Regional Myocardial Free Fatty Acid Extraction in Normal and Ischemic Myocardium

K. Vyska, PhD, H.J. Machulla, PhD, W. Stremmel, MD, D. Faßbender, MD,
W.H. Knapp, MD, G. Notohamipродjo, MD, U. Gleichmann, MD,
H. Meyer, MD, E.J. Knust, PhD, and R. Körfer, MD

The rate constant for free fatty acid influx \( (k_1) \) was studied in normal and ischemic myocardium. In 15 normal subjects and 30 patients with coronary artery disease, \(^{201}\text{Tl}\) and \(^{15-}(p{^-}{\text{123I}}\text{-iodophenyl})\text{-pentadecanoic acid (IPPA)} \) were administered during exercise under fasting conditions and at rest. In 10 patients, the study was repeated after percutaneous transluminal coronary angioplasty; in three patients, the study was repeated after infarction. The initial accumulation of IPPA, related to that of \(^{201}\text{Tl}\) (both background and crossover corrected), was used for determinations of the regional rate constant of IPPA influx into myocardial tissue \( (k_1^*) \). In normal subjects, no significant differences in \( k_1^* \) between major myocardial segments were found; the average value of \( k_1^* \) was \( 0.57 \pm 0.13/\text{min} \) (mean \( \pm \text{SD} \)) at rest and \( 0.42 \pm 0.06/\text{min} \) at exercise (average workload, \( 123 \pm 47 \) W). With increasing free fatty acid plasma concentration and perfusion, free fatty acid influx increased in a saturable fashion. The Michaelis-Menten constant \( (K_M^*) \) and the maximal velocity \( (V_{\text{max}}^*) \) for IPPA influx into myocardial tissue were estimated to be \( 470 \) nmol/g and \( 430 \) nmol/g \cdot \text{min} \), respectively. In ischemic areas, \( k_1^* \) was reduced to \( 57 \pm 18/\% \) of \( k_1^* \) value in nonaffected segments. The areas were larger than those showing reduced \(^{201}\text{Tl}\) uptake. Preinfarction and postinfarction studies showed that the size of \(^{201}\text{Tl}\) defects in postinfarction images corresponded with the size of the area with reduced \( k_1^* \) observed in preinfarction scintigrams. Revascularization led to an increase of \(^{201}\text{Tl}\) uptake and to normalization of \( k_1^* \). (Circulation 1988;78:1218-1233)

Fatty acids are transported to the heart by blood as albumin-bound fatty acids or as triglycerides complexed to hydrophobic lipoproteins.\(^1\)\(^2\) Triglycerides are hydrolyzed at the surface of the endothelial cells.\(^1\)\(^2\) Monomeric fatty acids are efficiently taken up by the myocardium, revealing a single-pass extraction rate of 40% in the resting heart.\(^1\)\(^3\)\(^4\)

Although fatty acids are the major energy source of the myocardium,\(^5\)\(^6\) little is known about their cellular uptake mechanism. The hypothesis of a passive diffusional process was recently challenged.\(^7\)\(^8\)

Influx of fatty acids into isolated rat cardiomyocytes was shown to reveal criteria of a carrier-dependent system and is mediated by a specific 40-kDa membrane protein.\(^7\) This membrane transport protein is different from the 12-kDa cytosolic fatty acid–binding protein, which may serve in the distribution of internalized fatty acids to the various intracellular lipid pools and pathways.\(^9\)

The identification of a membrane fatty acid transporter is of physiological significance because it might represent a site of metabolic control of fatty acid uptake according to the energy requirements of the heart.

Therefore, it was of potential interest to elucidate whether myocardial fatty acid uptake in humans reveals criteria of a facilitated diffusional process and whether this transport competence is altered under pathological conditions. For such in vivo metabolic studies, a radioiodinated phenyl fatty acid, \( 15-(p{^-}{\text{123I}}\text{-iodophenyl})\text{-pentadecanoic acid (IPPA)} \) was used, which in previous studies has been shown to be analogous to the physiological serum fatty acids.\(^10\)\(^11\)\(^17\) This study examined...
whether myocardial fatty acid uptake follows saturation kinetics with increasing plasma free fatty acid concentrations (criterion of carrier-mediated transport) and how the fatty acid uptake pattern is altered in ischemic regions of the myocardium. For evaluating the clinical significance of such studies, we also analyzed whether areas of reduced fatty acid extraction in coronary artery disease indicate a potential region of risk for a myocardial infarction.

**Subjects and Methods**

**Subject Population**

Control subjects were 15 individuals without risk factors, with normal coronary arteries (as demonstrated by coronary angiography), normal wall motion, and no abnormal findings in echocardiography or in electrocardiography. Either these subjects were examined for social medical indications or they were finally found to have, for example, esophagitis or chest pain originating from thoracic nerves, nerve roots, or spinal cord. Each subject was examined by a physician, and informed consent was obtained for the radionuclide study. The study has been conducted according to a protocol approved by the Committee on Ethics of Human Investigation of the Heart Center North-Rhine Westphalia, Bad Oeynhausen, FRG.

During clinical study, 30 patients with coronary artery disease were examined. All patients underwent selective coronary and left ventricular biplane cineangiography. Coronary angiograms were reviewed by at least two experienced angiographers, and the maximal luminal narrowing for each major coronary artery was estimated visually and classified by consensus. Only patients with a lesion of at least 80% diameter narrowing (on visual assessment of coronary arteriograms) were selected for the investigations of the free fatty acid uptake under ischemic conditions. A myocardial segment was regarded jeopardized when it showed eukinesia or hypokinesia of and being supplied by a severely stenotic major coronary artery. In 10 of these patients, the study was repeated after percutaneous transluminal coronary angioplasty (PTCA). In three patients, the measurement was repeated after myocardial infarction. Each patient gave written, informed consent.

**Study Protocol**

All subjects fasted for at least 14 hours before the start of the study to enhance myocardial free fatty acid utilization and to standardize study conditions.

**Control Group**

In control subjects, the studies were carried out under exercise and at rest conditions. Each study began by measurement under exercise conditions, and 4 hours later, the study was repeated at rest conditions. This protocol enables the background correction to be carried out by the second examination.

