Total and Effective Coronary Blood Flow in Coronary and Noncoronary Heart Disease

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ABSTRACT There are no data available concerning total coronary blood flow to the whole heart (CBF) in man. "Effective" or "nutrient" coronary blood flow to the whole heart (MBF), supposedly a measure of flow through exchanging channels of the coronary circulation, has been measured but its validity has not been established. Accordingly, CBF and MBF were measured in 9 normal subjects, 26 patients with coronary heart disease (CHD), and 19 with noncoronary, mostly valvular heart disease (NCHD), by coincidence counting ^{84}Rb technique. Two methods were used: single bolus (24 cases) and continuous infusion (30 cases). Various other parameters including myocardial oxygen utilization (MVO_2) and lactate extraction ratio were determined.

In the normal subjects CBF (386±77 ml/min) was significantly higher ($P < 0.05$) than in CHD (288±124 ml/min) and NCHD (292±111 ml/min). Likewise the normal MBF (380±81 ml/min) was significantly higher ($P < 0.01$) than in CHD (251±105 ml/min) as well as NCHD (258±104 ml/min). The myocardial Rb extraction ratio (^{E}Rb) was significantly lower in normal subjects (39±9%) than in CHD (50±7%) and NCHD (52±11%) and this supports the view that ^{E}Rb is flow-dependent.

In both CHD and NCHD there was significant diminution of MVO_2 as well as CBF. In CHD this was accompanied by a significant anaerobic trend but in NCHD it was not. It might therefore appear that in CHD, MVO_2 is determined by perfusion whereas in NCHD, perfusion is determined by MVO_2. In comparing CBF with MBF by paired observation testing, there was no significant difference in the normals ($P > 0.3$), whereas the differences were significant in CHD ($P < 0.01$) and NCHD ($P < 0.02$). This was merely a reflection of a reduced ratio of myocardial to total body ^{E}Rb in CHD and NCHD, and available evidence indicates that this may be an expression of depressed transport of Rb^+ rather than true shunting.

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INTRODUCTION

Many methods have been put forward for the measurement of coronary blood flow in man but none can be considered entirely satisfactory.

Wide use has been made of techniques based on indicator substances which diffuse passively into the myocardial cell. They provide flow data which must be expressed per unit of heart muscle (unit flow) and yet cannot be accepted as true average or mean values in all circumstances. The nitrous oxide technique (1), depending on coronary sinus sampling, purports to measure blood flow per unit of heart muscle drained by this system. However, in a heterogeneously perfused organ reduced flow to certain zones may well prolong the time required for myocardial equilibration beyond the usual 10 min period of N_2O breathing. Furthermore, because of the relatively high solubility of N_2O in blood, even a stable arterial concentration cannot be attained within this period. Prolonged small differences in arteriovenous gas concentration become highly significant in this situation and because of this, especially sensitive techniques of measurement (which are beyond the scope of the traditional nitrous oxide method) are required (2–4). Thus, in the presence of coronary disease this method has tended to overestimate average flow.

Washout techniques using bolus injection of ^{133}Xe (5) or ^{85}Kr (6) require isolation of the coronary circulation either by selective arterial injection of indicator or coronary venous sampling, and thus can claim only to measure flow per unit of heart muscle perfused by, or drained by the vessel in question. The same disadvantage, that

of inhomogeneity of flow both topographically and between layers, as occurs particularly in coronary disease, limits their reliability. The adequacy of delivery of the tracer to areas of below average flow is questionable. The unit flow value is not a valid average but an overestimate since the isotope clearance curve is dominated by well perfused areas. These and other difficulties inherent in the various inert gas techniques have been discussed by several authors (2–4, 7–9).

Indicator dilution methods have been used for the measurement of coronary sinus flow (10–12). These have the advantage of measuring absolute rather than unit flow, but nevertheless, only a fraction of the entire coronary flow is involved. If one accepts the normal values for man which have been published to date then coronary sinus flow (12) is not greater than approximately 50% of myocardial blood flow (13–15).

By the use of substances that are actively transported into the myocardial cell, it is possible to measure whole heart blood flow. ^{84}Rb is particularly useful in this respect since it is a positron emitter and its activity can therefore be measured by coincidence counting. This is an extremely effective method of field isolation (16) and with the use of a double coincidence counting technique the whole heart can be "separated" from its surroundings. Since the entire organ uptake of isotope is measured, all zones are represented according to their degree of perfusion. Bing et al. have developed this technique for measurement of "nutrient" or "effective" myocardial blood flow (MBF)[1] (17) and values for normal subjects and patients with coronary disease have been reported by them and by other investigators (13–15, 18).

The relation of nutrient flow, which is supposedly a measure of flow through exchanging channels of the coronary circulation, to coronary blood flow (CBF), defined as the entire flow through all channels of the coronary circulation (exchanging or otherwise) is unknown. The very term nutrient flow is of uncertain validity. Its measurement by the technique of Bing et al. (17), based on Sapirstein's hypothesis (19) assumes that the uptake of Rb^+ by an organ is directly proportional to the flow through its nutrient channels and a corollary of this is that the rate of transfer of ion across the myocardial cell membrane is identical to that of the remainder of the body under all circumstances. However, it is unlikely that the Na/K pump which controls active Rb^+ transport (20–23) could conform to such rigid requirements; it is difficult to believe that this mechanism would not be affected by myocardial pathology.

