Fatty acid uptake is preserved in chronically dysfunctional but viable myocardium

MAJÄ A. T. MÄKI,1 MERJA T. HAAPARANTA,2 MATTI S. LUOTOLAHTI,3 PIRJO NUUTILA,4 LIISA-MARIA VOIPIO-PULKKI,4 JÖRGEN R. BERGMAN,2 OLOF H. SOLIN,2 AND JUHANI M. KNUUTI1,2
Departments of 1Nuclear Medicine, 2Clinical Physiology, and 4Medicine, University of Turku, and 2Turku Positron Emission Tomography Center, University of Turku, FIN-20520 Turku, Finland

Fatty acid uptake is preserved in chronically dysfunctional but viable myocardium. Am. J. Physiol. 273 (Heart Circ. Physiol. 42): H2473–H2480, 1997.—Glucose uptake appears preserved or even enhanced in the chronically dysfunctional but viable myocardium. However, the use of other fuels such as free fatty acids (FFA) remains unknown. We studied FFA uptake in the chronically dysfunctional but viable myocardium in seven patients with an occluded major coronary artery and a corresponding chronic wall motion abnormality but no previous infarction. Myocardial FFA uptake kinetics in the fasting state were measured with positron emission tomography (PET) and [18F]fluoro-6-thia-heptadecanoic acid ([18F]FTHA). The FFA uptake index was calculated by multiplying the fractional [18F]FTHA uptake with serum FFA concentration. Myocardial blood flow (MBF) was measured with [15O]H2O and PET. Myocardial viability was confirmed with a static [18F]-labeled 2-fluoro-2-deoxy-D-glucose PET imaging and a follow-up echocardiography in the revascularized patients. Regional MBF was slightly but not significantly lower in the dysfunctional compared with normal myocardial segments (0.76 ± 0.18 vs. 0.81 ± 0.14 ml·min⁻¹·g⁻¹, means ± SD; P = 0.16). The fractional [18F]FTHA uptake rates [0.11 ± 0.03 vs. 0.11 ± 0.04 ml·g⁻¹·min⁻¹; not significant (NS)], and the FFA uptake indexes (5.8 ± 1.7 vs. 5.8 ± 2.1 µmol·100 g⁻¹·min⁻¹; NS) were similar in the dysfunctional but viable and in the normal myocardial regions. Thus, in the chronically dysfunctional but viable (collateral-dependent) myocardium, the fatty acid uptake probed by [18F]FTHA appears preserved. Taken together with preserved glucose uptake, the results indicate that there is uncoupling of substrate uptake and mechanical function in the chronically dysfunctional but viable myocardium.

coronary artery disease; heart; hibernation; ischemia metabolism

FREE FATTY ACIDS (FFA) are the primary physiological substrates for myocardial energy production (23, 24). The contribution of fatty acids to total fuel oxidation depends to a large extent on their plasma concentration in relation to other oxidizable fuels (23, 34). Furthermore, the rate of fatty acid utilization is dependent on the energy demands of the tissue (34). Long-chain fatty acids (LCFA) represent the main energy supply for the heart in the fasting state (23, 24). The β-oxidation process involves breakdown of the LCFA to two carbon fragments, which then become finally oxidized through the citric acid cycle, generating the energy (ATP) needed for contractile and other work (16, 23, 34). Fatty acid uptake (16, 24, 35) and oxidation (9, 16, 23, 24, 34) are suppressed in acutely ischemic hearts, whereas glucose uptake is simultaneously increased (25). Glucose can yield energy by nonoxidative glycolysis, whereas FFA lack alternative nonoxidative metabolic pathways (16, 29).

