Myocardial Blood Flow as Measured by Fractional Uptake of Rubidium-84 and Microspheres

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Under conditions of varying flow rates, total myocardial blood flow, measured by fractional uptake of rubidium-84, using a coincidence counting system, was compared with myocardial flow measured by microspheres (15 ± 5 μm). The methods were compared, open-chested, in 47 dogs: 17 during control, ten following 5 min of ligation of left anterior descending coronary artery, five following i.v. isoproterenol, six following ligation and isoproterenol, and nine after ligation plus dipyridamole. Regional flows by Rb-84 and by either Ce-141 or Cr-51 microspheres were also compared for left ventricle, as well as for nonischemic posterior wall, which served as a reference area, and for anterior wall with ligation of left anterior descending artery in the same preparations. There were no significant differences in total or regional flow measured by the two methods, nor in the estimate of ischemic area size. The data indicate that measurement of myocardial blood flow by fractional uptake of a potassium analog is a reliable method in the presence of ischemia and drug intervention. It is suggested that the inequalities of extraction ratio that occur with differing flow rates do not invalidate fractional-uptake methods over the flow ranges examined.

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It is generally accepted that the fractional uptake method for the measurement of myocardial blood flow and the distribution of blood flow within the heart, using potassium analogs as indicators, is valid if the extraction ratio for the diffusible indicator is the same for the region under study as the overall extraction ratio for the body (*1–6*). When the extraction ratios are equal, the regional (or organ) flow fraction equals the regional indicator content divided by the amount injected. Content divided by amount injected can be converted to flow terms by multiplying by the cardiac output (*4*). It is less generally accepted that fractional-uptake methods can be reliable in the presence of marked heterogeneity of flow (*3*). In this case extraction ratios are certain to be significantly different between total body and heart and within the myocardium, since extraction ratios for diffusible potassium analogs vary inversely with flow (*7*).

Developmental efforts in myocardial scintigraphy are being directed increasingly toward the achievement of tomographic maps of cardiac sections showing quantitatively the content of diffusible radioactive tracer. Specific application of such systems will be limited by uncertainties about the equality of extraction ratios and the effects of unequal extraction ratios on flow calculations, and this will be true even given the ability to measure quantitatively the tissue content of the diffusible radiotracer. The confidence limits for the relationship between tracer content and flow must be known (*8–10*). While one approach would be to measure extraction ratios during control and intervention situations, the following considera-

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tions complicate, and perhaps nullify, that concept. In the presence of heterogeneous myocardial flow such as that present during ischemia, prolonged measurement time may be required to ensure adequate representation of underperfused areas in the coronary sinus (*11*) and, thus, accurate determination of extraction ratio. In the clinical situation when a patient becomes symptomatic secondary to an imposed stress, it is necessary to make the flow measurement quickly and without the benefit of a steady state. Furthermore, alteration of an extraction ratio following an intervention could occur simply by a redistribution of flow to circuits with extractabilities different from those of the control state, and be entirely reflective of flow (*12*). The assumption would be, however, that because the extraction ratio changed, the flow measurement was invalid. Finally, when regional flows are the target, it is not possible to measure the extraction ratios for various regions in the human heart.

To circumvent the problem of extraction-ratio measurement—which, in our opinion, is one without a satisfactory solution—this study compares total and regional myocardial blood flows, as determined by fractional uptake of Rb-84, with the same flows determined by microsphere technique, under conditions of diverse regional flows. The hypothesis is that if the two indicators, one of which has an extraction ratio of unity, quantitatively measure similar flows, extraction-ratio alterations do not limit the validity of fractional-uptake techniques (*13–16*).

METHODS

Mongrel dogs weighing 12–20 kg were anesthetized with i.v. sodium pentobarbital, 35 mg/kg, and endotracheal intubation was carried out. Anesthesia was maintained throughout the procedure by additional i.v. sodium pentobarbital as required. Respiration was maintained with a Harvard respirator. A vertical sternum splitting incision was made, exposing the heart. A polyethylene snare was placed around the left anterior descending coronary artery for subsequent vessel occlusion. To obtain the arterial rubidium curve, the right femoral artery was tied off and the proximal end connected to a 2-ml radicoil placed in a standard well counter. The distal end of the radicoil was connected to a pump set to withdraw blood through the coil at a constant rate of 10 ml/min. A plastic catheter was inserted into the left atrial appendix for injection of microspheres. Plastic cannulae were also inserted into the left femoral and left brachial arteries, tied in place, and connected to a Harvard withdrawal pump. These cannulae were used for arterial sampling for reference blood flows. Another plastic catheter was inserted into the right jugular vein for intravenous drug infusion and Rb-84 injection.