[1] *Abbreviations used in this paper:* CBF, coronary blood flow; CHD, coronary heart disease; CI, continuous infusion; CO, cardiac output; $^{E}O_2$, myocardial oxygen extraction ratio; ^{E}Rb, Rb extraction ratio; MBF, myocardial blood flow; MVO_2, myocardial oxygen utilization; NCHD, noncoronary heart disease; TTI, tension-time index.

Rb has an advantage because it is actively taken up and retained within the cell and it is well suited for the application of the Fick principle to the measurement of flow. By this means total flow through the entire coronary circulation can be measured. No data with respect to this parameter have been published and therefore we have undertaken its measurement in a series of subjects of varied clinical composition. In this study, MBF has been simultaneously measured with CBF to determine their relationship.

METHODS

Patients were studied in the course of routine diagnostic cardiac catheterization and selective coronary angiography. The investigative protocol was carried out before any steps were taken in the diagnostic routine including angiography. Patients were in a fasting state and sedated approximately 1 h previously with diazepam intramuscularly in the dose range 5–15 mg.

Our subjects were divided into three groups.

Coronary heart disease (CHD). These patients had clinical and electrocardiographic evidence of established CHD and were functionally at least class II (NYHA). In all, subsequent angiograms revealed significant coronary arterial lesions (Table I). 16 subjects had triple artery disease, 6 double, and 4 single but not less than grade 2. Three of the patients had associated valvular disease. There were 22 males and 4 females aged 52±8 (mean±SD).

Noncoronary heart disease (NCHD). Patients with congenital heart disease were specifically excluded. All individuals had clinical, electrocardiographic, and radiological evidence of established organic heart disease and functionally were at least class II (NYHA). The great majority had valvular disease and were being evaluated for possible surgical correction. In all, significant coronary disease was excluded by subsequent angiography and their diagnoses (Table I) were confirmed by subsequent hemodynamic study. The group consisted of 11 males and 8 females aged 54±10.

A group designated as normal. These were patients with atypical chest pain in whom diagnostic study was being carried out to exclude CHD. All of these patients had normal coronary angiograms and normal hemodynamic findings on subsequent study. Five males and four females aged 40±6 were in this group.

The principles of the ^{84}Rb coincidence counting method of Bing et al. (17), in essence an application of the hypothesis of Sapirstein (19), were employed to measure cardiac output (CO) and MBF. CBF was estimated by the Fick principle simultaneously with MBF.

The instrumentation (16)[2] based on the concept of Bing et al. (17) represents a considerable improvement upon their original design in several respects. (*a*) The coincidence resolving time of 5×10^{-9} s is 10 times shorter. This reduces the error due to background body ^{84}Rb activity to less than 2.5% under worst case conditions. (*b*) The detector pairs are mounted on a mobile motorized yoke permitting 360° rotation in the horizontal and vertical planes as well as wide flexibility in positioning the probes relative to one another. Therefore precision in parallel alignment and centering on target organs is possible. (*c*) The

[2] Isotron. Conuclear Ltd., Ottawa, Canada.

entire instrument assembly is mobile and this permits its use in the cardiac catheterization laboratory where exact placement under fluoroscopic control of both the myocardial and reference probes is effected without moving the patient. These modifications allow more effective field isolation increasing the accuracy of calibration and organ activity measurement. The first 24 patients were investigated by the single bolus method (14, 18, 24). A catheter[3] was positioned approximately 2 cm within the coronary sinus and another was placed in the arch of the aorta and blood sampling was commenced at the same moment from both sites at a rate of 20 ml/min and continued for precisely 2 min, by which time the myocardial isotope level had reached a plateau. ^{84}Rb in a dose of 0.25 μCi/kg body weight was injected 10–15 s after the start of sampling via a catheter positioned in right ventricle or pulmonary artery. All residual activity within the entire infusion system was measured and subtracted. The arterial blood was led through a well scintillation counter set to 0.511 MeV gamma and its activity, integrated over 1-s intervals, was recorded by means of a high-speed digital printer. This information was used to calculate CO by the Stewart-Hamilton principle. The precordial activity was measured by counting 0.511 MeV gamma in coincidence mode with a 5×10^{-9} s time window using paired 4 inch scintillation detectors positioned over the center of the heart. When cardiomegaly was present, the crystals were placed so as to include as much of the ventricular mass as possible. Lung and chest wall activity, simultaneously measured by a similar pair of detectors positioned over the right lung, was subtracted from precordial activity to obtain myocardial uptake of ^{84}Rb. Counts integrated over 1-s intervals and recorded by means of the digital printer, were monitored until myocardial activity had reached a plateau which was invariably within 2 min after injection. The myocardial uptake was read at this level since it represented the stage of complete body distribution and maximum blood clearance. The dose given was assumed to be the same as the total body uptake since 98% of Rb^+ is taken up by tissues (19). The contribution of the intracavitary component to the precordial activity can therefore be ignored as it is less than 2%. The activity of the two blood samples was read in the well counter and the results used to calculate myocardial arteriovenous difference and hence CBF by the Fick principle. MBF was derived by the Bing-Sapirstein formula (17).

