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ω-^{123}I-Hexadecanoic acid metabolic probe of cardiomyopathy

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Abstract. The utility of ω-^{123}I-hexadecanoic aicd myocardial scintigraphy as a metabolic probe of cardiomyopathies was investigated. Sixteen patients with a variety of cardiomyopathies and myopathies that involve cardiac muscle and ten volunteers were imaged in the postabsorptive state in a 40° LAO projection after a standard dose of ω-^{123}I-hexadecanoic acid. An elimination $T_{1/2}$ was calculated from the left ventricular myocardial time-activity curve. An uptake index, corrected for chest wall attenuation, was also computed in 7 of 10 volunteers and 8 of 16 patients.

Of the 16 patients, only 2 had distinctly abnormal ω-^{123}I-hexadecanoic acid myocardial tracer kinetics. The first patient had a metabolic disorder of which carnitine deficiency was one component. The second patient had endocardial fibroelastosis, a process which has been linked to disorders which deprive the myocardium of oxygen and energy. Therefore, the cardiomyopathy may have been caused by some abnormality of cardiac metabolism other than carnitine deficiency. Although of limited utility in the overall cardiomyopathic population, ω-^{123}I-hexadecanoic acid myocardial scintigraphy should be further investigated as a screening test for carnitine deficiency and related metabolic abnormalities in patients at risk.

The cardiomyopathies are a group of myocardial disorders of diverse etiology and pathophysiology (Goodwin et al. 1982). They account for a significant percentage of cardiac morbidity and mortality. In a small number of cases, the cardiomyopathy can be traced to some inborn error of cardiac metabolism (Goodwin et al. 1982; Taylor 1982). Since certain of these defects such as carnitine deficiency (Engel 1980) may be amenable to specific therapy, their clinical identification is of great importance. Unfortunately, the tools available to the clinician for the work-up of patients presenting with cardiomyopathy are limited. Echocardiography and cardiac blood pool scintigraphy can provide important anatomical and physiological information, but are lacking when an etiological diagnosis is sought. Myocardial biopsy has been useful for the detection of inflammatory processes and amyloidosis (Melvin and Mason 1982), and potentially could be used to diagnose metabolic defects as well (Peters et al. 1977). However, its invasive nature is a detraction. Also, patchy disease can often be missed when a tiny endomyocardial biopsy is taken (Ferrans and Roberts 1978).

Myocardial imaging with radiolabeled metabolic tracers might provide an important noninvasive means of identifying metabolic defects in the cardiomyopathies. The state of myocardial fatty acid metabolism can be depicted by the myocardial tracer kinetics of positron emitting ^{11}C-palmitate (Klein et al. 1979; Lerch et al. 1982; Schön et al. 1982). Positron emission tomography with ^{11}C-palmitate has thus enabled the in vivo study of myocardial fatty acid metabolism in the relatively few centers equipped with an onsite cylotron (Lerch et al. 1981; Schelbert et al. 1983). An alternative, more widely applicable method involves the imaging of radioiodinated long chain fatty acid substrates with an Anger camera. Terminally radioiodinated long chain fatty acids have been found to be extracted and cleared by the myocardium in a fashion similar to carbon labeled counterparts (Machulla et al. 1978). Using the conventional gamma camera, the elimination $T_{1/2}$ of these ω-^{123}I-fatty acids has been quantified in man (Freundlieb et al. 1980). Abnormal regional myocardial tracer kinetics have been observed during exercise-induced ischemia (van der Wall et al. 1981), unstable angina (van der Wall et al. In press), and acute myocardial infarction (van der Wall et al. 1981). The aim of this study was to determine whether ω-^{123}I-hexadecanoic acid myocardial scintigraphy might be useful for the detection of myocardial metabolic defects in patients with cardiomyopathy.

