COMPARATIVE MYOCARDIAL UPTAKE OF INTRAVENOUSLY ADMINISTERED RADIONUCLIDES

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The myocardial and blood clearance rates and the myocardium-to-blood ratios for radiopharmaceuticals such as ^{43}K, ^{86}Rb, ^{129}Cs, radioiodinated oleic acid, ^{203}Pb, ^{69}Zn, and $^{99m}TcO_4^-$ as a function of time were compared in rats. Attempts were made to alter these parameters by various pharmacological and dietary interventions. While ^{69}Zn, ^{203}Pb, and $^{99m}TcO_4^-$ showed ratios below or only little greater than 1, ^{43}K, ^{86}Rb, and ^{129}Cs reached myocardial concentrations about 27 times higher than their corresponding blood levels. Radioiodinated oleic acid showed ratios between 1 and 6.5 depending on the specific activity. Insulin in 20% glucose was shown to cause substantial increases in the ratios for potassium, rubidium, cesium, and radioiodinated oleic acid. Digoxin and isoproterenol caused significant changes in myocardial clearance rates and therefore in the myocardial-to-blood ratios. The ratios for oleic acid were decreased when the compound was injected in the fasting state. The described animal model can be helpful for determining the suitability of radionuclides for myocardial scanning and for examining the effects of pharmacologic and dietary interventions.

During recent years an increasing number of radiopharmaceuticals have become available for myocardial imaging (*1–15*). When injected directly into the coronary arteries, they yield high-quality images with little or no background activity. These techniques, however, require cardiac catheterization. In contrast, it has been shown that the intravenous administration of a variety of radiopharmaceuticals does provide a simple and noninvasive means of visualizing normally perfused myocardium. In addition, in theory, these noninvasive methods have the potential to yield information relating to the viability of myocardial cells because their uptake depends upon both regional myocardial blood flow and upon the active transport of the agents across the cell membrane.

Unfortunately the intravenously administered radioactive agents often remain in the blood at rather high concentrations, accumulate in skeletal muscle or in the liver in addition to the myocardium, or are excreted into the upper gastrointestinal tract, each contributing to relatively high background activities surrounding the heart. Consequently, the images are often difficult to interpret. Moreover, it appears that the perfusion pattern seen on the scan depends upon the rate of uptake or washout or both and thus upon the time after the injection that imaging is performed.

It became of interest, therefore, to compare the myocardial uptake as a function of time for a variety of intravenously administered radiopharmaceuticals such as potassium, cesium, rubidium, and radioiodinated lipids as well as less commonly studied drugs in the same animal preparation. In addition, it was attempted to alter the myocardial concentrations or blood levels of these radiopharmaceuticals by various pharmacologic and dietary techniques and to examine the effects of carrier substances on the myocardial extraction of several of these agents.

METHODS

Sprague-Dawley rats weighing between 250 and 300 gm and fed ad lib were used. Under ether anesthesia each radiopharmaceutical was injected through a leg vein and the animals were allowed to recover. They were reanesthetized in groups of four rats at 10, 30, 60, 90, and 120 min after injection. Using a 19-gage needle, blood (2–3 ml) was withdrawn from a cardiac chamber through the chest wall and the

Received Feb. 15, 1974; revision accepted June 26, 1974.

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heart was then rapidly excised. After removing the atria and great vessels and opening the ventricular chambers, the remaining blood was washed off using a 20% formaldehyde solution. The heart and blood specimens were collected in tightly sealed counting tubes and weighed on an analytical balance. At the end of each study the activity of each sample was determined in a well scintillation counter (Automatic Gamma Counting System, Searle Radiographics, Inc., Des Plaines, Ill.) and expressed in counts per minute per milligram. By dividing the specific activity in myocardium by the specific activity in blood, a myocardium-to-blood (M/B) ratio was established.

Twenty microcuries of $^{99m}TcO_4^-$, ^{43}K (Medi-Physics, Emeryville, Calif.), ^{129}Cs (New England Nuclear, North Billerica, Mass.), ^{86}Rb (International Chemical & Nuclear Corp. (ICN), Irvine, Calif.), ^{203}Pb (New England Nuclear, North Billerica, Mass.), and ^{69}Zn (Union Carbide Corp. Tuxedo, N.Y.) were individually injected in a total volume of 0.3 ml. Except for ^{69}Zn, which was contaminated with carrier Zn during production, all radioisotopes were carrier-free.