In the chronically dysfunctional but viable (hibernating) myocardium, depressed myocardial function has been believed to be a consequence of chronically reduced resting myocardial blood flow (MBF) (28). However, recent human studies have shown that resting MBF is either normal or only slightly reduced in the reversibly dysfunctional regions in noninfarcted (22, 36), infarcted (21), and unselected (6, 10) patient populations. However, the flow reserve appears to be very limited in these regions (36). We have previously shown that although absolute glucose uptake is slightly increased in the dysfunctional but viable myocardium in the fasting state, the hormonal control of myocardial metabolism is preserved (22). On the basis of these findings, it can be suggested (in contrast to ongoing ischemic conditions) that FFA metabolism might also be preserved in the chronically dysfunctional but viable myocardium. However, the FFA metabolism in the chronically dysfunctional but viable (collateral-dependent) myocardium has not been previously studied in humans.

[18F]-labeled 14(R,S)-fluoro-6-thia-heptadecanoic acid ([18F]FTHA) is a new LCFA tracer analog and inhibitor of fatty acid metabolism (5). [18F]FTHA has a high first-pass uptake in the heart. After [18F]FTHA is transported into the mitochondria, it undergoes initial steps of β-oxidation and is thereafter trapped in the cell. Only a small fraction of the tracer (5–10%) has been detected to incorporate to triglycerides (5). Thus the rate of [18F]FTHA retention by the myocardium is suggested to reflect mainly the β-oxidation rate of LCFA (5).

This study was designed to investigate fatty acid uptake kinetics in the chronically dysfunctional but viable and normal myocardial regions as probed by [18F]FTHA and positron emission tomography (PET) in the fasting state. MBF was measured by [15O]H2O and PET.

METHODS

Subjects

The study group consisted of seven male patients (Table 1). Six patients had total occlusion of the left anterior descending
coronary artery (LAD), and one patient had an occluded right coronary artery (RCA). The regions distal to the occluded coronary arteries demonstrated chronic wall motion abnormalities in three consecutive echocardiography examinations during the study, but there was no history or electrocardiographic evidence of myocardial infarction in any subject. None of the patients had diabetes. Patients continued their normal medication during the study. Six patients were taking long-acting nitrates, six were taking \( b \)-blockers, three were taking calcium antagonists, one was taking diuretics, and two used lipid-lowering agents. There were no coronary events between the angiographic and PET studies. Each subject gave a written informed consent. The study protocol was accepted by the Ethical Committee of the Turku University Central Hospital.

### Study Design

Angiography was performed 2.1 ± 1.1 mo before the PET study. To enhance myocardial FFA utilization and standardize the study conditions, all subjects fasted 15–18 h before the PET studies. MBF was measured with \([^{15}O]H_2O\) and FFA uptake kinetics were measured with \([^{18}F]FTHA\) and PET (Fig. 1). Arterialized venous plasma glucose concentrations were determined every 5–10 min, and FFA, insulin, and lactate concentrations were determined every 30 min. The laboratory tests were analyzed as previously described (22). Heart rate and blood pressure were monitored during the studies to calculate the rate-pressure product. Electrocardiograms (ECG) were continuously monitored during the PET study. Echocardiograms were obtained immediately before and after the PET study and repeated 1–2 days later to confirm the chronic nature of the wall motion abnormality. A static PET study 60 min after intravenous \([^{18}F]FDG\) injection was performed to confirm myocardial viability together with the follow-up echocardiography. The \([^{18}F]FDG\) study was performed after 15–18 h fast on a separate day within four days of the \([^{18}F]FTHA\) study. A follow-up echocardiography was obtained 8–11 mo after revascularization.

### Coronary Angiography

A significant lesion was defined as that compromising the luminal diameter by 50% or more. Angiographic data were aligned to eight segments as follows: the LAD was considered to supply the anterobasal, anterior septal, anterior, and apical regions; the left circumflex artery, to supply the lateral and posterobasal regions; and RCA, to supply the posterior septal and inferior segments.