In exercise studies, upright bicycle ergometry was performed by stepwise increase of the workload (25 W for each step) and was terminated in case of exhaustion. The duration of one workload step was 1 minute. At maximum exercise level, 1 mCi $^{201}$TI and 2 mCi IPPA were injected simultaneously followed by a 10-cc saline flush by an intravenous cannula inserted before the start of the study. Exercise was continued for 60 seconds. During the indicator application, a dynamic dual-isotope study at a frame rate of 1 frame/min at a left anterior oblique angle (LAO) of 30° was started. Total collection period was 10 minutes. The emissions were detected with a single-crystal camera (DATAMO, Picker, Cleveland, Ohio) equipped with a high-resolution collimator. For dual-isotope counting, dual-channel analyzer windows were centered at 75 (123$^1$TI) and 160 keV (121$^1$I), in which a width of 20% was used for both windows. Subsequently, the subjects were positioned in a supine position in front of the single-crystal camera (Dyna 4/15, Picker) equipped with a converging collimator, and static images in anterior, LAO 45°, and LAO 75° projections were registered. The collection period was 6 minutes for each image; a 64 × 64 matrix was used. Before exercise and at maximal workload, blood samples for the determination of lactate, glucose, and free fatty acid levels were collected.

For the examinations at rest conditions 4 hours later, four images with the same camera (anterior, LAO 30°, LAO 45°, and LAO 75° projections) were registered to determine the residual activity (collection period was 6 minutes for each image). Subsequently, blood samples for determination of lactate, glucose, free fatty acids, and hematocrit levels were collected. After administration of 1 mCi $^{201}$TI and 2 mCi IPPA, a dynamic study in LAO 30° and static studies in anterior, LAO 45°, and LAO 75° projections were carried out in a supine position as described above. During these examinations, precaution was taken to keep the patient in the same position so that the correction for residual activity was possible. The correction for residual activity was carried out by subtraction of corresponding scintigrams detected before and after the second indicator application.

All scintigrams were corrected for crossover effects and for background activity. For the crossover effects, correction data determined in separate measurements of standard sources were used. For background corrections, a modified interpolative background-subtraction algorithm of Goris and colleagues$^{18}$ was used.

**Patient Studies**

In all patients, the cardiac medications were withheld overnight. The patients were examined solely under exercise conditions. Upright bicycle ergometry described above was terminated in case of exhaustion, typical angina with at least a 2-mm horizontal ST segment depression 60 msec after the
Q wave deflection point, or tachycardia. All patients achieved at least 75% of their age-adjusted maximal heart rate. In this case, 2 mCi $^{201}\text{Tl}$ and 4 mCi IPPA were administered at maximal workload. Subsequently, dynamic study in LAO 30° and static studies in anterior, LAO 45°, and LAO 75° projections were carried out as described above.

**Kinetic Studies**

In five control subjects after intravenous bolus injection of IPPA and $^{201}\text{Tl}$, the activity distributions in the chest were registered in one projection (LAO 30°) during a period of 80 minutes at a rate of 1 frame/min. All subjects exercised in a supine position. After correcting the data obtained for crossover effects, the regions of interest were assigned to the left ventricular myocardium and to the background area (superior caval vein or aorta). The time-activity curves were generated and normalized to the number of pixels in respective regions of interest. The myocardial IPPA and $^{201}\text{Tl}$ retention time–activity curves were obtained by subtracting the normalized time activity curves registered in the background region of interest (superior caval vein or aorta) from the normalized left ventricular time-activity curves.

Parallel to the external measurements, the IPPA and $^{201}\text{Tl}$ activities in blood were determined. For this, blood samples were taken during the whole examination period. Withdrawal of blood samples was begun 1 minute before injection. The collection rate in the first 15 minutes of examination was 1 ml/min. Thereafter, the rate of withdrawal was reduced to 1 ml/5 min. The samples were centrifuged and weighed, and IPPA, as well as $^{201}\text{Tl}$ activity in plasma and erythrocytes, was measured in a well counter.

**In Vitro Determinations**

For the determination of free fatty acids in serum, an in vitro enzymatic colorimetric method (NEFAC-kit, Wako Chemicals Neuss, FRG) was used. For the determinations of lactate and glucose, kits supplied by Boehringer Mannheim (FRG) were used.

**Calculations**

As described in the Appendix, the rate constant for IPPA influx in myocardial tissue ($k_{1*}$) is given by

$$k_{1*} = k_{1t*} \cdot \frac{A_{2*/A_{3*}}}{A_{2*}} \cdot \frac{\int f_{lb*} dt}{f_{lb*} dt} \cdot (1 - H)$$

In our studies, the regional distribution of the quotient $A_{2*/A_{3*}}$ was determined by means of pixel-by-pixel division of the background and crossover-corrected IPPA and $^{201}\text{Tl}$ images. The quotient image ($A_{2*/A_{3*}}$) thus obtained was multiplied by the factor $(1 - H)$ (where H is hematocrit) and the ratio $\int f_{lb*} dt/\int f_{lb*} dt$ (these factors being the same for all segments of the left ventricular myocardium).

The ratio $\int f_{lb*} dt/\int f_{lb*} dt$ was determined as a ratio of the count rates registered in the blood regions of interest (aorta) in the crossover-corrected $^{201}\text{Tl}$ ($f_{lb*}$) and IPPA ($\int f_{lb*} dt$) integral images, obtained by summation of the data collected in the first 10 minutes after indicator application in the LAO 30° projection. The period of 10 minutes was selected because kinetic studies demonstrated that the changes of the ratio $\int f_{lb*} dt/\int f_{lb*} dt$ after this period are very low.

Subsequently, the parametric image thus obtained was multiplied by $k_{1*}$ (a segmental correction for variation of $^{201}\text{Tl}$ extraction at a high flow rate was carried out as described in the Appendix). The area corresponding to left ventricular myocardium was subdivided into 36 radial segments, and the average values per pixel of a given segment were plotted as a linear diagram. The segment numbering was clockwise. Zero was selected at a point corresponding to 12 o'clock. This diagram was considered to reflect the circumferential distribution of $k_{1*}$ in the left ventricular wall.

The relative increase of myocardial blood flow during exercise was determined by the ratio of the average count rates in myocardium registered in $^{201}\text{Tl}$ scintigrams at rest and during exercise (see Appendix).

**Tracer Kinetics**

Representative normal IPPA and $^{201}\text{Tl}$ time–activity curves are demonstrated in Figures 1A and 1B. These curves were registered in a control subject in regions of interest selected over the left ventricular myocardium as well as over vena cava superior or aorta (reference region for background activity) after intravenous bolus injection of IPPA and $^{201}\text{Tl}$. The total registration period was 80 minutes.

By subtracting the pixel-normalized background time-activity curves from the myocardial curves, the myocardial indicator-residue time-activity curves were obtained (Figure 2). The IPPA-residue time–activity curve is characterized by a steep increase that is followed by a plateau phase and a period of a biphasic elimination. The half-times of the rapid and slow phases were 8.5 and 66.7 minutes, respectively. The corresponding $^{201}\text{Tl}$ curve shows a steep increase followed by a very slow indicator elimination phase.