Materials and methods

Study Population

ω-^{123}I-hexadecanoic acid myocardial scintigraphy was performed in a group of ten healthy adult volunteers to establish normal ranges for myocardial tracer kinetics. There were eight males and two females with a mean age of 26 years, range 23–40 years (Table 1). Then sixteen patients with a variety of cardiomyopathies and neuromyopathies that involve cardiac muscle were studied (Table 2).

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Patient 1 had the Kearns-Sayre syndrome, a disorder characterized by: (a) progressive external ophthalmoplegia, (b) pigmentary retinal degeneration, and (c) heart block (Kearns et al. 1958; Berenberg et al. 1977). Although she had not yet developed heart block, there was a left anterior hemiblock and an incomplete right bundle branch block. Since this patient had clinical similarities to previously reported patients with folic acid malabsorption (Lanzkowsky et al. 1969) and in view of the recent evidence linking folic acid and carnitine metabolism (Allen et al. 1980), plasma folate (Rothenberg et al. 1972) and skeletal muscle carnitine (McGarry and Foster 1976) were measured in this patient. These studies showed: (a) a low plasma folate level of 1.9 ng/ml (normal 5–15 ng/ml), (b) ragged-red fibers on a skeletal muscle biopsy, (c) subnormal skeletal muscle free carnitine of 2.70 nmol/mg noncollagen protein (normal 17.10 ± 7.6 nmol/mg based on 35 controls) and slightly increased esterified carnitine content. Skeletal muscle carnitine levels were performed in the laboratory of Dr. Salvatore Di Mauro by a modification of the method of McGarry and Foster (1976).

Patient 2 was a 2-year-old female with severe congestive heart failure since the age of 6 weeks. Cardiac catherization was suggestive of endocardial fibroelastosis. She died within a week of ω-^{123}I-hexadecanoic acid myocardial scintigraphy. Postmortem examination revealed endocardial fibroelastosis, myocardial hypertrophy, and extensive myocardial fibrosis. She had a skeletal free muscle carnitine of 2.03 mmol/g wet tissue and cardiac free muscle carnitine of 0.64 mmol/g wet tissue. Both these values are within the normal range.

Table 2 lists the other patients studied with their diagnoses and noninvasive assessment of left ventricular function. As can be seen, a full spectrum of cardiomyopathies and myopathies which involve cardiac muscle was studied. Also, left ventricular function varied widely within the patient group.

Table 1. ω-^{123}I-Hexadecanoic acid myocardial uptake-washout indices of volunteers

No.	Sex	Age (yrs)	Myocardial $T_{1/2}$ (min)	Myocardial uptake index[a]
1	F	40	39	61.9
2	M	27	29	65.0
3	M	24	30	77.9
4	M	24	21	
5	F	24	36	
6	M	24	26	45.3
7	M	23	41	64.1
8	M	23	27	58.6
9	M	23	32	60.6
10	M	26	44	
Mean ± SD		26 ± 5	33 ± 7	62 ± 10

[a] The myocardial uptake index, corrected for chest wall attenuation, is expressed in counts/pixel/min

Imaging methods

ω-^{123}I-hexadecanoic acid was synthesized by iodine replacement labeling of 16-bromohexadecanoic acid in refluxing methylethyl ketone followed by evaporation to dryness and formulation in sterile, pyrogen-free 5% HSA solution (Otto et al. 1981). The ^{123}I utilized for this synthesis was produced by the ^{127}I (p,5n) ^{123}Xe → ^{123}I reaction with radionuclide purity specification of 98.6% ^{123}I and 1.4% ^{125}I at the time of calibration. ^{123}I was obtained from Crocker Laboratories, Davis, Calif. Radiochemical purity of the final preparation was greater than 95% as determined by anion exchange chromatography using Bio Rad AG1-X8 resin preluted with 5% HSA solution.

