Iodine 123–phenylpentadecanoic acid myocardial scintigraphy: usefulness in the identification of myocardial ischemia

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ABSTRACT In this study, we tested the hypothesis that myocardial ischemia induced by exercise in patients is associated with diminished metabolism and/or delayed clearance of an intravenously injected fatty acid, iodine 123–labeled phenylpentadecanoic acid (IPPA). Fifteen normal volunteers and 18 patients with significant coronary heart disease (CHD) received IPPA during exercise. In the patients with CHD, radionuclide ventriculograms were also obtained during exercise. The normal volunteers had relatively uniform initial left ventricular segmental IPPA activity after exercise and uniform IPPA clearance in the interval from 4 to 20 min immediately after exercise. In contrast, the patients with CHD had increased initial left ventricular segmental IPPA activity (63%, p < .001) and delayed IPPA clearance (44%, p < .01) in segments supplied by significantly narrowed coronary arteries. Based on analysis with the mean values ± 1 SD for initial IPPA activity, clearance, or both in normal volunteers, the sensitivity and specificity of exercise IPPA scintigraphy for detecting CHD were 89% and 67%, respectively; when ± 2 SD differences from the mean values in the normal volunteers were considered, the sensitivity and specificity were 72% and 100%, respectively. Among the total of 27 noninfarcted left ventricular segments supplied by significantly narrowed coronary arteries in the study patients, 26 (96%) had an abnormality (mean ± 1 SD) of either initial IPPA activity or clearance compared with corresponding segments in the normal volunteers and/or with other left ventricular segments in the same image that were not supplied by significantly narrowed coronary arteries. Thus, these data suggest that IPPA scintigraphy may be used in the identification of myocardial ischemia in patients with CHD by demonstrating abnormal initial left ventricular segmental IPPA activity and/or delayed clearance after exercise.


Under aerobic and fasting conditions, free fatty acids are the preferred substrate of normal myocardium, providing up to 90% of resting energy requirements. Therefore, radiolabeled fatty acids have attracted great interest for cardiac imaging and as potential probes of myocardial metabolism. Studies by Sobel, Schelbert, and Weiss and their colleagues and others using 13C-palmitate with positron tomography have shown great promise for this technique in defining ischemic and infarcted myocardium. However, such studies require a cyclotron to produce short-lived radioisotopes as well as specialized imaging systems. Thus, these methods are expensive and not presently available for routine clinical use at most institutions.

Several fatty acids, including hexadecanoic and heptadecanoic acids, have been synthesized and labeled with single photon-emitting radioisotopes. Modifications of fatty acid chain length, degree of methylation, incorporation of metallic heteroatoms such as tellurium have been attempted to alter myocardial uptake or metabolism. In some instances, however, interpretation of the myocardial kinetics of these agents has been hampered by poor image contrast due to release of free radiiodine by the myocardium and by hepatic β-oxidation. Freundlieb et al. have proposed correction procedures for identify-
ing the free $^{123}$I activity not specifically bound to myocardial cells, but an iodine-labeled fatty acid that is metabolized without liberation of free radiiodine is desirable.

Recently, Machulla et al. synthesized $\omega$-(p-I-123 phenyl)-pentadecanoic acid (IPPA), a long-chain free fatty acid that undergoes $\beta$-oxidation without significant deiodination. The chemical structure of IPPA is $^{123}$I-$\omega$-(CH$_2$)$_n$-COOH. In our laboratory, Kulkarni et al. have modified the synthesis of IPPA with improved radiochemical yields of greater than 90%, thus enhancing its utility in human imaging. Chien and Reske and their colleagues have shown rapid myocardial uptake of IPPA and biexponential clearance similar to that of $^3$H-palmitate in animal preparations. IPPA is metabolized to iodobenzoic acid with subsequent rapid renal excretion. Using single photon-emission tomography or computed tomographic imaging, we have also previously demonstrated that acutely infarcted canine myocardium shows decreased uptake and/or delayed clearance of IPPA, even when coronary blood flow is restored by reperfusion.

The goal of the present study was to characterize the uptake and clearance of IPPA at rest and during exercise in normal volunteers and patients with coronary heart disease. In these studies, we tested the hypothesis that regions of myocardial ischemia exhibit diminished metabolism and/or delayed clearance of intravenously injected IPPA, thus allowing detection of ischemic regions as areas of increased IPPA activity on myocardial scintigraphic images.

