Comparison of Myocardial Imaging with Iodine-123-Iodophenyl-9-Methyl Pentadecanoic Acid and Thallium-201-Chloride for Assessment of Patients with Exercise-Induced Myocardial Ischemia

Pierre Chouraqui, Jamshid Maddahi, Robert Henkin, Stephen M. Karesh, Elizabeth Galie, and Daniel S. Berman

Departments of Medicine (Divsion of Cardiology) and Nuclear Medicine, Cedars-Sinai Medical Center; Department of Medicine, University of California School of Medicine, Los Angeles, California; and the Department of Nuclear Medicine, Loyola University Medical Center; Maywood, Illinois

Iodine-123-iodophenyl-9-methyl-pentadecanoic acid ([^{123}I] MPDA) and thallium-201 (^{201}Tl) were sequentially injected in 11 patients during exercise-induced myocardial ischemia. Simultaneous dual-energy planar images were obtained at 5 min, 3 and 5 hr. All studies were concordantly either positive (8/11) or negative (3/11) by both radionuclides. Exact agreement for segmental uptake was 93%, 94% and 94% for 5-min, 3- and 5-hr images, respectively. Exact agreement for defect reversibility by 3 and 5 hr were 95% and 92%. The initial defect contrasts and myocardial-to-lung ratios were similar by both agents but myocardial-to-liver ratio was lower by [^{123}I]MPDA at 5 min, which became similar to ^{201}Tl at 5 hr. Normal percent myocardial clearances of both agents were comparable and significantly higher than those in defect zones. Thus [^{123}I]MPDA is suitable for myocardial imaging and correlates closely with ^{201}Tl for initial postexercise myocardial uptake and defect reversibility. Defect reversibility appears to result from differential myocardial clearance from normal and ischemic regions.

J Nucl Med 1991; 32:447–452

Assessment of regional myocardial perfusion and viability has prognostic and therapeutic implications in patients with coronary artery disease. Thallium-201 (^{201}Tl) myocardial imaging has been widely applied for these assessments. Thallium-201, however, is not optimal for assessing myocardial viability because nonreversible defects may be observed in viable myocardial regions (1–4). Myocardial viability may also be assessed

by determining the metabolic integrity of the myocardium using radiolabeled metabolic substrates. Free-fatty acids serve as the primary metabolic energy source for the myocardium under normal circumstances. Extensive research using positron emission tomography has shown that normal fatty acid metabolism is altered in the ischemic or necrotic myocardium (5,6), suggesting that fatty acids may be useful for assessment of myocardial viability.

Recently, a new single-photon agent, iodine-123-iodophenyl-9-methyl-pentadecanoic acid ([^{123}I]MPDA) has been developed. Iodine-123-MPDA is a modified long-chain (15 carbons) fatty acid which differs from [^{123}I]iodophenylpentadecanoic acid (IPPA) by a methyl branch on its 9 carbon location (Fig. 1). Iodine-123-MPDA was previously used in an open label noncomparative Phase 1 study to evaluate its biodistribution and safety in normal volunteers (7). The purpose of this study was to compare [^{123}I]MPDA and ^{201}Tl imaging in patients with exercise-induced ischemia with respect to regional myocardial distribution, defect reversibility, target-to-background ratios, defect contrast, initial uptake, and subsequent clearances from normal and ischemic myocardial regions.

