Effects of Heterogeneous Myocardial Perfusion on Coronary Venous H_2 Desaturation Curves and Calculations of Coronary Flow

FRANCIS J. KLOCKE, ROBERT C. KOBERSTEIN, DAVID E. PITTMAN, IVAN L. BUNNELL, DAVID G. GREENE, and DOUGLAS R. ROSING

From the Department of Medicine, State University of New York at Buffalo School of Medicine, Buffalo, New York 14214

ABSTRACT The present investigation was intended to evaluate myocardial inert gas desaturation curves for manifestations of heterogeneous coronary perfusion. The test gas was hydrogen (H_2) and blood H_2 analyses were performed with a gas chromatograph capable of detecting small but prolonged venous-arterial H_2 differences produced by areas of reduced flow. Curves were initially obtained after 4-min left ventricular infusions of H_2-saturated saline in six patients with arteriographically proven coronary artery disease, three patients with normal coronary arteries, and nine closed-chest dogs. The dogs were studied before and after embolic occlusion of a portion of the left coronary artery. Although the slopes of their semilogarithmically plotted venous desaturation curves varied with time before embolization, they showed more distinct deviations from single exponentials after embolization (after H_2 concentrations had fallen below 15% of their initial values). The human curves divided similarly, those from coronary artery patients deviating appreciably from single exponentials. A similar separation was also evident in studies of coronary venous-arterial H_2 differences after 20 min of breathing 2% H_2; data were obtained in four dogs before and after coronary embolization, and in three normal patients, and five patients with coronary artery disease. Additional data indicated that the findings were not the result of right atrial admixture in sampled coronary venous blood, although admixture occurred frequently when blood was sampled in the first 2 cm of the coronary sinus (as seen in the frontal projection). Finally, average coronary flows calculated from a given set of data varied significantly with different methods of calculation. Areas of below-average flow seemed likely to be overlooked when single rate constants of desaturation, relatively insensitive analytical techniques, or relatively short periods of saturation and (or) desaturation are employed.

This work was presented in part at the 40th Annual Scientific Sessions of the American Heart Association, San Francisco, Calif., 21 October 1967.

Received for publication 8 July 1968.

INTRODUCTION

Although inert gas techniques have been used to measure coronary blood flow for two decades, their suitability when flow is not uniform has remained difficult to evaluate. This situation is particularly troublesome when myocardial perfusion is known to be distributed heterogeneously, e.g., in coronary artery disease (1). Of particular interest are alterations in the patterns of tissue-blood gas exchange produced by areas of myocardium which have a flow per unit volume lower than the average flow per unit volume for the entire tissue. Failure to identify these areas may cause total flow to be overestimated and sites of clinically significant disease to be overlooked. In the original nitrous oxide technique (2, 3), arterial and venous nitrous oxide concentrations are followed during a period of nitrous oxide breathing. Areas of low flow are expected to prolong the time required for

the arterial-venous nitrous oxide difference to become negligible. When these areas contribute only a small fraction of the total venous drainage, the magnitude of the prolonged difference will be small and its identification may require unusually sensitive analytical techniques (4). In applications of the nitrous oxide technique in which flow is determined from desaturation rather than saturation curves (5), areas of low flow are expected to produce prolonged venous-arterial gas differences. The quantitation of small differences during desaturation is aided by the fact that the absolute gas concentrations are lower than during saturation. On the other hand, it is crucially important that the preliminary period of test gas breathing is adequate to achieve the same partial pressure of test gas in areas of low flow as in areas of high flow. If this is not the case, the areas of low flow will be incompletely represented in the venous washout curve and even the most sensitive analytical methods will be of limited value. The same principles apply when desaturation curves are obtained after introduction of a solution containing a dissolved test gas into the left ventricle or a coronary artery. These washouts have most frequently utilized ^{85}Kr or ^{133}Xe and have employed both coronary venous blood sampling (6) and precordial monitoring of myocardial radioactivity (7). With a gas of low solubility, recirculation through the lungs is minimal and arterial gas concentrations drop to negligible levels when gas administration is discontinued. When the ensuing venous (or myocardial) desaturation curve is plotted semilogarithmically against time, heterogeneity of myocardial perfusion causes the slope of the curve to become less negative with time, i.e., to deviate from a single exponential. The ability to detect this type of deviation is again related to the sensitivity of the techniques used for gas analysis and to the delivery of test gas to areas of low flow.

The present study was intended to evaluate coronary venous desaturation curves for evidence of nonuniform perfusion by employing a specially designed thermal conductivity gas chromatograph (8). The chromatograph is appreciably more sensitive and specific than Van Slyke analyses and can detect 10^{-5}–10^{-6} ml of virtually any gas in a 2.0 ml blood sample. Studies were initially performed in anesthetized, closed-chest dogs, where desaturation curves could be obtained before and after embolic occlusion of a portion of the left coronary artery. They were then extended to patients undergoing diagnostic cardiac catheterization, the majority of whom had clinical and arteriographically documented coronary artery disease. The test gas was hydrogen (H_2) and the duration of myocardial exposure to the test gas was either 4 or 20 min. In addition, precautions were taken to ensure that the results were not influenced by right atrial admixture in the sampled coronary venous blood. The findings indicate that nonuniform myocardial perfusion can be detected in coronary desaturation curves. The degree of nonuniformity is increased in dogs after embolic occlusion of a portion of the left coronary artery, and is generally greater in patients with coronary artery disease than in patients without coronary artery disease. The findings also reaffirm that inert gas estimates of total flow can be seriously affected if heterogeneity of myocardial perfusion is overlooked.

METHODS

Studies after delivery of test gas by dissolved gas infusion

Experimental animals. Nine mongrel dogs weighing between 20 and 36 kg were anesthetized with sodium pentobarbital, 30 mg/kg, intubated, and allowed to ventilate spontaneously. An 8F Sones catheter was inserted through an external jugular vein and advanced under fluoroscopic control through the coronary sinus and into the proximal portion of the great cardiac vein (9). A second Sones catheter was inserted through a carotid artery and advanced retrograde into the left ventricle. A short polyvinyl catheter was placed in the lower abdominal aorta through a femoral artery and the animal was anticoagulated with sodium heparin, 100–150 mg i.v. After the catheters had been positioned, a control venous desaturation curve was obtained after a 4 min left ventricular infusion of isotonic saline or 5% dextrose-in-water (D/W) containing dissolved H_2. The infusate was prepared by bubbling H_2 through the saline (or D/W) for approximately 20 min. Its administration was accomplished with a consant-rate infusion pump at rates varying between 12 and 24 ml/min. 10 to 15 2.0-ml blood samples were drawn through the coronary venous catheter during the last minute of the infusion and the 6–10 min immediately after its conclusion. In five animals, systemic arterial samples were also obtained from the aortic sampling site during desaturation. All samples were analyzed for H_2 concentration using the gas chromatograph described above. After the control washout had been completed, the left ventricular catheter was repositioned in either the left circumflex or left anterior descending coronary artery, and 0.1–0.2 ml of mercury was injected through the catheter in order to occlude a portion of

the artery. (Preliminary experiments verified that the mercury did not pass through the capillary bed and occluded appreciable segments of the embolized vessel, thereby producing an acute but not immediately lethal myocardial infarction.) The catheter was then replaced in the left ventricle and, after waiting 30–90 min, a second desaturation curve was obtained in the same manner as the first. In five animals, systemic arterial samples were again obtained from the aortic sampling site during desaturation.

