Identification of impaired metabolic reserve by atrial pacing in patients with significant coronary artery stenosis

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ABSTRACT We investigated myocardial $^{11}$C-palmitate clearance kinetics at a resting heart rate (control) and during pacing using positron-emission tomography in 10 patients with significant coronary artery stenosis (>70%) and evidence of exercise-induced ischemia. Serial $^{11}$C-palmitate images acquired at control and during pacing revealed biexponential myocardial $^{11}$C clearance both in myocardium supplied by a stenotic coronary artery (myocardium "at risk") and in myocardium supplied by a normal coronary artery (normal myocardium). At control, the average rate of myocardial $^{11}$C clearance from the early rapid curve component (the clearance half-time) was similar in normal myocardium and in that at risk (22.2 ± 5.2 vs 21.0 ± 5.4 min, NS), as was the amount of myocardial $^{11}$C activity at the end of the early rapid phase (residual fraction 56.3 ± 7.2% vs 54.7 ± 7.3%, NS). Thus, myocardial clearance was homogeneous at control, suggesting a similar rate and amount of $^{11}$C-palmitate oxidation in normal myocardium and in that at risk. PACing shortened clearance half-times and decreased residual fraction in both normal myocardium and that at risk compared with control. However, clearance half-times were 17% longer and residual fractions 14% higher in myocardium at risk compared with normal myocardium (p < .005 and p < .01, respectively). Therefore, during pacing myocardial $^{11}$C clearance became heterogeneous, suggesting impaired $^{11}$C-palmitate oxidation in myocardium at risk compared with normal myocardium. Increased substrate utilization in response to increased workload can be thought of as a measure of metabolic reserve. Our data suggest metabolic reserve for free fatty acid oxidation is impaired in myocardium supplied by a significantly stenosed coronary artery and that this impairment can be detected by analysis of myocardial $^{11}$C-palmitate clearance.


EVALUATION of regional myocardial fatty acid metabolism, including differentiation of normal, ischemic, and infarcted myocardium, is possible without obtaining samples of myocardial tissue with the use of $^{11}$C-palmitate and positron-emission tomography. 1-13 In normal myocardium, $^{11}$C activity clears in a biexponential manner after an intravenous or intracoronary injection of $^{11}$C-palmitate. The amount and rate of $^{11}$C clearance from the myocardium during the first component of the clearance curve (the early rapid phase) corresponds to the amount and rate of $^{11}$C-CO$_2$ release. 9-11 This finding indicates that the early rapid phase is related to oxidation of free fatty acids. The second curve component, or late slow phase, may reflect incorporation of the $^{11}$C label into the endogenous lipid pool. The fractional distribution of tracer between the two curve components and the two slopes are altered by changes in plasma substrate concentrations of free fatty acids and glucose, cardiac work, 9, 14, 15 and ischemia. 6, 10, 11 Experimental evidence in dogs during pacing compared with control suggested $^{11}$C-palmitate oxidation was increased in normal myocardium but was impaired in acutely ischemic myocardium. 6, 11

Given that the fractional distribution and clearance rates of $^{11}$C-palmitate in canine myocardium detected...
both pacing-induced increases in cardiac work and pacing-induced myocardial ischemia, the following clinical study was undertaken to test whether pacing-induced alterations in myocardial $^{11}$C clearance (1) could also be observed in humans for normal myocardium, (2) differed between myocardium supplied by normal and that supplied by stenosed coronary arteries, and (3) correlated with clinical, electrocardiographic, and/or echocardiographic evidence of ischemia.

**Methods**

**Patient population.** We studied 10 patients (nine men and one woman) with a mean age of 53 (range 40 to 61) years (table 1). On visual assessment of coronary arteriograms each patient had a lesion of at least 70% diameter narrowing in either the left anterior descending or circumflex coronary artery, but not both, so that myocardium supplied by normal and stenosed coronary arteries could be compared in each patient. All patients had exertional angina. Ischemia during exercise was indicated by electrocardiography and/or $^{201}$TI scintigraphy. Two patients had a prior anterior myocardial infarction and three had significant lesions in the right coronary artery.

**Study protocol.** The study protocol and consent form had been approved by the UCLA Human Subject Protection Committee, and each patient gave informed written consent. Cardiac medications were withheld overnight. All patients fasted for at least 14 hr to enhance myocardial free fatty acid utilization and to standardize study conditions.

For the positron-emission tomographic study, one set of $^{13}$N-ammonia images at control and two sets of serial $^{11}$C-palmitate images were obtained, one at control and one during pacing.