Methods

Study groups. Fifteen normal volunteers (12 men and three women with a mean age of 29 ± 7 years) were evaluated. None had clinical evidence of coronary artery disease. Fifteen underwent resting and nine underwent exercise IPPA examinations, with nine individuals having both. In six of the normal volunteers resting and maximal exercise radionuclide ventriculographic studies were also performed.

Eighteen patients who presented with stable angina pectoris at Parkland Memorial Hospital in Dallas between August 1984 and June 1985 were studied with IPPA (Table 1). Fifteen patients were men and three were women. Their mean age was 54 ± 11 years. Seventeen patients underwent coronary arteriography, and all were found to have greater than or equal to 70% luminal diameter narrowing of one or more major coronary arteries. Four of the patients had single-vessel, eight had double-vessel, and five had triple-vessel coronary arterial stenoses. The patient who did not undergo coronary arteriography presented with classic exertional angina and demonstrated left ventricular global and segmental deterioration during exercise radionuclide ventriculography. In total, 11 patients had prior myocardial infarctions as documented by clinical history, classic alterations on the electrocardiogram, abnormal enzymes, and/or subsequently abnormal regional left ventricular wall motion. Two patients had undergone previous coronary artery revascularization surgery.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Patients with coronary heart disease studied with IPPA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CHD = coronary heart disease; MI = myocardial infarction; CABG = coronary artery bypass graft surgery.

In these patients, 11 resting and 18 exercise IPPA studies were performed. Eleven patients underwent both resting and exercise IPPA studies. In addition, all 18 patients underwent resting and maximal exercise radionuclide ventriculographic examinations. The cardiac catheterizations and IPPA examinations were completed within a mean time of 216 ± 344 days and the resting and exercise radionuclide ventriculograms were obtained within 188 ± 311 days of IPPA imaging. There was no major change in the clinical conditions of these patients between these studies.

Radiochemical preparation. Phenylpentadecanoic acid (PPA) was radioiodinated via a PPA-thallium intermediate as proposed by Kulkarni et al. with minor modifications. With radionuclide purity of greater than 99% was obtained from Atomic Energy of Canada, Ltd., Ottawa. The labeled product was reconstituted in ethyl alcohol-albumin saline matrix and sterilized by 0.22 $\mu$m membrane filtration (Millipore). Pyrogen testing was performed with a limulus amoebocyte lysate test.

Exercise radionuclide ventriculographic protocol. Red blood cell labeling with technetium pertechnetate was accomplished in vitro. Radionuclide ventriculography was performed with a standard-field-of-view gamma camera (Picker Dyna Mo, Northford, CT) equipped with a general-purpose, low-energy, parallel-hole collimator interfaced to a dedicated nuclear medicine computer for data acquisition, storage, and analysis (Technicare 560, Solon, OH). A 12-lead electrocardiogram was obtained before the beginning of exercise.

Supine bicycle exercise was begun generally at 150 to 300 kilopond-meters (kp-m) and workload was increased in increments until a near-maximal effort was achieved or the patient developed severe fatigue, angina, ST segment depression of 2 mm or more, or complex ventricular ectopic activity. The 12-lead electrocardiographic examinations were repeated at 1 min intervals during exercise and for 10 min after exercise.

Left ventricular ejection fraction (LVEF) and end-systolic volume were measured and a subjective assessment of segmental wall motion was obtained at rest and at each level of exercise with methods we have described previously.

Exercise IPPA protocol. Fifteen normal volunteers and 18 patients with coronary heart disease were studied with IPPA. Most patients with coronary heart disease were treated with individually maximal antianginal medications, and these were continued without modification. Subjects were allowed a no-fat diet for breakfast, and then fasted for 4 to 8 hr before injection and imaging. One milliliter of Lugol’s solution was given orally 30 to 60 min before the injection of IPPA. Two to six millicuries of IPPA was injected intravenously with the patient upright at rest (in those patients in whom resting evaluations were obtained) or 1 min before termination of exercise in all of the patients studied during and after exercise. Exercise testing in-
volved symptom-limited maximal upright bicycle exercise; exercise was terminated if the patient developed severe fatigue, angina, ST segment depression of 2 mm or more, or complex ventricular ectopic activity.

