Comparison of 17-Iodine-131 Heptadecanoic Acid Kinetics from Externally Measured Time-Activity Curves and from Serial Myocardial Biopsies in an Open-Chest Canine Model

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The relation between the externally measured myocardial time-activity curve and the radiochemically determined kinetics of iodine-131(^{131}I) heptadecanoic acid was studied in an open-chest canine model under different metabolic interventions. Kinetics were assessed by analysis of 12 biopsies taken in an assay period of 90 min. Time-activity curves were fitted with a monoexponential plus constant. The halftime value of the exponential of the external curve corresponded well with the elimination rate of ^{131}I from the myocardium: 14.6 ± 4.5 min vs. 14.6 ± 5.3 min. The constant was build up of three components: free ^{131}I in cardiac tissue, the almost constant activity of the radiolabeled free fatty acid (FFA) in the myocardial lipid pool, and the radioactivity of blood and noncardiac tissues. The contribution of blood and noncardiac tissue to the constant amounted to a mean value of 77%. These findings support the analysis of externally measured time-activity curves with a monoexponential plus constant curve fit, in which background correction is not necessary. In cases where lipid storage is predominantly present, high $T_{½}$ values, both internally and externally, were found, which were fitted with a monoexponential curve. It can be concluded that externally measured time-activity curves reflect satisfactorily the kinetics of radioiodinated heptadecanoic acid.

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In the past decade the interest in myocardial metabolism has increased. An important stimulus was the availability of radiolabeled free fatty acids enabling the exploration of myocardial metabolism in a noninvasive way. One class of fatty acids are the radioiodinated free fatty acids (*1,2,3*). After i.v. injection of fatty acids labeled with radioiodide in the terminal position, the uptake by the myocardium is about the same as found for natural fatty acids (*4,5*). The extracted fatty acids are partly stored in lipids and partly oxidized (*6*). In the latter process radioiodide is released from the fatty acid and leaves the myocardium (*7,8*), most probably by passive diffusion. The radioiodide can be detected with a gamma camera and a time-activity curve is generated by plotting the count rates as a function of time.

In patient studies differences in half-time values are found between normal, ischemic, and necrotic myocardial regions (*9,10,11,12,13,14*). The half-time values also change in patients with cardiomyopathy (*15,16*), during infusion of glucose/insulin (*17*), after acute ethanol consumption (*18*), and after rehabilitation training in patients with myocardial infarction (*19*).

Animal experiments have been performed to increase the knowledge of the metabolic pathways of radioiodinated free fatty acids and to elucidate an interpretation of external time-activity curves (*8,20,21,22,23,24*). Nevertheless, the correlation between time-activity curves measured with a gamma camera and the actual kinetics of radiolabeled free fatty acid in myocardium and blood, has not been studied extensively. This relation is important for correct interpretation of the time-activity curves of patients.

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Thus, the aim of the present study was to elucidate the relation between a myocardial time-activity curve, measured externally and the underlying kinetics of radioiodinated fatty acids, measured radiochemically.

MATERIALS AND METHODS

The 17-iodo-heptadecanoic acid (IHDA) labeled with iodine-131 (^{131}I) in the terminal 17-position was prepared as described earlier (*23*). Fifteen mongrel dogs were studied after 24 hr of fasting. After premedication with 10 mg methadon and 15 mg droperidol i.m., dogs were anaesthetized with nitrous oxide and oxygen, together with i.v. droperidol, methadon and lidocaine. Blood pressure was monitored via catheters in the femoral artery and femoral vein. A coronary sinus catheter was introduced under fluoroscopy to obtain venous blood samples.

Thoracotomy was performed at the left fifth intercostal space. The pericardium was opened widely and fixed to the chest wall to form a cradle. By means of an external pacemaker the heart rate was maintained at 150 bpm. After injection of 4–10 mCi IHDA via the cephalic vein, myocardial biopsies were obtained with a fast spinning hollow needle as described earlier (*6,7*). The average weight of the biopsies was 60 mg. The biopsies were taken at 0.5, 1, 2, 3, 5, 10, 20, 30, 45, 60, 75, and 90 min after injection. Arterial and coronary sinus blood samples of 2 ml were drawn simultaneously.

The biopsies were immediately stored on a surface cooled in liquid nitrogen and subsequently weighed and counted in a gamma well counter. Thereafter the biopsies were ground while adding methanol/chloroform 1/2 (v/v) and acidified urea 40%. The aqueous fraction containing free iodide, the pellet, and the organic fraction containing lipids were separated by means of centrifugation.

Blood samples were stored on melting ice. After centrifugation, 0.2 ml aliquots of plasma samples were counted and the plasma lipids were separated from the free radioiodide by means of centrifugation. All fractions were counted in a gamma well counter. Radioactive contents of the biopsies, blood plasmas, aqueous (iodide), and organic (lipid) fractions were expressed as cpm/mg/mCi of injected IHDA.

At the start of the experiment and 90 min later, cardiac output was determined using the thermodilution method. Arterial and coronary sinus samples drawn at 0 min (moment of administration of IHDA) and at 90 min were analyzed for substrate concentrations of unlabeled FFA, glucose, and lactate. From the analysis of arterial and coronary sinus samples, the extraction fractions of the various substrates were calculated.

