Methods of measurement of myocardial blood flow in patients: a critical review

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ELEGANT, sophisticated methods developed in the past several decades have allowed investigators to gain a rich fund of knowledge concerning regulation of coronary blood flow in animals. Under experimental conditions, perfusion in the myocardium can be measured with a spatial resolution in microns and with a temporal resolution in milliseconds. In addition, flow, pressure, and diameter in individual microarterial vessels (100 μm in diameter) on the surface of the beating heart can be assessed. Myocardial perfusion can be measured accurately under a variety of conditions, including studies in animals during exhaustive exercise. Compared with the sophisticated measurements of myocardial perfusion that can be obtained in animals, current approaches of studying coronary flow in humans are crude and the new improved approaches are only available in a few laboratories. In view of these methodologic limitations it is not surprising that knowledge concerning regulation of coronary flow in humans is decades behind the wealth of information about regulation of myocardial perfusion in animals.

What little data are available concerning regulation of the coronary circulation in humans suggest that under normal conditions the control of the coronary circulation in large mammals (dogs, pigs, cats, and calves) is reasonably similar to that observed in man. Thus far only one modest difference in reflex control has been observed between dogs and man. Just the opposite is true in the presence of disease. Pathologic states simulated in animals (hypertrophy, coronary obstruction, myocardial ischemia, and coronary collaterals) produce alterations in the coronary circulation that are markedly different from those observed in patients with disease processes. These large differences between data obtained in animal and human studies of the coronary circulation in the presence of disease or altered physiology to simulate disease underline the great importance of developing a method to make sophisticated measurements of myocardial flow in humans.

The purpose of this Perspective is to review critically currently available methods of studying coronary flow in man and to provide a glimpse of several exciting relatively new methods that are being developed. Most of the methods in current use are primarily utilized to measure changes in coronary blood flow. Although flow per gram can be measured with gas clearance and positron-emission tomography, at present even these approaches are employed in most clinical applications to measure alterations in myocardial perfusion as opposed to absolute measurements of perfusion. The existing methods can be grouped into six general categories: thermodilution, gas clearance, densitometry, electromagnetic and Doppler flow probes, positron-emission tomography, and newer approaches (ultrafast computed tomography, contrast echocardiography, and magnetic resonance imaging).

Thermodilution. Coronary sinus thermodilution is an inexpensive, widely available technique for the measurement of coronary flow and is the most frequently applied approach to studying coronary flow in humans. This method, introduced by Ganz et al., is theoretically sound. It requires only right heart catheterization to cannulate the coronary sinus and is therefore remarkably safe. This technique can be used to measure a broad range of flows. Despite these attractive features, the method has severe limitations that are often unappreciated by investigators employing it. The limitations of this technique can be classified in two categories: fundamental and practical.

The fundamental limitations are as follows: (1) pha-
sic coronary flow or rapid changes in mean flow cannot be assessed because the time constant of the technique is slow, (2) perfusion to the right ventricle or atria cannot be assessed because the venous drainage of these chambers is not primarily via the coronary sinus, (3) perfusion in specific transmural layers cannot be estimated, and (4) regional left ventricular flow measurements are confined to crude separation of great anterior vein flow (left ventricular anterior wall and septum) and perfusion to a large but indeterminate area of the left ventricle (distal coronary sinus).

Even though these fundamental limitations are considerable, the thermodilution technique would still be useful if the practical limitations were not overwhelming.

First and foremost, convincing validation studies (coronary sinus, thermodilution employed under clinically relevant conditions vs an accepted gold standard) have never been presented. In an in vitro system or with the thermodilution catheter fixed with a ligature around the coronary sinus, it has been shown that coronary flow can be measured accurately with this method. These data confirm that the mathematical formulations of the method are correct. In contrast to the studies in vitro, validation studies performed under clinically relevant conditions when the thermodilution catheter can move in the coronary sinus have shown only weak correlations with actual flow measurements. The notion that the exact position of the catheter in the coronary sinus can be determined by fluoroscopy under conditions in which heart size and shape may be changing has not been verified.