Oleic acid was labeled with carrier-free ^{131}I according to the method described by Anghileri (*16*). In brief, $Na^{131}I$ (1–5 mCi) was evaporated to dryness under a stream of nitrogen. Iodine monochloride was allowed to exchange with the radioactive residue for 30 min after which the oleic acid was added. Following 2 hr at room temperature the reaction was terminated by adding an alcoholic solution of sodium metabisulfite. The iodinated oleic acid was purified by anion-exchange chromatography. Examining the "iodinated oleic acid" by thin-layer chromatography showed less than 1% inorganic iodide. For the majority of the experiments ^{131}I-oleic acid was dissolved in aqueous propylene glycol and the pH adjusted to 8 with 1 *M* NaOH. In a number of experiments radioiodinated oleic acid was added to 25% human serum albumin (HSA) and the mixture shaken until complete solution was obtained. The average dose of ^{131}I-oleic acid per animal was 1.5 mg contained in 0.3 ml solution.

Because iodination of oleic acid in the manner described leads to a loss of a double bond, the resulting compound no longer can be considered biologically as true oleic acid. The term ^{131}I-oleic acid, however, will be used in this communication for convenience.

The experiments were divided into four groups: in Group 1 (140 rats), control M/B ratios and the time course of accumulation were established for each radiopharmaceutical. The effects of carrier upon the M/B ratios for $^{99m}TcO_4^-$, ^{129}Cs, and ^{203}Pb were examined in Group 2 (60 rats) by adding sodium perrhenate, cesium chloride, and lead acetate to the corresponding radiopharmaceutical so that each animal received 1 mg of carrier. In Group 3A (60 rats) an attempt was made to improve the M/B ratios by injecting insulin (Reg. Insulin USP 80, E. R. Squibb & Sons, Inc., New York, N.Y.) (1 I.U./kg) in 0.3 ml of 20% glucose IV simultaneously with the potassium, cesium, and rubidium. In Group 3B (32 rats), ^{43}K was injected into 12 rats

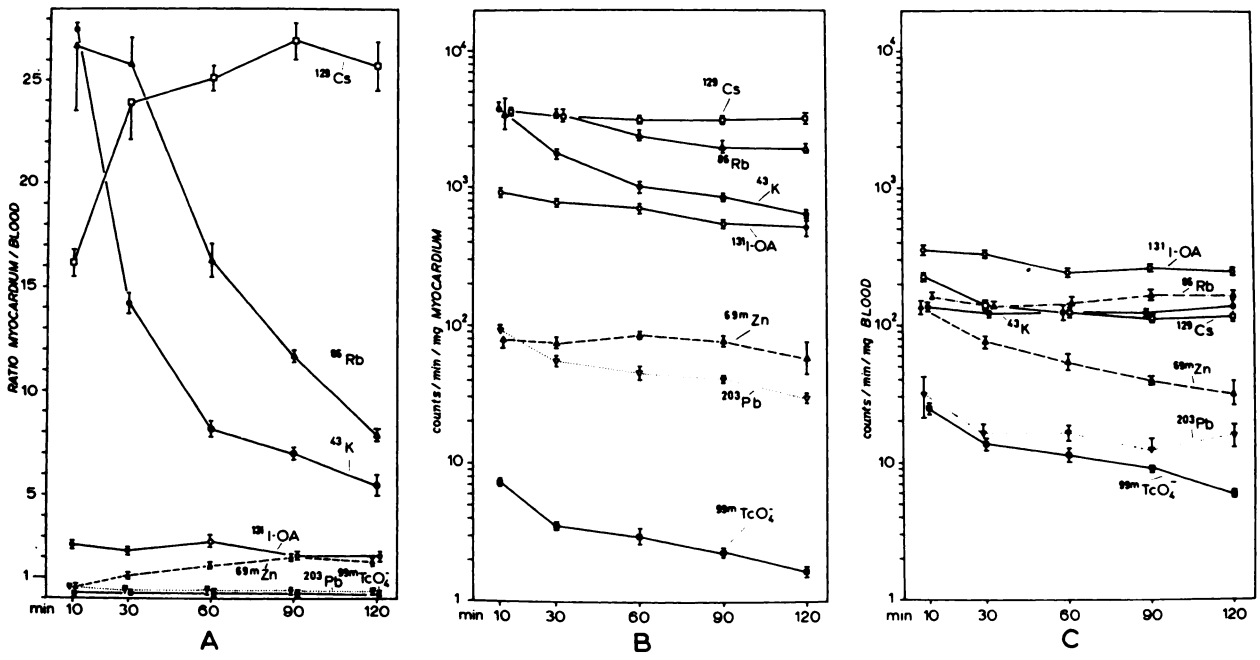

FIG. 1. Comparison of myocardium-to-blood ratios (A), myocardial concentrations (B), and blood levels (C) for all radiopharmaceuticals studied. Each point represents average of four animals and 1 s.e.