In the last 30 patients, CBF and MBF were measured by the continuous infusion (CI) technique. Sampling catheters were placed in the coronary sinus and aorta as for the bolus technique. In addition, a catheter was positioned in the outflow tract of the right ventricle for sampling of mixed venous blood. Iostope in a dose of 0.5 μCi/kg body wt was diluted in 50 ml of normal saline and this solution was infused by means of a Harvard pump (Harvard Apparatus Co., Inc., Millis, Mass.) into the distal pulmonary artery. The interposition of the pulmonary valve is believed to have assisted in preventing contamination of the mixed venous sample by infusate. In those cases in which transseptal catheterization had been performed, the infusion was given into the left atrium. Approximately 25 ml was delivered over a period of 12–14 min and the overall infusion rate was precisely determined. The remainder of the infusate was subsequently given as part of a repeat set of determinations during cardiac pacing and these results will be reported separately. The mean of the differences between infusion rates during the two runs was not significantly different from 0 ($P > 0.2$). This degree of reproducibility implies constancy of delivery; furthermore direct testing of the system under simulated conditions showed that the infusion rate varied by less than 0.5% during a continuous 20 min run. At some point no earlier than 6 min after the start of infusion, by which time a steady state in blood concentration was expected, mixed venous, myocardial venous, and systemic arterial blood samples were drawn. Myocardial activity was measured, again after correction for lung and chest wall activity, and recorded as counts per minute integrated over 1-min periods. These results were then plotted as a function of time and a linear fit obtained by the method of least squares to derive the rate of myocardial uptake. The rate of body uptake at the time of sampling was assumed to be equivalent to the rate of infusion. From these data both CBF and CO were calculated according to the Fick principle. MBF was then derived by the Bing-Sapirstein formula (17).

^{84}Rb extraction ratio (^{E}Rb) is defined as (A-V/A) $\times$ 100, where A and V are respectively arterial and venous concentrations of isotope. Myocardial ^{E}Rb using coronary venous concentrations and whole-body ^{E}Rb using systemic mixed venous concentrations were calculated.

Separate blood samples were taken for the estimation of arterial and coronary venous lactate levels and also for arterial and coronary venous O_2 content. Lactate concentration was measured by enzymatic determination (25). Blood P_{O_2} measured with a Clark type electrode was converted to percent oxyhemoglobin saturation at 37°C (26). Hemoglobin was measured by the cyanmethemoglobin method. Whole blood O_2 content was then calculated using methods described by Kelman and Nunn (27). Myocardial oxygen consumption was calculated as the product of myocardial arteriovenous oxygen content difference and CBF.

Tension-time index (TTI) was calculated as the product of heart rate and the integral of left ventricular pressure with respect to time during systole.

Total heart volume was measured according to the Jonsell formula utilizing three dimensions (long, broad, and sagittal) taken from posteroanterior and lateral chest radiographs (28).

The data on 54 patients are presented. An additional 17 patients were studied but their data are not included: in 15 CBF was not measured because coronary sinus sampling was either not satisfactory or not done at all. In two patients in which the bolus method was used, the CO measurement was not deemed reliable because of the amount of distortion of the arterial indicator dilution curve due to severe valvular insufficiency. Thus, MBF could not be estimated.

CALCULATIONS

According to the Sapirstein hypothesis (19) the ratio of MBF to CO is the same as the ratio of myocardial uptake of ^{84}Rb to body uptake of the isotope (or dose injected). Thus, using the single bolus method:

$$\mathrm{MBF} = \frac{\mathrm{uH}(t)}{\int_0^\infty A_1(t)\mathrm{d}t} \qquad (1)$$

where A_1 = ^{84}Rb arterial concentration during first circula-

[3] Zucker multipurpose catheter. USCI Div., C. R. Bard Inc., Glens Falls, N. Y., Cat. no. 5620.

TABLE I

List of Data in 54 Patients

Study no.	Diagnosis	Technique	CO	MBF	CBF	Myocardial lactate extraction	Myocardial oxygen consumption	TTI	Cardiac volume
			liters/min	*ml/min*	*ml/min*	*%*	*ml/min*	*mm Hg s/min*	*ml*
13	Normal	Bolus	5.50	314	315	—	35.97	2,263	795
38	Normal	Bolus	4.11	261	260	44.00	29.04	2,587	788
53	Normal	CI	6.42	404	421	31.82	50.10	2,827	752
54	Normal	CI	7.24	445	473	31.58	58.56	3,363	584
61	Normal	CI	6.59	541	506	20.93	53.18	3,779	627
67	Normal	CI	7.08	346	353	—	37.88	4,072	810
69	Normal	CI	8.48	345	344	56.00	26.18	3,265	447
70	Normal	CI	6.37	395	405	23.16	53.62	3,223	687
71	Normal	CI	3.89	372	400	4.0	44.44	3,134	640
11	Mitral regurgitation; Tricuspid regurgitation; Aortic regurgitation	Bolus	6.70	343	383	18.57	32.56	2,741	1,760
23	Aortic regurgitation; Prosthetic valve	Bolus	3.78	224	246	63.64	25.93	4,615	1,176
24	Mitral stenosis and regurgitation	Bolus	4.98	407	382	26.67	48.06	3,462	1,176
28	Mitral regurgitation	Bolus	4.62	165	140	35.71	14.94	2,815	981
32	Hypertrophic obstructive cardiomyopathy	Bolus	6.56	188	328	25.37	43.10	2,341	868
33	Hypertensive heart disease	Bolus	4.65	231	384	30.23	38.78	4,280	685
34	Aortic stenosis and regurgitation	Bolus	5.01	304	310	28.30	28.71	2,979	970
37	Aortic regurgitation	Bolus	4.48	481	480	33.33	39.46	4,466	1,580
40	Aortic stenosis and regurgitation	CI	4.73	190	197	44.44	23.31	4,016	520
42	Aortic regurgitation	CI	6.64	197	194	16.67	19.21	2,925	1,104
43	Aortic stenosis	CI	5.55	138	140	30.00	16.10	3,212	868
44	Mitral stenosis	CI	3.75	117	150	53.70	13.16	3,637	1,082
45	Mitral stenosis; Cardiomyopathy	CI	5.46	164	224	8.75	21.80	2,423	1,683
46	Aortic regurgitation	CI	5.20	255	278	21.43	32.19	2,904	1,094
48	Aortic regurgitation	CI	4.46	152	205	20.00	19.05	1,795	898
51	Aortic regurgitation	CI	5.84	325	403	31.25	35.95	3,610	1,134
62	Aortic stenosis	CI	8.74	308	250	30.00	31.55	4,730	951
64	Mitral stenosis and regurgitation	CI	3.42	280	327	6.49	31.75	3,025	714
65	Aortic stenosis	CI	5.39	425	461	40.00	52.83	4,185	630
9	CHD (003)	Bolus	8.11	433	475	—	—	2,954	851
10	CHD (203)	Bolus	6.04	404	414	—	31.46	2,015	558
12	CHD (333)	Bolus	4.46	145	172	—	—	2,755	1,124
14	CHD (333)	Bolus	3.08	159	235	—	27.33	3,022	855
15	CHD (131)	Bolus	3.01	244	249	−5.56	34.99	1,529	996