During the experiment the right side of a dog was positioned over a gamma camera with a parallel-hole collimator. Registration of scintigrams of 1-min duration took place during the assay period of 90 min.

To enhance the ranges of the parameters of the time-activity curves the effects of several metabolic interventions were studied in five groups of dogs. Group 1: control dogs, n = 4, no intervention; Group 2: infusion of glucose/insulin, n = 4, glucose levels were kept above 8 mmol/l; Group 3: dipyridamol 20 mg/hr, n = 2; Group 4: noradrenalin 0.25 μgr/kg/hr, n = 2; Group 5: infusion of sodium lactate, n = 3, lactate levels were maintained above 6 mmol/l.

Data analysis

After summing up the first ten scintigrams, a region of interest (ROI) was drawn comprising the whole heart. Both from the scintigraphic registration and from the radioactive contents derived from the biopsies, time-activity curves were generated. The time-activity curves derived from the scintigrams, from the biopsy samples measured prior to grinding, from the free iodide in the aqueous phase, and from the lipid fraction were fitted either with a monoexponential plus constant or a monoexponential curve whenever appropriate. From the curve fit with a monoexponential plus constant, both the half-time ($T_{½}$) value of the monoexponential and the ratio of the amplitude (A) of the monoexponential and the total activity (amplitude plus constant A+C) expressed in % (A/A+C) were calculated. From monoexponential curve fitting only the $T_{½}$ value was studied. Time-activity curves of the biopsies and arterial plasma were fitted starting at the maximum of the curve, and the curves derived from the scintigrams were fitted beginning 10 min after administration of the IHDA.

Extraction fractions were calculated as the difference between arterial and coronary sinus count rate expressed as a percentage of the arterial count rate.

To test differences between internally (radiochemical) and externally (scintigraphic) measured halftime values, the paired t-test was applied.

RESULTS

Hemodynamic and Substrate Data

In Table 1 the mean arterial blood pressure and cardiac output are given at the start of the experiment (0 min) and at the end of the experiment (90 min). Arterial concentrations and extraction fractions of free fatty acid, glucose, and lactate are given in Table 2. The extraction fractions of IHDA in the groups are shown in Table 3.

Scintigrams

In Figure 1 (upper panel) an example of the scintigraphically measured time-activity curve of a control dog is presented. The time-activity curve is composed of two components. The decreasing exponential repre-

TABLE 1
Hemodynamic Measurements in the Groups

		Mean Arterial Blood Pressure in mm Hg		Cardiac Output in 1/min	
Intervention	n	0 min mean ± s.d.	90 min mean ± s.d.	0 min mean ± s.d.	90 min mean ± s.d.
Control	4	98 ± 7	89 ± 11	5.0 ± 1.2	5.2 ± 1.8
Glucose	4	98 ± 24	85 ± 8	5.4 ± 1.5	4.7 ± 1.2
Dipyridamol	2	81 ± 17	74 ± 9	4.5 ± 0.1	5.2 ± 0.3
Noradrenalin	2	138 ± 17	110 ± 5	4.6 ± 0.1	5.8 ± 0.1
Lactate	3	95 ± 13	92 ± 28	4.0 ± 0.4	4.8 ± 1.6

TABLE 2
Arterial Substrate Concentrations and Extraction Fractions

Intervention	n	Concentration in mmol/l		Extraction fraction in %	
		0 min mean ± s.d.	90 min mean ± s.d.	0 min mean ± s.d.	90 min mean ± s.d.
Free fatty acids					
Control	4	0.44 ± 0.26	0.36 ± 0.11	56 ± 16	53 ± 26
Glucose	4	0.20 ± 0.31	0.17 ± 0.23	31 ± 21	12 ± 15
Dipyridamol	2	1.61 ± 1.39	0.07 ± 0.01	22 ± 21	25 ± 35
Noradrenalin	2	2.40 ± 1.38	1.33 ± 0.52	27 ± 4	25 ± 4
Lactate	3	0.32 ± 0.14	0.20 ± 0.09	8 ± 34	4 ± 37
Glucose					
Control	4	6.8 ± 2.4	5.9 ± 1.1	2 ± 6	−5 ± 3
Glucose	4	9.1 ± 1.9	13.6 ± 5.0	−6 ± 1	1 ± 5
Dipyridamol	2	5.9 ± 0.8	6.3 ± 1.2	1 ± 8	1 ± 5
Noradrenalin	2	5.2 ± 2.0	6.5 ± 0.9	2 ± 0	5 ± 4
Lactate	3	6.7 ± 1.2	7.8 ± 2.7	3 ± 4	2 ± 9
Lactate					
Control	4	1.4 ± 0.7	1.8 ± 1.2	25 ± 21	13 ± 15
Glucose	4	1.2 ± 0.6	1.4 ± 0.5	15 ± 48	26 ± 13
Dipyridamol	2	0.8 ± 0.4	1.0 ± 0.1	14 ± 1	41 ± 2
Noradrenalin	2	0.7 ± 0.1	1.0 ± 0.1	27 ± 1	4 ± 8
Lactate	3	8.4 ± 3.2	6.7 ± 5.0	14 ± 8	37 ± 9

