A Study of Hemodynamics and Coronary Blood Flow in Man with Coronary Artery Disease

By George G. Rowe, M.D., James H. Thomsen, M.D., Roger R. Stenlund, M.D., David H. McKenna, M.D., Salvador Sailer, M.D., and Robert J. Corliss, M.D.

SUMMARY
Coronary blood flow was measured by the nitrous oxide method, and cardiac output was measured by the Fick principle, in a series of 31 human subjects with the clinical diagnosis of angina pectoris. Coronary arteriography was carried out on the same subjects as a part of the same procedure, and the extent and severity of the coronary artery lesions was determined. A numerical value was assigned to the severity of the coronary artery disease, an attempt was made to correlate the severity of coronary artery disease with the measured coronary blood flow and with various hemodynamic parameters which traditionally describe the systemic and pulmonary circulation. There was no correlation between any of the parameters measured and the severity of coronary artery disease demonstrated by angiography. It is concluded, therefore, that the nitrous oxide method for measuring coronary blood flow is not helpful in separating subjects with normal coronary arteries from those with coronary artery disease, nor are resting hemodynamic observations helpful.

Maximum flow through the coronary arteries of the dog heart was measured by post-mortem perfusion. This flow rate is sufficient to provide a considerable factor of safety as far as constriction of the major coronary arteries is concerned. If these data are extrapolated to the coronary vessels of man, it would seem that a very large "safety factor" exists, and this may explain why severe coronary disease is not revealed by studies of coronary blood flow.

Additional Indexing Words:
Myocardial metabolism Cardiac catheterization Coronary arteriography

Although many reports are available on the determination of myocardial blood flow by the nitrous oxide method in subjects prone to have angina pectoris,1-8 there are few in which the coronary arteries were studied by angiography. We have found no study in which an attempt has been made to correlate the severity of coronary artery disease as demonstrated by coronary arteriography with coronary flow as determined by the nitrous oxide method, although some observations have been made by radioactive gas methods.9, 10 It seems important, therefore, to obtain such information since previous studies have indicated a normal average value.1-8 There is always considerable spread in values for coronary flow from the highest to the lowest point. Similarly, there is considerable difference in the severity of coronary artery lesions in those with arteriosclerotic heart disease.11-14 Thus, it is possible that meaningful correlations do exist but have not been found because they have not been sought with all necessary information at hand.

Because of the normal coronary blood flow in humans who are prone to have angina, a series of dog coronary arteries were perfused with blood to determine their maximal flow rates. These data seemed pertinent to the
question of how much of the lumen of coronary arteries can be compromised without significantly restricting coronary blood flow.

Methods

In 31 human subjects in whom angina pectoris was diagnosed clinically or was strongly suspected (table 1) coronary arteriography was combined with determination of coronary blood flow by the nitrous oxide saturation technique.16 A needle was placed percutaneously in the left femoral artery, and two no. 6 Lehman catheters were inserted into the right brachial comitans veins. The catheters were manipulated under fluoroscopy so that the tip of one lay in the main pulmonary artery, whereas the other lay in the coronary sinus. Pressures in the femoral artery, pulmonary artery, and coronary sinus were recorded by Statham strain-gauge pressure transducers on a Waters photographic recorder with pressure means determined by electrical damping. Subjects were attached through a series of one-way valves and large bore tubing to a Tissot spirometer and to a source of either room air or nitrous oxide. Valves were so arranged that expired air could be collected in the spirometer when desired, and a mixture of approximately 15% nitrous oxide, 21% oxygen, and 64% nitrogen could be given when the coronary blood flow determination was made. Expired air was collected over a 3-min period during the determination of cardiac output and was analyzed for oxygen and carbon dioxide by the Scholander method. Blood specimens were analyzed for oxygen by the Van Slyke-Neill method with duplicate

*The method of determining this index of remaining coronary artery lumen is discussed in the text.
analyses required to check within 0.2 ml/100 ml. Analyses for nitrous oxide were done by the technique of Orcutt and Waters. Arterial and coronary sinus blood pH was determined by the Radiometer Corporation Model 22 pH meter. Hemoglobin was measured by the Coleman Junior Model 6/20 spectrophotometer.

Cardiac output was calculated by the direct Fick principle. Cardiac work was determined by the traditional Starling formula as the mean arterial blood pressure multiplied by cardiac output and appropriate constants, and expressed by kilogram-meters of work for the right and left ventricles. Coronary vascular resistance was expressed in units as determined by systemic arterial mean pressure in mm Hg divided by coronary blood flow in ml/100 g of myocardium per minute. The “r-values” for correlation were determined by the Olivetti-Underwood Programma 101 digital desk-top computer.