TABLE 1. MYOCARDIUM-TO-BLOOD RATIOS FOR THE RADIOPHARMACEUTICALS STUDIED

Radiopharmaceutical	Intervention	Myocardium-to-Blood-Ratio (minutes after injection) 10	30	60	90	120
$^{99m}TcO_4^-$	Control	0.30 ± 0.02	0.26 ± 0.01	0.26 ± 0.1	0.25 ± 0.01	0.28 ± 0.01
	+ rhenium	0.26 ± 0.004	0.27 ± 0.007	0.26 ± 0.006	0.26 ± 0.01	0.26 ± 0.002
^{69}Zn	Control	0.58 ± 0.04	1.0 ± 0.04	1.58 ± 0.05	2.05 ± 0.15	1.82 ± 0.17
^{203}Pb	Control	0.48 ± 0.26	0.41 ± 0.11	0.29 ± 0.11	0.36 ± 0.10	0.17 ± 0.02
	+ lead acetate	0.11 ± 0.09	0.08 ± 0.02†	0.09 ± 0.01†	0.09 ± 0.02†	0.10 ± 0.01†
^{129}Cs	Control	16.2 ± 0.7	23.9 ± 1.8	25.1 ± 0.7	26.9 ± 0.9	25.7 ± 1.2
	+ CsCl	10.8 ± 1.4†	16.9 ± 1.1†	18.9 ± 1.1†	21.1 ± 2.3	21.7 ± 1.9
	+ insulin in 20% glucose	15.4 ± 0.5	27.0 ± 0.7†	30.4 ± 0.6†	31.1 ± 0.7†	32.2 ± 1.6
^{43}K	Control	27.6 ± 0.3	14.2 ± 0.5	8.2 ± 0.4	7.0 ± 0.3	5.5 ± 0.5
	+ insulin in 20% glucose	32.0 ± 2.6	21.1 ± 1.1	12.4 ± 0.5	8.1 ± 0.2	6.6 ± 0.1
	+ digoxin	26.5 ± 0.6	16.5 ± 0.5†	11.4 ± 0.4†	8.7 ± 0.2†	7.5 ± 0.2†
	+ isoproterenol	23.9 ± 1.5	22.2 ± 0.6†	11.9 ± 0.7†		
^{86}Rb	Control	26.7 ± 3.2	25.8 ± 1.3	15.6 ± 1.0	11.9 ± 0.4	9.0 ± 1.1
	+ insulin in 20% glucose	29.4 ± 8.0	26.8 ± 1.5*	19.3 ± 2.4*	14.1 ± 0.7†	11.5 ± 0.7†
^{131}I oleic acid	in propylene glycol	2.63 ± 0.12	2.28 ± 0.1	2.79 ± 0.17	2.08 ± 0.25	2.26 ± 0.07
	fasting state	2.64 ± 0.24	1.45 ± 0.01†	1.13 ± 0.12†	1.15 ± 0.18†	1.61 ± 0.21*
	insulin-glucose	2.21 ± 0.11	2.35 ± 0.23	2.95 ± 0.26	3.17 ± 0.34†	3.34 ± 0.41*
	heparin	3.00 ± 0.25	2.90 ± 0.23	3.20 ± 0.20	2.47 ± 0.19	2.36 ± 0.15
	in human serum albumin	2.40 ± 0.01	2.08 ± 0.09	2.26 ± 0.39	2.20 ± 0.40	2.33 ± 0.09

Significantly different from control * $p < 0.05$; † $p < 0.01$.

5 min following a subcutaneous injection of isoproterenol (0.08 μg/kg) and into 20 rats 30 min after the intraperitoneal administration of digoxin (8 μg/kg). In Group 4 (80 rats) ^{131}I-oleic acid dissolved in aqueous propylene glycol was used. The effects of insulin in hypertonic glucose in 20 rats, of heparin [Lipohepin (aqueous sodium heparin), Riker Laboratories, Inc., Northridge, Calif.] (100 μg/kg given i.p. 10 min after the oleic acid) in 20 rats, and of altering the dose of oleic acid in eight rats were studied. In addition, the effect of a 24-hr fast upon the M/B ratios of labeled oleic acid was determined in 20 rats and finally in a series of 20 rats the myocardial uptake of radioiodinated oleic acid dissolved in human serum albumin was evaluated in comparison with the same agent dissolved in propylene glycol.

For statistical analysis, Student's t-test for grouped and paired data was used (*17*).

