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Radiopharmaceuticals XXVII. ^{18}F-Labeled 2-Deoxy-2-Fluoro-D-Glucose as a Radiopharmaceutical for Measuring Regional Myocardial Glucose Metabolism In Vivo: Tissue Distribution and Imaging Studies in Animals

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^{18}F-2-Deoxy-2-fluoro-D-glucose (^{18}FDG) is rapidly extracted by the mouse heart, and the radioactivity in heart (3–4% per organ) remains relatively constant for 2 hr post injection. The brain uptake (2–3% per organ) remained relatively constant throughout the time course of the study. Liver, lungs, kidneys, small intestine, and blood all showed a rapid clearance of radioactivity after injection of ^{18}FDG. At 120 min the heart-to-lung ratio was 12 and heart-to-liver ratio was 32. Urinary excretion of activity was ~16% of the injected dose at 60 min. The uptake of radioactivity by dog heart following the intravenous administration of ^{18}FDG was 2.8–4.1% at 60 min and 2.4% at 135 min; it was regionally distributed, the areas of highest activity being the left ventricle and the interventricular septum. The brain activity was 2.1–3.5% at 120 min, with a ratio of gray matter-to-white matter of 2–3:1. Urinary excretion in dogs was 16% and 50% of the injected dose at 60 and 135 min. The chemical form of the activity in the urine, although unidentified, was not $^{18}F^-$. Cross-sectional images of the myocardium of the dog after intravenous injection of ^{18}FDG were obtained using emission tomography.

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Recent attempts to measure the in-vivo myocardial distribution of C-11 labeled glucose utilizing emission tomography have not been successful, as the result of a low extraction of this compound from the coronary circulation and the widespread distribution of [^{11}C] glucose throughout many other organs such as the lung (*1*). Glucose transport is a passive, carrier-facilitated process. Thus, selective accumulation within a tissue against a concentration gradient does not occur and there is merely an equilibration of intracellular and extracellular glucose concentrations (*2*). Since glucose rapidly enters several metabolic

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pathways, however, the tendency toward equilibrium would constantly affect net glucose influx, and the subsequent redistribution of labeled metabolites would result in a continuous loss of radioactivity from the organ. It would be desirable to have a glucose analog labeled with a gamma-emitting nuclide that would be transported and phosphorylated and thus trapped intracellularly as is glucose, but that would not undergo subsequent metabolic steps with a redistribution of radioactivity. Because the hydroxyl groups at C-1, C-3, C-6, and perhaps C-4 of glucose are involved in the binding of glucose to hexokinase, glucose analogs with substituents only on the relatively non-critical 2 position—such as 2-deoxy-2-fluoro-D-glucose (FDG)—are substrates for hexokinase (*3*).

Local cerebral glucose metabolism has been demonstrated recently in animals and humans by the use of emission tomography and the gamma-emitting glucose analog, F-18-labeled 2-deoxy-2-fluoro-D-glucose (^{18}FDG) (*4*). A discussion of the basis for the use of the deoxyglucose method for measuring local glucose metabolism has been recently published (*5*). This compound is a suitable substrate for hexokinase (*3*), and 2-deoxy-2-fluoro-D-glucose phosphate was the only observed product of this reaction (*4*). Since this metabolic is a poor substrate for subsequent metabolic steps (*6*) and since the permeability of hexose phosphates is quite low, we have explored the use of ^{18}FDG as a radiopharmaceutical for studies of myocardial metabolism and imaging. Because the ischemic or hypoxic heart is dependent upon glucose as its major energy source, this compound might provide a method for the in-vivo measurement of regional myocardial glucose utilization as a probe for myocardial ischemic conditions. Our initial studies were carried out in normal animals to explore the time-distribution patterns of this compound as an agent for myocardial imaging and metabolism. In addition, cross-sectional images of the dog myocardium were obtained after i.v. injection of ^{18}FDG using positron emission transaxial tomography.

MATERIALS AND METHODS

Synthesis of ^{18}F-2-deoxy-2-fluoro-D-glucose (^{18}FDG). High specific activity anhydrous ^{18}F-F_2 was produced using the $^{20}Ne(d,\alpha)^{18}F$ reaction with 13.8 MeV deuterons on a target consisting of 0.1% F_2 in neon (*7–9*). The reaction of ^{18}F-F_2 with 3,4,6-tri-0-acetyl-D-glucal gave [^{18}F] 3,4,6-tri-0-acetyl-2-deoxy-2-fluoro-D-glucopyranosyl fluoride that was hydrolyzed to ^{18}FDG (*10,11*). The radiochemical yield of ^{18}FDG has been increased by a factor of 2 over the previously reported procedure (*10,11*) by using a 0.7 × 10 cm column of silica gel and elution with ether:hexane (1:1) to separate the gluco- and mannopyranosyl fluorides. The radiochemical purity was >96% as determined by thin layer chromatography (*10,11*).

