

The Comparison of 2-¹⁸F-2-Deoxyglucose and 15-(ortho-¹²³I-phenyl)-Pentadecanoic Acid Uptake in Persisting Defects on Thallium-201 Tomography in Myocardial Infarction

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The myocardial uptake of glucose and fatty acids into ²⁰¹Tl redistribution defects were studied in 32 patients with myocardial infarction by tomography using 2-¹⁸F-2-deoxyglucose (FDG) and 15-(ortho-¹²³I-phenyl)-pentadecanoic acid (oPPA). A total of 1153 segments were analyzed, 408 (35%) of which showed a persistent thallium-defect in stress-redistribution images. Of the segments with a decreased ²⁰¹Tl uptake in these redistribution tomograms, 50.5% had a decreased uptake of both FDG and oPPA; in 21.8% FDG as well as oPPA uptake was within normal range. Normal FDG uptake but decreased oPPA uptake was detected in 17.4%, whereas 10.3% of the segments had normal oPPA uptake but decreased FDG uptake (chi-square test, $p < 0.001$). A significant correlation of FDG and oPPA uptake ($r = 0.51$) was found in the segments with persistent ²⁰¹Tl defect. Thus, a substantial fraction of persistent thallium-defects after healed myocardial infarction exhibit FDG as well as oPPA uptake, probably due to residual fatty acid metabolism in partially ischemic regions.

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The detection of viable myocardium in infarcted regions, so called hibernating myocardium, is a major goal in clinical cardiology today. Stress-redistribution ²⁰¹Tl scintigraphy has been widely used to address this question (1). In several studies of recent years, however, tissue with preserved glucose metabolism was detected in some segments of persistent ²⁰¹Tl defects (2-5). Tillisch (6) has suggested that these segments with preserved FDG uptake have a better functional recovery following aorto-coronary bypass grafting than do segments without significant FDG uptake.

The aim of this study was to compare 2-¹⁸F-2-deoxyglucose (FDG) and 15-(ortho-¹²³I-phenyl)-pentadecanoic acid (oPPA) uptake in chronically infarcted regions and to

determine the relative value of the fatty acid analog ¹²³I-oPPA for the identification of viable myocardium. The potential advantage of this radiopharmaceutical would be a wider availability compared to FDG and the potential to perform dual-isotope SPECT, for example, with ²⁰¹Tl and ¹¹¹In. oPPA has been shown to be readily transported across cytoplasmic membranes into the myocardial cells and to be bound to coenzyme A. It is then retained mainly in the free-fatty acid pool and there is minimal β -oxidation compared to its para isomer. Backdiffusion is minimal in man (7). Thus oPPA is well suited to trace fatty acid uptake using SPECT.

METHODS

Study Population

Thirty-two patients were studied using SPECT with ²⁰¹Tl and ¹²³I-oPPA and PET with FDG. All patients had acute myocardial infarction by both electrocardiographic and serum enzyme criteria at least 4 wk prior to the scintigraphic studies. There were 31 men and 1 woman with a mean age of 59.1 yr. Each patient underwent ventriculography and coronary angiography. Wall motion was classified as normal, hypokinetic, akinetic, and dyskinetic by two independent observers and the presence of coronary stenosis (>50%) was tabulated from coronary angiograms. In addition, a total of 32 normal participants without any evidence of coronary heart disease were studied, 15 subjects using ²⁰¹Tl, 10 using oPPA, and 7 using FDG. A single study was performed on each of the normal participants in order to minimize radiation exposure to this group.

Thallium-SPECT

Thallium scintigraphy was done after an overnight fast. A symptom-limited exercise/stress test was performed with an upright bicycle ergometer starting at 25 watts and increased at 25-watt increments every 2 min. The exercise was continued until 90% of the age-predicted maximal heart rate was reached, or until onset of severe angina pectoris or dyspnea, or if ST depressions of more than 2 mV appeared in the EKG. At peak exercise, 2 mCi (75 MBq) of ²⁰¹Tl-chloride were injected intravenously. The stress-SPECT was started at 5 min, followed by the delayed SPECT 3-4 hr later. The gamma camera (Philips Diagnost) was rotated from 45° left posterior oblique to right anterior oblique

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by 32 angles over 180°, each step lasting for 40 sec. Transverse sections in a zoomed mode were reconstructed by a filtered backprojection algorithm after filtering the profiles using a Butterworth filter of the 4th order. Short- and long-axis cuts of the heart were obtained using a 12–17-mm slice thickness.

