Kinetics of 14(R,S)-Fluorine-18-Fluoro-6-Thia-Heptadecanoic Acid in Normal Human Hearts at Rest, During Exercise and After Dipyridamole Injection

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The myocardial uptake kinetics of 14(R,S)-[^{18}F]fluoro-6-thia-heptadecanoic acid (FTHA) were evaluated in humans with PET. The relationship between human myocardial FTHA uptake kinetics and the rate-pressure product (RPP) as an index of myocardial oxygen consumption was investigated in seven normal subjects under fasting conditions. **Methods:** Seven studies were performed at rest and under submaximal continuous supine bicycle exercise with elevated RPP. An additional five studies were performed after dipyridamole injection to increase myocardial blood flow independent of the myocardial energy requirement. **Results:** In all studies, rapid tracer uptake was found within 2–3 min after injection, which remained nearly constant during the 30-min study. Patlak plots of myocardial FTHA kinetics showed a linear increase, indicating metabolic trapping. The mean uptake rate constant, K_i, obtained from Patlak plot analysis was 0.11 ± 0.02 ml/g/min at rest and increased significantly to 0.26 ± 0.06 ml/g/min during exercise. The dipyridamole study yielded a comparatively small elevation with a mean K_i of 0.15 ± 0.02 ml/g/min, which was not significant in the analysis of variance and the Duncan range test. There was a significant correlation between K_i and RPP, with $r = 0.85$ ($p < 0.01$). **Conclusion:** Analysis of FTHA uptake kinetics with PET may be useful for noninvasive assessment of myocardial utilization of exogenous long-chain fatty acids in general and of beta oxidation in the fasting state.

Key Words: dipyridamole; exercise testing; fatty acid imaging; heptadecanoic acid

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In order to study myocardial energy metabolism with positron emission tomography (PET), radiolabeled long-chain fatty acids (LCFAs) such as ^{11}C-palmitate (*1–3*) and ^{18}F-fluoroheptadecanoic acid (*4*) have been proposed. Because beta oxidation of LCFAs represents the main energy supply for the heart in the fasting state, the measurement of their turnover would give information about myocardial oxidative metabolism. The metabolic pathways of these fatty acids, however, are complex and comprise backdiffusion (*5*), turnover in various lipid fractions, beta oxidation and final oxidation in the tricarboxylic acid cycle. Thus, kinetic analysis in a multiple-compartment model remains uncertain (*6*) and there has been no success so far to assess myocardial oxidative metabolism directly with LCFA radiotracers. Presently, ^{11}C-acetate is regarded as the only indicator which reflects myocardial oxygen consumption clearly under various conditions (*7,8*).

The recently introduced thia-fatty acids, which have a sulfur heteroatom in the chain, stand out for their defined metabolic fate (*9–11*). Although accepted by many steps of LCFA metabolism, thia-fatty acids do not undergo complete beta oxidation because this process is blocked by the sulfur atom (*12*). Therefore, the external measurement of tracer kinetics is not distorted by the appearance of catabolites of the oxidative pathway. DeGrado et al. synthesized and evaluated an ^{18}F-labeled thia-fatty acid, 14-[^{18}F]fluoro-6-thia-heptadecanoic acid (FTHA), and studied its in vivo distribution and metabolism in mice (*13*). They found that FTHA was rapidly taken up in the heart followed by a slow clearance of the activity with a half-life of about 2 hr. The hypothesis of oxidative metabolic trapping of FTHA was tested with [5(4-chlorophenyl)-pentyl]oxirane-2-carboxylate (POCA) which inhibits the carnitine palmitoyl-transferase I (CPT I). CPT I is located at the outer surface of the inner mitochondrial membrane and catalyses the formation of acyl-carnitine, the compound by which LCFAs are transported into the inner space of the mitochondria where they are metabolized by beta oxidation. The inhibition of CPT I by POCA blocks the beta oxidation for several hours (*14*). In mice pretreated with POCA, myocardial uptake of FTHA was reduced by 81% at 1 min and 87% at 60 min (*13*). These data suggest that the trapping site is the mitochondria and that ^{18}F-labeled metabolite accumulation is dependent on beta oxidation.