RESULTS

Comparison of radiopharmaceuticals (Group 1). The concentration in myocardium and blood as a function of time and the corresponding M/B ratios for each radiopharmaceutical are shown in Fig. 1. For $^{99m}TcO_4^-$ the highest myocardial concentration was noted 10 min following injection (Fig. 1B). Within the next 20 min the concentration decreased by 52% followed by a phase of slower washout having a half-time of approximately 1.4 hr. The decrease in myocardial content was paralleled by a fall in blood concentration (Fig. 1C) and the resulting M/B ratio of 0.26 ± 0.01 (s.e.m.) remained approximately the same throughout the entire period studied (Fig. 1A). Lead-203 was cleared from myocardium and blood in a somewhat similar manner to $^{99m}TcO_4^-$ with peak myocardial concentration observed at 10 min postinjection. The rate of myocardial washout ($T_{1/2}$ = 1.4 hr between 30 and 120 min), however, exceeded that of its blood disappearance ($T_{1/2}$ = 2.2 hr) and caused the M/B ratio to fall from an initial value of 0.48 ± 0.26 at 10 min to 0.17 ± 0.02 after 2 hr. For ^{69}Zn, a M/B ratio of 0.58 ± 0.04 was found at 10 min, which gradually rose to 2.05 ± 0.15 at 90 min. This increase in ratio primarily resulted from a decrease in blood levels since the myocardial concentration stayed approximately unchanged throughout the 2-hr period.

Potassium-43, ^{86}Rb, and ^{129}Cs were taken up by the myocardium at strikingly higher ratios. Potassium-43 and ^{86}Rb attained the highest M/B values within 10 min, averaging 26.7 ± 3.2 and 27.6 ±

0.3, respectively. These values, however, fell rapidly to 8.2 ± 0.4 and 15.6 ± 1.04 at 1 hr and to 5.5 ± 0.5 and 9.0 ± 1.1, respectively, at 2 hr. The decrease in myocardial concentrations with both agents occurred in a multiexponential fashion. From the late phase (60–120 min), biologic half-times of 2.18 hr for ^{43}K and 3.35 hr of ^{86}Rb were calculated. The corresponding blood levels failed to decrease to the same degree as the myocardial concentrations and the M/B ratios therefore fell rapidly. In contrast, myocardial ^{129}Cs concentration decreased only by 10.1% from 10 to 120 min postinjection resulting in a biologic half-life of 12.5 hr. Although blood levels fell slowly, a M/B ratio of 16.2 ± 0.7 was observed at 10 min and reached a peak value of 26.9 ± 0.9 at 90 min.

Iodine-131-oleic acid accumulated in the myocardium in lower concentrations producing markedly lower M/B ratios. They averaged only 2.64 ± 0.12 10 min postinjection and remained between 2.0 and 3.0 throughout the entire 2 hr. Myocardial concentration fell gradually with a biologic half-time of 2.18 hr, accompanied by a similar decrease in blood concentration ($T_{1/2}$ = 3.58 hr).

Effects of carrier (Group 2). The effects of carrier (or pseudocarrier) upon the M/B ratios were studied for $^{99m}TcO_4^-$, ^{203}Pb, and ^{129}Cs. The results were compared with their control values and are listed in Table 1. No changes in myocardial uptake could be observed when rhenium (pseudocarrier, 1 mg/animal) was added to $^{99m}TcO_4^-$. The M/B ratios did not differ significantly from the control values and neither myocardial nor blood clearances were significantly affected. This was different for ^{203}Pb for which the addition of lead acetate (1 mg/rat) reduced the M/B ratios by an average of 74.3% between 30–90 min ($p < 0.01$). A similar carrier effect was noted when CsCl (1 mg cesium/rat) was given in addition to the ^{129}Cs. The ratios reached only 66.7–84.4% of their corresponding control values ($p < 0.01$ at 10, 20, and 60 min).

Effects of drug interventions. *Insulin and glucose (Group 3A).* Glucose and insulin given simultaneously with ^{43}K, ^{86}Rb, ^{129}Cs, and ^{131}I-oleic acid lead to a significant increase in myocardial uptake. The results were compared with the control experiments and the new data are listed in Table 1. Figure 2 compares the percent change in the values. Using the same amount of insulin and glucose in all experiments, the average increase in the M/B ratios for ^{43}K was 50.9 ± 5.7% at 60 min ($p < 0.001$), for ^{129}Cs 21.2 ± 2.2% at 60 min ($p < 0.001$), and for ^{86}Rb 28.4 ± 8.9% at 120 min ($p < 0.01$). The M/B ratios for ^{131}I-oleic acid were increased by 52.5 ± 16.1% at 90 min ($p < 0.01$).

