Average Coronary Blood Flow Per Unit Weight of Left Ventricle in Patients With and Without Coronary Artery Disease

By Francis J. Klocke, M.D., Ivan L. Bunnell, M.D., David G. Greene, M.D., Stephen M. Wittenberg, M.D., and John P. Visco, M.D.

SUMMARY

Average left ventricular flow per unit mass (F/W) has been evaluated at rest in 20 normal individuals and 26 patients with arteriographically proven, advanced coronary artery disease, using inert gas techniques modified to take into account methodological problems presented by heterogeneous perfusion within the ventricle. Preliminary studies in a canine model in which coronary flow could be measured directly before and after coronary occlusion indicated (1) that inert gas techniques utilizing venous sampling are suitable for abnormal situations when appropriately long periods of saturation and desaturation, and careful resolution of prolonged venous-arterial differences, are employed; and (2) that traditional inert gas methods are not adequate when F/W is abnormally heterogeneous. Using helium as a tracer, coronary disease patients showed a systematic reduction, in comparison to normal individuals, in average left ventricular F/W at rest (54 ± 11 vs 70 ± 13 ml/min/100 g, P < 0.01). Simultaneous studies with traditional nitrous oxide and krypton techniques did not show this difference because of the methodological limitations of these techniques in the presence of abnormally heterogeneous F/W. We conclude: (1) that useful, accurate measurements of F/W can be obtained in coronary disease if appropriate methodological precautions are taken; and (2) that appreciable portions of the left ventricle have an abnormally low F/W, even at rest, in patients with advanced coronary disease.

Additional Indexing Words:
Coronary blood flow
Gas chromatography
Heterogeneous myocardial perfusion
Tissue-blood partition coefficients
Inert gas flow measurements
Validation of flow-measurement techniques

Although the clinical manifestations of coronary atherosclerosis are agreed to be related to an imbalance between myocardial oxygen demand and supply, measurements of coronary blood flow have been of limited value in clarifying specific clinical situations and general pathophysiological principles. Most existing measurements have been obtained using modifications of the inert gas technique developed by Kety and Schmidt for the cerebral circulation\(^1\) and subsequently modified by Eckenhoff et al.\(^2\) for the coronary circulation. There has been general agreement that average flow per unit weight (F/W) for the left ventricle does not show a systematic reduction in patients with coronary artery disease studied at rest in the cardiac catheterization laboratory.\(^3\) However, in view of the known heterogeneity of flow in coronary disease, it has not been clear that the reported measurements have been methodologically adequate to ensure inclusion of localized areas within the heart having a below-average perfusion. One difficulty in resolving this question has been the lack of experimental data validating specific inert gas techniques in situations in which myocardial perfusion is abnormally heterogeneous. The present investigation was intended (1) to examine the validity of measurements employing three different inert gas techniques in an animal model in which coronary flow could be measured directly before and after coronary occlusion; and (2) to re-examine testing levels of average F/W in conscious patients with and without coronary disease. During the latter studies, measurements...
employing recent modifications of inert gas techniques were compared with simultaneous measurements employing more traditional approaches. The findings indicate that traditional methodology is not adequate in the presence of coronary disease and that there is indeed a systematic reduction in average F/W in patients with arteriographically advanced coronary disease studied at rest in the cardiac catheterization laboratory.