PET

This study was performed 2 hr after the delayed ²⁰¹Tl scan. Patients received a 50-g oral glucose load 45 min prior to the intravenous injection of 10 mCi of FDG, which was synthesized according to Hamacher et al. (8). A transmission scan for attenuation correction was performed with a rotating ⁶⁸Ge/⁶⁸Ga pin source before the FDG injection. The emission scan was acquired from 45 to 75 min after FDG-injection. A Scanditronix PC4096 WB scanner (Uppsala, Sweden) with eight detector rings that deliver 15 contiguous slices each with a thickness of 7 mm was used. Short- and long-axis cuts were obtained. The short-axis cuts had slice thicknesses corresponding exactly to the SPECT images.

Fatty Acid Tomography

This study was done after an overnight fast and under resting conditions 4 days after the thallium-SPECT and FDG-PET-studies. oPPA with a specific activity of 3000 Ci/mol was synthesized as described by Machulla et al. (9). Four millicuries (150 MBq) of this agent were then injected intravenously. Data acquisition was started 10 min later. The other conditions and the processing of the scans were identical to those used for ²⁰¹Tl scintigraphy.

Image Analysis

Six contiguous PET and SPECT short-axis slices were used for data evaluation. All slices were normalized to the respective maximal myocardial activity. The distribution of thallium, oPPA, and FDG were qualitatively graded as normal or diminished uptake in the anterior, lateral, posterior and septal regions. Quantitative analysis was performed using a polar map of the heart. The apex was represented by a circle, the subsequent five myocardial slices by concentric rings divided into eight sectors resulting in a total of 41 segments per map. The counts in each sector were normalized to the sector with the maximum counts. Segments that were not completely in the field of view of both the

TABLE 1

Number of Quadrants with Persistent Thallium Defect and Normal or Reduced FDG and oPPA Uptake

FDG oPPA	Low Low	Normal Normal	Low Normal	Normal Low
Wall motion score				
Normokinesia	3	4	0	1
Hypokinesia	9	6	1	1
Akinesia	6	3	0	4
Dyskinesia	5	0	0	0
mean value	1.57*	0.92*	1	1.50
s.d.	0.99	0.76	—	0.84
Stenosis				
≥99%	12	7	0	1
≥70%, <99%	6	5	0	3
<70%	5	1	1	2

* p < 0.06.

TABLE 2

Number of Segments with Persistent Thallium Defect and Normal or Reduced FDG and oPPA Uptake

	oPPA low	oPPA normal	Total
FDG low	206	42	248
FDG normal	71	89	160
Total	277	121	408

Chi-square test, p < 0.001.

PET and SPECT cameras were excluded from further analysis and thus 1153 segments were evaluated instead of 1312.

Observed count data were compared with normal values obtained in the same manner in normal subjects who had no evidence of cardiovascular or pulmonary disease. The segments with a relative uptake less than the mean value –2 s.d. in the delayed ²⁰¹Tl-SPECT were further classified concerning their oPPA and FDG activity. If the oPPA or the FDG uptake in these segments was below the mean value –2 s.d. in the normal group studied with FDG or oPPA, respectively, the uptake in this segment was termed to be low, otherwise normal.

Differences between mean values were tested by Student's t-test (Table 1), differences between proportions were tested by chi-square test with Yates correction (Table 2).

RESULTS

All patients revealed perfusion defects on ²⁰¹Tl tomograms in the electrocardiographically assigned areas. The results of qualitative evaluation of the FDG and oPPA tomograms and their relation to the clinical data are given in Table 1. Of a total of 128 analyzed quadrants, 43 (34%) exhibited ²⁰¹Tl defects in the redistribution tomogram. Out of these, 23 (53%) had low FDG and oPPA uptake, 13 (30%) normal FDG and oPPA uptake, 1 (2%) low FDG but normal oPPA, and 6 (14%) normal FDG but low oPPA uptake. In areas with concordantly reduced FDG and oPPA uptake, there was a trend towards reduced wall motion in comparison with normal FDG and oPPA uptake (p < 0.06). In addition, a total of 1153 segments were quantitatively assessed. Of these, 408 (35.4%) exhibited a defect in the ²⁰¹Tl-redistribution study (uptake < mean –2 s.d. of the normal group). Of the segments with a decreased ²⁰¹Tl uptake in the redistribution tomogram, 206 (50.5%) had a decreased FDG and oPPA uptake (Fig. 1). In 89 (21.8%) segments, FDG as well as oPPA uptake was within normal range (Fig. 2). Seventy-one (17.4%) segments revealed normal FDG uptake but decreased oPPA uptake, whereas 42 (10.3%) segments had normal oPPA uptake but decreased FDG uptake (Table 2).

