

## Regional Myocardial Blood Flow \*

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**Summary.** A method is described which measures the local effectiveness of the myocardial circulation, expressed as a clearance constant. Uniform clearance constants have been demonstrated in the normal canine and human myocardium. A distinct difference in clearance constants has been demonstrated between the normal canine myocardium and areas of naturally occurring disease. Heterogeneous clearance constants have been found in a majority of human subjects with coronary artery disease—the lowest rates being noted in areas of fibrous aneurysm.

### Introduction

In 1948 Kety suggested that the clearance rate of local deposits of radioactive material could be used as an index of effective regional blood flow (2). Using 0.5–1.0 ml of isotonic  $^{24}\text{Na}$  solution, he successfully determined the clearance constant of skeletal muscle, and suggested that this method could also be used as a means of measuring myocardial blood flow. In 1952, this method was used by Cullen and Reese (3) to measure myocardial circulation in dogs. In 1960, Hollander et al. (4) reported the use of direct injection of  $\text{Na } ^{131}\text{I}$  to measure myocardial blood flow in man and in the

dog and later reported a decreased disappearance rate in subjects with coronary artery disease (5). Subsequently, the direct deposition of radiosodium has been used to assess regional myocardial circulation in dogs by Connolly and coworkers (6) in 1960 and Salisbury and associates (7) in 1962. In 1964, this technic was used by Kirk and Honig (8) to demonstrate a slower rate of clearance in the subendocardial layers of the myocardium when compared with subepicardial layers.

The studies mentioned above have measured the myocardial clearance of radiosodium and radioiodine. Renkin (9), studying the transport of electrolytes from blood to tissue, pointed out that the extraction ratio of hydrophilic ions fell to 0.5 at flow rates of 10 ml/100 g per min. Lassen (10) compared clearances in skeletal muscle and found that  $^{24}\text{Na}$  and  $^{133}\text{Xe}$  measured virtually the same flow rate at rest (2.3 and 2.5 ml/100 g per min). A much higher flow rate was measured by  $^{133}\text{Xe}$  during reactive hyperemia (56 ml/100 g per min in normal subjects), while that measured by  $^{24}\text{Na}$  was 12.9 ml/100 g per min. This was attributed to increasing limitation to sodium exchange at the capillary level with increasing flow. As myocardial blood flow is relatively fast, it would appear advantageous to use an inert, lipophilic tracer such as  $^{133}\text{Xe}$  or  $^{85}\text{Kr}$  to measure myocardial perfusion, as these gases are able to cross the entire capillary-cell interface and are not limited by diffusion through pores as are  $^{24}\text{Na}$  and  $^{131}\text{I}$ .

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The safety of injection of small volumes of fluid into the human myocardium has been established by Hollander et al. (4), and the safety of radiation exposure involved established by Lassen (11). This communication reports on the use of intramyocardial injections of radiokrypton to assess the degree of myocardial perfusion in normal and diseased dog hearts and in human subjects with angiographically localized coronary artery disease.

### Methods

$^{85}\text{Kr}$  was used as an indicator in all experiments. Supplied as a gas, it was agitated into solution with isotonic saline. 0.3 ml of this solution (containing  $10\ \mu\text{c}$ ) was injected via a No. 27 needle along a diagonal tract to a depth of approximately 3 mm beneath the epicardium. The surface of the myocardium was then sponged to eliminate minor initial bleeding from the injection site, and a shielded scintillation probe with a 1 inch Na I crystal was placed 5 cm above the injection site. A rate meter, counting 30,000 cpm (time constant 1 sec), and attached to a direct-writing recorder, provided a record of the disappearance of isotope. After subtraction of background radiation, the above data were plotted on semilogarithmic paper, and the clearance constant of the exponential portion of the curves was calculated from the equation

$$K = \frac{\log C_1 - \log C_2}{0.4343 (T_2 - T_1)} = \frac{0.6931}{\text{half-time in min}}$$

where  $C_1$  and  $C_2$  = counts per minute at  $T_1$  and  $T_2$ , respectively. With this basic technic, six animal experiments were performed. Mongrel dogs (10–20 kg in weight) were anesthetized with morphine sulfate (5 mg/

kg) and 1:16 saturated chloralose-urethane solution as needed. After induction of anesthesia, the dogs were placed in the right lateral decubitus position, and a thoracotomy was performed in the fourth left interspace. Blood pressure and heart rate were monitored throughout the study.

In the first animal, a segment of the proximal left anterior descending artery was dissected free, and a thin polyethylene cannula placed in the arterial lumen. Propranolol (2 mg) was given intravenously to slow heart rate and suppress ventricular irritability. Six pairs of measurements of myocardial  $^{85}\text{Kr}$  clearance constants were made with injection into the myocardium adjacent to the left anterior descending artery along with injections directly into the artery.

In a second animal a Goldblatt clamp was placed on the proximal left anterior descending artery. An intramyocardial injection of  $^{85}\text{Kr}$  was made distal to the clamp, and the decay curve monitored continuously during intermittent occlusion of the vessel.

In a third experiment, in three animals with grossly normal hearts 41 intramyocardial deposits were made at random sites, but at uniform depths along the anterior descending artery and over the anterior left ventricle, and isotope decay curves were recorded.

In the sixth animal, the fortuitous discovery of an area of fibrous scarring on the anterior left ventricle (probably secondary to canine small vessel arteritis) enabled four random measurements to be made over the area of scar and four over normal myocardium.