Patients. Nine patients were studied in conjunction with diagnostic cardiac catheterization and selective cine coronary arteriography. Six of the patients had clinical and arteriographically documented coronary artery disease, with greater than 50% occlusion of at least two of the three major coronary vessels. In five of the six patients, there was also arteriographic evidence of collateral circulation to the areas supplied by the diseased vssels. Three patients had anatomically normal coronary arteries. One was a 42 yr old male being evaluated for chest pain which was concluded to be muscular in origin; complete catheterization was normal. Another was a 33 yr old male with mild aortic insufficiency but normal left ventricular pressures and volumes. The final patient was a 56 yr old female with an unexplained cardiomyopathy. In each case, a 7F or 8F Sones catheter was inserted through an antecubital vein and advanced into the coronary sinus or great cardiac vein. Catheter position was verified by a cineangiogram made during a hand-injection of meglumine diatrizoate and, as will be discussed below, the catheter tip was always more than 2 cm from the coronary sinus ostium in the frontal projection. Isotonic saline or 5% D/W containing dissolved H_2 was then infused through a left ventricular catheter for 4 min, using a constant-rate infusion pump and rates between 24 and 48 ml/min. The infusate was prepared by passing the H_2 through a sterile filter [1] and water trap before bubbling it through the saline or D/W. 15 to 20 2.0-ml blood samples were drawn through the coronary venous catheter during the infusion and the 15 min immediately thereafter. Clotting of the sampled blood was prevented by filling the dead space of the sampling syringes [2] with heparinized saline. In three patients, samples were also obtained from a peripheral arterial sampling site during the desaturation process. All samples were again analyzed for H_2 concentration with the gas chromatograph.

Studies after delivery of test gas by gas breathing

Experimental animals. Four mongrel dogs weighing between 22 and 35 kg were anesthetized with sodium pentobarbital, 30 mg/kg, intubated, and allowed to ventilate spontaneously through a low resistance three-way valve. An abdominal aortic sampling catheter was inserted through a femoral artery and an 8F Sones catheter was positioned in the proximal portion of the great cardiac vein. After anticoagulation with sodium heparin, 100–150 mg i.v., control arterial and coronary venous desaturation curves were obtained after a 20 min period in which the animal breathed a gas mixture containing 2% H_2 and the usual 21% O_2. 12 to 15 pairs of 2.0-ml blood samples were drawn through the arterial and coronary venous catheters during the last few minutes of the H_2 breathing and the first 15–20 min thereafter. After the control washout had been completed, another Sones catheter was inserted through a carotid artery and positioned in either the left circumflex or left anterior descending coronary artery so that a portion of the artery could be occluded with mercury. The catheter was withdrawn as soon as the mercury was administered and, approximately 30–90 min later, a second set of arterial and coronary venous desaturation curves was obtained after another 20 min of H_2 breathing.

Patients. Eight additional patients were studied in conjunction with diagnostic cardiac catheterization and cine coronary arteriography. Five of the patients had clinical and arteriographically documented coronary artery disease, with greater than 50% occlusion of at least two of the three major coronary vessels. In all five patients, there was also arteriographic evidence of collateral circulation to the areas supplied by the diseased vessels. The three remaining patients were classified as having normal coronary arteries. One was a 39 yr old female with atypical chest pain for which no organic basis could be documented; complete catheterization, including coronary arteriography, was normal. Another was a 16 yr old boy being evaluated for what turned out to be an innocent murmur. Although coronary arteriography was not performed, routine right and left heart catheterizations were entirely normal. The final patient was an 18 yr old girl with postnecrotic cirrhosis, portal hypertension, and arterial hypoxemia; her cardiac catheterization was normal except for an arterial oxygen saturation of 80%, which was related to multiple intrapulmonary arteriovenous fistulae; coronary arteriograms were not obtained.

In each patient a 7F or 8F Sones catheter was positioned in the coronary sinus or great cardiac vein and cineangiographic verification that the catheter tip was more than 2 cm from the coronary sinus ostium in the frontal projection was obtained as described above. A previously placed arterial catheter or needle was used to sample arterial blood. The nostrils were occluded and the patient breathed through a mouthpiece and low resistance three-way valve. Arterial and coronary venous desaturation curves were obtained after a 20 min period in which the patient breathed a mixture containing 2% H_2 and 21% O_2. 12 to 15 pairs of 2.0-ml arterial and coronary venous blood samples were obtained during the last few minutes of the H_2 breathing and the 15–20 min immediately thereafter.

Studies on right atrial admixture in coronary venous blood

Studies in this area were confined to patients, since a previous investigation (10) has indicated that right

[1] Model SXHA0130S, Millipore Filter Corp., Bedford, Mass.

[2] Model 2YP, Becton-Dickinson Co., Rutherford, N. J.

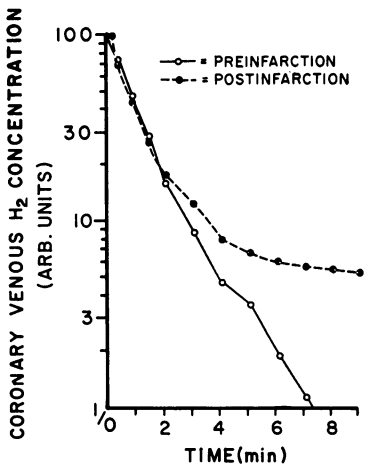

FIGURE 1 Coronary venous desaturation curves after H_2 infusions in an anesthetized dog.

atrial "contamination" of canine coronary venous blood is unlikely when the tip of the sampling catheter is in the great cardiac vein. The basic plan was to examine coronary venous blood for the presence of dissolved H_2 during a constant-rate infusion of H_2-saturated saline into the systemic venous circulation. Because of its extremely low solubility in blood, over 95% of the infused H_2 was expected to be eliminated in the lungs before it could reach the myocardium (11). The concentration of H_2 in the blood sampled during the infusion should therefore have been minimal unless the sample was "contaminated" with right atrial blood. A total of 18 patients with various abnormalities was studied. 2.0-ml samples of coronary venous blood were drawn through a Sones catheter during infusions of H_2-saline into the superior vena cava (13 patients) or inferior vena cava (5 patients) at rates between 24 and 36 ml/min. Catheter positions relative to the coronary sinus ostium were measured (with appropriate correction for magnification) on cineangiograms taken in the frontal projection during hand injections of meglumine diatrizoate. Peak rates of sample withdrawal were 15–25 ml/min and the H_2 concentration of each sample was measured chromatographically. Samples were obtained in more than one position in the coronary sinus and (or) great cardiac vein in 11 of the 18 patients. In all 18 patients samples were also obtained after the