MATERIALS AND METHODS

Patient Population

The patient population consisted of 11 patients with stable exertional angina and exercise-induced ischemic electrocardiographic changes ($\geq$ 1.0 mm horizontal or downsloping ST depression of $\geq$ 1.5 mm upsloping ST depression at 0.08 sec after the J point). One patient had a previous myocardial infarction. The age ranged from 53 to 73 yr with a mean of 63 yr. There were 1 female and 10 male patients, recruited in two different medical centers: Loyola University Medical Cen-
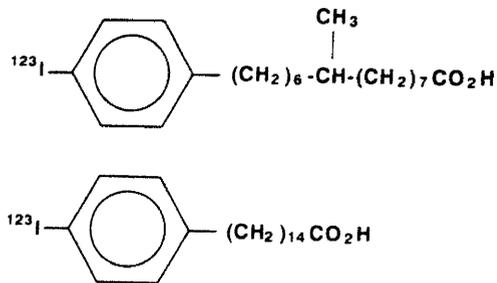
FIGURE 1
Structural formulae of [^{123}I]MPDA (top) and [^{123}I]IPPA (bottom). The only structural difference between the two compounds is that the former has a methyl branch of the carbon 9 location.

ter in Maywood, Illinois and Cedars-Sinai Medical Center in Los Angeles, California. Informed written consent was obtained prior to enrollment in the study.

Study Protocol

Patients were asked to fast for at least 4 hr prior to stress testing and were instructed to be off nitrates for at least 4 hr, calcium channel blockers for at least 12 hr, and beta blockers for 48–96 hr (depending on the type used) prior to the exercise study. Each patient received 1 ml Lugol's solution orally 15–30 min before the exercise test to block subsequent thyroid uptake of radioiodine. All patients underwent a symptom-limited multistage treadmill exercise test according to the Bruce protocol. Modified 12-lead electrocardiograms were recorded at rest, during each minute of exercise, and during recovery. At peak exercise, 2 mCi of ^{201}Tl and 3 mCi of [^{123}I] MPDA were intravenously injected sequentially and the patient continued to exercise for 1 min.

Imaging Protocol

Simultaneous dual-energy images were obtained by a gamma camera (Siemens 7500 Orbiter). Two separate 20% windows were centered one on the ^{201}Tl photopeak (69–83 keV) and the other on the ^{123}I photopeak (159 keV). A medium-energy, all-purpose collimator was used. Planar images were obtained in the anterior, 45°, and steep (85°) left anterior oblique views at 10 min, 3 hr, and 5 hr postinjection repeating identical views.

Visual Analysis of Images

Each planar view was divided into three segments and each segment was visually scored by consensus of two experienced blinded observers. Iodine-123-MPDA images were analyzed without knowledge of the scores of ^{201}Tl images. A 5-point scoring system was used in which 1 = severely reduced activity, 2 = moderately reduced activity, 3 = mildly reduced activity, 4 = probably normal activity, and 5 = definitely normal activity.

The pattern of defect reversibility was determined by comparing stress images to 3-hr and 5-hr redistribution images. Reversibility patterns were defined based on the segmental score change from the initial to the delayed study as follows: a segment was considered *reversible* if it had a stress score ≤3 that improved to 4 or 5 at delayed imaging. A segment was

considered *nonreversible* if it had a score of ≤3 which did not improve at redistribution imaging. Segments with *reverse-redistribution* were defined as segments with initial score ≥4 that decreased to ≤3.

Quantitative Analysis of Images

Three regions of interest (ROIs) were assigned to each image: (1) over a normal myocardial zone, (2) over a myocardial defect area, and (3) over the lung background. In the anterior view, a fourth ROI was also assigned over the liver area (Fig. 2). Identical ROIs were used on [^{123}I]MPDA and ^{201}Tl images. For each ROI, the average counts per pixel was determined by the computer. Myocardium-to-lung count ratios and myocardium-to-liver count ratios were determined by dividing the average counts per pixel of the normal myocardial zone by those of the lung and liver, respectively.

Background was subtracted using the Watson interpolative algorithm (8). After correction by appropriate physical decay factors (^{201}Tl decay factor = 0.991/hr; ^{123}I-123 decay factor = 0.948/hr) myocardial clearances of ^{201}Tl and [^{123}I]MPDA were calculated in the normal and defect zones at 3-hr and 5-hr imaging times by subtracting the average counts per pixel of delayed images from the average counts per pixel of initial images and dividing the result by the average counts per pixel of initial images. Percent clearance was obtained by multiplying the result by 100. Defect contrast was calculated by subtracting average counts per pixel of a defect zone from that of the normal myocardial zone and dividing the result by the average counts per pixel in the normal zone. This value was expressed in percent after multiplying the result by 100. Because energy spillover between the two radionuclides was negligible, correction was not performed.