### Echocardiography

Digitized two-dimensional echocardiography (Acuson 128XP/5, Acuson; or Aloka SSD 870, Aloka) was performed according to standard protocols (31) and previously described modifications to correspond to the PET studies (15). Images from the parasternal long and short axes and apical four-and two-chamber views were registered and videotaped. Regional function was interpreted in the eight myocardial segments (anterobasal, anterior, anterior septal, lateral, posterior sepa-
The function in each segment was scored as 1 for normal; 2, hypokinetic; or 3, akinetic. Normal wall motion was defined as >5 mm of endocardial excursion and systolic thickening. Hypokinesia was defined as <5 mm of endocardial excursion and reduced wall thickening in systole. Akinesis was defined as near absence of endocardial excursion or thickening. The segment was considered to be thinned if wall thickness was reduced by 25% compared with the adjacent normal segment. The results of individual pre- and postrevascularization echocardiograms were ultimately verified by comparison of videotape recordings. Echocardiograms were analyzed by an experienced physician (M. Luotolahi) blinded to both PET and clinical data. Special attention was focused on the detection of any fluctuation in the wall motion abnormality in different studies. In follow-up echocardiography, improvement of contractile function was diagnosed if normal wall motion was detected in a previously hypokinetic segment. Ejection fraction (EF) was determined by the biplane method (modified Simpson’s rule) (31).

Classification of Myocardial Segments

Angiographic and echocardiographic data were combined to identify two types of myocardial segments: 1) dysfunctional (collateral-dependent) but viable or 2) normal as precisely as possible. A segment was classified as dysfunctional but viable when the corresponding coronary artery was occluded and a chronic wall motion abnormality but no myocardial thinning was detected. The segment was classified as normal if it was associated with a nonsignificant (<50%) coronary artery stenosis and no wall motion abnormalities. Because of severe coronary artery disease in two patients (patients 3 and 5), one segment supplied with a 75% stenotic artery was accepted as normal. Forty-five segments in seven patients were included in the final analysis. The remaining segments (n = 11) represented various combinations of abnormalities and were excluded from further analysis. In six patients dysfunctional segments were localized to the anterior, anteroseptal, and apical walls, and in one patient, to the inferior and posterior septal walls.

Positron Emission Tomography

Production of [18F]FTHA. [18F]FTHA was synthesized by nucleophilic radiofluorination of benzyl 14(R,S)-tosyloxy-6-thia-heptadecanoate (4). The radiochemical purity of the final product was >98%. The nonmetabolized [18F]FTHA was analyzed by high-performance liquid chromatography on a μ Bondapak C18 column using methanol:water:acetic acid (85:15:0.4) as eluant at a flow rate of 3.0 ml/min. The radioactivity on the column outlet flow was monitored with a coincidence probe consisting of two 3 × 3 NaI-crystals.

Image acquisition, processing, and corrections. The patients were positioned supine in a 15-slice ECAT 931/08–12 tomograph (Siemens/CTI, Knoxville, TN) with a measured axial resolution of 6.7 mm and 6.5 mm in plane. To correct for photon attenuation, transmission scanning was performed for 20 min before the emission scan with a removable ring source containing 68Ge (total counts 15–30 × 106) per plane. The flow study was performed as previously described (22). The mean doses of [15O]CO and [15O]H2O were 3,780 ± 460 and 1,720 ± 130 MBq, respectively. Fifteen minutes after the flow study was completed, 180 ± 25 MBq [18F]FTHA was injected intravenously over 30 s. Dynamic scanning of the cardiac region was started simultaneously for 32 min (12 × 15, 4 × 30, 2 × 120, 1 × 180, and 4 × 300 s). Nineteen blood samples were taken to measure [18F]FTHA radioactivity in plasma. In the FDG study, static 20-min imaging was started after 1 h of injection of [18F]FDG (270 ± 10 MBq). All data were corrected for dead time, decay, and photon attenuation and reconstructed in a 128 × 128 matrix. The final in-plane resolution in reconstructed and Hann-filtered (0.3 cycles/pixel) images was 9.5 mm full width of half maximum.