For the comparison, the myocardial indicator-residue time-activity curve was registered in a normal subject also after application of $^{17,123}\text{I}$-heptadecanoic acid (IHA) (Figure 2). When compared with the IPPA curve, the IHA curve is distinguished by a sharp maximum.

In Figure 3, the ratio of the IPPA-residue and $^{201}\text{Tl}$-residue time-activity curves presented in Figure 2 is plotted as a function of time. After a slight initial overshoot, the ratio remains constant (within the range of experimental error) between 7 and 25 minutes after indicator application. (The initial overswing is probably due to the sequential application of IPPA and $^{201}\text{Tl}$, which leads to the time shift in the IPPA and $^{201}\text{Tl}$ curves.) In five subjects, the beginning of the plateau phase ranged from 6 to 8 minutes. The end of the plateau ranged from 25 to
Figure 1. Plots of time-activity curves that were registered in regions of interest selected over left ventricular myocardium (upper curve) and aorta (lower curve). Panel A: After administration of 15-(p-123I-iodophenyl)-pentadecanoic acid (IPPA). Panel B: After administration of 201Tl. All curves were normalized to 1 pixel and multiplied by a factor of 100. This was a dynamic study with a registration rate of 1 frame/min.

30 minutes. The time interval between 10 and 25 minutes was therefore chosen for determination of regional distribution of the rate constant $k_1^*$. Normal Subjects

Figure 4 shows a typical example of 201Tl (left upper corner) and IPPA (right upper corner) scintigrams in the LAO 75° projection from a normal subject after simultaneous administration of 1 mCi 201Tl and 2 mCi IPPA at maximal workload. The workload applied was 200 W. The parametric image obtained by division of background-corrected IPPA and 201Tl scintigrams is shown in the left lower corner. The regional distribution of the quotient IPPA/201Tl in the left ventricular myocardium is homo-

Figure 2. Plots of myocardial indicator-residue time-activity curves registered in a normal subject after administration of 201Tl (upper curve), 15-(p-123I-iodophenyl)-pentadecanoic acid (IPPA) (middle curve), and 17-123I-heptadecanoic acid (IHA) (lower curve). All curves were normalized to a common maximum.

Figure 3. Plot of ratio of the IPPA- and 201Tl-residue time-activity curves plotted as a function of time. IPPA, 15-(p-123I-iodophenyl)-pentadecanoic acid.
FIGURE 4. Color scintigrams from normal subject. Scintigram of $^{201}$TI in the left anterior oblique (LAO) 75° projection (upper left), scintigram of 15-(p-$^{23}$I-iodophenyl)-pentadecanoic acid (IPPA) in the LAO 75° projection (upper right), distribution pattern of the quotient IPPA/$^{201}$TI (bottom left), and the linear diagram demonstrating the radial distribution of the rate constant for IPPA influx ($k_1^*$) (bottom right) in normal left ventricular myocardium. In the $k_1^*$ distribution pattern, all data not related to the myocardial regions were eliminated. Applied workload was 200 W; free fatty acid plasma concentration was 500 nmol/ml; lactate plasma concentration was 23.4 mg/dl; and glucose plasma concentration was 107 mg/dl.

geneous. The segmental distribution of the rate constant for IPPA influx, $k_1^*$, is shown in the right lower corner. In this particular subject, the average of the $k_1^*$ values determined in 36 radial segments was 0.37/min; the standard deviation was 0.02/min.

In 15 normal subjects examined during exercise, the average $k_1^*$ was $0.42 \pm 0.06$/min (Table 1). The average workload and heart rate were $123 \pm 47$ W and $136 \pm 23$ beats/min, respectively. The average plasma concentrations of fatty acid, lactate, and glucose were $0.63 \pm 0.18$ mmol/l, $22.27 \pm 14.52$ mg/dl, and $100 \pm 6.34$ mg/dl, respectively. In the same subjects at rest, the average $k_1^*$ was $0.57 \pm 0.13$/min; the heart rate was $80 \pm 13$ beats/min; the average plasma concentrations of fatty acid, lactate, and glucose were $0.66 \pm 0.39$ mmol/l, $8.76 \pm 3.61$ mg/dl, and $99 \pm 15$ mg/dl, respectively.

Perfusion Rate Determinations

The perfusion rates, which were registered in normal subjects who exercised at different workloads, are presented in Figure 5 as a function of the heart rate. The increase of perfusion rate during exercise is a linear function of the heart rate. The regression line was calculated as

$$f_p/f_{p0} = -0.20 + 0.0167\times HR; \quad (R^2 = 0.93) \quad (2)$$
TABLE 1. Studies During Exercise and at Rest

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>k_l*(min⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>0.42</td>
<td>0.06</td>
<td>0.02</td>
</tr>
<tr>
<td>Rest</td>
<td>0.57</td>
<td>0.13</td>
<td>0.03</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>136</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td>Rest</td>
<td>80</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Workload (W)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f/f70 Exercise</td>
<td>2.07</td>
<td>0.47</td>
<td>0.12</td>
</tr>
<tr>
<td>Rest</td>
<td>1.14</td>
<td>0.20</td>
<td>0.05</td>
</tr>
<tr>
<td>Free fatty acid plasma concentration (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>0.63</td>
<td>0.18</td>
<td>0.05</td>
</tr>
<tr>
<td>Rest</td>
<td>0.66</td>
<td>0.39</td>
<td>0.10</td>
</tr>
<tr>
<td>Lactate plasma concentration (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>22.27</td>
<td>14.52</td>
<td>3.88</td>
</tr>
<tr>
<td>Rest</td>
<td>8.76</td>
<td>3.61</td>
<td>0.90</td>
</tr>
<tr>
<td>Glucose plasma concentration (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>100</td>
<td>6.34</td>
<td>1.76</td>
</tr>
<tr>
<td>Rest</td>
<td>99</td>
<td>15</td>
<td>4</td>
</tr>
</tbody>
</table>

k_l*, regional rate constant of influx of 15-(p-[¹²³]I-iodophenyl)pentadecanoic acid; f/f₇₀, relative plasma flow rate.

where f_p is plasma flow in the subject, and f_p70 is the average plasma flow rate at a heart rate 70 beats/min in normal subjects (0.44 ml/g·min), f_p/f_p70 is the relative plasma flow rate, and HR is the heart rate in beats per minute.

A linear relation exists also between the flow and the applied workload (Figure 6); the regression line was determined as

\[ \frac{f_p}{f_p70} = 0.992 + 0.008724*W \]  \( (R^2 = 0.88) \) (3)

where W is workload in watts.