Statistical Analysis

The kappa statistic was used to measure the agreement between [^{123}I]MPDA and ^{201}Tl images in evaluating segmental scores and segmental reversibility scores. The significance of kappa statistic was determined by calculating a t-like statistic defined as kappa value divided by its asymptotic standard error. This value was also compared to Z-table values to obtain the corresponding p value. A p value < 0.05 was considered statistically significant. Paired t-tests were used to compare
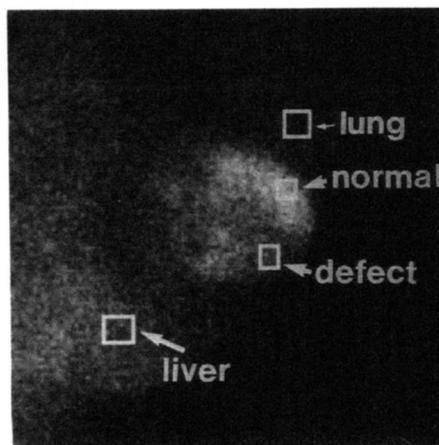
FIGURE 2
Assignment of the four ROIs on an [^{123}I]MPDA anterior image.

initial defect contrasts, myocardial-to-background ratios, and percent clearance in normal and defect regions between the two radionuclides.

RESULTS

Detection of Perfusion Defects on Initial Images

In the 11 patients, 8 studies were concordantly positive and 3 were concordantly negative by [123I]MPDA and 201Tl (Fig. 3). Of the eight positive studies, seven showed reversible defects by both 201Tl and [123I]MPDA and one (the patient with prior myocardial infarction) showed both reversible and nonreversible defects by both radionuclides. Agreement between the two radionuclides for visual segmental scores of the initial, 3-hr and 5-hr images is shown in Figure 4. On initial images, 92 of 99 segments were scored identically resulting in 93% exact agreement (kappa = 0.858, p < 0.0001). Of 71 myocardial segments with normal 201Tl uptake, 70 (99%) had normal [123I]MPDA uptake. Moreover, the degree of reduction of activity also correlated highly between the two agents: Of 28 myocardial segments with reduced 201Tl uptake, 24 (86%) also had abnormal [123I]MPDA uptake. Exact agreement was 94% (93/99) on 3-hr postinjection images and was 94% (82/87) on 5-hr postinjection images (kappa = 0.807 and 0.753 respectively, p < 0.0001). Of note, one patient did not undergo the 5-hr imaging and in one patient only two views were obtained at 5 hr, resulting in a reduction of the number of analyzable segments at 5-hr delayed imaging.

Defect Reversibility

Figure 5 shows correlation between the two radionuclides for segmental defect reversibility patterns. Exact agreement was 95% (94/99) (kappa = 0.898, p < 0.0001) for initial 3-hr redistribution and was 92% (80/

FIGURE 4
Agreement for visual segmental scores between [123I]MPDA and 201Tl on initial 3-hr and 5-hr images.

87) for initial 5-hr studies (kappa = 0.823, p < 0.0001). The pattern of reversibility from initial postexercise to 3-hr delayed imaging was found to be discordant between the two agents in 5 of 99 segments. Of these, three segments were considered reversible by 201Tl that were normal by [123I]MPDA and one segment was reversible by 201Tl but showed reverse redistribution by [123I]MPDA. It is of note that despite this apparent discordance, four of five segments were considered to be viable by both agents. Of the 87 myocardial segments that were compared for the pattern of 5-hr reversibility, 7 showed discordant patterns between the two agents. Of these, six were reversible or showed reverse redistribution by 201Tl but were normal (five segments) or showed reverse redistribution (one segment) by [123I] MPDA. Therefore, in this subgroup of seven apparently discordant results, six showed concordance for regional myocardial viability.