After completion of measurements of cardiac output and coronary blood flow, coronary arteriography was done by the Sones technique through the right brachial artery. An attempt was made to obtain views of the left coronary artery at 60°, 45°, and 30° in the left anterior oblique position as well as 30° in the right anterior oblique position. Views of the right coronary artery were obtained at 45° in the left anterior oblique position and 30° in the right anterior oblique position. Pictures were recorded by an Arriflex camera with a 100-mm lens of 35-mm double-X Type 5222 panchromatic negative film and developed in Ethol 90 developer. A Machlett 6-inch x-ray intensifier tube was used, and its image was magnified somewhat by altering voltage on the electrostatic field in the

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intensifier. The camera was rotated so that the long (cephalocaudal) axis of the patient's heart was displayed transversely on the film. This gives approximately 25% greater film surface area on which to display the coronary vessels.

In one of the 31 subjects coronary arteriograms were considered unsatisfactory for rating of the left anterior descending coronary artery. In four subjects, coronary arteriograms were not satisfactory but were considered good enough to permit reasonable rating of the vessels. A system for mathematical rating of the degree of stenosis in the coronary arteries was as follows: The subject was considered to have three coronary arteries, the right, the left anterior descending, and the circumflex. Each normal vessel was given a rating of 100. If the vessels were diseased, an estimate was made of the percentage of the lumen which remained open in increments of 25%. Thus, as an example, if the left anterior descending coronary artery was considered to be 75% occluded and the other two vessels were normal, the assigned rating would be (anterior descending) 25 + (circumflex) 100 + (right) 100 = 225 for the total score. If disease was found in a branch of one of the mean vessels, the size of the branch was estimated as compared to that of its parent vessel, the degree of occlusion of the branch was estimated, the overall effect of the occlusion approximated, and this figure was subtracted from the total. For example, if the anterior descending coronary artery bifurcated, giving off a branch which was estimated to be 50% of the size of the parent vessel and if this vessel were 50% occluded, the estimated occlusion of the anterior descending coronary artery was 50% of 50%, or equivalent to 25% occlusion of the anterior descending coronary artery.

Disease of the left mainstem coronary artery was considered to be a special circumstance since it supplies both the circumflex and the anterior descending arteries. Consequently a value of 200 was assigned to the left mainstem coronary artery and the percentage of occlusion of this vessel for rating purposes was considered to be twice as significant as an equal occlusion would be in either the anterior descending or circumflex coronary arteries. Thus, if there were 50% occlusion of the left mainstem coronary artery, the two-vessel rating became 100 and, providing the right coronary artery was normal, the three-vessel rating was 200.

In order to obtain greater objectivity the coronary arteries were rated by two observers independently. Having reached an independent rating, the figures that had been assigned by the previous observer were examined. If there appeared to be a wide discrepancy between the two ratings, the films were reviewed to determine whether something had been overlooked. If a change in the rating appeared to be justified, and, this was usually the case, it was made. If opinions remained divergent, the two ratings were averaged. The final rating was always the average of that assigned by the two observers. The hemodynamic data were not available to those who rated the vessel disease at the time of the rating so no bias could have occurred from this source.

Utilizing this rating system for coronary arteries, correlation coefficients were calculated between the rating given to the coronary arteries

| Table 2 |
| Correlation of Hemodynamic Parameters and the "Three Vessel Rating" |

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Correlation coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>3.27 ± 0.73</td>
<td>-0.0033</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Left ventricular work index (kg-m/min/m²)</td>
<td>4.5 ± 1.3</td>
<td>-0.0545</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Coronary blood flow (ml/100 g/min)</td>
<td>82 ± 20</td>
<td>-0.1745</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Coronary vascular resistance (units)</td>
<td>1.26 ± 0.32</td>
<td>+0.0773</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Coronary sinus O₂ content (ml/100 ml of blood)</td>
<td>5.7 ± 1.3</td>
<td>-0.0584</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Left ventricular O₂ (ml/100 g/min)</td>
<td>9.8 ± 2.4</td>
<td>-0.0627</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Mean coronary sinus blood pressure (mm Hg)</td>
<td>7 ± 3</td>
<td>-0.1055</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Mean pulmonary arterial blood pressure (mm Hg)</td>
<td>20 ± 6</td>
<td>-0.2387</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Stroke index (ml/beat)</td>
<td>43 ± 12</td>
<td>+0.0030</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Coronary sinus pH (units)</td>
<td>7.39 ± 0.07</td>
<td>+0.1873</td>
<td>&gt;0.1</td>
</tr>
</tbody>
</table>