Planar imaging was performed with a standard-field-of-view gamma camera (Picker Dyna Mo) equipped with a general-purpose, low-energy, parallel-hole collimator interfaced to a dedicated nuclear medicine computer for data acquisition, storage, and analysis (Technicare 560, Solon, OH). Energy discrimination was provided by a 20% window centered on the 159 keV photopeak of $^{123}$I. Images were acquired in a 40 degree left anterior oblique projection. Individual images of 4 min duration were acquired with a digital resolution of $128 \times 128$ beginning at 4, 20, 40, and 60 to 90 min after IPPA injection. Count densities in normal left ventricular segments before background subtraction averaged 80 counts/pixel.

Quantitation of myocardial IPPA activity. Images were aligned and spatially smoothed. Background activity was measured in a region of interest constructed two to three pixels outside the left ventricular boundary and adjacent to the apical-lateral segment of the left ventricle. Left ventricular regions of interest were constructed over the high or basal-septal, low or apical-septal, low or apical-lateral, and high or basal-lateral segments of each image (figure 1). The left ventricular apex was avoided to minimize confusion due to normal thinning of the left ventricular muscle mass in that region. IPPA activity in segments 1 and 2 was assumed to reflect the distribution of the left anterior descending coronary artery (LAD), that in segment 3 the right coronary artery (RCA), and that in segment 4 the circumflex coronary artery (LCX). Activity within each region was normalized to the mean activity of all segments within the image. Segmental washout rates were calculated from the mean activity in each segment before normalization. IPPA distributions and washout rates were compared with values derived from the normal volunteers and with those in normal segments within the same image.

Statistical analyses. Results are expressed as the mean $\pm$ 1 SD. Student’s t test and chi-square goodness-of-fit analyses were performed for statistical comparisons ($p < .05$ was considered indicative of a statistically significant difference). Abnormal left ventricular segments were those in which there was a 1 SD increase or decrease in segmental IPPA activity or clearance compared with that in corresponding left ventricular segments of normal volunteers. Values for left ventricular segmental clearance more than 1 SD different from the maximal mean values in normally perfused segments within the same image were also considered abnormal.

Results

Consequences of administration of IPPA. No changes in resting heart rate, respiratory rate, or blood pressure were recorded after the intravenous injection of IPPA. Administration of Lugol’s solution resulted in near-complete suppression of thyroid uptake of radioactivity in all subjects studied.

Normal volunteers

Exercise responses. Six normal volunteers underwent exercise radionuclide ventriculography. They exercised to a mean workload of 942 $\pm$ 307 kp-m, a mean heart rate of 142 $\pm$ 18 beats/min, and a mean systolic blood pressure of 184 $\pm$ 29 mm Hg. None of the normal volunteers developed chest pain or ST segment alterations suggestive of ischemia with exercise. All volunteers had the expected normal increase in global LVEF, decrease in left ventricular end-systolic volume index, and lack of deterioration in left ventricular segmental motion.

During the exercise IPPA examination, the volunteers exercised to a mean workload of 936 $\pm$ 221 kp-m, a mean heart rate of 166 $\pm$ 25 beats/min, and a mean systolic blood pressure of 183 $\pm$ 19 mm Hg.

IPPA images. Initial IPPA activity in normal volunteers (figure 2) was relatively uniform, with the mean maximal difference in left ventricular segmental activity varying by 18 $\pm$ 7% at rest and 13 $\pm$ 5% after exercise (table 2). The apical-septal and apical-lateral segments consistently demonstrated greater IPPA activity relative to the basal segments in normal volunteers. This may have been caused by hepatic overlap of the apex in these planar images, which affects the apical segments to the greatest extent.

IPPA segmental washout rates in normal volunteers were also relatively uniform. IPPA washout from 4 to 20 min after IPPA injection at rest and during exercise was 21.1 $\pm$ 10.0% and 12.6 $\pm$ 8.4%, respectively ($p < .001$).

Patients with coronary heart disease

Exercise responses. All patients underwent exercise radionuclide ventriculographic examinations and they exercised to a mean workload of 439 $\pm$ 153 kp-m, a mean heart rate of 102 $\pm$ 20 beats/min, and a mean systolic blood pressure of 177 $\pm$ 26 mm Hg. With
exercise, seven of 18 (39%) developed angina and four of 18 (22%) developed 1 mm or more horizontal or downsloping ST depression as measured 80 msec after the J point. A fall in global LVEF occurred in nine of 18 or 50% of patients, an increase in left ventricular end-systolic volume index was noted in 10 of 18 (56%), and left ventricular segmental deterioration in wall motion was observed in 16 of 18 (89%). Each patient had at least one of the abnormal responses to exercise described above, indicating the development of myocardial ischemia with exercise.

