INVESTIGATIVE NUCLEAR MEDICINE

Myocardial Imaging and Metabolic Studies with [17-^{123}I]Iodoheptadecanoic Acid

Christian Freundlieb, Anton Höck, Karel Vyska, Ludwig E. Feinendegen, Hans-Jürgen Machulla, and Gerd Stöcklin

Nuclear Research Center Jülich GmbH, Jülich, Federal Republic of Germany

After intravenous administration of the stearic acid analogue [17-^{123}I]iodoheptadecanoic acid (I-123 HA), myocardial metabolism was studied in ten normal individuals, eight patients with coronary artery disease and three patients with congestive heart failure. High-quality images were obtained in sequential scintigraphy of I-123 metabolically bound in myocardial tissue. Infarcted zones as well as ischemic regions are indicated by reduced tracer uptake. Iodine-123 in the blood pool and interstitial space consists mainly of radioiodide that is liberated by fatty-acid metabolism and was corrected for. Using the proposed correction not only are the images improved but the uptake and elimination of the I-123 in the myocardial cells can be followed. The average disappearance half-time of I-123 HA from the myocardium of normal persons was 24 ± 4.7 min. In patients with coronary artery disease significant differences between myocardial regions were observed.

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Long-chain free fatty acids (FFA) are an important source for myocardial energy production (*1–3*). Because FFA are efficiently extracted from the blood by the myocardial cells, Evans and coworkers in 1965 proposed the use of labeled FFA for myocardial imaging (*4*). They produced the first scintigrams of the heart with I-131-labeled stearic acid, prepared by addition of iodine to the double bond of oleic acid. Further studies, however—mainly by Poe et al. (*5,6,8,9*) and Robinson and Lee (*7*) and recently by Machulla et al. (*10*)—have demonstrated that the iodination of FFA at double bonds strongly influences myocardial extraction and elimination of the labeled compound. These difficulties restricted the use of radioiodinated FFA almost exclusively to experimental studies.

Initial animal experiments with various labeled FFAs have shown that [17-^{123}I]iodoheptadecanoic acid (I-123 HA), labeled in the ω position with I-123, is taken up by the myocardium almost exactly as is [1-^{11}C]palmitic acid (*10*). Labeling with I-123 permits an excellent external detection of this tracer by any conventional gamma camera, and the radiation exposure of the patient can be kept reasonably low (*8–11*).

This paper presents clinical results using I-123 HA for myocardial studies in normal persons and in patients with heart disease. An image correction for I-123 that is not specifically bound to the myocardial cells is described. It emphasizes the usefulness of I-123 HA for studies of myocardial metabolism (*12*).

MATERIALS AND METHODS

Iodine-123 was obtained from the Swiss Institute of Reactor Research, Würenlingen (Switzerland) or was produced at the isochronous cyclotron of the KFA Jülich by the ^{127}I (d, 6n) ^{123}Xe (β^+, EC) ^{123}I process (*13*). Iodine-123 HA was synthesized by nonisotopic halogen exchange using 17-bromo-heptadecanoic acid as parent compound (*10*). Final high-pressure liquid chromatography was applied for purification and radioanalytical quality control of the labeled product (*14*). Usually 1–2

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For reprints contact: L. E. Feinendegen, MD, Institute of Medicine, Nuclear Research Center Jülich GmbH, P.O. Box 1913, D-5170 Jülich, Federal Republic of Germany.

mCi I-123 HA, dissolved in 2 ml of patient's own serum and sterilized by Millipore filtration, was administered i.v., once per patient.

The patients were placed in the supine position with the chest under the head of an Anger scintillation camera equipped with a high-resolution, low-energy, converging collimator. Anterior and left anterior oblique projections were used. Simultaneously with the injection of I-123 HA, serial imaging was started. In three cases the camera images were triggered using the R wave of the patient's ECG.

