Measurement of Myocardial Fatty Acid Metabolism: Kinetics of Iodine-123 Heptadecanoic Acid in Normal Dog Hearts

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To define the potential of iodine-123 heptadecanoic acid (IHA) for the noninvasive assessment of myocardial fatty acid metabolism with gamma camera imaging, the influence of myocardial oxygen consumption (MVO_2) and blood flow (MBF) on extraction and half-times of IHA were investigated in dogs. Following IHA injection into the left circumflex coronary artery, extraction fraction and half-times were derived from the peak and slope of the IHA time activity curve, which consisted of a vascular, early, and late phase. Single-pass extraction fraction of IHA averaged 0.53 ± 0.11 s.d. at control and was not influenced by MVO_2 and MBF. The half-time of the early phase (T = 9.3 min ± 2.8 s.d. in controls) as well as the ratio between the size of the early and late phase increased with MVO_2 (r = 0.82, r = 0.87, respectively). Thus, early phase intracellular turnover of IHA increased, yet clearance of ^{123}I activity was slowed by augmented cardiac work. Preliminary data of HPLC and electrophoretic analysis of myocardial arterial and venous blood samples over time indicate that the early phase is characterized by a decreasing washout of IHA and a relative increase of radioiodine washout. The half-time of the late phase (T = 245 min ± 156 s.d. at control) was not related to MVO_2 and MBF. In conclusion, myocardial fatty acid metabolism cannot be measured from the half-time of the early phase but might be analyzed from the ratio between the size of the early and late phase when using IHA.

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Free fatty acids (FFA) represent the preferred energy substrate for the heart under physiologic conditions (*1, 2*), where their oxidation accounts for as much as 90% of myocardial oxygen consumption (MVO_2) (*3,4*). In the past, a various number of FFA have been proposed for the noninvasive assessment of myocardial FFA metabolism (*5–9*), among which only the physiologic carbon-11 (^{11}C) palmitic acid (CPA) with positron computed tomography was considered an accurate agent for the quantitation of regional myocardial FFA utilization (*10–17*). However, the major limitation of positron imaging is the worldwide scarcity of the relatively expensive imaging devices and cyclotrons. Therefore, research has drawn its attention to gamma emitting radioisotopes [i.e., iodine-123 (^{123}I)] labeled to FFA which could be used by more widespread gamma cameras. Among these iodinated FFA, ^{123}I heptadecanoic acid (IHA) offered a potential value for the study of myocardial FFA metabolism (*18–20*). The resemblance of the clearance curves of IHA and CPA under normal conditions and during altered substrate availability suggested that the clearance of IHA during the early phase might be a measure of myocardial FFA oxidation (*20–22*). However, none of these studies has proven the direct relationship between the early clearance rate of IHA and MVO_2. As this relationship is absolutely necessary to evaluate the potential of IHA as a metabolic tracer, it was the purpose of this study to characterize the kinetics of IHA in normal myocardium and relate these kinetics directly to MVO_2 as an index of myocardial oxidative metabolism under different levels of cardiac work.

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MATERIALS AND METHODS

Experimental Preparation

Eight mongrel dogs weighing 20 to 26 kg were fasted 24 hr prior to the experiment and anesthetized with

fentanylbase (0.15 ml/kg) and etomidate (initially 0.5 mg/kg i.v., then 5 mg/kg/hr at a constant infusion rate). The ventilation was maintained with a 34% oxygen/66%N_2O mixture using a Pulmomat respirator*. A catheter was advanced through the femoral artery into the aorta to monitor systemic blood pressure (Statham P 23 Db pressure transducer) and withdraw arterial reference blood samples for flow measurement. After a left thoracotomy the heart was exposed and suspended in a pericardial cradle. Two polyethylene cannulas were inserted into the left atrium for injection of labeled microspheres and arterial blood sampling. For collection of coronary venous blood the great cardiac vein was cannulated with an 0.8-mm Teflon cannula connected to a fine plastic tubing. After preparation of the left circumflex coronary artery (LCX) an electromagnetic flow probe (Type B, Hellige) was placed around the LCX and distally to it a 25-gauge needle connected to a fine polyethylene tube was inserted into the LCX for intracoronary tracer administration. The ECG, arterial blood pressure and LCX flow were monitored continuously on a strip chart recorder†. Myocardial ^{123}I activity was recorded with a lead-shielded and collimated 7.5 × 5.0 cm NaI(Tl) scintillation detector positioned over the myocardium supplied by the LCX. The detector was connected to an on-line digital computer system‡.