During the evaluation with IPPA, the patients exercised to a mean workload of 528 ± 149 kp-m (p < .001 compared with normal volunteers), a mean heart rate of 115 ± 22 beats/min (p < .001), and a mean peak systolic blood pressure of 179 ± 27 mm Hg (p = NS). During the exercise test, nine of 18 patients (50%) developed angina and seven of 18 (38%) developed significant ST depression.

**TABLE 2**

Normal volunteers studied with IPPA

<table>
<thead>
<tr>
<th></th>
<th>Mean maximal difference in LV segmental IPPA activity (%)</th>
<th>IPPA washout from 4 to 20 min (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting study (n = 15)</td>
<td>18±7</td>
<td>21.1±10.0</td>
</tr>
<tr>
<td>Exercise study (n = 9)</td>
<td>13±5</td>
<td>12.6±8.4A</td>
</tr>
</tbody>
</table>

LV = left ventricular.

*p < .001 compared with IPPA washout from 4 to 20 min at rest.

IPPAs. Although most IPPA studies demonstrated clear abnormalities that could be appreciated visually, quantitative analyses were required to detect abnormalities in approximately 30% of patients studied. Figures 3 and 4 are IPPA images that illustrate the left ventricular segmental heterogeneity of IPPA activity at rest and immediately after exercise in two patients. The maximal differences in left ventricular segmental activity averaged 36% and 30% at rest and after exercise, respectively (p < .001; table 3).

The sensitivity and specificity of exercise IPPA scintigraphy for the detection of coronary heart disease were determined by comparing the variation in initial left ventricular IPPA activity and/or clearance on the patients’ images with those on images of the normal volunteers (table 4). Based on analysis with the mean normal values ±2 SD for initial left ventricular segmental IPPA activity, clearance, or both, the sensitivity of IPPA scintigraphy for detecting coronary heart disease was 67%, 22%, and 72%, respectively. The specificity was 100% when alterations in initial IPPA activity, clearance, or both were considered. When the mean normal values ±1 SD were considered, the sensitivity increased to 89%, 39%, and 89%, respectively, and the specificity fell to 78%, 89%, and 67%, respectively.

**FIGURE 3.** Images from a patient with significant three-vessel coronary heart disease and exertional angina who demonstrated increased initial IPPA activity in the interventricular septum (upper arrow) at the postexercise IPPA examination. Also demonstrated on the exercise radionuclide ventriculogram was global and segmental left ventricular functional deterioration in the region in which IPPA uptake and washout were altered, i.e., the ventricular septum. Lower arrow points to the liver. Color code is as in figure 2.
In the patients studied during exercise, there were 27 coronary arteries with stenoses of 70% or more supplying noninfarcted myocardium (12 LAD, six RCA, and nine LCX). Compared with the left ventricular segmental IPPA distribution in the normal volunteers, in the patients initial IPPA activity in left ventricular regions supplied by significant coronary stenoses was increased in 17 of 27 patients (63% of the total), it was normal in seven of 27 (26%), and it decreased in three of 27 (11%) (p < .001; table 5). One patient with severe three-vessel coronary arterial stenoses without prior infarction had homogeneous activity in all segments and they were not classified as abnormal by our distribution criteria. However, this patient had markedly delayed IPPA washout in all left ventricular segments.

### TABLE 3
Normal volunteers and patients with coronary heart disease studied with IPPA

<table>
<thead>
<tr>
<th>Mean maximal difference in LV segmental IPPA activity (%)</th>
<th>Normal volunteers</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting study</td>
<td>18 ± 7</td>
<td>36 ± 14^A</td>
</tr>
<tr>
<td>Exercise study</td>
<td>13 ± 5</td>
<td>30 ± 13^A</td>
</tr>
</tbody>
</table>

LV = left ventricular.

^A p < .001 compared with normal volunteers.

