Iodophenylpentadecanoic Acid-Myocardial Blood Flow Relationship During Maximal Exercise with Coronary Occlusion

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Imaging ^{123}I-labeled iodophenylpentadecanoic acid (IPPA) uptake and clearance from the myocardium following exercise has been advocated as a means of detecting myocardial ischemia because fatty acid deposition is enhanced and clearance prolonged in regions of low flow. However, normal regional myocardial blood flows are markedly heterogeneous, and it is not known how this heterogeneity affects regional metabolism or substrate uptake and thus image interpretation. In five instrumented dogs running at near maximal workload on a treadmill, ^{131}I-labeled IPPA and 15-micron ^{46}Sc microspheres were injected into the left atrium after 30 sec of circumflex coronary artery occlusion. Microsphere and IPPA activity were determined in 250 mapped pieces of myocardium of ~400 mg. Myocardial blood flows (from microspheres) ranged from 0.05 to 7.6 ml/min/g. Deposition of IPPA was proportional to regional flows ($r = 0.83$) with an average retention of 25%. The mean endocardial-epicardial ratio for IPPA (0.90 ± 0.43) was similar to that for microspheres (0.94 ± 0.47; $p = 0.08$). Thus, initial IPPA deposition during treadmill exercise increases in proportion to regional myocardial blood flow over a range of flows from very low to five times normal.

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Imaging the heart with radiolabeled free fatty acids to evaluate myocardial perfusion and/or metabolism has been an area of investigation since Evans et al. reported their early experience with iodine-131- (^{131}I) labeled oleic acid (*1*). However, this was not clinically practical until highly purified iodine-123 (^{123}I) became available in conjunction with the current gamma cameras and computer systems. Straight chain fatty acids, e.g., pentadecanoic or hexadecanoic, labeled with ^{123}I on the omega carbon, have been used for estimating myocardial perfusion by their deposition and metabolism by their clearance (*2–4*). They have significant limitations, for example, clearance from the myocardium which may occur by washout of the tracer-labeled substrate, without metabolism or metabolic deiodination with the resultant contamination of the myocardial radioactivity clearance by the free radioiodide. This has been reviewed in detail by Visser et al. (*5*). Analogs of these free fatty acids have been developed by placement of a phenyl or methyl group at various sites on the straight chain. The omega-phenyl iodinated compound is retained as iodobenzoate, iodopropionate and iodopropenate, whereas beta-methyl substitution greatly reduces beta oxidation and release of the iodine (*6*). The biologic characteristics of these compounds have been reviewed by Westera et al. (*7*).

The analog which has received the most investigation, and which has been used in conjunction with exercise testing to detect myocardial ischemia in humans is 15-(para-^{123}I-phenyl)pentadecanoic acid (IPPA) (*8–11*). However, in spite of this clinical application, relatively little is known about its delivery and initial uptake by the myocardium during exercise or ischemia. Reske et al. have reported a strong linear correlation between IPPA deposition and myocardial blood flow measured by microsphere technique under normal to low flow conditions (*12*). However, at higher flows between 1.7–2.5 ml/min/g, regional IPPA activity was found in diminished proportion to flow. If this is generally the case, then IPPA activity could not serve as a marker of myocardial perfusion during exercise testing. Furthermore, if its initial myocardial concentration is not solely a function of delivery by flow but is impeded by transmembrane transport into the cell, then interpretation of its clearance kinetics as a measure of myocardial metabolism would be difficult. Therefore, the purpose of this study was to examine the relationship between the initial deposition of IPPA and regional myocardial blood flow in an exercising dog with acute ischemia in one portion of the coronary bed.