TABLE I—(*Continued*)

Study no.	Diagnosis	Technique	CO	MBF	CBF	Myocardial lactate extraction	Myocardial oxygen consumption	TTI	Cardiac volume
			liters/min	*ml/min*	*ml/min*	%	*ml/min*	*mm Hg s/min*	*ml*
16	CHD (323)	Bolus	2.00	142	174	25.67	15.36	1,872	957
18	CHD (320)	Bolus	4.20	319	346	0.00	42.77	2,297	699
20	CHD (332)	Bolus	3.81	183	192	15.15	26.52	2,223	731
21	CHD (233)	Bolus	3.52	321	363	8.33	40.11	2,503	649
26	CHD (331)	Bolus	7.10	299	565	19.48	65.82	3,496	1,091
27	CHD (002)	Bolus	4.09	207	222	39.81	18.29	2,779	693
29	CHD (032)	Bolus	6.15	352	389	32.84	48.16	3,053	857
30	CHD; Mitral stenosis; Aortic stenosis (131)	Bolus	4.25	214	229	40.00	27.73	2,809	1,580
25	CHD; Mitral regurgitation (203)	Bolus	5.33	155	181	17.32	26.25	2,085	1,115
50	CHD (333)	CI	5.73	251	257	33.33	30.30	2,967	690
41	CHD (333)	CI	5.93	198	212	9.33	25.55	2,216	802
52	CHD (330)	CI	4.26	248	257	0.00	28.01	4,391	851
49	CHD; Mitral regurgitation (332)	CI	2.55	118	147	5.56	15.01	2,462	1,244
55	CHD (313)	CI	4.64	149	155	27.48	17.42	3,110	546
56	CHD (030)	CI	5.42	201	265	−1.72	24.06	3,136	694
57	CHD (323)	CI	7.81	204	218	21.26	21.28	3,552	951
59	CHD (333)	CI	9.83	511	533	18.18	44.08	2,310	1,367
60	CHD (202)	CI	6.01	182	213	33.33	28.54	4,164	1,011
63	CHD (300)	CI	5.47	320	382	19.23	51.42	3,254	810
66	CHD (233)	CI	6.10	414	480	0.00	55.82	2,549	1,155
68	CHD (333)	CI	4.42	153	164	21.57	20.78	4,710	879

In patients with CHD numbers in parentheses in diagnosis column indicate grade of severity of lesions in anterior descending, circumflex, and right coronary arteries in that order. (0 = normal; 1 = < 50% stenosis; 2 = 50–75% stenosis; 3 = > 75% stenosis.)

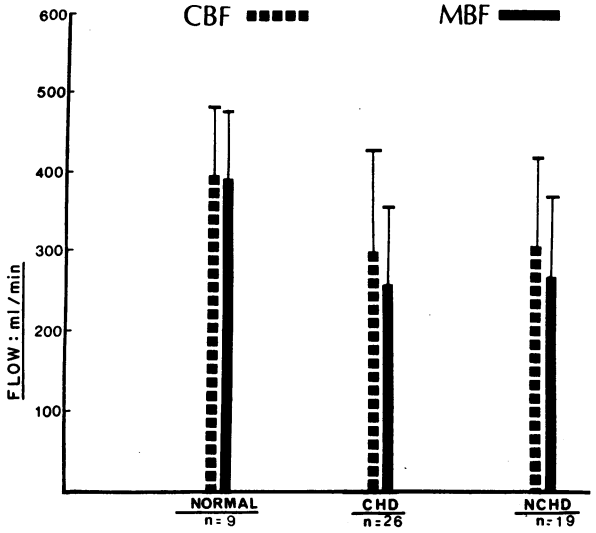

FIGURE 1 Summary of whole-heart perfusion data. The differences between normal on the one hand and CHD and NCHD on the other are significant. CBF and MBF differ significantly from one another in CHD and NCHD.

tion; uH =-myocardial uptake of Rb.

$$\text{CBF} = \frac{\text{uH}(t)}{\int_0^t A(t)\text{d}t - \int_0^t V(t)\text{d}t} \qquad (2)$$

where A = ^{84}Rb concentration in arterial blood; V = ^{84}Rb concentration in coronary sinus blood. Arterial and venous blood are collected simultaneously and continuously over a 2-min period.