Methods

Validation Studies

A right heart bypass preparation was utilized so that total coronary outflow could be measured directly by timed collection in a graduated cylinder during inert gas measurements of average F/W (fig. 1). Seventeen mongrel dogs were anesthetized with sodium pentobarbital, intubated and ventilated with a constant volume pump. Atelectasis was minimized by 2-4 cm of continuous expiratory positive pressure. The chest was opened through a median sternotomy, appropriate structures were isolated and the heart suspended in a pericardial cradle. Sodium heparin, 10,000 units, was administered intravenously and supplemented with additional 5,000 unit doses at 30 min intervals. Systemic venous return drained through superior and inferior vena caval cannulae into an external reservoir primed with blood from a donor animal. An occlusive roller pump passed blood at a constant rate from the reservoir through a heat exchanger and a Bardic cannula inserted into the main pulmonary artery through a right ventricular stab wound. Retrograde leakage of blood into the right ventricle was avoided by doubly ligating the main pulmonary artery around the cannula. Total coronary outflow drained to a second reservoir through another cannula, having multiple side holes, which was inserted into the right ventricle through the ayzyos vein. The contents of this reservoir were returned to the systemic venous reservoir at 2-4 minute intervals. When coronary flow was to be measured directly, right heart outflow was diverted to a graduated cylinder for timed 30-60 sec collections. Flow to the nonworking right ventricle was minimized by ligating the right coronary artery high in the A-V groove and its superficial branches to the conus as they reached the anterior portion of the ventricle. This procedure produced obvious cyanosis of the right ventricular free wall except for the few millimeters nearest the septum (supplied by tributaries of the left coronary artery). Surface gas transfer, which is known to occur in open-chest preparations, was minimized by enclosing the ventricles in a closely fitting latex covering. Arterial pressure was monitored through a catheter in the aortic arch, which was also used to sample systemic arterial blood during inert gas measurements. A left ventricular catheter was available for injection of dissolved gas tracer. Coronary venous blood was sampled through a 7 or 8 F Sones catheter introduced into the coronary sinus from the right atrial appendage and advanced 2-3 cm beyond the coronary sinus ostium. Systemic arterial temperature was monitored with a thermistor inserted into the descending aorta and the heat exchanger adjusted to maintain aortic temperature constant within ±1°C at 35-38°C. Prior to coronary ligation, systolic and diastolic arterial pressures ranged from 80 to 175 mm Hg (average 121 mm Hg) and 60 to 110 mm Hg (average 74 mm Hg), respectively. Corresponding values after coronary ligation were 85 to 160 mm Hg (average 117 mm Hg) and 60 to 100 mm Hg (average 73 mm Hg). Heart rate varied from 75 to 165 beats/min (average 122 beats/min) before coronary ligation, and from 80 to 145 beats/min (average 111 beats/min) after ligation.

Different inert gases were studied simultaneously to evaluate the effects of varying periods of saturation and desaturation on the measurement of average F/W. Measurements employing helium (He) were particularly designed to include areas of low flow while those employing nitrous oxide (N₂O) and krypton (Kr) were intended to duplicate techniques commonly used in other laboratories. For He measurements, the inspirate was switched from room air to a mixture containing 75% He, 4% N₂, and 21% O₂ twenty minutes prior to the onset of desaturation. For N₂O measurements, 4% N₂O was substituted for the 4% N₂ during the last 10 minutes preceding desaturation. For Kr measurements, 5-10 ml of isotonic saline saturated with dissolved Kr was injected into the left ventricle at the onset of desaturation. Fifteen to twenty pairs of 2.0 ml arterial and coronary venous blood samples were drawn during the last few minutes prior to desaturation and the 20-25 minutes immediately thereafter and analyzed for inert gas concentrations with a gas chromatograph. Helium analyses were performed on alternate pairs using a unit described previously. N₂O and Kr analyses were performed on the remaining pairs, using a similar unit. The carrier gas was helium and the test gas sample passed successively through an 8-10 foot column of Poropak Q (for isolation of N₂O from the remainder of the sample), a thermistor detector (for measurement of N₂O), an 8-10 foot column of activated charcoal (for isolation of Kr) and a second thermistor detec-

![Figure 1](http://circ.ahajournals.org/DownloadedFrom/000000158200000021662.pdf)

Canine right heart bypass preparation for validation studies. (Ao = aorta; PA = pulmonary artery; LA = left atrium; LV = left ventricle; SVC = superior vena cava; IVC = inferior vena cava; RA = right atrium; RV = right ventricle; CS = coronary sinus; LAD = left anterior descending coronary artery; RCA lig. = right coronary artery ligature; CS samp. cath. = coronary sinus sampling catheter; Res. = reservoir; Heat exc. = heat exchanger).
tor (for measurement of Kr). Tracer concentrations were quantified from the heights of the appropriate chromatographic peaks and expressed in arbitrary units (preliminary experiments having verified linear relationships between tracer concentration and peak height). Helium values for average F/W were obtained using the Kety-Schmidt formula and desaturation curves covering the entire 20-25 minute period of observation. N2O values for F/W were obtained using the same formula and curves covering only the initial 10 minutes of desaturation. Tissue-blood partition coefficients were calculated as described subsequently.

Measurements of average F/W were obtained before and/or approximately one hour after production of a localized myocardial infarction. The latter was accomplished by ligating several adjacent diagonal branches of the left anterior descending coronary artery supplying the anterior free wall of the left ventricle (fig. 1). Total coronary outflow was measured repeatedly prior to the onset of tracer administration to verify the existence of a stable state. Timed outflow collections were obtained at 1-2 min intervals throughout desaturation and average values for directly measured outflow converted from total flow (ml/min) to F/W (ml/min/100 g) by dividing measured outflow by the postmortem weight of the left ventricle, septum and small perfused segment of adjacent right ventricular free wall (the latter averaging 7.5 ± 0.9 [sn% of the total weight).