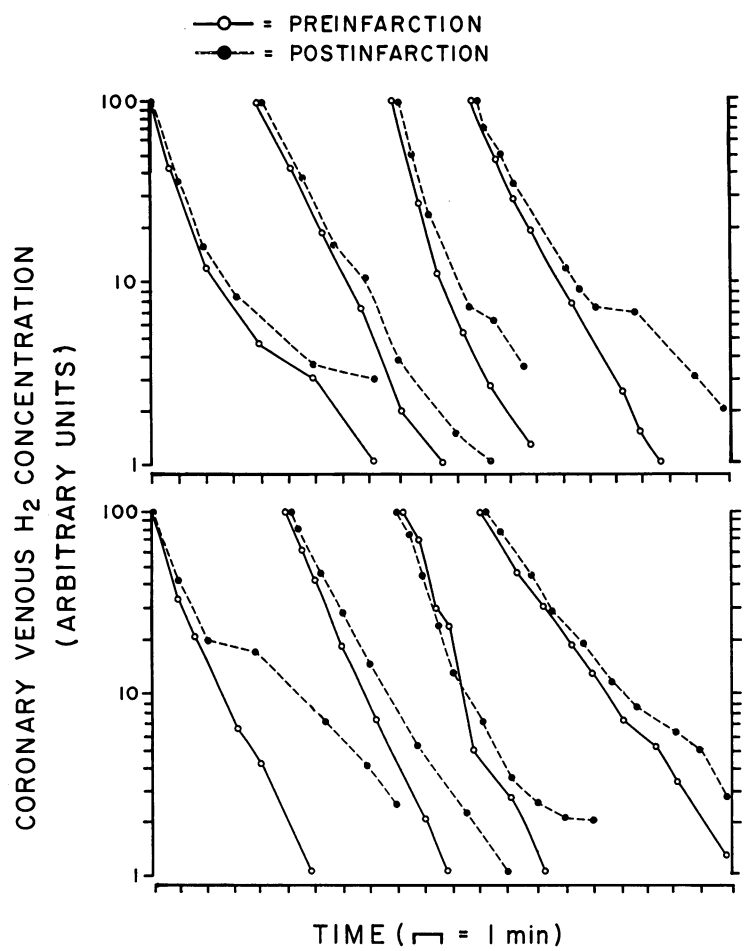

FIGURE 2 Coronary venous desaturation curves after H_2 infusions in eight additional anesthetized dogs.

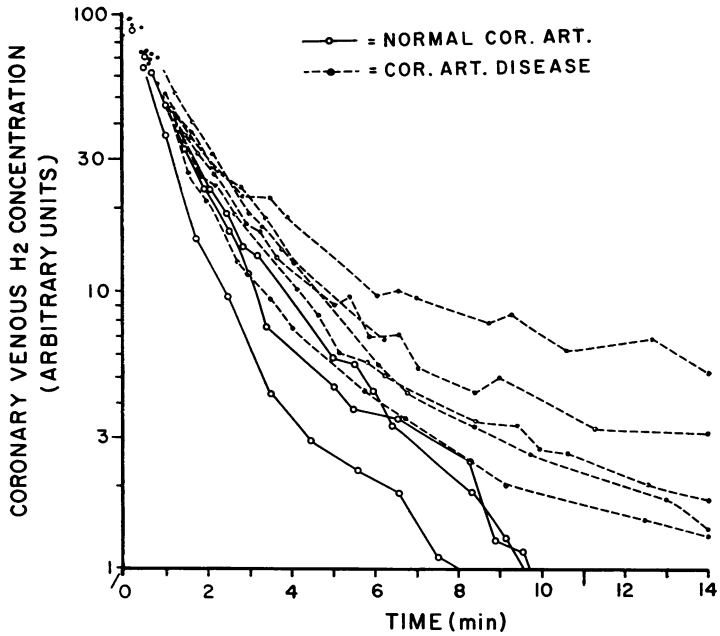

FIGURE 3 Coronary venous desaturation curves after H_2 infusions in patients with arteriographically normal coronary arteries and arteriographically proven coronary artery disease.

catheter had been withdrawn into the right atrium adjacent to the coronary sinus ostium.

RESULTS

Studies after delivery of test gas by dissolved gas infusion

Experimental animals. Coronary venous desaturation curves before and after coronary occlusion are shown for each of the nine animals in Figs. 1 and 2. Although none of the curves forms a truly single exponential, the deviations from a single exponential are more pronounced in the postinfarction curves. In most cases, however, the deviations become apparent only after the venous gas concentrations have fallen below 10–15% of their initial values. Systemic arterial H_2 concen-

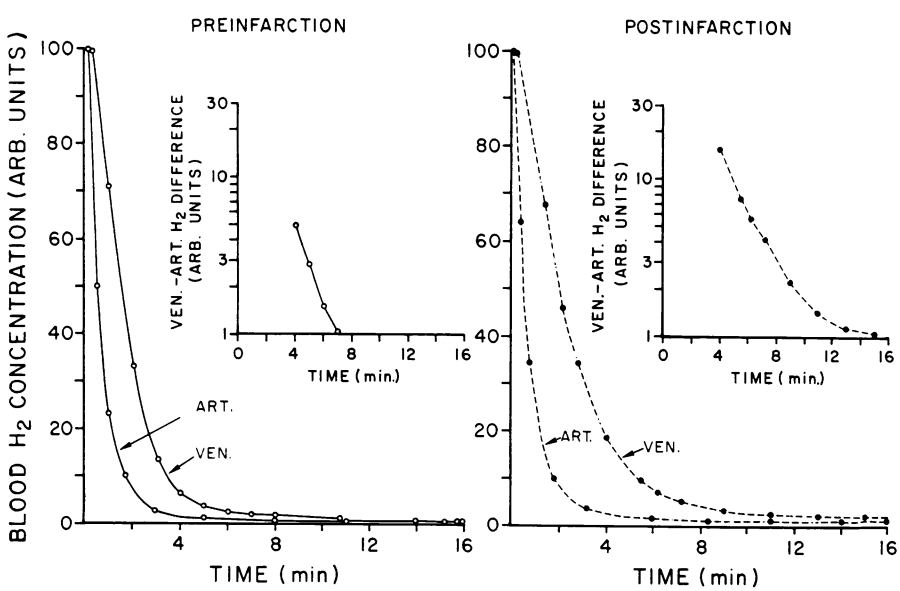

FIGURE 4 Arterial and coronary venous desaturation curves and venous-arterial H_2 differences after H_2 breathing in an anesthetized dog.