When the continuous infusion method is used:

$$\text{CBF} = \frac{\text{uH}(t)}{C_a - C_{cv}} \qquad (3)$$

where uH(t) or myocardial uptake is measured by plotting precordial counts per minute as a function of time during infusion. C_a and C_{cv} are arterial and coronary venous concentrations of isotope respectively.

$$\text{MBF} = \frac{\text{uH}(t)}{C_a - C_v} \qquad (4)$$

where C_v is concentration of isotope in right ventricular outflow tract.

RESULTS

Detailed findings are presented in Table I.

CBF. In nine normal subjects CBF measured 386±77 ml/min (mean ±SD). In 26 patients with CHD the mean value measured 288±124 ml/min and in 19 patients with NCHD it was 292±111 ml/min. Using the t test for group observations CBF was significantly less than normal in both CHD and NCHD ($P < 0.05$).

MBF. The mean values for normal, CHD, and NCHD were 380±81, 251±105, and 258±104 ml/min, respectively. Again, the flows in both CHD and NCHD were significantly reduced ($P < 0.01$).

TABLE II

^{84}Rb Extraction Ratio (^{E}Rb)

Normal			CHD			NCHD		
Study no.	Myocardial ERb	Whole-body ERb	Study no.	Myocardial ERb	Whole-body ERb	Study no.	Myocardial ERb	Whole-body ERb
	%	%		%	%		%	%
53	46	48	50	52	53	40	61	64
54	41	44	41	44	47	42	34	32
61	37	34	52	60	62	43	60	60
67	28	29	49	66	82	44	70	90
69	28	27	55	51	53	45	61	81
70	40	39	56	44	58	46	48	52
71	51	54	57	45	48	48	41	56
			59	43	45	51	55	69
			60	52	61	62	53	44
			63	43	51	64	44	52
			66	43	50	65	49	53
			68	51	55			
Mean	38.7%	39.4%	Mean	49.5%	55.3%	Mean	52.4%	59.3%
SD	±8.8	±10.1		±7.3	±9.8		±10.7	±16.2
Significance of difference (paired t test)		$P > 0.4$	Significance of difference (paired t test)		$P < 0.01$	Significance of difference (paired t test)		$P < 0.05$

CBF–MBF. In all three groups CBF and MBF showed a good positive linear correlation. The correlation coefficients (r) were respectively 0.981, 0.914, and 0.877 in normal, CHD, and NCHD groups. Values for these two parameters showed good agreement in the normal group but in CHD and NCHD, MBF was consistently lower. Thus, MBF was 98±4% of CBF in the normals, 88±10% in CHD and 90±18% in NCHD. In comparing MBF with CBF by paired observation testing, there was no significant difference ($P > 0.3$) in the normals, whereas the differences were significant in CHD ($P < 0.01$) and NCHD ($P < 0.02$).

The situation with respect to the above flow data is summarized in Fig. 1.

Cardiac output. The mean value for normal was 6.2± 1.5 liters/min, for CHD, 5.1±1.8 liters/min, and for NCHD, 5.3±1.3 liters/min. The difference between normal on the one hand and CHD and NCHD on the other is of borderline significance ($0.1 > P > 0.05$).

^{81}Rb Extraction ratios. The myocardial ^{E}Rb was not significantly affected by the method of delivery of isotope; to whit the mean value of myocardial ^{E}Rb in 23 cases in which the CI method was used was 51±9% whereas in 22 cases studied by bolus method it was 56± 10% ($P > 0.1$). Since the latter method was used in only two cases in the normal group, all nine normals are excluded from this comparison.

The findings detailed in Table II are confined to the CI studies since whole-body ^{E}Rb data were available only in those cases. In the normal group the myocardial and whole-body ^{E}Rb values were 39±9 and 39±10%, respectively. The corresponding values in CHD were 50±7 and 55±10%; and in NCHD were 52±11 and 59±16%. The myocardial: body ^{E}Rb differences were significant in the latter groups ($P < 0.05$) by paired t testing.

Myocardial as well as whole body ^{E}Rb values were significantly lower in the normal group compared with CHD ($P < 0.01$) and NCHD ($P < 0.02$).

Myocardial oxygen utilization (Fig. 2a). Mean arterial oxygen content values in ml/100 ml were: normal, 17.4±3.8; CHD, 17.8±2.5; NCHD, 17.0±1.7. These are normal levels.

In the normal patients mean myocardial oxygen utilization (MVO_2) was 43.2±11.5 ml/min; in CHD it was 32.0±13.4 ml/min. This difference is statistically significant ($P < 0.05$).

In NCHD the value was 29.9±11.3 ml/min which is also significantly lower than normal ($P < 0.01$).

Myocardial lactate extraction (Fig. 2b). The mean values were as follows: normal, 34.6±13.3%; CHD, 17.3±13.6%; NCHD, 29.7±14.1%. Whereas the normal and NCHD values were not significantly different from one another ($P > 0.3$), they were significantly higher than CHD ($P < 0.01$).