Second, several anatomic and physiologic features of the coronary venous circulation adversely affect the ability to accurately measure coronary flow with coronary sinus thermodilution. The venous drainage pattern of the left ventricle is variable and substantial venous collaterals are present. In the dog, for example, coronary sinus occlusion produces minimal adverse effects because of the availability of numerous alternative venous pathways. The actual source of venous drainage from most sites except the great cardiac vein into the coronary sinus is indeterminate. Also, in the presence of severe coronary disease or myocardial infarction, it is likely that the coronary venous drainage pattern is distorted.

Third, no convincing animal or clinical validations studies have documented the accuracy of coronary flow measurements with the thermodilution technique in the presence of severe coronary disease. The frequently quoted study of Pepine et al. employed electromagnetic flow probes placed intraoperatively on vein bypass grafts at the time of open heart surgery as a gold standard. Under these conditions the electromagnetic flow probes are nearly impossible to calibrate accurately. The importance of these deficiencies is magnified when investigators use the technique to measure minor differences in coronary flow (± 30%) resulting from modest perturbations in myocardial oxygen consumption produced by small changes in heart rate, aortic pressure, or ventricular contractility. Conclusions based on small changes in calculated coronary vascular resistance are even worse because the proper formulation for computing coronary vascular resistance remains controversial.

Even though the coronary sinus thermodilution technique has major deficiencies, some conceptually useful information has been obtained with this method. Until additional convincing validation studies are presented, measurements of coronary flow with the coronary sinus thermodilution technique should be interpreted cautiously. At present, only large changes (> 30%) in great cardiac vein flow in patients with normal coronary arteries are likely to be qualitatively accurate. The widespread application of the coronary sinus thermodilution method of measuring coronary flow under other conditions, particularly in patients with severe coronary disease and myocardial infarction, should be discouraged.

Gas clearance methods. Gas clearance methods of measuring myocardial perfusion emanate from the pioneering work of Kety. Several nonradioactive gasses (nitrous oxide, hydrogen, helium, and argon) and radioactive xenon-133 (133Xe) have been used in such studies.

The techniques using nonradioactive gas measure average perfusion in most of the left ventricle. The equipment required is simple and inexpensive and the method is safe. Regional specificity is marginal and flow to selected transmural layers cannot be measured. This approach requires obtaining simultaneous arterial and coronary sinus blood for measurements of gas concentration during the saturation or desaturation phase of gas administration. The time constant of these methods is seconds to minutes; thus, rapid changes in flow cannot be assessed. Accurate measurement requires stable conditions. The time course of the effects of any intervention on coronary blood flow in man must be known a priori so that the few measurements of flow that can be obtained by the gas clearance technique can be properly timed. All the problems of venous drainage patterns that plague the thermodilution method are equally applicable to nonradioactive gas.
clearance. If the left ventricular myocardium is not homogenously perfused (because it contains ischemic, necrotic, or fibrotic areas), measurements with this method are of limited value unless a meticulous technique is used.\textsuperscript{19}

This approach is primarily applicable in patients with normal coronary vessels and no major regional abnormalities in left ventricular structure or function. In spite of these limitations, this approach has been used effectively by several groups of German and American investigators to obtain valuable information concerning the effects of various cardiac diseases on resting and maximal coronary flow.\textsuperscript{19–22}

The use of radioactive $^{133}$Xe to measure myocardial perfusion introduced by Cannon et al.\textsuperscript{23} increases the spatial resolution of the gas clearance approach. At the same time this modification increases the risk to the patient because $^{133}$Xe must be introduced directly into the coronary arteries. It also increases cost since a multicrystal gamma camera and computer are required for data acquisition and analysis. This method cannot delineate differences in perfusion to selected transmural layers. Because $^{133}$Xe is highly soluble in cardiac fat, only a limited number of measurements can be obtained in each study.\textsuperscript{24} In addition, the temporal resolution is limited and hence rapid changes in flow cannot be measured accurately. Because of the limited number of flows that can obtained and the long time constant of the method, the temporal course of the effects of an intervention (e.g., drug infusion, exercise) must be well established so that the few measurements allowed can be properly timed. In practice, this is a major limitation. Although it is generally acknowledged that flow rates below 200 ml/100 g can be measured with reasonable accuracy, validation studies have not yielded consistent results.\textsuperscript{25–27} Significant concern about measurements at high flow rates with $^{133}$Xe clearance ($>200$ ml/100 g) persists. The assumption that the partition coefficient of $^{133}$Xe is not altered by myocardial ischemia, fibrosis, or hypertrophy remains untested.