### TABLE 1  
Clinical data and those from control and pacing studies

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Cath</th>
<th>Prior infarction</th>
<th>ETT/201TI</th>
<th>Pacing ECG</th>
<th>Control echo</th>
<th>Pacing echo</th>
<th>Pacing $^{11}$C-palmitate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>M</td>
<td>70% LAD</td>
<td>Anterior</td>
<td>Inferior ischemia</td>
<td>Minimal anterolateral ST elevation</td>
<td>Anterior infarct</td>
<td>Anterior infarct</td>
<td>Anterior infarct</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>M</td>
<td>70% LAD, 100% RCA</td>
<td>Inferior</td>
<td>Exertional angina</td>
<td>No ischemia</td>
<td>No obvious wall motion abnormality</td>
<td>No qualitative abnormality</td>
<td>Anteroseptal retention</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>M</td>
<td>90% LAD</td>
<td>Anterior</td>
<td>Exertional angina</td>
<td>No ischemia</td>
<td>Anterior infarct, adjacent akinesia</td>
<td>Retention both anterior infarct (figure 6)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>F</td>
<td>70% LAD, 70% RCA</td>
<td>None</td>
<td>Inferolateral ischemia</td>
<td>Possible inferolateral ischemia</td>
<td>Ni</td>
<td>Anteroseptal severe hypokinesis</td>
<td>Anteroseptal retention</td>
</tr>
<tr>
<td>5</td>
<td>57</td>
<td>M</td>
<td>95% LAD</td>
<td>None</td>
<td>Inferolateral ischemia</td>
<td>Minor T wave changes</td>
<td>Ni</td>
<td>No wall motion abnormality</td>
<td>Anteroseptal retention</td>
</tr>
<tr>
<td>6</td>
<td>61</td>
<td>M</td>
<td>100% LAD</td>
<td>None</td>
<td>Septal redistrib.</td>
<td>No ischemia</td>
<td>Ni</td>
<td>Anteroseptal severe hypokinesis</td>
<td>Anteroseptal retention</td>
</tr>
<tr>
<td>7</td>
<td>52</td>
<td>M</td>
<td>90% Circ</td>
<td>None</td>
<td>Posterior redistrib.</td>
<td>Nonspecific ST changes</td>
<td>Ni</td>
<td>Lateral severe hypokinesis</td>
<td>Anterolateral retention</td>
</tr>
<tr>
<td>8</td>
<td>49</td>
<td>M</td>
<td>90% LAD</td>
<td>None</td>
<td>Anteroseptal redistrib.</td>
<td>Possible inferolateral ischemia</td>
<td>Ni</td>
<td>Anteroseptal mild hypokinesis</td>
<td>No qualitative abnormality</td>
</tr>
<tr>
<td>9</td>
<td>51</td>
<td>M</td>
<td>90% LAD, 100% RCA</td>
<td>Inferior</td>
<td>Inferior infarct, some redistrib.</td>
<td>No ischemia</td>
<td>Ni</td>
<td>Anteroseptal severe hypokinesis</td>
<td>Anteroseptal retention (figure 5)</td>
</tr>
<tr>
<td>10</td>
<td>60</td>
<td>M</td>
<td>95% LAD</td>
<td>None</td>
<td>Inferolateral ischemia</td>
<td>Nonspecific T wave abnormality</td>
<td>Ni</td>
<td>Anteroseptal mild hypokinesis</td>
<td>No qualitative abnormality</td>
</tr>
</tbody>
</table>

*Cath = coronary artery disease documented by cardiac catheterization; LAD = left anterior descending coronary artery; RCA = right coronary artery; Circ = circumflex coronary artery; ETT = exercise to clearance test; ECG = electrocardiogram; echo = echocardiogram.

Wenckebach rhythm prevented higher heart rate.

$^{201}$TI results.
Before each injection of $^{11}$C-palmitate, heart rate and blood pressure were measured to estimate cardiac workload. A 12-lead electrocardiogram and a two-dimensional echocardiogram were obtained. Venous blood was drawn to determine plasma substrate levels.

After completion of the control $^{11}$C-palmitate study, a temporary pacemaker was inserted into each patient's right atrium under fluoroscopic guidance in the UCLA Cardiopulmonary Special Procedures Room. The pacemaker rate was increased gradually until the patient experienced angina. Then the pacemaker was turned off and the patient was returned to the Nuclear Medicine Clinic. The patient was carefully repositioned in the tomograph, and the pacemaker rate was slowly increased to a heart rate 10% below that which produced angina. This heart rate was maintained while a second dose of $^{11}$C-palmitate was injected and throughout acquisition of a second set of serial $^{11}$C-palmitate images. A 12-lead electrocardiogram and echocardiogram were recorded during pacing. A modified chest lead was continuously monitored throughout both $^{11}$C-palmitate studies for detection of ST segment changes and/or arrhythmias.