Free Fatty Acid Influx Rate

We studied the relation between the rate constant for IPPA influx, k_l*, and the free fatty acid plasma concentration, c_p, at a constant flow rate. For this study, we selected only those data obtained in subjects with a ratio f_p/f_p70 between 1.0 and 1.2. As can be seen in Figure 7, at a constant flow rate, the increase of c_p from 200 to 1,200 nmol/ml results in a reduction of k_l* from 0.78 to 0.4/min. Figure 8 demonstrates the relation between k_l* and the flow at a constant free fatty acid plasma concentration. The lower curve demonstrates the data detected in subjects with free fatty acid plasma concentration ranging from 700 to 820 nmol/ml. The upper curve reflects the corresponding relation observed in subjects with free fatty acid plasma concentration ranging between 390 and 560 nmol/ml. In both cases, the threefold increase of the flow rate resulted in 30% decrease of k_l*.
The dependence of $k_{1*}$ on the rate of free fatty acid supply per gram of tissue ($c_p \cdot f_p$) is shown in Figure 9. This figure demonstrates a close relation between these two variables. The relation could be approximated by a hyperbolic function.

We also studied the dependency of $k_{1*}$ on the lactate plasma concentration (Figure 10). No significant changes of $k_{1*}$ can be observed with increasing lactate plasma concentrations.

**Patients With Coronary Artery Disease**

Figure 11 shows scintigrams of a patient with an 85% proximal stenosis of the left anterior descending coronary artery (LAD). Right coronary artery (RCA) and left circumflex coronary artery (LCx) had no luminal narrowing. Ventriculography revealed a good global left ventricular contraction. No reflux was detected. Left ventricular ejection fraction was 80%. The $^{201}$Tl scintigraphy (maximum workload was 100 W) revealed slightly reduced accumulation and a vague redistribution after 4 hours in the septum. In the LAO 75° projection, only a slightly reduced $^{201}$Tl accumulation in the apical segment of the anterior wall can be perceived (left upper corner). The average value of $k_{1*}$ in the noninvolved segment was, as can be seen in the right lower corner of this figure, $0.40 \pm 0.05$/min. In contrast, the value of $k_{1*}$ in the supply area of LAD (whole anterior wall) (average $k_{1*} = 0.25$/min) is significantly reduced.

After this investigation, PTCA was performed. Two weeks later, the patient was reinvestigated (Figure 12). After PTCA, the average value of $k_{1*}$ in the area of anterior wall was $0.41 \pm 0.03$/min, whereas the value of $k_{1*}$ observed in normal subjects at corresponding conditions was $0.43$/min. This indicates that in this patient the revascularization led to normalization of IPPA influx.

In 20 patients with one-vessel disease examined in this study, the average value of $k_{1*}$ in the supply area of the affected coronary artery was found to be reduced on average to $57 \pm 18\%$ of the value of $k_{1*}$ in nonaffected segments. This reduction of $k_{1*}$ was statistically significant ($p<0.001$).

Data obtained in a 57-year-old patient with a history of unstable angina are demonstrated in Figure 13. Ventriculography revealed good global ventricular contraction with discrete segmental early relaxation phenomena in the anterior wall (left ventricular ejection fraction = 0.76). Coronary angiography revealed 90% LAD stenosis, peripheral to the origin of the first diagonal branch, 25% proximal...
stenosis of RCA, and 50% stenosis of the large right ventricular branch. The LCx appeared normal. In this patient, the LAO 75° 201Tl scintigram did not show any significant alterations (Figure 13, right upper corner). IPPA uptake, however, was clearly reduced in the whole anterior wall. Accordingly, the $k_1^*$ distribution pattern showed a significant alteration in the anterior wall ($k_1^* = 0.22/\text{min}$). Apart from this obvious finding, the average value of $k_1^*$ in the inferior wall (0.34/min) was found to be lower than the corresponding values in normal subjects. One month later, the patient was readmitted because of severe chest pain and the electrocardiographic evidence of subacute anterior wall infarction. Recatheterization revealed an increase of the LAD luminal narrowing to 95%. The 201Tl scintigraphy (Figure 14) revealed an infarct area that corresponded with the defect in the preinfarction $k_1^*$ distribution pattern. Similar observations were made in all three patients examined so far in the preinfarction and postinfarction periods.

The results obtained in a preliminary study in patients with two-vessel disease ($n = 10$) revealed a significant reduction of $k_1^*$ in both affected areas (average, $54 \pm 22\%$ of $k_1^*$ observed in normal subjects at corresponding conditions). After successful PTCA
in all patients, a reduction of the ventricular dimensions was observed accompanied with an improvement of the $^{201}$TI accumulation and normalization of the $k_1^*$ (average, 89 ± 10% of $k_1^*$ observed in normal subjects at corresponding conditions) in the supply area of the dilated artery. The normalization of the $k_1^*$ distribution pattern, however, was frequently incomplete. In several patients, the improvement of $k_1^*$ was observed even in the supply area of nontreated stenosed coronary artery. This indicates that in these patients the PTCA also led to reduction of the “steal effect” existing before PTCA.

**Discussion**

**Kinetic Studies**

In normal subjects, the myocardial IPPA-residue time-activity curve was characterized by a steep increase of activity and a plateau phase that was followed by a two-phase elimination period (Figure 2). In the plateau phase, no significant changes of IPPA tissue concentration were externally detectable even when the IPPA blood concentration was significantly decreased (Figure 1A, lower curve). Because of this particular property, the IPPA represents an indicator that reflects the myocardial free
fatty acid uptake under the metabolic conditions existing during the short period after indicator application (instant picture) and that provides this information for a longer time (frozen state), even when the myocardial metabolism is already changing (a property necessary for a time-consuming myocardial scintigraphy).

The constancy of IPPA tissue concentration in the plateau phase indicates, moreover, that during this period the IPPA efflux from the myocardium is negligible and that in this period the catabolism of IPPA is either not proceeding or the elimination of catabolic products is so retarded that no changes of IPPA tissue concentration are externally detectable. This means that by external detection the IPPA behaves as an indicator that is trapped in tissue, that is, the myocardial IPPA uptake registered in the plateau phase has to be considered as a measure for the free fatty acid influx. The IPPA uptake was found to be proportional to both regional myocardial blood flow and the IPPA plasma concentration\textsuperscript{14,15} with a proportionality constant
usually being designated as a rate constant for IPPA influx \( (k_{1}^{*}) \). Therefore, for the analysis of the behavior of \( k_{1}^{*} \) by use of IPPA, the IPPA uptake data obtained by scintigraphy in the plateau phase had to be corrected for the regional myocardial blood flow. 