Experimental Protocol

A total of 13 experiments were performed in eight dogs. Six studies were done under control conditions, while in five experiments MVO_2 was altered by atrial pacing§. In two experiments myocardial arterial and venous blood samples were analyzed up to 40 min after high-dose (2 mCi) intracoronary bolus injection of IHA by means of high pressure liquid chromatography (HPLC) (250 × 4 mm and 125 × 4,6 mm columns)¶ and electrophoresis**.

Immediately before IHA administration regional myocardial blood flow (MBF) was measured with tin-113- or scandium-46-labeled carbonized microspheres (15 ± 3 μ in diameter)†† and the arterial reference sample technique (*23*). A bolus of 200 to 250 μCi of IHA‡‡ contained in 0.2 ml of a 6% albumin solution was then flushed into the LCX and myocardial time activity curve recorded for 65 min. In five dogs, a second 0.3 ml IHA bolus with an activity of ~500 μCi was injected into the LCX 2 hr later. For these experiments the residual activity of the first run was corrected.

Myocardial arterial and venous blood samples were drawn before and 5 min after intracoronary IHA administration to analyze blood gases and plasma levels of triglycerides, glucose, and lactic acid. Determination of MVO_2, myocardial FFA, glucose, and lactic acid consumption are described elsewhere (*14*).

Data Analysis

The recorded time activity curves of myocardial ^{123}I activity were corrected for physical decay and processed with a multiexponential least-square fitting routine using a digital computer‡. Data correction for blood pool activity was not performed, as, with the intracoronary bolus injection technique, radioiodine activity in arterial blood was found to be negligible.

All mean values are given with their standard deviations. Statistical tests of the results were performed with linear regression analyses or, when appropriate, with Student's t-test for paired and unpaired data.

RESULTS

Hemodynamic and Biochemical Findings

In the six control experiments, heart rates averaged 132 ± 18 bpm, mean arterial blood pressure was 118 ± 20mm Hg and MVO_2 averaged 9.15 ± 2.75 ml/min/100 g. Myocardial consumption of triglycerides at control was 0.27 ± 0.32 mmol/min/100 g, of glucose 30.4 ± 27.1 μmol/min/100 g, and lactic acid consumption averaged 12.8 ± 13.6 μmol/min/100 g. With atrial pacing, heart rates increased to 192 ± 13 bpm ($p < 0.001$), whereas mean blood pressure did not change significantly from control. MVO_2 was augmented to 15.9 ± 3.31 ml/min/100 g ($p < 0.001$) during pacing, while myocardial consumptions of triglycerides, glucose, and lactic acid did not differ significantly from control. However, with enhanced cardiac work the ratio of myocardial triglyceride to glucose utilization was higher than in the control experiments (12.1 ± 6.8 vs. 8.5 ± 4.3, $p < 0.05$).

Myocardial Iodine-123 Time Activity Curve after Intracoronary IHA Injection

A typical ^{123}I time activity curve of a control experiment is demonstrated in Fig. 1. Counts were recorded for 65 min following intracoronary bolus injection of IHA. After a vascular phase which at its end was contaminated by recirculating ^{123}I activity from the coronary sinus through the right and left heart, an early and a late curve component were detected. The half-time of the early component or early phase for all control experiments averaged 9.3 ± 2.8 min. The half-time of the late phase was considerably longer with a mean of 245 ± 158 min in the six control studies. The relative size of the early phase (E_e) averaged 0.24 ± 0.05 and the size of the late component (E_l) was 0.29 ± 0.07 for controls.