Table 2. ω-^{123}I-Hexadecanoic acid myocardial kinetics of patients

Number	Sex	Age	Diagnosis	LV function		$T_{1/2}$		Uptake index	
				Fract. shortening	LVEF	min	Z score[a]	counts/pixel/min	Z score
1	F	24	KSS + carnitine deficiency	36		60	+3.9	27.9	−3.4
2	F	2	CM + endocardial fibroelastosis	10	23	105	+10.3		
3	F	20	Progressive ext. ophthalmoplegia			15	−2.6		
4	M	20	Duchenne's muscular dystrophy			20	−1.9	68.9	+0.7
5	F	2	Myotonic dystrophy	40		16	−2.4		
6	F	27	Myotonic dystrophy	34		20	−1.9	29.8	−3.2
7	M	50	Myotonic dystrophy			20	−1.9		
8	M	35	Myotonic dystrophy	40		20	−1.9	28.5	−3.4
9	M	24	Freidreich's ataxia	38		31	−0.3		
10	F	14	Congestive CM + mitral regurg		14	39	+0.9	30.1	−3.2
11	F	58	Congestive CM		27	34	+0.1		
12	M	35	Congestive CM		13	33	0.0	49.0	−1.3
13	F	57	Adriamycin CM	28		27	−0.9		
14	M	64	Hypertrophic obstructive CM			36	+0.4	87.0	+2.5
15	M	65	Atrial fib + Alcohol abuse	44		30	−0.4	49.4	−1.3
16	F	1	Complex congenital heart disease	27		16	−2.4		

Abbreviations: KSS = Kearns Sayre syndrome, CM = cardiomyopathy, ext = external, regurg = regurgitation, fib = fibrillation, LV = left ventricular, Fract = fractional, LVEF = left ventricular ejection fraction.

Fractional shortening was determined by echocardiography and left ventricular ejection fraction by gated cardiac blood pool scintigraphy.

[a] Z score = number of standard deviations beyond the normal mean

All volunteers and patients were studied in the postabsorptive state (at least 4 h from the last meal) after ingesting SSKI to block thyroidal uptake of the tracer. All adults received a standard 3-mCi dose and all pediatric patients received the equivalent dose adjusted to body surface area. Images were obtained in the 40° left anterior oblique projection with a standard field of view gamma camera, medium-energy parallel-hole collimator (360 KeV), employing a 20% window around the 159 KeV photopeak of ^{123}I. Beginning with injection of the tracer, serial 1-min images were acquired in a 64 × 64 word mode for 30 min.

Data analysis

Data processing was identical for all studies. From the composite 30 min image a myocardial region of interest was flagged encompassing both ventricles. Then, all 1-min raw images were subjected to horizontal interpolative background subtraction by a modification of the method of Watson et al. (1981). Next, a time-activity curve of the left ventricular myocardium excluding the inferoapical segment was generated from the processed images. The inferoapical segment was excluded to avoid the problem of hepatic overlap which occurred in some patients. An elimination $T_{1/2}$ was determined by plotting the curve on semilog paper and subjecting the straight downsloping part beyond 6 min to a monoexponential least squares fit. An uptake index was derived by first summing images 6–10 and calculating the average counts/pixel/min over the left ventricular moycardium excluding the inferoapical segment. To correct for chest wall attenuation, this value was then divided by $e^{-\mu d}$, where μ is the linear attenuation coefficient of ^{123}I in water and d is the distance in cm from the surface of the chest to the mid-left ventricular cavity measured on a parasternal long-axis M-mode echocardiogram.