A coincidence counting system equipped with two opposed 4-in. crystals provided for cylindrical detection of the myocardial uptake of rubidium (*17*). The upper crystal was lowered to within ½-in. of the anterior surface of the heart, and care was taken to position the entire heart under the crystal and to avoid the dome of the liver.

Total myocardial blood flow by Rb-84 ($TMBF_{Rb}$) was calculated by the following formula:

$$TMBF_{Rb} = K \times q(t)/\int_0^\infty A_o(t)dt,$$

where K represents a factor determined for each experiment to convert the value q (myocardial counts) from coincidence counts to values comparable to the arterial counts from the well counter and to correct for transmission factors present when the experimental animal is in place, and $q(t)$ represents the myocardial counts of rubidium. The K factor is determined by using a standard source dish of known volume so that counts per milliliter from the well counter and the coincidence counters can be made comparable. The denominator represents the integrated arterial blood concentration of rubidium during the first circulation, determined by extrapolation after recirculation begins. The method and its verification have been described in detail (*5,6,18,19*). Cardiac output was determined with the standard indicator-dilution technique using Rb-84 as the indicator (*18*).

Regional myocardial flows by rubidium ($RMBF_{Rb}$) were similarly calculated except that the myocardial content was determined by gamma counting of the tissue samples rather than precordial detection with the coincidence system.

For the microsphere measurements, carbonized microspheres* 15 ± 5 μm in diameter, were labeled with Ce-141 or Cr-51, injected into the left atrium, and followed with a 5-ml saline flush. The microspheres were obtained as 1 mCi of nuclide in 10 ml of 10% dextran to which one drop of Tween 80 had been added. The stock solution was diluted with 10% dextran so that each milliliter contained approximately 2 million microspheres. Before injection, the microspheres were mixed by agitation for at least 30 min in an ultrasonic bath and vortex agitator. Two milliliters of the solution were drawn into a syringe, which was vigorously agitated until the moment of injection. The injection was given, over a period of 10–20 sec, into the left-atrial cannula and the syringe was flushed with 5 ml of normal saline. A drop of each microsphere injectate was microscopically checked for clumping. Starting 30 sec before injection and continuing for

90 sec thereafter, blood was withdrawn simultaneously from the right brachial and right femoral arteries at 10 ml per minute with a Harvard pump.

When the data collection was concluded, the majority of the hearts were quickly excised, washed free of blood, stuffed with gauze to preserve shape, and stored in formalin at 18°C for 24 hr to facilitate sectioning. Two hearts were quick-frozen and sectioned immediately in order to verify that the diffusion coefficient for rubidium over longer periods of fixation did not significantly modify the relationship between myocardial rubidium and microsphere content (7). At the time of sectioning, gross epicardial fat and major vessels were removed from the heart and the total heart weighed. The heart was cut into six slices. Each slice was then divided into seven sections of left ventricle and one section of right ventricle. The former were divided into epicardial and endocardial halves and numbered so that Section 1 always corresponded to the area transected epicardially by the anterior descending artery. The samples were placed in plastic vials, weighed, digested, adjusted for constant geometry, and counted for at least 5 min in a gamma well counter using window settings corresponding to the peak energies emitted by each of the three radionuclides. The reference arterial blood samples were counted in aliquots in the same manner as the myocardial samples. The activities recorded in each energy window, and the corresponding sample weights, were then entered into a digital computer programmed to correct activity recorded in each window for contaminant activity contributed by the other nuclides, and for background activity.

Microsphere flows were calculated in ml/min per total heart by the formula:

$$TMBF_M = Cm \times RBF/C_R,$$

where $TMBF_M$ is myocardial blood flow by microspheres, *Cm* is counts per total weight of myocardium, *RBF* is reference blood flow in milliliters per minute from the brachial and femoral arteries, and C_R is total counts in the averaged reference blood samples (*20*). If the reference samples varied by greater than 20%, the calculated flows were discarded (*21*). For smaller myocardial samples, the flows per gram, $RMBF_M$, were similarly calculated.

Study groups. *Series 1.* These animals (N = 17) had $TMBF_{Rb}$, $TMBF_M$, $RMBF_{Rb}$, and $RMBF_M$ determined during the control state when flow was normally distributed and extraction was therefore presumed to be normally distributed.