Single Pass Extraction Fraction of IHA in Myocardium

IHA extraction fraction after a single capillary transit (E), calculated as the sum of the size of the early and late phase, averaged 0.54 ± 0.12 in the six control

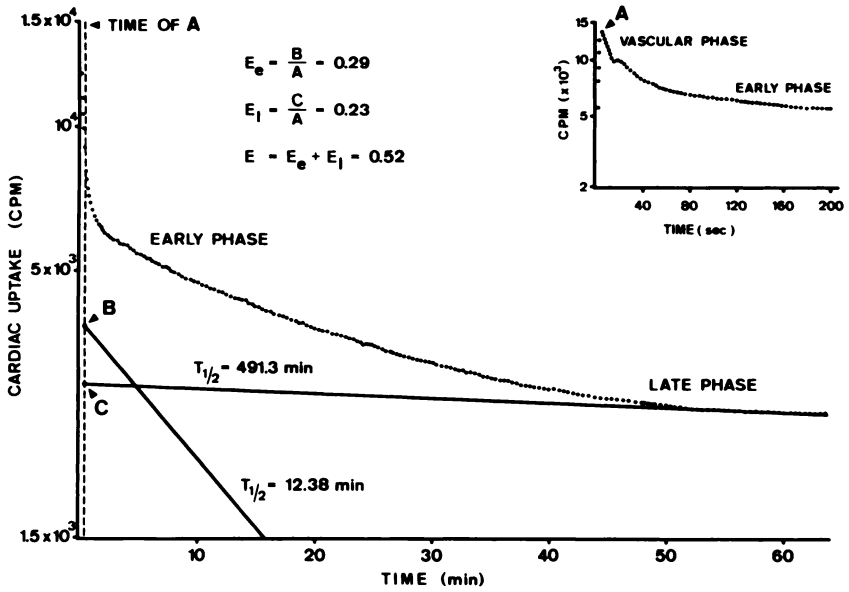

FIGURE 1
Myocardial ^{123}I time activity curve recorded for 65 min after intracoronary bolus injection of IHA. Curve is displayed in low time resolution mode (30-sec intervals) and shows characteristic biphasic appearance with early and late phase. Inset in upper right depicts initial 300 sec of curve in higher frequency mode (2-sec time samples). Peak activity A equalizes total injected activity and is followed by vascular phase. Sizes of early (E_e) and late curve component (E_l) are determined by extrapolating slopes of each phase back to time of A and dividing intercepts B and C by A. Sum of E_e and E_l represents total single pass extraction fraction of IHA

experiments. Neither myocardial consumptions and arterial concentrations of triglycerides and glucose nor arterial pH revealed a significant influence on E (all p >0.05). Subsequently, MVO_2 and MBF were examined for their effect on E. As shown in Fig. 2, both an increase in MVO_2 and MBF did not alter E significantly. Thus, despite changes in MVO_2 due to enhanced cardiac work, and concomitant alterations in MBF, E remained essentially constant.

Influence of Cardiac Work on the Early Phase

In order to prove the assumption that the early phase is characterized by myocardial oxidation of IHA, the effect of different levels of cardiac work on the early phase was examined. Figure 3A demonstrates a positive relationship between the half-time of the early phase and MVO_2, however in an unexpected way: ^{123}I activity cleared from myocardium the slower, the more MVO_2 or cardiac work was augmented. In other words, with increased MVO_2 and a subsequent increase in myocardial FFA oxidation (*14*) the turnover of IHA during the early phase decreased. Hence, the half-time of the early phase is no direct measure of IHA oxidation. In addition, the half-time of the early phase was not related to myocardial triglyceride consumption (r = +0.18, p >0.05) as a measure of actual fatty acid metabolism.