For the purpose of correction for I-123 in the blood pool and interstitial space as described below, 0.5 mCi carrier-free $Na^{123}I$ was administered intravenously 30–32 min after the injection of I-123 HA, while serial imaging continued. The total time of measurement was 40–50 min.

For simple myocardial imaging without analysis of tracer washout, a total of up to 800,000 counts were collected 7–10 min after I-123 HA injection. For the myocardial images gated by ECG triggering, only counts recorded in the last third of each cardiac cycle were registered.

All data were stored in list mode and further processed by a computer. Images were replayed in a 64 × 64 matrix with a frame rate of 1/min, corrected for background as described below, and smoothed.

Tracer clearance from the peripheral blood was measured in ten normal persons by counting serial samples of venous blood in a well scintillation counter. Blood samples were taken at regular intervals up to 30 min after I-123 HA administration. Inorganic I-123 was separated from the blood of five of these individuals by high-pressure liquid chromatography, and was counted as usual. The data were expressed as a percentage of the total I-123 in the blood.

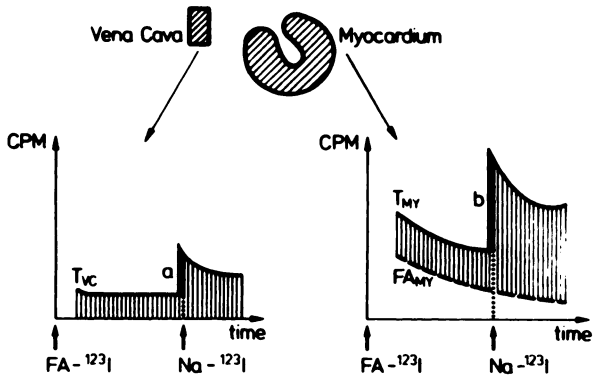
Five female and 16 male subjects, ranging in age from 29 to 84 yr were studied in three groups. Group 1 was composed of ten individuals who showed no signs of heart disease; they had undergone diagnostic workup and were finally treated for noncardiac disorders.

Group 2 consisted of eight patients with coronary artery disease (CAD). The degree of stenosis was estimated by angiography and was 50% or more in at least one vessel. Four of these patients had suffered from myocardial infarction 1–9 yr previously.

Group 3 included three patients with severe congestive heart failure resulting from hypertensive or arteriosclerotic heart disease.

In order to minimize radiation exposure from uptake of I-123 in the thyroid, 500 mg sodium perchlorate were given orally 30 min before the injection of I-123 HA.

Correction for I-123 in the blood pool and interstitial space, i.e., not specifically bound to the myocardial cells. In order to correct the serial images for activity from the I-123 in the blood pool and interstitial space—i.e., for



$$\frac{a}{b} = \frac{T_{VC}}{T_{MY} - FA_{MY}}$$

$$FA_{MY} = T_{MY} - \frac{b}{a} T_{VC}$$

FIG. 1. Correction procedure for nonmyocardial background activity after I-123 HA injection. T_{VC} = count rates over control ROI (vena cava); T_{MY} = count rates over myocardial ROI; FA_{MY} = count rates related to organically bound I-123; *a* and *b* = increments due to $Na^{123}I$ injection.

I-123 that was not bound to the myocardial cells—a special correction method was used. The procedure is based on the quantitative evaluation of the contribution to the image by the pool of inorganic I-123. The principle is diagrammed in Fig. 1. It shows two regions of interest: one the vena cava area, used as a control region outside the myocardium, and the other is the myocardium, where fatty acids accumulate. Both regions are examined after I-123 HA injection and again after injection of $Na^{123}I$. Thus, following i.v. injection of 1–2 mCi I-123 HA, serial scintigrams are made at a rate of one per minute. The two diagrams of Fig. 1 give the counting rates per region as a function of time. The sudden rise of counting rates at 30 min after injection of I-123 HA is due to the second injection, this time of $Na^{123}I$, while serial scintigraphy is continued. The diagrams of the two regions show shaded areas indicating the counting rate per image region related to activity in the blood pool and interstitial space, i.e. free activity. The total counting rate of the myocardial region, T_{MY}, includes both free, or