Because the regional \( ^{201}\text{Tl} \) uptake was shown to be proportional to regional myocardial blood flow, we used the parametric image obtained by dividing the background corrected IPPA and \( ^{201}\text{Tl} \) images as a basis for our determinations of \( k_{1}^{*} \). The kinetic properties of the quotient IPPA/\( ^{201}\text{Tl} \) thus obtained are shown in Figure 3. The time course of the quotient IPPA/\( ^{201}\text{Tl} \) detected in humans during a period of 80 minutes is characterized by a steep increase and initial overswing, which are followed by a broad plateau phase. (The initial overswing is probably due to the sequential application of IPPA and \( ^{201}\text{Tl} \), which leads to the time shift in the IPPA and \( ^{201}\text{Tl} \) curves.) The plateau phase begins 6–8 minutes and is finished 25–30 minutes after indicator application. In this period (used for data collection), the ratio of IPPA to \( ^{201}\text{Tl} \) uptake can be considered as constant.

As explained in the Appendix, the parametric image of the quotient IPPA/\( ^{201}\text{Tl} \) is not only a function of \( k_{1}^{*} \) but also of the ratio of IPPA to \( ^{201}\text{Tl} \) plasma concentrations \( (I_{p}^{*} \text{ dt})/(I_{w}^{*} \text{ dt}) \). Therefore, for the quantitative analysis of \( k_{1}^{*} \), it was necessary to correct the parametric image for this ratio. Because the IPPA and \( ^{201}\text{Tl} \) plasma concentrations are the same for all segments of the left ventricular myocardium, we carried out this correction by multiplying the parametric image by a ratio of the count rates registered in the blood regions of interest (aorta) in \( ^{201}\text{Tl} \) \( (I_{b}^{*} \text{ dt}) \) and IPPA \( (I_{b}^{*} \text{ dt}) \) integral images, which were obtained in the first 10 minutes after indicator application. The image thus obtained was used for the quantitative evaluation of the regional distribution of \( k_{1}^{*} \).

**Normal Subjects**

The parametric image of IPPA influx rate constant, \( k_{1}^{*} \), registered in a normal subject (Figure 4) demonstrates a homogeneous distribution of \( k_{1}^{*} \) in left ventricular myocardium. The average left ventricular \( k_{1}^{*} \) was found to be at rest 0.57 ± 0.13/min. This value agrees closely with corresponding data reported by Most and others2 and Wisneski and others.3 By this comparison, we considered that the rate constant for IPPA influx determined in our measurements corresponds to the unidirectional free fatty acid extraction rate determined by Most and others4 and Wisneski and others.4 Similar to the data of Most and colleagues4 and Wisneski and colleagues,3 our data are higher than the extraction rates determined for unlabeled free fatty acids (chemical extraction ratio). This, however, is expected because according to Most and others5 and Wisneski and others6 the chemical extraction ratio

---

**FIGURE 14.** Color scintigram of \( ^{201}\text{Tl} \) in the left anterior oblique 75° projection in same patient as in Figure 13 after infarction.

**FIGURE 15.** Plot of relation between the reciprocal value of the rate constant for 15-(p-\(^{125}\text{I})\text{-iodophenyl})-pentadecanoic acid influx and the amount of free fatty acid supplied to a gram of myocardial tissue in 1 minute \((d_{w} = u \cdot c_{p} \cdot f_{p}; c_{p} \text{ is the free fatty acid plasma concentration; } f_{p} \text{ is plasma flow; and } u \text{ is unit of time}).
underestimates the actual uptake of the free fatty acid by the myocardium because of the release of unlabeled free fatty acid in venous effluent.

The average left ventricular $k_i^*$ was found to decrease with an increasing perfusion rate (Figure 8). These results agree closely with observations of Weiss and others, who found in experiments with isolated canine hearts that a fourfold increase of the perfusion led to a 50% reduction of fatty acid extraction. Weiss and others explained this by the flow-dependent time of exposing the substrate to the myocardium (residence time).

Because our studies were carried out under exercise conditions that may lead to an increase of the arterial lactate levels, one might expect that the changes of influx rate are also influenced by the increase of lactate level in our studies. This possibility was, however, eliminated by the results demonstrated in Figure 10, which indicate that with increasing lactate plasma concentration no significant changes of $k_i^*$ are detectable. These results agree well with findings of Rose and others, who showed that lactate acts as an allosteric inhibitor of long-chain fatty acyl thiokinase, whereas it does not inhibit the sarcocellular transport of palmitate. Fox and others found that under ischemic conditions, under which the intracellular lactate, and free fatty acid levels are high, the efflux of $^{11}$C-labeled palmitate in the first 3 minutes after indicator application increases by 5% at normal conditions to 15% of initially sequestered $^{11}$C-labeled palmitate at ischemia. Thus, the reduction of free fatty acid utilization observed at high lactate plasma levels is probably a consequence of increased free fatty acid influx and not due to decreased free fatty acid influx. Because in our method the influx and not the efflux is assessed, it is evident that the effects of lactate on net sequestration of free fatty acid observed by detection of arterial minus coronary sinus differences cannot be detected with this method.

At a constant flow rate, $k_i^*$ was reduced with increased levels of free fatty acid plasma concentration (Figure 7). The increase of free fatty acid plasma concentration from 200 to 1,200 nmol/ml led to a decrease of $k_i^*$ from 0.78 to 0.4/min. These results indicate that the fatty acid uptake follows with increasing free fatty acid plasma concentrations the saturation kinetics (criterion of facilitated transport).

The literature dealing with the mechanism of the myocardial uptake of nonesterified fatty acid is controversial. Some authors describe it as a passive, diffusional process. On the other hand, experimental evidence has accumulated that suggests that the uptake of fatty acid involves membrane-associated carrier-mediated transport (saturability of fatty acid uptake; competitive inhibition between different fatty acids; inhibition of fatty acid uptake by 1-bromopalmitate or by pretreatment of the cells with trypsin or stilbene compounds. Moreover, Stremmel and Stremmel and others, who isolated a plasma membrane fatty acid-binding protein (40 kDa) from heart myocytes, have demonstrated that the rabbit antibody to the rat plasma membrane fatty acid-binding protein inhibits fatty acid influx in a dose-related manner, and Nunn and others showed that the bacterial mutants deficient in the gene coding for the carrier do not take up long-chain fatty acids. Therefore, by interpretation of our data we assumed that the influx of fatty acid in myocardial tissue is not a simple diffusion process but mainly a carrier-facilitated process.

To relate our data to the variables characterizing the carrier-facilitated process (maximal transport velocity, $V_{max}$, and Michaelis-Menten constant, $K_M$), it was necessary to repeat the IPPA examination in each patient at two different metabolic conditions and to consider that carrier-facilitated process is an enzymatic reaction.