sents the fast part and the constant represents the slow part. In this example the $T_{½}$ value was 11.5 min and A/A+C was 66%. In the intervention studies with infusion of glucose, dipyridamol, and noradrenalin, the same course of the time-activity curves was found. In the lactate group the time-activity curves revealed a monoexponential course (Fig 1, lower panel). The results of the different groups are presented in Table 4. In the lactate group the range of scintigraphic $T_{½}$ values was 168–500 min and in the remaining groups the range of $T_{½}$ values was 10.6–24.0 min and the range of A/A+C ratios 7.8–65.1%.

Myocardial Biopsies

In Figure 2 (upper panel) the time-activity curves of the total radioactivity and the radioactive contents of the lipid and aqueous fractions of the biopsies of a control dog are depicted. The statistical means and standard deviations of data derived from the myocardial biopsies and scintigrams are shown in Table 4.

A further subdivision of the myocardial radioactivity into the aqueous and lipid phases is presented in Table 5. A monoexponential plus constant course was found

TABLE 3
Extraction Fractions of Radiolabeled IHDA

Intervention	n	5 min mean ± s.d.	10 min mean ± s.d.	20 min mean ± s.d.
Control	4	40 ± 16	51 ± 13	38 ± 15
Glucose	4	43 ± 25	12 ± 19	4 ± 27
Dipyridamol	2	42 ± 12	40 ± 8	19 ± 9
Noradrenalin	2	29 ± 1	31 ± 7	19 ± 9
Lactate	3	29 ± 9	12 ± 2	−5 ± 12

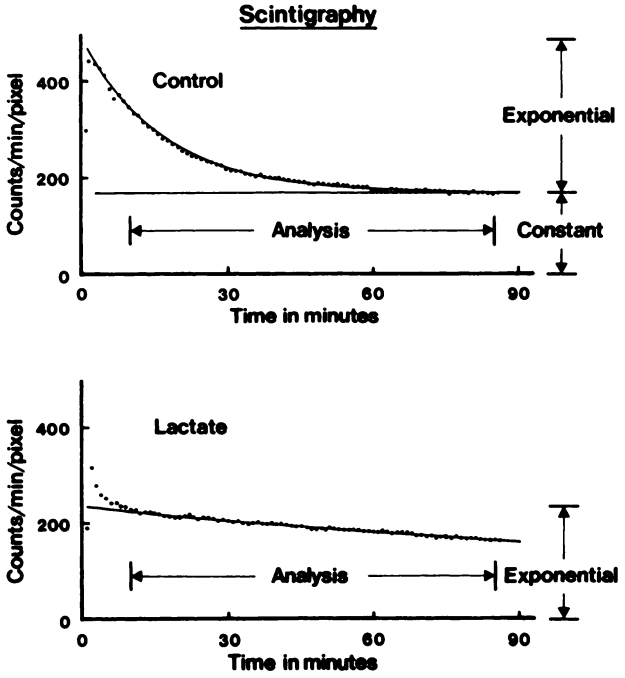

FIGURE 1
Time-activity curves from scintigraphy. Control dog (upper panel); increased lactate level (lower panel).

TABLE 4
Analysis of Externally and Internally Measured Time-Activity Curves

Intervention	n	Scintigraphy		Biopsies	
		$T_{½}$ in min mean ± s.d.	A/A+C % mean ± s.d.	$T_{½}$ in min mean ± s.d.	A/A+C % mean ± s.d.
Control	4	14.0 ± 2.3	54.6 ± 10.2	14.6 ± 3.1	83.0 ± 5.4
Glucose	4	15.3 ± 16.0	42.1 ± 23.5	15.6 ± 8.5	68.3 ± 28.9
Dipyridamol	2	11.2 ± 0.9	64.5 ± 0.4	10.2 ± 3.5	88.8 ± 4.5
Noradrenalin	2	18.2 ± 6.9	43.5 ± 3.4	17.2 ± 0.7	80.1 ± 5.7
Lactate	3	316 ± 168		337 ± 330	

A/A+C:
A = amplitude monoexponential.
C = constant.

for the total radioactivity and the aqueous fraction. In contrast, the lipid fraction showed a monoexponential course. In Figure 2 (lower panel) the same information is presented for a dog from the lactate group.

Arterial Plasma

The time-course of radioactivity in arterial plasma and the results of the curve fitting in one of the dogs of the control group are shown in Figure 3 and the results in the separate groups in Table 6. The highest $T_{½}$ value in the total group was 1.8 min.

