Myocardial Imaging and Metabolic Studies with [17-^{123}I]Iodoheptadecanoic Acid in Patients with Idiopathic Congestive Cardiomyopathy

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In twenty patients with primary congestive cardiomyopathy (COCM) the patterns of accumulation and washout of the fatty acid analogue [17-^{123}I]iodoheptadecanoic acid (I-123 HA) were studied. In contrast to patients with ischemic heart disease, where reduced I-123 HA accumulation was correlated with stenosis of the main coronary arteries, thus usually involving larger wall segments, the patients with COCM concentrated I-123 HA heterogenously in small spotty segments throughout the entire left-ventricular myocardium. The regional washout half-times varied between 15.1 and 116.2 min. It seems that in patients with severe COCM the elimination half-times are more prolonged than in early stages of the disease. There was no correlation between the regional uptake and the elimination half-times. Sequential myocardial imaging with I-123 HA appears useful for noninvasively diagnosis of COCM.

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Congestive cardiomyopathies have been recognized increasingly in recent years through improved diagnostic procedures, but a full understanding of etiology and pathophysiology still awaits a clear answer (*1*,*2*). The diagnostic criteria are often equivocal, for example regarding diminished cardiac output and stroke volume, elevated left-ventricular end-diastolic pressure, elevated pulmonary-artery pressure, and increased left- and right-ventricular volumes with reduced ejection fractions. None of these findings is specific for this disease. Tissue biopsy with optical- and electron-microscopic examination (*3*,*4*) is invasive, but it may show one or more of the following changes: cellular necrosis, hypertrophy of cardiac muscle cells, interstitial fibrosis, decreasing or increasing numbers of mitochondria and interstitial cells, mitochondrial swelling, or enlargement of the nuclei (*5–11*). Most of these findings are in no way different from those found in other types of cardiac disorders (*4*,*6*).

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Most forms of cardiomyopathies are either primarily or secondarily related to alterations in cellular metabolism (*12–18*). Since fatty acids are the primary source of energy supply for the myocardium, metabolic changes are expected to involve the utilization of fatty acids.

Myocardial metabolism may be studied noninvasively with labeled fatty acids using [17-^{123}I]iodoheptadecanoic acid (I-123 HA), and tracer accumulation and turnover may be assayed separately (*19*). It was the purpose of the present study to investigate accumulation and turnover of fatty acids in the myocardium of patients with congestive cardiomyopathy in order to find out whether global or regional accumulation and elimination of labeled fatty acids is changed in this disease. A preliminary report has already appeared (*20*).

MATERIALS AND METHODS

The study included six healthy volunteers, 13 patients with severe primary congestive (dilative) cardiomyopathy (COCM) and 7 patients with normal ventricular function at rest but with signs of dysfunction during stress, considered in an early stage of cardiomyopathy

(*21*). The six healthy volunteers had normal resting and exercise ECG and normal chest radiographs but were not examined with invasive methods. Since they were free of symptoms they were considered normal.

The patients with severe COCM were all in NYHA class III and IV. They showed enlarged hearts by chest radiograph (cardiothoracic ratio >50%). Diagnosis was confirmed by left- and right-heart catheterization, demonstrating dilated ventricles with poor wall motion, wide coronary arteries without signs of atherosclerosis, and lack of hypertension or valvular disease.

The patients with a potentially early stage of cardiomyopathy had normal-sized hearts by radiograph. Coronary angiography performed because of chest pain and abnormal exercise ECG revealed normal coronary arteries and normal-sized left and right ventricles, with normal wall motion as well as normal intraventricular pressures. During bicycle ergometer exercise, however, they demonstrated abnormally elevated pulmonary-artery wedge pressure. Measurement of myocardial lactate extraction, performed in three patients, revealed an abnormal extraction during high-rate ventricular stimulation.

In two patients (F. A. and H. M. in Table 2) myocardial tissue was histologically examined following transarterial catheter biopsy. Biopsy material from patient H. M. showed moderate hypertrophy of cardiac muscle fibres; the nuclei were enlarged and often surrounded by vacuoles. The myofibrils were heterogenously distributed. Patient F. A. had normal microscopy findings, but electron microscopy indicated variations in mitochondrial structure. Some myelin figures were observed. Rarely small lipid droplets were seen. Otherwise there were few degenerative changes in this patient.