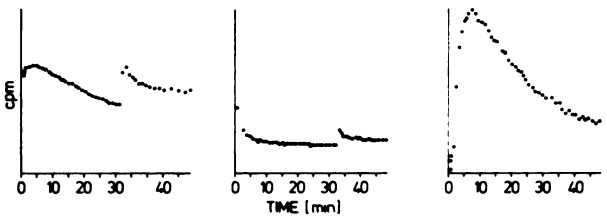


FIG. 2. Time-activity curves after i.v. injection of I-123 HA and (32 min later) $Na^{123}I$. Left, raw myocardial ROI; middle, control ROI; right, background-corrected myocardial ROI.

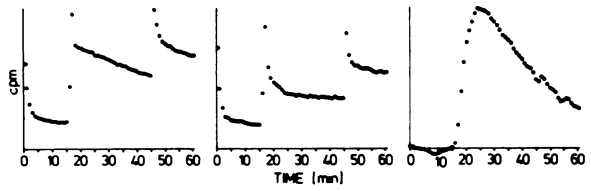


FIG. 3. Quality check for background correction: precordial clearance curves after injection of $Na^{123}I$ 15 min before and 30 min after I-123 HA injection (normal subject). Left and middle: original curves over myocardial and control ROIs. Right: corrected curve over myocardial ROI. Note almost complete suppression of count rates caused by both radioiodide injections.

background, I-123 and I-123 bound to the myocardial cells, the latter being identified as FA_{MY}. It is assumed that the ratio of *a*, the cpm increment in the control region, over *b*, the same in the myocardial region, is proportional to the ratio of free I-123 in the control and myocardial regions. The time course of the nonmyocardial background is given by the time-activity curve, T_{VC}, recorded over the control region. Thus, the time course of the background in the myocardial region is obtained by the expression $b/a \cdot T_{VC}$. The counting rates related to the fatty-acid-bound I-123 in the myocardium (FA_{MY}), is calculated by the formula $FA_{MY} = T_{MY} - b/a \cdot T_{VC}$.

The increments *a* and *b* are obtained by subtracting the count rates recorded during the last 2 min before the I-123 injection from the count rates registered in the second and third minutes after injection.

Figure 2 shows the counting rates from serial images of the myocardial region of interest (left), the caval ROI (middle), and the background corrected counting rates from the myocardial region (right). I-123 HA accumulation and elimination can be easily recognized from the corrected curve.

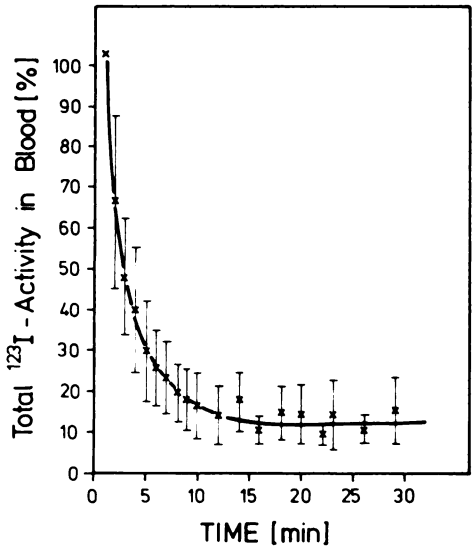


FIG. 4. Blood clearance of I-123 HA after i.v. administration (mean ± s.d.). Data were normalized to value found at 1 min after injection.