Twelve of 27 or 44% of noninfarcted segments supplied by significantly narrowed coronary arteries exhibited delayed washout of IPPA from 4 to 20 min after exercise compared with washout from the same left ventricular segments in the normal volunteers (−2.4 ± 8.7%, p < .001). Fifteen left ventricular segments demonstrated normal or enhanced IPPA washout compared with normal. However, in eight of these 15 segments IPPA washout rates were slower than those in normally perfused left ventricular segments within the same images, with abnormality defined as the mean maximal variation in left ventricular segmental IPPA washout ± 1 SD in normal subjects. Thus, delayed early IPPA left ventricular segmental washout was found in 20 of 27 or 74% of noninfarcted left ventricular segments supplied by significantly narrowed coronary arteries.

In all, 26 of 27 or 96% of the left ventricular segments supplied by significantly narrowed coronary arteries exhibited some associated abnormality in either initial IPPA activity or clearance compared with that in similar segments in the normal volunteers and/or other left ventricular segments in the same images.

### TABLE 4
Sensitivity and specificity of exercise IPPA scintigraphy for the detection of coronary heart disease

<table>
<thead>
<tr>
<th>Sensitivity (%)</th>
<th>Normal mean values ± 2 SD</th>
<th>Normal mean values ± 1 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial activity</td>
<td>67</td>
<td>89</td>
</tr>
<tr>
<td>Clearance</td>
<td>22</td>
<td>39</td>
</tr>
<tr>
<td>Both</td>
<td>72</td>
<td>89</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial activity</td>
<td>100</td>
<td>78</td>
</tr>
<tr>
<td>Clearance</td>
<td>100</td>
<td>89</td>
</tr>
<tr>
<td>Both</td>
<td>100</td>
<td>67</td>
</tr>
</tbody>
</table>

Twelve of 27 or 44% of noninfarcted segments supplied by significantly narrowed coronary arteries exhibited delayed washout of IPPA from 4 to 20 min after exercise compared with washout from the same left ventricular segments in the normal volunteers (−2.4 ± 8.7%, p < .001). Fifteen left ventricular segments demonstrated normal or enhanced IPPA washout compared with normal. However, in eight of these 15 segments IPPA washout rates were slower than those in normally perfused left ventricular segments within the same images, with abnormality defined as the mean maximal variation in left ventricular segmental IPPA washout ± 1 SD in normal subjects. Thus, delayed early IPPA left ventricular segmental washout was found in 20 of 27 or 74% of noninfarcted left ventricular segments supplied by significantly narrowed coronary arteries.

In all, 26 of 27 or 96% of the left ventricular segments supplied by significantly narrowed coronary arteries exhibited some associated abnormality in either initial IPPA activity or clearance compared with that in similar segments in the normal volunteers and/or other left ventricular segments in the same images.

### TABLE 5
Initial IPPA activity and early washout after exercise in left ventricular segments supplied by significantly narrowed coronary arteries^A

<table>
<thead>
<tr>
<th>Narrowsed coronary artery</th>
<th>Initial IPPA activity</th>
<th>Washout of IPPA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>LAD</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>RCA</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>LCX</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>(53%)</td>
<td>(26%)</td>
</tr>
</tbody>
</table>

^A Luminal diameter narrowing ≥70%.

^B p < .001 by chi-square analysis; ^C p < .01 by chi-square analysis.
TABLE 6
Clinical characteristics and results of exercise radionuclide ventriculography, IPPA scintigraphy, and cardiac catheterization in patients with coronary heart disease