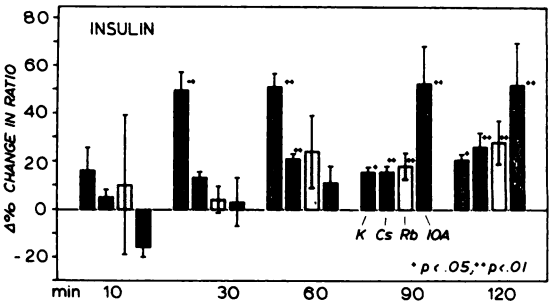

FIG. 2. Effects of insulin in 20% glucose on myocardium-to-blood ratios (shown as Δ% change from control) for ^{43}K (K), ^{129}Cs (Cs), ^{86}Rb (Rb), and radioiodinated oleic acid (IOA).

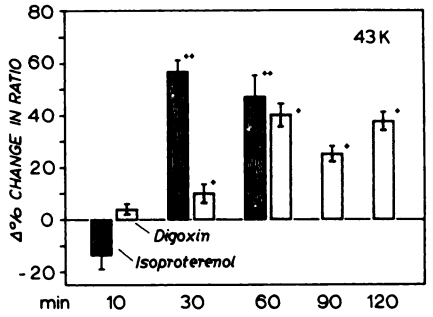

FIG. 3. Effects of digoxin and isoproterenol on myocardium-to-blood ratios for ^{43}K (Δ% change statistically different from control, $^{+}p < 0.05$, $^{2+}p < 0.01$).

No significant changes in blood clearances were noted although the myocardial ^{129}Cs concentration continued to rise slowly throughout the entire period while decreasing in the control. Furthermore, myocardial ^{43}K and ^{86}Rb concentration decreased during the first 60 min at slower rates after insulin and glucose was given (^{43}K: $T_{1/2}$ = 19 min, control versus 26 min with insulin and glucose; ^{86}Rb: $T_{1/2}$ 58 min, control versus 75 min with insulin and glucose).

Insulin and glucose prolonged the myocardial half-life of ^{131}I-oleic acid from 2.18 hr to 7.17 hr whereas the blood half-life decreased from 3.28 hr to 2.28 hr (determined from 10–120 min).

Effects of digoxin and isoproterenol upon myocardial uptake of potassium (Group 3B). In the digitalized animals, the M/B ratios for ^{43}K were enhanced by 39.9% at 60 min and 37.4% at 120 min ($p < 0.01$ when compared with their controls (see Table 1 and Fig. 3). This was primarily due to a slower myocardial clearance rate ($T_{1/2}$ = 75 min control versus, 95 min after digoxin).

Administration of isoproterenol prior to the ^{43}K injection clearly reduced the myocardial clearance of the radioisotope, its half-life being 1.14 hr (control 0.46 hr). Although the initial myocardial concentration was lower than in the control, the slower washout resulted in 57.0% and 31.6% higher ratios

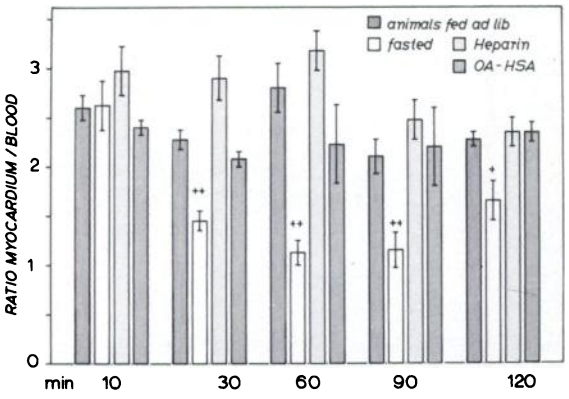

FIG. 4. Myocardium-to-blood ratios for radioiodinated oleic acid (in propylene glycol) in rats fed ad lib, fasted for 24 hr, following intraperitoneal injection of heparin and with radioiodinated oleic acid dissolved in HSA (*significantly different from control, $p < 0.01$).

at 30 and 60 min, respectively (Fig. 3). Furthermore, isoproterenol caused a more rapid initial decrease in ^{43}K blood level ($T_{1/2}$ = 2.79 hr control, versus 1.67 hr after isoproterenol.

Myocardial uptake of ^{131}I-oleic acid (Group 4). The effects of various interventions upon the M/B ratios are shown in Table 1 and Fig. 4. Although myocardial concentrations of the radiopharmaceutical fell very slowly in the animals fed ad lib ($T_{1/2}$ = 2.18 hr), they decreased rapidly in the rats fasted for 24 hr ($T_{1/2}$ = 1.2 hr) causing significantly lower ratios. After insulin and glucose, myocardial concentrations decreased slowly ($T_{1/2}$ = 7.17 hr as compared with 2.18 hr in control). Blood levels, however, fell more rapidly and, therefore, the M/B ratios exceeded the control levels by 52.4 and 51.8% ($p < 0.01$) at 120 and 90 min, respectively. Heparin administration produced no significant changes in the M/B ratios.

