Anatomic and Physiologic Considerations in Measurements of Myocardial Blood Flow

By RICHARD S. Ross, M.D., and GOTTLIEB C. Friesinger, M.D.

THE CLINICAL importance of ischemic heart disease has provided a powerful stimulus for the development of new and better methods for the study of the coronary circulation. In the animal laboratory, the electromagnetic flowmeter has replaced the rotameter as the standard method of measuring coronary blood flow. Flowmeter probes can be implanted around a dog’s coronary artery and utilized to study the coronary circulation during exercise in an intact unanesthetized animal. These excellent methods cannot, for obvious reasons, be applied to the study of patients, and therefore clinical investigators have been forced to develop other methods for the study of patients with ischemic heart disease.

The coronary circulation can be defined as a peripheral circulatory bed, and therefore any discussion of the method of measuring myocardial blood flow should logically begin with a consideration of the simplest kind of peripheral circulatory bed as diagrammed in figure 1. The artery and vein are both accessible, and an indicator can be injected into the blood flowing in through the artery and its concentration measured in venous blood leaving the bed, and there is no pathway whereby it can recirculate. The indicator substance may be identified by virtue of its color, its chemical properties, or its radioactivity. If a radioactive indicator is used, and a scintillation probe is placed over the vascular bed, a concentration time plot can be obtained by means of a ratemeter and a direct-writing recorder. The indicators employed in the study of the myocardial circulation can be divided into two groups according to their volume of distribution. Some of the indicators are large molecules that stay within the blood vessels during their transit of the myocardial circulation, whereas others pass through the capillary walls and equilibrate with the extravascular tissues. In either case, the time course of the indicator through the myocardium can be analyzed to yield a measure of flow. In the case of a vascular indicator such as I\textsuperscript{131} albumin, the time-concentration curve is analyzed by the application of indicator-dilution principles. When an extravascular indicator is employed, flow is derived from the measured rate at which the indicator is either taken up by or washed out from the myocardium. The commonly used extravascular indicators are nitrous oxide, I\textsuperscript{131} iodo-antipyrine, Kr\textsuperscript{85}, Xe\textsuperscript{133}, Rb\textsuperscript{86}, Rb\textsuperscript{84}, K\textsuperscript{42}, and Na I\textsuperscript{125}. A new approach to the calculation of flow from isotope clearance data has recently been suggested by Zierler.

Unfortunately, the myocardial circulation is not as simple as the peripheral circulation dia-

Figure 1
Schematic diagram of simple peripheral vascular bed.
grammed in figure 1. The important differences between the myocardial circulation and a schematized simple peripheral vascular bed are outlined in figure 2. Of first importance is the intimate relationship of the myocardial circulation to the chambers of the heart, the lungs, and the chest wall. The heart chambers as well as the lung and the chest wall all contain blood, and hence all contain any indicator introduced into the systemic circulation. Therefore, a radiation detector placed over the chest wall will measure changes in radioactivity in the heart chambers, the lung, the myocardium, and the chest wall. The anatomy of the arterial and venous circulation of the myocardium becomes of great importance when methods of measuring flow are considered. There are two coronary arteries coming off the aorta, thus it is impossible to introduce indicator into both of these vessels at the same time and in equal concentration without also introducing it into other segments of the systemic circulation which are perfused by aortic blood. The venous system is also complicated in that the majority of the left ventricular myocardium and hence the drainage from the left coronary artery passes through the coronary sinus into the right atrium. The drainage of the right ventricle is not into a single channel but rather through multiple small channels into the right atrial wall. Venous sampling of left ventricular drainage is possible, but right ventricular drainage is not available for sampling.

If myocardial blood flow is to be measured, the myocardial circulation must be isolated from other segments of the circulation in some manner. The methods of myocardial blood flow measurement can be divided into three general groups on the basis of the method of isolation employed. This classification is shown in table 1. First are the methods that isolate the myocardium on an anatomic basis. As indicated in figure 2, it is difficult if not impossible to separate the myocardium from the chest wall, lung, and heart chambers by any form of simple collimation, but some methods depend upon this technic. The method of coincidence counting to be discussed by Dr. Bing is a form of anatomic or physical separation depending on the ingenious utilization of the properties of the particular isotope rubidium-84. Other investigators employing temporal isolation have depended upon the

![Figure 2]

Schematic diagram of coronary vascular bed in relation to chest wall and a radiation detecting probe. LCA, left coronary artery; RCA, right coronary artery.