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TABLE 1
Hemodynamic and Glucose Data of Study Group

Subject no.	Age (yr)	Study	Heart rate (1/min)	RR systolic (mmHg)	RPP (mmHg/min)	Glucose (mg/ml)
1	41	Rest	50	107	5350	69
		Dipyridamole	46	109	5014	77
		Exercise	74	140	10360	89
2	33	Rest	78	117	9126	75
		Dipyridamole	76	118	8968	73
		Exercise	102	140	14280	71
3	40	Rest	71	103	7313	74
		Dipyridamole	93	110	10230	74
		Exercise	120	130	15600	66
4	52	Rest	68	105	7140	74
		Dipyridamole	68	101	6868	76
		Exercise	125	134	16750	79
5	30	Rest	60	120	7200	83
		Dipyridamole	63	106	6678	77
		Exercise	97	143	13871	73
6	52	Rest	69	108	7452	68
		Exercise	95	135	12825	96
7	66	Rest	60	107	6420	90
		Exercise	84	122	10248	88
Mean ± s.d.	45 ± 13	Rest	65 ± 9	110 ± 6	7143 ± 1140	76 ± 8
		Dipyridamole	69 ± 7	109 ± 6	7552 ± 2052	75 ± 2
		Exercise	100 ± 18	135 ± 7	13419 ± 2469	80 ± 11

RPP = heart rate × RR systolic = rate-pressure product.

The aim of this PET study was: (1) to study the myocardial kinetics of FTHA; (2) to evaluate its imaging characteristics in humans; and (3) to determine the sensitivity of FTHA kinetics to changes in myocardial oxygen demand and myocardial blood flow. The myocardial kinetics of FTHA were studied in fasting normal humans at rest, during stress and after dipyridamole injection. The dipyridamole study was designed to evaluate the dependence of FTHA uptake on myocardial blood flow. Dipyridamole increases coronary blood flow by approximately four times that of the baseline flow (*15*), while treadmill exercise increases coronary flow at most by approximately twice the baseline flow (*15*). The rate constant of tracer accumulation calculated by Patlak plot analysis (*16*) was correlated to the product of heart rate and systolic blood pressure (rate-pressure product = RPP). RPP is known to correlate closely with oxygen consumption in subjects with normal and ischemic hearts (*17–21*).

METHODS

FTHA Synthesis

No-carrier-added (n.c.a.) synthesis of FTHA was performed using an aminopolyether supported nucleophilic radiofluorination of benzyl 14(R,S)-tosyooxy-6-thiaheptadecanoate (*22*) concurrent with the preparation of 17-[^{18}F]fluoroheptadecanoic acid (*23*). For improvement of purification, an excess of the tosylate was converted by potassium phenolate to the 14-phenylether before ester cleavage by 0.2 N KOH. The n.c.a. FTHA was isolated from the phenyl ether by reverse-phase HPLC on a 20 × 250-mm C-18 column with methanol-to-water-to-acetic acid (88:12:0.4) as eluent. After formulation of n.c.a. FTHA in the serum of the patient and sterile filtration, the radiochemical yield was 35% ± 5% with a total synthesis time of 90 min. The radiochemical purity of this tracer was >98%.

Study Population

Seven healthy male subjects (age 30–66 yr, mean 45 yr) were enrolled in this study. In addition, two normal volunteers were investigated before the onset of the study in order to design the duration of the single measurements. All gave written informed consent. Each subject was interviewed to elicit a complete medical history. None had diabetes or thyroid disease, used medication or had a history of chest pain. The average weight of the study group ranged from 68 to 88 kg (mean 78 kg). There were no significant differences in plasma glucose between the rest, exercise or dipyridamole study. Heart rate and systolic blood pressure measurements were recorded every 5 min throughout the imaging period. The averages of these parameters were multiplied to determine the RPP (Table 1).

Positron Emission Tomography

PET studies were performed using a PC4096-15WB camera. The reconstructed in-plane resolution was 7.1 mm and the z-resolution was about 6 mm (*24*). Attenuation was corrected by using ^{68}Ge-derived transmission scans obtained over 10 min before tracer injection. After intravenous administration of 100–200 MBq of FTHA, myocardial radioactivity was measured up to 30 min. Single scans were initially taken every 15 sec and then extended to 5 min for the last four scans. In two additional normal subjects who were investigated in pilot measurements at rest, uptake kinetics were followed up to 90 min.