All patients were investigated immediately after an exercise over 3 min in the upright position on a bicycle ergometer with a load of 25 W. The normal individuals underwent the investigation first at rest and a second time 8 days later immediately after a maximal exercise test. Work load on a bicycle ergometer was increased stepwise to the maximum determined by reaching age-dependent maximal heart rate or exhaustion.

Two to three mCi of the stearic acid analog, [17-^{123}I]iodoheptadecanoic acid (I-123 HA), were dissolved in the serum obtained from each individual shortly before the test run, and were administered intravenously during the last minute of exercise. Images were taken in the supine position in LAO-45° projection under the head of an Anger scintillation camera, equipped with a low-energy converging collimator. The measurement was usually started 3 min after the end of exercise, or at rest 7 min after tracer injection. One mCi of carrier-free Na^{123}I was administered i.v. 30 min after injection of I-123 HA to derive a correction for I-123 in the blood pool and interstitial space. Accumulation of I-123 HA was assayed qualitatively, whereas turnover rates are given quantitatively.

Dynamic studies. These studies of metabolic turnover were carried out in one projection only. In order to eliminate myocardial movement during the cardiac cycles, which would have impaired regional analysis, the multiple ECG-gated registration mode was applied. A total of 40 ECG-gated images were registered per examination. The collection period for each gated image was 1 min. From all gated images thus obtained, the scintigrams corresponding to diastole were selected and used for evaluating regional fatty-acid turnover. For the determination of diastolic images, the ECG-gated studies registered between the 5th and 10th minute were

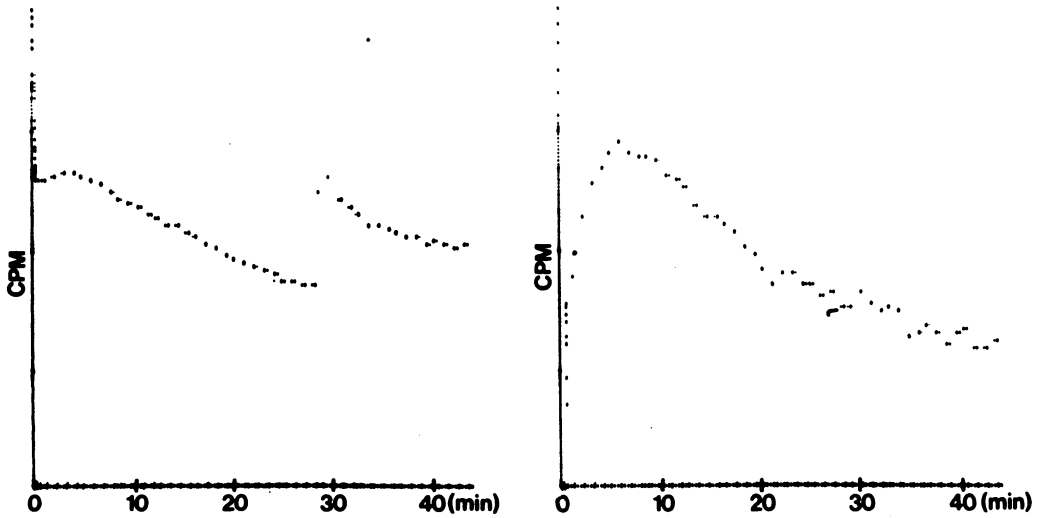


FIG. 1. Time-activity curve over myocardial ROI after successive intravenous injections of I-123 HA and Na ^{123}I: before left and after right correction for catabolically released I-123.

summed. In the ECG-study thus obtained, the left-ventricular cavity was delineated with the ROI technique in all matrixes. From these ROIs the one with the highest number of pixels/ROI was selected and the time-activity curve was created over the entire ECG-study. This time-activity curve, which is a reflected image of a cardiac volume curve, was used for selecting diastolic images in the original study. From the sequence of diastolic images, regions of interest were selected for creating regional washout curves according to the distribution of the three main coronary arteries—e.g., LAD., CIRC., and PAD. as published (*22*).