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Double products</th>
<th>Angina</th>
<th>ST depression</th>
<th>LVEF at rest</th>
<th>LVEF during exercise</th>
<th>Change in LVESVI</th>
<th>LV segmental deterioration</th>
<th>RCA (% stenosis)</th>
<th>LAD (% stenosis)</th>
<th>LCX (% stenosis)</th>
<th>Dominance</th>
<th>LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. R.</td>
<td>49</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>0.42</td>
<td>0.33</td>
<td>+8</td>
<td>2.3</td>
<td>50</td>
<td>60</td>
<td>100</td>
<td>R</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>A. A.</td>
<td>70</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>0.58</td>
<td>0.45</td>
<td>+35</td>
<td>2.3</td>
<td>100</td>
<td>95</td>
<td>—</td>
<td>R</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>H. B.</td>
<td>71</td>
<td>M</td>
<td>-</td>
<td>+</td>
<td>0.54</td>
<td>0.49</td>
<td>+5</td>
<td>1.2,4</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>J. J.</td>
<td>41</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>0.61</td>
<td>0.45</td>
<td>+22</td>
<td>2.3</td>
<td>—</td>
<td>99</td>
<td>—</td>
<td>Codom</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>W. C.</td>
<td>47</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>0.70</td>
<td>0.68</td>
<td>+3</td>
<td>3.4</td>
<td>60</td>
<td>—</td>
<td>50</td>
<td>R</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>R. C.</td>
<td>48</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>0.55</td>
<td>0.47</td>
<td>+8</td>
<td>2.3</td>
<td>100</td>
<td>70</td>
<td>99</td>
<td>R</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>R. D.</td>
<td>49</td>
<td>M</td>
<td>-</td>
<td>+</td>
<td>0.63</td>
<td>0.76</td>
<td>—9</td>
<td>2</td>
<td>PG</td>
<td>PG</td>
<td>OG</td>
<td>R</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>D. C.</td>
<td>52</td>
<td>M</td>
<td>-</td>
<td>+</td>
<td>0.45</td>
<td>0.53</td>
<td>—7</td>
<td>—</td>
<td>80</td>
<td>60</td>
<td>—</td>
<td>R</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>J. H.</td>
<td>52</td>
<td>M</td>
<td>21,850</td>
<td>+</td>
<td>0.61</td>
<td>0.50</td>
<td>+10</td>
<td>1.2,3</td>
<td>50</td>
<td>75</td>
<td>75</td>
<td>R</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>R. F.</td>
<td>59</td>
<td>M</td>
<td>10,240</td>
<td>+</td>
<td>0.51</td>
<td>0.58</td>
<td>—5</td>
<td>2.3</td>
<td>99</td>
<td>—</td>
<td>100</td>
<td>R</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>N. H.</td>
<td>43</td>
<td>M</td>
<td>20,280</td>
<td>+</td>
<td>0.45</td>
<td>0.52</td>
<td>—19</td>
<td>3</td>
<td>100</td>
<td>75</td>
<td>99</td>
<td>R</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>C. H.</td>
<td>46</td>
<td>M</td>
<td>12,180</td>
<td>+</td>
<td>0.61</td>
<td>0.52</td>
<td>+14</td>
<td>1.2,4</td>
<td>100</td>
<td>—</td>
<td>100</td>
<td>R</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>W. G.</td>
<td>47</td>
<td>M</td>
<td>27,600</td>
<td>-</td>
<td>0.62</td>
<td>0.70</td>
<td>—5</td>
<td>2</td>
<td>75</td>
<td>75</td>
<td>L</td>
<td>0.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. P.</td>
<td>46</td>
<td>M</td>
<td>22,220</td>
<td>-</td>
<td>0.68</td>
<td>0.71</td>
<td>—5</td>
<td>2</td>
<td>50</td>
<td>90</td>
<td>75</td>
<td>99</td>
<td>R</td>
<td>0.77</td>
</tr>
<tr>
<td>E. D.</td>
<td>42</td>
<td>F</td>
<td>11,960</td>
<td>+</td>
<td>0.53</td>
<td>0.68</td>
<td>—10</td>
<td>—</td>
<td>—</td>
<td>99</td>
<td>R</td>
<td>—</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>J. G.</td>
<td>39</td>
<td>M</td>
<td>19,264</td>
<td>+</td>
<td>0.67</td>
<td>0.72</td>
<td>—7</td>
<td>4</td>
<td>90</td>
<td>75</td>
<td>99</td>
<td>R</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>J. K.</td>
<td>70</td>
<td>F</td>
<td>16,368</td>
<td>+</td>
<td>0.73</td>
<td>0.64</td>
<td>+14</td>
<td>2</td>
<td>100</td>
<td>99</td>
<td>75</td>
<td>R</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>B. W.</td>
<td>53</td>
<td>M</td>
<td>26,208</td>
<td>+</td>
<td>0.66</td>
<td>0.54</td>
<td>+24</td>
<td>2.3</td>
<td>90</td>
<td>—</td>
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<td>R</td>
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</tr>
</tbody>
</table>

LV = left ventricular; MI = myocardial infarction; LVESVI = left ventricular end-systolic volume index; Inf-lat = inferolateral; PG = patent graft; OG = occluded graft; Ant = anterior; Inf = inferior; SEMI = subendocardial myocardial infarction; Ant-sep = anteroseptal; H-lat = high lateral.