*SD = standard deviation.
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and the various hemodynamic parameters listed in table 2. These correlation coefficients were calculated on the basis of the rating of all three coronary vessels and were repeated, utilizing the ratings for only the anterior descending and circumflex coronary arteries. On this scale obviously the score for perfect vessels is 200 since only two vessels are involved, but other details of the calculations were the same as discussed previously. Ratings for the calculations which involve three vessels are referred to in the tables as “three-vessel rating,” whereas those calculated from the rating for the anterior descending and circumflex coronary arteries alone are listed as “two-vessel rating.”

It seems probable that the normal major coronary arteries are capable of carrying such a sufficient quantity of blood that they seldom, if ever, restrict flow. To investigate this possibility, hearts freshly removed from dogs were suspended from a large glass tube tied within the proximal end of the transected aorta. Care was taken not to damage the aortic valve so that significant aortic insufficiency would occur. A quantity of fresh, heparinized blood from the dog whose heart was under study was used for modified Langendorff perfusion. The right coronary artery was completely occluded by a ligature close to the aorta, while the anterior descending and circumflex coronary arteries were dissected from their bed and their ends transected and clamped about 2 cm distal to the bifurcation of the left mainstem coronary artery. Thus the area of the coronary arteries most commonly involved with coronary disease remained attached to the aorta. With the heart suspended from its aorta and attached to the tube filled with blood under 85 to 90 mm Hg pressure, preliminary collections were made to measure the amount of blood which flowed through the heart while the coronary arteries were clamped. This quantity of blood (not more than 10 to 15 ml/min) was presumed to have leaked through the aortic valve or proximal branches of the coronary vessels or both. Having measured this “artifactual” flow several times, the clamps were removed from the left anterior descending and the circumflex coronary arteries and flow was timed, collected, and measured as it ran through the open ends of the arteries. This measured flow was then corrected by subtracting from it the amount of blood collected during the test periods prior to opening the transected coronary arteries. After having made this observation several times, its average was assumed a fair representation of the maximal rate of flow. The left mainstem coronary artery was then transected and similar observations were made to determine the maximal rate of flow through the left main coronary artery.

Results

The results of this study are displayed in tables 1 to 3. In 30 human subjects the three vessels could be rated. The mean values of all the hemodynamic parameters listed are within normal limits for this laboratory. In only one of these subjects were the coronary arteries considered to be normal by both observers, so that the highest rating for three

<table>
<thead>
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<th>Table 3</th>
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<tbody>
<tr>
<td>Correlation of Hemodynamic Parameters and the &quot;Two Vessel Rating&quot;</td>
</tr>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
</tr>
<tr>
<td>Left ventricular work index (kg-m/min/m²)</td>
</tr>
<tr>
<td>Coronary blood flow (ml/100 g/min)</td>
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<td>Coronary vascular resistance (units)</td>
</tr>
<tr>
<td>Coronary sinus O₂ content (ml/100 ml of blood)</td>
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<td>Left ventricular Q O₂ (ml/100 g/min)</td>
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<td>Mean pulmonary arterial blood pressure (mm Hg)</td>
</tr>
<tr>
<td>Stroke index (ml/beat)</td>
</tr>
<tr>
<td>Coronary sinus pH (units)</td>
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</tbody>
</table>

*sd = standard deviation.
vessels was 300. The lowest rating in a subject in this group was 28 indicating that in the opinion of the observers only 9.3% of the normal cross section area of the three coronary arteries remained. Four subjects were considered to have ratings of 200 for two vessels indicating that both the left anterior descending and circumflex coronary arteries were normal. The lowest rating in this group was 25 indicating that only 12.5% of the normal lumen was available for supplying blood throughout the distribution of the left anterior descending and circumflex coronary arteries. On the basis of the three vessel rating, the average figure for the 30 subjects was 161 out of a possible 300 (53.7%), whereas the average two-vessel rating was 108 out of a possible 200 (54.0%). These subjects then, revealed generally rather severe coronary artery disease but with considerable spread, from normality through severe disease. A considerable spread in the hemodynamic data is evident when the lowest and the highest figures are compared. Yet when the severity of coronary artery disease as determined by the present rating is related to the various hemodynamic parameters measured, the r values indicate no significant correlation between the degree of obstruction in the coronary vessels and the alteration of the hemodynamic parameter in question.

