarction to define the clinical feasibility of planar myocardial FDG imaging and to investigate the relationship between ^{201}Tl and FDG in myocardial areas with normal and abnormal left ventricular function.

MATERIALS AND METHODS

Patients

The study was approved by the Ethical Committee on Human Research of the Free University Hospital. Fifty-one consecutive patients (41 men; mean age 60 ± 12 yr) admitted to the coronary care unit with myocardial infarction were studied. All patients were admitted with a typical history of prolonged chest pain, transiently elevated serum enzyme levels including CK-MB fractions, and electrocardiographic signs of either a Q-wave or a non-Q-wave infarction. Forty-four patients had Q-wave infarction and seven patients had non-Q-wave infarction by electrocardiographic criteria. Thirty-three patients were treated with thrombolytic agents in the acute stage of infarction.

Exclusion criteria for entering the study were unstable angina pectoris, insulin-dependent diabetes mellitus, severe congestive heart failure (Killip class III–IV) and major noncardiac disease. After informed consent was obtained, all patients underwent scintigraphic evaluation by ^{201}Tl and FDG at rest on the same day; which was within 5 ± 2 days of infarction.

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Thallium-201 Scintigraphy

Rest ^{201}Tl scintigraphy was performed in the morning after a light meal. Ten to 15 min after intravenous administration of 74–90 MBq ^{201}Tl views were obtained in the standard left anterior oblique 45 (LAO45), anterior and left anterior oblique 70 (LAO70) positions. The gamma camera was equipped with a 9-mm crystal and a low-energy all-purpose collimator. Images were obtained using 8 min per view in the zoom mode in a wordframe matrix of 128×128 pixels and the scintigraphic data were stored on disk. To ensure correct patient positioning during FDG imaging, the scintigraphically determined position of the center of the left ventricle was marked on the chest of the patient using a marker (^{57}Co) and a pen with water-insoluble ink after each ^{201}Tl image.

FDG Scintigraphy

Deoxyglucose was labeled with ^{18}F at the Radionuclide Center of the Free University; no carrier was added to the ^{18}F . A typical purity of greater than 95% was obtained. Transportation to the hospital lasted 20 min. Forty-five minutes before intravenous administration of 185 MBq FDG, an oral glucose load of 20–50 g was given together with a light carbohydrate meal. The meal was to prevent fasting conditions during the study, promote FDG uptake and minimize the heterogeneity of myocardial FDG uptake (9,10). Forty minutes after injection, scintigraphy was started. Standard LAO45, anterior and LAO70 views were obtained. The same conventional Anger gamma camera equipped with a 511-keV collimator (van Mullekom, Nuclear Fields, Boxmeer, The Netherlands) was used. Starting with a 360-keV collimator, adjustment to a 511-keV collimator was achieved by increasing the bore length and septal thickness. The hole diameter had to be increased to 4.6 mm to ascertain that the collimator weight did not exceed 150 kg. The septal thickness of this collimator is 2.11 mm and the spatial resolution of this imaging system using a line spread function FWHM has been estimated to be 14 mm for ^{18}F in 10 cm water (7).

The FDG images were acquired with an energy window of 20% around the photopeak of ^{18}F (511 keV) in the zoom mode in a wordframe matrix of 128×128 pixels during 8 min per view. All scintigraphic data were stored on disk. Blood samples were taken to measure plasma glucose and insulin levels shortly before the administration of FDG in 23 patients.

Cardiac Catheterization

Cardiac catheterization with coronary angiography and left ventriculography was performed in 22 patients using the Judkins' technique. Cardiac catheterization was performed within 6 ± 5 days of infarction. Left ventriculograms were obtained in all patients in a 30° right anterior oblique (RAO30) projection and in the 50° left anterior oblique (LAO60) position. The ventriculograms and coronary angiograms were reviewed by two experienced observers without knowledge of the scintigraphic data. Maximal luminal diameter narrowing of each major coronary artery was estimated visually and differences in interpretation were resolved by consensus with a third observer. A luminal diameter narrowing greater than 50% was considered significant.

Left ventricular wall motion was assessed qualitatively by dividing the left ventricle into anterior, apical and inferior regions in the RAO30 view and the septal, inferoapical and posterolateral regions in the LAO60 view. Wall motion was scored as normal, hypokinetic, akinetic or dyskinctic.