TABLE I

*Coronary Flows Calculated from Desaturation Curves after H_2 Infusions**

Method of calculation		Conventional equation for average flow‡	Rate constant, beginning with onset of desaturation§	Rate constant, beginning 30–45 sec after onset of desaturation‖
		ml/100 g per min	*% of conventional average flow*	*% of conventional average flow*
Dogs before coronary occlusion				
1		89	101	99
2		84	121	118
3		69	104	104
4		128	118	106
5		78	101	100
6		82	120	104
7		79	102	102
8		86	115	115
9		50	102	102
	Mean	83	109 ($P < 0.02$)¶	106 ($P < 0.05$)¶
	SEM	6.9	3.0	2.2
Same dogs after coronary occlusion				
1		51	160	153
2		64	155	141
3		63	110	103
4		107	118	107
5		65	117	107
6		48	177	Indeterminate
7		59	107	107
8		85	125	128
9		44	114	107
	Mean	65	131 ($P < 0.01$)¶	119 ($p < 0.02$)¶
	SEM	6.6	8.5	7.2
Patients without coronary artery disease				
1		73	104	100
2		62	108	102
3		98	109	109
	Mean	78	107	104
Patients with coronary artery disease				
1		46	122	109
2		47	127	119
3		64	118	114
4		48	125	121
5		38	155	118
6		55	125	114
	Mean	50	129 ($P < 0.01$)¶	116 ($P < 0.01$)¶
	SEM	3.6	5.6	1.8

* All values have been calculated assuming a tissue-blood partition coefficient (λ) of 1.0 and a myocardial specific gravity of 1.0.

‡ $F/V = 100\ \lambda\ (C_{v_0} - C_{v_t})/\int_0^t C_v\, dt$ where C_{v_0} and C_{v_t} are the H_2 concentrations of coronary venous blood at the beginning and end of the observed period of desaturation. $\int_0^t C_v\, dt$ was obtained by planimetric integration of the area under the linearly plotted venous desaturation curve. (This is the traditional Kety-Schmidt formula; arterial H_2 concentration does not appear since it is negligible after cessation of dissolved H_2 infusion.)

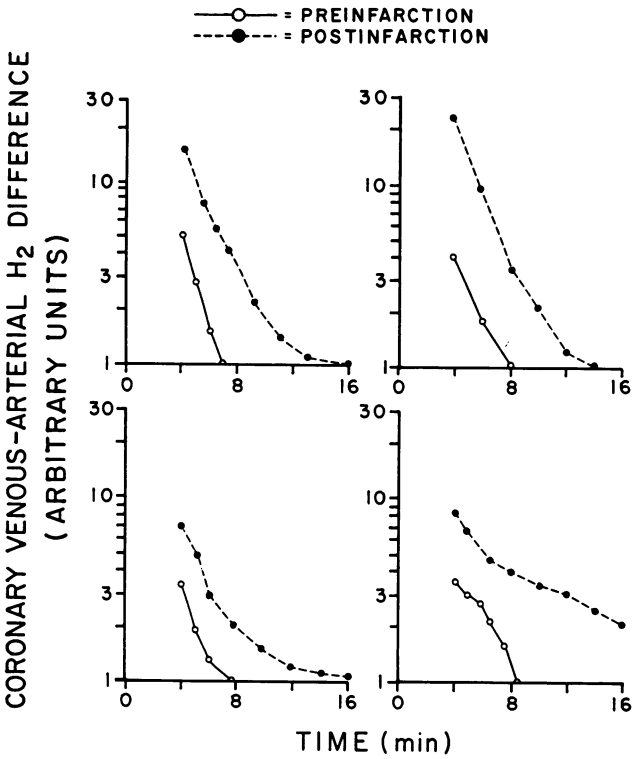

FIGURE 5 Coronary venous-arterial H_2 differences after H_2 breathing in anesthetized dogs.

trations were always negligible after the first 30–90 sec of desaturation in the five animals in which they were measured. Coronary flows calculated by three different approaches are shown in the upper half of Table I.

Patients. Fig. 3 illustrates coronary venous desaturation curves in the three patients without coronary artery disease and the six patients with coronary disease. Although none of the curves is adequately described by a single exponential, the deviations from a single exponential are appreciably more pronounced in the coronary artery patients than in the noncoronary artery patients. In addition, the deviations from a single exponential become apparent only after the venous gas concentrations have fallen below 10–15% of their initial values. Systemic arterial H_2 concentrations were negligible after the first minute or two of desaturation in the three patients in whom they were measured. Calculated coronary flows are shown in the lower half of Table I.

Studies after delivery of test gas by gas breathing

Experimental animals. Representative arterial and coronary venous desaturation curves are illustrated in Fig. 4. The venous-arterial H_2 difference is prolonged after coronary occlusion and, as shown on the inset, can be plotted semilogarithmically against time in a manner similar to the latter portion of desaturation curves after H_2 infusions. Fig. 5 shows venous-arterial H_2 differences before and after coronary occlusion in all four animals. Coronary flows calculated by three

§ $F/V = k\lambda$ where k = 0.693/half-time of desaturation, expressed in minutes. k was determined from the straight line best fitting the semilogarithmically plotted data between the onset of desaturation and the time when the venous H_2 concentration reached approximately 10% of its initial value.

‖ $F/V = k\lambda$ as above, but k was determined from the best-fitting straight line for the period between 30–45 sec after the onset of desaturation and the time when the venous H_2 concentration reached approximately 10% of its initial value. As mentioned in the text, initial venous concentrations and the first 30–45 sec of desaturation are difficult to evaluate precisely after sudden single injections of dissolved gases, and are often neglected in calculations of flow using this type of gas delivery (6, 7, 16). Numerically greater flows obtained with the rate constant beginning with the onset of desaturation presumably indicate a decreasing slope of the initial portion of the desaturation curve.

¶ Values for P were calculated using the paired t test method and the corresponding flows expressed in ml/100 g per min.