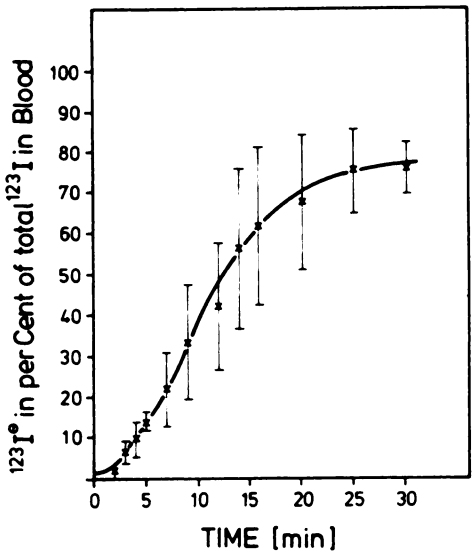


FIG. 5. Relative concentrations of radioiodide in blood after I-123 HA injection, determined by high-pressure liquid chromatography.

In order to test the validity of the correction procedure, one volunteer was given 0.5 mCi $Na^{123}I$ intravenously 15 min before, and again 30 min after, the injection of 1 mCi I-123 HA. The second iodide injection was used for the correction procedure as described above. The extent of the disappearance of the counting rates related to the first iodide injection was used as a quality check of the correction. The original data and the corrected curve are shown in Fig. 3. Clearly in the corrected curve the contributions from the two radioiodide injections are almost completely suppressed.

RESULTS

Blood clearance. The elimination of I-123 from blood of ten normal persons after injection of I-123 HA is summarized in Fig. 4. The counting rates were normalized to the first value, which was measured 1 min after

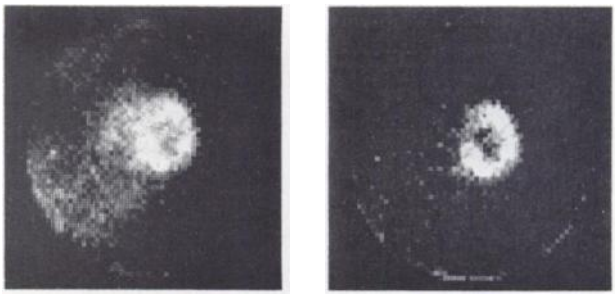


FIG. 6. Anterior images of normal myocardium at 10 min after i.v. administration of 1.5 mCi I-123 HA; (a, left) before and (b, right) after background correction. Collection period: 4 min, giving 600,000 counts.

tracer injection. The elimination of the indicator is characterized by an initial rapid decrease with a half-time of about 2 min. This phase is followed by a period of slower elimination that leads to a plateau averaging 10–15% of the initial value.

The decrease of total I-123 activity in blood is accompanied by a rise of the inorganic I-123 fraction, as shown in Fig. 5. Beyond 15 min after I-123 HA injection, an average of 55–75% of the blood activity is attributed to inorganic I-123.

Imaging. Figure 6 shows typical anterior chest scintigrams after injection of I-123 HA into a normal person: (a) before and (b) after background correction. It is recognized that our background correction results in an optimal contrast between myocardium and the surrounding tissue.

Figure 7 illustrates a corrected and gated image of a normal myocardium: 800,000 counts were collected in diastolic time intervals starting 7 min after injection of 2 mCi I-123 HA.

Figure 8 illustrates the gated and corrected anterior myocardial image of a 63-year-old patient with coronary artery disease who had suffered an apical infarction 9 yr ago. The infarcted area is clearly visualized as an activity defect in the apical region.

Figure 9 presents a nongated but corrected myocardial image of an 84-year-old patient with severe congestive heart failure resulting from arteriosclerotic heart disease. There is a large area of reduced tracer uptake in the anterolateral parts of the left-ventricular wall, whereas the septal and inferior parts of the myocardium show a relatively increased tracer uptake that extends to the wall of the right ventricle.

Figure 10A shows the corrected and gated 60° LAO myocardial image of a 49-year-old patient. One can clearly recognize a reduced I-123 HA uptake in the posterolateral wall. The coronary arteriogram of this patient (Fig. 10B) shows one-vessel disease with 30 and 50% narrowings of the right coronary artery.