The size of the early phase was directly proportional to MVO_2 (Fig. 4A). Thus, with enhanced cardiac work more IHA entered the early phase. Both the half-time (Fig. 3B) and the size (r = 0.23; p >0.05) of the early phase were independent of MBF at a flow range from 60–178 ml/min/100 g.

Influence of Cardiac Work on the Late Phase

The size of the late phase of the time activity curve decreased as MVO_2 was increased (Fig. 4B). The rate of clearance of ^{123}I activity from myocardium during the late phase, expressed as the half-time, was not influenced by changes in MVO_2 (r = 0.13; p >0.05).

In addition, there was no relationship between the size (r = 0.08; p >0.05) and half-time (r = 0.11; p >0.05) of the late phase and MBF. The late phase most likely reflected storage of IHA.

Relation Between the Early and Late Phase

With augmented MVO_2 the ratio between the size of the early and late phase increased linearly (r = 0.87; p <0.01) and was independent of MBF (r = 0.32, p >0.05). As E of IHA was not significantly influenced by MVO_2 (Fig. 2A), more IHA entered the early phase and less IHA was stored during the late phase when cardiac work was increased.

DISCUSSION

Myocardial free fatty acid metabolism is well understood at present (*1–3,14,15*). FFA are extracted by the myocardial cell and activated to FFA-CoA by way of thiokinase. FFA-CoA is either oxidized or esterified. When using the physiologic FFA ^{11}C-labeled palmitic acid (CPA) the oxidative pathway is characterized by an early phase of the time activity curve, which is associated with release of ^{11}C-CO_2, whereas the esterified pathway is identified by a slow late phase (*14*). Both pathways compete for FFA-CoA.

The decision of which pathway is preferred primarily depends on MVO_2, and second, on substrate availability in plasma (*24*). With high MVO_2 more FFA-CoA is utilized or oxidized and more CO_2 is released from myocardium. In fact, the clearance rate of ^{11}C activity or half-time during the early phase was inversely related to MVO_2 (*14*). Thus, the half-time of the early phase of the ^{11}C time activity curve represents a measure of myocardial FFA oxidation and provides quantitative

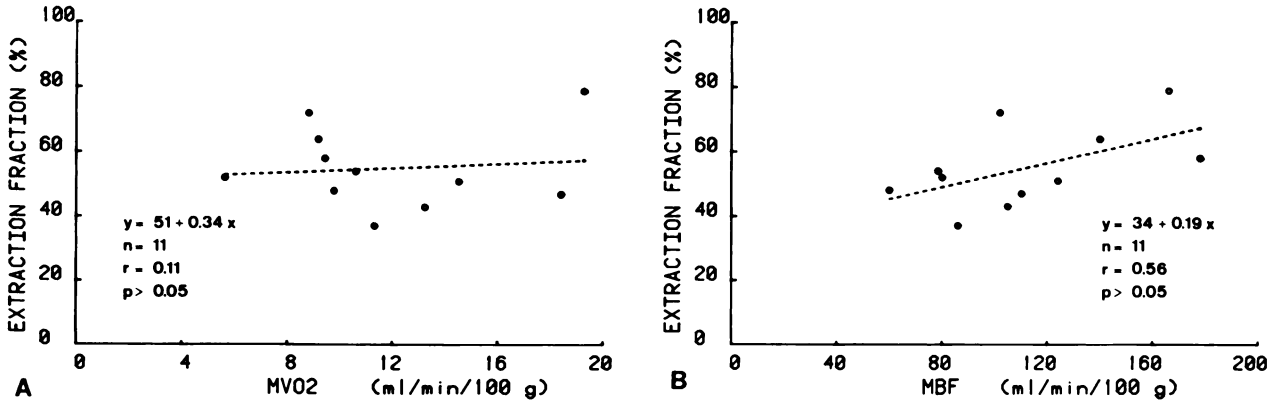

FIGURE 2
Relationship of myocardial single pass extraction fraction (E) of IHA to myocardial oxygen consumption (panel A) and myocardial blood flow (panel B). Despite marked changes in flow and oxygen consumption, extraction fraction remained relatively constant

means for the noninvasive assessment of regional myocardial FFA metabolism (*25*).