METHODS

Experimental Model

Five mongrel dogs (32–40 kg) were trained to run on a treadmill. Three of the dogs achieved a workload of 7–8 miles

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per hour at a 15–20% grade. The other two could reach only a 10% grade. Subsequently, under halothane anesthesia with O_2 supplementation, each animal was instrumented in a sterile manner through a left thoracotomy. A 2 mm i.d. tygon catheter was placed in the aorta immediately distal to the arch and attached with 4-0 silk suture. Two similar catheters were inserted through the left atrial appendage, positioned so the orifices were in the body of the left atrium, and sutured in place. A hydraulic occluder was placed on the circumflex coronary artery ~1 cm distal to its origin. The air pressure needed to occlude the artery was determined by measurement of flow with a Doppler flow probe on the artery immediately upstream from the occluder. The ends of the intravascular catheters and the occluder were brought out through the chest incision, tunneled subcutaneously to the paraspinal region and brought out through the skin. The chest was then closed, pneumothorax evacuated, and the animal allowed to recover from anesthesia. The animal was fitted with a jacket to protect and hold the ends of the catheters. In addition to the standard post thoracotomy care, the animals received 325 mg of aspirin and 75 mg of dipyridamole orally, daily for 14 days post-op to help maintain catheter patency. Dipyridamole was stopped 24–48 hr before the study. Three to 5 days postsurgery, the animals were restarted exercising at a low level on the treadmill with a gradual increase over a 7–10 day period until their preoperative level of exertion was reached.

Exercise Study

After a 12-hr fast, but with free access to water, the animals were positioned on the treadmill, the arterial line attached to a pump calibrated to withdraw at 15 ml/min, and the hydraulic occluder attached to a pressure regulator on a CO_2 source. Exercise was started with an increase of workload over a 5-min period to the peak level reached during training. After 1 min at peak exercise, pressure was applied to the hydraulic occluder and set 10% above the pressure previously shown to cause occlusion of the coronary artery. Thirty seconds after occlusion, and while still running at maximum, arterial blood withdrawal was begun. Five seconds later, 200–500 μCi of ^{131}I-labeled IPPA (synthesized by Jeanne M. Link) in 6% human serum albumin and 3–4 million, 15-micron scandium-46-(^{46}Sc) labeled microspheres (E.I. DuPont New England Nuclear, Boston, MA) were simultaneously injected into the left atrium. The animal was kept running at peak level for an additional 55 sec while arterial blood withdrawal continued (total 60 sec). Immediately thereafter, a lethal dose of sodium pentobarbital, followed by 40 mEq of potassium chloride, was injected into the left atrium. The heart was excised (less than 2 min after completion of blood withdrawal), rinsed in cold saline, the ventricular cavities filled with polyurethane foam which expands to fill the ventricle to its premortum size and then hardens (*13*). The heart was then cut into four equal thickness, cross-section slices parallel to the A-V ring, the right ventricle excised leaving the full thickness of the septum as part of the left ventricle. Dry ice was used to cool the slices to a state of hardness facilitating subsequent cutting of each slice into 32 radial segments, which were then divided into endo- and epicardial sections, 64 pieces per slice and 256 pieces per left ventricle. Each of these sections were then weighed, ^{131}I and microsphere activity determined in a gamma scintillation well counter (3-in. NaI cyrstal) along with blood samples from the withdrawal pump and standards of the injected radionuclides. After appropriate correction for decay, the matrix inversion technique was used to correct for scattered radiation between radionuclides. IPPA activity was calculated as counts/g/min. Local myocardial blood flow, F_i ml/min/g, in each myocardial piece, subscripted i, was determined from the microsphere data assuming 100% deposition, by the formula:

$$F_i = \frac{F_{ref}}{m_i} * \frac{q_{i\,ms}}{q_{ref\,ms}},$$

where q_{ims} is microsphere activity in the i^{th} piece (cpm), m_i is the mass of the i^{th} piece, F_{ref} is the flow in the reference syringe (ml/min), and q_{refms} (CPM) is the total microsphere activity in the reference sampling syringe (*14*).

The regional deposition of IPPA, d_i ml/g/min, was estimated from the IPPA activity by the formula:

$$d_i = \frac{F_{ref}}{m_i} * \frac{q_{ifa}}{q_{reffa}},$$

where q_{ifa} is the IPPA activity in the i^{th} piece (cpm), m_i is the mass of the i^{th} piece, F_{ref} is the flow in the reference syringe (ml/min), and q_{reffa} (cpm) is the total IPPA activity in the reference sampling syringe.