**Tomographic studies.** All studies were acquired with the UCLA whole body positron-emission tomograph (ECAT II). The instrument's performance characteristics have been described previously. The patient was placed in the tomograph and a rectilinear transmission scan (resembling a low-resolution chest x-ray) was obtained to ensure accurate patient positioning. Cross-sectional transmission images were acquired to correct the emission images for photon attenuation. Regional myocardial blood flow images were obtained at five or six contiguous myocardial levels after intravenous injection of $^{11}$N-ammonia (15 to 20 mCi). These images also served to determine the mid left ventricular imaging plane. Using the low-power neon laser beam of the tomograph, we marked with a felt-tipped pen the level of the mid left ventricular imaging plane on the patient's chest. These markings enabled not only maintenance of the patient's position throughout acquisition of the $^{11}$C-palmitate images, but also repositioning of the patient for the second tomographic study.

To ensure adequate decay of $^{11}$N-ammonia (9.9 min physical half-life) we waited at least 50 min between injections of $^{11}$N-ammonia and those of $^{11}$C-palmitate. Ten to twenty millicuries of $^{11}$C-palmitate was injected intravenously and serial images through the mid left ventricle were recorded, beginning at the time of tracer injection and continuing for approximately 60 min. A second dose of $^{11}$C-palmitate (20 mCi) was injected during pacing and another set of serial cross-sectional images was recorded for the same amount of time while pacing was maintained.

Images were acquired in the medium-resolution mode (18 mm at full-width half-maximum of a line source). $^{11}$N-ammonia images were recorded in the decay-compensated mode; the time per image increased as $^{11}$N decayed so that comparable counts (approximately one million) were collected for each image. The serial $^{11}$C-palmitate images were acquired for successively longer times so that a minimum of 400,000 counts was collected per image (maximum counts were as high as 2,400,000). Images were acquired for 90, 180, 300, and occasionally 600 sec for approximately 15, 21, 15, and 10 min, respectively. $^{11}$N-ammonia and $^{11}$C-palmitate were produced as described previously.

**Analysis of myocardial $^{11}$C clearance.** Nine circular regions of interest (1.0 cm in diameter) were assigned to the left ventricular myocardium and a tenth was assigned to the left ventricular blood pool (figure 1). The myocardial cross section was divided into two segments, one supplied by a normal coronary artery and the other supplied by a stenosed coronary artery. The segments are subsequently referred to as those that were "normal" and those "at risk." For patients with left anterior descending coronary artery stenosis, the septal and anterior regions (i.e., regions S1 through A2; figure 1) comprised the segment at risk and the lateral regions (i.e., regions L1 through L3) comprised the normal segment. In the two patients with a prior anterior myocardial infarction, a portion of the anterior wall in which $^{11}$N-ammonia uptake was two standard deviations below normal was defined as the infarcted segment. In these two patients the segment at risk consisted of the remaining septal and anterior myocardium. Observed regional $^{11}$C myocardial concentrations were corrected for partial volume effect, for spillover of activity from the cardiac chambers, and for the myocardial vascular compartment, as described previously.

$^{11}$C myocardial concentrations were averaged for the regions of interest in a given segment. Segmental myocardial time-activity curves were generated from the serial images.

Three variables were determined from these time-activity curves (figure 2): (1) the relative uptake of $^{11}$C-palmitate, (2) the half-time of the early rapid phase, and (3) the fraction of $^{11}$C activity remaining in myocardium at the end of the early rapid phase, subsequently referred to as residual fraction and expressed as a percent of the maximal $^{11}$C activity. Maximal $^{11}$C activity occurred approximately 6 min after the injection of tracer. The maximal uptake in the normal segment was defined as 100%. Maximal tracer uptake in the segment at risk was expressed as a percent of maximal tracer uptake in the normal segment, and was defined as relative uptake. Monoexponential rather than biexponential analysis of the $^{11}$C myocardial clearance curve was performed due to the lack of adequate definition of the late slow phase. The half-time of the early rapid phase was determined by least squares fit of the myocardial clearance curve starting at the time of maximal tracer uptake and ending at the last point before the curve inflection, as shown in figure 2. The residual fraction was defined as the myocardial $^{11}$C activity tissue concentration at the end of the early rapid phase and was expressed as percent of maximum activity. The residual fraction represents the relative amount of $^{11}$C activity that has not cleared from the myocardium at the end of the early rapid phase, whereas the size of the early rapid phase, as described by Schon et al. and Schelbert et al., represents the amount of $^{11}$C.

**FIGURE 1.** Schematic drawing of a cross-sectional image of the left ventricular myocardium with regions of interest. Circular regions were assigned, three each to the septal (S1 to S3), anterior (A1 to A3), and lateral (L1 to L3) walls. A region of interest was drawn outlining the entire myocardium to enable correction for the partial volume effect. Regions of interest were drawn for the left ventricular (LV) cavity and the blood pool (BP) to correct for cross-contamination of counts from the blood pool.

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activity has cleared from the myocardium at the end of the early rapid phase. Therefore, the size of the early rapid phase and the residual fraction provide complementary information and their sum equals 100%. The serial ¹¹C-palmitate images were examined visually for differences in tissue ¹¹C clearance rates between normal myocardium and that at risk (figures 3 and 4), and the variables determined from the ¹¹C time-activity curves were analyzed (figure 5).