Study Protocol

The studies were done after fasting overnight. All subjects were examined at rest and at submaximal bicycle exercise in the supine position. A 50-W workload remained constant throughout the entire imaging period. Once steady-state had been achieved, the tracer was injected intravenously and dynamic positron imaging was carried out in the same way as in the baseline study. In five of the seven volunteers at rest, an intravenous dipyridamole solution of 0.56 mg/kg was infused for 4 min. Because of the delayed vasodilatory effect, FTHA was injected 7 min after infusion onset. The single studies per individual were performed on different days within 1 wk. In order to obtain the plasma input curve, arterialized venous blood samples were withdrawn in intervals of up to 5 min after tracer injection. The blood samples drawn at 5, 10, 15 and 20 min were also used for the determination of plasma glucose levels. Plasma analysis at these times was done by HPLC using the conditions described above for the purification of FTHA with analytical columns. This allowed for the determination of the original nonmetabolized FTHA to be used for the correction of the plasma input function.

Data Analysis

One region of interest (ROI) over the left myocardium was defined at a 30% isocontour level and decay-corrected time-activity curves were calculated for kinetic analysis. Because no regional differences were found by visual inspection of the whole series of 15 reconstructed slices recorded in the normal volunteers, the single ROI was considered to be representative for the entire myocardium. Spillover correction was not performed because FTHA was cleared rapidly from the blood.

The time curves of myocardial activity were analyzed by the Patlak plot method (*16*) using the decay-corrected plasma time-activity curve corrected for metabolized FTHA. In this method, the tissue-to-plasma activity ratio (c_T/c_p) is plotted over the normalized plasma time which is expressed as $\int c_p\, dt/c_p$. For a tracer which irreversibly accumulates in tissue, the plot yields a straight line whose slope represents the uptake rate constant K_i (*16*).

For statistical tests, an analysis of variance with the factors "subject" and "study condition" was used to check the significance of the influence of these parameters on K_i. The factor "subject" was introduced to take into account the repeated measurements in the study subjects. Subsequent comparisons of group means were performed with the Duncan multiple range test (*25*). Regression analysis was done by linear least-squares fitting. The level of significance was set to 0.05.

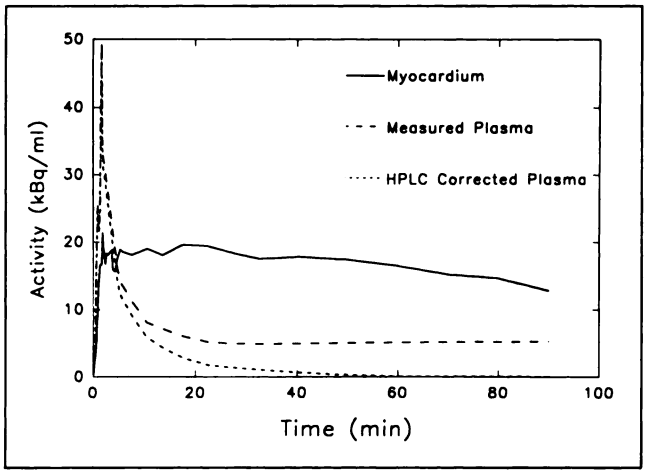

FIGURE 1. Time-activity curves of myocardial FTHA uptake, measured plasma and plasma corrected for unchanged tracer.

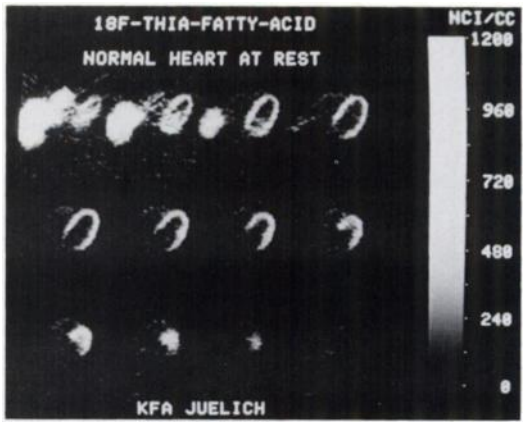

FIGURE 2. Twelve adjacent reconstructed slices obtained in a patient at rest from 10 to 30 min p.i., demonstrating homogeneous myocardial uptake of FTHA.