Series 2. These animals (N = 30) were studied in order to determine the relationships between total and regional myocardial blood flow as measured by microspheres and the Rb-84 fractional uptake, under conditions where myocardial flow patterns demonstrated heterogeneity, and under conditions where cardiac output and myocardial flow might be changing in different directions or to different degrees. The determinations made were: a) $TMBF_{Rb}$ and $TMBF_M$; b) $RMBF_{Rb}$ and $RMBF_M$ for total left ventricle and in the anterior wall (distal to occlusion) with posterior wall serving as a reference flow area; and c) the regions of the left ventricle, and their percentage by weight, in which rubidium and microspheres showed flow rates (a) less than 50%, and (b) less than 25%, of the mean flow in the posterior wall. Series 2 animals were divided into four subgroups:

Series 2A. Ten dogs following 5-min occlusion of the left anterior descending artery.

Series 2B. Five dogs following 3 min of i.v. infusion of isoproterenol at 5 μg per minute.

Series 2C. Six dogs following 5 min of left anterior descending occlusion plus isoproterenol at the same rate as in 2B animals.

Series 2D. Nine dogs studied after 5 min of left anterior descending artery occlusion plus dipyridamole† at 250 μg per kilogram per minute.

Series 3. This series of 30 animals was undertaken to determine the relationship between cardiac output and total myocardial blood flow by fractional extraction of rubidium, with the same interventions used for the comparative flow studies. Ten animals were studied before and after occlusion of left anterior descending artery; six after isoproterenol infusion (5 μg/min for 3 min); five following occlusion of left anterior descending artery for 5 min plus

TABLE 1. STUDY GROUPS

Measurements: $TMBF_{Rb}$, $TMBF_M$, $RMBF_{Rb}$, $RMBF_M$	
Series 1	(N = 17). No intervention
Series 2	(N = 30). Intervention studies
Series 2A	(N = 10). LAD occlusion
Series 2B	(N = 5). Isoproterenol infusion
Series 2C	(N = 6). LAD occlusion plus isoproterenol
Series 2D	(N = 9). LAD occlusion plus dipyridamole
Measurements: $TMBF_{Rb}$, cardiac output	
Series 3	(N = 30).
Series 3A	(N = 10). LAD occlusion
Series 3B	(N = 6). Isoproterenol infusion
Series 3C	(N = 5). LAD occlusion plus isoproterenol
Series 3D	(N = 4). Dipyridamole
Series 3E	(N = 5). LAD occlusion plus dipyridamole

$TMBF_{Rb}$, $TMBF_M$ = total myocardial blood flow by rubidium and microspheres, respectively; $RMBF_{Rb}$, $RMBF_M$ = regional myocardial blood flow by rubidium and microspheres, respectively; LAD = ligation of left anterior descending artery.

TABLE 2. COMPARISON OF TOTAL AND REGIONAL MYOCARDIAL BLOOD FLOW AS DETERMINED BY MICROSPHERES AND BY FRACTIONAL UPTAKE OF RUBIDIUM-84

	Number of observations	$TMBF_{Rb}$ ml/min	$TMBF_{St}$ ml/min	Left ventricle Rb ml/min/g	Left ventricle Microspheres ml/min/g	Anterior wall Rb ml/min/g	Anterior wall Microspheres ml/min/g	Posterior wall Rb ml/min/g	Posterior wall Microspheres ml/min/g
Series 1 (controls)	17								
Mean		76	84	0.99	0.90				
s.e.		8	11	0.19	0.21				
		NS		NS					
Series 2									
2A—Postocclusion LAD	10								
Mean		55	58	0.7309	0.7690	0.609	0.657	0.7890	0.7831
s.e.		6	4	0.0186	0.0214	0.0398	0.0516	0.0345	0.0323
		NS		NS		NS		NS	
2B—Isoproterenol	5								
Mean		114	128	1.252	1.202	1.164	1.068	1.567	1.514
s.e.		10	9	0.0485	0.0452	0.716	0.0585	0.122	0.122
		NS		NS		NS		NS	
2C—Postocclusion LAD and isoproterenol	6								
Mean		70	83	1.200	1.134	0.608	0.531	1.653	1.660
s.e.		12	15	0.0531	0.0482	0.0660	0.0662	0.112	0.108
				NS		NS		NS	
2D—Postocclusion LAD and dipyridamole	9								
Mean		76	80	1.692	1.657	1.688	0.435	1.733	1.680
s.e.		12	12	0.0919	0.0746	0.196	0.218	0.164	0.141
				NS		NS		NS	

$TMBF_{Rb}$, $TMBF_{St}$ = myocardial blood flow for total heart (including right ventricle and atrial) by rubidium-84 and by microspheres, respectively; Rb = rubidium-84; NS = no significant difference between the columns on either side; LAD = left anterior descending artery.

isoproterenol; four dogs following dipyridamole (250 μg/kg i.v. for 5 min); and five dogs following left anterior descending artery occlusion (5 min) and dipyridamole during the period of occlusion.