Table 1

"Isolation" of the Coronary Circulation

<table>
<thead>
<tr>
<th>Group</th>
<th>Method</th>
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</thead>
<tbody>
<tr>
<td>I. Anatomical—physical</td>
<td></td>
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<tr>
<td>Collimation Rb-86, Kr-84</td>
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<tr>
<td>Coincidence counting Rb-84</td>
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<td>II. Temporal—vascular indicators</td>
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<tr>
<td>Dilution curve &quot;splitting&quot; I-131 albumin</td>
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<td>Comparison of slopes I-131 albumin</td>
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<tr>
<td>III. Circulatory</td>
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<tr>
<td>Venous sampling (coronary sinus)</td>
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<tr>
<td>Inhalation: N-20, Kr-85</td>
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<tr>
<td>Injection:</td>
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<tr>
<td>LV—Kr-85</td>
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<tr>
<td>IV—I-131 Iodo-antipyrine i.v. injection</td>
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<tr>
<td>Arterial injection (coronary arteries)</td>
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<td>Precordial counting: Xe-133, Kr-85</td>
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<tr>
<td>Intramyocardial injection</td>
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<tr>
<td>Precordial counting: Na I-131</td>
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fact that the coronary components of the precordial dilution curve can be separated from the components due to the passage of indicator through the heart chambers and great vessels. In some instances, the coronary component has been identified by comparing it with the dilution curve derived from another segment of the systemic circulation. The errors inherent in these methods have been carefully studied by Tsagaris et al., who have pointed out that the concentration time curves of many segments of the systemic circulation overlap and that there is no consistent and significant difference between the time course of the coronary circulation and other segments of the central circulation. Lastly, there are the technics of vascular isolation which have in general been employed to make the currently popular clearance technics effective, and we will discuss these in some detail.

In figure 3, the principle of venous isolation is outlined. An indicator is introduced into the systemic circulation, either by inhalation or by injection. Both nitrous oxide and krypton-85 have been administered by inhalation, and krypton-85 has also been used by injection into the left ventricle. I$^{131}$ amino-

![Figure 3](http://circ.ahajournals.org/)

**Figure 3**

*Schematic diagram showing technics of myocardial blood flow measurement by "venous isolation" employing coronary sinus catheterization.

pyrine, unlike the gaseous indicators, can be injected intravenously in that it is not excreted as it passes through the lung. All four of these indicators by virtue of their introduction into the systemic circulation will be present in the chambers of the heart, lung, and chest wall. Thus, a precordial scintillation probe would be influenced by radioactive material contained in all three of these beds in addition to that in the myocardium. The volume of indicator contained in the heart chambers is especially important in this regard in that it is usually much larger than that in the myocardium itself. The level of radioactivity at the surface of the chest is a function of total quantity of radioactivity and not just concentration. It is necessary therefore to isolate the myocardial circulation by introducing a catheter into the coronary sinus and sampling venous drainage. All three of these indicators are assumed to equilibrate with the myocardium, and their rate of disappearance is measured and considered as a function of flow. It is also of course a function of the volume of myocardium and the partition coefficient between blood and myocardium for the particular indicator in use. By virtue of the peculiar properties of the venous circulation, only the left ventricular myocardial circulation can be studied in this way.

The technic of arterial isolation is indicated in figure 4. This technic makes it possible to analyze the disappearance of radioactivity from the myocardium with a scintillation detector positioned over the chest wall. It is not necessary to sample venous drainage as well. Sones catheters used for coronary arteriography are employed to deliver solutions of xenon-133 directly into the coronary arteries. Essentially all the injected indicator enters the coronary artery and hence the myocardium. Thus, it is reasonable to assume that the precordial radioactivity all comes from the myocardium and that the rate of disappearance of radioactivity from the precordium is a function of myocardial blood flow. A small amount of radioactive material is spilled into the aortic root and enters the systemic circulation.
Myocardial blood flow measurement by coronary arterial catheterization and injection of xenon-133. The coronary ostia are localized by means of the image amplifier and arteriographic studies completed. The radioactive gas is injected and the image amplifier replaced by a scintillation detector. The disappearance of radioactivity from the precordium is recorded by a ratemeter and strip chart recorder.