The release of organically bound I-123. Figure 11 shows a typical time-activity curve (corrected for blood-pool and interstitial tracer) indicating the release of I-123 from the myocardium. The declining part of the curve can be approximated by a monoexponential function. The half-times of disappearance thus measured in all patients so far examined are given in Table 1. For normal persons the average half-time was 24 ± 4.7 min. The average half-time from the entire myocardium of the patients with coronary artery disease did not differ significantly from this value.

DISCUSSION

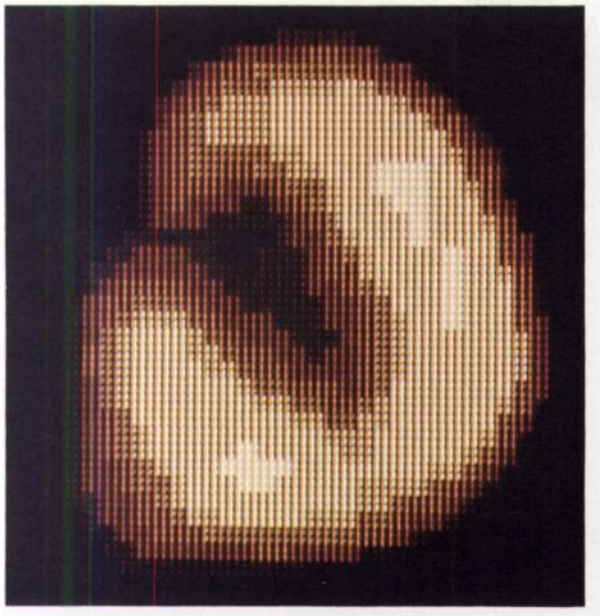
Long-chain free fatty acids play an important role in cardiac metabolism. Apart from their potential as imaging agents, labeled FFA should therefore be valuable for noninvasive studies of cardiac metabolism, provided they retain the biological characteristics of the unlabeled FFA. Labeling with C-11 should be ideal, but optimal imaging using the 511-keV annihilation radiation from C-11 needs special equipment, which currently limits the wider use of C-11-labeled compounds. An I-123 label has the advantage of favorable physical characteristics, permitting easy detection with ordinary imaging systems.

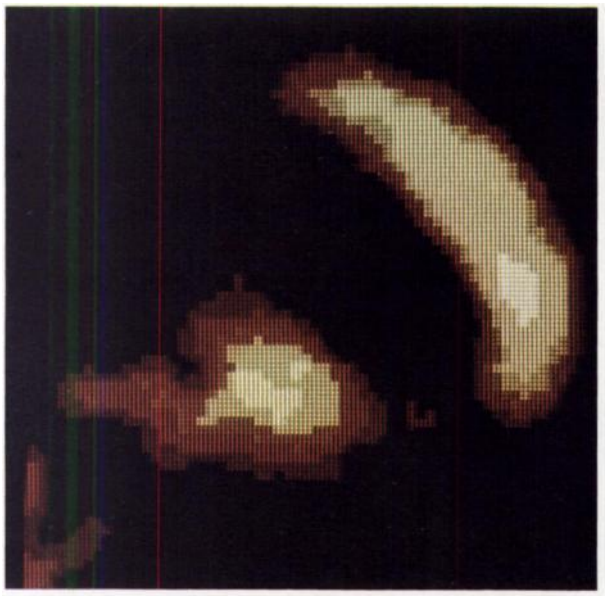
The site of FFA labeling with radioiodine may alter the chemical and biological characteristics of fatty acids (*5,7,10*). Iodination at a double bond or in the alpha position of the carbon chain strongly reduces the myocardial extraction of long-chain FFA. In contrast, long-chain FFA carrying iodine at the terminal carbon atom show an extraction efficiency by myocardial cells that is indistinguishable from that found for C-11-labeled oleic and palmitic acids (*7,10*). To avoid iodine addition to a double bond during the labeling procedure, we decided to label the saturated heptadecanoic acid with I-123 in the ω position. Because of the steric similarities of iodine and the methyl group, both having a radius of about 2 Å, ω-labeled I-123 HA may be considered as a true stearic acid analog. Solution of I-123 HA in a patient's own serum is simple and yields an injectable tracer practically free from hazardous side effects. Moreover, side experiments showed that I-123 HA dissolved in human serum albumin (HSA) solutions accumulated mainly in liver and lung while the uptake in the myocardium was reduced. This finding may be explained by the presence of polymerized and denatured albumin in commercially available HSA solutions.