Animal experiments. ^{18}FDG was dissolved in isotonic saline and injected intravenously into 8- to 10-week-old Swiss Albino mice (BNL strain) through a lateral tail vein, or into female mongrel dogs (15–17 kg) through a leg vein. The dogs were anesthetized with sodium pentobarbital (20 mg/kg) either 15 min before administration of ^{18}FDG, or were first injected with ^{18}FDG and anesthetized 60 min later. At the desired time interval after the injection of ^{18}FDG the animals were killed by cervical fracture (mice) or by barbiturate overdose (dogs). The organs were removed, blotted to minimize adhering blood, weighed, and counted in an automated NaI well counter and the activity corrected for decay. Data are expressed as percentage of the injected dose per organ or per gram of tissue as indicated.

In some experiments, urine was collected from the animals and analyzed for the possible presence of $^{18}F^-$ by passing aliquots of urine over 1- by 5-cm alumina column and washing with 8 ml of water, after which effluent and the alumina (containing $^{18}F^-$) were counted to determine by difference the amount of $^{18}F^-$ in the sample. The validity of this method for measuring $^{18}F^-$ in samples was tested by passing known aliquots of $^{18}F^-$ over identical columns and measuring both the adsorbed radioactivity and the column effluent. Less than 0.02% of the $^{18}F^-$ broke the alumina column. Note that this

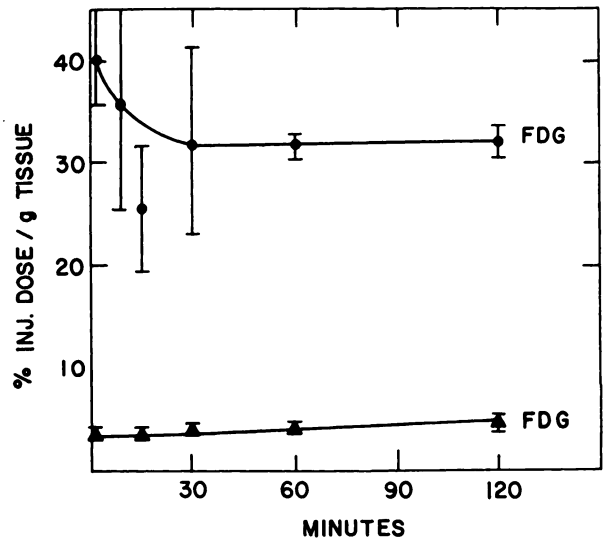

FIG. 1. Uptake of total radioactivity in mouse cardiac muscle, ●—● and mouse skeletal muscle, ▲—▲ following injection of ^{18}FDG as indicated. Each point represents the mean ± SDM of four to eight mice.

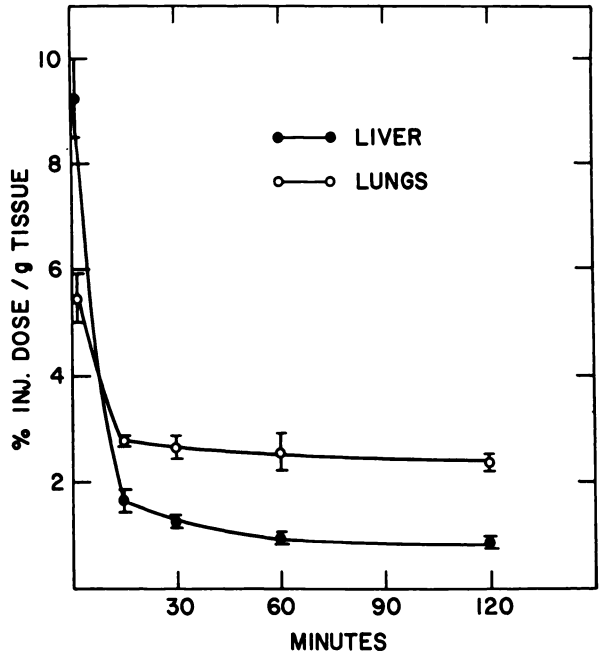

FIG. 2. Clearance of total radioactivity from mouse lungs and liver following injection of ^{18}FDG. Each point represents the mean ± SDM of four to eight mice.

