Regional Myocardial Blood Flow

THE INCREASING incidence of coronary artery disease has provided an intense stimulus for expansion of our present knowledge of the coronary circulation. In the experimental animal laboratory, the electromagnetic flowmeter has proved to be an excellent tool by which one can study dynamic aspects of the coronary circulation. A flowmeter is clearly unsuitable for human investigation; therefore, the search for a simple method of analyzing myocardial blood flow has intensified.

Over 20 years ago, Eckenhoff et al. described a method based upon the principle that an inert gas, nitrous oxide (N₂O), diffuses across the capillary membrane proportional to the rate of coronary blood flow. Coronary venous sampling at regular intervals provides a time-concentration curve that permits calculation of myocardial blood flow according to the Fick principle. Myocardial blood flow is expressed as ml/100 g of tissue per minute and represents the “average flow” of those regions of the myocardium draining into the coronary sinus. Unfortunately, a 10-min desaturation period with “steady-state” conditions is required, the gas analysis is cumbersome, and the technique requires coronary sinus catheterization. Although N₂O flows give reasonably good agreement with rotameter flows, the search for alternative methods of measuring myocardial flow has been spurred by the several disadvantages inherent in the N₂O method.

In 1949, Kety first employed the clearance of a locally injected radioisotope indicator to measure the effectiveness of the regional circulation of skeletal muscle. This technique was adapted to the study of local circulation in the myocardium by several investigators. Measurement of myocardial clearance rates by the direct injection of radioactive material into the myocardium obviously has limited clinical application primarily because the method can only be performed during a thoracotomy. In these studies, nonuniform perfusion was observed for the first time in patients with coronary artery disease, as significant reductions in clearance rates were found in myocardial regions rendered ischemic by diseased coronary vessels.

Attempts have been made to measure myocardial blood flow following injection of radioisotopes into the systemic circulation. ⁸⁶Rubidium, which is extracted by the myocardium, and nondiffusible radioisotopes such as radioiodinated albumin have been employed. In these studies myocardial blood flow rates were calculated from counts monitored by a precordial detector. Unfortunately, radioactive material, injected intravenously, appears at approximately the same time and concentration in the lung, cardiac chambers, and chest wall, as well as in the myocardium, which virtually precludes an accurate measurement. One approach, described by Bing et al., attempts to circumvent this difficulty by using a double-coincidence counting technique. This method employs simultaneous counting by detectors positioned over both right and left precordium to distinguish between extracardiac and myocardial radioactivity. The ⁸⁶Rb-clearance method probably adequately reflects directional changes of total myocardial blood flow but has been questioned as a quantitative measurement, particularly under circumstances where total myocardial blood flow is compared following an intervention that might alter velocity of flow or the size of the capillary bed.

A second approach designed to separate the myocardial vascular bed from surrounding structures was described in 1962 by Herd and associates in dogs and was shortly thereafter adapted to use in humans by both Ross et al. and by Cohen and his co-workers. Address for reprints: Dr. Edward M. Dwyer, Jr., Roosevelt Hospital, Cardiovascular Laboratory, 428 West 59th Street, New York, New York 10019.
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technique requires a selective injection of a radioactive inert gas ($^{133}$xenon or $^{85}$krypton) into either coronary artery and is done in conjunction with coronary arteriography. Washout of the isotope is monitored by means of an external gamma-detector, and myocardial blood flow is calculated from the disappearance slope. Since most of the xenon or krypton is excreted through the lungs in one passage, recirculation of the remaining isotope is minimal and does not produce significant radioactivity in surrounding structures.

All of these techniques have proved disappointing because they fail to detect lowered myocardial blood flow in patients with coronary artery disease. The consistent demonstration of normal myocardial blood flow in such patients has understandably created uncertainty about the validity and clinical usefulness of such methods. At best, it appears that these studies can offer reliable estimates of an "average" or total myocardial blood flow but fail to dissect out the component flows that comprise the "average" flow. It is not difficult to envision that with single-curve analysis by single-crystal precordial counting techniques or coronary sinus sampling, small areas of reduced perfusion might be totally obscured by a remaining larger volume of normally perfused myocardium. Such a situation was strongly suggested by a recent report, in which myocardial blood flow was measured by intracoronary injection of xenon during atrial pacing. Conti and associates\textsuperscript{12} unexpectedly found a greater increase in myocardial blood flow in patients with an ischemic response to pacing than in those who did not manifest ischemia. As the authors point out, it is likely that their "average" myocardial blood flow was dominated by normal regions of myocardium, which probably contract, consume oxygen, and require blood flow to a "supernormal" extent when adjacent myocardial regions become ischemic.