Similarly, there was no significant change in myocardial uptake when the ^{131}I-oleic acid was dissolved in HSA instead of propylene glycol. The ratios, however, were affected when altering the amount of labeled oleic acid. The results are shown in Fig. 5 and suggest an inverse relationship between dose and the M/B ratio.

DISCUSSION

Comparison between the radiopharmaceuticals studied. The use of the same animal preparation and the same experimental protocol permitted a comparison of the myocardial concentrations and blood half-time clearances of each radiopharmaceutical. The specific myocardial activity and its changes over time were determined for each radionuclide by establishing a M/B ratio. From the results, distinct differences between the radiopharmaceuticals examined became apparent. Although ratios as high as 27 : 1 were observed for potassium, rubidium, and cesium, these values ranged only between 2 and 3 to 1 for radioiodinated oleic acid and zinc and remained well below 1.0 for lead and pertechnetate.

The specific myocardial activity of pertechnetate became of interest since it is used with increasing frequency for radionuclide angiocardiography (*18,19*) and only little is known of its myocardial uptake. Myocardial-to-blood ratios at 10 min averaged only 0.26 and remained virtually unchanged throughout the entire observation period. Ratios of this magnitude suggest that only little if any pertechnetate had entered the intracellular space and that it had remained primarily in the extracellular compartments which are known to represent 18–25% of total myocardial mass (*20,21*).

Lead-203 and ^{69}Zn, in contrast, achieved slightly higher ratios but only the latter reached a myocardial concentration exceeding that of blood. Compared with pertechnetate, both ions are more likely to have entered the intracellular space. Metallic ions are known to participate in enzymatic reactions (*22*). Therefore, we might anticipate that they would accumulate in the intracellular space at rather high concentrations. Nayler and Anderson (*23*) have observed that the inotropic effect of zinc upon cardiac muscle contraction is most prominent 90 min after injection at which time in the present study the highest concentrations occurred. These authors postulated that its action depended upon a site located on the cell membrane. In contrast earlier reports have suggested that the action of this divalent cation upon skeletal muscle cells is caused by its intracellular accumulation and its ability to mobilize Ca^{2+} within the cell (*24*).

From the high M/B ratios observed for potassium, rubidium, and cesium, it would appear that these ions were concentrated primarily in the intracellular

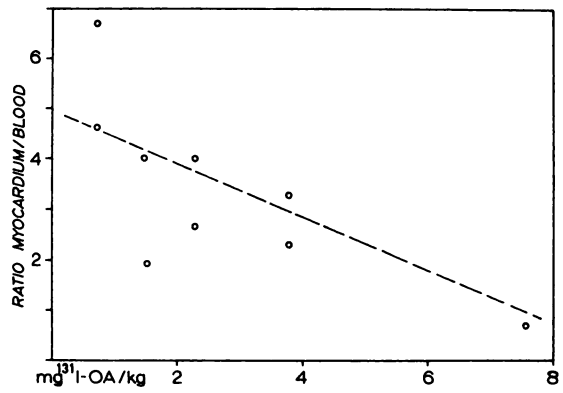

FIG. 5. Relationship between amount of radioiodinated oleic acid injected and myocardium-to-blood ratio. n = 9; y = 2.40 × 4.97; and r = 0.739.

space. The results are in good agreement with previous reports describing ratios for potassium and cesium of similar magnitudes (*5,6*) to those observed in our series of rat experiments. The apparent differences between the myocardial uptakes of potassium and cesium have been pointed out by Poe (*6*) who reported myocardial and blood clearance rates similar to those determined in the current study. In both studies, potassium (and rubidium) were rapidly lost from myocardium whereas the myocardial content of cesium even increased during the first 90 min following injection.

In view of their similar physical, electrical, and chemical properties, the differences between potassium, rubidium, and cesium are of interest. Before entering the myocardial cell, they must transverse a multicomponent barrier consisting of capillary wall, interstitial fluid compartment, and cell membrane, each of which presumably exerts a certain resistance to the passage of these ions. Owing to differences in ion size or their hydration shell size, the resistance to passive diffusion across the capillary wall may differ for individual ions (*25,26*) and could account in part for the observed differences in myocardial uptake and clearance.