method does not distinguish between radiofluoride and other metabolites of ^{18}FDG that might also be retained by alumina; it served only to show that the major part of urinary activity was not $^{18}F^-$. Precipitation of the activity in the urine as $Pb^{18}F_2$ confirmed that<0.8% of the total activity was present as $^{18}F^-$ or some labeled metabolite behaving like fluoride. In several dogs, serum glucose measurements were made in triplicate by the S.V.R. method*, on blood drawn from a peripheral leg vein immediately before the injection of ^{18}FDG. The glucose levels ranged from 80–107 mg %.

Imaging experiment. Five mCi of ^{18}FDG were injected intravenously into one dog (anesthesized as described above), and imaging was begun 5 min later. A series of 6-min scans were taken with the PETT III (*12*) instrument, with total coincidence counts ranging from 1.2–1.9 × 10^6 for each of four levels investigated. The different slices were approximately 1.5 cm apart and extended from the base to the apex of the heart. Transmission scans at the various levels were made before emission tomography. A repeat scan at the level above the apex, taken at 90 min after injection, showed virtually no change from that obtained at 28 min after injection.

RESULTS

Mice. Tissue distributions of [^{18}F] 2-fluoro-2-deoxy-D-glucose in mice at 1, 15, 30, 60, and 120 min after injection were studied; the data are shown in Figs. 1 and 2 and Table 1. The uptake by the heart is rapid (3–4% per organ) (Fig. 2) and remains essentially unchanged up to 2 hr after injection The rather large biologic variability in the heart uptake in mice at early times (Fig. 1) contributes to large standard deviations and therefore, from this data, it is unclear as to whether there is any significant heart clearance. The uptake by cardiac muscle was not typical of muscle tissue in general, since accumulation of ^{18}FDG in skeletal muscle was significantly less than that of the heart (Fig. 1). The lungs and liver—both organs which might interfere with myocardial imaging—rapidly cleared of radioactivity (Fig. 2), and at 120 min post injection the heart-to-lung ratio was 12 and the heart-to-liver ratio was 32. Several other tissues, particularly the

TABLE 1. DISTRIBUTION OF RADIOACTIVITY IN MOUSE TISSUES FOLLOWING THE INTRAVENOUS INJECTION OF ^{18}FDG

	% Injected dose/Gram tissue*				
	1 min	15 min	30 min	60 min	120 min
Heart	39.76 ± 3.36	27.5 ± 6.4	32.7 ± 8.6	31.66 ± 2.66	32.33 ± 2.7
Lungs	5.38 ± 0.41	2.71 ± 0.03	2.45 ± 0.03	2.53 ± 0.23	2.39 ± 0.13
Muscle	2.59 ± 0.11	3.81 ± 0.53	3.21 ± 0.43	4.01 ± 0.54	4.97 ± 0.78
Liver	9.60 ± 0.38	1.64 ± 0.21	1.10 ± 0.07	0.82 ± 0.08	0.89 ± 0.10
Blood	7.07 ± 0.69	1.54 ± 0.18	0.89 ± 0.11	0.55 ± 0.10	0.40 ± 0.11
Femur	1.19 ± 0.19	—	1.85 ± 0.38	2.75 ± 0.58	—
Skull	2.39 ± 0.38	3.45 ± 0.47	2.22 ± 0.64	2.62 ± 0.56	2.79 ± 0.72
Brain	4.33 ± 0.46	6.07 ± 0.94	5.31 ± 0.94	4.57 ± 0.75	3.42 ± 0.28
Kidneys	13.27 ± 1.42	2.47 ± 0.14	2.09 ± 0.54	1.14 ± 0.11	0.52 ± 0.05
Spleen	2.07 ± 0.38	2.02 ± 0.14	1.94 ± 0.18	1.88 ± 0.34	1.93 ± 0.19
Sm. intestine	5.39 ± 0.26	2.59 ± 0.21	2.01 ± 0.41	1.73 ± 0.22	1.39 ± 0.20
Pancreas	2.57 ± 0.39	—	2.36 ± 0.22	2.45 ± 0.25	—

* Mean ± SDM for 4–8 animals per point.

blood, kidneys, and small intestine, showed a similar rapid clearance of ^{18}FDG (Table 1). The brain activity remained relatively constant through the time course of the study. There was no significant increase with time in the ^{18}F activity in the skull or femur indicating minimal, if any, in vivo defluorination. This latter result was also indicated by the finding that the activity in the urine, which was 16% of the injected ^{18}FDG dose after 60 min, never showed >0.8% of the total activity as fluoride or some metabolite similar to fluoride. Of the organs studied, the spleen and pancreas showed the lowest accumulation of radioactivity.