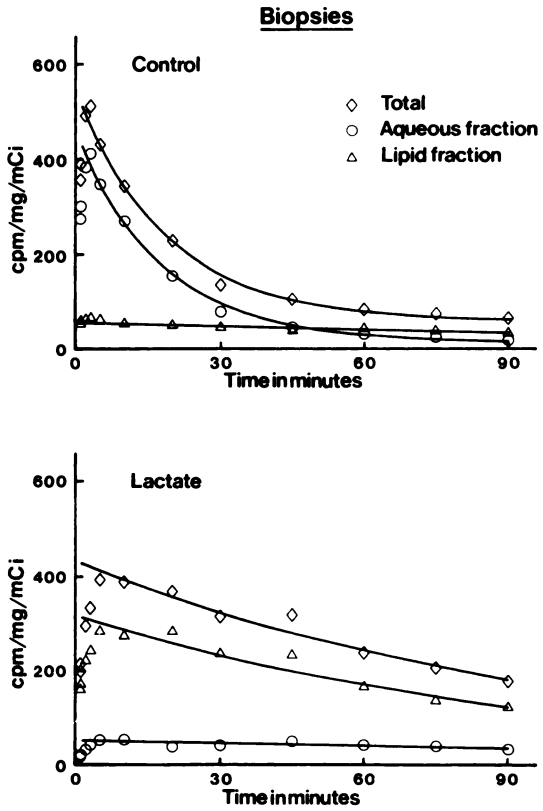

FIGURE 2
Time-activity curve from biopsies. Control dog (upper panel); increased lactate level (lower panel).

Relation Between Scintigraphy and Kinetics of IHDA

In Figure 4 the $T_{½}$ values from the scintigrams are compared to the $T_{½}$ values derived from the total radioactivity curves of the myocardial biopsies. For the control and intervention groups other than lactate, the mean $T_{½}$ value ± s.d. from the scintigraphic data was 14.6 ± 4.5 min and from the myocardial biopsies, 14.6 ± 5.3 min. The t-test revealed a 95% confidence interval for the difference between internally and externally measured halftime values of −2.4 min to 2.4 min.

For the lactate group these values are: scintigraphy 316 ± 168 min and biopsies 337 ± 330 min.

The relation between the A/A+C values from scintigrams and total radioactivity of myocardial biopsies is depicted in Figure 5. After applying linear regression, the correlation coefficient was found to be 0.92.

DISCUSSION

For understanding the time-activity curves of IHDA scintigrams, two factors have to be known: 1) the kinetics of IHDA and its metabolites during the assay period, and 2) the contribution of background radioactivity, i.e., noncardiac tissues and blood, to the original myocardial time-activity curve. For these reasons dogs were studied in which scintigraphy and biopsy-analysis were performed simultaneously.

Scintigraphy

Scintigraphic curves have been analyzed using a monoexponential or biexponential curve fit. In a recent study we demonstrated that a monoexponential did not fit the time-activity curve adequately and we demonstrated further that biexponential curve fitting lacked precision because more than one pair of half-time values for the fast and slow exponential could be found for the same curve (*25*). Moreover, we demonstrated that the applied background correction procedures are incorrect (*26,27*). The optimal analysis proved to be a monoexponential plus constant without previous back-

TABLE 5
Results of Curve Fitting of Internally Measured Time-Activity Curves in Control and Intervention Groups

		Total activity		Aqueous fraction		Lipid fraction
Intervention	n	$T_{½}$ in min mean ± s.d.	A/A+C % mean ± s.d.	$T_{½}$ in min mean ± s.d.	A/A+C % mean ± s.d.	$T_{½}$ min mean ± s.d.
Control	4	14.6 ± 3.1	83.0 ± 5.4	13.2 ± 3.5	95.1 ± 2.1	97.1 ± 30.4
Glucose	4	15.6 ± 8.5	68.3 ± 28.9	9.4 ± 1.7	83.9 ± 24.9	114.2 ± 52.3
Dipyridamol	2	10.2 ± 3.5	88.8 ± 4.5	9.1 ± 3.2	95.7 ± 2.1	85.2 ± 18.7
Noradrenalin	2	17.2 ± 0.7	80.1 ± 5.7	14.8 ± 0.6	90.6 ± 5.7	115.9 ± 48.6
Lactate	3	337 ± 330				335 ± 327

A/A+C:
A = amplitude monoexponential.
C = constant.

ground correction. In the present study a monoexponential plus constant course of the external and internal time-activity curve was found. In dogs with lactate infusion this course degraded to a monoexponential course and a constant could not be found. The latter results do not implicate the absence of a constant, but, because of the low discrimination power of the curve fitting method (noise), only monoexponential curve fitting could be accomplished.

In the presence of noise, the discrimination power of curve fitting with one or more exponentials, such as here, will decrease with increasing $T_{½}$ values. While the $T_{½}$ values in the control study and during interventions other than lactate were in the 10.6–24.0 min range, in the lactate group a range of 168–500 min was found. Thus, the finding of a monoexponential in the lactate group can be attributed to the high $T_{½}$ values compared to the acquisition time. For an accurate determination of the half-time value, the assay period should be more than two times the half-time value (*28*).