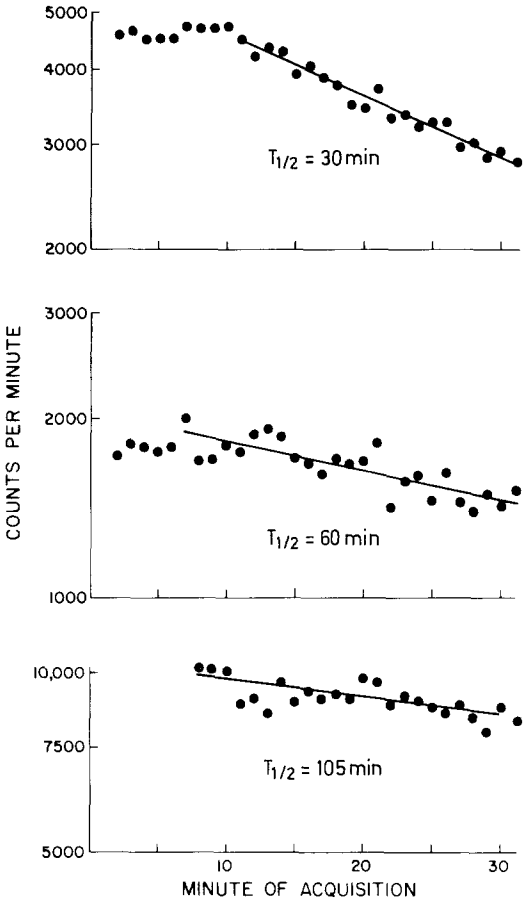

Fig. 1. Contrasts the myocardial time-activity curves of a representative volunteer (*top*), patient 1 with Kearns Sayre syndrome and carnitine deficiency (*middle*), and patient 2 with idiopathic cardiomyopathy and endocardial fibroelastosis (*bottom*)

Results

Normal volunteers and patients

The ω-^{123}I-hexadecanoic acid myocardial tracer kinetics of the volunteers are shown in Table 1. The mean elimination $T_{1/2}$ was 33±7 min with a range of 21–44 min. The mean attenuation corrected uptake index was 62±10 counts/pixel/min with a range of 45–78. The ω-^{123}I-hexadecanoic acid myocardial tracer kinetics of the patients are shown in Table 2. Only 2 of the 16 patients had a markedly prolonged $T_{1/2}$. Patient 1 with Kearns Sayre syndrome and carnitine deficiency had a $T_{1/2}$ of 60 min. Patient 2 with idiopathic cardiomyopathy and endocardial fibroelastosis had a elimination $T_{1/2}$ of 105 min. Three patients had a very slightly accelerated $T_{1/2}$: patient 5, the 2-year-old female with myotonic dystrophy and patient 16, the 1-year-old female with complex congenital heart disease, had a $T_{1/2}$ of 16 min, and patient 3 with progressive external ophthalmoplegia had a $T_{1/2}$ of 15 min. All other patients had a $T_{1/2}$ within 2 standard deviations of the normal mean.

Attenuation corrected uptake indices are also listed in Table 2. Pediatric patients were excluded from the uptake index analysis for lack of suitable controls. Patient 1 with Kearns Sayre syndrome and carnitine deficiency had the most depressed uptake index −28 counts/pixel/min. Patients 6 and 7 with myotonic dystrophy and patient 12 with idiopathic congestive cardiomyopathy and severe mitral regurgitation also had depressed uptake indices. Patient 14 with hypertrophic obstructive cardiomyopathy had a slightly increased uptake index.

Figure 1 depicts the myocardial time-activity curves of a representative volunteer (*top*), patient 1 with Kearns Sayre syndrome and carnitine deficiency (*middle*), and patient 2 with idiopathic cardiomyopathy and endocardial fibroelastosis (*bottom*).

In Fig. 2, early and late smoothed images of patient 1 are contrasted with the corresponding images of a normal volunteer. There is a lower count density in the patient's myocardial images and less of a change in myocardial activity between early and late images in comparison with the normal example. Also note that the patient's hepatic activity was eliminated at a faster rate than her myocardial activity, the reverse of what is normally found.

Discussion

At the outset, it was hoped that various patterns of ω-^{123}I-hexadecanoic acid myocardial tracer kinetics would be identified in this diverse patient group. However, strikingly abnormal ω-^{123}I-hexadecanoic acid myocardial tracer kinetics were observed in only 2 of the 16 patients studied.