Dogs. The clearance of radioactivity from dog blood was best described by fitting the data to 3 components (Fig. 3). The initial component was quite rapid, with a half-life of 0.54 min, the second component had a half-life of 5.92 min, and the slow component had a half-life of 80.4 min.

With dogs, at 60 min post injection, the organs having the highest F-18 activity were the heart, brain, liver, and lungs. Although by 2.25 hr the lungs and liver had lost significant activity, the heart retained considerable activity (Tables 2, 3). Dog urine contained about 14–19% of the injected activity by 1 hr and 42–57% by 2.25 hr as determined from the activity per gram of urine and assuming a rate of urine formation of ~44 ml/kg-day (*13*). As in the mouse, negligible amounts of the F-18 activity in the urine appeared as $^{18}F^-$ (0.9%). The bone activity in dogs was also very low (Table 2).

The activity in the heart was regionally localized rather than uniformly distributed (Table 3). The lowest activities at 60 and 135 min were found in the left atrium, right atrium, and right ventricle; the

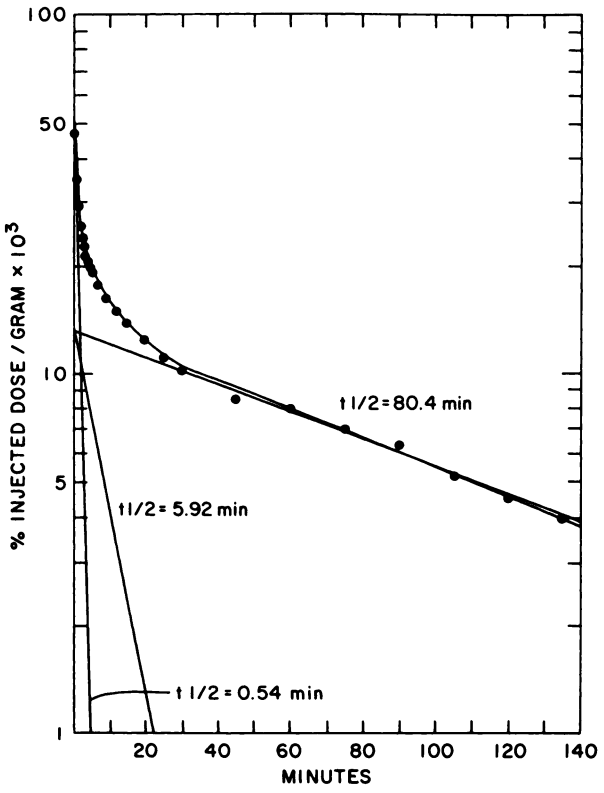

FIG. 3. Clearance of total radioactivity from blood in the dog following injection of ^{18}FDG. Results are the average values from three separate experiments.

TABLE 2. DISTRIBUTION OF RADIOACTIVITY IN DOG TISSUES FOLLOWING INJECTION OF ^{18}FDG*

	60 min				135 min			
	%/gram	%/gram	%/organ	%/organ	%/gram	%/gram	%/organ	%/organ
Lungs	0.0103	0.0112	3.56	1.25	0.0103	0.0101	1.19	1.44
Heart	†	†	2.82	4.10	†	†	2.40	2.45
Brain	‡	‡	2.14	—	‡	‡	3.54	2.10
Ovaries	0.0091	0.0105	0.01	0.01	0.0115	0.0338	0.001	0.017
Spleen	0.0076	0.0094	0.51	1.79	—	0.0064	—	0.90
Liver	0.0107	0.0093	3.67	2.80	0.0062	0.0069	1.82	2.54
Pancreas	0.0075	0.0064	0.23	0.17	0.0125	0.0074	0.37	0.30
Kidneys	0.0139	0.0118	0.97	0.62	0.0097	0.0076	0.50	0.50
Bone	0.0040	0.0026	—	—	0.0008	0.0016	—	—
Blood	0.0055	0.0077	—	—	0.0035	0.0040	—	—
Urine§	0.2980	0.2900	13.9	12.7	0.4170	0.5800	42.1	57.1
Muscle	0.0033	0.0057	—	—	0.0029	0.0027	—	—

* Data is presented for 2 dogs at each time. Duplicate tissue samples from each organ were used to determine the radioactivity in each organ and the average of the two samples is shown for each determination. In all cases, the values for the two samples differed by less than 5%.