Myocardial biopsies

The time-activity curves of the total radioactivity of biopsies show a monoexponential plus constant course, except in the lactate group. From the upper panel of Figure 2, it is concluded that the monoexponential part of the total radioactivity is related to the radioactivity in the aqueous fraction. The constant of the total radioactivity is build up of the radioactivity of the lipid fraction and the constant of the aqueous fraction. At the peak of total myocardial radioactivity, the contribution of the lipid fraction to the total myocardial radioactivity is <20%, as can also be deduced from the high A/A+C ratios in Table 5.

Because the time-activity curve of the aqueous fraction is a monoexponential plus constant and the time-activity curve of the lipid fraction a monoexponential, the time-activity curve of the total radioactivity is the sum of two exponentials plus a constant. Thus, curve fitting should have revealed a biexponential plus constant. However, the signal to noise ratio of the total radioactivity is too low to calculate the two exponentials. The same holds for the scintigraphic time-activity curves. As a consequence a monoexponential plus constant has been found.

In the lactate group a different pattern emerges. In

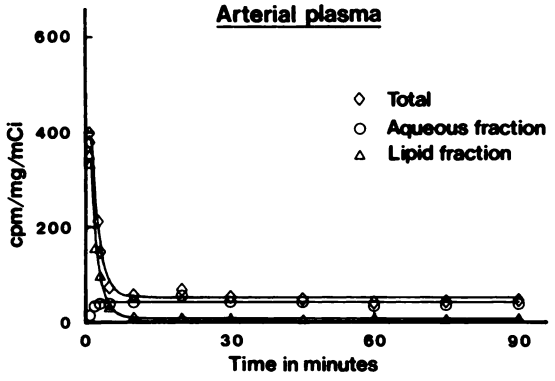

FIGURE 3
Time-activity curves from arterial plasma.

TABLE 6
Total radioactivity in arterial plasma

Intervention	n	$T_{½}$ in min. mean ± s.d.	A/A+C % mean ± s.d.
Control	4	1.2 ± 0.2	93.0 ± 1.0
Glucose	4	1.0 ± 0.5	92.9 ± 1.5
Dipyridamol	2	1.5 ± 0.1	93.2 ± 1.8
Noradrenalin	2	1.4 ± 0.1	92.7 ± 1.2
Lactate	3	1.7 ± 0.2	91.6 ± 0.6
Total	15	1.3 ± 0.3	92.8 ± 1.2

A/A+C :
A = amplitude monoexponential.
C = constant.

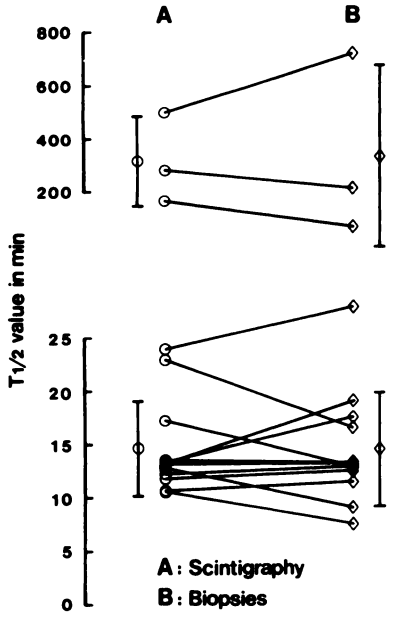

FIGURE 4
Comparison of $T_{½}$ values of externally and internally measured time-activity curves.

this group, the aqueous fraction is small and the total myocardial radioactivity is mainly dictated by the radioactivity of the lipid fraction.

Free ^{131}I, found in the aqueous fraction, showed also a monoexponential plus constant course. This course suggests a passive elimination of free ^{131}I from the myocardium by diffusion. In studies of isolated perfused guinea pig hearts, Kloster et al. found that the diffusion of the halide from the mitochondria to the blood was the rate-determining step in halofatty acid turnover in normal myocardium (*8,21*). Visser et al. studied the kinetics of IHDA in open-chest dogs and concluded that the washout of free radioiodide determines the elimination rate found in scintigraphy (*6, 23*). Our present results confirm the earlier results of Kloster and Visser. A two-compartment model is sufficient to explain these findings. One compartment

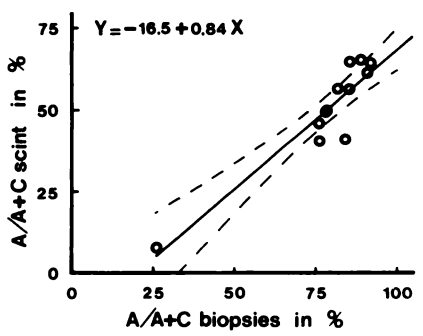

FIGURE 5
Relation of A/A+C ratios of externally measured time-activity curves and the internal A/A+C ratio. Broken lines indicate the 95% confidence interval.

represents the mitochondrial space of the myocardium and the second compartment represents the blood pool together with noncardiac tissues. See also Appendix 1. In this model the course of the radioactivity in the compartment representing the myocardium indeed follows a monoexponential plus constant course. The $T_{½}$ value depends on the diffusion parameters, including diffusion constant, area and diffusion pathway, and the constant is the resulting radioactivity in both compartments after diffusion has been completed and depends on the capacities of the compartments.