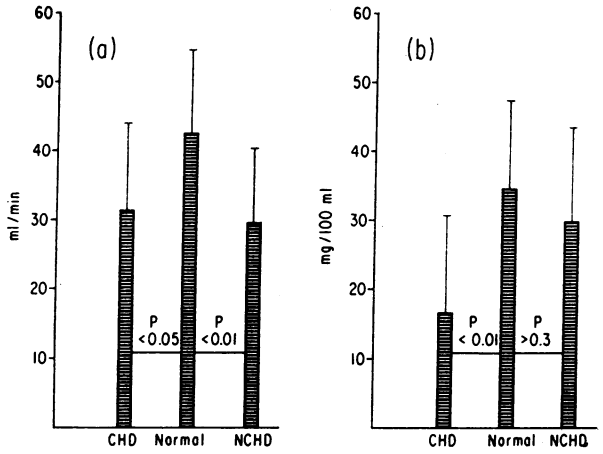

FIGURE 2 Both (*a*) MVO_2 and (*b*) lactate extraction ratio are significantly depressed compared with normal in CHD; only MVO_2 is depressed in NCHD.

Tension-time index (TTI). The following mean values were obtained. Normal, 3,168±561 mm Hg s/min; CHD, 2,854±765 mm Hg s/min; NCHD, 3,377±833 mm Hg s/min. The difference between the CHD and NCHD values were significant ($P < 0.05$) but neither was significantly different from normal ($P > 0.2$; $P > 0.4$, respectively).

Cardiac volume. The normal mean value for cardiac volume was 681±120 ml. The mean value for CHD was 914±249 ml which was significantly higher than normal ($P < 0.02$); and for NCHD it was 1,046±337 ml which was also significantly greater than normal ($P < 0.01$).

DISCUSSION

Before a discussion of the results themselves is entered into, certain aspects of the methodology should be considered.

Two different techniques (CI and single bolus) were used. The single bolus technique (14, 15, 18) has been advocated for the measurement of whole heart MBF because it is relatively simple and noninvasive; most of the published human data have been obtained by this means. Since one of our goals was to compare this parameter with CBF, we commenced the study with the bolus technique, applying it in the first 24 patients. However two disadvantages must be stated (*a*) The calculation of MBF depends on measurement of CO and when this in turn is based on the Stewart-Hamilton (indicator dilution) principle, there may be a tendency for it to be underestimated in the presence of valvular regurgitation (29, 30). Seven patients studied by bolus technique had some degree of valvular regurgitation (NCHD, 6; CHD, 1) and it is possible that their MBF values may consequently have been artificially low. We attempted to

minimize such errors by rejecting from the series those patients (2 in number) found to have a marked degree of distortion of their arterial indicator curves. (*b*) For measurement of CBF, blood has to be sampled from the coronary sinus at a steady rate for a period of 2 min, as part of the procedure for determining the integrated coronary arteriovenous ^{84}Rb concentration difference. Not infrequently however, flow is not free; we were obliged to reject several patients from the series because the sampling rate was either erratic or too low.

In deference to these objections the single bolus technique was supplanted by the CI technique in the last 30 patients. Since this allowed the measurement of CO by the Fick method, its accuracy and therefore that of MBF was not affected by possible errors due to the presence of valvular reguritation. For the estimation of CBF, only single samples of 5 ml size were needed. It should be realized that relative to the bolus technique, that of CI is relatively invasive, even if limited to measurement of MBF; it is more complicated and each determination takes considerably longer than the 2 min required for the single bolus method to allow for the collection of sufficient data from which to plot the rate of accumulation of ^{84}Rb in the myocardium. (Although we used a 12–14 min infusion period, 6–8 min should be sufficient).

Notwithstanding the aforementioned considerations, technique did not appear to be a factor in determining the pattern of results. In CHD the mean CBF measured by the bolus method was not significantly different from the mean CBF measured by the CI method ($P > 0.5$). The same is true for MBF ($P > 0.5$) and the CBF-MBF difference ($P > 0.4$). The corresponding values in NCHD were $P > 0.1$, $P > 0.2$, and $P > 0.5$. All but two of the normal cases were studied by the CI method. The similarity of the mean myocardial ^{E}Rb values for the two methods (51 and 56%) implies that blood sampling techniques were valid. Reassurance in this regard is especially important as far as the bolus method is concerned. This similarity, incidentially, is to be expected in spite of considerable contrasts between the methods in terms of magnitude and rate of change of Rb^{+} blood levels, since an active transport mechanism is involved.

With continuous infusion blood levels of ^{84}Rb rise steeply and then reach a plateau indicating a steady state in which rate of delivery of isotope equals rate of tissue uptake (16). It may be questioned whether our blood samples were always drawn after the onset of this plateau. Assuming uniform and constant whole-body extraction, the relative blood level of a substance infused at a constant rate will be a function of the number of complete circuits through the vascular system after the start of infusion. The number of circulations required to reach a plateau will depend inversely on the extraction ratio. Thus, with an ^{E}Rb of 39% (the mean value in the normals group) the blood level reaches within 1% of its plateau in 10 circulations. This is equivalent to 4.2 min assuming a circulation time of 25 s.[4] In all cases our blood sampling commenced no earlier than 6 min after the start of infusion, which appears thus to have afforded an adequate margin of safety, especially since the higher ^{E}Rb in the non-normal groups would be expected to provide an even earlier plateau.