Clinical Studies

Forty-six patients were studied in conjunction with diagnostic cardiac catheterization after having given informed consent. Twenty were classified as having normal values for the Kety-Schmidt formula and desaturation curves covering the entire 20-25 minute period of observation. N2O values for F/W were obtained using the same formula and curves covering only the initial 10 minutes of desaturation. Tissue-blood partition coefficients were calculated as described subsequently.

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Partition Coefficients

Partition coefficients were measured directly in additional in vitro experiments. Twenty to sixty gas specimens of left ventricular myocardium were obtained from human hearts at the time of autopsy and from dog hearts immediately following pentobarbital anesthesia. The human tissues were from individuals in whom the primary cause of death was not heart disease; a few specimens showed patchy myocardial fibrosis due to coronary atherosclerosis but results were not demonstrably different from other specimens. All specimens were initially stripped of epicardium and endocardium and cut into small slices, omitting visible blood vessels and connective tissue. The slices were divided into two or three portions, weighed, diluted on a 1:1, 1:2 or 1:3 basis with isotonic saline and homogenized with a small Waring blender and an ultrasonic homogenizer. Each homogenate was equilibrated in a Farhi tonometer at 37°C with a gas mixture containing He, N2O or Kr, or a combination of these tracers. Isotonic saline was tonometered with the same gas mixture and 2.0 ml aliquots of each equilibrated homogenate and saline were analyzed chromatographically as outlined above. A tissue-saline partition coefficient expressing the amount of tracer contained in 1 g of tissue as a fraction of that contained in 1 ml of saline was calculated for each gas from the fraction of myocardium in the homogenate and the chromatographic peak heights for the test gas in the homogenate and saline (assuming myocardial specific gravity to be 1.05). Coefficients for the 2-3 homogenates prepared from each tissue specimen were averaged (the individual values always agreeing within ±10% of one another).

Since the solubilities of He, N2O and Kr differ significantly in plasma and erythrocytes, data were also collected relating the relative solubility of each gas in blood and saline to hematocrit. Blood specimens were collected from six healthy laboratory workers as well as seven dogs anesthetized with pentobarbital. A portion of each specimen was centrifuged to obtain plasma and a high-hematocrit concentrate. Isotonic saline, plasma, the original specimen and the high hematocrit concentrate were equilibrated in a Farhi tonometer with a gas mixture containing He, N2O and Kr and analyzed as described above. The chromatographic peak height of each plasma or blood sample was expressed as a fraction of the peak height of the corresponding saline sample, and human and canine data were each pooled to obtain least-squares regression lines relating blood-saline partition coefficient (the amount of tracer contained in 1 ml of blood expressed as a fraction of that contained in 1 ml of saline) to hematocrit.

Tissue-blood partition coefficients for individual measurements of F/W were obtained by dividing the average human or canine tissue-saline partition coefficient by the blood-saline partition coefficient appropriate to the hematocrit.
Table 1

Partition Coefficient Determinations

<table>
<thead>
<tr>
<th></th>
<th>Human</th>
<th>Canine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N mean ± sd</td>
<td>N mean ± sd</td>
</tr>
<tr>
<td>He</td>
<td>11</td>
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</tr>
<tr>
<td></td>
<td>0.85 ± 0.04</td>
<td>0.85 ± 0.05</td>
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<tr>
<td>Kr</td>
<td>7</td>
<td>10</td>
</tr>
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<td>1.09 ± 0.07</td>
<td>1.08 ± 0.04</td>
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<tr>
<td>N₂O</td>
<td>11</td>
<td>7</td>
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<tr>
<td></td>
<td>0.95 ± 0.06</td>
<td>0.96 ± 0.06</td>
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</table>

Blood-Saline (37°C):

Regression equation

He
- Human: P.C. = 0.96 - 0.17 (Hct) 0.018
- Canine: P.C. = 0.95 - 0.17 (Hct) 0.021
Kr
- Human: P.C. = 1.06 + 0.50 (Hct) 0.036
- Canine: P.C. = 1.02 + 0.78 (Hct) 0.032
N₂O
- Human: P.C. = 0.95 + 0.16 (Hct) 0.046
- Canine: P.C. = 0.97 + 0.19 (Hct) 0.032

Abbreviations: N = number of left ventricles tested; sd = standard deviation; P.C. = partition coefficient; Hct = hematocrit (ml/100 ml); see = standard error of estimate.