Initial Defect Contrast

On the initial images, the average ± s.d. defect contrast for [123I]MPDA was 42% ± 17%, which was not significantly different from that of 201Tl which was 38% ± 16% (p = 0.142).

Myocardial Percent Clearances in Normal and Defect Regions

In normal regions, the 3-hr percent clearances of 201Tl and [123I]MPDA were 40 ± 4 and 43 ± 5, respectively (p = ns) (Fig. 6). In the defect regions, the 3-hr

FIGURE 3
Comparison of initial radionuclide distributions of [123I]MPDA and 201Tl. Planar myocardial images are shown in the anterior (ANT), 45° and steep left anterior oblique (LAO) views. Iodine-123-MPDA and 201Tl uptakes are similarly decreased in the apical, inferior, and distal posterolateral segments. Of note is the higher liver uptake of [123I]MPDA (anterior view).

FIGURE 5
Visual agreement for segmental defect reversibility between [123I]MPDA and 201Tl on initial 3-hr and initial 5-hr redistribution studies. (NL = normal; REV = reversible defect; NR = nonreversible defect; and RR = reverse redistribution).
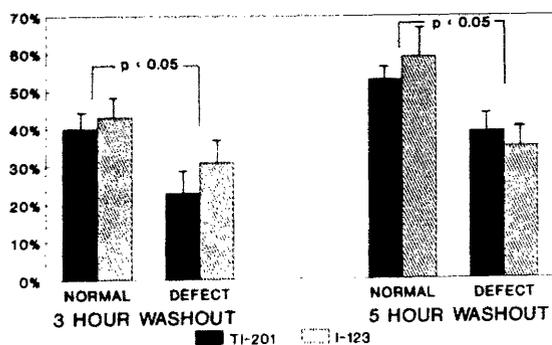
FIGURE 6
Comparative [^{123}I]MPDA and ^{201}Tl percent clearances in normal and defect regions at 3 hr (3 HOUR WASHOUT) and 5 hr (5 HOUR WASHOUT).

percent clearances were similar for both agents (23 ± 6 and 31 ± 6, respectively) but were significantly lower than the corresponding values in normal regions (p < 0.05). Similar differences between normal and defect percent myocardial clearances were noted on 5-hr delayed images for ^{201}Tl (53 ± 3 versus 39 ± 5, respectively) and for [^{123}I]MPDA (59 ± 7 versus 35 ± 5, respectively). Of note, for the patient with a prior myocardial infarction, [^{123}I]MPDA percent clearance from the infarct zone was 47% at 3 hr and 68% at 5 hr, both higher than the corresponding normal values.

Myocardial-to-Background Ratios

These were determined for the initial and 5-hr images (Fig. 7). Thallium-201 myocardium-to-lung ratios on initial and 5-hr images were 2.43 ± 0.49 and 1.84 ± 0.27, respectively. Iodine-123-MPDA myocardium-to-lung ratios on initial and 5-hr images were 2.65 ± 0.34 and 1.73 ± 0.17, respectively, which were not statistically different from the values observed with ^{201}Tl. In contrast, the initial [^{123}I]MPDA myocardium-to-liver ratio was significantly lower than that of ^{201}Tl (respectively 1.12 ± 0.30 versus 1.41 ± 0.37, p < 0.05). The 5-hr myocardium-to-liver ratios for [^{123}I]MPDA and ^{201}Tl were not statistically different (respectively 1.07 ± 0.19 versus 1.17 ± 0.11).
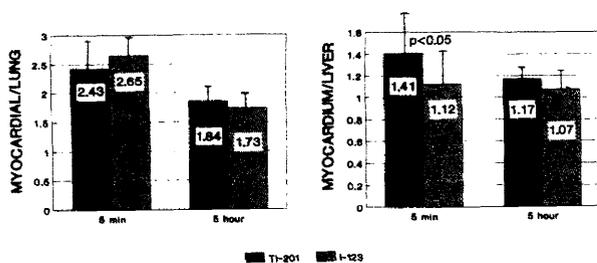
FIGURE 7
Myocardial-to-lung (left) and myocardial-to-liver (right) ratios of [^{123}I]MPDA and ^{201}Tl for initial (5-min) and delayed (5-hr) images.