The study groups are outlined in Table 1.

Derived data and data management. Data were calculated as mean ± s.e. of the mean and the significance of the difference between paired data determined by student's t-test. Correlation coefficients were calculated by standard analysis of variance as well as by rank correlation (Wilcoxen) test.

"Ischemia" was arbitrarily assumed to be present to a moderate degree if a myocardial section had a calculated flow of less than 50% of the mean flow in the posterior wall; and a section was arbitrarily considered "severely ischemic" if the flow was less than 25% of the mean flow in the posterior wall.

RESULTS

Total and regional myocardial blood flows. The myocardial blood-flow values ± s.e. of the mean, expressed as ml/min for all study groups, are shown in Table 2. Total myocardial blood flow by Rb-84 uptake and by the microsphere technique were not significantly different in any of the groups. The correlation coefficient for the two flows was 0.932 across all dogs. Average flow/g of left ventricle and for anterior wall (Slices 2–5, Sections 1, 2, 7) and for posterior wall (Slices 2–5, Sections 3, 4, 5) are also collated in Table 2. As in the case of total flow, there were no significant differences between Rb-84 and microsphere flows in any area. By standard analysis of variance, the correlation coefficients between the Rb-84 and microsphere determinations were 0.882 for left-ventricular flow per gram, and 0.895 and 0.946 for anterior- and posterior-wall flow per gram, respectively. Analysis of variance values by rank order for the same areas were 0.913, 0.916, and 0.960, respectively.

The flow rates across all animals ranged from 0.03 to 6.47 ml/min per gram. The highest flow values per gram were in the posterior wall under dipyridamole infusion, the lowest in Group 2A in the anterior wall following ligation of left anterior descending artery and without drugs.

"Ischemic" area size. The data for ischemic area size, expressed as grams of left ventricle, are shown in Table 3. In the control group (Series 1), no ischemic areas were identified. For the animals with ligation, there were no significant differences between area classification in any of the groups. For sections with flows/g less than 50% of the mean

TABLE 3. GRAMS OF LEFT VENTRICLE WITH FLOWS LESS THAN 25% OF MEAN NORMAL FLOW (<25%) AND GREATER THAN 25% BUT LESS THAN 50% (>25%, <50%)

	Number of observations	Total LV weight (grams)	<25% Rubidium (grams)	<25% Microspheres (grams)	>25%, <50% Rubidium (grams)	>25%, <50% Microspheres (grams)
LAD ligation	10					
Mean		80.3	8.4	10.6	7.7	5.7
s.e.			4.1	4.4	1.8	0.9
			NS		NS	
LAD ligation plus isoproterenol	6					
Mean		91.1	12.5	14.9	18.8	16.9
s.e.			5.6	6.0	6.4	5.7
			NS		NS	
LAD ligation plus dipyridamole	9					
Mean		64.9	6.1	8.3	8.3	9.8
s.e.			3.3	2.9	1.3	1.1
			NS		NS	

LV = left ventricle; LAD = left anterior descending artery; NS = no significant difference between the columns on either side.

for the posterior wall, the correlation coefficient for all animals was 0.889; for areas with less than 25% of mean posterior wall flow, $r = 0.956$; and for areas with greater than 25% but less than 50% of mean posterior wall flow, $r = 0.795$. The average difference between rubidium and microsphere area identification was 2 g; and these were in contiguous areas constituting from one to three pieces of myocardium having an average weight of 0.87 g.

Cardiac output and myocardial blood flow. Series 3 studies are collated in Table 4. In 22 of 30 studies, myocardial blood flow and cardiac output changed in the same direction. With occlusion of left anterior descending artery, myocardial flow decreased by 23% and cardiac output by 18% ($p < 0.05$). With isoproterenol, myocardial flow increased 58% ($p < 0.05$) and cardiac output 33% ($p < 0.05$). With occlusion of left anterior descending artery plus isoproterenol, apparent increases in myocardial flow and cardiac output, not significant, were 9% and 15%, respectively. Before occlusion of the left anterior descending artery, dipyridamole infusion in-