Data Analysis

FDG images were projected on a monitor screen without background correction or smoothing for visual interpretation by two

experienced observers. Scintigrams were visually scored as good, moderate or poor. Anterior views were used to draw regions of interest (ROI) over myocardium with qualitatively normal ^{201}Tl and FDG uptake. Scintigraphic information combined with data from coronary angiography was used to assure that ROIs were drawn in flow areas of normal coronary arteries when these angiographic data were available. In addition, ROIs were drawn over the lung area adjacent to the left ventricle and over the liver area. The numbers of pixels per myocardial, lung and liver ROIs were 100, 425 and 115, respectively in all patients. Heart/lung and heart/liver ratios for ^{201}Tl and FDG were calculated from the counts per pixel in the ROIs.

Quantitative Analysis of Myocardial Thallium and FDG Images

The images were quantitatively analyzed with an operator-interactive computer program. This program involved the following steps. A circle was drawn around the left ventricle. The interpolative background subtraction technique as described by Goris et al. (11) and modified by Watson et al. (12) using a proximity weighting function was applied. After background subtraction, nine-point image smoothing was performed. The left ventricle was divided into 60 radii spaced 6° apart, originating from the center of the ventricle. Along each radius, the pixel with maximum ^{201}Tl or FDG activity was chosen and plotted as the number of counts versus angle. The combination of all 60 radii resulted in a circumferential profile of myocardial uptake. Profiles were then aligned such that the 90° radius in each view corresponded to the visually located apex. The outflow tract radii, chosen between 204 and 330° (13), were excluded from further data analysis. In addition, the left ventricle without the outflow tract was divided into 13 sectors of 18° . Of each myocardial view, the myocardial sector with the maximal ^{201}Tl uptake was used as the individual reference sector for the ^{201}Tl and FDG study. FDG uptake within this sector was considered 100% and FDG activities of other sectors were normalized to this maximal ^{201}Tl uptake. Thus, relative myocardial ^{201}Tl and FDG uptake in sectors were expressed as a percentage of this reference region. The three planar images were divided into a total of nine regions (Fig. 1). Average relative ^{201}Tl and FDG uptake for these regions were calculated. Relative regional ^{201}Tl uptake was categorized into normal ($\geq 75\%$ of peak activity), moderately reduced (50%–75%) and severely reduced ($< 50\%$). These tracer defects were classified as viable and nonviable. Regions were considered viable if FDG uptake exceeded ^{201}Tl uptake by 20% or more or if FDG uptake was normal ($\geq 75\%$). All regions with FDG uptake less than 20% of ^{201}Tl uptake were considered nonviable.

Imaging two tracers with different photon energies may result in different circumferential profiles. For this purpose, a phantom study was performed with an ellipsoidal sphere with an inner and outer wall. In the 1-cm space between these walls, a small compartment (2×2 cm) was introduced to create a tracer defect. Both the sphere and the defect were filled with ^{201}Tl and FDG activity. If the defect activity was less than 33%, the normalized profiles of ^{201}Tl and FDG differed less than 7% from each other. If the defect activity was more than 60%, the normalized ^{201}Tl and FDG profiles differed less than 2% from each other. Hence, a 20% criterion for the difference between normalized ^{201}Tl and FDG profiles can safely be used for the detection of myocardial viability.