TABLE II

*Coronary Flows Calculated from Desaturation Curves after H_2 Breathing**

Period of desaturation considered:	Onset to 20 min after onset	Onset to 10 min after onset	Onset to point where $(C_v - C_a) = 5\%$ of C_{v0}
	ml/100 g per min	*% of 0–20 min value*	*% of 0–20 min value*
Dogs before coronary occlusion			
1	90	104	115
2	90	102	113
3	147	103	126
4	87	102	117
Mean	104	103 ($P < 0.02$)‡	118 ($P < 0.05$)‡
Same dogs after coronary occlusion			
1	70	106	114
2	63	105	113
3	101	112	132
4	68	116	134
Mean	76	110 ($P < 0.05$)‡	123 ($P < 0.05$)‡
Patients without coronary artery disease			
1	86	105	116
2	68	104	114
3	113	101	118
Mean	89	103	116 ($P < 0.05$)‡
Patients with coronary artery disease			
1	61	122	128
2	61	116	119
3	46	115	123
4	65	109	117
5	68	113	123
Mean	60	115 ($P < 0.01$)‡	122 ($P < 0.01$)‡

* $F/V = 100\ \lambda/(C_{v0} - C_{vt})/\int_0^t (C_v - C_a)\ dt$ where C_{v0} and C_{vt} are the H_2 concentrations of coronary venous blood at the beginning and end of the observed period of desaturation. The latter was taken as 20 min, 10 min, or the number of minutes after the onset of desaturation when the venous-arterial H_2 difference, $(C_v - C_a)$, was 5% of C_{v0}. λ was again taken as 1.0 and $\int_0^t (C_v - C_a)\ dt$ was obtained by planimetric integration of the area between the linearly plotted venous and arterial desaturation curves. (This is again the traditional Kety-Schmidt formula.)

‡ Values for P were calculated using the paired t test method and the corresponding flows expressed in ml/100 g per min.

different approaches are shown in the upper half of Table II.

Patients. Fig. 6 shows arterial and coronary venous desaturation curves for one "normal" patient and one patient with coronary artery disease. The venous-arterial H_2 difference is appreciably more prolonged in the coronary artery patient and, as shown on the inset, can be plotted semilogarithmically against time as in Fig. 4. Fig. 7 shows venous-arterial H_2 differences for all patients studied in this fashion. Calculated coronary flows are shown in the lower half of Table II.

Studies on right atrial admixture in coronary venous blood

Detailed results are shown in Table III. 25 samples were obtained in 15 patients at points more than 2 cm from the ostium of the coronary sinus. Coronary venous H_2 concentrations never exceeded 3% of the H_2 concentrations in the right atrium adjacent to the coronary sinus ostium, and

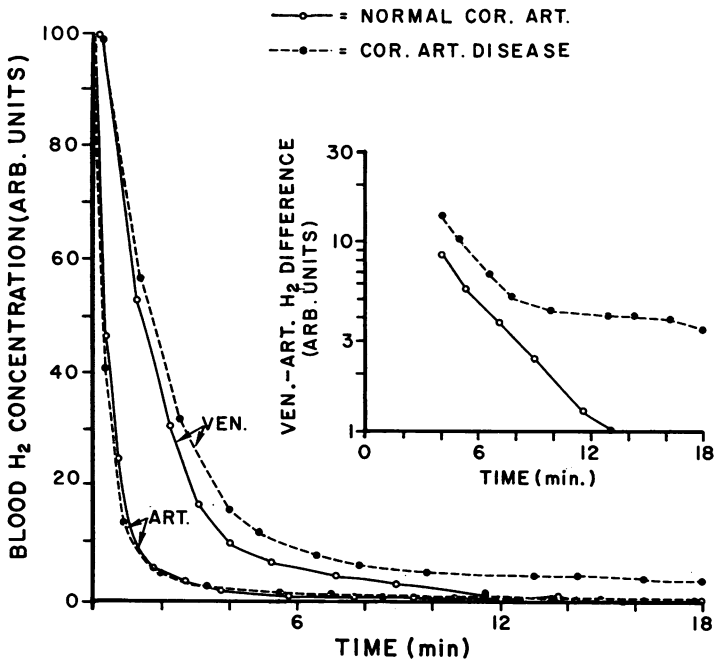

FIGURE 6 Arterial and coronary venous desaturation curves and venous-arterial H_2 differences after H_2 breathing in a normal patient and a patient with coronary artery disease.

averaged only 1.2% of these values. In nine of the 15 patients samples were also obtained in the first 2 cm of the coronary sinus. Coronary venous H_2 concentrations ranged from 2 to 42% and averaged 15% of right atrial H_2 concentrations, and six of the nine patients showed a distinct H_2 "step-up" in the more proximal position (the latter being defined as an increment of H_2 concentration greater than 5% of the right atrial H_2 concentration). In three patients in whom sampling was possible only in the first 2 cm of the coronary sinus, coronary venous H_2 concentrations were 7, 8, and 9%

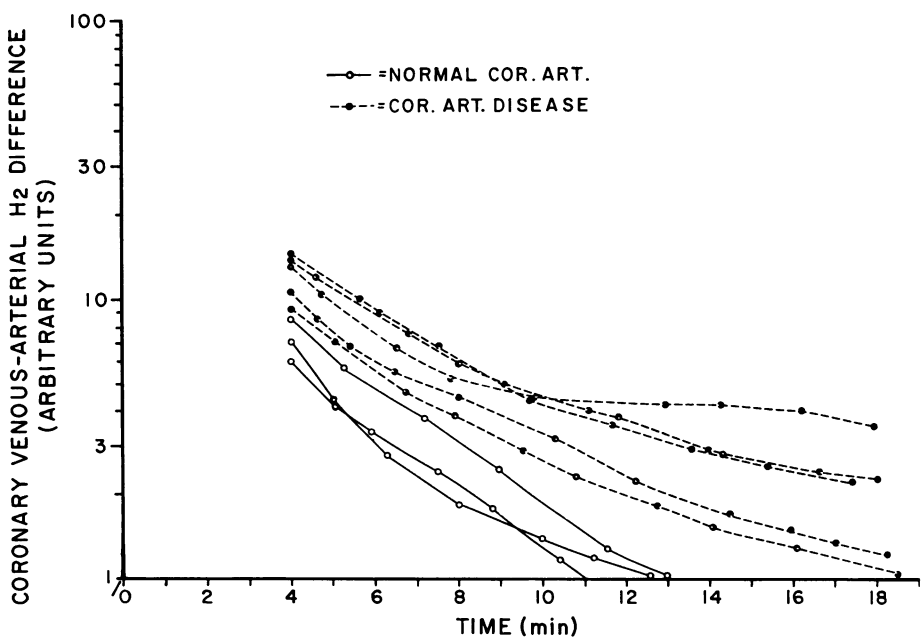

FIGURE 7 Coronary venous-arterial H_2 differences after H_2 breathing in patients with and without coronary artery disease.