Markedly reduced uptake and slowed washout of tracer was found in patient 1 with Kearns Sayre syndrome and carnitine deficiency. Carnitine is a quarternary amine essen-

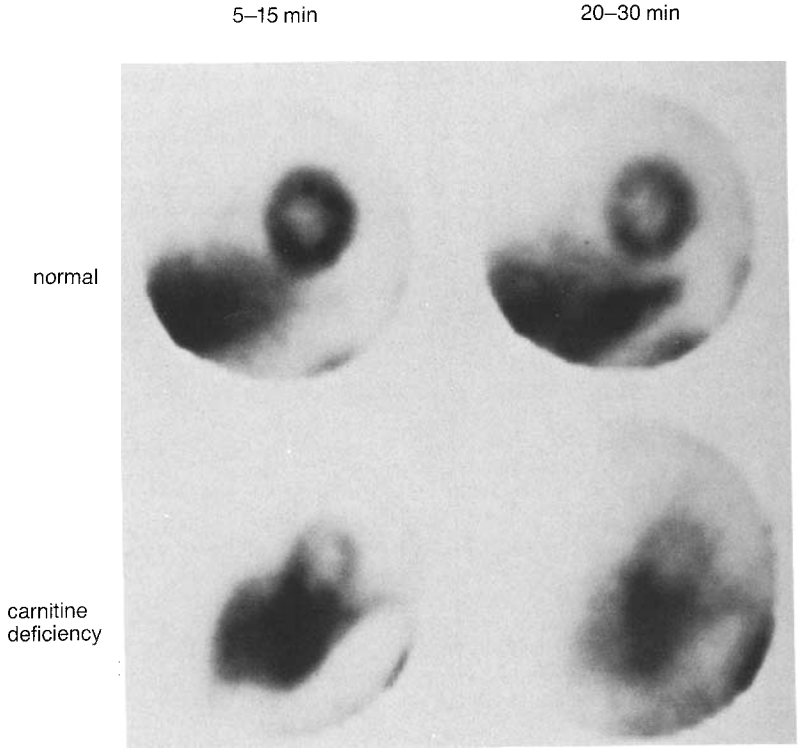

Fig. 2. Contrasts the ω-^{123}I-hexadecanoic acid myocardial images of a normal volunteer (*top*) with those of patient 1 (*bottom*). The early images (*left*) are derived by summing raw 1-min images 5–15 and the late images (*right*) are derived by summing raw 1-min images 20–30

tial for the transfer of cytoplasmic long chain fatty acids to their mitochondrial site of β-oxidation (Frenkel and McGarry 1980). Carnitine deficiency has been identified as a cause of myopathy and potentially fatal cardiomyopathy (Chapoy et al. 1980; DiMauro et al. 1980; Engel 1980). Although patient 1 lacked the striking left ventricular dilation and hypofunction which has been reported in some patients with carnitine deficiency (Chapoy et al. 1980; Tripp et al. 1981), she did have a cardiac conduction defect and mild left ventricular hypertrophy by echocardiography. The ω-^{123}I-hexadecanoic acid myocardial tracer kinetic pattern observed indicates that the technique was sensitive to this patient's abberrant long chain fatty acid metabolism. The alternative explanation that the results simply reflected reduced myocardial blood flow in this patient was considered unlikely. Abnormalities in coronary anatomy have not been documented in any previously described patients with a carnitine deficiency state (Frenkel and McGarry 1980).

Extremely slow washout of tracer was observed in patient 2 with fatal idiopathic cardiomyopathy and endocardial fibroelastosis. Endocardial fibroelastosis is often related to conditions causing myocardial hypoxia such as anomalous coronary artery circulation (Hastreiter 1968). Its familial occurrence suggests that endocardial fibroelastosis can also occur secondary to inborn errors of cardiac metabolism (Westwood et al. 1975). In one recently reported family, carnitine deficiency was found to be the cause (Tripp et al. 1981). Thus myocardial energy deprivation, either due to hypoxia, carnitine deficiency, or some other metabolic defect appears to be an important pathogenetic mechanism for this process. Of note, patient 2 had a normal coronary angiogram as well as normal skeletal and cardiac muscle free carnitine in specimens obtained immediately post mortem. It is likely that the severely retarded ω-^{123}I-hexadecanoic acid myocardial washout reflected some metabolic defect other than carnitine deficiency rather than a reduced myocardial blood flow in this patient.