Static images. For the static myocardial images, only the counts recorded in the last third of each cardiac cycle were registered. Each image was made by collecting 300,000 counts per view beginning 7 min (resting study) or 3 min (exercise study) after tracer injection. Activity differences of more than 20% within the distribution area of a coronary artery were called a heterogeneous accumulation pattern.

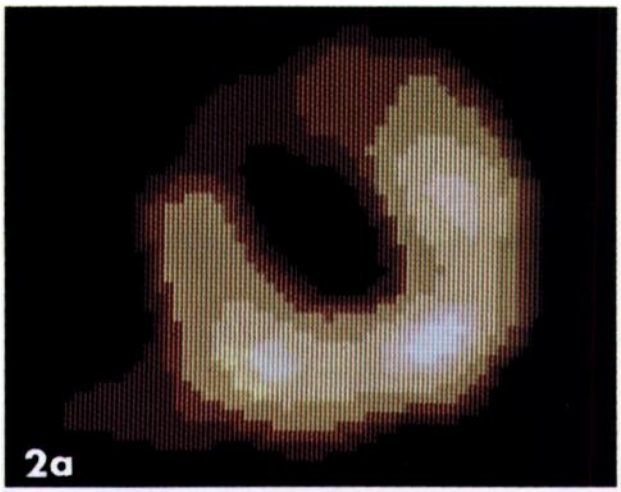
Correction for catabolically released free iodine-123. In order to correct the images for I-123 in the blood and interstitial space—i.e., radioiodide that was not bound to the myocardial cells—each myocardial image was corrected by a method modified from that reported previously (*19*).

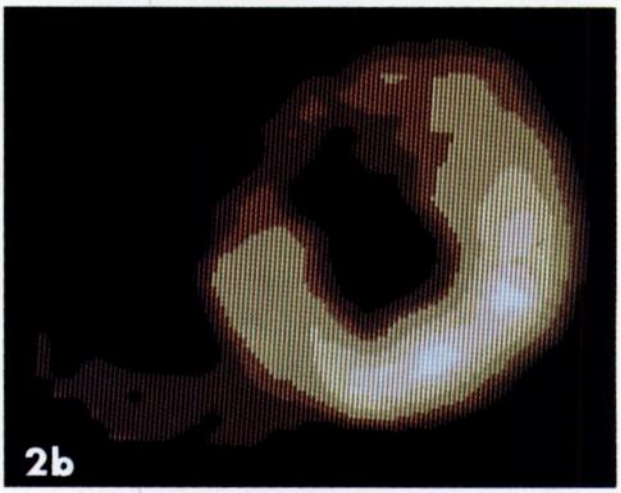
This background correction was possible because the substance causing the background (I-123 ion) is different from the original compound (I-123 HA) and because the distributions of these two substances in the chest are different (*19*).

The basic idea involved in performing the background correction is to create a well-defined artificial I-123 iodide background in the patient by injection of (usually) 1.0 mCi of $Na^{123}I$ at the end of the examination period while image acquisition is continued. The image registered 2 min before the I-123 injection is then substracted from the image registered 2 min after this injection.

The difference image thus obtained describes the distribution of I-123 in the chest, and is therefore proportional to the background activity distribution in the uncorrected I-123 HA scintigram.

To determine a proportionality constant that normalizes the $Na^{123}I$ distribution matrix to the background activity distribution, it is necessary to find in the uncorrected I-123 scintigram at least one region in which only the background activity is registered, i.e., in which no significant accumulation of I-123 HA occurs. We assume that this condition is fulfilled in the area of the superior caval vein. With this assumption, the mentioned proportionality constant can be determined as the ratio of counting rates registered in caval region of interest (ROI) in the original uncorrected I-123 HA scintigram to that determined in the same region of interest in the Na ^{123}I distribution scintigram (difference scintigram).