**Electrocardiograms.** Twelve-lead electrocardiograms obtained during the control and pacing studies were evaluated for presence of Q waves, conduction abnormalities, and ST-T segment changes both at control and during atrial pacing by one of the authors (J. S. C.) who was unaware of other patient data. Standard criteria were used to define pacing-induced ischemia (i.e., >2 mm flat or downsloping ST segment depression 0.08 sec after the J point)². Pacing-induced ST segment depression of 1 to 2 mm was defined as possible ischemia.

**Echocardiograms.** Regional myocardial wall motion was evaluated qualitatively on two-dimensional echocardiograms obtained in the standard views (i.e., long-axis, cross-sectional, and apical two- and four-chamber views) independently by two of the authors (J. K., J. S. C.) who were unaware of other patient data. Six echocardiographic regions were defined for the long-axis and two- and four-chamber apical views (figure 6). Regional wall motion was graded as follows: 3 = normal; 2 = mild hypokinesis; 1 = severe hypokinesis; 0 = akinesis; –1 = dyskinesis. Pacing-induced echocardiographic ischemia was defined as a deterioration of regional wall motion by at least two grades. These stringent criteria were applied to ensure the validity of the deterioration in wall motion. If the wall motion score for the two observers differed by more than one grade, they reviewed the echocardiograms together and settled the interobserver difference by consensus.

**Statistical analysis.** Mean values are given with standard deviations. A paired Student t test was used to compare observations within the same patient group, and the unpaired Student t test was used to compare observations between different patients. Results were also evaluated with a Wilcoxon signed-rank test to account for the possibility of nonnormal distribution of data. Confidence limits were calculated to indicate the range of possible differences that might exist between the groups. The accepted level of statistical significance was p < .05.

**Results**

**Clinical, hemodynamic, and laboratory data.** No complications occurred as a result of either the pacemaker insertion or pacing. Only one patient complained of chest discomfort after 40 min of pacing. The discomfort was not clearly angina; however, pacing was discontinued. This patient was included in the analysis because adequate data had already been acquired.

Heart rate at control averaged 65 ± 12 beats/min and increased during pacing to 102 ± 15 beats/min (p < .001). Neither mean resting systolic nor diastolic blood pressure changed significantly from control to pacing (138 ± 21 vs 141 ± 23 mm Hg and 83 ± 12 vs 80 ± 17 mm Hg, respectively). Venous glucose before the pacing study was slightly lower than before the control study (p < .05; table 2). Other venous substrate levels were similar at control and before pacing.
Venous substrate levels did not change significantly from the beginning to the end of the pacing period.

**Electrocardiograms and echocardiograms.** At control, no patient exhibited electrocardiographic evidence of ischemia (table 1). Two patients had Q waves in the anterior leads consistent with a documented prior myocardial infarction. Pacing failed to produce definite electrocardiographic evidence of ischemia, while possible evidence of ischemia (i.e., 0 to 2 mm flat or downsloping ST depression) developed in two patients.

At control, wall motion was normal in eight patients. The two patients with prior anterior myocardial infarctions had regions of akinesis or dyskinesis on echocardiography that corresponded to the site of electrocardiographic Q waves. Pacing induced areas of severe hypokinesis or akinesis in five patients. These patients were classified as having definite echocardiographic ischemia during pacing. Among the other five patients, pacing produced mild segmental hypokinesis (i.e., the wall motion score changed by one grade) in three and no apparent changes in the remaining two patients.

**13N-ammonia images.** Circumferential profile analysis at the midmyocardial level revealed normal, homogeneous myocardial 13N-ammonia uptake at control in

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**FIGURE 4.** $^{11}$C-palmitate images from a patient with a prior anterior myocardial infarction and a 90% stenosis of the left anterior descending coronary artery after the first septal perforator. The infarcted anterior myocardium is delineated by dots. Both at control and during pacing in the segment of infarcted myocardium, $^{11}$C-palmitate uptake was decreased compared with that in normal segments and segments at risk. During pacing, 40 min after tracer injection $^{11}$C-palmitate had not cleared from myocardium adjacent to the segment of infarcted myocardium, whereas it had cleared from the normal lateral wall and proximal septum.