These experiments have all been performed with the physiologic CPA. Since the time activity curves of terminally iodinated FFA such as IHA resembled somehow that of CPA, it was concluded by some authors (*18–22,26*), that FFA metabolism can also be measured quantitatively from the half-time of the early phase of IHA. The findings of this study indicate, however, that despite comparable methodology the kinetics of IHA are different from those of CPA (Table 1) and that the half-time of the early phase of IHA does not provide quantitative information about IHA oxidation.

Myocardial Extraction Fraction of IHA

For determination of myocardial E of IHA during a single capillary transit the intracoronary bolus injection technique was used. This approach was previously employed and validated to study myocardial tracer kinetics (*14,15,27–29*) and minimizes the effects of tracer recirculation on the primary myocardial time activity curve, thus permitting visual and quantitative analysis of the intrinsic turnover of tracer substances in myocardium.

In the six control experiments E averaged 0.54 ± 0.12 and was lower than E of CPA ($p < 0.005$) (*14*), which corresponds to the findings of Machulla et al. (*18*) about halogenated FFA. Since IHA and ^{123}I hexadecanoic acid were found to have similar myocardial extractions (*32*), the E value of the current study is also lower than the 0.70–0.78 extraction fraction of ^{123}I hexadecanoic acid observed by Westera (*30*) and Jatley (*31*), who proposed this radiopharmaceutical as a sufficient flow tracer. The difference of E might be explained by the different technique as well as the different species. According to our experiments, however, IHA does not satisfy the criteria for a good flow tracer mainly because of its medium range E at a single capillary transit.

Similar to CPA (*14*) single pass myocardial E of IHA was relatively constant despite considerable variations

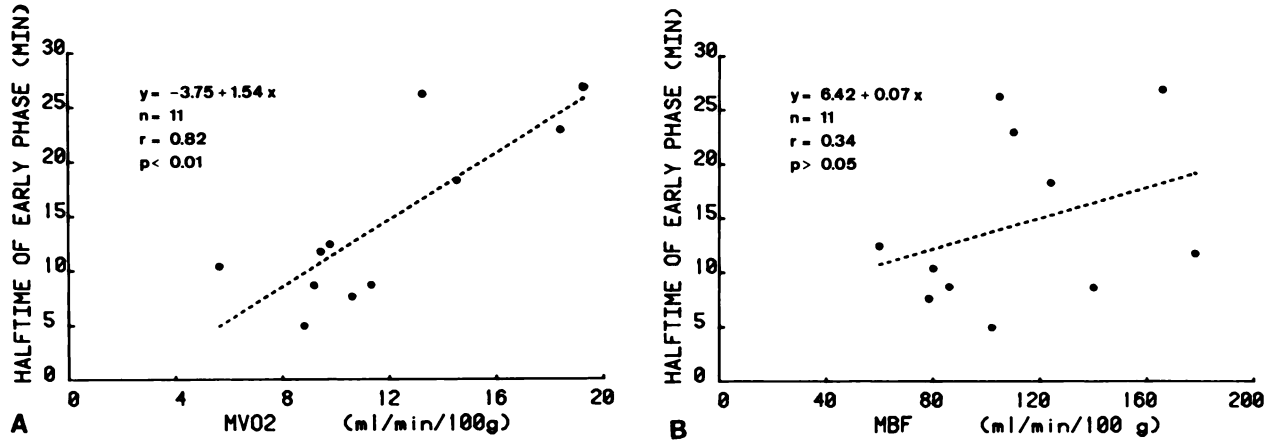

FIGURE 3
Relationship of half-time of early phase to myocardial oxygen consumption (panel A) and blood flow (panel B). While half-time of early phase is independent of flow, there seems to be positive relation to myocardial oxygen consumption: With increased cardiac work, ^{123}I clearance was slowed