(The flow could be estimated from this formula if the extraction of IPPA were complete in a single pass and if there were no recirculation from other organs.) The local extraction of IPPA is $E_i = d_i/F_i$ or $[q_{ifa}/q_{ims}]/[q_{reffa}/q_{refms}]$. (If the E_i were the same at all flows, and its value known, then IPPA deposition could serve as a measure of local flow.)

Myocardial blood flow data was also analyzed in terms of normal and ischemic zones. Normal myocardial blood flow was defined for each cross-sectional slice by calculating the mean and standard deviation of flow in 12 endocardial and 12 epicardial samples from the center of the region supplied by the normal coronary artery. All of the samples in each slice were then examined and those whose flow was more than 2 s.d.s below the mean value of the 12 normal samples were classified as being in an ischemic zone. Those whose flow was within 2 s.d. were considered normal.

STATISTICS

IPPA d_i and microsphere F_i in all samples for each heart were compared using linear regression analysis and statistical significance tested with analysis of variance. The F test was used to compare regression lines. Mean values were tested with the paired t-test. Analyses were performed using the BMDP statistical analysis package.

Results

Microsphere measured F_i flow in each myocardial sample as a function of endocardial or epicardial location is shown for each animal in Figure 1. Study 815 has fewer data points displayed than the other studies. This is because during data analysis it was recognized that inadequate numbers of microspheres had been injected to provide statistically valid numbers of them per sample for the small samples taken. Therefore, in this study, two adjacent endocardial or epicardial samples were combined in a circumferential manner resulting in only 16 endocardial and 16 epicardial samples for each slice.