**FIGURE 5.** Effect of pacing on segmental myocardial $^{11}$C time-activity curves in the patient presented in figure 3. The lateral myocardium (normal segment) is represented by triangles and the anteroseptal myocardium (segment at risk) by circles. At control the clearance half-times and residual fractions were similar. In contrast, during pacing the clearance half-time was longer and the residual fraction was larger in the segment at risk than in the normal segment, suggesting impaired free fatty acid clearance during pacing in the segment at risk.
eight patients. In the two patients with prior anterior myocardial infarction, 13N-ammonia in the anterior wall was two standard deviations below normal.19

Myocardial uptake and clearance of 11C-palmitate. Visual inspection of the initial 11C-palmitate images (6 to 10 min after injection) revealed homogeneous myocardial tracer uptake both at control and during pacing in the eight patients without a prior anterior myocardial infarction. At control, myocardial 11C activity remained homogeneous on the late 11C-palmitate images (40 to 60 min after injection), implying homogeneous myocardial clearance of 11C activity. During pacing, however, the late 11C-palmitate images of six patients demonstrated retention of more 11C activity in myocardium at risk than in normal myocardium (figures 3 and 4). Increased retention of tracer coincided in five of the six patients with pacing-induced severe hypokinesis or akinesis. The remaining four patients demonstrated no obvious abnormalities in segmental myocardial 11C activity clearance rates on visual inspection. In the two patients with a prior anterior myocardial infarction, visual inspection of the initial images revealed reduced 11C-palmitate uptake in the anterior wall both at control and during pacing. This reduction was proportional to the reduced 13N-ammonia uptake.

Segmental analysis of 11C time-activity curves confirmed the homogeneity of myocardial tracer uptake in normal myocardium and that at risk. The relative tracer uptake of 11C-palmitate was similar in segments at risk and in normal segments both at control and during pacing. For example, in segments at risk the relative tracer uptake was 97.3 \pm 14.3\% at control and 97.8 \pm 14.1\% during pacing (NS). Analysis of 11C time-activity curves also confirmed the marked decrease in uptake in the two infarcted segments, which averaged 28\% less than in normal myocardium at control and 23\% less during pacing.

Clearance half-times of the early rapid phase at control averaged 22.2 \pm 5.2 min in normal myocardium and were similar in segments at risk (figure 7). Pacing significantly shortened the average clearance half-times in both normal segments and those at risk. Also, clearance half-times were shorter in normal segments than in those at risk (p < .05). Clearance half-times decreased in all normal segments. In segments at risk, changes in clearance half-times were variable (figure 7). With regard to infarcted segments, the clearance half-time increased in one from 48.2 min at control to 58.3 min during pacing; in the other segment, the clearance half-time was normal (15.2 min) at control but increased with pacing to 54.6 min.

Residual fractions at control were similar in normal segments and those at risk (table 3; figure 8). Residual fractions declined significantly during pacing in both normal segments and those at risk (p < .001). These decreases averaged 31\% in normal segments and 18\% in segments at risk. Thus, residual fractions decreased less in segments at risk than in normal segments (p < .03). The residual fraction fell during pacing in all normal segments; the response in segments at risk was more variable (figure 8). In the patients with infarcted segments, residual fractions were abnormally large both at control and during pacing (86.4\% and 83.0\%, respectively) in one, and were normal in the other at control but increased to 84.3\% during pacing.

| Venous plasma substrate levels |  
|---|---|---|
|  | Control | Beginning | End |
| Free fatty acids (mmol/l) | 0.42 \pm 0.26 | 0.43 \pm 0.21 | 0.48 \pm 0.11 |
| Triglycerides (mg/dl) | 242 \pm 162^a | 284 \pm 212 | 311 \pm 295 |
| Glucose (mg/dl) | 99 \pm 22 | 92 \pm 16^b | 97 \pm 19 |
| Lactate (mg/dl) | 8.9 \pm 2.9 | 8.7 \pm 2.5 | 8.0 \pm 2.2^a |
| Pyruvate (mg/dl) | 0.59 \pm 0.25 | 0.58 \pm 0.20 | 0.49 \pm 0.22^a |

*a*The number of observations was one less than the sample size stated at the top of the column.

b*p < .05 compared with control by both paired t test and Wilcoxon signed-rank test.
TABLE 3
Segmental myocardial 11C-palmitate clearance kinetics at control and during pacing

<table>
<thead>
<tr>
<th></th>
<th>Normal segments (n = 10)</th>
<th>Segments at risk (n = 10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-time of the early rapid phase (min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>22.2 ± 5.2</td>
<td>20.8 ± 5.5</td>
<td>NS</td>
</tr>
<tr>
<td>Pacing</td>
<td>13.4 ± 2.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15.6 ± 4.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Residual fraction (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>54.0 ± 6.1</td>
<td>51.8 ± 7.4</td>
<td>NS</td>
</tr>
<tr>
<td>Pacing</td>
<td>36.4 ± 9.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>41.8 ± 10.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>p &lt; 0.03</td>
</tr>
</tbody>
</table>

Probability values refer to comparison of normal segments with those at risk. Statistical analysis was performed both by paired t test and Wilcoxon signed-rank test and yielded concordant results. The p values indicate the level of statistical significance as evaluated by paired t test:

<sup>a</sup>p ≤ .002; <sup>b</sup>p < .01 compared with control.

trol varied considerably between patients, probably due to differences in cardiac work and substrate and hormone levels. To reduce this interpatient variability in clearance half-time and residual fraction, we examined for each patient both at control and during pacing, the differences between segments at risk and normal segments (table 4). Myocardial 11C-palmitate uptake was similar in segments at risk and normal segments both at control and during pacing (table 4). At control, both clearance half-times and residual fractions were also similar in segments at risk and normal segments. However, pacing produced significant differences in clearance half-times and residual fractions in segments at risk and normal segments. Thus, in segments at risk, compared with normal segments, pacing shortened clearance half-times 17.2 ± 23.7% (p < .005) and resulted in 13.9 ± 17.3% larger residual fractions (p < .01).