DISCUSSION

Iodine-123-labeled free-fatty acids have been proposed as a means of studying myocardial metabolism in man (9,10), but their rapid mitochondrial degradation by beta-oxidation and rapid detachment of ^{123}I from the molecule have limited their clinical application. In the last decade, more suitable radiolabeled fatty acids were developed for myocardial imaging. The problem of rapid mitochondrial degradation was addressed by adding one or two methyl groups at the carbon-3 position (11-16), which prevented the compound to enter the beta-oxidation cycle. To stabilize the ^{123}I on the free-fatty acid molecule, a phenyl ring was added at the omega position (17-18). Recently, [^{123}I]MPDA, a new modified free-fatty acid was developed that contains a phenyl ring on carbon-15 and a methyl branch of the carbon-9. Preliminary study in normal volunteers (7) demonstrated that the methyl branching on carbon-9 significantly increased the myocardial residence time of [^{123}I]MPDA. In the present study, uptake and kinetics of [^{123}I]MPDA were compared to those of ^{201}Tl in patients with exertional ischemia.

Myocardial-to-Background Ratios

Our results demonstrate comparable myocardial-to-lung ratios between [^{123}I]MPDA and ^{201}Tl on the initial and 5-hr delayed images. We found, however, that the initial myocardial-to-liver ratio was lower with [^{123}I] MPDA because of its higher initial liver uptake. The [^{123}I]MPDA hepatic clearance is faster than that of ^{201}Tl, resulting in similar myocardial-to-liver ratios for both agents 5 hr after injection.

Initial Myocardial Uptake

Iodine-123-MPDA paralleled ^{201}Tl segmental myocardial distribution very closely. Quantitative assessment of defect contrast confirmed this finding by demonstrating no significant difference between [^{123}I] MPDA and ^{201}Tl. These findings suggest that the initial postexercise distribution of [^{123}I]MPDA, like ^{201}Tl is related to regional myocardial blood flow distribution. However, it is possible that decreased [^{123}I]MPDA regional uptake, as observed with other fatty acids (19-21), is not only flow related but may be also affected by diminished extraction accompanying reduction of aerobic metabolism.

Defect Reversibility

The agreement between [^{123}I]MPDA and ^{201}Tl for different patterns of defect reversibility was high. This was observed when the initial postexercise images were compared to either the 3-hr or the 5-hr delayed images. Correlation between the two agents for defect reversibility is also reflected in the high degree of correlation that was found in regional myocardial distribution of both agents on the 3- and 5-hr delayed images. Similarity between the two agents with respect to defect revers-

ibility stems from similar [^{123}I]MPDA and ^{201}Tl myocardial clearance patterns.