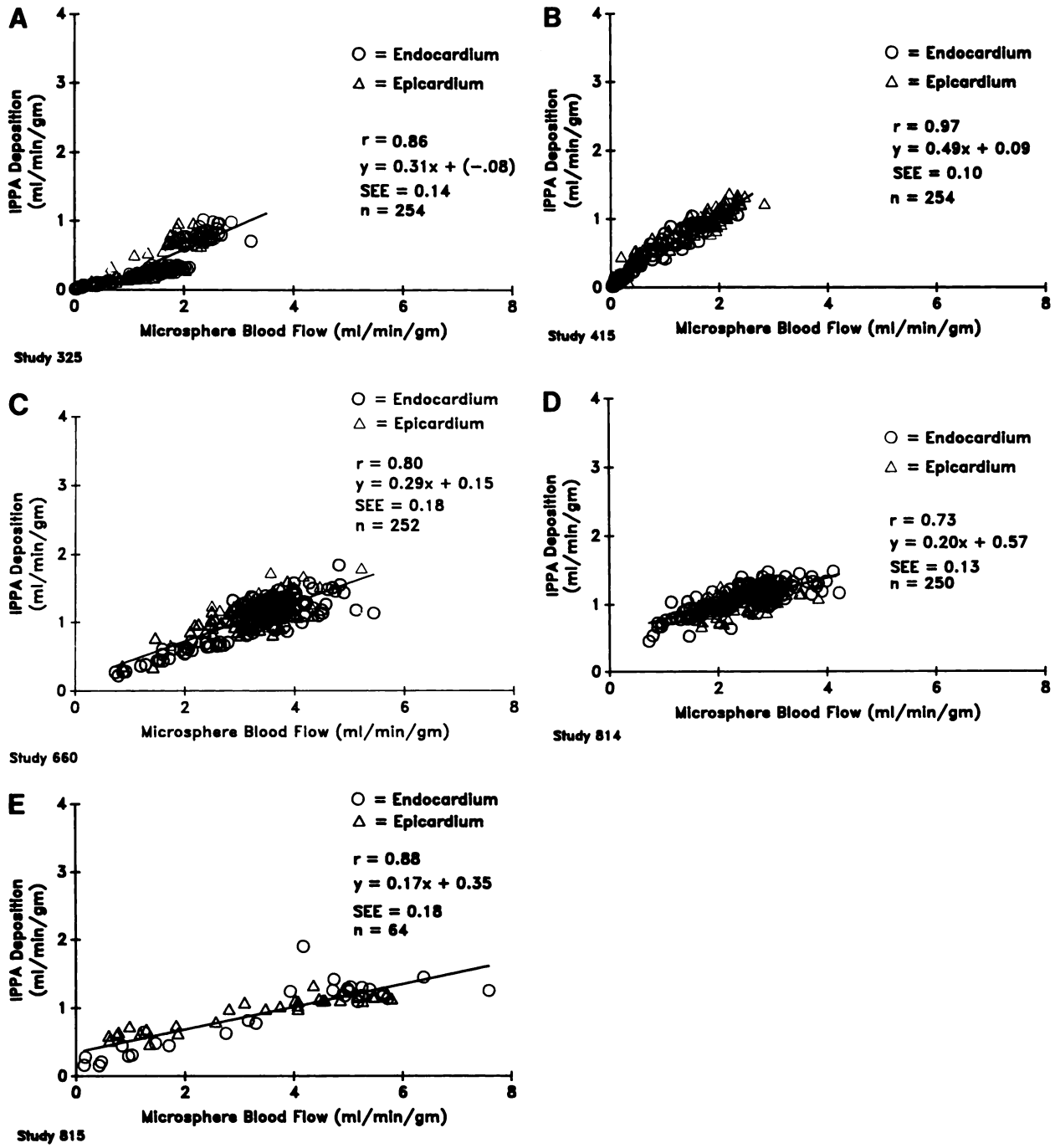

FIGURE 1
Endocardial and epicardial IPDA deposition in ml/min/g is expressed as a function of microsphere measured myocardial blood flow for each of the individual animals. The regression line shown represents the comparison between the IPDA and microspheres for all samples combined.

Global left ventricular myocardial blood flow measured by microspheres during exercise for each of the dogs is shown in Table 1. As anticipated, because dogs 325 and 415 did not exercise to as high a treadmill workload (7 mph, 10% grade), mean flow in these two animals (averaging 0.91 ml/min/g) was significantly less than in the other three (averaging 3.07 ml/min/g). Among all five animals, flow at peak exercise ranged from 0.05 ml/min/g to 7.58 ml/min/g (only one animal had flow above 6 ml/min/g). The range was 0.11–3.2 ml/min/g for the two dogs that achieved only a low level of exercise. For the 3 dogs that exercised to a high workload, mean endocardial blood flow (3.15 ± 1.31 ml/min/g) was essentially the same as epicardial flow (3.00 ± 0.95, Table 2) and was considerably higher than for the other two dogs. The endo-epicardial ratio was greater than 1.0 for four of the five animals (Table 2).

As shown in Figure 1 and Table 1, there was a strong,

TABLE 1
Global Mean Values

Study no.	Microsphere ml/min/gm*	IPDA ml/min/gm*	r=	Slope	Intercept	s.e.e.
325§	1.29 ± 0.74	0.33 ± 0.27†	0.86	0.31	−0.08	0.14
415§	1.04 ± 0.74	0.60 ± 0.38†	0.97	0.49	0.09	0.10
660	3.29 ± 0.82	1.09 ± 0.29†	0.80	0.29	0.15	0.18
814	2.45 ± 0.67	1.08 ± 0.19†	0.73	0.20	0.57	0.13
815	3.48 ± 1.95	0.93 ± 0.37†	0.88	0.17	0.35	0.18
Mean‡	¶	¶	0.72	0.25	0.33	0.32

* Mean ± s.d.
† $p < 0.05$ compared to microspheres.
‡ Mean ± s.d. for 1070 samples combined.
§ Achieved only a level of 10% grade, 7 miles per hour instead of the goal of 15% grade 7 miles per hour reached by the others.
¶ Because of the marked differences in mean flow of studies 325 and 415 and the other three studies, a mean flow for all studies was not calculated.

linear correlation between global IPPA d_i and microsphere F_i (mean correlation coefficient r = 0.83) for all five animals, and ranged from 0.73 to 0.97. The mean endocardial-epicardial (endo-epi) ratio for the IPPA d_i (0.90 ± .43) (Table 2) tended to be less than for microsphere F_i (0.94 ± 0.47), but was statistically different only for two animals. IPPA endo-epi ratio also correlated well with microsphere endo-epi ratio (r = 0.76).