33 human subjects, ranging in age from 35 to 62 yr were studied at thoracotomy. All subjects underwent prior cardiac catheterization and selective cine coronary angiography by the Sones technic. The four subjects with normal coronary arteries included one with mitral stenosis and two with aortic stenosis who were undergoing surgical correction of their valvular lesions. The

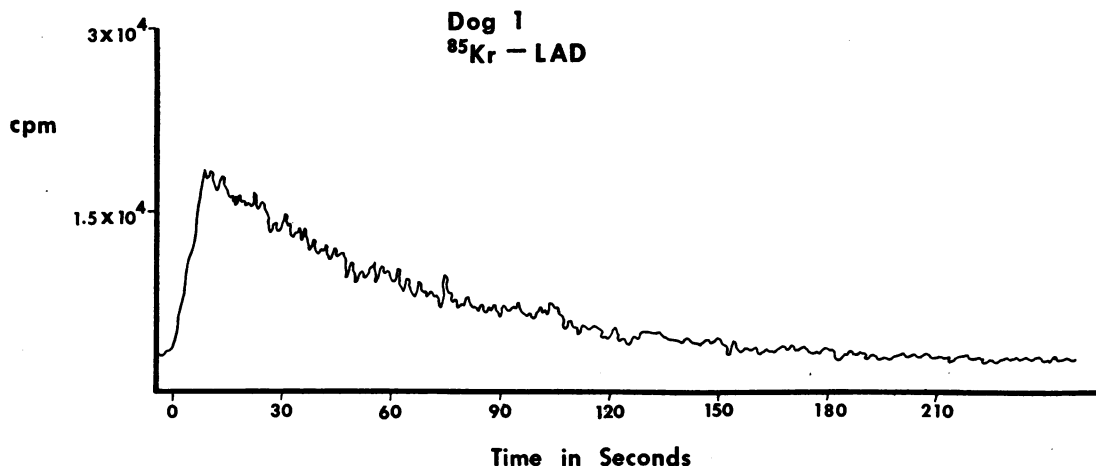


FIG. 1. DOG 1: PRECORDIAL  $^{85}\text{Kr}$  CLEARANCE CURVE AFTER INJECTION OF TRACER INTO CANINE LEFT ANTERIOR DESCENDING ARTERY. LAD, left anterior descending artery.

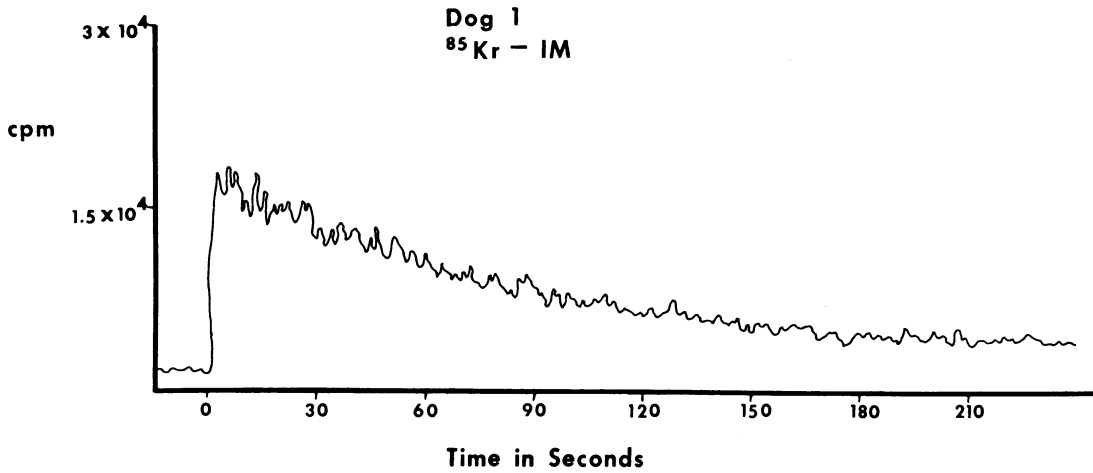


FIG. 2. DOG 1: PRECORDIAL <sup>85</sup>Kr CLEARANCE CURVE AFTER DEPOSITION OF TRACER INTO CANINE MYOCARDIUM ADJACENT TO LEFT ANTERIOR DESCENDING ARTERY. *IM*, intramyocardial.

TABLE I  
<sup>85</sup> Krypton clearance constants\*  
Experiment 1, normal canine left ventricle.

Intra-arterial injection	Intramyocardial injection	Mean blood pressure	Pulse rate
		<i>mm Hg</i>	
0.47	0.61	86	123
0.37	0.43	82	130
0.40	0.55	70	132
0.44	0.35	58	134
0.46	0.45	60	130
0.41	0.31	56	132
0.425 ± 0.038 SD	0.450 ± 0.115	68	131

\* With in-dwelling left anterior descending arterial cannula after beta-adrenergic blockade.

first normal subject was found to have minimal narrowing of the distal anterior descending artery with angiography, but was found to have palpably normal vessels and a grossly normal myocardium at surgery.

29 patients with diseased coronary arteries were studied at the time of surgery for internal mammary artery implantation. The patients were selected because of refractory angina pectoris and demonstration of a greater than 50% stenosis of the left anterior descending artery. Halothane-oxygen, meperidine, and curare were used for anesthesia in all patients. Arterial blood pressure and electrocardiograms were monitored in all patients. Blood pressure, heart rate, and rhythm did not change significantly during the period of intramyocardial clearance constant determinations.