Myocardial Clearance

Iodine-123-MPDA myocardial clearances in normal regions at 3 and 5 hr were similar and statistically not significantly different from those observed with ^{201}Tl in the same corresponding regions. In myocardial segments with initial defect, percent clearance rates of [^{123}I]MPDA at 3 and 5 hr were lower than those observed in normal myocardial regions. These values were also not significantly different from those of ^{201}Tl. The results suggest that the observed defect reversibility from initial post-stress to 3- and 5-hr delayed imaging times are due to differential clearance rate of [^{123}I]MPDA from normal and defect regions such that the relatively faster clearance rate of [^{123}I]MPDA from normal areas and relatively slower clearance rate from defect areas result in normalization of activity over time. In this regard, [^{123}I]MPDA appears to behave very similarly to ^{201}Tl. Our finding of slower than normal clearance rate of [^{123}I]MPDA in defect zones is consistent with previous work by Lerch et al. (19) using carbon-11-palmitate, Van der Wall et al. (22) using heptadecanoic acid, and Kennedy et al. (23) using [^{123}I]IPPA. The proposed mechanism for reduced fatty acid clearance from regions of myocardial ischemia has been that once the fatty acid has undergone esterification with acetyl co-enzyme A, it is no longer able to diffuse out of the cell. Schoen (24) described this phenomenon as "metabolic sequestration" of the fatty acids in the myocardial cells. Our study, however, does not evaluate the underlying metabolic alterations that may have been responsible for slower clearance of [^{123}I]MPDA from defect regions. In the one patient in this study with a myocardial segment with prior myocardial infarction, the [^{123}I]MPDA clearance from the defect zone was higher than that from the normal zone. This observation is consistent with a previous report by Van der Wall (25). Since myocardial imaging was performed at three time intervals only, more detailed kinetics of [^{123}I]MPDA cannot be evaluated based on this study.

Study Limitations

Since only 11 patients were included in this study, the results should be considered preliminary. There were only four nonreversible defects by ^{201}Tl imaging. Therefore, we could not evaluate the limitations of ^{201}Tl and the possible advantages of [^{123}I]MPDA with respect to evaluation of myocardial viability.

CONCLUSIONS

This study demonstrates that [^{123}I]MPDA is a suitable agent for myocardial imaging and is comparable to ^{201}Tl. Similar initial myocardial distribution of these two radionuclides suggests that [^{123}I]MPDA initial dis-

tribution is related to regional myocardial perfusion. Reversibility of the initial postexercise myocardial defects appears to be due to slower clearance from defect regions rather than active accumulation of fatty acids in these areas. Further clinical investigation is needed to define comparative abilities of [^{123}I]MPDA and ^{201}Tl to assess myocardial viability.

REFERENCES

1. Brunken R, Kottou S, Nienaber C, et al: PET detection of viable tissue in myocardial segments with persistant defects at thallium-201 SPECT. Radiology 1989;172:65–73.
2. Liu P, Kiess MC, Okasa RD, et al. The persistent defect on exercise thallium imaging and its rate after myocardial revascularization: does it represent scar or ischemia? Am Heart J 1985;110:996–1001.
3. Gibson RS, Watson DD, Taylor GJ, et al. Prospective assessment of regional myocardial perfusion before and after coronary revascularization surgery by quantitative thallium-201 scintigraphy. J Am Coll Cardiol 1983;1:804–815.
4. Kiat H, Berman DS, Maddahi J, et al. Late reversibility of tomographic myocardial thallium-201 defects: an accurate marker of myocardial viability. J Am Coll Cardiol 1988; 12:1456–1463.
5. Lerch RA, Ambos HD, Bergmann SR, Welch MJ, Ter-Pogossian MM, Sobel BE. Localization of viable, ischemic myocardium by positron-emission tomography with C-11-palmitate. Circulation 1981;65:731–738.
6. Goldstein RA, Klein MS, Welch MJ, Sobel BE. External assessment of myocardial metabolism with C-11-palmitate in vivo. J Nucl Med 1980;21:342–348.
7. Miller DD, Barlai-Kovach M, Gill JB, et al. Imaging characteristics of a new single-photon myocardial metabolic tracer. Circulation 1986;74:II-62.
8. Sinusas AJ, Beller GA, Smith WH, Vinson EL, Brookeman V, Watson DD. Quantitative planar imaging with technetium-99m-methoxyisobutyl isonitrile: comparison of uptake patterns with thallium-201. J Nucl Med 1989;30:1456–1463.
9. Poe ND, Robinson GD, Zielinski FW, et al. Myocardial

imaging with I-123-hexadecanoic acid. *Radiology* 1977;124: 419–424.

10. Freundlieb C, Hock A, Vyska K, Feinendgen LE, Machulla HJ, Stocklin G. Myocardial imaging and metabolic studies with [17-I-123]iodoheptadecanoic acid. *J Nucl Med* 1980;21: 1043–1050.