Because Fox and others demonstrated the efflux of nonmetabolized fatty acid from myocardial tissue, the postulated carrier-facilitated process has to be expected to be a reversible one. This type of transport is comparable with a reversible, unimolecular enzyme-catalyzed reaction of the type:

$$S + C_1 \rightleftharpoons (SC)_1 \rightleftharpoons (SC)_2 \rightleftharpoons C_2 + S_2$$

where $S$ is the effective fatty acid concentration in plasma ($S_i$) and tissue ($S_j$). $C$ is the carrier when it is on the blood side ($C_1$) and on the tissue side ($C_2$), and $(SC)$ is the fatty acid–carrier complex on the blood side $[(SC)]]$ and on the tissue side $[(SC)_2]]$.

We assumed that, similar to glucose, the transport of free fatty acid is symmetrical. Under these conditions, the rate constant for the forward reaction, $k_1$, is an example of a unimolecular enzyme-catalyzed reaction described by:

$$k_1 = \frac{V_{max}}{K_M + S_i + S_j}$$

where $K_M$ and $V_{max}$ are the Michaelis-Menten constant and maximal reaction velocity, respectively. The transport of free fatty acid from flowing plasma into myocardial tissue is performed by a membrane-bound (immobilized) carrier. This is a reaction in which the substrate is not homogeneously mixed with an enzyme (carrier). Therefore, neither the input (arterial) nor the output (venous) free fatty acid concentrations can be considered as effective concentrations determining locally the rate of free fatty acid transport ($S_i$). As explained in the Appendix, the best estimate for the free fatty acid plasma concentration that is locally determinant for the transport rate, $S_i$, represents the amount ($a_p$, nmol/g) of fatty acid that is supplied to a gram of myocardial tissue in a unit of time. Thus, the rate constant for fatty acid influx into myocardial tissue, $k_i$, is described by:

$$k_1 = \frac{V_{max}}{K_M + a_p + S_j}$$

where $c_2$ is the free fatty acid tissue concentration.
If it is considered that IPPA is applied in tracer amounts and assumed that the affinity of IPPA to the carrier is the same as that of other fatty acids, then the rate constant for IPPA influx is given by

\[ k_1^* = \frac{V_{\text{max}}^*}{K_M^* + a_p + c_2} \]  

where \( V_{\text{max}}^* \) and \( K_M^* \) are the maximal velocity and Michaelis-Menten constant for IPPA influx, respectively.

Because \( c_2 \) (in dog heart, about 25–32 nmol/g wet wt\(^{32}\)) is very low as compared with \( a_p \) (average, 300 nmol/g), it was, in the first approximation, neglected. Under these conditions, the reciprocal value of \( k_1^* \) is given by

\[ \frac{1}{k_1^*} = \frac{1}{V_{\text{max}}^*} + \frac{1}{V_{\text{max}}^*} \cdot a_p \]  

This relation indicates that if the free fatty acid uptake is a carrier-facilitated process, then \( 1/k_1^* \) is a linear function of \( a_p \). In Figure 15, the values of \( 1/k_1^* \) observed in this study are plotted as a function of \( a_p \). It can be seen that this is a linear relation. (The comparison of the regression line obtained from our data with the data presented by Most and colleagues\(^4\) demonstrated a close correlation.) On the basis of these data, which strongly support the hypothesis that fatty acid uptake is a carrier-facilitated process, it was possible to calculate \( K_M^* \) and \( V_{\text{max}}^* \) for IPPA influx in normal myocardium, which were 470 nmol/g and 430 nmol/g min, respectively.

**Patients With Coronary Artery Disease**

We also determined \( k_1^* \) in patients suffering from coronary artery disease. The results obtained suggest that the free fatty acid extraction is reduced in poststenotic segments. As can be seen in Figure 11 in poststenotic segments, \( k_1^* \) is reduced to 63% of the value in nonaffected segments (the average value observed in poststenotic segments was 57 ± 18% of the value in nonaffected segments). In nonaffected areas, the extraction of IPPA corresponded to values observed in normal subjects examined under the comparable conditions. The reduction of \( k_1^* \) in ischemic segments reflects, at least to some extent, the reduction of free fatty acid utilization caused by an increase of cytoplasmic fatty acid concentration due to decrease in \( \beta \)-oxidation. According to Schelbert\(^{33}\) and Schelbert and others,\(^{34}\) who showed an increased uptake of 2-fluoro-deoxyglucose by ischemic myocardium, this reduction of fatty acid utilization is compensated by an increase of glucose utilization.

Even if the animal studies of van der Vusse and others\(^{32}\) indicate that the ischemia may lead to about a threefold increase of free fatty acid concentration in cytoplasm (\( c_2 \)) (normal \( c_2 \) was 32 nmol/g; under ischemic conditions, a value of 111 nmol/g was detected), it can be demonstrated that these changes of \( c_2 \) alone cannot account for the changes of \( k_1^* \) observed in this study in ischemic areas. Therefore, the possibility should be considered that the reduction of \( k_1^* \) in ischemic areas is due to the changes of \( K_M^* \) and \( V_{\text{max}}^* \).

As can be seen in Figures 11 and 13, the dimensions of \(^{201}\)Tl defects in poststenotic segments and the size of areas with reduced \( k_1^* \) are different. The size of the areas showing reduced \( k_1^* \) significantly exceeded that of the \(^{201}\)Tl-accumulation defects.

In preinfarction and postinfarction studies (Figures 13 and 14), it could be demonstrated that the extension of the \(^{201}\)Tl defects registered after infarction corresponded closely with the size of the areas of reduced \( k_1^* \) detected before the event. This observation suggests that the areas of reduced \( k_1^* \) might reflect the extension of jeopardized myocardium, whereas \(^{201}\)Tl scintigraphy tends to underestimate it.

The results obtained in patients examined before and after revascularization indicate that in the \( k_1^* \) distribution pattern the residual defects are still detectable even if after revascularization the normalization of perfusion and improvement in fatty acid influx rate are observed.

In a preliminary study, we observed in patients with two-vessel disease (LAD and RCA stenosis) after PTCA of LAD the improvement of perfusion and fatty acid extraction even in areas supplied by RCA. Thus, it is suggested that PTCA of the LAD may result in an improvement of the blood flow even within the area supplied by the nontreated coronary artery. In two-vessel disease (LAD and RCA), this potential reaction may be due to the fact that the RCA provides the collateral flow to the poststenotic segments.

These data indicate that 1) in poststenotic segments, free fatty acid extraction is significantly reduced; 2) the extension of free fatty acid extraction defects may be significantly larger than \(^{201}\)Tl defects; and 3) the revascularization leads to normalization of regional free fatty acid extraction.

We expect that in the future the method developed might provide a powerful tool for clinical use and open new insights into the biochemistry of myocardial disease.

**Appendix**

In this section, the model describing myocardial IPPA uptake is developed.