† See Table 3.

‡ See Table 4.

§ % in urine calculated by multiplying the % injected dose per gram times the rate of urine formation in dogs (~44 ml/kg/day) over the 60 min and 135 min period.

TABLE 3. DISTRIBUTION OF RADIOACTIVITY IN DOG HEART FOLLOWING INJECTION OF ^{18}FDG*

	60 min (%/gram)		135 min (%/gram)	
Right auricle	0.0124 (0.0115–0.0133)	0.0244 (0.0228–0.0260)	0.0098 (0.0096–0.0100)	0.0130 (0.0122–0.0138)
Right ventricle	0.0126 (0.0123–0.0129)	0.0178 (0.0174–0.0182)	0.0128 (0.0120–0.0136)	0.0093 (0.0092–0.0094)
Left auricle	0.0090 (0.0086–0.0094)	0.0155 (0.0147–0.0163)	0.0088 (0.0087–0.0089)	0.0092 (0.0089–0.0095)
Left ventricle	0.0271 (0.0257–0.0285)	0.0401 (0.0390–0.0412)	0.0270 (0.0266–0.0274)	0.0172 (0.0167–0.0177)
IVS	0.0300 (0.0290–0.0310)	0.0441 (0.0426–0.0456)	0.0332 (0.0317–0.0347)	0.0195 (0.0188–0.0202)

* Data is shown for two dogs at each time; values represent the mean and in parentheses, the range, of triplicate determinations from each region.

highest activity was found in the left ventricle and interventricular septum (IVS).

Tomographic images of the myocardium of a normal dog were obtained after administration of 5 mCi of ^{18}FDG (Fig. 4). Computer reconstruction of a series of 1 cm cross-sectional images taken beginning 5 min after injection clearly showed the left ventricle and interventricular septum.

As in the heart, the brain activity was not uniformly distributed (Table 4). The cerebral cortex showed the highest % dose/g followed by the cerebellum and medulla. In the cerebral cortex, the gray matter had approximately two to three times the activity per gram than was found in the white matter.

DISCUSSION

As shown by the blood clearances in both mice and dogs, the distribution of i.v. ^{18}FDG to various organs was quite rapid. The kidneys, liver, lungs, and small intestine all showed high initial levels of activity, followed by very rapid clearance. The heart and the brain showed a rapid accumulation of activity and this remained relatively constant during the time course of the study period. The uptake of radioactivity in human brain after injection of ^{18}FDG has recently been shown to be sufficient for tomographic studies for the determination of local cerebral glucose metabolism (*4*). These studies have demonstrated the selective distribution of ^{18}FDG in different regions of the human brain corresponding with the differential rates of glucose metabolism. The present studies on the distribution of ^{18}FDG in dog brain as determined by excision and counting (Table 4) agree quite well with tomographic data (*4*). The ratio of the average gray-matter metabolic rate for glucose to that of the white matter was 2.7 for humans. The similar tissue ratio for radioactivity in the dog brain ranged from ~2 to 3:1.

Although identification of the chemical form of radioactivity in the various organs was not undertaken in the present studies, the results for ^{18}FDG distribution in the heart strongly suggest that this radiopharmaceutical is rapidly extracted from the coronary circulation and is metabolically trapped intracellularly by phosphorylation through hexokinase. In the dog the lungs and liver, both organs which might potentially serve as interfering background for imaging, undergo a rapid clearance of F-18 activity