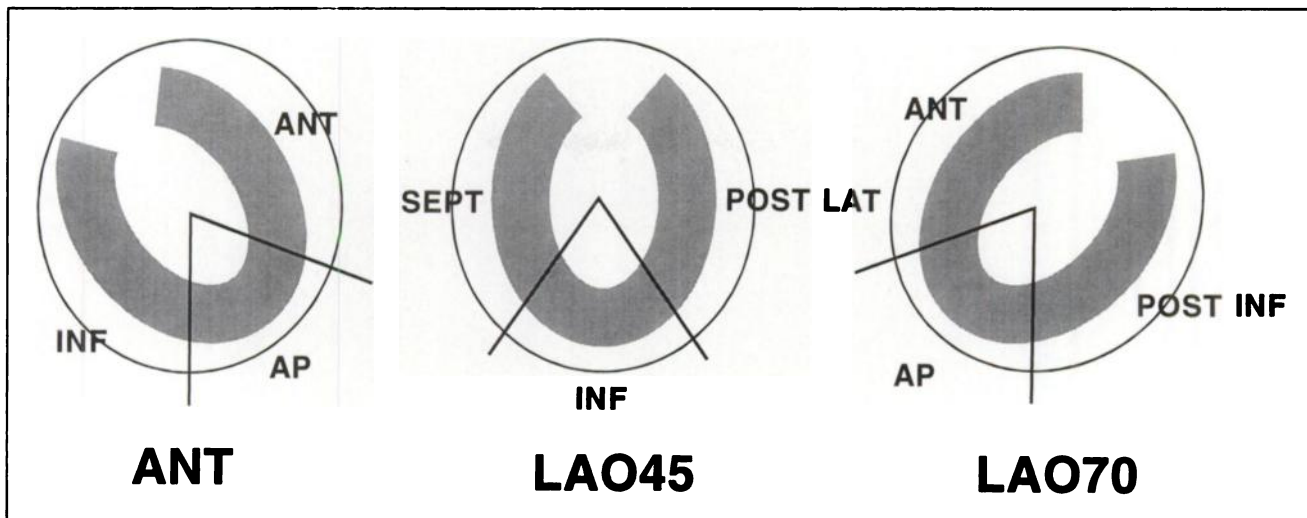


FIGURE 1. Myocardial regions used for the quantitative analysis of the scintigrams. ANT = anterior; LAO45 = left anterior oblique, 45°; LAO70 = left anterior oblique, 70°.

Comparison of Left Ventricular Wall Motion with Scintigraphic Data

For correlation of wall motion and scintigraphic data, corresponding myocardial regions were compared. The anterior scintigrams were compared with the RAO30 ventriculograms and the LAO45 scintigrams with the LAO60 ventriculograms (14,15).

Statistical Analysis

Values are expressed as mean \pm standard deviation. Statistical analysis was performed with the Student's t-test for paired and unpaired data. A p value $<$ 0.05 was considered statistically significant.

RESULTS

Image Quality

Visually, the image quality of 27 (53%) FDG studies was good, 17 (33%) were moderate and 5 (10%) were poor. Two of the five poor FDG studies were of such bad quality that they were uninterpretable and were excluded from further data analysis. Heart-to-lung ratios of ^{201}Tl images were 2.37 ± 0.44 and of FDG, 2.45 ± 0.39 ($p = \text{ns}$). Heart-to-liver ratios were 1.06 ± 0.19 and 1.78 ± 0.34 ($p < 0.001$), respectively.

Regional Analysis

Figure 2 shows the relation of relative regional ^{201}Tl and FDG uptake ($\text{FDG} = 0.68\text{Tl} + 35.59$; $r = 0.63$; $n = 441$). FDG uptake in normal myocardium was homogeneously distributed with a $\text{FDG}/^{201}\text{Tl}$ ratio of 1.10 ± 0.15 . The $\text{FDG}/^{201}\text{Tl}$ ratio in abnormal myocardium was 1.30 ± 0.27 ($p < 0.05$ versus normal myocardium). Figure 3 shows a flow chart of the analyzed myocardial regions. Four hundred forty-one myocardial regions was analyzed for ^{201}Tl and FDG uptake: 200 regions showed normal ^{201}Tl uptake, 241 regions had reduced uptake, 191 had moderately reduced ^{201}Tl uptake (50–75%) and 50 regions had severely reduced uptake ($<$ 50%).

Viability was preserved in 62% and 48% ($p = \text{ns}$) of

moderately reduced and severely reduced regions. A concordance between blood flow and metabolism was observed in 38% and 52%, respectively. The average ^{201}Tl and FDG uptake in relation to the severity of reduction in flow is expressed in Table 1. Thallium uptake differs in the normal, moderately and severely reduced regions, but it cannot differentiate between viable and nonviable regions within severely reduced regions (43.1% versus 42.0%).

Coronary Angiography and Regional Wall Motion

Nine patients had single-vessel disease, seven patients had double-vessel disease and six patients had triple-vessel disease. The mean left ventricular ejection fraction was $49\% \pm 9\%$. Ninety myocardial areas showed normal wall motion on ventriculography (Fig. 4). The average ^{201}Tl uptake was $75.7\% \pm 11.2\%$ ($p < 0.01$ versus hypokinetic and akinetic regions) and FDG uptake was $86.2\% \pm 13.0\%$