*a*Change from rest to exercise in left ventricular end-systolic volume index (ml).

*b*Coronary arteriographic findings before CABG (IPPA study was performed after CABG).

not supplied by significantly narrowed coronary arteries.

Clinical correlations and results of IPPA studies in individual patients are shown in table 6. The interindividual (two different observers) and intra-individual correlations for the same observer making the same measurements of IPPA uptake and washout at 2 month intervals were 0.95 and 0.98, respectively, for 168 measurements.

Rest and exercise IPPA studies in patients with coronary heart disease. Eleven patients underwent IPPA studies at rest and immediately after exercise. Among these patients there was a total of 18 noninfarcted left ventricular segments supplied by significantly narrowed coronary arteries. In these left ventricular segments, mean initial IPPA left ventricular segmental activity was increased after exercise compared with values in similar left ventricular segments in the normal volunteers (p = .03). Left ventricular segmental IPPA clearance from 4 to 20 min after exercise was 9.6 ± 13.4%.

During the IPPA studies at rest, the initial activity of IPPA in 18 noninfarcted left ventricular segments supplied by significantly narrowed coronary arteries was not significantly different than the IPPA distribution in the same left ventricular segments in the normal volunteers. IPPA clearance from 4 to 20 min after its injection in patients at rest was 18.4 ± 6.8% (p = .02 compared with exercise).

**Discussion**

In the present study, we used resting and postexercise IPPA myocardial scintigraphy in normal volunteers and patients with known coronary heart disease to test the hypothesis that left ventricular myocardium supplied by significantly stenosed coronary arteries exhibits abnormal initial IPPA uptake and/or metabolism or delayed clearance that can be detected by this method. The left ventricular segmental uptake and washout of IPPA was relatively uniform in normal volunteers, and our more recent studies have also demonstrated that submaximal exercise in normal volunteers does not cause reduced left ventricular segmental IPPA uptake or clearance. In contrast, myocardial segments supplied by significantly narrowed coronary
arteries frequently demonstrated increased early IPPA activity and delayed washout after exercise. After exercise, 63% of noninfarcted myocardial segments supplied by significantly narrowed coronary arteries demonstrated increased initial IPPA activity and 74% demonstrated delayed early IPPA clearance. Therefore, regions of myocardial ischemia may frequently be identified with IPPA scintigraphy as left ventricular regions of relatively increased segmental IPPA activity after exercise.

Previous studies in experimental animals have demonstrated that the duration of myocardial ischemia is important in determining myocardial extraction of fatty acids. After reducing mean blood flow to the LAD by 60% for a period of 12 min in a canine preparation, Schönh et al. found equivalent extraction fractions for 11C-palmitate in ischemic and control myocardial regions. Weiss et al., using an isolated perfused beating rabbit heart preparation, found that 1 min of a 75% reduction in coronary flow caused an increased extraction fraction of 11C-palmitate. However, 30 min of ischemia caused a decrease in 11C-palmitate extraction fraction. Thus, the myocardial extraction fraction of fatty acids appears to be increased after brief periods of reduced coronary blood flow, presumably due to a prolonged duration of exposure to the myocardial cell membrane, i.e., increased residence time. Prolonged reductions in flow may decrease myocardial uptake or retention of fatty acids, possibly by reducing the activity of the enzyme acyl-CoA synthetase. Free fatty acid and CoA are substrates for acyl-CoA synthetase, and the acyl-CoA product is sequestered in the cell. If administered free fatty acid is not transformed into an acyl-CoA derivative, it may diffuse out of the myocardial cell.

The early phase of IPPA metabolism and clearance is similar to that observed with 11C-palmitate, with a half-life of 3.0 to 6.5 min, and almost certainly represents direct oxidation of IPPA rather than delayed incorporation into triglyceride stores. The early phase of free fatty acid oxidation has been demonstrated to be diminished in magnitude and prolonged in duration in regions of myocardial ischemia. Since our first scintigrams were acquired between 4 and 8 min after injection of contrast, significant direct oxidation of fatty acid had already occurred, especially in the normally perfused segments. Therefore, the initial IPPA activity we measured reflected both segmental myocardial uptake and early washout of the IPPA that had already undergone direct oxidation. Thus, in ischemic myocardial segments, the relatively increased segmental IPPA activity we measured in some patients was most likely caused by a combination of decreased direct oxidation of IPPA and enhanced IPPA extraction. Miller et al. also found increased activity of radioiodinated fatty acid in the ischemic "border zone" left ventricular segments using a canine preparation of temporary coronary arterial occlusion and reperfusion.