11. Livni E, Elmaleh DR, Levy S, Brownell GL, Strauss WH. Beta methyl [1-C-11]heptadecanoic acid: a new myocardial metabolic tracer for positron emission tomography. *J Nucl Med* 1982;23:169–175.

12. Goodman MM, Kirsch G, Knapp FF Jr. Synthesis of radioiodinated omega-(p-iodophenyl)substituted methyl-branched long-chain fatty acids. *J Lab Compds Radiopharm* 1982; 19:1316–1318.

13. Goodman MM, Kirsch G, Knapp FF Jr. Synthesis and evaluation of radioiodinated terminal p-iodophenyl-substituted alpha and beta-methyl-branched fatty acids. *J Med Chem* 1984;25:390–397.

14. Goodman MM, Knapp FF Jr, Elmaleh DR, Strauss HW. New myocardial imaging agents: synthesis of 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid by decomposition of a piperidimyl trizene precursor. *J Org Chem* 1984;49:2322–2325.

15. Knapp FF Jr, Goodman MM, Callahan AP, Kirsch G. Radioiodinated 15-(p-iodophenyl)-3,3-dimethyl pentadecanoic acid (DMIPP): a useful new agent to evaluate myocardial fatty acid uptake. *J Nucl Med* 1986;27:521–531.

16. Van der Wall EE, Barret E, Strauss HW, et al. Altered uptake and kinetics of radioiodinated 15-p-(I-125)-iodophenyl-3-methylpentadecanoic acid in diabetic myocardium [Abstract] *Circulation* 1985;72:424.

17. Reske SN, Simon H, Machulla HJ, Biersack HJ, Knopp R, Winkler C. Myocardial turnover of p-(I-123 phenyl)-penta-

18. decanoic acid in patients with CAD [Abstract]. *J Nucl Med* 1982;23:P34.

18. Dudczak R, Schmoliner R, Angelberger P, Kletter K, Frischauf H. Myocardial studies with I-123-p-phenylpentadecanoic acid in patients with coronary artery disease and cardiomyopathy [Abstract]. *J Nucl Med* 1982;23:P35.

19. Lerch RA, Bergman SR, Ambos HD, Welch MJ, Ter-Pogossian MM, Sobel BE. Effect of flow-independent reduction of metabolism on regional myocardial clearance of C-11-palmitate. *Circulation* 1982;65:731–738.

20. Fox KAA, Ambos HD, Homura H, Bergman SR, Sobel BE. The importance of back-diffusion on myocardial kinetics of C-11-palmitate. *J Am Coll Cardiol* 1984;3:574.

21. Fox KAA, Nomura H, Sobel BE, et al. Consistent substrate utilization despite reduced flow in hearts with maintained work. *Am J Physiol* 1983;244:H799–H806.

22. Van der Wall EE, Heidendal GAK, Den Hollander W, Westera G, Ross JP. Metabolic myocardial imaging with I-123-labeled heptadecanoic acid in patients with angina pectoris. *Eur J Nucl Med* 1981;6:391–396.

23. Kennedy PL, Corbett JR, Kulkarni PV, et al. Iodine-123-phenylpentadecanoic acid myocardial scintigraphy: usefulness in the identification of myocardial ischemia. *Circulation* 1986;74:1007–1015.

24. Schoen HR, Schelbert HR, Najafi A, et al. C-11-labeled palmitic acid for the noninvasive evaluation of regional myocardial fatty acid metabolism with positron-computed tomography. II. Kinetics of C-11-palmitic acid in acutely ischemic myocardium. *Am Heart J* 1982;103:548–561.

25. Van der Wall EE, Den Hollander W, Heindendal GAK, Westera G, Majid PA, Roos JP. Dynamic myocardial scintigraphy with I-123-labeled free-fatty acids in patients with myocardial infarction. *Eur J Nucl Med* 1981;6:383–389.