The validity of the CI technique depends upon accurate measurement of the rate of uptake of isotope by the myocardium. Some investigators have found this to be troublesome and furthermore have claimed that such uptake is not a linear function of time (13, 31, 32). Nevertheless, we have encountered no difficulty in this regard: in the cases studied by CI technique, we obtained excellent linear correlation between myocardial ^{84}Rb uptake and time, as evidenced by an r value of 0.985 ± 0.018 (mean$\pm$SD; $n = 30$).

The linearity of infusion rate is likewise an important consideration. We believe our technique was satisfactory in this regard (see Methods).

In considering precordial detector size one can certainly question whether a diameter of 4 inches would effectively cover the range of heart sizes to be encountered and whether the myocardial uptake would not be underestimated in large hearts. Valid though we felt this point to be, we considered that the installation of larger crystals would have allowed insufficient room for the two detector pairs in most patients. In the presence of cardiomegaly we endeavored to include as much of the ventricular region as possible, sacrificing atrial and vascular areas when necessary.

CBF is calculated by a *direct* application of the Fick principle and therefore a good deal of confidence can be reposed in the measurement. An inherent assumption is that activity measured in the coronary sinus sample is equal to the mean myocardial venous activity. Since, at any given arterial blood level, the only determinant of coronary venous isotope level is myocardial ^{E}Rb, this assumption implies that ^{E}Rb does not vary between regions of the myocardium, or that if it does, such variation is randomly distributed throughout the heart. The coronary sinus sample remains representative of any variation within its region of drainage since the effluents from the different zones are pooled in this sample and their activities automatically averaged. However, a difference between the mean ^{E}Rb of the region drained by the coronary sinus and that of the rest of the myocardium would invalidate the above assumption and we cannot deny that this possibility exists. We suspect that, if present, any such difference is unlikely to be gross since CBF was found to have a high degree of correlation with MBF—a parameter whose calculation does not require the mean coronary venous isotope level.

[4] Peak to peak recirculation time in 33 subjects given a bolus of ^{84}Rb Cl = 24.6±3.4 s (mean ±SD).

Systematic overestimation of CBF would result from the existence of myocardium of lower ^{E}Rb confined to the coronary sinus drainage system and its degree would be no greater than the extent of the CBF-MBF difference. The difference of 10–12% occurring in this series represents the limit of our possible error from this source. It is not, however, pathognomonic of such an error.

Normal MBF values reported by other investigators using the ^{84}Rb method (13–15, 18) are some 35% lower than ours. We suspect a methodological basis for this difference: the increased resolution of our instrumentation as well as advantages conferred by improved mechanical design, as discussed in Methods, would be expected to yield higher net myocardial counts.

We have found CBF and MBF to be significantly below normal in the group of patients with CHD. This is in agreement with the findings of Cowan et al. (15) who measured MBF by means of ^{84}Rb coincidence counting technique. Their mean values were 74% of normal while ours are 65%. While this is what might logically be expected, the majority of investigators hitherto have been unable to distinguish CHD from normality on the basis of resting flow values. Many used inert gas methods which are now acknowledged to overestimate flow in the presence of coronary disease (2, 4, 7, 33). More recently, however, Klocke and his collaborators (3) have used a hydrogen desaturation method in which attention is paid to the crucial importance, because of heterogeneous flow, of delivery method, sampling period, and precision of measuring technique. They found lower average flows in CHD. However, their patients were few in number and several of those "without coronary artery disease" we would have placed in the NCHD category. Cannon, Dell, and Dwyer (34) have approached the problem of nonuniform flow by using a multiple-crystal scintillation camera for external monitoring of myocardial ^{133}Xe washout. They also found average unit flows to be lower in the presence of coronary artery disease than in patients with normal coronary arteries. However, the great majority of the latter had cardiac pathology and therefore were not truly normal.

In the NCHD group we have found both CBF and MBF to be significantly less than normal. Why this should be so is a challenging puzzle. In the case of CHD, MVO_2 was subnormal and this was accompanied by a significant trend toward anaerobic metabolism (Fig. 2). Since the TTI was not significantly less than normal and gross cardiac volume was significantly greater, it is likely that the demand of the myocardium for oxygen was greater than the coronary circulation could supply and hence the tendency to anaerobiasis. On the other hand in NCHD, MVO_2 was similarly diminished but this was not accompanied by a significant anaerobic trend. It might, therefore, appear that in CHD, MVO_2 was determined by perfusion whereas in NCHD perfusion was determined by MVO_2. It is paradoxical that this parameter was reduced despite a significantly increased gross heart volume and a TTI that was certainly not less than normal. One may speculate that these determinants of MVO_2 important though they may have been, were counterbalanced by that of myocardial contractile state, depression of which is known to occur in the presence of myocardial hypertrophy or failure (35, 36). Thus, it could be argued that depression of CBF in NCHD is the result of autoregulation.