Alignment of myocardial segments in PET. As previously described (15, 22), transaxial PET slices were visually aligned and the left ventricular myocardium was assigned to the eight segments (anterobasal, anterior septal, anterior, lateral, posterior septal, apical, posterobasal, and inferior) with the help of a heart map phantom designed for our studies. A mean of 34 elliptical regions of interest (ROI) were placed on an average of 9 transaxial ventricular slices in both the [18F]FTHA and [18F]FDG studies, avoiding myocardial borders. A mean of 17 elliptical ROIs were drawn on representative transaxial ventricular slices in the flow study. The larger ROI were used in the flow studies to enhance the accuracy of the measurements. The segmental results from each PET study and also the angiographic and echocardiographic data were finally combined and pooled together (M. T. Mäki and J. M. Knuuti).

A regional blood flow (MBF) measurement of regional blood flow. Values of regional MBF (ml·min⁻¹·g water-perfusible tissue⁻¹) were calculated according to the previously described method employing the single compartment model (12, 14). The arterial input function was obtained from the left ventricular time activity curve using a previously validated method in which corrections were made for the limited recovery of the left ventricular ROI and spillover from the myocardial signals (13). The mean blood flow values in the dysfunctional and normal myocardial regions in each patient were calculated and used for further analysis.

Calculation of regional FFA uptake. The nonmetabolized fraction of [18F]FTHA was used to correct the plasma input function. Metabolite analysis was not available in patients 2 and 4. Because the nonmetabolized fraction of the tracer was quite comparable between the patients, we used the mean metabolite fraction in those two studies to correct the input function. Plasma and tissue time-activity curves were analyzed graphically (26). The slope of the plot in the graphic analysis is equal to the fractional uptake constant of [18F]FTHA (Kᵢ). In this study, the last seven time points were used to determine the slope by linear regression. The mean Kᵢ for each myocardial segment was calculated (average: 4 ROI/segment). The regional myocardial FFA uptake index in each segment was calculated as Kᵢ × Pᵣᵢ, where Pᵣᵢ is mean serum FFA level during PET imaging. The mean values of all dysfunctional and normal segments were calculated in each patient and used in the final analysis (Table 2).

Calculation of relative [18F]FDG uptake. The [18F]FDG uptake rate of the dysfunctional regions in each patient was expressed as a percentage of the counts in the normal regions.

Statistical Analysis

All results are expressed as means ± SD. The difference between the dysfunctional and the normal regions was statistically tested using a paired comparisons t-test. P values <0.05 were interpreted as statistically significant. The statistical computation was performed with SAS statistical program package (SAS Institute, Cary, NC).

RESULTS

Metabolic and Physiological Characteristics During Study Period

Plasma glucose was 5.3 ± 0.4 mmol/l, plasma lactate was 0.9 ± 0.5 mmol/l, serum insulin was 8 ± 3 mU/l,
Table 2. Summary of individual metabolic and flow results in normal and dysfunctional myocardium

<table>
<thead>
<tr>
<th>Patient</th>
<th>Region Type</th>
<th>$K_i$, ml·g$^{-1}$·min$^{-1}$</th>
<th>Serum FFA, µmol/l</th>
<th>FFA Uptake Index, µmol·100 g$^{-1}$·min$^{-1}$</th>
<th>MBF, ml·min$^{-1}$·g$^{-1}$</th>
<th>Relative MBF, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dysfunctional</td>
<td>0.10</td>
<td>550</td>
<td>5.3</td>
<td>0.67</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>0.12</td>
<td>6.2</td>
<td></td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Dysfunctional</td>
<td>0.16</td>
<td>590</td>
<td>8.9</td>
<td>0.66</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>0.17</td>
<td>9.6</td>
<td></td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Dysfunctional</td>
<td>0.06</td>
<td>710</td>
<td>4.2</td>
<td>1.14</td>
<td>104</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>0.05</td>
<td>3.4</td>
<td></td>
<td>1.10</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Dysfunctional</td>
<td>0.09</td>
<td>430</td>
<td>3.9</td>
<td>0.79</td>
<td>108</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>0.09</td>
<td>3.6</td>
<td></td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Dysfunctional</td>
<td>0.14</td>
<td>530</td>
<td>7.3</td>
<td>0.64</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>0.13</td>
<td>6.8</td>
<td></td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Dysfunctional</td>
<td>0.10</td>
<td>550</td>
<td>5.5</td>
<td>0.68</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>0.10</td>
<td>5.5</td>
<td></td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Dysfunctional</td>
<td>0.10</td>
<td>590</td>
<td>5.8</td>
<td>0.72</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>0.09</td>
<td>5.2</td>
<td></td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>Dysfunctional</td>
<td>0.11 ± 0.03</td>
<td>560 ± 80</td>
<td>5.8 ± 1.7</td>
<td>0.76 ± 0.17</td>
<td>93 ± 10</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>0.11 ± 0.04</td>
<td>5.8 ± 2.1</td>
<td>0.81 ± 0.14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FFA, free fatty acid; FFA uptake index, $K_i$ × FFA; $K_i$, uptake constant of $^{18}$F-labeled 14-fluoro-6-thia-heptadecanoic acid; MBF, myocardial blood flow.