In in vitro experiments in which the myocardial cells are dispersed in the medium with the homogeneously distributed free fatty acids, the influx rate of radioactively labeled free fatty acid into the cell (\( v_i^* \)) was found to be proportional to the radioactively labeled free fatty acid concentration in the solution (\( c_{\text{eff}}^* \)):

\[ v_i^* = \text{const}_1 \cdot c_{\text{eff}}^* \]  

Under in vivo conditions, the albumin-bound fatty acids are transported to the heart in blood plasma. Because of the extraction of free fatty acid
by the myocardial tissue, the distribution of free fatty acid concentration in the capillary cross section is not homogeneous. It has a maximum in the middle of the capillary and a minimum at the capillary wall. Moreover, the average free fatty acid concentration in a capillary cross section decreases from the arterial to the venous side of the capillary. Thus, neither the arterial nor the venous radioactively labeled free fatty acid concentrations can be used for the calculations of \( v_2^* \).

On the other hand, the in vivo measurements indicate that at a constant plasma flow rate \( f_p, \text{ ml/min g} \) the amount of radioactively labeled free fatty acid sequestered in the heart tissue \( (c_2^*, \text{ dpm/g}) \) is proportional to the radioactively labeled free fatty acid plasma concentration \( (c_p^*, \text{ dpm/ml}) \), and at a constant \( c_p^* \) the amount of radioactively labeled free fatty acid sequestered in myocardium is proportional to \( f_p \).\(^{14,15,19} \)

This suggests that under in vivo conditions, the \( v_1^* \) is proportional to the product of \( f_p \) and \( c_p^* \):

\[
\text{\( v_1^* = c_{\text{eff}}^* \cdot c_{p}^* \cdot f_p \, \tag{10} \)}
\]

By comparing Equations 9 and 10, it appears that \( c_{\text{eff}}^* = c_{\text{eff}}^* \cdot c_{p}^* \cdot f_p \), where const is the proportionality factor having dimension min. That is, the average effective local radioactively labeled free fatty acid concentration \( (c_{\text{eff}}^*) \) determining the transport process is proportional to the amount \( (a_p^*, \text{ dpm/g}) \) of radioactively labeled free fatty acid supplied to a gram of tissue in a unit of time \( (a_p^* = u \cdot f_p \cdot c_p^*, \text{ where } u \text{ is the unit of time}) \). Therefore, when the transport of radioactively labeled free fatty acid from the plasma into the myocardial tissue is to be modeled, neither the arterial nor the venous radioactively labeled free fatty acid concentration but rather \( a_p^* \) has to be taken into consideration.

The rate of IPPA accumulation in myocardial tissue is then

\[
\text{\( dc_p^*/dt = (\text{influx rate}) - (\text{efflux rate}) - (\text{metabolic rate}) = \)}
\[
\text{\( k_1^* \cdot a_p^* - (k_2^* + k_3^*) \cdot c_p^* \, \tag{11} \)}
\]

where \( k_1^* \) (min\(^{-1}\)), \( k_2^* \), and \( k_3^* \) are the rate constants for IPPA influx, efflux, and catabolism, respectively.

As our measurements demonstrate, by external detection, during the period from 7 to 25 minutes after indicator application the IPPA acts as an indicator that is trapped in tissue and not further metabolized. Under these conditions, both \( k_2^* \) and \( k_3^* \) can be considered to be zero, \( dc_p^*/dt = k_1^* \cdot a_p^* \) and

\[
\text{\( c_{2t}^*(T) = \int_0^T k_1^* \cdot a_p^* \cdot dt = k_1^* \cdot u \cdot f_p \cdot \int_0^T c_p^* \cdot dt \, \tag{12} \)}
\]

By the use of the double-isotope technique in which a flow indicator \( (201\text{Tl}) \) is administered with IPPA, the flow component in Equation 12 can be eliminated. Because \( 201\text{Tl} \) is trapped in the myocardial tissue, its sequestration is described by

\[
\text{\( c_{2t}^*(T) = k_{1t}^* \cdot u \cdot f_p \cdot \int_0^T c_{p}^* \cdot dt \, \tag{13} \)}
\]

where the \( k_{1t}^*, c_{2t}^*(t), \) and \( c_{p}^*(t) \) are the rate constants for \( 201\text{Tl} \) influx, \( 201\text{Tl} \) tissue concentration, and \( 201\text{Tl} \) plasma concentration, respectively.

By dividing Equation 12 by Equation 13, the following is obtained:

\[
\frac{c_{2t}^*(T)}{c_{p}^*(T)} = k_{1t}^* \cdot \frac{\int_0^T c_{p}^* \cdot dt}{\int_0^T c_{p}^* \cdot dt} \tag{14}
\]

In this relation, in which the flow component is eliminated, the ratio \( \int_0^T c_{p}^* \cdot dt/\int_0^T c_{p}^* \cdot dt \) is identical for all segments of the ventricular wall and can be determined from the amount of IPPA \( (\int_0^T c_{p}^* \cdot dt) \) and of \( 201\text{Tl} \) \( (\int_0^T c_{pp}^* \cdot dt) \) registered in a region of interest selected over a blood region in IPPA and \( 201\text{Tl} \) integral images obtained in the first 10 minutes after indicator application as follows:

\[
\frac{\int_0^T c_{pp}^* \cdot dt}{\int_0^T c_{p}^* \cdot dt} = \beta_p \cdot \frac{\int_0^T c_{p}^* \cdot dt \cdot (1-H_t)}{\int_0^T c_{p}^* \cdot dt} \tag{15}
\]

where \( \beta_p \) is the ratio of the tissue absorption coefficients for \( ^{125}\text{I} \) and \( 201\text{Tl} \); \( c_{p}^* \) and \( c_{pp}^* \) are the IPPA and \( 201\text{Tl} \) blood concentrations, respectively.

Because the accumulation of IPPA in erythrocytes is very low (less than 5% of the total blood activity), the IPPA plasma and blood concentrations can be related to each other by \( c_{p}^* = c_{n}^*/(1-H_t) \), where \( H_t \) is the hematocrit level. On the other hand, shortly after indicator application, the concentration of \( 201\text{Tl} \) in erythrocytes is practically the same as that in plasma, that is, \( c_{p}^* = c_{ipt}^* \). Yet, Equation 15 can be written as follows:

\[
\frac{\int_0^T I_{tp}^* \cdot dt}{\int_0^T I_{tp}^* \cdot dt} = \beta_p \cdot \frac{\int_0^T c_{pp}^* \cdot dt \cdot (1-H_t)}{\int_0^T c_{pp}^* \cdot dt} \tag{16}
\]

The ratio \( c_{p}^*/c_{2t}^* \) in Equation 14 is proportional to the ratio of the amount of IPPA \( (A_2^*) \) and \( 201\text{Tl} \) \( (A_{2t}^*) \) detected in IPPA and \( 201\text{Tl} \) images corrected for the background and crossover effects in a region of interest assigned to myocardium, that is, \( A_2^*/A_{2t}^* = \beta_\text{ip} \cdot c_{p}^*/c_{2t}^* \), where \( \beta_\text{ip} \) is the ratio of tissue absorption coefficients for \( ^{125}\text{I} \) and \( 201\text{Tl} \).