The chi-square test revealed that FDG and oPPA uptake in defects in the ²⁰¹Tl redistribution scan are interrelated (chi-square = 70.4, p < 0.001). Thus, the sensitivity of oPPA for the detection of normal FDG uptake in persistent thallium-defects was 56% and its specificity was 83%. The

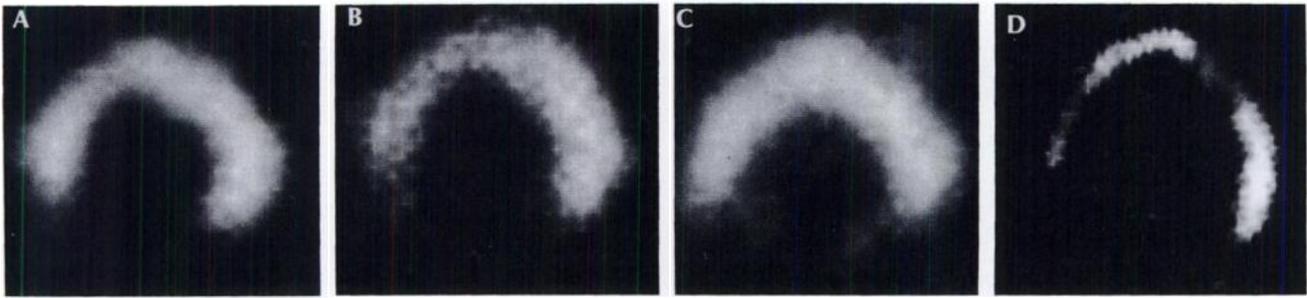


FIGURE 1. Thallium-201 defect after stress (A), in late image at rest (B), and with a matched activity defect in the oPPA (C) and FDG (D) images.

positive and the negative predictive values were 68% and 74%, respectively. In addition, the quantitatively determined uptake of oPPA and FDG in these segments revealed significant correlation. Spearman's rank correlation coefficient between oPPA and FDG uptake in ^{201}Tl redistribution defects was 0.51 ($p < 0.001$). A scatter plot of the uptake data is shown in Figure 3. In the segments that had normal behavior in the stress and rest tomograms as well as in the segments with positive and negative redistribution, no significant inter-relationship of oPPA and FDG uptake was found.

DISCUSSION

The data presented here suggest that in persistent ^{201}Tl defects, metabolically active myocardium may be detected with FDG and oPPA emission tomography, both carried out at rest. This sustains the previous observation that thallium stress-3-hr redistribution scintigraphy underestimates the extension of viable tissue after myocardial infarction. An extensive comparison of FDG and PET with planar thallium scintigraphy has been performed by Brunken et al. (2). These findings were further confirmed using PET and thallium-SPECT (10). Modified protocols with redistribution SPECT imaging at 24 hr after ^{201}Tl injection, have also failed to significantly improve the detection of viable myocardium in persistent thallium defects (11). The thallium redistribution phenomenon is due to delayed accumulation of thallium in ischemic segments and the relatively rapid washout from nonischemic areas (12).

Therefore, the redistribution is dependent on the arterial input function of ^{201}Tl . If the arterial ^{201}Tl concentration declines rapidly, the redistribution phenomenon may be too slow to be observed in severely ischemic areas. Recently, Dilsizian et al. (13) reported that the reinjection of thallium after completing the conventional delayed images detects viable myocardium in about half of the fixed defects observed after stress-redistribution imaging.

In comparison to SPECT, modern PET systems have a considerably better spatial resolution resulting in diminished partial volume effect. Thus, the finding of normal oPPA uptake in segments with reduced FDG uptake may be explained in part by activity spillover from normal myocardium into scar area which is more pronounced in SPECT than in PET. A further possible explanation could be a nonspecific binding of the iodinated fatty acid analog to necrotic myocardial cells or a retention in the interstitial edema.

In chronic myocardial infarction, viable tissue is expected to be partially reperfused. In this instance, the relation of glucose and fatty acid uptake depends upon the extent of imbalance between oxygen demand and supply.

In contrast to pure flow markers, FDG exhibits an increased extraction fraction in ischemic compared to normal myocardium due to increased glycolysis. On the other hand, it has been reported that the initial tracer uptake of ^{14}C -palmitic acid in acutely ischemic myocardium is largely determined by the regional myocardial blood flow (14). However, Bilheimer et al. (15) observed an accumulation and abnormal lipid deposition in border