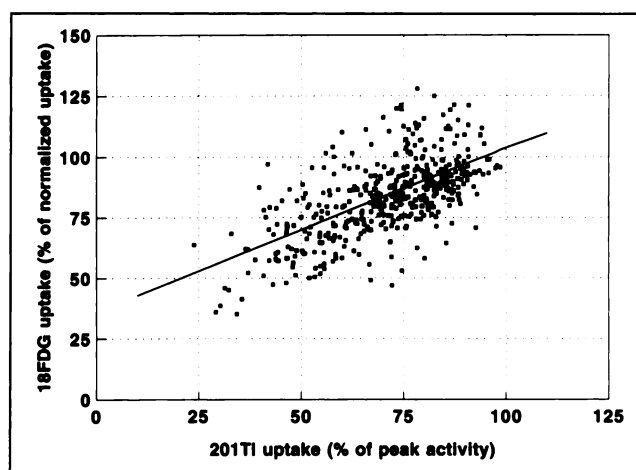


FIGURE 2. Scatter plot and regression analysis of relative ^{201}Tl and relative FDG uptake in myocardial regions with normal and reduced ^{201}Tl uptake.

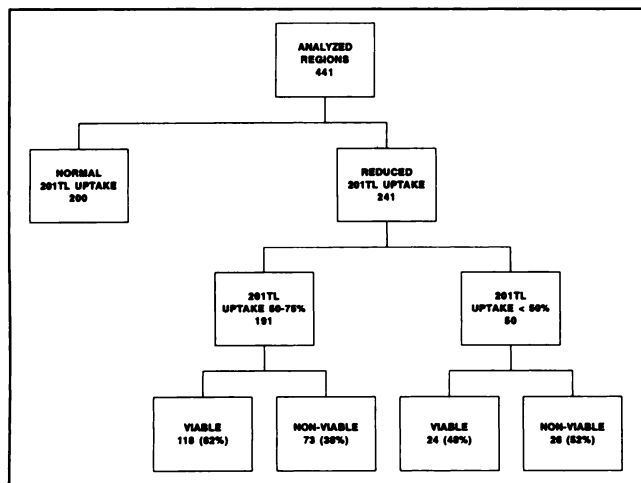


FIGURE 3. Flow chart of the analyzed myocardial regions.

($p = ns$ versus hypokinetic regions; $p < 0.01$ versus akinetic regions), respectively, in these areas.

Twenty-nine hypokinetic myocardial areas were observed. The average ^{201}Tl uptake was moderately reduced in these regions ($65.8\% \pm 12.9\%$, $p = ns$ versus akinetic regions), but FDG was comparatively increased ($86.0\% \pm 18.7\%$, $p = ns$ versus akinetic regions). Twenty-four (83%) hypokinetic areas were considered viable using the viability definitions, and five regions (17%) were considered nonviable.

In the 13 areas with akinesia, the average ^{201}Tl uptake was $65.7\% \pm 16.9\%$ and the FDG uptake was $78.4\% \pm 17.1\%$ ($p = ns$ versus hypokinetic regions). Nine (69%) regions were viable using the definitions for viability and four regions (31%) were nonviable. Viable myocardial regions were detected in 37 (76%) patients. Thirty patients with ECG signs of Q-wave infarction had myocardial areas with viability. An example of scintigraphic images of a patient with a match in ^{201}Tl and FDG uptake is shown in

TABLE 1
Average Regional ^{201}Tl and FDG Uptake in Regions with Normal, Moderately Reduced (50–75%) and Severely Reduced (< 50%) ^{201}Tl Uptake

Regions		Average ^{201}Tl uptake (%)	Average ^{18}F FDG uptake (%)
Normal		83.6 ± 5.5	92.2 ± 11.9
50%–75%	Total group	64.5 ± 7.3	$79.3 \pm 14.4^*$
	Nonviable	61.1 ± 6.9	$65.4 \pm 7.3^*$
	Viable	$66.6 \pm 6.8^\dagger$	87.8 ± 10.5
< 50%	Total group	42.5 ± 6.1	$63.2 \pm 13.6^*$
	Nonviable	42.0 ± 6.2	$52.8 \pm 8.1^*$
	Viable	43.1 ± 6.0	$74.5 \pm 8.2^*$

* $p < 0.01$ vs. FDG uptake in normal regions.

† $p < 0.001$ vs. ^{201}Tl uptake in nonviable moderately reduced regions.