and serum FFA concentration was $560 ± 80 \mu$mol/l during the PET studies. The mean rate-pressure product was $7,300 ± 1,340$ mmHg·beats·min$^{-1}$. No patient experienced chest pain or showed ischemic ECG changes during the PET study.

Regional Wall Motion Abnormalities During Study Period

The affected myocardial segments (Table 1) were constantly and severely hypokinetic in all seven patients in the three echocardiograms performed before revascularization. The mean preoperative EF was $58 ± 6\%$. Five patients underwent coronary bypass grafting, and one patient underwent percutaneous transluminal coronary angioplasty (Table 1). In five of the seven patients, wall motion was normalized in the dysfunctional regions. One patient was not revascularized, and another infarcted after angioplasty. After revascularization, EF increased to $63 ± 4\%$, but this increase was not statistically significant.

Relative Myocardial $^{18}$F-FDG Uptake and Blood Flow

The mean relative $^{18}$F-FDG uptake in the dysfunctional regions (expressed as the percentage of activity in the normal regions) was $103 ± 12\%$ (range 96–118\%). Resting MBF was not different in the dysfunctional ($0.76 ± 0.18$ ml·min$^{-1}$·g$^{-1}$) and normal ($0.81 ± 0.14$ ml·min$^{-1}$·g$^{-1}$; $P = 0.16$) myocardial regions (Table 2).

Fractional $^{18}$F-FTHA Uptake and FFA Uptake Indexes in Dysfunctional and Normal Myocardium

Rapid tracer uptake was detected in the heart within 2–3 min after injection, and it remained nearly constant during the next 30 min (Fig. 2A). Patlak plots of myocardial $^{18}$F-FTHA kinetics showed a linear increase, indicating metabolic trapping (Fig. 2B). The mean $K_i$ values in the dysfunctional and normal regions were $0.11 ± 0.03$ and $0.11 ± 0.04$ ·ml·g$^{-1}$·min$^{-1}$, respectively (NS). Consequently, the mean FFA uptake indexes were similar in the dysfunctional ($5.8 ± 1.7$ µmol·100 g$^{-1}$·min$^{-1}$) and normal ($5.8 ± 2.1$ µmol·100 g$^{-1}$·min$^{-1}$; NS) myocardial regions. The individual FFA uptake indexes in the dysfunctional and normal myocardial areas are shown in Fig. 3 and Table 2. A representative PET image from patient 5 with a wall motion abnormality but preserved $^{18}$F-FTHA uptake in the corresponding region is shown in Fig. 4.

DISCUSSION

The purpose of the present study was to investigate whether fatty acid uptake is altered in the chronically dysfunctional but viable (collateral-dependent) myocardium in humans. The myocardial FFA uptake indexes were determined with $^{18}$F-FTHA and PET in patients with an occluded major coronary artery and chronic myocardial dysfunction. The results show that although regional function is chronically reduced, FFA uptake is preserved.
Regional oxidative metabolism is intimately coupled to MBF (7). Furthermore, the rate of total oxidative metabolism measured by 13C-acetate and PET was nearly normal in the chronically dysfunctional but viable myocardium (11, 36). Currently, there is some evidence in human studies that chronic dysfunction in the viable myocardium might result from repetitive ischemic episodes with a persistent stunning effect (10, 36) rather than from chronic hypoperfusion or chronic hypoxia.