TABLE 2
Microspheres Myocardial Blood flow (ml/min/g*)

Study no.	Endocardium	Epicardium	Endo-Epi ratio
325	1.36 ± 0.86	1.22 ± 0.66‡	1.02 ± 0.51
415	0.84 ± 0.65	1.24 ± 0.78‡	0.65 ± 0.79
660	3.33 ± 0.98	3.26 ± 0.62	1.07 ± 0.48
814	2.49 ± 0.80	2.41 ± 0.48	1.06 ± 0.38
815	3.62 ± 2.16	3.34 ± 1.75	1.06 ± 0.44
Mean	§	§	0.94 ± 0.47

IPDA
Myocardial Deposition (ml/min/g)

Study no.	Endocardium	Epicardium	Endo-Epi ratio
325	0.34 ± 0.29†	0.32 ± 0.25†	0.99 ± 0.48
415	0.48 ± 0.34†	0.73 ± 0.37†‡	0.60 ± 0.46
660	1.06 ± 0.34†	1.13 ± 0.22†	0.96 ± 0.38†
814	1.11 ± 0.21†	1.05 ± 0.15†	1.07 ± 0.24
815	0.92 ± 0.47†	0.94 ± 0.25†	0.92 ± 0.33†
Mean	§	§	0.90 ± 0.43

* Mean ± s.d.
† $p < 0.05$ compared to microspheres.
‡ $p < 0.05$ compared to endocardium.
§ See Table 1 for explanation.

For endocardial samples (Table 3), there was a strong correlation between IPPA and microsphere deposition (r = 0.85; $p > 0.05$ compared to global) and was similar for the epicardial samples (r = 0.82). The regression values, slopes of the regression lines, the y intercepts and the standard error of the estimates comparing IPPA activity to microsphere measured flow for the endocardium and epicardium for each of the individual animals, as well as the values for all samples, are shown in Table 3.

When the IPDA-microsphere relationships were examined relative to normal and ischemic zones, global mean normal endocardial and epicardial zone d_i and F_i were significantly greater than in the ischemic zone for both microspheres and IPDA (Table 4). IPDA activity correlated with microsphere activity in both the normal and ischemic zones, although not as strongly as for all samples combined. Endo-epi flow ratios for microspheres were similar in both the normal and ischemic zones and for IPDA in the normal zone. However, there was a significant difference between IPDA normal and ischemic endo-epi zone ratios, as well as between microspheres and IPDA in the ischemic zone (Table 4). Ischemia also significantly altered the relationship between global F_i and d_i as evidenced by the increase in the slope of the regression line by ~44% (Table 4 and Fig. 2). However, this difference was totally the result of the ischemic zone slope in one study (415). If study 415 is excluded, the global normal zone slope is decreased from 0.25 to 0.20, while decreasing the global ischemic zone slope from 0.39 to 0.23, which is not different than the normal zone.

DISCUSSION

Because IPPA can be labeled with ^{123}I, a superior isotope for gamma camera imaging relative to thallium-201 (^{201}Tl), it offers an attractive alternative for single

TABLE 3
Comparison between Microspheres and IPDA

Study no.	Endocardium r=	slope	intercept	s.e.e.	Epicardium r=	slope	intercept	s.e.e.	Endo-epi ratio r=	slope	intercept	s.e.e.
325	0.88	0.30	−0.07	0.14	0.85	0.35*	−0.11	0.13	0.90	0.85	0.12	0.21
415	0.97	0.51†	0.05†	0.08	0.96	0.46*†	0.16*†	0.10	0.93	0.54†	0.24†	0.16
660	0.87	0.31‡	0.04†	0.17	0.68*	0.24*†‡	0.32*†‡	0.16	0.86	0.67†‡	0.24†	0.20
814	0.80	0.21†‡§	0.57†‡§	0.13	0.56*	0.17†‡§	0.63*†‡§	0.12	0.76	0.47†‡§	0.57†‡§	0.15
815	0.89	0.19†‡§	0.22†‡§¶	0.23	0.93	0.13*†‡§	0.50*†‡§¶	0.09	0.53	0.40†‡§	0.50†‡§	0.28
ALL**	0.85	0.28	0.17	0.24	0.82	0.29	0.21	0.23	0.76	0.65	0.28	0.26