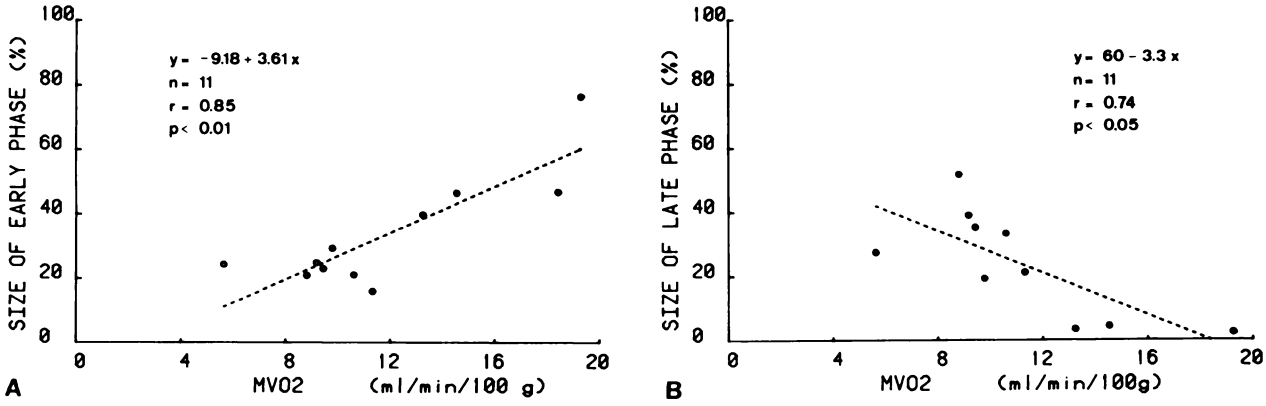

FIGURE 4
Relationship of size of early phase (panel A) and size of late phase (panel B) to myocardial oxygen consumption. With enhanced myocardial oxygen consumption, size of early phase increased, whereas size of late phase decreased

in MVO_2 and MBF. This, according to the Renkin-Crone model (*33,34*) unexpected finding, where a flow-related fall of E was described, must be explained by an isolated increase of E with MVO_2—as it was found with CPA (*14*)—so that E remains essentially constant when both flow and MVO_2 increase.

Turnover of IHA in Myocardium

After its myocardial sequestration IHA is cleared from myocardium in a biexponential manner. This was observed in nearly all investigations with intracoronary injection techniques (*18–20,22,26,35*) in all species. IHA therefore appeared to enter two pools with different turnover rates. The turnover rate or half-time of the early phase in the six control experiments averaged 9.3 ± 2.8 min and was slightly higher than the 7.3 min observed in calves by Dudczak et al. (*20*) after intracoronary administration of IHA under control conditions. Another group (*36*) found in isolated perfused rabbit hearts a half-time of 14.3 ± 2.1 min of a monoexponential IHA time activity curve. These differences may be species-related; they may, however, partly result from a too short monitoring of the ^{123}I time activity curve (*36*), where the reported half-time might represent the sum of the slopes of two curve components. Compared to the half-time of the early phase of CPA, our IHA half-time of the early phase was significantly longer (Table 1) in the control experiments (*14*). With CPA the turnover rate of the early phase depended on MVO_2 and correlated with the rate of ^{11}C-CO_2 production as a measure of myocardial CPA oxidation (*14*). If IHA was equivalent to CPA as stated by many authors (*21,22, 26*), then the half-time of its early phase should indeed decrease with augmented MVO_2 or the turnover of IHA during this phase should be accelerated. Our experiments revealed the contrary: With increased MVO_2 the half-time of the early phase was prolonged and the clearance of ^{123}I activity from myocardium became slower. Moreover, the ^{123}I clearance during the early phase did not correlate with actual myocardial fatty acid metabolism. Thus, metabolic turnover rates from myocardium cannot be measured from the half-time of the early component of the IHA time activity curve.