TABLE 4. MYOCARDIAL BLOOD FLOW (MBF_{Rb}) AND CARDIAC OUTPUT BY RUBIDIUM-84, AT REST AND FOLLOWING INTERVENTION

	Number of observations	MBF_{Rb} (ml/minute) Pre-	MBF_{Rb} (ml/minute) Post-	MBF_{Rb} %Δ	Cardiac output (l/minute) Pre-	Cardiac output (l/minute) Post-	Cardiac output %Δ
Series 3							
3A. Occlusion of LAD	10						
Mean		88	68	−23	1.7	1.4	−18
s.e.		14	10		0.28	0.25	
		$p < 0.05$			$p < 0.05$		
3B. Isoproterenol	6						
Mean		67	106	+58	1.2	1.6	+33
s.e.		9	10		0.15	0.13	
		$p < 0.05$			$p < 0.05$		
3C. Occlusion of LAD and isoproterenol	5						
Mean		80	87	+9	1.3	1.5	+15
s.e.		14	17		0.16	0.23	
		NS			NS		
3D. Dipyridamole	4						
Mean		71	92	+30	1.2	1.3	+8
s.e.		11	10		0.16	0.12	
		NS			NS		
3E. Occlusion of LAD and dipyridamole	5						
Mean		65	69	+6	1.5	1.4	−6
s.e.		17	19		0.14	0.11	
		NS			NS		

LAD = left anterior descending artery; NS = no significant difference between the columns on either side.

creased myocardial blood flow 30% and cardiac output 8%; after occlusion, myocardial flow appeared to increase by 6% and cardiac output to decrease by 6%, but neither change was significant.

DISCUSSION

These data show good agreement between total myocardial blood flow as determined by microspheres and by the fractional uptake of a diffusible indicator, rubidium-84, and they are compatible with a previous study demonstrating general equivalence of the two techniques (*6*). Other comparisons between total myocardial blood flow as determined by fractional uptake of radioactive rubidium or potassium and by the nitrous oxide method (*19*), the direct Fick principle (*5,22*), and the direct myocardial radiotracer content (*23*) have also shown that the methods have reasonably accurate equivalence at varying flow rates and in the presence of drug intervention. In the studies presented here, the equivalence between the findings from fractional uptake of Rb-84 and from microspheres was shown to hold in the presence of varying heterogeneity of myocardial flow induced by coronary-artery occlusion, by isoproterenol, and by dipyridamole, as well as under conditions where cardiac output and myocardial blood flow could have been changing in opposite directions or to varying degrees. Admittedly, the cardiac-output studies, by necessity, had to be done as studies separate from the comparative regional flow studies, since only one injection of rubidium could be given in each experiment.

In the case of regional flows, previous studies have demonstrated that the regional content of ionic potassium or potassium analogs and small radioactive microspheres bear a linear relationship (*16*), with disparity occurring only at very high or low flow rates (*13*) or with reperfusion following temporary ischemia (*15*). Since flow is the factor common to both diffusible indicator and microsphere content, these studies have been interpreted to indicate that, except under unusual conditions, measurement of myocardial content of a diffusible indicator such as potassium, rubidium, or thallium can provide a reliable noninvasive method for the determination of regional myocardial flow distribution. The data presented here have extended those observations to suggest that it is permissible to refer to flow in milliliters per minute as well as in the less quantifiable terms, distribution and perfusion.

Simple equivalence between microsphere and rubidium flows cannot be assumed to validate each other. Microspheres of the size used in this study (15 ± 5 μm) are measuring arteriolar flow and "instantaneous" flow, that is, the flow pattern that was present during the period of the primary arterial curve. Rubidium and potassium tracers necessarily must be extracted from capillaries, and thus are measuring capillary flow per minute. This may result in smoothing out temporal inhomogeneity of myocardial flow and extraction-ratio differences. In addition, both techniques have a fairly large potential for experimental error. This is somewhere between 10% and 20% for the microsphere technique in comparison with measurement of flow by total collection of coronary-venous drainage (*24*). To the best of our knowledge this same comparison—namely with total coronary-venous drainage under condition of ischemia—has not been done for fractional-uptake methods. The intent of our work was to add to and extend the observations of others that myocardial fractional uptake of diffusible indicators in the potassium-analog group is directly related to flow, and, that underperfused regions are not being masked or created by extraction-ratio differences, even in the presence of highly variable extraction ratios between regions, secondary to varying flow rates. The basis for the insensitivity of the flow estimate to variations in extraction probably derives from the fact that the fractional uptake of diffusible indicators is the product of extraction and flow. Extraction alone does not determine the final flow estimate.

FOOTNOTES

* Microspheres, Minnesota Mining and Manufacturing Corporation.

† Dipyridamole supplies courtesy of Boehringer Ingelheim, Ltd., Elmsford, N.Y.

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