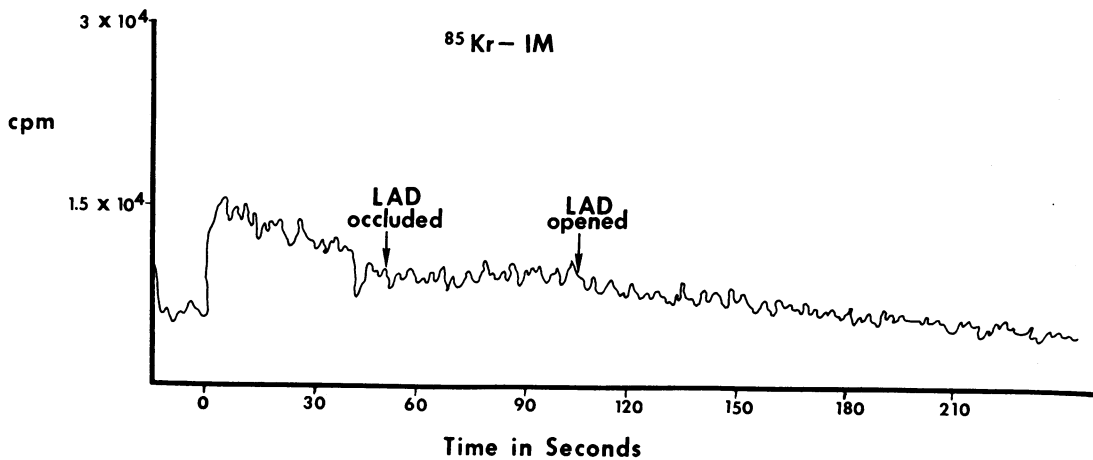


FIG. 3. DOG 2: PRECORDIAL <sup>85</sup>Kr CLEARANCE CURVE AFTER DEPOSITION OF TRACER INTO CANINE MYOCARDIUM, SHOWING ARREST OF DISAPPEARANCE WITH OCCLUSION OF NUTRIENT ARTERY AND RESUMPTION OF DECAY CURVE WITH RESTORATION OF FLOW. *LAD*, left anterior descending artery; *IM*, intramyocardial.

TABLE II  
Intramyocardial <sup>85</sup>Kr clearance constants in normal hearts

Study	Patient	Clearance constants (anterior left ventricle)				Mean K	SD
Human	E.D.	2.77	2.58	2.96	2.44	2.28	±0.454
	A.Mo.	2.85	2.34	2.42			
	O.S.	1.76	2.50	1.94	2.18		
	A.Ma.	1.97	1.64	1.53			
Study	Subject	No. of observations (anterior left ventricle)		Mean K	SD		
Animal	Dog 3	13		1.73	±0.337		
	Dog 4	16		1.45	±0.264		
	Dog 5	12		1.20	±0.220		

Results

The results of the first experiment are shown in Figs. 1 and 2 and are tabulated in Table I. Fig. 1 reproduces an isotope decay curve after injection of tracer into the left anterior descending artery. Fig. 2 shows a similar curve obtained after intramyocardial injection. Table I shows the clearance constants obtained after beta-adrenergic blockade ( $0.425 \pm 0.038$  SD vs.  $0.450 \pm 0.115$ ). The re-

sults obtained by the two methods are not significantly different ( $P > 0.5$ ). The low clearance constants may have been due to the presence of a partially occluding cannula in the coronary artery studies plus beta-adrenergic blockade.

The results of the second experiment are shown in Fig. 3. An intramyocardial deposit of <sup>85</sup>Kr was placed and an isotope decay curve recorded with an initial clearance constant of 0.69. With

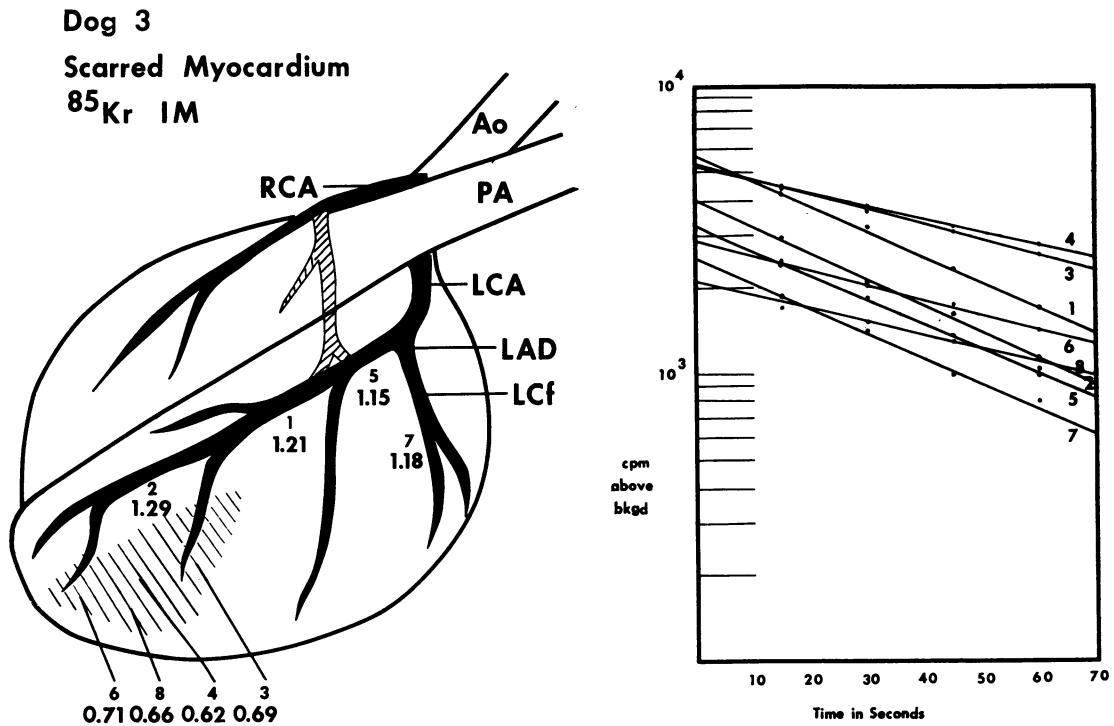


FIG. 4. DOG 3: SCARRED CANINE HEART DEMONSTRATING REPRODUCIBLY REDUCED <sup>85</sup>Kr CLEARANCE CONSTANTS IN DISEASED AREA. Graph at right shows semilogarithmic plot of decay curves; small numbers designate random sequence of injection. Ao, aorta; PA, pulmonary artery; RCA, right coronary artery; LCA, left coronary artery; LAD, left anterior descending artery; LCf, left circumflex artery; IM, intramyocardial.