We then examined whether myocardial uptake and clearance of 11C-palmitate differed between segments with and without pacing-induced regional wall motion abnormalities (table 4). The changes in percent differences in clearance half-times from control to pacing for the group with pacing-induced wall motion abnormalities (65.8%, 51.6%, 12.5%, 3.5%, −2.8%) and the group without pacing-induced wall motion abnormalities (26.3%, 8%, 6.1%, 4.9%, −4.4%) exhibited some overlap. However, clearance half-times were significantly longer in segments at risk than in normal segments in the five patients with pacing-induced wall motion abnormalities (p < .01), but not in patients without pacing-induced wall motion abnormalities.

Discussion

Alterations in 11C-palmitate clearance in myocardium supplied by normal or stenosed coronary arteries could be detected and were similar to changes previously observed in animal experiments. In normal myocardium the faster tissue clearance rates and smaller residual fractions were consistent with a pacing-induced increase in fatty acid oxidation. In contrast, pacing produced less pronounced changes in myocar-
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![Residual Fraction](image)

**FIGURE 8.** Changes in the residual fraction in normal segments and segments at risk. During pacing (P), the residual fractions decreased significantly compared with control (C) values. This suggests more $^{11}$C-palmitate was oxidized during pacing compared with at control. However, during pacing the residual fraction was greater in segments at risk than in normal segments suggesting less $^{11}$C-palmitate was oxidized in segments at risk. *p < .002 compared with control.

Diameter supplied by stenosed coronary arteries, suggesting an attenuated or an inadequate increase in $^{11}$C-palmitate oxidation.

**Methodologic considerations.** Although others have used physical stress such as supine bicycle exercise to study blood flow and glucose metabolism during increased cardiac work,23, 24 we chose atrial pacing in this study for several reasons. First, plasma substrate levels change dramatically during physical exercise.25 Such altered substrate levels can affect myocardial substrate utilization, thereby influencing both the amount of myocardial $^{11}$C-palmitate uptake and its fractional distribution between the early and late clearance phases.14, 21 As has been demonstrated previously in animals,11 plasma glucose, lactate, and free fatty acid concentrations were not significantly different at the beginning and end of pacing in this study. Before pacing, venous glucose was slightly lower than control. This decreased availability of glucose would tend to enhance global myocardial free fatty acid utilization, but would not account for regional differences. Therefore, the pacing-induced alterations in myocardial $^{11}$C-palmitate clearance cannot be ascribed to changes in plasma substrate availability. Second, acquisition of $^{11}$C-palmitate time-activity curves requires a minimum of 40 to 60 min of serial imaging during steady-state conditions. Maintaining a constant level of exercise for the entire imaging period would be difficult. Third, increased patient motion during exercise would degrade image quality, thus impairing acquisition of myocardial time-activity curves.

On the other hand, insertion of the atrial pacemaker required removal of the patient from the tomograph between the first and second $^{11}$C-palmitate studies. Despite meticulous patient repositioning to obtain the same cardiac imaging levels for both studies, small positional differences occurred. Therefore, only patients with identical or nearly identical control and pacing cross-sectional images were accepted for this study. One additional patient was excluded from analysis for this reason.

In our previous animal experiments, myocardial $^{11}$C-palmitate tissue clearance curves were analyzed with the use of a biexponential least squares fit. However, myocardial $^{11}$C-palmitate clearance was slower in humans than in dogs because cardiac work was lower in human studies (i.e., lower heart rates and mean arterial blood pressures). The 20 min physical half-life and the relatively lower doses of $^{11}$C-palmitate used in the patients precluded acquisition of statistically adequate images beyond 1 hr after administration of tracer. Consequently, the late slow clearance phase did not contain enough curve points to permit accurate biexponential curve fitting. As an alternative approach, only the slope of the early rapid clearance curve component and the residual fraction were determined. This approach provides reasonably accurate estimates of the fractional distribution of tracer between the two major metabolic pools in tissue. This approach has been used earlier in patient studies and results compare well with those of the biexponential analysis used in dogs.21

**Increased cardiac work and production of acute myocardial ischemia during pacing.** Blood pressure remained unchanged during pacing, as has been reported previously.26 The pacing heart rate was maintained below that which produced angina. Only one patient complained of chest discomfort, and it was not clearly angina. The average pacing heart rate was less than 70% of the maximal predicted heart rate for a 60-year-old patient during maximal exercise (the average age of our patients was 59 years). Thus, atrial pacing in this study produced only a moderate level of stress. However, this stress was sufficient to induce alterations in myocardial $^{11}$C-palmitate clearance and regional wall motion abnormalities, a conventional crite-
TABLE 4
Percent difference in myocardial $^{11}$C-palmitate clearance from normal segments and those at risk