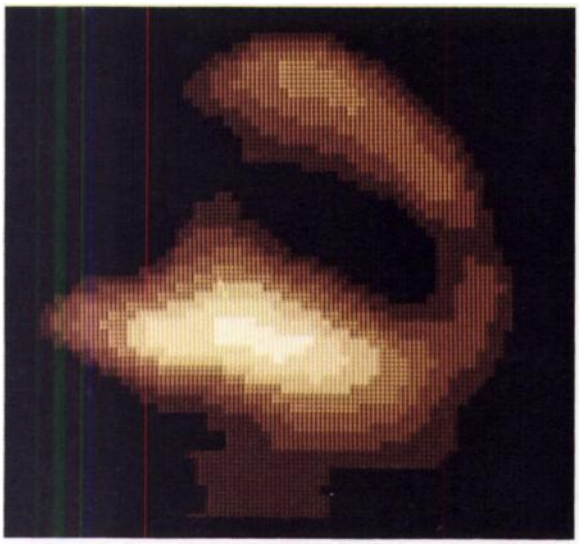
After intravenous injection of I-123 HA there is a rapid tracer accumulation in myocardium and liver and a rapid disappearance of tracer from the blood. Thus myocardial imaging can be started about 5–10 min after tracer injection. Even without further data processing and correction for free I-123, images of comparatively good quality are obtained.

Due to the known metabolic degradation of FFA in the myocardium, the activity over the heart decreases with time. The period during which optimal myocardial images are recorded is limited to the 5–30 min after I-123 HA injection. Following injection of 1 mCi I-123 HA, a normal four-projection study can be completed within 20 min. According to the dosimetry calculations of Poe (*8*), the absorbed radiation dose to the heart amounts to 0.04 rad/mCi and the dose to the whole body is 0.03 rad/mCi.

As with other suitable radiopharmaceuticals, such as K-43, Cs-129, and Tl-201, I-123 HA myocardial scintigrams show old infarct scars as photon-deficient areas. Moreover, in patients with coronary artery disease, ischemic regions may be clearly recognized even in the resting state; in these regions tracer accumulation is also reduced. This is in agreement with the experimental







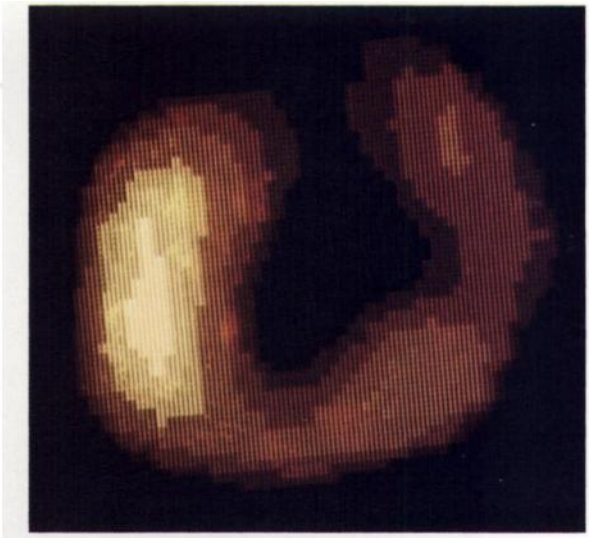


FIG. 7. (Top left) Anterior image of normal myocardium at 7 min after 2 mCi I-123 HA i.v. Background-corrected and gated for diastole only; 800,000 counts total.