Results

Partition Coefficients

Data for tissue/saline partition coefficients and regression lines relating blood/saline partition coefficients to hematocrit are shown in table 1. Tissue/blood partition coefficients calculated for a hematocrit of 40 in man were 0.95 for He, 0.94 for N₂O and 0.87 for Kr.*

Validation Studies

Representative sets of desaturation curves before and after left anterior descending ligation are illustrated in figures 2 and 3. Data from all 17 animal studies are given in table 2 and figure 4. Prior to left anterior descending ligation, values for F/W obtained from He desaturation curves averaged 99 ± 10 (sd)% of directly measured F/W and the mean of the differences between He and metered flow was 7% of metered flow. Corresponding averages for N₂O and Kr were 104 ± 11% and 98 ± 11%. Following left anterior descending ligation, small prolonged venous-arterial differences were apparent in the He desaturation curves, while differences from pre-ligation curves could not be identified for N₂O and Kr. He flows averaged 96 ± 9% of directly measured flow and the mean of the differences between He and metered flow was 9% of metered flow. N₂O and Kr flows exceeded directly measured flow (N₂O = 124 ± 22% of directly measured flow, P < 0.02 [paired t using absolute values for F/W] and Kr = 122 ± 14% of directly measured flow, P < 0.01 [also paired t using absolute values for F/W]).

Clinical Studies

Data from all patients, including arteriographic "scores" as described by Rowe et al.,† are given in

* Tissue-blood partition coefficients in this paper relate the equilibrium concentrations of tracer in 1 g of myocardium and 1 ml of blood. In some other studies, these coefficients have been expressed in terms of the relative concentrations of tracer in 1 ml of myocardium and 1 ml of blood, with a value for myocardial specific gravity being added subsequently in the calculation of F/W. The present values would be 5% larger if expressed in this form.

Figure 2
Arterial and coronary sinus desaturation curves for He before and after coronary ligation in a canine right heart bypass study (animal 7, table 2).

Figure 3
Arterial and coronary sinus desaturation curves for N₂O and semilogarithmically plotted coronary sinus desaturation curves for Kr in the same canine study illustrated in figure 2.
Table 2
Comparisons of Inert Gas and Directly Measured Flows in Dogs on Right Heart Bypass

<table>
<thead>
<tr>
<th>No.</th>
<th>Weight-LV and septum g</th>
<th>Total outflow ml/min ± sd</th>
<th>Outflow per unit weight ml/min/100 g</th>
<th>Inert gas flows ml/min/100 g</th>
<th>He</th>
<th>N₂O</th>
<th>Kr</th>
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<td>12</td>
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<td>13</td>
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</table>
MEASURED values of as pressed closed circles indicate validation studies.

Comparisons of inert gas and directly measured flows in canine validation studies. Each data point represents an inert gas flow expressed as a percentage of the simultaneous directly measured flow. Absolute values of flow are not shown. Lines connecting open and closed circles indicate observations before and after coronary ligation in individual animals. Solid horizontal bars represent mean values for each set of data. P values were calculated using paired t-tests and absolute values of inert gas and directly measured F/W. (NS = not significant).

Tables 3 and 4 and figure 5. Representative studies from a normal patient and a patient with coronary artery disease are illustrated in figures 6 and 7. Values for average F/W using He averaged 70 ± 13 ml/min/100 g in the normal patient group and 54 ± 11 ml/min/100 g in the coronary disease group (P < 0.01). Measurements employing N2O averaged 70 ± 9 ml/min/100 g in 12 normal patients (108 ± 16% of simultaneous measurements employing He) and 69 ± 11 ml/min/100 g in 13 coronary disease patients (138 ± 18% of simultaneous measurements employing He, P < 0.01, paired t, fig. 8). Measurements employing dissolved Kr averaged 83 ± 19 ml/min/100 g in 12 coronary disease patients (154 ± 29% of simultaneous measurements employing He, P < 0.01, paired t, fig. 8). Only one such comparison was available in a normal patient (figs. 6 and 8).

Discussion

Methodological Considerations and Previous Validation of Inert Gas Measurements of F/W

These studies indicate a systematic difference in average F/W at rest in patients with and without coronary artery disease. Since this finding is at variance with previous reports, it is pertinent to consider methodological differences between this and other studies and to review animal studies in which inert gas
measurements have been compared with direct measurements of coronary flow. As discussed in more detail previously,\(^9\) three requirements are especially important for commonly used inert gas techniques:

1. Concentration of tracer must be uniform throughout the myocardium at both the onset and completion of the flow measurement. If F/W is truly homogeneous, this requirement can be achieved with any duration of saturation or desaturation. When flow is not homogeneous, venous outflow originates predominantly from areas having a higher-than-average F/W and changes in average tissue gas concentration (the numerator of the Kety-Schmidt equation) which are inferred from changes in venous (or arterial) gas concentration are incorrectly high until a uniform tissue gas concentration has been achieved.