The transport across the cell membrane is assumed to be an active process. From previous reports it appears that in the muscle cell this transport mechanism distinguishes poorly between potassium and rubidium (*26,27*), an observation which might serve to explain why both ions were accumulated in the myocardial cell at similarly high concentrations early after administration. With regard to cesium, only few details on its active transport across the cell membrane are available. In the present study, early myocardial concentrations of cesium were low but increased with time, which might suggest that this ion is transported across the cell membrane at a significantly slower rate (*28*) than potassium and rubidium.

The net intracellular concentration of these ions depends, furthermore, upon the rate of leakage from the cell. Different efflux rates for potassium (high) and cesium (low) have been reported (*27,29,30*), thus appearing to explain the rapid decrease in myocardial ^{43}K concentrations over time and the slow decrease for cesium. Myocardial rubidium concentrations fell less rapidly than with potassium, suggesting a slightly slower clearance rate than potassium.

Radioiodinated oleic acid achieved M/B ratios ranging only between 2 and 3. Because the blood clearance rate was similar to that of the myocardium, the M/B ratios remained essentially unchanged throughout the entire observation period. Free fatty acids are known to represent the major energy source for the myocardium. When myocardial extraction rates for several free fatty acids were compared, the AV difference for oleic acid was highest (*31*) suggesting that it might be useful as a myocardial scanning agent. Evans and coworkers (*9,32*) used radioiodinated free fatty acids in dogs and patients and reported myocardium-to-blood ratios as high as 9.4 to 1. These ratios were derived from dog experiments and it is possible that the lower ratios observed in the present study might be due to differences in the species studied and the methodology of the labeling process. During the iodination procedures used in the present study a double bond of the oleic acid is saturated resulting in a compound that does not represent true oleic acid. The same authors dissolved free fatty acid in human serum albumin. This different mode of solubilizing oleic acid, however, seems to produce no significant effect on the myocardial uptake as determined in the current study.

Effects of carrier. The addition of carrier produced no significant effects on the M/B ratios for $^{99m}TcO_4^-$ but significantly lowered the M/B ratios for ^{203}Pb and ^{129}Cs. It is possible, of course, that despite physical and chemical characteristics similar to $^{99m}TcO_4^-$, rhenium did not represent a true carrier. On the other hand, the higher plasma concentrations of the rhenium and pertechnetate might have interfered with the transport mechanism across the cell membrane by saturating the carrier system. However, from the data obtained it cannot be concluded whether this decrease in ratios was due to truly lower myocardial or to higher blood concentrations. It is conceivable that the intracellular space for Pb and Cs is limited and that maximal myocardial concentrations had been achieved already with the amounts of radionuclides given in the control studies. Any further increase in the dose of the ion, e.g., by adding a carrier, would not enhance myocardial concentrations but would lead to higher blood levels and accordingly lower the M/B ratios.

In the case of ^{69}Zn, which was not used in a carrier-free form in the present study (yet achieved M/B ratios as high as 2:1), it is possible that much higher ratios could be obtained with the radiopharmaceutical in a carrier-free state.

Effects of drug interventions. *Glucose and insulin.* The results clearly indicate that the M/B ratios can be improved when insulin in 20% glucose solution is given simultaneously with potassium, rubidium, and radioiodinated oleic acid. The effect was most prominent for potassium (at 30 and 60 min) and radioiodinated oleic acid (at 90 and 120 min). Insulin in hypertonic glucose has been used clinically

to alter the extra-to-intracellular potassium distribution in patients. More recently, insulin and potassium infusions (GIK) have been used (*33*) to "improve the fate" of ischemic myocardium. There is evidence that hypertonic glucose and insulin may play independent roles in altering the potassium distribution between the intra- and extracellular spaces (*34*). Rapid injection of 20% glucose alone can rapidly lower circulating potassium levels. Moreover, it has a direct effect on transmembrane potential (*35*). Insulin, on the other hand, may alter myocardial ion transport. It enhances inorganic phosphate uptake in the liver, which may be accompanied by an intracellular migration of potassium (*22,36*). A decrease in blood potassium levels together with an enhanced potassium migration into the myocardium thus could account for the higher M/B ratios as observed in the present study. Because rubidium and cesium are similar in their physical, electrical, and chemical characteristics to potassium, it is conceivable that similar mechanisms could account for the enhancement of their M/B ratios.

Insulin and glucose have been used previously to improve myocardial scans obtained after intravenous injection of radioiodinated free fatty acids (*9*). The results of the present study suggest that the higher myocardium-to-blood ratios were primarily due to prolonged myocardial half-times. Insulin and glucose are known to alter lipid and carbohydrate metabolism. Supplying the myocardium with large amounts of carbohydrates, e.g., by injecting 20% glucose, may shift its energy supply from lipids to carbohydrates (*37*) resulting in a slower turnover rate for radioiodinated oleic acid. This could result in the radioiodinated oleic acid remaining in myocardium for a longer duration as suggested by our data. In the present study, blood clearance remained essentially unchanged following the insulin and glucose; the prolonged myocardial half-time was probably responsible for the higher M/B ratios at 90 and 120 min.