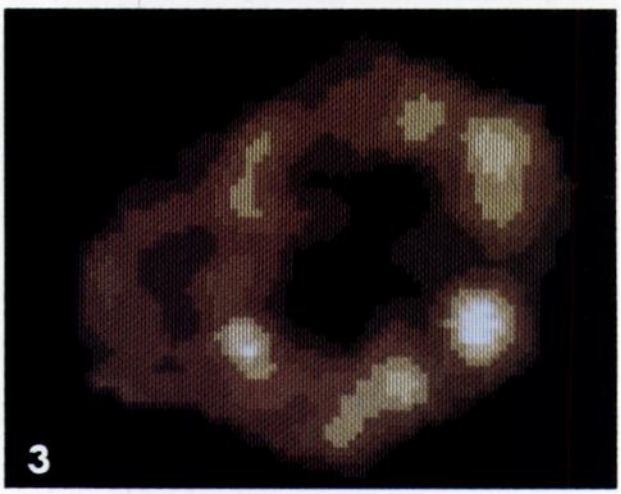


FIG. 2. Diastolic images in LAO 45° projection, from a normal person after a dose of 2.5 mCi I-123 HA (a: at rest; b: after exercise).

FIG. 3. Diastolic image in LAO 45° projection of a patient with severe COCM. Note uneven distribution pattern of I-123 HA.

After multiplying the Na ^{123}I distribution scintigram by this constant, the background activity distribution matrix is obtained. Substraction of the background activity distribution matrix from the uncorrected I-123 HA

TABLE 1. REGIONAL MYOCARDIAL ELIMINATION TIMES (MIN) OF I-123 HA IN NORMALS

	Total heart		Septum		Inferior wall		Posterolateral wall	
	R*	E†	R	E	R	E	R	E
1	24,0	20,6	24,5	18,7	21,4	15,5	25,3	18,2
2	27,6	24,9	24,7	17,4	26,8	24,9	25,0	22,0
3	27,9	22,1	27,5	22,0	28,0	21,7	27,0	21,5
4	23,0	18,8	20,2	23,9	21,3	18,8	22,9	21,0
5	21,9	21,7	21,9	21,3	25,3	22,6	21,7	24,3
6	23,9	22,1	16,4	19,1	21,7	19,4	26,4	28,6
$\bar{X}$	24,72	21,7	22,53	20,4	24,08	20,5	24,72	22,6
$S_{\bar{x}}$	2,47	2,0	3,92	2,4	2,99	3,3	2,04	3,5

* R = Rest.
† E = Exercise.

scintigram yields the background-corrected image.

If this background correction is applied not only to one but to all scintigrams of the dynamic study, the background-corrected study is obtained. The improvement of information achieved by the described correction is illustrated in Fig. 1. The time-activity curves created from the myocardial region of interest in the original uncorrected study from a normal person (Fig. 1 (left)) is characterized by an initial steep increase and followed by a slow elimination phase that approaches the background level asymptotically. The sudden increase in the activity in the last third of the registration period corresponds to the injection of Na ^{123}I used as an internal standard for correction. In contrast to this uncorrected time-activity curve, in which background contamination is still present, the corrected time-activity curve, (Fig. 1 (right)) clearly shows uptake and washout of I-123 HA in the myocardium.

RESULTS

Normal individuals show a homogeneous distribution pattern of I-123 HA in the left-ventricular myocardium at rest as well as after exercise (Fig. 2). As in scintigraphy with thallium-201, only the left-ventricular wall is visible under normal conditions. For these images 300,000 counts were collected for the diastolic time intervals by gated data acquisition. The applied correction produces good contrast between myocardium and the surrounding tissue.

In patients with COCM, the accumulation pattern of I-123 HA is heterogeneous. An example is shown in Fig. 3. This heterogeneity does not follow the perfusion areas of individual coronary arteries; this means that normal as well as reduced accumulation of I-123 HA may be observed within the field of one coronary artery.

In normals the average washout half-time for the whole heart was 24.0 ± 5 min at rest and 21.7 ± 2 min after exercise (Table 1). The regional washout half-times for septum, and the inferior and posterolateral walls did not differ significantly from these values.