Fig. 2. A: myocardial and blood [18F]FTHA time-activity curves in dysfunctional (anterolateral and septal) and normal (lateral) myocardial regions (patient 5). Similar [18F]FTHA uptake was detected in all these myocardial regions. Metabolite-free fraction was calculated by subtracting plasma [18F]FTHA metabolite radioactivity from plasma total radioactivity. B: graphic analysis (Patlak) of [18F]FTHA uptake in corresponding myocardial regions in A showed similar fractional uptake constants of [18F]FTHA (i.e., slope of plot). Cplasma, tissue radioactivity concentration; Cplasma, plasma radioactivity concentration.

Fig. 3. Free fatty acid (FFA) uptake indexes in normal and dysfunctional myocardial regions. FFA uptake index was calculated by multiplying fractional uptake constant of [18F]FTHA with serum FFA concentration.

Fig. 4. Representative positron emission tomography (PET) image (patient 5). Midventricular slice of [18F]FTHA PET study shows homogenous trace uptake in myocardium.
ischemia. This is further supported by the findings of this study, because FFA oxidation was preserved in the postischemic and stunned extraoperatively perfused pig heart (17) and reperfused, isolated rat heart (19), whereas ongoing ischemia resulted in a clear reduction in uptake (16, 24, 35) and \( \beta \)-oxidation of FFA (9, 16, 23, 24, 33, 34). Recently Young et al. (38) measured FFA uptake in canine heart during short-term (50–80 min) low-flow ischemia. They found that myocardial FFA extraction was increased and net FFA uptake was preserved compared with the preischemic values (38).

Principally, measuring the cardiac uptake of a substrate does not indicate whether the substrate is immediately oxidized or stored for later metabolism. Therefore, the accumulation of a FFA tracer in the myocardium probes the net utilization rate of long-chain FFA, the sum of esterification and oxidation (5). However, Wisneski et al. (37) found that in humans 84 ± 17% of the FFA extracted by the myocardium undergo rapid oxidation within 30 min, and a smaller fraction enters the intracellular lipid pool in the fasting state. Recently, Bergmann et al. (3) found similar results using palmitate in dogs. Additionally, the percentages of FFA undergoing rapid oxidation were similar in healthy volunteers and in patients with coronary artery disease (37).

\([18\text{F}]\)FTHA is a new LCFA tracer analog. After transport into the mitochondria, \([18\text{F}]\)FTHA undergoes the initial steps of \( \beta \)-oxidation and is thereafter trapped in the cell (5). Because of this phenomenon, the accumulation rate of radioactivity in the myocardium has been suggested to reflect the uptake and \( \beta \)-oxidation rate of LCFA (5, 8). The hypothesis that \([18\text{F}]\)FTHA traces \( \beta \)-oxidation has been tested in mice by pretreatment with the CPT I inhibitor 2[5(4-chlorophenyl)pentyl]oxirane-2-carboxylate. In that study (5), cardiac \([18\text{F}]\)FTHA uptake decreased by 81 and 87% at 1 and 60 min, respectively. These findings suggest that the accumulation rate of \([18\text{F}]\)FTHA appears to be mainly associated with FFA \( \beta \)-oxidation and that only 5–10% is esterified, at least, in the nonischemic myocardium. Recently, Stone et al. (33) studied cardiac \([18\text{F}]\)FTHA retention in swine during ischemia and hypoxia. They found that in the normal and ischemic tissues \([18\text{F}]\)FTHA uptake relates to \( \beta \)-oxidation, although during (nonphysiologically) hypoxia \([18\text{F}]\)FTHA uptake appears to slightly overestimate \( \beta \)-oxidation activity compared with tritiated palmitate. Taken together, current evidence indicates that \([18\text{F}]\)FTHA might be a metabolic probe of energy-providing FFA \( \beta \)-oxidation in myocardium. However, metabolism of FFA is complex, and the tissue kinetics of this novel tracer are not fully investigated in humans and under different physiological and pathological conditions.