* $p < 0.05$ compared endocardium.
† $p < 0.05$ compared to study 325.
‡ $p < 0.05$ compared to study 415.
§ $p < 0.05$ compared to study 660.
¶ $p < 0.05$ compared to study 814.
** all samples combined.

photon emission computed tomography. Several investigators have suggested use of ^{123}IPPA as a myocardial perfusion and metabolic imaging agent (*8–11*). However, Reske et al. have suggested that at myocardial blood flows >1.7 ml/min/g the deposition of tracer decreases relative to the flow. This would complicate interpretation of IPPA kinetics in the absence of a quantitation of myocardial concentration which is not possible with gamma imaging (*12*).

The relationship of IPPA d_i to microsphere F_i during exercise has not previously been examined. Our model was chosen because it closely reflects the clinical situation of exercise testing and has been used by Nielson et al. to examine the relationship between ^{201}Tl deposition

TABLE 4
Normal and Ischemic Zones

	Microspheres ml/min/g	IPDA ml/min/g	r=	Slope	Intercept	s.e.e.
		Global				
Normal (698)	2.64 ± 1.12	0.93 ± 0.38**	0.74	0.25	0.26	0.25
Ischemic (372)	1.12 ± 0.86*	0.52 ± 0.49* **	0.68	0.39*	0.09	0.35
		Endocardium				
Normal (345)	2.76 ± 1.18	0.94 ± 0.38**	0.74	0.24	0.28	0.25
Ischemic (190)	0.96 ± 0.80†	0.43 ± 0.56†**	0.53	0.37†	0.07	0.47
		Epicardium				
Normal (353)	2.52 ± 1.04†‡	0.95 ± 0.38‡**	0.74	0.27‡	0.23	0.26
Ischemic (182)	1.29 ± 0.90†‡¶	0.62 ± 0.38†‡¶**	0.92	0.39†¶	0.12†¶	0.15
		Endo-Epi ratio				
Normal (345)	1.10 ± 0.31	1.06 ± 0.29	0.66	0.59	0.41	0.21
Ischemic (182)	1.00 ± 1.43	0.74 ± 0.92§**	0.49	0.31§	0.43	0.79

* $p < 0.05$ compared to global normal.
† $p < 0.05$ compared to normal endocardium.
‡ $p < 0.05$ compared to ischemic endocardium.
¶ $p < 0.05$ compared to normal epicardium.
§ $p < 0.05$ compared to normal endo-epi ratio.
** $p < 0.05$ compared to microspheres.
( ) = Number of samples

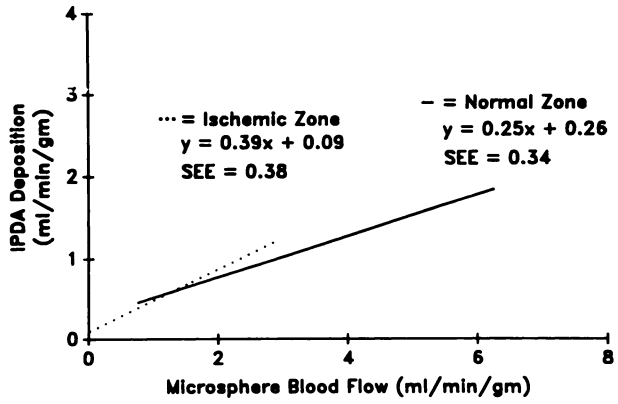

FIGURE 2
The correlation between IPDA deposition and microsphere flow in normal and ischemic zones is shown for all samples. The extremes of the lines reflect the limits of flow for the normal and ischemic zones.

and myocardial blood flow (*15*). Our results demonstrate globally that during exercise the initial myocardial IPPA deposition is proportional to blood flow over a wide range of flow. The deposition, however, is only about 25% of the IPPA delivered by the flow, i.e., local extraction and retention is ~25%, which is typical for barrier-limited solutes. A similar relationship between microspheres and IPPA was found for endo- and epicardium (Table 3).