RESULTS

Figure 1 presents time-activity curves of myocardial FTHA uptake as well as of measured and tracer-corrected FTHA plasma input function over a period of 90 min. As indicated above, such a long period of measurement was utilized only in the pilot studies. The myocardial uptake of the tracer reached a plateau after about 1 min. After 20 min, a slow clearance was observed with a half-time of 130 min. HPLC analysis of FTHA activity in the plasma yielded less than 2% nonmetabolized FTHA after 60 min. Thus, the tracer-corrected FTHA plasma curve approached values near zero at that time. With the Patlak plot, a considerable error propagation was found for times greater than 60 min because errors in the small values of measured nonmetabolized tracer led to large errors in the corrected plasma data and hence in the tissue-to-plasma ratio that is needed in the Patlak plot calculation. Therefore, it was decided to shorten the duration of the study to less than 60 min. Because data analysis yielded practically identical results even within 30 min after injection, this duration was chosen for the study protocol. Figure 2 shows 12 adjacent reconstructed slices obtained in a patient at rest from 10 to 30 min postinjection, demonstrating a homogeneous myocardial uptake of FTHA.

The hemodynamic data of all subjects and their means

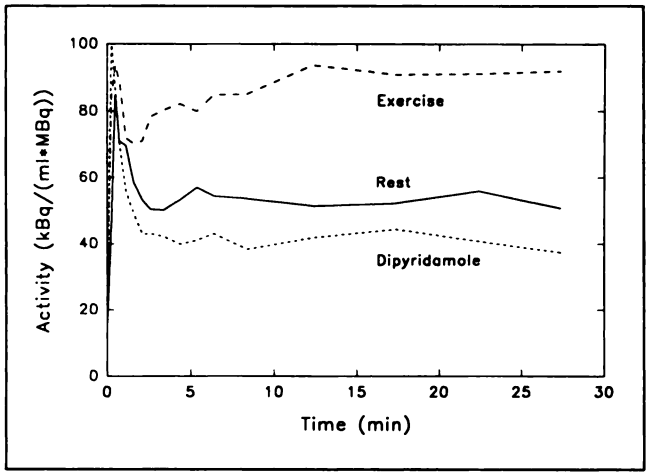

FIGURE 3. Myocardial uptake curve of FTHA at rest, during bicycle exercise and after dipyridamole infusion. The curves are normalized to the injected dose.

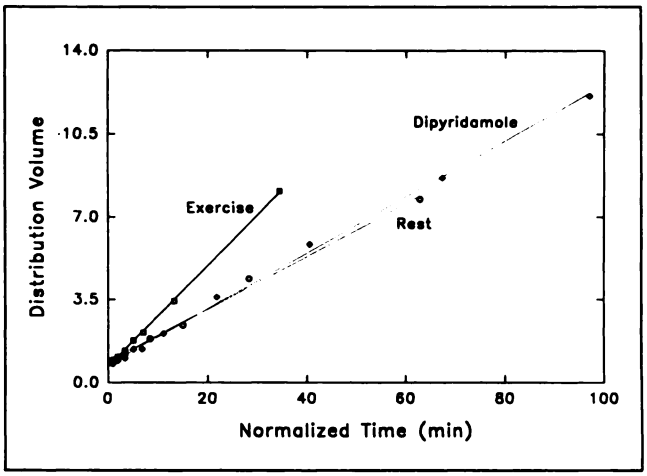

FIGURE 5. Patlak plots of FTHA in the myocardium at rest, during bicycle exercise and after dipyridamole infusion.

are summarized in Table 1. Exercise significantly ($p < 0.001$) increased heart rates by 54%, systolic blood pressure by 32% and RPP by 88%, when compared to the rest studies. In the dipyridamole study there was a 6% increase in heart rate, a 1% decrease in systolic pressure and a 6% increase of RPP. None of these changes were significant. Blood pressure and heart rate remained stable throughout all experiments. Table 1 also presents the glucose levels measured in the single studies and the averages for the three study conditions for which no significant differences were found.