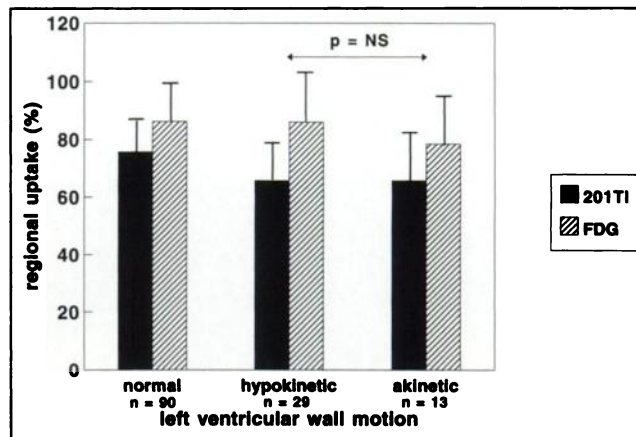


FIGURE 4. Bar graph showing relative ^{201}Tl and FDG uptake in relation to left ventricular wall motion.

Figure 5. Figure 6 shows an example of a mismatch between flow and metabolism.

Plasma Glucose and Insulin Levels

Plasma glucose and insulin levels were, respectively, 6.8 ± 1.4 mmole/liter and 43.7 ± 19.1 mU/liter.

DISCUSSION

We have described the use of planar myocardial FDG imaging in patients shortly after myocardial infarction using a rest ^{201}Tl and FDG protocol. Regional left ventricular function was correlated to regional ^{201}Tl and FDG uptake.

Planar FDG imaging yielded images of adequate quality in most patients. Seventy-six percent of the patients had normal or relatively increased FDG uptake within the infarct area, which probably indicates the presence of viable myocardial tissue. This incidence is in line with previous FDG studies after myocardial infarction. Signs of residual ischemia after infarction were reported in 55%–77% of patients (2,8,16,17).

Table 1 and Figure 3 show that FDG uptake can be preserved (79.3%), especially in regions with moderately reduced ^{201}Tl uptake. This is in contrast to FDG uptake in regions with severely reduced ^{201}Tl uptake (63.2%), but it is similar to the results of a study by Kalff et al. (18). They found that a blood flow reduction of 50% did not change relative glucose utilization in ischemic canine myocardium. In contrast, low flow conditions resulted in marked impairment of FDG uptake. Our findings also correlate with the study by Dilsizian et al. (19) who found that the magnitude of ^{201}Tl uptake after reinjection could distinguish between viable and nonviable myocardium. Mild-to-moderate ^{201}Tl defects may represent viable myocardium. With planar scintigraphy, we found a high incidence of residual tissue viability in ventricular regions with reduced flow and impaired function during the subacute phase of myocardial infarction. These results indicate, as do previous FDG-PET studies, that (1) viable myocardium can be characterized by a small decrease in ^{201}Tl uptake combined with a normal FDG uptake, and (2) viable myocardium can be

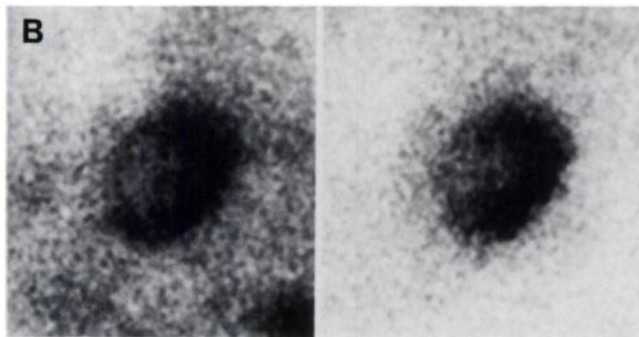
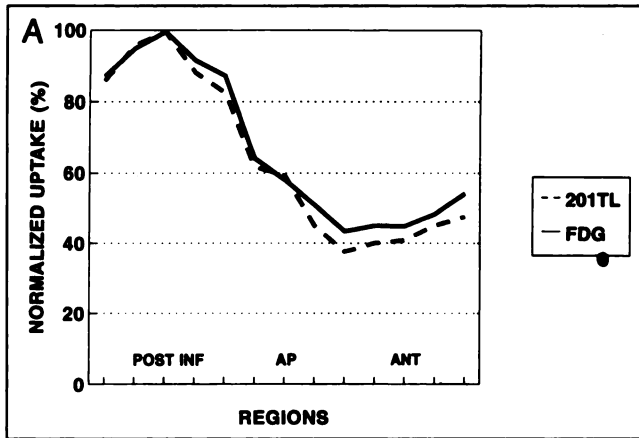


FIGURE 5. Quantitative analysis (A) and left anterior oblique, 70° view (B) of ^{201}Tl (left) and FDG (right) scintigram. The reduction in both ^{201}Tl and FDG uptake in the anterior region of the left ventricle showed concordance (nonviable tissue).