TABLE III  
*Human intramyocardial <sup>85</sup>Kr clearance constants in subjects with coronary artery disease*

Difference < 1 SD				Difference > 1 SD				Difference > 2 SD				Difference > 3 SD							
Pa- tient	Clearance constants			Pa- tient	Clearance constants			Pa- tient	Clearance constants			Pa- tient	Clearance constants						
L.B.*	1.72	1.59	1.59	F.F.	2.58	2.44	2.77	3.45	J.R.	1.66	1.06	1.62	1.80	H.K.	1.34	2.58	2.77	2.08	3.45
G.W.†	2.06	2.12	1.84	J.V.	1.97	2.58	2.43		B.K.	1.22	1.97	1.09		H.S.	1.88	1.13	2.58		
S.R.§	1.53	1.84	1.80	P.H.	3.18	3.18	2.24		A.C.	1.20	1.66	2.58		R.M.	1.15	2.76	0.91		
				G.L.	2.07	1.88	1.48		N.B.	0.90	1.91	1.86		P.F.	2.46	2.16	0.67		
				W.S.	1.06	1.47	1.64		A.F.	2.08	2.12	1.25	1.78	W.B.	3.45	1.66	1.18		
				I.G.	2.23	2.38	1.59		F.B.	1.72	3.45			M.B.	2.86	1.56	0.77		
				A.V.	0.52	0.75	0.67	0.69	ALC.	0.97	1.01	2.06		A.M.	3.06	0.96	0.0		
				L.L.	1.97	1.88	2.94		P.D.	0.84	1.47	0.81		E.M.	2.06	2.85	0.52	2.54	3.06
									K.H.	1.80	2.52	1.53		B.C.	1.88	0.63	0.0		

\* Stenosis of left anterior descending artery and left circumflex artery.

† Stenosis of left anterior descending artery, left circumflex artery, and right coronary artery.

‡ Stenosis of left anterior descending artery.

TABLE IV  
<sup>85</sup>Kr clearance patterns in relation to morphology of left anterior descending artery (LAD)

Patient	Clearance constants			LAD lesion	Myocardium
	Proximal	Mid	Distal		
Increasing clearance along LAD					
H.K.	1.34	2.58	2.77	Proximal stenosis	Normal
B.K.	1.22	1.97	1.09*	" "	* in apical scar
R.M.	—	1.15	2.76	Mid stenosis	Apical & lateral fibrosis
A.C.	1.20	1.66	2.58	Proximal occlusion	" fibrosis
N.B.	0.90	1.91	1.86	" narrowing	" systolic expansion
W.S.	—	1.06	1.47	" occlusion	Inferior fibrosis
ALC.	—	0.97	2.06	" narrowing	Anterior fibrosis
P.D.	—	0.84	1.47	Diffuse narrowing	Normal
Area of reduced clearance along LAD					
J.R.	1.66	1.06	1.62	Proximal stenosis	Apical & posterior fibrosis
H.S.	1.88	1.13	2.58	Mid stenosis	Normal
Decreasing clearance along LAD					
P.F.	2.46	2.16	0.67	Diffuse narrowing	Apical & lateral fibrosis
A.M.	3.06	0.96	0.0	" "	" aneurysm
B.C.	1.88	0.63	0.0	" "	" aneurysm
W.B.	3.45	1.66	1.18	Proximal stenosis	" fibrosis
M.B.	2.86	1.56	0.77	" "	" systolic expansion
No significant change along LAD or incompletely studied					
A.Mo.	2.42	2.34	2.42	None	Normal
O.S.	1.76	1.94	—	"	"
A.Ma.	1.97	1.64	—	"	"
E.D.	—	2.77	2.58	"	"
F.F.	2.58	2.44	2.77	Proximal narrowing	Apical fibrosis
S.R.	1.53	1.84	1.80	Mid stenosis	Normal
L.B.	1.72	1.59	1.59	Proximal stenosis	Posterior fibrosis
K.H.	1.80	2.52	1.53	Diffuse narrowing	Apical fibrosis
G.W.	—	2.06	2.12	Proximal stenosis	" systolic expansion
A.F.	—	2.08	2.12	" "	" fibrosis
J.V.	1.97	2.58	2.43	" "	Proximal scar
E.M.	—	2.06	2.85	" "	Lateral aneurysm
F.B.	1.72	—	3.45	Diffuse narrowing	Proximal fibrosis
L.L.	—	1.97	2.94	" "	Normal
G.L.	2.07	1.88	1.48	" "	Apical fibrosis
P.H.	3.18	3.18	2.24	Mid occlusion	Normal
A.V.	—	—	0.52	Proximal stenosis	Apical aneurysm
I.G.	—	—	1.59	" "	Normal

occlusion of the vessel, the clearance immediately fell to 0, and returned to 0.73 when the vessel was opened. An intra-arterial cannula was present in this animal, partially obstructing flow and possibly preventing reactive hyperemia after release of the clamp.

The results of the third set of experiments are shown in Table II. 41 determinations of the intramyocardial  $^{85}\text{Kr}$  clearance constant were made at various sites over the normal canine anterior left ventricle, with an average of  $1.73 \pm 0.337$ ,  $1.45 \pm 0.264$ , and  $1.20 \pm 0.220$ .