ω-^{123}I-hexadecanoic acid myocardial scintigraphy was normal or marginally abnormal in the remaining 14 patients studied. Patient 3 with progressive external ophthalmoplegia had pigmentary retinal degeneration but no evidence of a generalized myopathy and no cardiac involvement. Therefore, the biochemical defect underlying the syndrome may not have involved cardiac muscle. No distinctly abnormal ω-^{123}I-hexadecanoic acid myocardial tracer kinetics emerged from patients 4–9 with a variety of heredofamilial neuromyopathies having cardiac expression (Duchenne's muscular dystrophy, myotonic dystrophy, Friedreich's ataxia). Recently, positron emission computed tomography with ^{18}F2-fluorodeoxyglucose revealed accelerated regional exogenous glucose utilization in the posterobasal and posterolateral walls in patients with Duchenne's muscular dystrophy (Perloff et al. 1984). Whether an accompanying decline in regional fatty acid metabolism exists, remains to be proven. Such a defect could have been missed in patient 4 because the 40° left anterior oblique projection utilized in this study, did not permit optimal visualization of the posterobasal wall of the left ventricle. The somewhat low ω-^{123}I-hexadecanoic acid myocardial uptake index in two of the four patients with myotonic dystrophy is of uncertain significance.

Patients 10–14 had a variety of cardiomyopathies with a wide range of resting left ventricular function. Only patient 10 had a depressed ω-^{123}I-hexadecanoic acid myocardium uptake index. Interestingly, this patient had the lowest left ventricular ejection fraction (14%). These results differ from those of Höck et al. (1983) who reported delayed ω-^{123}I-heptadeconoic acid washout in the majority of their patients with severe congestive cardiomyopathy and normal or marginally delayed washout in patients with early stage cardiomyopathy.

Patient 15 had paroxysmal atrial fibrillation and a history of alcohol abuse. Alcohol is known to impair acutely fatty acid oxidation (Bing 1978). The fact that this patient had abstained from alcohol for several months and had good ventricular function at the time of this study, may explain the normal myocardial tracer kinetics observed. Finally, patient 16 with congenital heart disease (double outlet right ventricle and valvular pulmonic stenosis) had intrinsically normal left ventricular muscle. Therefore, normal myocardial tracer kinetics were to be expected.

Conclusions

The results of this study have both disappointing and promising aspects. No distinctly abnormal patterns of ω-^{123}I-hexadecanoic acid myocardial tracer kinetics emerged from the patients with common types of cardiomyopathy, e.g. congestive cardiomyopathy, hypertrophic obstructive cardiomyopathy, or heredofamilial neuromyopathy. It is therefore unlikely that ω-^{123}I-hexadecanoic acid myocardial scintigraphy will be clinically useful in classifying human cardiomyopathies on the basis of fatty acid metabolic patterns. The positive aspect of this study was the fact that ω-^{123}I-hexadecanoic acid myocardial scintigraphy singled out patients 1 and 2 from the entire group of 16. Patient 1 had a carnitine deficiency state known to impair the intracellular transport of long chain fatty acids and patient 2 may have had a related defect in cardiac metabolism. While carnitine deficiency and related metabolic abnormalities are thought to be rare congenital conditions, they are potentially treatable causes of cardiomyopathy (Engel 1980; Mastaglia et al. 1980). Also, acquired carnitine deficiency has been found in more commonly encountered clinical settings such as uremia (Bohmer et al. 1978). The potential of ω-^{123}I-hexadecanoic acid myocardial scintigraphy as a noninvasive screening test for carnitine deficiency states in patients at risk should therefore be explored.

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