2. Analytical methods for measuring changes in tissue or blood gas concentration must be sufficiently sensitive to quantitate small changes in tracer concentration reflecting areas of below-average F/W. These changes become evident only after the initial portion of the measurement and appear as small but prolonged venous-arterial (or tissue-arterial) test gas differences.

3. For calculation of F/W from a monoexponential rate constant of desaturation following bolus injection of tracer, F/W must be uniform throughout the area of myocardium being evaluated. In addition, the rate of exchange of tracer between tissue and capillaries must not be limited by the physical process of diffusion.

(A) Techniques Employing Sampling of Coronary Venous Outflow

Previous comparisons of inert gas measurements of F/W and direct measurements of F/W have been limited in number and have not included circumstances in which heterogeneity of F/W has been increased to an abnormal degree. Direct validation of techniques employing coronary sinus sampling rests heavily on the careful work of Gregg and co-workers with N\(_2\)O.\(^4\) After defining problems related to surface gas loss and other factors, N\(_2\)O measurements during 10-15 minute saturation periods were compared to values of F/W obtained from measurements of left coronary inflow and postmortem left coronary injection. In nine animals, N\(_2\)O flows averaged 101 ± 14% of directly measured flows (range 78-121%). The initial work of Eckenhoff et al.\(^2\) also attempted this type of comparison but, for reasons outlined by Gregg, a definitive conclusion was not possible. More recently, Aukland et al.\(^10\) reported 19 comparisons of directly measured venous outflow and F/W calculated from monoexponential clearance constants following several minutes of dissolved H\(_2\) infusion in six isolated, nonworking hearts. H\(_2\) values for F/W averaged 97 ± 7% (range 72-105%) of directly measured F/W, the latter being expressed as cc/min/100 g of total heart. The successful use of the monoexponential clearance constant implied that flow was relatively homogeneous in the particular experimental preparation. This conclusion was supported by the similarity of additional curves following bolus injection of H\(_2\) to those following the more prolonged H\(_2\) infusion.

The present observations in the right heart bypass preparation prior to coronary ligation support the validity of measurements employing conventional N\(_2\)O techniques and bolus injection of tracer with coronary sinus sampling in the working heart when regional variations in F/W are small. However, in view of the findings after coronary ligation, conventional techniques have important limitations when coronary perfusion is abnormally heterogeneous. The overestimates of average F/W with Kr seem readily understandable. When employing bolus injection, distribution of tracer corresponds to distribution of total flow and it is impossible to achieve the requisite uniformity of tissue tracer concentration when regional F/W varies. The use of a monoexponential rate constant reduces the likelihood of even partial representation of areas of below-average F/W in the value for average F/W and, when employed in conjunction

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Figure 5

**Individual values of average LV F/W in normal individuals and coronary disease patients.** Solid horizontal bars represent mean values for the two groups. Note reasonably good separation of groups above 70 and below 50 ml/min/100 g, but large overlap between 50 and 70 ml/min/100 g. As discussed in the text, the group means differ significantly (P < 0.01).
Arterial and coronary sinus desaturation curves for He and N₂O and semilogarithmically plotted desaturation curve for Kr in a normal individual (case 1, table 3).

Arterial and coronary sinus desaturation curves for He and N₂O and semilogarithmically plotted desaturation curve for Kr in a coronary disease patient (case 9, table 4).
Comparisons of \( N_2O \) and Kr values of F/W with simultaneous He values of F/W in human studies. Each data point represents an \( N_2O \) or Kr flow expressed as a percentage of the simultaneous He flow. Absolute values of F/W are not shown. Solid horizontal bars represent mean values for each set of data; P values were calculated using paired t-tests and absolute values of F/W.

(B) Coronary Sinus Drainage as an Index of LV Perfusion

As pointed out by Gregg and Fisher,\(^1\) the use of coronary sinus blood samples as an index of F/W for the left ventricle and septum is less well established in man than in dog. The postmortem injection studies of Hood\(^12\) are encouraging in demonstrating (1) drainage into the coronary sinus of 96% of veins >1.0 mm in diameter originating in the left ventricular free wall and septum; and (2) only 17% of veins entering the coronary sinus originating from other structures. In the present studies, the coronary sinus catheter was inserted at least 2 cm beyond the coronary sinus ostium (as seen in the frontal projection) to avoid right atrial admixture.\(^5\) This no doubt minimized the contribution to our measurements of the postero-medial left ventricular free wall and the posterior portion of the interventricular septum and values for “average” F/W should be interpreted with this in mind. It happened that our coronary patient group included only one individual with isolated right coronary artery disease. The position of our coronary sinus catheters also makes it unlikely that the observed decreases in F/W in coronary artery disease were due to sampling a larger than usual portion of right ventricular drainage.