Fig. 4 illustrates the fourth experiment performed in a canine heart exhibiting an area of naturally occurring scar on the anterior left ventricle. The average intramyocardial  $^{85}\text{Kr}$  clearance in normal muscle was  $1.21 \pm 0.06$ ; that in scarred muscle was reduced at  $0.67 \pm 0.039$  ( $P < 0.01$ ).

The results of 14 determinations of intramyocardial  $^{85}\text{Kr}$  in four human subjects with normal coronary arteries are shown in Table II. The re-

sults of 105 determinations in 29 patients with angiographically identified coronary artery disease are shown in Table III. Each figure represents a single determination. The mean clearance constant in human hearts without coronary artery disease was  $2.28 \pm 0.454$ . The observed range was 1.53–2.96. The average standard deviation of this method was  $\pm 19\%$  of the mean, measured in these four human subjects and three dogs with normal coronary arteries. The highest clearance constants in normal areas of diseased human hearts fell within the range of  $2.28 \pm 2$  standard deviations with the exception of one subject with diffuse disease and uniformly reduced clearance constants and three subjects with a clearance constant of 3.45 in hyperdynamic areas.

Determinations made in areas distal and/or adjacent to coronary artery lesions were compared to determinations made in normal areas of the same heart and to the range of values recorded in subjects free of coronary artery disease. Table III lists the results of all determinations made in

H.K. 42 yo WF  
5-76-63

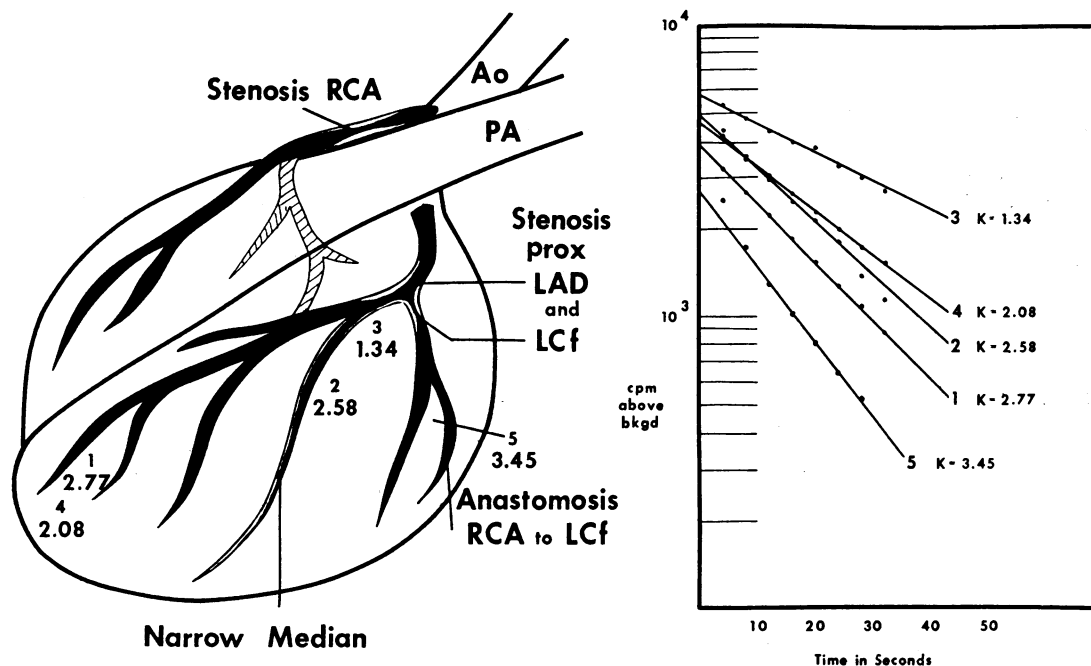


FIG. 5. PROXIMAL STENOSIS OF ALL MAJOR VESSELS, DEMONSTRATING REDUCTION OF CLEARANCE ADJACENT TO PROXIMAL LEFT ANTERIOR DESCENDING LESION. Ao, aorta; PA, pulmonary artery; RCA, right coronary artery; LAD, left anterior descending artery; LCf, left circumflex artery.