For a better understanding of the ^{123}I clearance rates from myocardium especially during the early phase, HPLC and electrophoretic analysis over a 40-min period of several simultaneously drawn myocardial arterial and venous blood samples were performed in our lab. Preliminary results indicate an over time decreasing washout of IHA as well as an over time increasing washout of free ^{123}I without evidence of intermediate metabolic products. These findings coincide with the results of Freundlieb et al. (*33*), who, also using HPLC, described an increased ^{123}I concentration over time in peripheral blood after i.v. administration of IHA. Stöcklin (*37*) postulated that the transportation of halide ions out of cell membranes and especially out of the mitochondria, where β-oxidation occurs, takes place by way of diffusion. Furthermore, the size of the solvated anion influences the rate of diffusion. Hence, the elimination of the ^{123}I ion out of the mitochondrion and cell membrane most likely represents the rate-determining step of the ^{123}I clearance rate during the early phase. This could explain the different half-times of CPA and IHA in control experiments. As with increased cardiac work the elimination of ^{123}I is prolonged, the membrane permeability for ^{123}I ions could decrease proportionally

TABLE 1
Comparison of the Kinetics of ^{123}I Heptadecanoic Acid (IHA) to ^{11}C Palmitic Acid (CPA) in Control Experiments Using Comparable Experimental Conditions*

Parameters at control	IHA (n = 6)	CPA (n = 10)	
Extraction fraction E	0.54 ± 0.12	0.65 ± 0.10	p <0.01
$T_{½}$ of early phase (min)	9.3 ± 2.8	3.4 ± 0.9	p <0.005
$T_{½}$ of late phase (min)	245 ± 158	159 ± 58	p <0.01
Size of early phase / Size of late phase	0.81 ± 0.39	1.71 ± 0.83	p <0.005

*For details of the kinetics of CPA see Ref (*14*).

to MVO_2. Since prolonged half-times of the early phase have also been described in myocardial ischemia (*20*, *32*,*26*,*37*), the half-time of the early phase can no longer be used specifically for identifying ischemic areas. Moreover, prolonged half-times of the early phase have to be interpreted with extreme caution as representing a probe for mitochondrial or cellular membrane integrity.

Different than the half-time, the size of the early phase increased with augmented MVO_2, whereas the size of the late phase decreased. This indicates that during the early phase with increased cardiac work more IHA is utilized and simultaneously less IHA enters the second pool or late phase. In the control experiments the ratio between the size of the early and late phase averaged 0.81 ± 0.39 which did not differ significantly to the ratio of 0.94 found by Dudczak (*20*) in calves. The positive relationship between this ratio and MVO_2 indicates that the ratio between the size of the early and late phase might serve as a measure of IHA metabolism, although with IHA this ratio was significantly lower than with CPA. Further investigation is needed to prove whether this parameter can be used for the analysis of regional myocardial fatty acid metabolism in health and disease.

The second pool or late phase is associated with storage of IHA into triglycerides and phospholipids. Its turnover rate from myocardium varied with a mean of 245 min, which was higher than that of Dudczak (*20*) and also that of CPA (*14*). Similar to CPA (*14*) the clearance half-time of the late phase was independent of MBF and MVO_2.

In conclusion, the findings of this study indicate that the tracer kinetics of IHA in control experiments are different than those of the physiologic CPA. In detail, myocardial IHA metabolism cannot be measured from the half-time or clearance rate of the early phase of the myocardial ^{123}I time activity curve. However, the ratio between the size of the early and late phase might provide qualitative information about regional myocardial fatty acid metabolism in health and disease.

FOOTNOTES

* Draegerwerk, FRG.
† Hellige Recomed System, Freiburg, FRG.
‡ Tectronix 4052, Beaverton, OR.
§ Grass S 88 stimulator, Quincy, MA.
¶ Waters Inst., Eschborn, FRG.
** Hormuth-Vetter Pherograph model 64, Wiesloch, FRG.
†† NEN, Dreieich, FRG.
‡‡ Squibb Laboratories, Würenlingen, Switzerland.

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