TABLE III

Studies of Right Atrial Admixture in Sampled Coronary Venous Blood in Man

Patient	Catheter position (cm beyond coronary sinus ostium)*	$C_{cv_{H_2}}$ as % of $C_{RA_{H_2}}$‡	Coronary venous O_2 saturation	
			Van Slyke	Oximeter§
			%	%
1	7	0	—	19
	4	3	—	—
	1	19	—	—
2	4	2	35	36
	2	2	—	—
3	5	3	37	37
	1	9	—	—
4	5	1	—	10
	2	7	—	—
5	5	1	—	—
	3	2	—	—
	1	5	—	—
6	4	2	—	17
	3	2	—	—
7	1	8	19	14
8	4	0	28	28
	2	12	33	32
	1	13	42	42
9	4	3	—	16
10	7	1	24	16
11	4	3	26	31
12	2	9	32	36
13	8	3	22	21
14	4	0	31	24
	3	2	—	—
	1	42	—	—
15	8	0	29	20
	6	0	24	14
	4	0	—	16
	3	0	—	—
	1	30	—	27
16	6	0	27	23
	4	0	—	—
	3	1	—	—
17	5	1	13	20
	3	1	13	20
	1	2	—	20
18	1	7	26	35

* As measured cineangiographically in the frontal projection.

‡ $C_{cv_{H_2}}$ and $C_{RA_{H_2}}$ = coronary venous and right atrial H_2 concentrations.

§ American Optical Company, Southbridge, Mass.

of the right atrial H_2 concentrations. These patients were not included in the desaturation studies.

DISCUSSION

Principles involved in the detection of heterogeneous coronary blood flow by inert gas techniques have been discussed in detail in recent reviews (12–17). Of particular importance in the present studies were the use of the gas chromatograph and the relatively long periods of inert gas saturation. The chromatograph's sensitivity facilitated the measurement of smaller venous-arterial differences than usually detected with Van Slyke analyses for nitrous oxide or with precordial counting techniques. In addition, since each H_2 analysis required only 2 ml of blood, a large number of samples could be employed to assist further in curve resolution. The problem of delivering test gas to all areas of the heart before the onset of desaturation has been mentioned in the introduction. To provide some quantitative index in this regard, it is helpful to consider situations which might obtain if the heart were composed of a number of homogeneous compartments arranged in parallel. If saturation were initiated by a sudden, "square-wave" increment in arterial gas concentration, the venous gas concentration in each individual compartment would approach the arterial gas concentration in an exponential fashion,[3] as expressed by the following equation:

$$C_{v_t} = C_a\,(1 - e^{-[(F/V/\lambda)\times t]})$$

where C_{v_t} = gas concentration in venous blood draining the compartment at time t (the latter being expressed in minutes), C_a = arterial gas concentration, F/V = flow per unit volume for the compartment, expressed as ml/g per min (taking myocardial specific gravity to be 1.0), and λ = tissue-blood partition coefficient.

Assuming that the tissue-blood partition coefficient is 1.0 in all compartments, the degree of saturation achieved in compartments having different flows can be calculated for different periods of test gas delivery. For example, at the end of a saturation period of 4 min, venous gas concentrations would have achieved at least 80% of the

[3] Assuming, as is conventionally done, that equilibrium for partial pressure of inert gas is always reached between tissue and blood at the capillary level, i.e., that tissue-blood gas exchange is limited solely by perfusion and not also by diffusion.

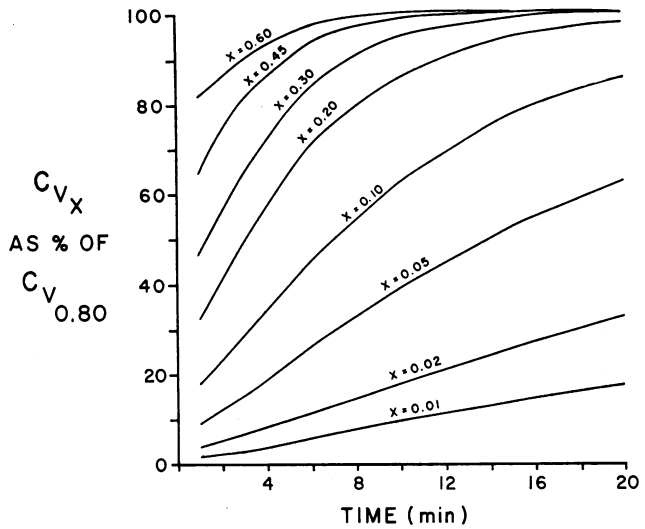

FIGURE 8 Relative venous test gas concentrations for myocardial compartments having different flows per unit volume, after a sudden increment in arterial test gas concentration. The ordinate is the venous gas concentration in a compartment (C_{v_x}) expressed as a percentage of the corresponding venous gas concentration in a compartment having a flow per unit volume of 0.80 ml/g per min ($C_{v_{0.80}}$). The different lines represent compartments with flows per unit volume varying between 0.01 and 0.60 ml/g per min.

arterial gas concentration in compartments having flows of 40 ml/100 g per min or more. Similarly, at the end of a 20 min saturation period, venous gas concentrations would have achieved at least 80% of the arterial gas concentration in compartments having flows of 8 ml/100 g per min. Fig. 8 expresses this same type of information in a slightly different fashion. Venous gas concentrations in compartments with widely varying flows are plotted as percentages of the simultaneously attained venous gas concentration in a compartment having a flow of 80 ml/100 g per min. If the latter value represents a "normal" coronary flow, the figure provides an indication of how completely areas with lower flows will be represented in desaturation curves obtained after different periods of test gas delivery. It is evident that areas having flows between 5 and 30 ml/100 g per min will be represented significantly more completely in curves obtained after a 20 min saturation period than in curves obtained after a 4 min saturation period. It is also evident that very short saturation periods will put areas of low flow at the greatest disadvantage. Indeed, 10–30-sec saturation periods were employed in a few early experiments and were much less effective for demonstrating known heterogeneity of flow than the periods subsequently employed.

One additional and important consideration when evaluating areas of low flow is that over-all coronary venous blood is weighted in favor of areas of higher flow and larger volume. This can be expressed by the following equation:

$$C_v = f_1 C_{v_1} + f_2 C_{v_2} + f_n C_{v_n}$$

where C_v = test gas concentration in over-all coronary venous blood, $C_{v_{1,2...n}}$ = test gas concentration in venous blood draining compartments 1,2...n, and $f_{1,2...n}$ = fraction of total coronary flow originating in compartments 1,2...n. Each individual f is related to the compartment's flow and volume:

$$f_1 = \frac{(F/V)_1}{(F/V)_T} \times \frac{V_1}{V_T}; \quad f_2 = \frac{(F/V)_2}{(F/V)_T} \times \frac{V_2}{V_T}; \text{ etc.}$$

where $(F/V)_{1,2,\text{etc.}}$ = flow per unit volume in compartments 1,2,etc., $(F/V)_T$ = over-all or "average" flow per unit volume for the entire heart, $V_{1,2,\text{etc}}$ = volume of compartments 1,2, etc., and V_T = volume of entire heart.

f is a useful term for considering limitations imposed by the sensitivities of analytical techniques for measuring venous-arterial gas differences. For example, if 20% of the heart has a F/V which is only 15% of the average F/V for the entire heart, its venous drainage will constitute only 3% of total venous outflow. Even assuming complete saturation of such an area before desaturation, the area will be overlooked by analytical techniques incapable of resolving venous-arterial differences of less than 3% of the over-all venous gas concentration at the beginning of desaturation. Since the chromatographic system employed for the present studies could quantitate venous-arterial differences of less than 1% of the initial venous and arterial

gas concentrations, its advantage over conventional techniques is evident.