Despite the many limitations noted, this invasive approach to measuring myocardial perfusion has yielded valuable information concerning the regulation of coronary circulation in humans.\textsuperscript{28–30} This method is at its best when perfusion in a presumably normal myocardial region (circumflex bed) is measured simultaneously with perfusion in an abnormal bed (severe left anterior descending obstruction).

\textbf{Densitometry.} The initial clinical application of videodensitometry by Rutishauser et al.\textsuperscript{31–33} and Smith et al.\textsuperscript{34} concentrated on measurements of flow in coronary bypass grafts. This was based on the measurement of contrast transit time from videodensitometric data. Because vein bypass grafts are large in caliber, long, straight, and free of branches, this approach worked well when appropriate background corrections were applied. Validation studies were convincing over a wide range of flow rates. The method requires intraarterial injection of contrast and has a time constant of a few seconds. It is surprising that videodensitometric measures of graft flow rates never became popular among investigators or practicing cardiologists. When this method is applied to the measurement of flow in native coronary vessels, the smaller caliber, complex three-dimensional course, multiple branch points, and short lengths of the vessels combine to seriously limit the accuracy of transit time measurement, especially at high flow rates.

A new approach using similar assumptions involves measurements of bypass graft flow reserve with ultrafast computed tomography.\textsuperscript{35} Because density resolution with computed tomography is much better than with conventional angiography, the contrast for computed tomography studies can be administered intravenously. Preliminary studies suggest that bypass graft patency and flow reserve can be measured very accurately with this technique.\textsuperscript{35, 36} This approach has not been applied to the measurement of flow in coronary vessels. The method should be of value in evaluating bypass graft patency and flow reserve, which continues to be an important problem in clinical cardiology today.

Another new modification of the videodensitometric approach involves the measurement of contrast transit time in various regions of the myocardium in association with digital subtraction angiography. This imaginative method popularized by Vogel et al.\textsuperscript{37} adds substantial spatial resolution to this technique. The time constant of the technique, however, is slow and hence rapid changes in flow cannot be measured. The transmural distribution of perfusion cannot be assessed with this technique. Because absolute flow cannot be determined, application of the method depends on assessing changes in perfusion usually before and after coronary dilation. Variables that may influence the accuracy of these measurements include the method and volume of intra-arterial contrast injection of contrast (electrocardiographically gated power injections are best), effects of the contrast agent itself on flow (contrast has a complex biphasic effect), the precise digital-subtraction angiography protocol, and the algorithm used to compute the changes in perfusion.\textsuperscript{32–40}

The majority of studies published thus far have used
contrast media as a coronary dilator to provide an index of coronary reserve. This has been an unfortunate choice because this dilator is not potent, the dose-response relationship is variable between patients and between vessels, and the duration of the peak flow response is brief and thus easily missed by a technique with a slow time constant. The average coronary flow reserve in normal vessels initially reported with digital-subtraction angiography was inordinately low (typically 2:1). Measurements of flow reserve with other techniques in normal humans are 4 to 5:1. If digital-subtraction angiography is to become a standard approach for assessment of maximal coronary reserve in patients, it will be necessary to make improvements in the technology that will permit accurate measurements of increases in flow as great as 500% and to establish a normal range of flow reserve values that is more consistent with those obtained with other techniques. Despite these limitations, some qualitative information on the regulation of coronary flow in pathologic states has been obtained with the use of the digital-subtraction angiographic technique as originally described.

Recent studies from Mistretta’s laboratory, additional refinements suggested by Vogel’s group, and the use of intracoronary papaverine as the dilator instead of contrast have resulted in substantial improvement in the digital-subtraction angiographic approach to assessment of coronary reserve. These refinements eliminate some of the major problems that have previously plagued this method. Most importantly, coronary flow reserve measurements obtained by the improved technique in normal subjects now report flow ratios in the range of 5:1. Although digital-subtraction angiography with this new modifications is very promising, additional carefully performed validation studies are needed.

Electromagnetic flow probes and Doppler techniques. Measurements of volume flow or blood flow velocity with electromagnetic flow probes or Doppler catheters are attractive. With both approaches flow is measured continuously with a time constant in milliseconds.