<table>
<thead>
<tr>
<th></th>
<th>Control (%)</th>
<th>Pacing (%)</th>
<th>p value</th>
<th>Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative uptake</td>
<td>$-3.1 \pm 15.6$</td>
<td>$-2.7 \pm 15.4$</td>
<td>NS</td>
<td>$-6.0$ to $5.2$</td>
</tr>
<tr>
<td>Clearance half-times</td>
<td>$-8.0 \pm 15.1$</td>
<td>$17.2 \pm 23.7$</td>
<td>&lt;.005</td>
<td>$-40.1$ to $-10.1$</td>
</tr>
<tr>
<td>Residual fractions</td>
<td>$-4.3 \pm 9.6$</td>
<td>$13.9 \pm 17.3$</td>
<td>&lt;.01</td>
<td>$-31.7$ to $-4.8$</td>
</tr>
<tr>
<td>Patients with pacing-induced wall motion abnormality$^\lambda$ (n = 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative uptake</td>
<td>$2.8 \pm 8.7$</td>
<td>$-1.0 \pm 7.4$</td>
<td>NS</td>
<td>$-6.3$ to $13.8$</td>
</tr>
<tr>
<td>Clearance half-times</td>
<td>$-5.8 \pm 13.2$</td>
<td>$26.1 \pm 30.6$</td>
<td>.01</td>
<td>$-59.5$ to $-4.3$</td>
</tr>
<tr>
<td>Residual fractions</td>
<td>$-1.5 \pm 7.9$</td>
<td>$12.3 \pm 22.7$</td>
<td>NS</td>
<td>$-34.6$ to $7.1$</td>
</tr>
<tr>
<td>Patients without pacing-induced wall motion abnormality$^\lambda$ (n = 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative uptake</td>
<td>$-9.0 \pm 19.6$</td>
<td>$-4.4 \pm 21.7$</td>
<td>NS</td>
<td>$-11.4$ to $2.4$</td>
</tr>
<tr>
<td>Clearance half-times</td>
<td>$-10.1 \pm 18.2$</td>
<td>$8.2 \pm 11.2$</td>
<td>NS</td>
<td>$-42.6$ to $5.9$</td>
</tr>
<tr>
<td>Residual fractions</td>
<td>$-7.2 \pm 11.2$</td>
<td>$15.5 \pm 12.3$</td>
<td>NS</td>
<td>$-49.6$ to $4.2$</td>
</tr>
</tbody>
</table>

Differences are given as (at risk — normal)/normal in percent. Statistical analysis was performed by paired t test and Wilcoxon signed-rank test and yielded concordant results. The p values indicate the level of statistical significance as evaluated by paired t test.

$^\lambda$Documented by echocardiography. See text for details.

determination for development of ischemia. Average heart rates during pacing were not significantly different in patients with and those without definite echocardiographic ischemia. Therefore, the failure to produce wall motion abnormalities was not attributable to lower cardiac work.

Induction of electrocardiographic and echocardiographic evidence of ischemia depends on the level of stress. Because pacing increased the heart rate only moderately in this study, it is not surprising that only two patients had 1 to 2 mm flat or downsloping ST depression. Consistent with earlier observations, pacing induced wall motion abnormalities without associated clinical symptoms and/or electrocardiographic changes. The overall sensitivity of stress-induced echocardiographic wall motion abnormalities for identification of significant coronary artery disease (defined as >50% stenosis) is at least 70%. Sensitivity and specificity may be increased to approximately 90% by adding an abnormal ejection fraction response to stress as another criterion. However, using both criteria, single-vessel disease is detected with a sensitivity of only 50% to 64%. Seven of the 10 patients in our study had single-vessel disease, which may partly explain why definite echocardiographic ischemia was detected in only half of our patients. However, if in our study deterioration of wall motion by one grade rather than two grades had been defined as ischemia, then pacing would have been found to produce ischemia in eight of the 10 patients. Finally, it is not possible to determine whether wall motion abnormalities were nonexistent or whether echocardiography simply failed to detect them.

Myocardial $^{11}$C-palmitate clearance at control and during pacing. $^{11}$C-palmitate clears from canine and human myocardium in a biexponential fashion. Animal experimental studies have provided evidence that the size of the early rapid clearance curve component reflects the fraction of $^{11}$C-palmitate that is rapidly oxidized to $^{11}$C-CO$_2$, and the slope of this component reflects the rate of oxidation. This is further confirmed by recent studies in our laboratory in which the early curve component was almost completely abolished by inhibition of the carnitine acyltransferase I with tetradecylglycidic acid, which prevented $^{11}$C-palmitate from reaching the inner mitochondrial membrane and thus from being oxidized. The slow clearance phase appears to be related to $^{11}$C-palmitate, which is esterified to triacyl esters and phospholipids, and deposited in the slow turnover endogenous lipid pool.