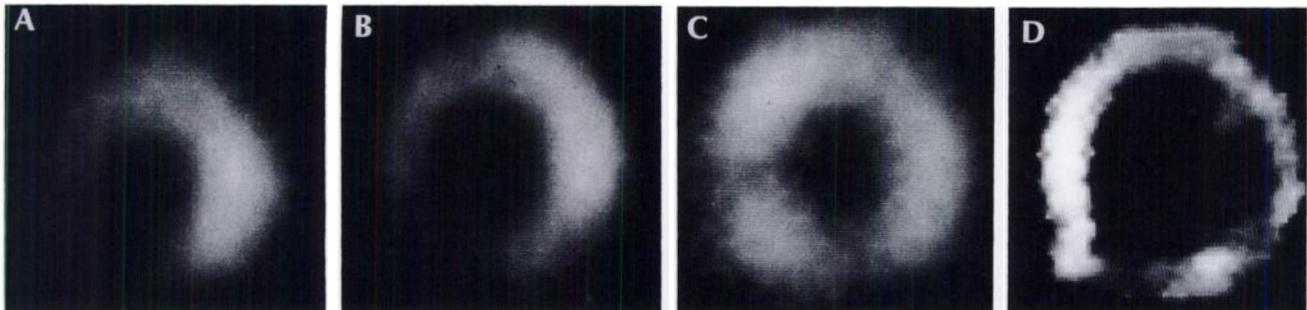


FIGURE 2. Thallium-201 defect in the stress (A) and redistribution (B) image, but with preserved activity uptake in the oPPA (C) and FDG (D) image.

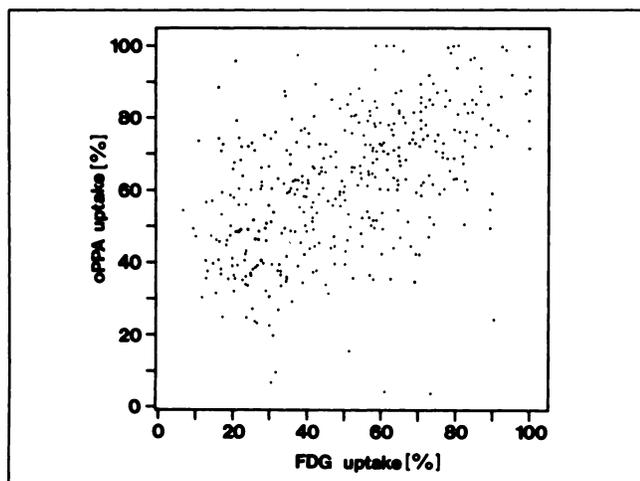


FIGURE 3. Scatter plot of FDG and oPPA uptake in persistent thallium-defects. The counts of the segments are given as the percentage of the maximal counts in a segment of the respective polar map.

zones of myocardial infarction using ^{14}C -oleic acid. The branched fatty acid [^{11}C] β -methyl heptadecanoic acid exhibited an increased extraction fraction in ischemic compared to normal myocardium in dogs (16). In a dog occlusion-reperfusion model, an accumulation of 15-(para-iodophenyl)-3-methyl pentadecanoic acid was detected that exceeded thallium accumulation (17). Results of studies using PET and ^{11}C -palmitate have shown that the fatty acid uptake in the early postischemic period is indicative of subsequent histochemical viability and presages later palmitic acid uptake and recovery of contractile function (18–20). Recently, Chappuis et al. (21) have demonstrated that ^{123}I -heptadecanoic acid uptake is a better predictor of myocardial viability as measured by means of triphenyltetrazolium chloride than ^{201}Tl uptake and myocardial blood flow in dogs. In the present group of patients with chronic myocardial infarction, the majority of segments characterized by preserved FDG uptake exhibited preserved oPPA uptake as well.

A minor number of segments showed FDG uptake only, indicating a tendency toward glycolysis and inhibition of fatty acid uptake. The decrease of oPPA uptake under these conditions may be caused by a decrease in intracellular binding due to inhibition of acyl CoA synthetase by increased lactate concentrations (22). The inhibition of carnitine palmitoyl transferase I due to increased lactate or carbohydrate concentrations, which is effective on palmitate metabolism (23), is not expected to influence oPPA uptake, because this tracer barely crosses into the mitochondria via the carnitine shuttle. Furthermore, inhibition of carnitine acyl transferase I by means of 2-[5-(4-chlorophenyl)pentyl]-oxirane-2-carboxylate does not alter oPPA kinetics in isolated perfused rat hearts (7). oPPA is therefore supposed to have a greatly reduced binding affinity to carnitine acyl transferase I.

FDG and oPPA may accumulate to various degrees in

different cells in a perfusion defect. Flow heterogeneity may cause metabolic heterogeneity with small areas of tissue exhibiting preferentially glycolysis or fatty acid metabolism.

The results of this study and of others cited herein suggest that in thallium redistribution defects there may be not only FDG uptake but also uptake of oPPA and thallium under resting conditions, thus indicating viable myocardium. The sensitivity for detection of viable myocardium using oPPA seems to be lower compared to FDG; the significance of the difference in fatty acid and glucose uptake for predicting the recovery of contractile function after revascularization is as yet unknown. On the other hand, there is the advantage of wider availability of ^{123}I -labeled oPPA and SPECT. This may be of relevance in the decision making for PTCA or bypass grafting.

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