MBF determines the delivery of \([18\text{F}]\)FTHA to the myocardium, but the retention is dependent on subsequent steps of metabolism (5). In the study by Ebert et al. (8), no significant increase in the uptake rate of \([18\text{F}]\)FTHA in the human heart was detected when MBF was elevated fourfold by dipyridamole. However, the myocardial uptake rate of \([18\text{F}]\)FTHA increased significantly during exercise-induced increase in myocardial energy consumption (doubling of coronary flow from baseline). In our study the mean fractional uptake rate constant \( K_t \) in the normal myocardial regions is similar to the values obtained by Ebert et al. (8) in healthy young men. Recently, \([18\text{F}]\)FTHA was applied also to study myocardial viability in a patient with left bundle branch block (1).

The results of this study together with the previous findings showing preserved glucose uptake lead us to conclude that uncoupling of substrate uptake and contractile function exists in the chronically dysfunctional but viable myocardium in humans. However, the mechanism of these changes remains unknown. Asynchronous wall motion may increase regional diastolic wall stress and, consequently, energy demand in the dysfunctional segments (27). Another possible explanation is altered intracellular calcium transport, which may enhance energy expenditure (2). The short-term uncoupling of substrate oxidation from mechanical function has been previously shown in the isolated working rat heart subject to no-flow ischemia followed by reperfusion (2, 18) and in postischemic, regionally stunned myocardium in the open-chest anesthetized dog (32). Glucose uptake studied by PET and \([18\text{F}]\)FDG does not differentiate between glucose storage and oxidation (34). Therefore, preserved glucose uptake in the dysfunctional tissue may reflect only increased shunting of glucose to the glycogen and/or increased anaerobic glycolysis and not increased glucose oxidation. Indeed, excess glycogen stores (6, 20, 36) (but no signs of degeneration, which would suggest acute ischemic damage) have been found in the chronically dysfunctional but viable myocardium, and \([18\text{F}]\)FDG uptake correlated positively with the amount of cardiomyocytes showing excess glycogen stores (6).

Limitations
Because the goal of this study was to investigate FFA metabolism in the chronically dysfunctional but viable myocardium, the study population was highly selected. Because patients with previous myocardial infarction were excluded, the global left ventricular EF was only mildly affected but not very different from what Vanoverschelde et al. (36) found when studying similar patients. We cannot completely exclude the possibility that some tissue necrosis might have existed in the dysfunctional regions, because no myocardial biopsies were taken. However, \([18\text{F}]\)FDG uptake was preserved in these myocardial regions, and wall motion was normalized in the five successfully revascularized patients, confirming the existence of myocardial viability. Because the study subjects were highly selected, we do not know whether the results are generalizable to patients with multiple vessel disease, more severe wall motion abnormality, or compromised global systolic function. \( \beta \)-Blocking agents are known to decrease global metabolic demand and might therefore also reduce myocardial FFA uptake. However, it is unlikely that they would change the difference of \([18\text{F}]\)FTHA...
uptake between the normal and dysfunctional myocardium.

In conclusion, FFA uptake probed by \(^{18}F\)FTHA and PET is preserved in the chronically dysfunctional but viable, noninfarcted (collateral-dependent) myocardium. Taken together with preserved glucose uptake, these findings demonstrate uncoupling between substrate uptake and mechanical function in the chronically dysfunctional but viable myocardium.

We express gratitude to Tuula Niskanen, Hannu Sipilä, and Mika Teräs for excellent technical assistance and to Jorma Mikko for analyzing the angiograms.

Address for reprint requests: M. Mäki, Dept. of Nuclear Medicine, Univ. Central Hospital, Kiinamyllynkatu 4–8, FIN-20520 Turku, Finland.

Received 27 May 1997; accepted in final form 30 July 1997.

REFERENCES