The lipid fraction showed a monoexponential course with a $T_{½}$ value in the order of 85 min or more.

Arterial Plasma

The course of radioactivity in arterial plasma revealed a monoexponential plus constant course. Separating arterial plasma into a lipid fraction and an aqueous fraction revealed that the exponential found in plasma represents the lipid fraction and the constant the aqueous fraction, Figure 3. Due to a fast elimination rate (mean $T_{½}$ = 1.3 min), the radioactivity in blood is almost constant after 10 min. Therefore, scintigraphically measured time-activity curves were analyzed starting at the tenth minute.

Relation Between Scintigraphy and Kinetics of IHDA

To maintain the condition of the dog hearts in our experiments as optimal as possible, only 12 biopsies were taken in an acquisition time of 90 min. Because of this small number of biopsies, the $T_{½}$ values of the biopsies could only be calculated with a limited precision and, thus, discrepancies between the scintigraphic $T_{½}$ values and those of the biopsies can be expected, Figure 4. Nevertheless the mean values correspond well.

During the intervention with lactate only low radioactivity was found in the aqueous fraction. The radioactivity in the myocardium was mainly found in the lipid pool, which had a slow turnover rate. This corresponds with the time-activity curves of the scintigram where high $T_{½}$ values were found. In an acquisition time of 90 min these $T_{½}$ values are too high to distinguish between the radioactivity contents from the myocardium and blood. Consequently, a monoexponential course was found.

A linear relationship was found between the A/A+C ratio measured scintigraphically and the A/A+C ratio found in the biopsies. The A/A+C ratio derived from the external time-activity curve is small compared to the A/A+C ratio of the biopsies, due to the presence of background radioactivity in the scintigram.

From the external (scintigram) and internal (biopsies) A/A+C ratios the contribution of background to the constant was calculated to be 77% ± 6%, Appendix 2.

The constant of the scintigram is buildup of three components, the constant of free ^{131}I in cardiac tissue, the almost constant radioactivity of the myocardial lipid

pool, and the constant radioactivity in blood together with the activity of noncardiac tissues.

Extrapolation to Human Studies

The purpose of the study was to demonstrate that the external time-activity curve reflects myocardial kinetics of IHDA. Grossly, IHDA kinetics is characterized by oxidation with a fast clearance rate and lipid storage with a slow clearance. In a previous study we have demonstrated that the external time-activity curve found in humans can be described by a monoexponential plus constant (*25*). As the same type of curve was found in this animal study, we may assume that scintigraphic curves adequately reflect IHDA kinetics in man.

Most methods of analyzing time-activity curves depended on a preceding correction for background activity. Several methods have been applied, one of the most popular methods is based on the administration of radioiodide near the end of the acquisition period of the scintigrams (*29*). In a previous study (*26*), we demonstrated that this method of background correction lacks the necessary precision. In many studies, after correction for background activity, monoexponential curve fitting has been applied (*12,13,15,16,17,18,19,20, 30*). But, from the results of the present study, we conclude that even after perfect correction for the activity of free ^{131}I in noncardiac tissue and the radioactivity in blood, the remaining activity curve is composed of the monoexponential (free iodide) plus a constant (lipids). A commonly used parameter is the size of the oxidation pool derived from the external time-activity curve. Due to the major contribution of background radioactivity to the constant, only gross changes in oxidation and storage can be seen. Although gross, the changes in relative size of the oxidation pool have been demonstrated by us in a paired patient study with glucose intervention (*31*). During ischemia, uptake of the fatty acid in the myocardium is decreased, again increasing the influence of background radioactivity. On the other hand, during ischemia, the radiolabel is mainly stored in lipids. These curves resemble the curves during lactate intervention and are thus clearly different from normal curves.

CONCLUSION

The course of the external as well as the internal time-activity curve obeys a monoexponential plus constant curve. Only in cases where lipid storage is predominantly present, a monoexponential curve has been found.

The results of our studies have shown that the half-time value of the external time-activity curve corresponds with the half-time value calculated from the time-activity curve of biopsies. In addition, the A/A+C ratio of the external time-activity curve is linear (first order approximation) related to the A/A+C ratio of the internal time-activity curve. Finally, we have shown that the mean 77% of the externally measured constant originates from the background. It can be concluded that externally measured time-activity curves reflect satisfactorily the kinetics of radioiodinated heptadecanoic acid.

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APPENDIX 1

A simple model of the diffusion of radioiodide is given in Figure 6. M represents the mitochondrial space of the myocardium and B the blood pool and all tissues into which radioiodide diffuses.

At time t = 0 radioiodide, as an end product of oxidation, is present in M but not in B. Assuming that transport of radioiodide from M to B is completely accomplished by diffusion, the radioiodide content of M as a function of time can be calculated with the help of an electrical model (Fig. 6 lower part). The amount of radioiodide in M at time t is designated by $Q_M(t)$ and at time t = 0 with $Q_M(0)$, the initial amount of radioiodide in the mitochondrial compartment. C_M and C_B are the capacities for radioiodide of M and B, respectively.