Because \( \beta_\text{ip} \) is approximately equal to \( \beta_t \), the following is obtained:

\[
k_{1t}^* = k_{1t}^* \cdot \frac{A_2^*(T) \cdot \int_0^T I_{tp}^* \cdot dt \cdot (1-H_t)}{A_{2t}^*(T) \cdot \int_0^T I_{tp}^* \cdot dt} \tag{17}
\]

At normal (rest) and low flow rates (ischemic regions), the myocardial uptake of \( 201\text{Tl} \) is linearly related to regional myocardial blood flow\(^{35-37} \); that

\(^{3} \)The value of \( A_2^*/A_{2t}^* \) would be slightly higher than the ratio \( c_{p}^*/c_{2t}^* \) because it is contaminated by the activity in the blood of the myocardium. However, 10 minutes after indicator administration when the registration of static images begins, the concentration of IPPA in blood is much lower than that in myocardium (in animal experiments, a factor of 5 was observed). The blood volume in myocardium amounts to about 20%. Thus, the error that is due to this contamination can be expected to be lower than 4%. Because this value is in the range of experimental error, it was neglected.
is, the extraction fraction of $^{201}\text{Tl}$ (EF$_\text{t}$*) is constant. According to Weich and others,\textsuperscript{33} it is 0.88. At high flow rates, the EF$_\text{t}$* was found to be related to a plasma flow rate by the following:\textsuperscript{20}

$$\text{EF}_\text{t}^* = 0.98 \cdot e^{-0.11F}$$

(18)

where $F = f_p/0.44$ is the plasma flow rate normalized to plasma flow rate of 0.44 ml/min $\cdot$ g.

Because in all these studies the EF$_\text{t}$* was determined in first-pass experiments after application of $^{201}\text{Tl}$ in the left atrium, no significant exchange between plasma and erythrocytes can be expected and the indicator accumulation in heart tissue can be related to the EF$_\text{t}$* by

$$\frac{dc_{\text{t}E}^*}{dt} = \text{EF}_\text{t}^* \cdot f_p \cdot c_{\text{pl}E}^*$$

(19)

$^{201}\text{Tl}$ is trapped in tissue. Thus, the EF$_\text{t}$* is the unidirectional extraction rate, and Equations 13 and 19 can be compared. This comparison indicates that $k_{m}\cdot c_{\text{pl}E}^*$ = EF$_\text{t}^* u$, where $u$ is 1 minute. Consequently, we took $k_{m}\cdot c_{\text{pl}E}^*$ to be 0.88/min for normal and low flow rates and 0.98 $e^{-0.11F}$/min for all other flow rates. To determine F, we considered that according to Equation 19 the ratio of the $^{201}\text{Tl}$ uptake during exercise ($c_{\text{te}E}^*$) and at rest ($c_{\text{tr}E}^*$) is given by

$$\frac{c_{\text{te}E}^*}{c_{\text{tr}E}^*} = \frac{\text{EF}_{\text{te}E}}{F_{\text{tr}E}^*} \cdot f_p \cdot \int_0^t c_{\text{pl}E}^* dt$$

(20)

where EF$_{\text{te}E}$ and EF$_{\text{tr}E}$ are the $^{201}\text{Tl}$ extraction fractions, $f_p$ and $f_r$ the plasma flow rates, and $c_{\text{pl}E}^*$ and $c_{\text{tr}E}^*$ $^{201}\text{Tl}$ plasma concentrations at exercise and at rest, respectively.

By analogy to Equation 17, this equation can be written as follows:

$$\frac{TL_{\text{te}E}^*}{TL_{\text{tr}E}^*} = \frac{\text{EF}_{\text{te}E} \cdot f_p}{\text{EF}_{\text{tr}E} \cdot f_r} \cdot \int_0^t I_{\text{te}E}^* dt$$

(21)

where TL$_\text{te}$* and TL$_\text{tr}$* are the count rates registered in region of interest myocardium and $I_{\text{te}E}^*$ and $I_{\text{tr}E}^*$ are the count rates registered in region of interest blood in exercise and rest $^{201}\text{Tl}$ scintigrams, respectively.

The increase of perfusion rate in normal myocardium was shown to be a linear function of the heart rate.\textsuperscript{39} Therefore, for flow rates at rest, the following relation was considered to be valid in normal myocardium:

$$f_p/f_p^0 = \text{HR}_{\text{r}}/70$$

(22)

where HR$_r$ is the heart rate at rest, and $f_p^0$ is the plasma flow in normal myocardium at a heart rate of 70 beats/min.

After substituting Equations 22 in 21 and after considering that the EF$_\text{t}$* at normal flow rates (EF$_\text{t}^*_{\text{tr}}$) equals 0.88 and that the perfusion rate in normal myocardium at a heart rate of 70 beats/min is about 0.80 ml/min $\cdot$ g\textsuperscript{40} (corresponding to a plasma flow rate 0.44 ml/min $\cdot$ g ($f_p^0$)), the following relation is obtained:

$$\frac{TL_{\text{te}E}^* \int_0^t I_{\text{te}E}^* dt}{f_r HR_{\text{r}}} = \frac{\text{EF}_{\text{te}E} \cdot f_p}{\text{EF}_{\text{te}E} \cdot f_r^0} = \frac{0.98 \cdot e^{-0.11F}}{0.88} \cdot F$$

(23)

This equation was used for the determination of F on the basis of our measurements of $^{201}\text{Tl}$ uptake at exercise and at rest.

References

6. Opie LH: Metabolism of the heart in health and disease: Part II. Am Heart J 1969;77:100–122
12. Knoop F: Der Aufbau aromatischer Fettssäuren in Tierkörper. Freiburg, Buchdruckerei Ernst Kuttruff, 1904
35. Weich HF, Strauss HW, Pitt B: The extraction of thallium-201 by the myocardium. Circulation 1977;56:188–191

KEY WORDS • fatty acid metabolism • fatty acid transport • 15-(p-131I-iodophenyl)-pentadecanoic acid
Regional myocardial free fatty acid extraction in normal and ischemic myocardium.


Circulation. 1988;78:1218-1233
doi: 10.1161/01.CIR.78.5.1218

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/78/5/1218

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/