Isoproterenol and potassium. When ^{43}K was injected during the period of maximum pharmacologic effect of the isoproterenol, the early M/B ratios were lower than their controls but exceeded them markedly at 30 and 60 min. Isoproterenol is known to cause a substantial increase in heart rate which is associated with changes in myocardial potassium balance (*38*). At the onset of the isoproterenol effect, potassium is lost from the myocardium. At the return of heart rate to normal, the myocardium recovers potassium from the blood and this probably explains the enhanced ratios at 30 and 60 min. This observation might be applied clinically if ^{43}K were injected towards the end of an exercise test (*2*) so that as the heart rate returned to pre-exercise levels, maximal concentrations may occur.

Digoxin and potassium. Since a large number of patients undergoing myocardial scanning procedures receive digitalis, its effects on the myocardial uptake of ^{43}K became of interest. Although no significant changes in M/B ratios were noted at 10 min, blood clearance was slightly increased and myocardial clearance slightly prolonged causing significant increases in M/B ratios between 30 and 120 min after injection. The mechanisms involved remain unclear, which is in contrast to numerous reports in which digoxin has been shown to cause a loss of potassium from the myocardial cell (*39*). In a study by Waser, et al (*40*), two intracellular compartments for potassium were postulated and digoxin was assumed to increase potassium binding to actomyosin. Tuttle, et al (*41*) suggested that digoxin in small quantities produces an increase in the rate of potassium influx whereas higher doses decrease myocardial potassium concentration. In the present study, only a small dose of digoxin was given (8 μg/kg body wt), which could account for the increased ratios.

Effects of fasting, heparin, preparation, and dosage on the myocardium-to-blood ratios for radioiodinated oleic acid. In comparison with the high M/B ratios achieved with potassium, rubidium, and cesium, there is still substantial interest in labeled oleic acid as a myocardial scanning agent even though its M/B ratios were found to be only between 2 and 3 to 1 in the control study. The commonly available radioactive isotopes of potassium, rubidium, and cesium, however, do not possess gamma energies as ideal for scintillation camera imaging as, for example, ^{123}I which potentially could be labeled to free fatty acids. For this reason we attempted to influence favorably the M/B ratios of radioiodinated oleic acid. Insulin in 20% glucose has previously been shown to enhance these ratios. Heparin, known as a plasma-clearing agent, was given i.p. following the oleic acid assuming that a fall in blood levels would ensue and increase the ratios. However, no significant changes were observed since, very likely, only the plasma triglycerides and chylomicrons were affected (*42*).

Fasting the animals for 24 hr caused the myocardial concentrations to fall more rapidly than in the control situation resulting in lower M/B ratios. Similar results have been reported previously (*9*). In the fasting state the myocardial energy supply appears to depend mainly upon lipids (*43*). Presumably, radioiodinated oleic acid is metabolized at a faster rate and removed more rapidly from the myocardium.

Significantly greater M/B ratios were noted when

the amount of radioiodinated oleic acid per animal was reduced. The results suggest an inverse relationship between dose and M/B ratio. Ratios less than one were observed with doses as high as 8 mg radioiodinated oleic acid per kilogram body weight. Giving only 0.76 mg/kg resulted in ratios as high as 6.7. This would indicate that high specific-activity oleic acid is preferable since large amounts may exert a carrier effect upon the myocardial uptake. In order to obtain reasonable myocardial images, however, a minimum dose is required. Moreover, it is possible that myocardial uptake of oleic acid occurs only above a certain threshold level (*44*).

From the results it is concluded that the described animal model can be used to examine the suitability of radiopharmaceuticals for myocardial scanning, to examine the effects of pharmacologic and dietary interventions upon myocardial uptake, and to select the optimum time for scanning after injection. Determination of myocardial and blood clearance rates, furthermore, might be important when myocardial scanning is repeated serially although further investigation of myocardial washout rates in ischemic tissue appears to be necessary. When applying the current data to the clinical situation, differences in species must be considered although M/B ratios in the same general range have been reported in both the canine and human heart (*1,9*).

ACKNOWLEDGMENTS

This work was supported in part by the following grants: USPHS NHLI No. HL14197, MIRU Contract No. HL81332 and American Heart Association No. 71-1004. The authors wish to acknowledge the skillful technical assistance of Jane Lindsey and Arnold J. Nuttall.

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