FIG. 8. (Center left) Gated I-123 HA anterior projection of myocardium with old apical infarction.

FIG. 9. (Bottom left) Anterior I-123 HA scintigram, ungated but background-corrected, from patient with congestive heart failure. Note reduced tracer uptake in anterolateral part of left-ventricular wall.

FIG. 10. Gated and background-corrected 60° LAO myocardial image (A, top right) and right coronary arteriogram (B, bottom right) of patient with 30 and 50% narrowings in course of RCA. Note reduced I-123 HA uptake in posterolateral wall.

results of Weiss et al. (*15*) who worked with C-11 palmitate in the isolated perfused heart. These results indicate that decrease of coronary perfusion is accompa-

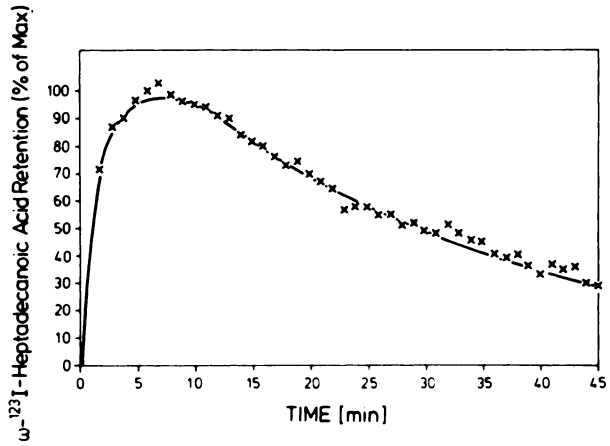


FIG. 11. Typical background-corrected precordial clearance curve of normal individual. Rates are percentages of maximum value. Note that additional injection of 0.5 mCi $Na^{123}I$ at 30 min is not recognizable in this corrected curve.

nied by a marked diminution of myocardial FFA uptake. This decreased uptake is not only an expression of the decreased delivery of FFA due to a decreased blood flow; there is also evidence that in the ischemic myocardium the extraction rate of FFA is reduced (*16,17*). This will enhance the effect of reduced perfusion. Thus in contrast to the situation with glucose, where a decrease of delivery is partially offset by an increase of the extraction rate (*15,16*), myocardial FFA uptake has to be regarded as a very sensitive index of myocardial ischemia.

The quality of the myocardial I-123 HA images can be strongly enhanced by the correction for I-123 in the blood pool and interstitial space, as described above. The rapid increase of radioiodide in blood after injection of I-123 HA indicates the degradation of the I-123 HA. The release of the label is probably the result of β oxidation of FFA, with final deiodination of labeled catabolites (*7*). Twenty minutes after injection of I-123 HA, ~70% of the blood activity is due to inorganic I-123 that enters the inorganic iodine pool. Because this pool is 3–5 times as large as the intravascular space, the result of I-123 release is an appreciable contribution of activity to the relatively large tissue space that is included in a myocardial image. The I-123 in blood and tissue changes with time, and its time course must be known for an optimal correction. Accordingly, we measure it over a nonmyocardial but intrathoracic control region where I-123 HA accumulation is negligible compared with the myocardium. The correction thus performed is possible in only one view per study. As control region the superior vena cava or the aortic root may be chosen, depending upon whether the anterior or the left anterior oblique projection is used. As we show in the control of Fig. 3, the correction for free I-123 is indeed effective. It not only