In five consecutive coronary artery perfusion experiments conducted on the hearts of dogs whose weights varied between 21 and 24.5 kg (table 3) the average flow through the open circumflex and anterior descending coronary arteries was 628 ml/min. This level was achieved even though one dog in this group had a small left coronary artery through which a flow of only 195 ml/min occurred. The average flow through the left main coronary artery was 1,061 ml/min.

Discussion

Prior to the availability of a method for measuring coronary blood flow in man, it was accepted that subjects with angina pectoris as a result of arteriosclerotic heart disease had reduced coronary blood flow. Anginal pain was thought to be a manifestation of inadequate blood flow to the myocardium to supply oxygen and to remove metabolites. This concept is still widely accepted even though current methods for measuring coronary blood flow in anginal subjects have failed to reveal any reduction in resting coronary flow per unit of myocardial weight or for the heart as a whole. When such an apparent discrepancy occurs between data accumulated by an experimental method and that presumed to be true on the basis of reasoning from the changes found at pathological examination, some explanation must be sought. The first explanation that suggests itself is that the methods for measuring coronary flow are inaccurate, and the newly acquired data are wrong. Even though attempts to validate the nitrous oxide flow method have appeared to be very good, potential sources of error should be considered; especially, one should examine the questions of adequate perfusion and the partition coefficient. The inert gas method depends upon uniform distribution of gas throughout the organ in which flow is being measured. Judging from the pattern of coronary artery lesions found in subjects with angina, blood flow may not be uniform throughout the heart. If it is not, the data obtained by methods which depend on rapid equilibration of gas and myocardium should be expected to give a different result than those which permit a longer period of exposure to the inert foreign gas. Yet, resting coronary flow is found to be within normal limits by three different methods—nitrous oxide, as reported in the literature and as shown here, radioactive xenon clearance, and coincidence counting. In these methods the duration of myocardial exposure to foreign gas varies from that of a single circulation time to 10 to 15 min. As a second consideration, it is possible that the partition coefficient of ischemic, fatty, or fibrous myocardium is different from that of the normal myocardium. Although no evidence is available on this point concerning myocardium itself, data have been presented for the
kidney in its normal state and, subsequent to considerable alterations in its structure, produced by agents given to induce anuria. These data for the kidney indicated no change in partition coefficient. Furthermore, the partition coefficients for the myocardium, brain, and kidney are all similar, indicating that in all probability nitrous oxide has a nearly similar partition coefficient in the variety of tissue which may be expected to be found in the ischemic myocardium.

Previous studies of coronary blood flow have revealed normal resting coronary blood flow in those subject to angina pectoris. However they have not reported an objective estimate of the severity of the coronary artery disease in each individual along with the determination of coronary flow, although there are some data in the studies using radioactive xenon clearance. Consequently it has not been possible to determine whether there is any relation between individual determinations of coronary blood flow by the nitrous oxide method and the severity of the coronary artery disease. It is particularly important that this be sought deliberately since the spectrum of normal in coronary flow and that of atherosclerotic changes in coronary artery disease is wide and correlations might have been obscured by the grouping of data. When the present data on coronary flow and coronary artery disease are related to one another, no systemic relation between the two sets of observations is revealed. The correlations are not significantly different whether the rating for all three coronary arteries or that for only the left anterior descending and circumflex coronary vessels is utilized. Both sets of correlations were calculated since, although it is agreed that under normal circumstances, in the dog, blood which flows from the coronary sinus enters the heart chiefly through the left main coronary artery, while in man, and especially in the presence of atherosclerotic coronary vascular disease, this may no longer be true. In many human subjects with extensive coronary artery disease the distal portion of an occluded coronary artery can be demonstrated to be filled from another vessel. Consequently, in the presence of coronary artery disease, blood appears to be supplied to the myocardium from whatever sources are available, and the left ventricular coronary flow depends more upon the total coronary and collateral arterial lumen and less specifically on the degree of occlusion in any one of the three coronary arteries.