As expected, both microsphere and IPDA delivery were reduced in the ischemic zone and statistically IPDA d_i was a higher fraction of F_i than in the normal zone, i.e., the slope of the regression line was higher. However, this was secondary to the contribution of one animal and thus there is probably no difference between normal and ischemic zone deposition. Although a strong relationship existed between F_i and d_i for each individual animal, there was variability in local extraction and retention among the animals. The reason(s) for these differences cannot be determined from our data. Possible explanations include a longer time between injection of IPPA and sacrifice in the animals with the highest extraction (i.e., longer time for recirculation of IPPA). This seems unlikely since all animals were sacrificed and the hearts excised within 2 min of completion of blood withdrawal. Greater metabolic demands by the dogs exercising to the higher level of blood flow should have caused increased extraction of IPPA which should have caused the slopes of the F_i-d_i relationship to be greater in these animals, unlike what was observed. However, the increased metabolic demands could have caused a more rapid beta oxidation of the IPPA with release of the radiolabeled metabolite into the blood and less apparent retention in the tissue samples. This would produce results similar to ours. Measurement of either E_i or retention would have to be made to resolve this. A shift to anaerobic metabolism with higher myocardial work would reduce beta oxidation and enhance IPPA retention unless there was a concomitant decrease in E_i. It seems unlikely that anaerobic metabolism developed in these normal animals running at a submaximal level of exertion. However, this cannot be addressed as hemodynamic parameters were not measured since it was assumed that they would be relatively normal in the intact exercising dog. Additionally, as the purpose of the study was to examine IPPA deposition to myocardial blood flow over a range of flows, knowledge of global hemodynamic parameters would provide information only as to why the maximal flows differed among the animals. Only with knowledge of regional differences in metabolic demand could the difference among the IPPA d_i-F_i relationship be discussed. Measurement of regional differences under these conditions would have been very difficult.

Our data differ from those reported by Reske et al. (*12*) who found that there was correlation between d_i and F_i over the flow range of 0 to 1.7 ml/min/g, but with flows between 1.7 and 2.5 ml/min/g, no further increase in IPPA uptake occurred. The difference between the two studies probably relates to the experimental models used. Our study was performed in an exercising dog, whereas Reske et al. used a pentobarbital anesthesized open chest dog in which coronary blood flow was increased by pacing. Aside from the anesthesia-induced differences, coronary blood flow during pacing is markedly different from flow at the same heart rate during exercise (*16*). In our study, myocardial oxygen demand presumably continued to increase throughout exercise, creating a need for increased extraction of IPPA to meet metabolic needs of the normal nonischemic myocardium. This may not occur during pacing.

The endocardial-epicardial deposition ratio for IPPA tended to be lower than for microspheres, as was reported by Reske et al. (*12*). Yipintsoi et al. showed similar results for potassium and antipyrine relative to microspheres (*17*). In our study, this was due almost exclusively to a marked decrease in the ratio in the low flow regions. Presumably, in the ischemic endocardium, the increase in extraction that accompanies the decreased flow was inadequate to offset the relative increase of epicardial flow that is known to occur (*16*). This was not observed with the microspheres. This difference between IPPA and microsperes cannot readily be explained since one would have anticipated similar decrease for microspheres. However, the validity of the microsphere method under these conditions should possibly be compared to some molecular marker of flow such as iodinated desmethylimipramine (*18*). Alternatively, in the very low flow regions, there may be preferential myocardial glucose utilization relative to free fatty acids which would tend to decrease IPPA uptake (*19*).

In summary, the initial deposition of radiolabeled IPPA during exercise linearly reflects regional myocardial blood flow in normal and ischemic tissue, although there is a systematic underestimation of absolute flow as a result of the limited rate of transmembrane transport into the cell. A gamma camera image taken within a short time following injection of IPPA will give a measure of relative regional flows. However, images acquired over times longer than the first minute or two will reflect the effects of combinations of delivery by flow, transmembrane uptake, metabolic transformations and reflux of metabolic products or of the non-metabolized parent compound. Thus, the adequacy of IPPA as a marker for myocardial ischemia will depend upon its subsequent kinetics which are not addressed in this study.

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