Delayed clearance of IPPA was observed in 74% of noninfarcted segments supplied by significantly narrowed coronary arteries in our study patients. Other investigators have demonstrated prolonged clearance of metabolizable labeled fatty acids in ischemic myocardial segments. IPPA washout rates measured in this study probably reflect turnover of esterified IPPA, and to a lesser extent IPPA incorporated into membrane phospholipids.

We found delayed clearance of IPPA after exercise compared with that in normal volunteers at rest. The delayed clearance of IPPA after exercise compared with that at rest was surprising, since the increased metabolic demands induced by exercise might be expected to increase oxidative metabolism and rates of fatty acid oxidation. Using positron imaging in an open-chest dog preparation, Schönh et al. demonstrated increased early oxidation of 11C-palmitate as myocardial oxygen demand was increased. Schelbert et al. demonstrated enhanced clearance of 11C-palmitate with pacing in man. However, we measured IPPA...
clearance 4 to 20 min after termination of exercise, not
during the stress of exercise. Under these circum-
cstances it is possible that delayed clearance of IPPA is
caused by a decrease in fatty acid oxidation due to
lactate accumulation in the myocardial cell and/or a
necessarily increased anabolism to replenish reduced
triglyceride stores. A third possibility is that plasma
levels of free fatty acids are increased with exercise,
thereby providing more nonradiolabeled substrate for
oxidation.

Although our findings with IPPA myocardial scinti-
graphy in normal volunteers and patients with coro-
nary heart disease are encouraging, there are several
factors that may have reduced the accuracy of our
measurement of left ventricular segmental IPPA activ-
ity as well as the overall sensitivity for detection of
abnormalities in the early distribution or clearance of
IPPA in the left ventricular segments that were studied.
All of the patients with coronary heart disease were
treated with their individual maximal doses of anti-
aginal medications, which would delay or prevent the
development of myocardial ischemia with exercise and
therefore attenuate ischemic alterations in fatty acid
metabolism. In addition, we used planar imaging in a
single projection. We anticipate that our ability to de-
tect myocardial ischemia as a regional area of relative-
ly increased IPPA activity using scintigraphy will be
substantially improved when patients are evaluated be-
fore institution of aggressive medical therapy and with
tomographic imaging.

In the analysis of the scintigrams from the patients,
we classified as abnormal IPPA activity or clearance
values that deviated by more than 1 SD from the mean
left ventricular segmental values in normal volunteers.
Using these criteria, we were able to identify regions
of abnormal IPPA initial activity or clearance. As our
number of normal volunteers increases in future stud-
ies, we anticipate that our range of normality will de-
crease and the use of the mean ± 2 SD may be feasible
to define a normal range. In fact, the sensitivity and
specificity of exercise IPPA scintigraphy for the de-
tection of coronary heart disease with the use of the
mean variation in initial IPPA activity and/or clearance
± 2 SD in normal volunteers were 72% and 100%,
respectively.

Our data suggest that IPPA myocardial scintigraphy
distinguishes normal myocardium from ischemic are-
as areas of increased IPPA activity and/or delayed washout
of IPPA compared to those in normally perfused left
ventricular segments. In contrast, 201Tl uptake is de-
creased in ischemic regions. Delayed images obtained
3 to 4 hr after injection are necessary with 201Tl to
distinguish myocardial ischemia from infarction. By
providing a marker of ischemia after a relatively brief
period of image acquisition, IPPA myocardial scinti-
graphy potentially provides an efficient means of detect-
ing segmental ischemia. However, in the future, direct
comparison studies with 207T1 scintigraphy will be nec-
essary to evaluate the relative sensitivity and specific-
ity of each diagnostic modality in the noninvasive de-
tection of coronary heart disease.

In conclusion, IPPA scintigraphy generally provides
high-quality myocardial images that appear to reflect
the metabolic integrity and/or perfusion of normal and
ischemic myocardium. Exercise IPPA scintigraphy
may allow the identification of myocardial ischemia as
regions of relatively increased IPPA activity, thus al-
lowing the noninvasive detection of segmental meta-
abolic abnormalities associated with severe coronary
heart disease.

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