H. S. 48 yo WF  
5-60-91

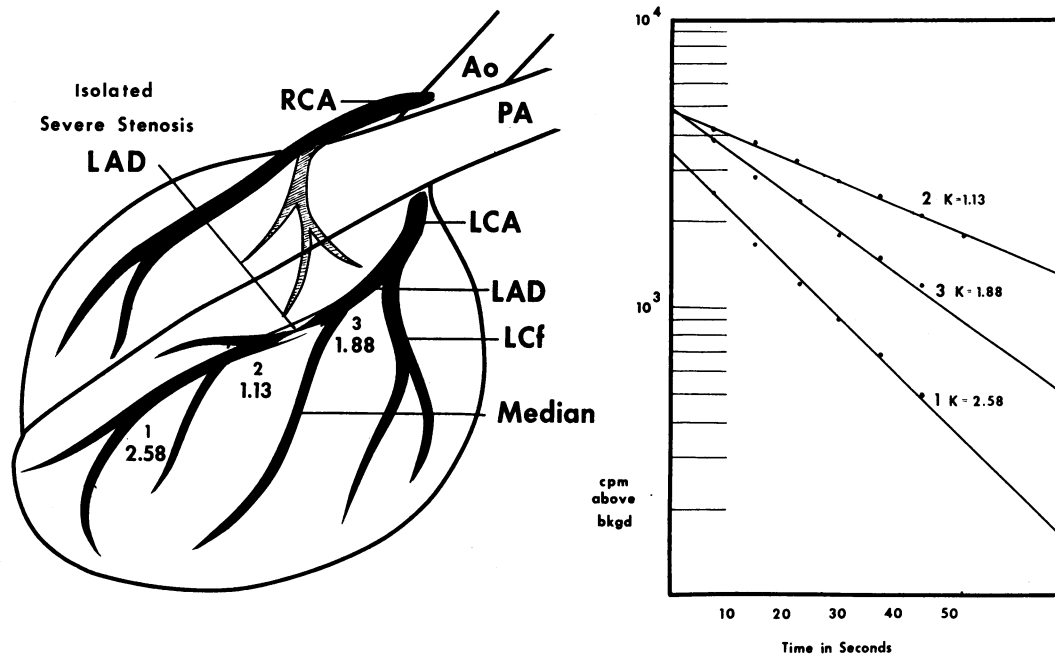


FIG. 6. HUMAN MYOCARDIUM WITH SINGLE STENOTIC LESION OF LEFT ANTERIOR DESCENDING ARTERY, SHOWING RELATIVE REDUCTION OF  $^{86}\text{Kr}$  CLEARANCE CONSTANT IMMEDIATELY DISTAL TO LESION. *LCA*, left coronary artery. Other abbreviations as in Fig. 5.

diseased subjects grouped according to the degree of difference of the lowest determination in a diseased area from the highest determination in a normal area, using  $\pm 19\%$  as the standard deviation. By these criteria, 9 of 29 patients had a low clearance in diseased areas differing from that in normal areas by 3 standard deviations, 9 differing by 2 standard deviations, 8 by 1 standard deviation, and 3 by less than 1 standard deviation. 18 of 29 patients had clearance constants in diseased areas below the range determined in subjects without coronary artery disease of  $2.28 \pm 2$  standard deviations or 1.37–3.19.

The patients in this study were preselected in that only those with predominant disease of the left anterior descending artery underwent surgery; therefore, the majority of measurements were made in this area. Comparison of the clearance constants with lesions of the left anterior descending artery revealed four patterns, listed in Table IV: (a) increasing clearance along the vessel; (b) area of reduced clearance along the vessel;

(c) decreasing clearance along the vessel; and (d) no change in clearance.

Fig. 5 illustrates a patient with a proximal stenosis of the left anterior descending artery, with a clearance constant of 1.34 adjacent to the lesion, 2.58 adjacent to mid vessel, and 2.77 along the distal vessel. Eight patients studied demonstrated this pattern; of these, seven had proximal stenotic lesions, and only one had diffuse narrowing of the vessel.

Fig. 6 illustrates a patient with an isolated stenosis of the mid left anterior descending artery with a clearance constant of 1.88 above the lesion, 1.13 just below the lesion, and 2.58 near the distal vessel. Two patients displayed this pattern, one with a proximal stenosis and one with a stenosis in mid vessel.

Fig. 7 illustrates a patient with diffuse narrowing of the left anterior descending artery with a fall in clearance constants along the vessel, 3.06 proximally, 0.96 near mid vessel, and 0 distally. Five patients were found to have this pattern,

A. M. 43 yo WM  
5-97-05

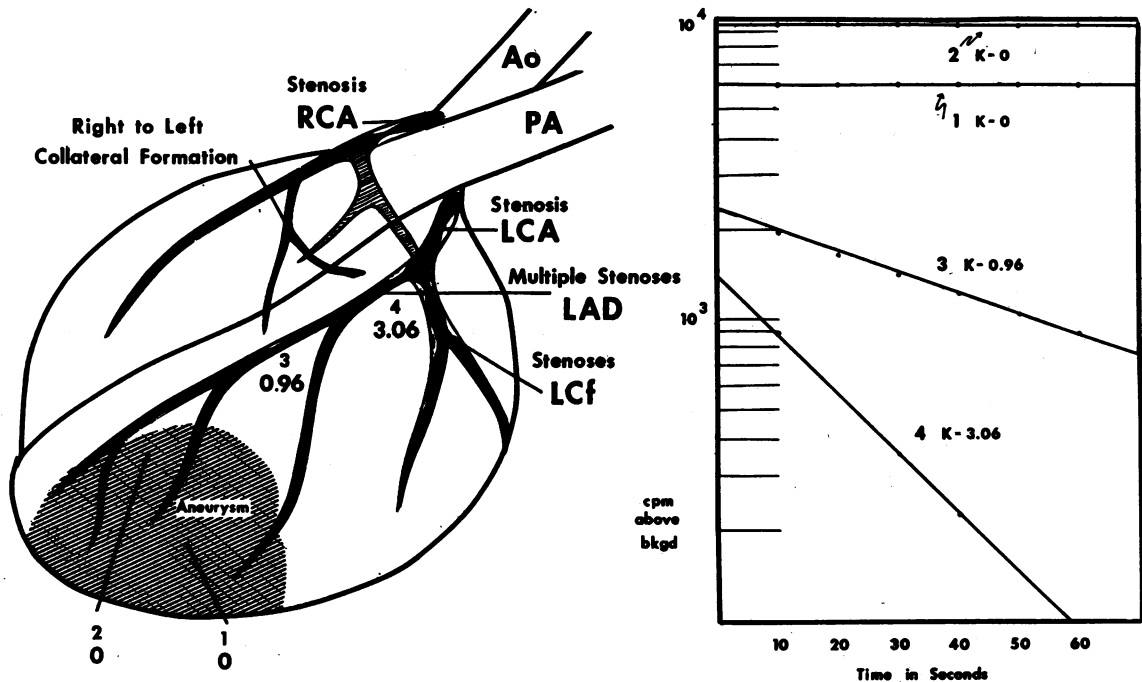


FIG. 7. DIFFUSELY DISEASED HUMAN LEFT ANTERIOR DESCENDING ARTERY WITH REDUCTION OF <sup>85</sup>Kr CLEARANCE CONSTANTS ALONG THE COURSE OF THE VESSEL. Ao, aorta; PA, pulmonary artery; RCA, right coronary artery; LCf, left circumflex artery; LCA, left coronary artery; LAD, left anterior descending artery.

three with diffuse narrowing of the vessel and two with proximal stenotic lesions.