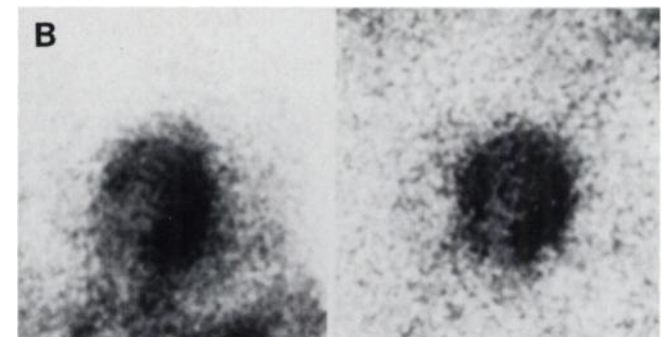
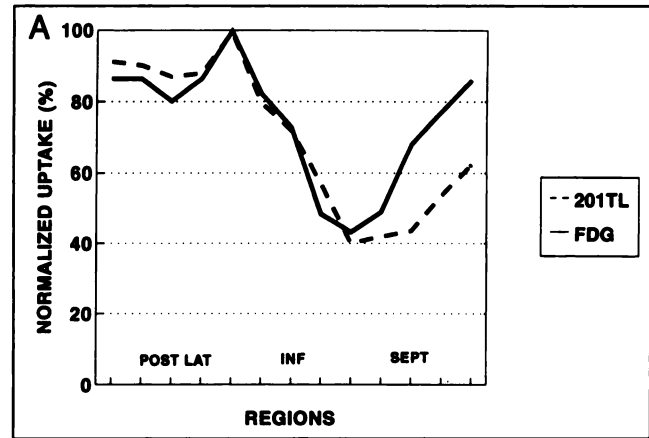


FIGURE 6. Quantitative analysis (A) and left anterior oblique, 45° view (B) of ^{201}Tl (left) and FDG (right) scintigram. A concordant reduction in the inferior uptake of ^{201}Tl and FDG can be observed. The relative enhanced septal uptake of FDG to ^{201}Tl exceeds the criteria for viability.

characterized by a FDG/ ^{201}Tl mismatch ($\geq 20\%$) with a more profound perfusion deficit and relative increase in FDG uptake. Nonviable myocardium is characterized by a matched FDG/ ^{201}Tl defect.

Early Imaging

Early identification of viable but jeopardized myocardium would support aggressive therapy to salvage endangered myocardial tissue. We found a high incidence of tissue viability in the subacute phase of infarction. As was shown by Schwaiger et al. (2), absence of residual tissue metabolism shortly after infarction is associated with irreversible injury, while remaining of metabolic activity indicates regions with a variable outcome. Although polymorphonuclear leukocytes accumulate in necrotic tissue as early as 4 hr after reperfusion of ischemic canine myocardium, preserved FDG uptake in the area of infarction is likely to reflect the metabolism of viable myocytes and is not just an inflammatory reaction, as was shown by a study of Wijns et al. (20). Our results show that FDG imaging to assess viability during the subacute phase of infarction is feasible; however, the need for complementary revascularization has to be determined.

Clinical Relevance

The clinical relevance and prognostic importance of the detection of myocardial viability with FDG in patients with

coronary artery disease was shown by Eitzman et al. (21) and Tamaki et al. (22). Their findings suggested that patients with impaired left ventricular function and metabolic evidence of myocardial ischemia appeared to have the most clinical benefit from a revascularization procedure. Whether these findings also apply to patients with recent myocardial infarction has to be established.