TABLE 1. CLINICAL DATA AND MYOCARDIAL CLEARANCE HALF-TIMES OF I-123 HA

Subject	Age (yr)	Sex	Diagnosis*	History of infarction	$T_{1/2}$ (min)	
D.H.	60	M	Normal		19.0	
B.H.	48	M	Normal		31.6	
C.G.	29	M	Normal		23.6	
R.R.	47	M	Normal		22.0	Group 1
E.M.	58	M	Normal		27.7	$\bar{x}$: 24.38
L.H.	56	M	Normal		27.5	
K.J.	51	M	Normal		23.4	(±4.72)
B.W.	43	M	Normal		30.0	
P.H.	50	F	Normal		17.0	
L.U.	57	F	Normal		22.0	
S.P.	51	M	CAD	+	21.2	
D.H.	61	M	CAD	+	25.0	Group 2
H.A.	49	M	CAD		21.2	
H.G.	50	M	CAD	+	23.7	$\bar{x}$: 31.80
K.H.	50	M	CAD	+	21.3	(±19.59)
S.S.	45	M	CAD		19.0	
H.H.	58	M	CAD		49.0	
W.H.	51	M	CAD		74.0	
S.H.	84	F	CHF		40.0	
M.E.	78	F	CHF		20.0	Group 3
S.E.	80	F	CHF		26.7	

* CAD = coronary artery disease; CHF = congestive heart failure.

improves the quality of the images, it also makes possible the external monitoring of the accumulation and elimination of the I-123 HA in the myocardium.

The correction technique is statistically sound. A typical 800,000-count myocardial image replayed in the form of a 64 × 64 matrix, contains in the myocardial ROI an average of 415 counts per pixel (range 390–440). The extracardiac background averages 184 c/pixel with a range of ~ ±8% (168–200). After correction, the myocardial ROI averages 183 c/pixel (range 173–193), and the control count falls between 0 and 10 per pixel. The ECG gating, with use of counts in the diastolic period only, improves spatial resolution by minimizing the effects of cardiac movement. The count rates per cardiac cycle are reduced to approximately one third of the values observed in nongated images and this holds true both for myocardial and nonmyocardial regions. The variations in the background are therefore in the same range as in the nongated images, and the background correction suffers from no significant inaccuracies.

The absorbed radiation dose caused by the additional injection of 500 μCi $Na^{123}I$ amounts to 0.02 rad for the whole body and 8 rad for the thyroid (*18*). These values are calculated for a case in which no thyroid-blocking agent is administered.

Myocardial uptake and elimination of I-123 HA is very similar to that observed with[1-^{11}C]palmitic acid (*10*). Since palmitic acid is readily metabolized in the heart and I-123 HA is metabolically accepted, one may conclude that release of the label from the heart after I-123 HA application signals IHA catabolism. The final fate of the labeled catabolite is uncertain, but the similarity of the clearance curves for C-11 palmitic acid and I-123 HA makes it likely that the process of β oxidation leads to an iodinated short-chain carboxylic derivative that is finally deiodinated.

Free fatty acid is also incorporated into triglycerides and phospholipids, but the turnover is relatively slow. It thus appears reasonable to assume that the release of I-123 from the myocardium signals FFA oxidation in the myocardium. From the average half-times of disappearance (24 min in normal subjects) and assuming that about half of the FFA extracted is rapidly catabolized by β oxidation (*17,19*), we calculate a rate constant of about 6%/min for the rapidly oxidizable FFA pool in the myocardium. Values between 8.6 and 19.2%/min were measured in dogs, in which the production of $^{14}CO_2$ in the left-ventricular myocardium after intracoronary C-14 palmitate injection was taken as a parameter (*20*).

In Table 1 the rates of elimination of I-123 from the entire myocardium show few significant differences between normal people and patients with coronary artery disease. This is not surprising since the measurements involved superposition of areas of different perfusion and perhaps of various metabolic states. Differences in the disappearance half-times of the myocardial indicator may be expected if distinct regions of interest are selected. For a quick check of this possibility, the half-times for parts of the myocardium with significant differences of tracer uptake were evaluated separately (Fig. 9). The values were 34 min for the septal-inferior parts and 60 min for the anterolateral region. In a patient with three-vessel CAD, half-times between 20 and 34 min were found for septal-inferior and anterolateral regions. These differences led one to expect that myocardial areas showing I-123 HA defects also show differences in elimination rates of the indicator. The final answer to this question requires regional analysis of multiple small myocardial areas. This work is in progress.

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