The present studies were designed with the above considerations in mind and indicate that nonuniformity of blood flow can be detected in venous desaturation curves if appropriate methods of test gas delivery and blood gas analysis are employed. The choice of H_2 as test gas was based on its extremely low solubility in blood ($\alpha = 0.015$ ml/ml per 760 mm Hg) and on its high intrinsic diffusibility. Since solubility of H_2 is only ¼ that of krypton and ⅙ that of xenon, elimination of recirculating H_2 from mixed venous blood in the lungs is appreciably more complete than elimination of krypton, xenon, or some more soluble gas (18). These differences in elimination become increasingly important as the duration of test gas infusion increases, and can complicate the analysis of semilogarithmically plotted venous desaturation data if the time required for the arterial gas concentration to become negligible is prolonged. In the present studies, the measurements of arterial H_2 concentration after H_2 infusions provided direct evidence that arterial H_2 recirculation was not, in these patients, an important consideration. In addition, the 4 min period of H_2 infusion allowed the venous concentration at the beginning of desaturation and the initial portion of the desaturation curve to be determined with more precision than when the dissolved test gas is administered as a sudden single injection (6, 7, 16). In desaturation studies after gas breathing, arterial gas concentrations are never negligible and represent gas entering pulmonary venous blood from poorly ventilated areas of the lungs (19) and gas not eliminated from mixed venous blood in other areas of the lungs. However, the arterial desaturation curve for a gas of slow solubility decreases more rapidly than the curve for a gas of high solubility and H_2 is again advantageous in this regard. In the present studies, arterial H_2 concentrations were sufficiently small and constant after the first few minutes of desaturation to allow the semilogarithmic plots shown in Figs. 4–7. These data also indicate a greater heterogeneity of flow in dogs after coronary occlusion than in dogs before coronary occlusion, and in patients with coronary artery disease than in patients without coronary artery disease. Although arbitrary, this manner of expressing increased heterogeneity is similar to that employing deviations from a single exponential in curves after H_2 infusions.

Two additional factors which merit discussion when evaluating small venous-arterial differences are right atrial admixture in sampled coronary venous blood and the representation in coronary venous blood of adipose tissue. As mentioned above, the possibility that right atrial blood "contaminates" blood sampled from the great cardiac vein in the dog has been excluded by a previous investigation (10). The data presented for patients indicate that right atrial admixture is unlikely in the distal coronary sinus and great cardiac vein but is frequent in the proximal coronary sinus. As shown in Table III, the admixture would frequently be undetected by isolated measurements of coronary venous oxygen saturation. Our current practice is to accept only samples drawn with the catheter tip more than 2 cm from the coronary sinus ostium as seen in the frontal projection.

The likelihood that venous drainage from adipose tissue contributed significantly to the presently reported venous-arterial differences seems remote. Although direct measurements of blood flow to cardiac adipose tissue are not available, flow to adipose tissue elsewhere in the body has been estimated to be 1–2 ml/100 g per min (20). If this estimate were applicable to cardiac adipose tissue and the adipose tissue comprised as much as 10% of the heart's total volume, its venous drainage would form only 0.1–0.3% of total coronary flow (assuming an over-all flow of 80 ml/100 g per min). In addition, because the tissue-blood partition coefficient of H_2 for adipose tissue is approximately 3 (21), the rate constant of saturation, $(F/V)/\lambda$, for adipose tissue should be only ⅓ that of a similarly perfused area of muscle. As a result, even after 20 min of H_2 breathing, the concentration of H_2 achieved in venous blood draining adipose tissue should be only a few per cent of that achieved in venous blood draining the rest of the heart. It is also of interest that the contribution of adipose tissue to measured gas exchange may be a considerably greater problem in studies employing precordial counting techniques (17).

Heterogeneity of coronary flow also has important implications for numerical calculations of flow (2, 4, 7, 12–17, 22). When desaturation follows test gas breathing, flow is calculated from the change in tissue gas concentration and the mean

venous-arterial gas difference. The dangers of failing to identify a prolonged venous-arterial gas difference have already been discussed. An additional problem is that the change in tissue gas concentration is calculated from the measured change in venous gas concentration and the tissue-blood partition coefficient. Since sampled coronary venous blood is weighted in favor of areas of high flow, the calculated change in tissue concentration will be too great for an area of low flow when saturation is incomplete, and will provide an inaccurate index of the change in average tissue concentration for the entire heart. Calculations of flow after dissolved gas infusions are currently controversial. When flow is calculated from the slope of the straight line which best fits the semilogarithmically plotted venous desaturation data during the first few minutes of desaturation, the assumption is made that flow is homogeneously distributed throughout the heart. Evidence indicating that flow calculated in this fashion agrees well with directly measured flow has been obtained in normal dogs by some (7) but not all (22) workers. Others avoid exponential treatments entirely and calculate flow per unit volume of distribution of tracer from the mean transit time of the tracer through the system (16). Table I illustrates some of the differences in calculated flow which can be obtained with the data in Figs. 1–3.[4] The fact that semilogarithmically plotted desaturation curves did not form single exponentials supports evidence that myocardial flow is not homogeneous (e.g., references 22, 24). The curves came closest to forming single exponentials in the anesthetized dogs before coronary occlusion, and flows calculated from rate constants of desaturation averaged only 6 and 9% more than those calculated from the conventional Kety-Schmidt equation for average flow. In the same animals after coronary occlusion, when desaturation curves deviated appreciably from single exponentials, flows calculated from rate constants averaged 19 and 31% more than those calculated from the conventional equation. This presumably indicates an overestimation of flow by the rate constant methods because of failure to include areas of reduced flow resulting from the occlusions. In addition, since the post-occlusion curves were integrated only for the time periods shown in Figs. 1 and 2, even the conventional average flows may have overlooked portions of persistent venous-arterial H_2 differences. Flows calculated from rate constants averaged 4 and 7% more than those calculated from the conventional equation in patients without coronary artery disease, but 16 and 29% more in patients with coronary artery disease. These findings also raise the possibility that resting flow per unit volume is indeed smaller in patients with coronary artery disease than in patients without coronary disease.