(C) Techniques Employing Precordial Counting

Although measurements employing coronary sinus sampling differ in important respects from those employing precordial counting,\(^9\) our reductions in average F/W in coronary patients are also at variance with findings of several groups using bolus injection of Xe\(^{133}\) into the left coronary artery and a monoexponential rate constant derived from a conventional scintillation crystal. While an area of below-average F/W has a potentially larger representation in a precordial desaturation curve than a coronary sinus desaturation curve,\(^\text{9}\) the basic requirements of even saturation and resolution of prolonged tissue-arterial differences again apply. As with Kr, bolus injection results in distribution of tracer according to flow rather than volume and the monoexponential calculation assumes homogeneity of F/W. Special problems are also presented by the slower rate of Xe clearance noted after the first minute or two of desaturation. This appears related to the movement of the highly lipid-soluble tracer into adipose tissue and/or delayed elimination of tracer from alveolar gas spaces included within the field “seen” by the external crystal. Calculations of F/W which include this latter portion of a desaturation curve give values which are patently unreasonable and have no doubt influenced the decision of several groups to resort to monoexponential calculation. The difficulties in fitting monoexponential clearance constants to Xe data have been emphasized by, among others, Zierler\(^3\) and Bassingthwaighte.\(^14\) Sampling of adipose tissue during Xe washout and simultaneous studies with antipyrine and Xe\(^14\) both suggest that even “early” rate constants are affected by movement of Xe into adipose tissue, and delayed clearance therefrom. These various potential problems were pointed out and considered carefully by Ross and his colleagues in their original description of Xe\(^{133}\) technique.\(^15\) In addition to a number of studies relating rate constants of clearance to variations of flow in relative terms, they demonstrated agreement between directly measured flow and 14 values obtained with Kr\(^{85}\) and Xe\(^{133}\) in three animals. The validity of measurements employing Kr\(^{85}\) and
precordial counting had also been considered by Herd and his colleagues in 1962. A close correlation was found between metered left coronary inflow and Kr\textsuperscript{85} F/W in each of four dogs, although measured inflow was not converted into F/W because of uncertainty about the volume of tissue perfused. Additional comparisons of Xe\textsuperscript{133} F/W and directly measured flow have been reported by Bassingthwaighte et al.\textsuperscript{14} and Shaw et al.\textsuperscript{17} However, validation of the most commonly used Xe methodology is not available in circumstances in which heterogeneity of perfusion has been increased to an abnormal degree. The pitfalls demonstrated by Shaw et al. using autoradiographic techniques after canine coronary occlusion\textsuperscript{17} emphasize the importance of further validation if the Xe technique is to continue to be used in coronary disease. While some of the difficulties related to heterogeneity of F/W can be obviated by the ingenious use of detector systems to examine localized areas within the heart,\textsuperscript{18, 19} the general limitations of bolus injection and monoexponential extrapolation apply to the localized area. In view of the increasing evidence for transmural variation of flow in abnormal hemodynamic states,\textsuperscript{20, 21} caution seems advisable in translating Xe rate constants into specific values for F/W even in topographically localized areas. Directionally incorrect conclusions about changes in average F/W related to interventions seem at least theoretically possible.

(D) Partition Coefficients

Direct measurements of partition coefficients have previously been reported for N\textsubscript{2}O by Kozam et al.\textsuperscript{22} The findings were similar to those reported in table 1 and there was verification that N\textsubscript{2}O solubility did not differ significantly in hearts with and without coronary artery disease. Since we were unable to measure the solubility of helium in scarred myocardium directly, we have assumed that partition coefficients for He also do not differ systematically in patients with and without coronary disease. The slope of our N\textsubscript{2}O regression line relating relative blood and saline solubilities to hematocrit is positive but small and the routine use of a tissue-blood partition coefficient of 0.94 ml/g would seem suitable. The slope of the corresponding regression line for helium is negative (because He is less soluble in erythrocytes than plasma), and 0.95 ml/g might be a reasonable value for routine use as tissue-blood partition coefficient. In the case of Kr, myocardial solubility is not known to have been measured directly previously. The usual procedure has been to assume a tissue-blood partition coefficient of 1.0, pointing out that this value has been measured directly for brain tissue. The present data suggest that the solubility of Kr in myocardium is systematically less than in blood and that tissue-blood partition coefficients for Kr vary significantly with hematocrit.