Fig. 8 illustrates a patient with virtually normal vessels and relatively uniform clearance constant of 2.58, 2.77, 2.44, and 2.96. 16 patients demonstrated this pattern, four with normal vessels, four with diffuse narrowing, and eight with a single stenosis. Two patients were incompletely studied in the region of the left anterior descending artery.

Discussion

Herd (12) and Ross (13) and their respective coworkers demonstrated that myocardial blood flow measured by injection of radioactive gases into the coronary arteries correlated well with blood flow measured by rotameter. Lassen (14) has reported a correlation between skeletal muscle blood flow measurements by venous occlusion plethysmography and intramuscular <sup>133</sup>Xe clearance. In the present study, it was found that <sup>85</sup>Kr

clearance constants measured after intramyocardial deposition of tracer did not differ significantly from those made after intra-arterial injection of tracer in the normal dog heart. The standard deviation of the intramyocardial determinations was considerably greater than that of the intra-arterial, demonstrating that the former method is less precise yet measures a clearance of the same order of magnitude as the intra-arterial determinations. It was also noted that the rate of disappearance of <sup>85</sup>Kr from the myocardium fell to zero when the blood supply to that area of myocardium was occluded and immediately rose to control levels when the blood supply was restored, demonstrating that <sup>85</sup>Kr clearance from intramyocardial deposits changed rapidly in response to changes in blood flow.

Measurement of myocardial blood flow by indirect tracer methods requires knowledge of the partition coefficient of the tracer, i.e., the ratio of distribution in myocardium and in coronary ve-



E.D. 47 yo WF  
3-25-48

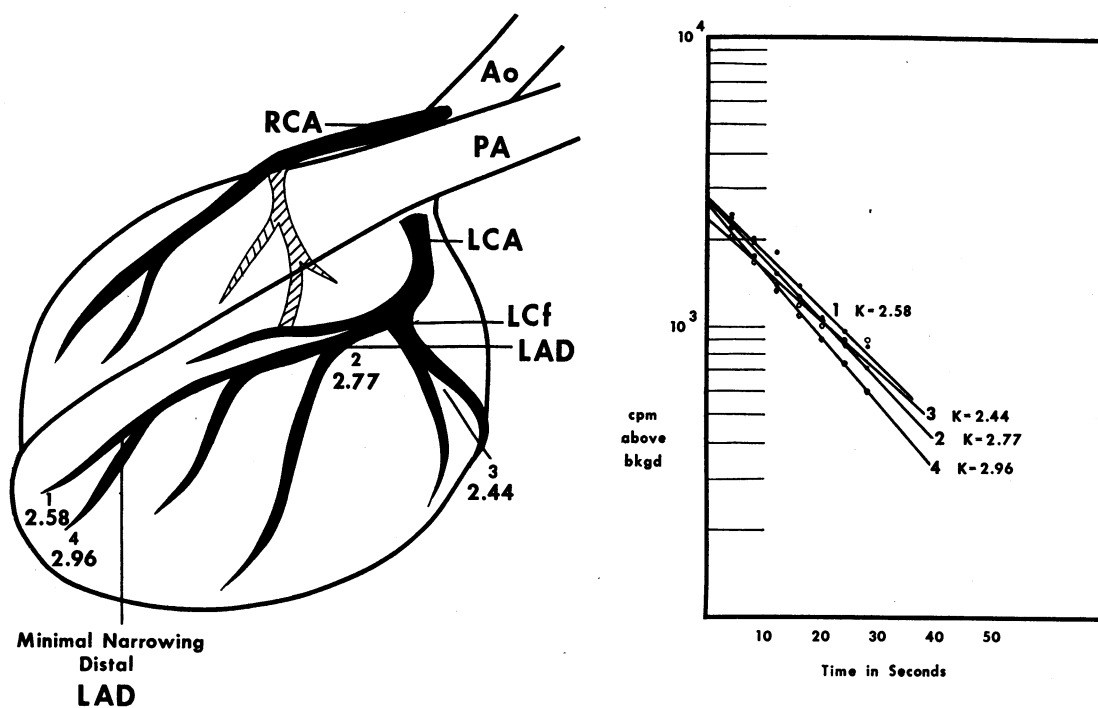


FIG. 8. GROSSLY NORMAL HUMAN MYOCARDIUM WITH UNIFORM INTRAMYOCARDIAL  $^{85}\text{Kr}$  CLEARANCE CONSTANTS. Abbreviations as in Fig. 7.

nous blood. Although the partition coefficient of  $^{85}\text{Kr}$  has been established in the normal dog heart, it has not been determined for local areas of pathology in the human heart. Further, in human subjects with coronary artery disease, a wide spectrum of pathologic changes in the myocardium exists, with varying degrees of inflammation, lipid deposition, and fibrosis. This would suggest that the partition coefficient might be expected to differ in each diseased area of each diseased subject. For this reason, it was believed that true regional myocardial blood flow could not be validly computed in the operating room, and therefore, only clearance constants have been used to describe areas of pathology.