A recent technique described by Klocke et al.\textsuperscript{13} is a significant improvement over earlier methods. They employ a chromatographic analysis of an inert gas (H$_2$) from the coronary sinus effluent following prolonged saturation of the myocardium with H$_2$. Using these sensitive analytic techniques, the authors were able to demonstrate additional low-flow washout curves, which serves to reemphasize the heterogeneous character of myocardial blood flow, especially in the group of patients with coronary artery disease. The inclusion of these diminished flows alters the calculation of average flow significantly and has permitted the demonstration of a reduced average myocardial blood flow in patients with coronary artery disease.

Since focal myocardial lesions and heterogeneous blood flow patterns are common features of patients with coronary artery disease, the capacity not only to recognize but to localize and quantitate regional impairments of perfusion assumes extreme importance. To this end, we have been engaged during the past few years in the development of a new method which, for the first time, quantitatively analyzes myocardial perfusion in multiple regions of the heart.\textsuperscript{14, 15} The technique utilizes a scintillation camera with multiple crystals, each individually collimated. The time-consuming construction of multiple washout curves and calculation of myocardial blood-flow rates are simplified by computer analysis.

Using this approach, we have measured regional flow to the left ventricle, right ventricle, and right atrium in patients with normal coronary arteries. The normal perfusion pattern determined in these subjects agrees closely with several studies in experimental animals in which regional myocardial blood-flow measurements were made with $^{86}$Rb or radioactive microspheres.\textsuperscript{5, 16, 17} Our data have demonstrated the presence of some heterogeneity of myocardial perfusion in normal subjects; however, myocardial blood flow becomes considerably less uniform in patients with coronary artery disease. With severe narrowing or occlusion of a major coronary artery, demonstrated by arteriography, associated regional reductions of myocardial blood flow have been found, while severe occlusive disease of multiple coronary

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vessels has usually resulted in a diffuse depression of perfusion rates.18-20

This approach is not without its limitations: intracoronary injection of isotopes is necessary; equipment and isotope are costly; and counting efficiency and intrinsic resolution of the scintillation camera are adequate but not ideal. The spherical anatomy of the heart presents difficulties, since in certain areas of the heart two or more myocardial surfaces supplied by one artery may overlap and be viewed by the same scintillation crystal. Also, certain limitations are imposed, at present, on our interpretations by the lack of quantitative data pertaining to either the partition coefficient of xenon in ischemic myocardium or the influence that isotope uptake in pericardiac adipose tissue has on the myocardial washout curve.

Currently, several investigators are exploring techniques that measure regional myocardial blood flow with Anger scintillation camera (single crystal with multihole collimation). This scintillation camera has demonstrated the capacity to localize visually the deficits in myocardial perfusion; however, its effectiveness in the quantitative measurements of regional rates of myocardial blood flow will await further study.

The quantitative assessment of perfusion to multiple myocardial regions, in conjunction with coronary arteriography, may have several additional clinical applications, such as (1) assessment of the effectiveness of collateral circulation beyond occlusive lesions, (2) pharmacologic investigation of the influence of drugs in ischemic regions of the heart, (3) study of diseases that may affect the coronary microcirculation, and (4) critical evaluations of surgical procedures proposed to revascularize the myocardium.

This type of approach is essential if we are to further our understanding of mechanisms operative in the pathogenesis and clinical manifestations of coronary artery disease. Data and conclusions from future studies based on methods that determine only an "average" myocardial blood flow should be viewed with caution. Such studies may inadvertently give misleading data, which impede rather than enhance our understanding of coronary artery disease.

Edward M. Dwyer, Jr.

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