Figure 3 shows myocardial time-activity curves obtained under three different study conditions in one subject from 0 to 27.5 min after injection. The curves are normalized to the injected dose. There is a rapid uptake, which reaches a plateau within 3 min. In this subject, the myocardial uptake of FTHA during exercise was nearly twice the uptake at rest, whereas less uptake was found when dipyridamole was applied.

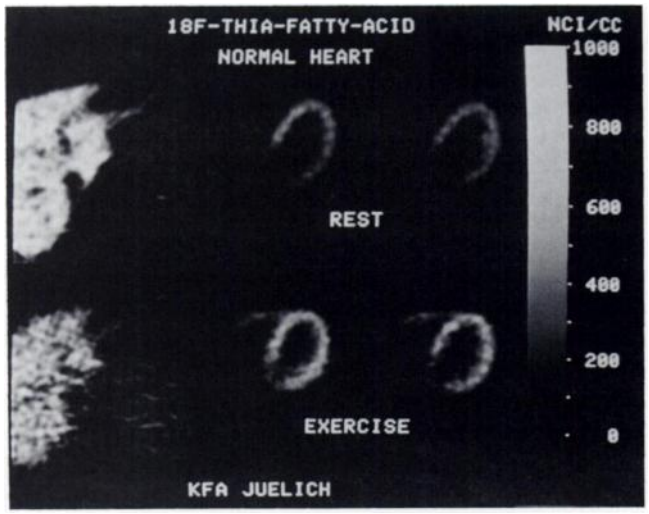

FIGURE 4. Left ventricular uptake distribution of FTHA during rest and exercise (accumulated from 10 to 30 min p.i.).

As shown in Figure 4, the left ventricular myocardial uptake increased in relation to the uptake in liver during exercise. Excellent imaging characteristics were observed. Heart-to-blood ratios increased significantly from 3.7 ($n = 7$) for rest to 6.3 for exercise ($p < 0.01$; $n = 7$), but not significantly to 4.6 ($n = 5$) for dipyridamole. No bone uptake was seen, indicating negligible fluoride formation. Thus, the placement of the fluorine atom at the (ω-3)-position hinders metabolic defluorination as suggested previously (*26*).

Patlak plots of myocardial uptake of FTHA in one subject at rest, during exercise and after dipyridamole are shown in Figure 5. Here, as in all other studies, the Patlak plots increased linearly for data acquired up to 30 min. In this subject, the slope of the Patlak plot increased by 91% during exercise, but remained nearly unchanged after administration of dipyridamole.

The mean K_i obtained from Patlak plot analysis was 0.11 ± 0.02 ml/g/min at rest and increased significantly to 0.26 ± 0.06 ml/g/min during exercise. The dipyridamole experiment yielded only a small, insignificant elevation with a mean K_i of 0.15 ± 0.02 ml/g/min. When K_i of all 19 studies was plotted over RPP, a significant correlation was revealed with a regression coefficient of 0.85 and $p < 0.01$ (Fig. 6).

DISCUSSION

LCFAs play an important role in cardiac metabolism (*27,28*). LCFA radiotracers are useful for noninvasive studies of cardiac metabolism (*29–35*). In agreement with previous animal studies (*13*), FTHA, a false substrate for fatty acid metabolism, is well retained in the myocardium presumably during beta oxidation at the sulfur heteroatom and therefore provides information on the rate of substrate delivery for beta oxidation of the myocardium. The inter-