After solving the differential equation we find:

$$Q_M(t) = Q_M(0)[K1 + K2 \exp(-K3.t)]$$

in which:

$$K1 = C_M / (C_M + C_B),$$

$$K2 = C_B / (C_M + C_B) = 1 - K1,$$

$$K3 = (C_M + C_B) / (R \cdot C_M \cdot C_B) = 1n2 / T_{½},$$

or

$$T_{½} = 1n2 \cdot R \cdot C_M \cdot C_B / (C_M + C_B)$$

$T_{½}$ is the half-time value of the exponential part of $Q_M(t)$.

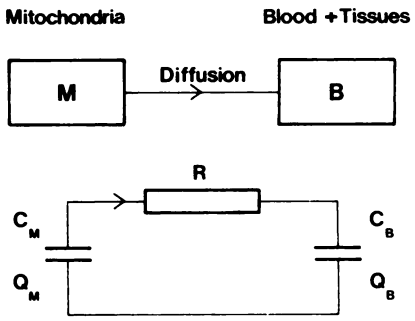

FIGURE 6
Model of radioiodide diffusion.

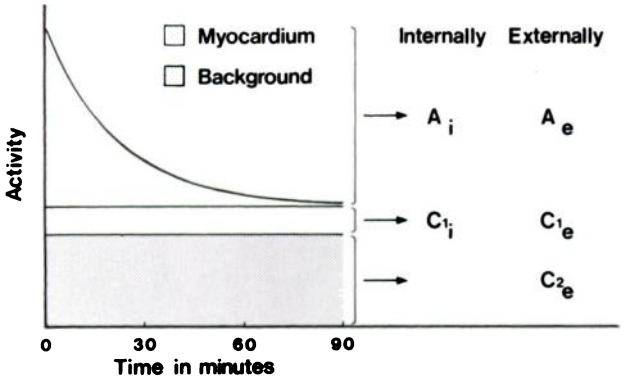

FIGURE 7
Calculation of the contribution of background to the scintigraphic time-activity curve.

C_B also receives radioiodide from other organs than the heart, increasing $Q_B(t)$. Because the radioactivity in blood increases within the first few minutes and remains constant thereafter, the behavior of other organs does not influence the results found with this model.

From these results can be concluded:

1. The course of radioiodide in the mitochondrial compartment is build up of two components, an exponential, and a constant.

2. The half-time value $T_{1/2}$ depends on R (diffusion) and the capacities C_M and C_B in series. Because $C_M << C_B$, C_M is the capacity which, in combination with R, determines the half-time value $T_{1/2}$.

APPENDIX 2

Contribution of background to the scintigraphic constant.

Curve fitting of the time-activity curve of the total radioactivity in the biopsies resulted in an amplitude A_i and a constant Cl_i (Fig. 7). Thus the internal A/A+C ratio is:

$$A_i/A_i+C1_i.$$

Externally an amplitude A_e is found and a constant $C1_e + C2_e$, where $C1_e$ is the contribution of myocardial tissues and $C2_e$ the contribution of background. While A_i is expressed in cpm/mg/mCi, A_e is expressed in cpm/pixel. Hence A_i and A_e are equivalent but not equal. The conversion of internal to external can be done by using:

$$A_i/A_e = C1_i/C1_e.$$

Because both internal and external A/A+C ratio's are known, $C2_e$ as a percentage of $C1_e + C2_e$ can be calculated.