Left Ventricular Function

Williams et al. (8) performed planar FDG imaging in patients after myocardial infarction who were evaluated before and after revascularization. Of 46 fixed ^{201}Tl defects (exercise ^{201}Tl and 24-hr redistribution imaging) preoperatively, 30 defects demonstrated improvement in regional exercise ^{201}Tl uptake or regional systolic function after revascularization. FDG- ^{201}Tl mismatches were present in 83% of these regions but were absent in the majority of the functionally unimproved regions. Therefore, their data suggest that viable myocardium can be identified using planar FDG scintigraphy. Our data indicate also that the detection of viability with the planar approach is feasible. Most regions with normal left ventricular function had a normal ^{201}Tl and FDG uptake. Hypokinetic regions showed a clear discordance between flow and metabolism, indicating the shift in energy production from free fatty acids to glucose. Three regions with a severely reduced

^{201}Tl uptake and a concordant low FDG uptake (< 50%) were akinetic at ventriculography. These regions probably represent real scar tissue. The other akinetic myocardial regions had either a mild ^{201}Tl defect or increased FDG uptake. Thus akinetic regions may represent scarred, hibernating or stunned myocardium. It supports previous findings that evaluation of regional function shortly after the onset of infarction may fail to distinguish necrotic from viable myocardium. Additional information about viability from metabolic studies or from ^{201}Tl activity are needed before proper clinical decisions can be made.

Methodologic Considerations

For viability assessment, myocardial FDG uptake should be related to a blood flow tracer (4,17). For this purpose, we used ^{201}Tl because early ^{201}Tl imaging reflects blood flow distribution in the myocardium (23).

The metabolic tracer, FDG, competes with glucose for phosphorylation by the enzyme hexokinase. In the myocardial cell, FDG is phosphorylated and trapped because FDG-6- PO_4 cannot be further metabolized (24,25). In ischemic myocardium, glucose becomes the major source of energy and may therefore lead to increased FDG uptake relative to nonischemic myocardium. This is the pathophysiological basis for normalization of FDG uptake to the region revealing maximal ^{201}Tl uptake. Because ^{201}Tl uptake depends on blood flow, oxygen consumption and myocardial mass, the region that shows maximal ^{201}Tl uptake represents the most "normal" myocardium.

Although planar 511-keV scintigraphy will not meet the standards of PET in terms of resolution and quantitation, the application of planar imaging systems seems justified, because, as Tillisch et al. (4) reported, only large myocardial areas with flow/metabolism mismatch improved after surgical revascularization.

Although overlap of myocardial activity from normal myocardium may mask areas with ischemia or infarction, from the data of Williams et al. (8), it can be inferred that viability can be demonstrated with planar imaging.

The fact that most myocardial areas with normal function had ^{201}Tl as well as FDG uptake of 75% or more supports the cut-off point of the lower limit of normal at 75% and the definition of viability. These criteria have been previously used by others (26) and are also supported by our experience with ^{201}Tl and FDG studies in 12 normal individuals (unpublished data), although it is acknowledged that revascularization data demonstrating improved regional function are needed to confirm these findings. Seventeen percent of hypokinetic regions was considered non-viable using the criteria for viability. This may have been caused by qualitative visual analysis of the wall motion data.

It has been shown that ^{201}Tl reinjection studies (19,27,28) can be performed to detect myocardial tissue viability. Our findings suggest that rest imaging, without the need of exercise-induced ischemia, may also identify viability.

The lack of ^{201}Tl rest-redistribution data is a major limitation of our study; however, this was not the primary goal of our study. In theory, many of the regions with reduced ^{201}Tl uptake but preserved FDG uptake would show ^{201}Tl redistribution if late ^{201}Tl imaging had been performed. Thus, the relative value of planar FDG scintigraphy compared to PET and compared to ^{201}Tl reinjection and rest-redistribution studies needs to be established. Also, the additional value of planar FDG scintigraphy to rest-redistribution imaging protocols needs investigation.

CONCLUSION

Myocardial FDG imaging is feasible with a standard gamma camera in patients shortly after myocardial infarction. Uptake of FDG in myocardial regions with normal ^{201}Tl uptake and normal left ventricular function is relatively homogeneously distributed; in regions with reduced ^{201}Tl uptake and abnormal function, it was significantly more heterogeneous due to the presence of relatively increased FDG uptake to flow. A considerable number of infarct patients (76%) had viable regions within the infarct area. Because an earlier planar FDG study has indicated that increased FDG uptake is related to functional recovery after revascularization, further studies are justified to evaluate the clinical relevance of planar myocardial FDG imaging.

Finally, because gamma cameras are used in the majority of community hospitals and because the physical half-life of ^{18}F allows offsite use of FDG, application in routine clinical practice may be possible for viability assessment, risk-stratification and prediction of functional recovery after myocardial infarction.

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