Table 2 summarizes the results from patients with severe COCM. Eleven of these 13 patients showed prolonged washout half-times for the total myocardium. Regionally the half-times ranged between 15.1 and 116.2 min. Significant differences between half-times occurred within the same area of coronary artery supply. No correlation between regional tracer accumulation and rate of elimination could be detected. Areas with diminished or normal uptake had shortened, normal, or prolonged half-times.

The results from patients with early stages of COCM are shown in Table 3. Again the accumulation pattern was heterogeneous and regional uptake and washout times were not correlated. Yet the degree of prolongation of half-times was less pronounced than in patients with severe COCM.

DISCUSSION

Normal persons show a homogeneous distribution of I-123 HA in the myocardium and, as in thallium-201 imaging, only the left-ventricular wall is seen. The washout half times for the total left-ventricular myocardium are in agreement with previously published results (*19*,*23*). Only small variations occur in single myocardial regions. The average turnover rate observed after exercise is statistically not significantly different from the resting data.

In patients with COCM, a heterogeneous accumulation pattern of I-123 HA is observed throughout the whole myocardium. This is in contrast to thallium-201, which may be normally distributed (*24*,*25*), increased (*26*), or regionally diminished, and thus may be in no way different from thallium uptake in patients with CAD (*25*,*27*,*28*). In this study Patient E.G. (severe COCM) had a normal thallium image but a highly inhomogeneous I-123 HA distribution pattern.

At rest, patients with CAD are characterized by a homogeneous accumulation defect of various extent and

TABLE 2. REGIONAL MYOCARDIAL ELIMINATION TIMES [MIN] OF I-123 HA IN PATIENTS WITH SEVERE COCM

Pat.	Total heart $t_{1/2}$	Septum $t_{1/2}$	Septum Acc.	Inferior wall $t_{1/2}$	Inferior wall Acc.	Postero-Lateral wall $t_{1/2}$	Postero-Lateral wall Acc.
K.R.	42,0	[§] a) 37,0	+	31,0	+*	a) 35,0	+
		[¶] b) 37,0	+			b) 42,0	++
S.E.	29,0	a) 24,0	−‡	34,0	++†	a) 31,0	+
		b) 22,0	+			b) 33,0	++
F.A.	24,6	a) 30,7	+	25,4	++	a) 21,3	+
		b) 25,0	+			b) 24,1	++
D.H.	25,0	a) 21,3	−	20,2	++	a) 27,0	++
		b) 19,0	+			b) 28,0	++
E.G.	40,6	a) 23,2	−	67,2	++	a) 35,8	+
		b) 30,0	++			b) 44,4	++
S.G.	52,7	a) 29,4	−	53,7	−	a) 86,6	+
		b) 30,2	++			b) 45,2	−
N.H.	44,2	a) 37,7	−	31,7	+	a) 43,5	++
		b) 28,6	−			b) 46,0	++
B.W.	37,2	a) 15,1	−	44,3	+	a) 51,3	++
		b) 34,1	++			b) 36,4	++
S.P.	49,5	a) 28,1	−	57,2	+	a) 33,0	−
		b) 42,4	+			b) 60,3	++
P.H.	40,3	a) 39,8	++	22,2	++	a) 22,4	+
		b) 21,3	−			b) 73,2	++
R.H.	53,1	a) 44,6	−	66,0	+	a) 53,1	+
		b) 32,0	++			b) 116,2	++
K.H.	72,8	a) 63,7	−	65,1	+	a) 62,7	++
		b) 54,0	+			b) 55,7	+
H.M.	35,4	a) 23,2	−	31,1	++	a) 40,9	+
		b) 19,7	−			b) 44,9	++

* Acc. diminished.
† Acc. normal.
‡ Acc. bad.
§ a = Basal part.
¶ b = Distal part.

degree in areas of narrowed arteries. In these areas the washout times are normal, shortened, or prolonged, and the alteration of elimination is uniform in the field of one coronary artery. Under exercise the extension and the degree of accumulation defects are more pronounced. In regions with nearly normal uptake at rest but with accumulation defects under exercise, the washout half-times may be prolonged even at rest. In regions with normal uptake at rest and under exercise, the washout times are normal, both at rest and under exercise. These observations reflect, in agreement with Weiss (*30*), Opie (*31*), and Most (*32*), a decreased delivery of free fatty acids due to a decreased blood flow and a diminished extraction rate in the ischemic myocardium. The alterations in washout rates in hypoxic regions may be an expression of changes in intracellular pool of fatty acids or of an altered absolute rate of fatty-acid metabolism.