Ninety per cent of that which returns to the right heart is cleared from the blood during a single passage through the lungs, and right atrial drainage of the coronary veins has been demonstrated to make no significant contribution to the precordial curve. Therefore, recirculation does not present a significant problem, and radioactivity in the heart chambers and pericardiac structures does not exist to a significant degree. This technic makes it possible to measure right and left coronary blood flow separately and also to make rapid serial measurements, and thus to study the effect of acute interventions on myocardial blood flow. Because the flow measurement technic is used in conjunction with arteriography, correlative studies between arteriographic appearance and physiologic measurements are possible.

It is with the method of arterial injection of xenon-133 that we have had most experience, and the practical application of this method in our laboratory is depicted in figure 5. The important features involve the placement of the Sones catheter in the ostium of a coronary artery and the injection of a solution of xenon-133. The position of the catheter is observed during injection with the image amplifier and television system. After injection, the catheter is pulled up into the aorta and a scintillation detector is immediately brought into position over the precordium. Within 10 seconds after delivery of the radioactivity into the coronary artery, the precordial monitoring of radioactivity washout is being recorded by a ratemeter and strip chart recorder. The results of a typical study are shown in figure 6, which shows an original washout curve, the replot of the slope on semilogarithmic paper, and the derivation of the flow from the rate constant.

It has not been possible to separate normal individuals from patients with ischemic heart disease on the basis of the myocardial blood flow as measured by any of the clearance methods. This failure is probably to be expected when it is recognized that the rate of disappearance of the isotope from the myocardium is a function of both flow and volume. If flow and volume are decreased proportionately, no change will be detected in the rate of disappearance. Such a proportionate
Calculation of myocardial blood flow from precordial disappearance rate of xenon-133. Upper left. Original strip chart record following intracoronary injection. Upper right. Semilogarithmic replot of original data. \( k \), the rate constant, is derived from the \( t \) measured on the semilog plot. The value for \( k \) is substituted in the equation \( F_{100} = k \left( \lambda \cdot \frac{100}{\rho} \right) \) to yield a value for flow in ml./min./100 Gm. \( \lambda \) = partition coefficient. \( \rho \) = specific gravity of myocardium.

decrease in blood flow and volume of myocardium might be expected in the natural course of ischemic heart disease. It is possible that scarred myocardium does not take up the indicator, and therefore only the flow to the remaining normal myocardium is measured.

The xenon clearance method has proved to be very useful in the study of the effect of acute interventions such as drug administration.\(^\text{16}\) It is superior to the nitrous oxide method for studies of this sort in that a measurement can be completed in 2 or 3 minutes as compared to 10 or more for the nitrous oxide method. An index of the usefulness of this method in acute studies can be gained from inspection of figure 7 in which the first of two measurements is plotted against the second. With a few exceptions, there is good agreement between the two control measurements. Lack of agreement represents either actual change in blood flow or error of the method. Obviously, only those experiments with controls in close agreement would be used, and it is apparent that there are a large number of points close to the line of identity. After suitable control measurements are made, a drug can be administered and then the
SYMPOSIUM: CORONARY ARTERY DISEASE

measurements repeated. It is the rate of disappearance that is measured, and, as pointed out previously, this is a function of flow, volume, and partition coefficient. It is reasonable to assume that volume and partition coefficient remain constant, and therefore a change in the rate of disappearance reflects a change in flow.

Summary

Indicators can be used to measure myocardial blood flow if the myocardial circulation can be isolated from other segments of the systemic circulation.

Methods of measuring myocardial blood flow can be divided into groups according to the technic employed to provide "isolation" of the myocardium.

There is no practical method of proved accuracy whereby coronary blood flow can be measured in man in absolute terms of ml./min.

All the so-called clearance methods measure myocardial blood flow in flow/volume units or ml./min./100 Gm.

Myocardial blood flow measurements in these flow/volume units have not proved useful in separation of normal individuals from those with ischemic heart disease at rest, but have been useful in the study of acute intervention such as exercise or the administration of drugs.

References

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