REFERENCES

1. Evans JR, Gunton RW, Baker RG, et al. Use of radioiodinated fatty acid for photoscans of the heart. *Circ Res* 1965; 16:1–10.
2. Robinson GD, Lee AW. Radioiodinated fatty acids for heart imaging: iodine monochloride addition compared with iodide replacement labeling. *J Nucl Med* 1974; 16:17–21.
3. Poe ND, Robinson Jr GD, MacDonald NS. Myocardial extraction of labeled long-chain fatty acid analogs. *Proc Soc Exp Biol and Med* 1975; 148:215–218.
4. Machulla HJ, Stöeklin G, Kupfernagel Ch, et al. Comparative evaluation of fatty acids labeled with C-11, C1-34m, Br-77, and I-123 for metabolic studies of the myocardium: concise communication. *J Nucl Med* 1978; 19:298–302.
5. Westera G, Visser FC. Myocardial uptake of radioactively labelled free fatty acids. *Eur Heart J* 1985; 6(suppl B):3–12.
6. Visser FC, van Eenige MJ, Westera G, et al. Metabolic fate of radioiodinated heptadecanoic acid in the normal canine heart. *Circulation* 1985; 72:565–571.
7. Visser FC, Westera G, van Eenige MJ, et al. The myocardial elimination rate of radioiodinated heptadecanoic acid. *Eur J Nucl Med* 1985; 10:118–122.
8. Kloster G, Stöeklin G. Determination of the rate-determining step in halofatty acid turnover in the heart. *Radioakt Isotope Klin Forsch* 1982; 15:235–241.
9. Van der Wall EE, Heidendal GAK, Den Hollander W, et al. Metabolic myocardial imaging with I-123 labeled heptadecanoic acid in patients with angina pectoris. *Eur J Nucl Med* 1981; 6:391–396.
10. Van der Wall EE, Den Hollander W, Heidendal GAK, et al. Dynamic myocardial scintigraphy with 123-I-labeled free fatty acids in patients with myocardial infarction. *Eur J Nucl Med* 1981; 6:383–389.
11. Van der Wall EE, Heidendal GAK, Westera G, et al. Myocardial scintigraphy with I-123 Labeled free fatty acids. In: Faiore G, Bertrand A, Cherrier F, Amor M, Neimann JL, et al. *Noninvasive methods in ischemic heart disease 1982.* Nancy, France, Specia; 1982:304–313.
12. Dudczak R. Myokardszintigraphie mit Jod-123-markierten Fettsauren. Wiener klinische Wochenschrift 1983; 95(suppl 143):1–35.
13. Fridrich L, Pichler M, Gassner A, et al. Tracer elimination in I-123-heptadecanoic acid: half-life, component ratio and circumferential washout profiles in patients with cardiac disease. *Eur Heart J* 1985; 6(suppl B):61–70.
14. Visser FC, van Eenige MJ, Van der Wall EE, et al. The elimination rate of I-123-heptadecanoic acid after intracoronary and intravenous administration. *Eur J Nucl Med* 1985; 11:114–119.
15. Rabinovitch MA, Kalff V, Allen R, et al. Omega-123-I hexadecanoic acid metabolic probe of cardiomyopathy. *Eur J Nucl Med* 1985; 10:222–227.
16. Höck A, Freundlieb C, Vyska K, et al. Myocardial imaging and metabolic studies with 17-I-123 iodoheptadecanoic acid in patients with idiopathic congestive cardiomyopathy. *J Nucl Med* 1983; 24:22–28.
17. Dudczak R, Kletter K, Frischauf H, et al. The use of 123-I-labeled heptadecanoic acid (HDA) as metabolic tracer: preliminary report. *Eur J Nucl Med* 1984; 9:81–85.
18. Höck A, Notohamiprodjo G, Spohr G, et al. Myocardial fatty acid metabolism after acute ethanol consumption. *Nucl Med Commun* 1986; 7:671–682
19. Höck A, Freundlieb Ch, Vyska K, et al. The influence of rehabilitation training on fatty acid metabolism in patients with myocardial infarction. In: *Non invasive methods in ischemic heart disease.* Nancy, France, Specia, 1982, 300–303.
20. Van der Wall EE, Westera G, Den Hollander W, et al. External detection of regional myocardial metabolism with radioiodinated hexadecenoic acid in the dog heart. *Eur J Nucl Med* 1981; 6:147–151.
21. Kloster G, Stöeklin G, Smith EF, et al. Omega-halofatty acids: a probe for mitochondrial membrane in-

tegrity. In vitro investigations in normal and ischaemic myocardium. *Eur J Nucl Med* 1984; 9:305–311.
22. Styles CB, Noujaim AA, Jugdutt BI, et al. Omega iodo fatty acid scintigraphy—What are we measuring? *Eur Heart J* 1985; 6(suppl B):103–106.
23. Visser FC, van Eenige MJ, Westera G, et al. Kinetics of radioiodinated heptadecanoic acid and metabolites in the normal and ischaemic canine heart. *Eur Heart J* 1985; 6(suppl B):97–101.
24. Schön HR, Senekowitsch R, Berg D, et al. Measurement of myocardial fatty acid metabolism: kinetics of iodine-123 heptadecanoic acid in normal dog hearts. *J Nucl Med* 1986; 27:1449–1455.
25. van Eenige MJ, Visser FC, Duwel CMB, et al. Analysis of myocardial time-activity curves of ^{123}I heptadecanoic acid I. Curve fitting. *Nucl Med* 1987; 26:241–247.
26. van Eenige MJ, Visser FC, Van Lingen A, et al. Evaluation of background correction methods. *Eur Heart J* 1985; 6(suppl B):57–59.
27. van Eenige MJ, Visser FC, Duwel CMB, et al. Iodinated free fatty acids: reappraisal of methodology. In: Van der Wall EE, ed. *Noninvasive imaging of cardiac metabolism.* Doadrecht Martin Nyhoff Publishers, 1987:95–107.
28. van Eenige MJ, Visser FC, Karreman AJP, et al. Analysis of myocardial time-activity curves of I-123 heptadecanoic acid II. The acquisition time. *Nucl Med* 1987; 26:248–252
29. Freundlieb C, Hoeck A, Vyska K, et al. Myocardial imaging and metabolic studies with 17-I-123 iodoheptadecanoic acid. *J Nucl Med* 1980; 21:1043–1050.
30. Stoddart PGP, Papouchado M, Wilde P. Prognostic value of 123-iodo-heptadecanoic acid imaging in patients with acute myocardial infarction. *Eur J Nucl Med* 1987; 12:525–528.
31. Duwel CMB, Visser FC, van Eenige MJ, et al. The influence of glucose on the myocardial time-activity curve during 17-iodo-123 heptadecanoic acid scintigraphy. *Nucl Med Commun* 1987; 8:207–215.