It is well known that the common variety of coronary artery disease which predisposes to angina pectoris is atherosclerosis and that it affects mainly the major coronary arteries rather than their smaller branches. It is also known that considerable constriction of a coronary artery must be produced before a reduction in flow is manifested by evidence of myocardial ischemia. Thus, even as the weakest link in a chain determines its strength, so the greatest resistance in a hydraulic system determines its flow in response to pressure. In this regard the increasing cross-sectional area of the vascular bed at each branching and the progressive enlargement of collateral channels must be weighed against the decreasing size of the individual vessels. The major pressure decrease in the vascular system occurs at the arteriolar level; hence it is generally agreed that the arterioles furnish the chief resistance to flow. This general phenomenon has recently been shown to apply to the heart as well. It seems acceptable then, on the basis of theoretical considerations, that coronary flow in subjects with coronary artery disease might be within normal limits at rest because the real resistance to flow lies peripherally in the coronary arterioles and precapillary sphincters, rather than in the region of the atherosclerotic plaques. The present data are consistent with this hypothesis.

Data concerning the maximum capacity for flow through the intact coronary arteries of living animals are not available. However, in large, normal dogs with a flowmeter embedded about the main left coronary artery, coronary flows were measured during heavy treadmill exercise. By estimating peak
phasic coronary flow from the graph, it appears that these animals may have transiently achieved 350 ml/min. From the data presented here, it is clear that the main trunks of the coronary arteries in the dog are capable of carrying a considerably greater coronary flow. Indeed, in studies of coronary blood flow during administration of dopamine, adenosine triphosphate, and adenosine, mean coronary blood flows of 531, 464, and 613 ml/100 g/min have been reported. Flows at this rate strain the nitrous oxide method and may well not be accurate, but they do indicate that considerable capacity for increase in coronary flow is available to the dog. Further credence that such flows can be achieved is supplied by data collected during exercise of a large unanesthetized dog in which mean flow through the circumflex coronary artery of 344 ml/min was recorded and in which peak flows, by extrapolation from the curve, appear to have been near 700 ml/min.

Extrapolating from the data taken from dog studies to that in man, seem to indicate that the maximal flow capacity of the main coronary arteries of man must be very great, yet during maximal treadmill exercise of otherwise normal men, changes in the electrocardiogram have been observed in some which are compatible with myocardial ischemia. It seems probable that these changes indicate asymptomatic coronary artery disease. It is clear from postmortem studies of American soldiers who were killed in the Korean conflict that many asymptomatic young Americans have anatomically severe coronary artery disease. Perhaps their disease would have been revealed by electrocardiographic monitoring during maximal treadmill exercise.

When myocardial ischemia occurs at rest, angina decubitus or infarction should result and the ischemic myocardium should be replaced by less demanding tissue. Individuals in the active phase of these latter syndromes have not had their coronary blood flow measured systematically, so no data are available during these states. In severely hypoxic dogs, or in those poisoned with cyanide, myocardial lactate production has been described. In some human subjects, myocardial lactate production during angina has occurred and has been equated with myocardial ischemia, suggesting that flow is inadequate. Un fortunately lactate production is not detected in all subjects who have angina and is present in some controls. Somewhere between the normal and the state of resting ischemia, as the constriction in the proximal portions of the coronary vessel increases, a point must be reached where coronary vasodilatation during exercise becomes inadequate to increase blood flow as much as is required. Under these circumstances angina of effort may occur. Attempts have been made to study this possibility by exercising, or giving isoproterenol or epinephrine to subjects with and without angina pectoris; however, coronary flow has increased as much or more in subjects with presumed coronary artery disease as in controls.

A method is needed for determining maximal coronary blood flow. Coronary blood flow in man has not been documented which approximates the maximum that one would expect by extrapolating from the data accumulated from the dog. It seems that when a good, simple, easily repeatable and reproducible method for measuring coronary flow is available, the physiological way to determine the significance of obstructing coronary artery disease would be to measure the maximum obtainable coronary flow and to relate this through suitable tables to the heart rate, cardiac work, left ventricular rate of pressure rise, coronary sinus oxygen content, left ventricular oxygen consumption, and suitable biochemical measures of ischemia. Until that time we must feel our way along and rely mostly on coronary arteriography.

References

2. Rowe, G. G., Maxwell, G. M., Castillo, C. A., Crumpton, C. W., Botham, R. J., and Young, W. P.: Evaluation of effect of bilateral internal mammary artery ligation on cardiac
HEMODYNAMICS AND CORONARY ARTERY DISEASE


30. MAXWELL, G. M., ROWE, G. G., CASTILLO, C. A., CLIFFORD, J. E., AFONSO, S., AND CRUMPTON,


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