In our patients at control, myocardial uptake and subsequent clearance of $^{11}$C-palmitate was similar in normal myocardium and that at risk. This finding indicates that fatty acid metabolism in myocardium supplied by a significantly stenosed coronary artery is normal, at least at rest. This is also in agreement with the normal wall motion and normal blood flow observed on the $^{13}$N-ammonia images, and the absence of electrocardiographic ischemia in segments at risk at control.
In this study, atrial pacing increased cardiac work only moderately without significantly changing substrate availability. In normal myocardium, pacing produced changes similar to those previously observed in canine experiments. The smaller residual fractions indicate that the fraction of 11C-palmitate entering the "oxidation pool" increased by an average of 33%, while tissue clearance rates increased by an average of 40%. These findings are consistent with the increased demand being met by increased oxidation of 11C-palmitate in normal myocardium.

Myocardial 11C-palmitate uptake was similar in normal myocardium and at risk. This uptake is largely a function of blood flow and the rate of metabolic sequestration of 11C-palmitate through the initial thio- kinase-mediated activation of free fatty acid to acyl-CoA. The effects of the mild-to-moderate stress of pacing on transmural myocardial blood flow and on metabolic sequestration of 11C-palmitate in this study was not examined. Therefore, the mechanism(s) for the similar 11C-palmitate uptake in normal myocardium and that at risk remains to be elucidated. Methodologic limitations such as insufficient temporal sampling and/or slight positional differences, which may be associated with partial volume-related effects, may in part account for this finding.

Experimental studies have demonstrated that when oxygen availability is mildly decreased, the rate of free fatty acid β-oxidation is reduced. The mild-to-moderate stress of pacing in our study appears to have impaired, rather than completely inhibited, 11C-palmitate oxidation. This is substantiated by the attenuated increases in the fraction of 11C-palmitate entering the early rapid turnover phase and the clearance half-time. Thus, although 11C-palmitate uptake may have remained normal in mildly ischemic myocardium during pacing, less tracer was oxidized and more was deposited in the slow turnover endogenous lipid pool, as evidenced by the relatively higher residual fractions.

The quantitative relationship between the attenuated myocardial 11C-palmitate clearance and an attenuated response in free fatty acid β-oxidation remains to be established. During severe myocardial ischemia, back-diffusion of extracted but nonmetabolized tracer from myocardium to blood is increased. The rate of back-diffusion may exceed the rate of 11C-CO2 release from myocardium. Increased back-diffusion would produce an apparent shortening of the clearance half-time. If back-diffusion of nonmetabolized tracer did indeed occur in our patients, it was outweighed by persistent 11C-palmitate oxidation and high 11C-CO2 release because clearance half-times in segments at risk decreased rather than increased during pacing.

In the two segments of infarcted myocardium studied, relative uptake of 11C-palmitate was lower, clearance half-time was longer, and residual fraction was higher than in normal segments or in segments at risk both at control and during pacing. The reduced tracer uptake in infarcted segments is largely a function of the decreased blood flow while longer clearance half-times and higher residual fractions indicate impaired free fatty acid oxidation. Residual free fatty acid metabolism in infarcted segments probably reflects the presence of some viable cells.

The pacing-induced changes in 11C-palmitate tissue clearance in segments at risk differed significantly from those in normal segments in the group of 10 patients. However, when patients with and without pacing-induced wall motion abnormalities were analyzed separately, clearance half-times during pacing differed significantly from those at control only in patients with pacing-induced wall motion abnormalities. While the absence of statistically significant differences for the other variables may be largely attributable to the small patient subgroups, the difference in clearance half-times in the two patient subgroups raises the question of a graded response of 11C-palmitate tissue clearance kinetics depending on the severity of pacing-induced ischemia.

Clinical implications. This study demonstrates that positron-emission tomography can be used to detect regional alterations in 11C-palmitate clearance during pacing in patients with significant coronary artery disease. These alterations are detected in the absence of angina and of definite electrocardiographic evidence of ischemia. Electrocardiographic abnormalities and abnormalities of regional myocardial blood flow have been documented in the absence of symptoms, and have been called "silent ischemia." Thus, abnormal or attenuated 11C-palmitate tissue clearance patterns in response to higher workloads may be more sensitive than conventional criteria for indicating the presence of ischemia. Normal myocardium responds to an increased workload by an appropriate increase in substrate oxidation. This can be thought of as a "metabolic reserve." Our data suggest that myocardium supplied by a significantly stenosed coronary artery has impaired metabolic reserve for oxidation of free fatty acid and that this impairment can be identified with positron-emission tomography and analysis of myocardial 11C-palmitate clearance.

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