(E) Other Considerations

From the practical point of view, the greatest limitation in obtaining a methodologically satisfactory measurement of F/W is the time involved (40 minutes after preliminary positioning of catheters, etc.). The standard deviations of directly measured F/Ws in table 2 indicate the degree to which the requirement of "stationarity"\textsuperscript{23} was met in the present animal studies. Comparable information is not available in the patient studies, although there seems no reason to suspect a selectively unsteady state in the coronary disease group. Also of potential concern is the contribution to the measured exchange of extracardiac structures. While the amount of superficial adipose tissue is greater in the human heart than the canine heart, measurements of oil-water solubility ratios in our laboratory indicate that this parameter is 50% greater for N\textsubscript{2}O than He. This is against the possibility that the observed differences between He and N\textsubscript{2}O F/Ws in coronary disease were due to an increased representation of adipose tissue in the He curves. Since He is inherently more diffusible than N\textsubscript{2}O, the possibility of a measurable contribution to He data from non-adipose structures near the heart cannot be excluded, although this circumstance would not provide an explanation for the observed differences in He F/Ws in patients with and without coronary disease. In any event, the volume of tissue represented in the present measurements is the volume of distribution of the sampled tracer.

Comparisons of He Values for F/W with N\textsubscript{2}O and Kr Values for F/W

Even though direct measurements of F/W are not possible in man, it is of interest to compare He, N\textsubscript{2}O and Kr values of F/W in the present human studies with each other and with previous measurements from other laboratories.* The absolute values of F/W obtained with He and N\textsubscript{2}O in normal patients agree reasonably with those summarized by Rowe,\textsuperscript{24} particularly when differences in assumed values for myocardial specific gravity and tissue-blood partition coefficients are taken into account. In addition, when

*Average values for F/W reported in this paper differ slightly from those given in preliminary publications. The differences are the result of (1) the use of a value for myocardial specific gravity of 1.05 (instead of 1.00); (2) the calculation of individual tissue-blood partition coefficients from the data in table 1; (3) the inclusion of the small segment of perfused right ventricular free wall adjacent to the septum in the calculation of directly measured F/W in the right heart bypass studies; and (4) the inclusion of a few more cases in the human studies.
present N₂O flows in normal individuals are expressed as percentages of simultaneous He flows (fig. 8), the two measurements do not differ significantly. This is compatible with the thesis that both techniques are satisfactory in man when flow is not abnormally heterogeneous. In the presence of coronary artery disease, absolute values for F/W with He averaged 23% lower than values obtained with He in normal patients, a reduction approximately similar in magnitude to that recently reported using the same technique in acute myocardial infarction by Hodges et al.²⁵ and in depressed inotropic states by Henry et al.²⁶ Our simultaneous N₂O and He flows differed significantly in coronary disease, N₂O flows exceeding He flows by an average of 38% (fig. 8). The absolute N₂O levels for F/W are similar to those obtained in coronary disease by others but presumably reflect an inability to include localized areas of reduced F/W in the measurement of average F/W. Comparisons of Kr and He flows were not performed systematically in patients with arteriographically normal coronary arteries but, in coronary patients, Kr flows showed even larger discrepancies from He flows, averaging 154 ± 29% of He flows (fig. 8). The reasons for this discrepancy are no doubt the same as described above for the animal studies after coronary ligation. The magnitude of the discrepancy would have been even greater had the tissue-blood partition coefficient for Kr been assumed to be 1.00.

F/W vs "Total" Flow in Man

When initial measurements of F/W did not reflect a systematic reduction in coronary artery disease, it was suggested that measurements of total flow (ml/min) might be more useful. Measurements of total flow for the entire heart (or, more specifically, that portion of the heart "seen" by four-inch external scintillation crystals) have been performed by several groups using Rb⁴¹ and coincidence counting. Results have conflicted, the data of some groups showing no difference at rest between individuals with and without coronary disease²⁷ and the data of other groups indicating a 25-35% reduction in coronary disease.²⁸ Measurements of total left ventricular flow using a continuous thermodilution measurement of coronary sinus outflow²⁹ have not shown a difference between individuals with and without coronary disease. The present data for F/W do not resolve the differences among these various measurements of "total" flow. However, as discussed below, a reduction in F/W and a normal "total" flow in coronary disease would be compatible if left ventricular size were increased systematically.