It is necessary to acknowledge the possible role played by probe size in the genesis of our results. In a heart too large to be entirely included within the field of a 4 inch detector pair, Rb uptake and therefore whole-heart flow will be underestimated. The flow value obtained might actually be normal if the mass of myocardium remaining within the field were sufficient, but if pure dilatation were present, then the absolute mass of myocardium seen by the detectors and therefore the flow, might appear less than normal without there having been any change in flow per unit mass. We indeed found that total heart volumes calculated from chest radiographs were higher than normal in CHD and NCHD; can it be that cardiac dilatation solely explains the apparent reductions in flow in the pathological groups? We cannot refute this possibility with complete certainty but the following observations may be pertinent. We do not find that the larger the heart, the lower the flow: CBF as a linear function of total heart volume ($n = 54$) yields a correlation coefficient of only -0.04. As our concern is only with volume increases which extend beyond the coincidence field, it is perhaps more appropriate to consider the discrepancy between the area of a 4 inch diameter circle and the frontal area of the heart, rather than total volume. CBF considered as a linear function of this area difference yields a similarly poor correlation ($r = 0.016$; frontal area calculated from the long and broad axes utilized in the volume estimations (28) assuming an elliptical shape; in none of our 54 cases was frontal area less than that of a 4 inch circle).

MBF is derived on the basis of the Sapirstein hypothesis (19) according to which organ uptake of Rb is proportional to flow and a corollary of which is that the ^{E}Rb of a given organ is equal to that of the whole body. Furthermore, MBF will be the same as CBF under these conditions.

In the case of our normal subjects the conditions of the Sapirstein hypothesis were met since myocardial and body ^{E}Rb values (Table II) were virtually the same ($P > 0.4$). The close agreement between CBF and MBF in this group ($P > 0.3$) was simply a reflection of this fact.

In the non-normal subjects this was not the case. The mean myocardial ^{E}Rb was significantly lower than

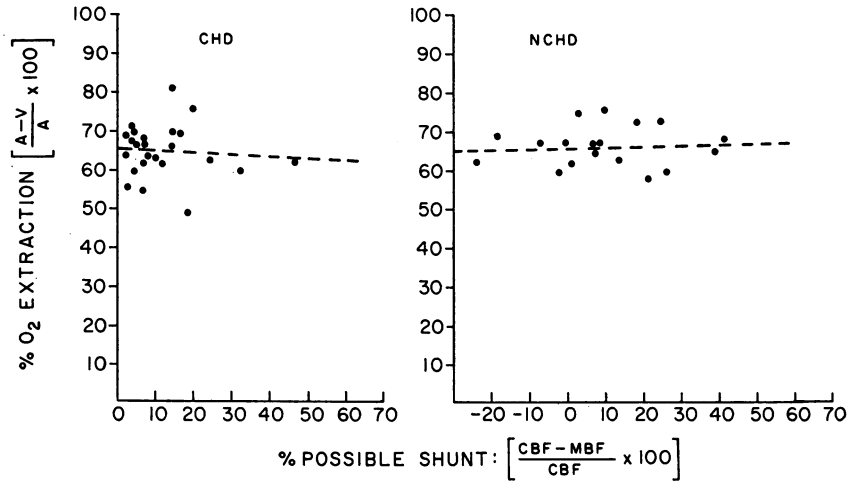

FIGURE 3 $^{E}O_2$, a likely correlate of any shunting, vs. percent CBF-MBF difference. These plots, showing virtual absence of correlation furnish no support for the shunt hypothesis.

that of the whole-body in CHD ($P < 0.01$) and NCHD ($P < 0.05$). Accordingly, MBF values were significantly lower than those of CBF ($P < 0.01$; $P < 0.02$). These findings could have been due either to the existence of a significant nonextracting component in the coronary circulation (i.e., a shunt) or depression of the active transport of Rb^+ across the myocardial cell membrane.

If shunting were present one would expect to find parallel changes in measured oxygen extraction. Assuming that myocardial oxygen extraction ratio ($^{E}O_2$) in extracting circuits is constant, then the greater the flow via nonextracting circuits the lower the overall $^{E}O_2$ would be. This assumption is certainly true when oxygen extraction is already at its maximum as is likely to be the case when myocardial ischemia is present or when the shunt is large. In Fig. 3 myocardial $^{E}O_2$ is plotted as a function of "possible shunting" expressed as percentage CBF-MBF difference. This figure shows coefficients of correlation of virtually zero in both CHD and NCHD. This tends to discount the possibility of true shunting.

The data in Table II show myocardial ^{E}Rb values in the normal patients to be significantly lower than those in the CHD ($P < 0.01$) and NCHD ($P < 0.02$) groups. This is the converse of the findings with respect to coronary flow in these groups. This relation between flow and ^{E}Rb is in accord with the observations of Moir (37). His studies on canine hearts showed coronary blood flow to be a major determinant of myocardial ^{E}Rb, the higher the flow, the lower the extraction.

On this basis, therefore, our ^{E}Rb data, whose measurement is independent of factors such as probe size, lend credence to the lower flow values obtained in CHD and NCHD.

Whole-body ^{E}Rb was found to be significantly lower in normal patients as compared with CHD ($P < 0.01$). Conversely mean CO values were higher in normals compared with the other groups and the differences close to being statistically significant ($P < 0.1$). It would seem reasonable indeed to conclude that these facts are not unrelated and that Moir's conclusions with respect to the heart are equally applicable to the body as a whole.

Thus, our experience indicates that in the case of CHD and certain other forms of heart disease, particularly valvular, the total CBF is significantly less than normal; myocardial extraction of Rb^+ is significantly greater than normal, most likely as a consequence thereof.

Yet, in abnormal hearts myocardial Rb^+ extraction is low relative to that of the whole-body. We tend to think that this is due to depressed myocardial Rb^+ transport rather than true shunting. In any event nutrient or effective CBF consistently underestimates total CBF in this group.

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