In contrast, patients with COCM show a inhomogeneous distribution of uptake and washout half-times throughout the total myocardium, with no relationship to the areas supplied by the coronary arteries. Moreover, no correlation could be seen between areas of altered uptake and areas with changed washout times. Thus, an inhomogeneous activity distribution with no relation to coronary supply, and a discordance between the accumulation pattern and the distribution of washout times seems to characterize COCM when compared with CAD.

It is unknown which of the numerous physical and biochemical factors are responsible for the inhomogeneous distribution of fatty acids in COCM. One possible reason may be a disturbance of fatty-acid transfer between extracellular binding sites on albumin and intracellular binding whatever subcellular structures are here involved (*33,34*). Yet, this disturbance must then

TABLE 3. REGIONAL MYOCARDIAL ELIMINATION TIMES [MIN] OF I-123 HA IN PATIENTS WITH COCM IN EARLY STAGE

Pat.	Total heart $t_{1/2}$	Septum $t_{1/2}$	Septum Acc.	Inferior wall $t_{1/2}$	Inferior wall Acc.	Postero-Lateral wall $t_{1/2}$	Postero-Lateral wall Acc.
T.H.	35,0	[§] a) 38,4	–[‡]	26,6	+[•]	a) 28,3	++
		[¶] b) 24,5	–			b) 27,8	++
T.P.	27,0	a) 14	++	27,0	++	a) 30,0	+
		b) 16	+			b) 24,9	++
K.G.	19,0	a) 17,0	+	16,4	++	a) 21,6	++
		b) 16,5	+			b) 18,4	++
R.A.	34,7	a) 33,5	+	21,8	–	a) 41,2	+
		b) 34,8	+			b) 30,9	++
B.M.	20,5	a) 20,8	+	17,7	+	a) 21,1	+
		b) 16,3	+			b) 18,3	++
K.H.	21,0	a) 16,8	++	16,5	+	a) 31,4	+
		b) 15,4	++			b) 19,6	++
D.H.	30,4	a) 28,8	+	32,0	+	a) 31,2	+
		b) 26,6	++			b) 35,6	++

[•] Acc. diminished.
[†] Acc. normal.
[‡] Acc. bad.
[§] a: Basal part.
[¶] b: Distal part.

be regionally uneven. Regional differences must also exist if alterations in cellular metabolism influence the rate of intracellular uptake.

On the other hand, the movement of fatty acids through the cell depends on the rates of oxidation and esterification (*35*), which are globally expressed by the washout half-times of I-123 HA in this study. As shown in patients with COCM, the regional washout half-times are not generally related to the accumulation pattern: regions with normal uptake had normal, shortened, or prolonged half-times. The same holds true for regions with diminished or grossly reduced uptake. Again, the interpretation of the washout times is also unclear at the present time. There may be changes in the lipid or triglyceride pool, a diminished demand for β-oxidation, an alteration of the distribution of coenzyme A between the cytosol compartment and the intramitochondrial compartment, or an incompetence of the carnitine shuttle across the mitochondrial membrane. It is supposed that the application of L-carnitine results in an improvement of fatty-acid metabolism (*17,36*).

Whatever the reason is for the topographical discordance between accumulation and elimination, these data indicate the potential of the method to obtain further insight into the pathophysiological processes in COCM. It also asserts that cellular uptake of I-123 HA obviously does not necessarily reflect the metabolic rate. The particular discordance between tracer uptake and metabolism described in this paper may well be a phenomenon shared by other labeled metabolites (*37*).

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