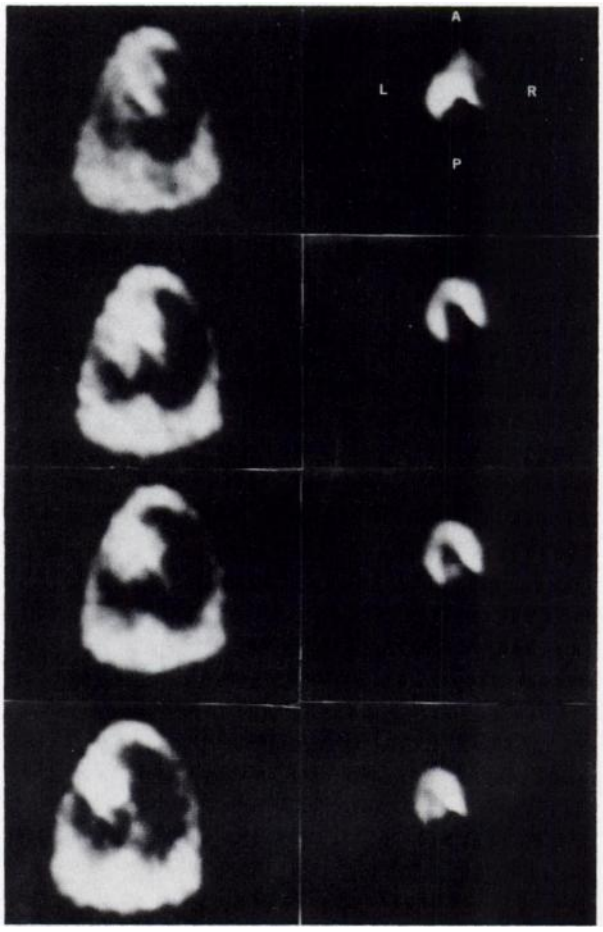

FIG. 4. Transmission and corrected emission from base to apex of heart (top to bottom of figure) in ca 1.5 cm steps after i.v. injection of 5 mCi of ^{18}FDG. Orientation is given in top panel of corrected emission image using letters A, P, L, and R to indicate anterior, posterior, left and right, respectively; left ventricular wall and interventricular septum are visualized.

TABLE 4. DISTRIBUTION OF RADIOACTIVITY IN DOG BRAIN FOLLOWING INJECTION OF ^{18}FDG*

	60 min	135 min	
	%/gram	%/gram	%/gram
Cerebral cortex	0.0289	0.0471	0.0273
Gray matter	0.0280	0.0589	0.0270
White matter	0.0168	0.0184	0.0148
Cerebellum	0.0246	0.0320	0.0260
Medulla	0.0234	0.0263	0.0209

* Data is shown for one animal at 60 min and two animals at 135 min and represent the mean for triplicate determinations.

after injection of ^{18}FDG. Thus the distribution after injection of ^{18}FDG. Thus the distribution of activity in the heart at later times may reflect primarily the initial removal of ^{18}FDG from the circulation.

Tomographic images of the normal dog heart after the i.v. injection of 5 mCi of ^{18}FDG were obtained and clearly showed the left ventricle and interventricular system (Fig. 4). By the use of tomographic imaging techniques and ^{18}FDG, it may be possible to detect regional differences in myocardial glucose utilization associated with abnormalities in myocardial metabolism. Glucose transport is closely associated with the energy demands of the cardiac muscle. For example, glucose uptake becomes progressively accelerated as the ventricle of a perfused rat heart develops more pressure. In the working rat heart there is stimulation up to five-fold in the rate of glucose uptake over that of the resting heart. Glycolysis predominates as the major energy source in the anoxic or ischemic myocardium, as opposed to β-oxidation, which is the primary energy source under physiologic conditions (*14*). Weiss et al. (*1*) found that the extraction of C-11-labeled glucose by the myocardium was not indicative of an altered metabolic extraction but merely reflected the result of decreased flow (increased residence time). Furthermore, the low extraction of glucose, particularly at high flow rates, coupled with the interference of lung radioactivity, precluded precise tomographic delineation of the heart with [^{11}C] glucose.

CONCLUSION

The results of these studies raise many questions that form the basis for research now in progress in our laboratory. For example, from the present results with ^{18}FDG, it is not clear how well the extraction efficiency of this compound is related to glucose transport and utilization and to what extent the hemodynamic state of the coronary circulation influences glucose metabolism. The determination of the metabolic fate of ^{18}FDG after injection, and the physiologic factors influencing uptake, are necessary of course, for the interpretation of the present results and their extension to the clinical diagnostic situation. Following the intravenous administration of ^{18}FDG, however, we have consistently observed the rapid accumulation of a small fraction of the total injected radioactivity, which persists in the myocardium with a much longer half-life than in any other organ. The apparently metabolic myocardial trapping displayed by ^{18}FDG is a unique feature absent with [^{11}C] glucose, and may provide the basis for the development of a technique to measure regional myocardial glucose metabolism. The potential importance of such a technique in the diagnosis and care of patients with cardiac disease is of considerable interest.

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FOOTNOTE

* Calbiochem, La Jolla, Cal.

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