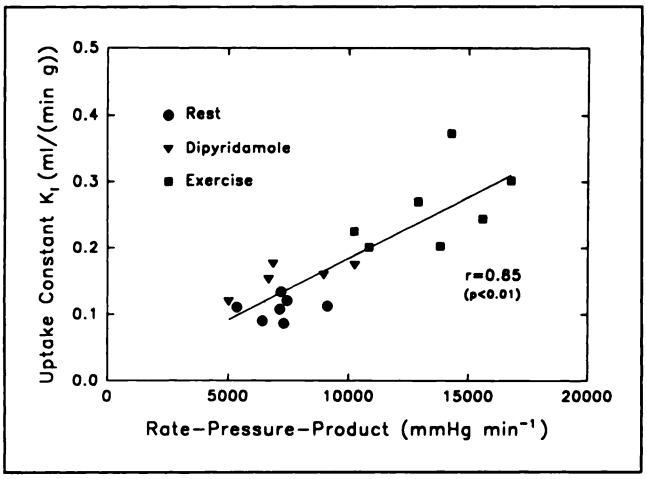

FIGURE 6. Correlation of the rate-pressure product (RPP) and the uptake rate constant K_i.

pretation that the accumulation of FTHA is related to mitochondrial beta oxidation is consistent with recent data from subcellular distribution studies in mouse hearts after intravenous administration of FTHA which showed a large amount (>80%) of radioactivity distributed to a fraction corresponding to mitochondria, nuclei and membranes (DeGrado TR, *unpublished data*).

In all studies of the present work, rapid, homogeneous myocardial uptake of FTHA was seen. In two subjects, myocardial FTHA kinetics were observed until 90 min after injection; the clearance half-time of 130 min was nearly the same as that in mice (*13*).

The high myocardial uptake of FTHA, its rapid clearance from the blood, and its low rate of release from myocardial tissue indicates a trapping phenomenon analogous to the kinetics of 2-deoxyglucose in carbohydrate metabolism (*36*). When activity curves of myocardial uptake of FTHA and of plasma FTHA activity over the first 30 min were analyzed by the Patlak plot technique, linearly increasing slopes were found consistently for all study conditions. This result suggests that the early accumulation of FTHA in the myocardium is nearly irreversible.

As expressed by the heart-to-blood ratio and the rate constant K_i, the myocardial uptake rate of FTHA increased significantly during exercise compared to rest. No significant increases were found when the myocardial flow was elevated by dipyridamole. These results indicate that FTHA accumulation into the myocardium depends almost exclusively on metabolic demand in the absence of coronary vascular disease.

This study, in which subjects with normal hearts were measured while fasting, yielded a significant correlation between the accumulation rate of FTHA and the myocardial oxygen demand, which was expressed by the rate-pressure product. Such a correlation is to be expected for a probe of LCFA delivery rate for beta oxidation. This is also in agreement with the previous finding (*13*) that nonspecific accumulation of FTHA into complex lipids is minimal. Thus, the analysis of FTHA uptake kinetics studied with PET may be useful for noninvasive measurement of LCFA utilization for beta oxidation in humans and may provide information for the understanding and diagnosis of myocardial disease. The simplified kinetics of the metabolically trapped FTHA might allow quantification of the myocardial beta oxidation rate of exogenous LCFA using appropriate tracer kinetic models. In this regard, FTHA may be preferable to ^{11}C-labeled palmitate which has a significant and variable uptake into complex lipids (*37*). In addition to the biochemical advantages of FTHA, its label with ^{18}F, which has a relatively long half-life, should be adequate for the demand of clinical PET. Until now, only ^{11}C-acetate with a short physical half-life was useful in assessing myocardial oxidative metabolism (*7,8*). More biochemical studies are required to test the usefulness of FTHA in the nonfasting state and in ischemic tissue.

CONCLUSION

FTHA shows excellent imaging characteristics for human cardiac studies. It has a rapid clearance from the bloodstream, high myocardial uptake and long retention in the myocardium. The uptake rate in the myocardium is dependent on metabolic demand and on myocardial perfusion to a minor extent. Thus, the changes observed in the myocardial kinetics of FTHA with exercise and vasodilation are consistent with expected changes in beta oxidation of exogenous LCFA and, in the fasting state, myocardial oxygen consumption. FTHA appears to be a promising agent for measuring myocardial metabolism and a possible one for quantitative assessment of the rate of LCFA delivery into mitochondria for beta oxidation. The simplified kinetics of metabolically trapped FTHA might allow quantification of the myocardial beta oxidation rate of exogenous LCFA using appropriate tracer kinetic models.

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