Table II illustrates differences in flow calculated from the data in Figs. 4–7. If desaturation curves had been terminated after 10 min instead of after 20 min, coronary flows would have averaged 103% of the 20 min values in the patients without coronary artery disease, but 115% of the 20 min values in patients with coronary disease. In dogs, the corresponding averages would have been 103% before coronary occlusion and 110% after coronary occlusion. Similarly, if the venous and arterial gas concentrations were considered to have been equal when the venous-arterial gas difference was reduced to 5% of the initial venous gas concentration, the corresponding averages would have been 116% for the normal patients, 122% for the coronary artery patients, 118% for the dogs before coronary occlusion, and 123% for the dogs after coronary occlusion. These latter calculations emphasize a limitation of analytical techniques which are incapable of resolving venous-arterial differences of less than 5% of the initial venous concentration. In considering all these figures, it must be emphasized that even the techniques which were employed may have overlooked areas of extremly low flow or of relatively low flow but extremely small volume. In addition, generalizations about absolute flow must be guarded because of the relatively small number of observations and the lack of a more "primary" standard of flow measurement against which inert gas methods may

[4] The flows calculated in this table and in Table II represent only a few of the possible treatments of the data presented. The calculations involving rate constants of desaturation were included because of their current, reasonably wide usage (but not because the authors believe myocardial flow to be homogeneous). Although a variety of multiexponential analyses could have been attempted, the observed curves could not be resolved into a consistent number of exponentials and, in view of the known limitations of these approaches (23), the matter was not pursued further.

be compared in man. The more important implication is that flows calculated from inert gas data can be heavily dependent upon the details of the technique which is employed when flow is heterogeneous. By judicious choice of techniques, it appears possible to improve capabilities for detecting heterogeneous flow and for quantitating total flow in the presence of heterogeneous flow.

ACKNOWLEDGMENTS

This work was supported by U. S. Public Health Service Research Grants HE-09587 and HE-07539 from the National Heart Institute, and by research grants from the Heart Association of Western New York and the United Health Foundation of Western New York.

REFERENCES

1. Sullivan, J. M., W. J. Taylor, W. C. Elliott, and R. Gorlin. 1967. Regional myocardial blood flow. *J. Clin. Invest.* **46**: 1402.
2. Eckenhoff, J. E., J. H. Hafkenschiel, M. H. Harmel, W. T. Goodale, M. Lubin, R. J. Bing, and S. S. Kety. 1948. Measurement of coronary blood flow by the nitrous oxide method. *Am. J. Physiol.* **152**: 356.
3. Bing, R. J., M. M. Hammond, J. C. Handelsman, S. R. Powers, F. C. Spencer, J. E. Eckenhoff, W. T. Goodale, J. H. Hafkenschiel, and S. S. Kety. 1949. The measurement of coronary blood flow, oxygen consumption and efficiency of the left ventricle in man. *Am. Heart J.* **38**: 1.
4. Sapirstein, L. A., and E. Ogden. 1956. Theoretic limitations of the nitrous oxide method for the determination of regional blood flow. *Circulation Res.* **4**: 245.
5. Goodale, W. T., and D. B. Hackel. 1953. Measurement of coronary blood flow in dogs and man from rate of myocardial nitrous oxide desaturation. *Circulation Res.* **1**: 502.
6. Cohen, L. S., W. C. Elliott, and R. Gorlin. 1964. Measurement of myocardial blood flow using krypton 85. *Am. J. Physiol.* **206**: 997.
7. Ross, R. S., K. Ueda, P. R. Lichtlen, and J. R. Rees. 1964. Measurement of myocardial blood flow in animals and man by selective injection of radioactive inert gas into the coronary arteries. *Circulation Res.* **15**: 28.
8. Klocke, F. J. 1967. Measurement of trace amounts of inert gases in blood by gas chromatography. *In* Lectures on Gas Chromatography, 1966. L. R. Mattick, and H. A. Szymanski, editors. Plenum Press Inc., New York. 75.
9. Goodale, W. T., M. Lubin, J. E. Eckenhoff, J. H. Hafkenschiel, and W. G. Banfield, Jr. 1948. Coronary sinus catheterization for studying coronary blood flow and myocardial metabolism. *Am. J. Physiol.* **152**: 340.
10. Koberstein, R. C., and F. J. Klocke. 1968. Right atrial admixture in coronary venous blood. *Federation Proc.* **27**: 631.
11. Klocke, F. J., D. G. Greene, and R. C. Koberstein. 1968. Indicator-dilution measurement of cardiac output with dissolved hydrogen. *Circulation Res.* **22**: 841.
12. Rowe, G. G. 1959. The nitrous-oxide method for determining coronary blood flow in man. *Am. Heart J.* **58**: 268.
13. Kety, S. S. 1960. Theory of blood-tissue exchange and its application to measurement of blood flow. *In* Methods in Medical Research. H. D. Bruner, editor. The Year Book Publishers Inc., Chicago. **8**: 223.
14. Gregg, D. E., and L. C. Fisher. 1963. Blood supply to the heart. *In* Handbook of Physiology, Section 2: Circulation. W. F. Hamilton and P. Dow, editors. American Physiological Society, Washington. **2**: 1517.
15. Rowe, G. G., C. A. Castillo, S. Afonso, and C. W. Crumpton. 1964. Coronary flow measured by the nitrous-oxide method. *Am. Heart J.* **67**: 457.
16. Zierler, K. L. 1965. Equations for measuring blood flow by external monitoring of radioisotopes. *Circulation Res.* **16**: 309.
17. Klocke, F. J., D. R. Rosing, and D. E. Pittman. 1968. Inert gas measurements of coronary blood flow. *Am. J. Cardiol.* In press.
18. Farhi, L. E. 1967. Elimination of inert gas by the lungs. *Respirat. Physiol.* **3**: 1.
19. Klocke, R. A., and L. E. Farhi. 1964. Simple method for determination of perfusion and ventilation-perfusion ratio of the underventilated elements (the slow compartment) of the lung. *J. Clin. Invest.* **43**: 2227.
20. Jones, H. B. 1951. Gas exchange and blood-tissue perfusion factors in various body tissues. *In* Decompression Sickness. J. F. Fulton, editor. W. B. Saunders Co., Philadelphia. 278.
21. Kety, S. S. 1951. The theory and applications of the exchange of inert gas at the lungs and tissue. *Pharmacol. Rev.* **3**: 1.
22. Bassingthwaighte, J. B., T. Strandell, and D. E. Donald. 1966. Coronary clearance of intra-arterial xenon and antipyrine. *Clin. Res.* **14**: 424.
23. Van Liew, H. D. 1962. Semilogarithmic plots of data which reflect a continuum of exponential processes. *Science.* **138**: 682.
24. Brandi, G., W. M. Fam, and M. McGregor. 1968. Measurement of coronary flow in local areas of myocardium using xenon 133. *J. Appl. Physiol.* **24**: 446.