Kety has argued that, "the effectiveness of the circulation in a tissue is better measured as its total ability to remove, and similarly to supply, freely diffusible substances. This total efficacy is accurately measured by the clearance constant, a concept which involves not only the volume of

flow of blood, but also all the adaptations or distributions which help or hinder the diffusion process (15)." Thus, a difference in clearance constant between two regions may reflect either a difference in nutrient flow or a difference in diffusion (partition coefficient), but cannot distinguish between the two. We have retained this concept, believing it particularly applicable to the method under discussion: a mechanical intervention in which a space-occupying tracer is forced into the myocardium probably inducing changes in local pressure-flow relationships. As indicated in Table III, the clearance constants determined by this method are invariably quite rapid, and may reflect a local hyperemia after temporary impairment or cessation of capillary blood flow produced by injection of tracer.

Clearance constants were found to be relatively uniform in the subepicardial region of the normal dog and human myocardium.  $^{85}\text{Kr}$  deposits were made at a uniform depth of 3 mm in all measure-

ments because of the known differences of Na <sup>131</sup>I disappearance rates between subendocardial and subepicardial regions (8). In scarred areas of the dog myocardium, <sup>85</sup>Kr clearance constants were found to be distinctly and reproducibly lower than those of surrounding normal myocardium, suggesting that the method would be useful in identifying areas of subepicardial scarring and ischemia in human subjects in whom a site for internal mammary implantation must be determined.

It must be emphasized that the clearance constants reported in human subjects represent a single determination. As multiple injections of tracer into the same area in the dog produced myocardial ecchymosis, this procedure was not considered justified in the remaining normal areas of the diseased human hearts studied. We chose to use the highest clearance constant obtained in an area of grossly normal muscle, away from known coronary lesions. As a point of reference, these values fell within the range determined in four subjects without coronary artery disease, with but four exceptions. One of the subjects had diffuse coronary artery lesions, in which a uniform reduction in flow might be expected, and three had hyperdynamic areas above areas of scar or aneurysm in which a higher oxygen demand and myocardial flow might be anticipated.

14 determinations in four human subjects without coronary lesions yielded a mean clearance constant of  $2.28 \pm 0.454$ , a standard deviation of 19.9% of the mean. This degree of reproducibility was confirmed by 41 determinations in three normal dog hearts, with an average standard deviation of 18.6% of the mean.

Clearance constants determined distally and/or adjacent to coronary artery lesions fell below the range of 1.37–3.19 in 18 of 29 patients. 18 of 29 patients had a reduction in clearance in diseased areas greater than 2 standard deviations when compared to the clearance in grossly normal areas of the same heart. These reduced clearance constants were below the range observed in subjects without coronary disease in all but two subjects, F.B. and K.H. (see Table III). Two additional subjects, W.S. and A.V. had clearance constants below 1.37 in diseased areas, but these did not differ by more than 2 standard deviations from values in their "normal" areas, perhaps be-

cause of uniform reduction of flow. Applying the most rigorous criteria, there remain, nevertheless, nine subjects in whom clearances in normal and diseased areas of myocardium differed by more than 3 standard deviations and fell 2 standard deviations below the mean normal clearance of 2.28 (i.e., less than 1.37). This group of nine patients confirms the conclusion that there is heterogeneous perfusion of the myocardium in the presence of sufficient coronary artery disease. In those subjects in whom a significant difference in clearance constants was not demonstrated, the assumption must be made that either this local perfusion is not reduced at all, or that it is not reduced sufficiently to be detected by this method.

In the four subjects studied with normal coronary arteries, <sup>85</sup>Kr clearance constants were found to be relatively uniform along the left anterior descending artery and over the anterior left ventricle. In 21 subjects with a single stenosis of the left anterior descending artery, <sup>85</sup>Kr clearance constants were reduced immediately adjacent to the lesion in nine patients. Farther along the vessel, clearance constants were higher than those close to the lesion and approximated values found elsewhere in the uninvolved myocardium. Low clearances in myocardial sites supplied by the distal portion of a vessel with a proximal stenosis were seen in only 2 of the 21 patients, suggesting that local areas of ischemia often result from occlusion of small branches of a major coronary artery by an atherosclerotic plaque in the wall of the major vessel, as opposed to reducing flow in the major vessel itself. This in turn suggests that a coronary stenotic lesion occupying less than 50% of the arterial lumen might still result in significant areas of ischemia solely by occluding side branches. Eight patients in this group showed no difference in clearance along the vessel. In eight patients with diffuse narrowing of the left anterior descending artery, <sup>85</sup>Kr clearance constant fell progressively along the vessel in three patients, was reduced proximally in one patient, and showed no change in four patients. In areas of fibrosis, with paradoxical systolic expansion, the clearance constant was zero and usually reduced in the myocardium immediately surrounding the area, but was often high in areas of grossly normal muscle as might

be expected in an area subjected to increased tension development to maintain cardiac output.<sup>1</sup>

It has long been a reasonable assumption that myocardial blood flow is unevenly distributed in the presence of sufficient coronary artery disease. To our knowledge, this report provides the first demonstration of the long suspected heterogeneity of myocardial perfusion in relation to angiographically localized coronary artery lesions in man.

Although universal agreement is lacking, there is evidence suggesting that implantation of an extracardiac artery into relatively ischemic regions of the myocardium (as opposed to well-perfused regions) increases the development of communications with the coronary arteries by influencing either the size, number, or extent of such communications (16). It is further suggested that implantation into areas of scar lessens the chance for success of the implant.<sup>2</sup> Although these areas are sometimes grossly visible at surgery, this method of charting regional myocardial perfusion, localizing areas of ischemia and avoiding areas of scar, has proved useful in determining the site for mammary artery implantation. This is particularly so when a choice must be made between placing the implant proximally or distally, or adjacent to one of two vessels with angiographic evidence of obstruction.

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<sup>1</sup> These areas of myocardium were hyperdynamic as judged by cine ventriculography.

<sup>2</sup> Sewell, W. H. Personal communication.