Implications of Present Measurements in Coronary Artery Disease

Since the differences in He F/Ws between patients with and without coronary disease appear not to be a methodological artifact, we conclude that average left ventricular F/W was decreased at rest in our coronary group. These individuals all had histories of angina pectoris and/or myocardial infarction and their arteriographic abnormalities were rather advanced. It seems reasonable that groups of individuals with less severe disease may have an abnormality of average F/W only during stress. Attempts were made to correlate the present values for F/W with the degree of arteriographic abnormality, as indicated by the Rowe "arteriographic score."³ A statistically significant correlation coefficient (r = 0.39, P < 0.01) could be obtained only if the seven patients in the normal group not subjected to arteriography were assumed to have normal coronary vessels. Thus, while there probably is a "weak" correlation between average left ventricular F/W in the cardiac catheterization laboratory and the degree of arteriographic abnormality, the correlation has limited usefulness in attempts to derive information about average F/W from individual arteriograms. More useful correlations might well result if the regional reductions in F/W which cause the diminution in average F/W could be related more specifically to localized arteriographic abnormalities.

In addition to considering group differences in average LV F/W at rest, it is also pertinent to consider the usefulness, and the limitations, of measurements of this parameter in individual patients. As illustrated in figure 5, nine of 10 cases in which F/W was 70 ml/min/100 g or more were normal individuals, while all 10 cases in which F/W was below 50 ml/min/100 g were coronary patients. However, the two groups showed considerable "overlap" in the range between 50 and 69 ml/min/100 g and it is clear that the measurement of average LV F/W at rest has limited sensitivity and specificity in defining the status of the coronary circulation in individual patients. A better separation between "normal" and "abnormal" perfusion might well be accomplished by additional measurements during a stressful intervention, or by measurements of regional F/W.

Increased heterogeneity of F/W has been illustrated in a small series of coronary disease patients in a previous report from our laboratory using semilogarithmic plots of venous-arterial test gas differences against time.⁶ Figure 9 shows a summary plot for all individuals in the present study. While there is significant overlap among individual curves in normal and coronary patients, venous-arterial differences for He are systematically more prolonged in the coronary group, thus again confirming the increased heterogeneity of F/W in this condition. Although individual curves are not shown in figure 9, there was a reasonably good separation between nor-
Semilogarithmic plot of average venous-arterial He differences vs time in normal individuals and coronary patients. Similar plots were constructed for each study in tables 3 and 4 and individual values tabulated from the smoothed curves at two-minute intervals. The points shown here are the resulting mean values (±1 SEM) for each group.

Figure 9

normal and coronary patients in the later stages of desaturation. At 20 minutes, for example, venous-arterial differences were less than 1% of initial He concentrations in all normal patients, but greater than 1% in 20 of 26 coronary patients. Attempts to construct more specific equivalent models of coronary perfusion using the information in figure 9 are complex and involve additional assumptions about diffusion equilibrium, constancy of arterial inert gas concentration, etc., and are beyond the scope of this paper.

Although definitive information concerning the nature of the areas of reduced flow in coronary disease patients is not available, the volume of these areas must be appreciable. Scar tissue related to previous ischemic episodes no doubt constitutes at least a portion of the "low-flow" tissue. We cannot exclude the possibility that the reduction in F/W in coronary patients is due entirely to scar tissue but were unable to document previous myocardial infarction by clinical, electrocardiographic, enzyme or angiographic data in four of the 10 coronary patients in whom F/W was below 50 ml/min/100 g. Areas of viable but "underperfused" muscle may also deserve consideration. Reports of normal values for total flow (ml/min) in coronary patients would be compatible with the present data for F/W (ml/min/100 g) if left ventricular size were increased systematically in patients with coronary disease. Interesting data in this regard are provided by recent pathological observations. While reviewing cases of cardiac rupture dur-

ing myocardial infarction, Naeim et al. noted heart weights to average 20-25% more in infarction patients without rupture than in a control group of noninfarction patients. In addition, Scott and Briggs reported cardiac weights exceeding 450 grams in males and 400 grams in females in 83 of 183 patients dying suddenly from coronary atherosclerosis in Albany County, New York. A similar incidence of cardiomegaly was reported by Titus et al. in a series of 86 autopsied cases of sudden unexpected death secondary to ischemic heart disease in Rochester, Minnesota.

Finally, the finding of a reduction in average F/W at rest in arteriographically advanced coronary disease in no way diminishes the importance of evaluating the coronary circulation in localized regions of the left ventricle, and during stress as well as at rest. The major challenge in measurements during atrial pacing and muscular exercise, and in efforts to quantitate topographical and transmural variations in flow in man, is still the development of methodologically adequate, widely applicable technology.

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