Studies with electromagnetic flowmeters have been used frequently to assess flow in vein bypass grafts and rarely to measure flow in native coronary vessels. Unfortunately, when flow probes are placed intraoperatively on vein bypass grafts, calibration is a major problem. Electromagnetic probes work best when they are implanted before use and fibrous adhesions stabilize contact between the vessel wall and the probe. With probes placed intraoperatively, vessel contact may be variable and change significantly with alterations in distending pressure in the conduit. Even if the flow probe could be calibrated, absolute measurements of flow in a graft are difficult to interpret because the size of the perfusion field is often undetermined. If the flow measurements are obtained before and after production of ischemia, typically by graft occlusion or injecting a pharmacologic dilator, these measurements are also difficult to interpret for several reasons. First, in the immediate postbypass period, coronary flow reserve is substantially reduced in normal coronary vessels perfusing normal ventricular muscle. Second, responses to graft occlusion and release are greatly influenced by flow from either the native coronary vessels or collaterals. Third, useful pharmacologic data require dose-response curves and knowledge of the absolute coronary flow or resistance under control conditions and during maximal dilation. These data are almost never reported. As a consequence of these confounding factors, intraoperative studies of graft flow rates with the electromagnetic flowmeter in the immediate post–cardiopulmonary bypass period are of limited value.

Electromagnetic flow probe measurements on native coronary vessels are unsafe because dissection of the vessel is needed to place the encircling probe. Calibration and probe/vessel contact are a problem. In view of these severe limitations and the availability of alternative approaches, in our opinion, measurements of coronary flow with electromagnetic flowmeters in patient studies should be abandoned unless a major breakthrough in this technology evolves. Clinical studies using this approach should be carefully scrutinized to ensure that the numerous limitations noted above are given appropriate consideration.

Doppler technology has several advantages vs electromagnetic flow probes for studies in patients. The piezoelectric crystal used in the Doppler technique is tiny and hence can be incorporated in small probes. If a pulsed-Doppler method is used, a single crystal can both send and receive the signal. This eliminates the need for a probe that must encircle the vessel; hence, dangerous coronary dissection is not required. Vessel wall/probe contact is less of a problem with the Doppler technique.

Extensive validation studies with the Doppler technique have been performed in which changes in velocity measured by the method have been compared with changes in perfusion measured with timed-venous coronary sinus collection and electromagnetic flow probes. These studies indicate that under a great variety of conditions, changes in coronary blood flow velocity measured by the Doppler technique accurately reflect changes in flow.
Several disadvantages are present when Doppler technology is used. With the conventional Doppler method only changes in velocity rather than absolute velocity or flow are measured. One must assume that the cross-sectional area of the vessel being interrogated remains fixed, that the velocity profile across the vessel is not severely distorted by disease, and that the angle between the crystal and the sample window in the blood stream being measured is stable. More advanced intraoperative Doppler techniques that will permit measurements of both coronary blood flow velocity profiles and coronary dimensions should allow direct calculation of absolute flow. Other limitations of the Doppler technique are that the method does not allow one to measure the distribution of perfusion in selected transmural layers of the left ventricle. Also, when the suction Doppler technique is used for intraoperative studies, only vessels on the anterior surface of the heart (right coronary artery, left anterior descending coronary, and diagonal branch) can be examined.

With the Doppler technique, coronary flow reserve in normal coronary vessels supplying a normal ventricle averages 5:1. Flow reserve is similar in awake and anesthetized open-chest patients, male and female subjects, and vessels perfusing the right and the left ventricles, and is independent of age in the absence of superimposed disease.

Studies with the intraoperative Doppler technique have made three contributions to knowledge concerning the regulation of coronary flow in humans: (1) coronary reserve and the quantitative characteristics of reactive hyperemia in normal vessels perfusing normal ventricles have been established, (2) the effects of cardiac hypertrophy on coronary reserve in patients have been defined, and (3) the major limitations associated with the use of percent stenosis to assess the physiologic significance of coronary obstructive lesions have been demonstrated.

Although the intraoperative Doppler technique is useful for research applications, the clinical applicability is minimal because the measurement can only be obtained during open heart surgery. Recently, a small No. 3F Doppler catheter has been developed. This instrument is a significant improvement over the previously described Doppler catheter because it measures flow selectively in major coronary vessels rather than in only the left main coronary artery or proximal right coronary artery. These new small catheters do not cause coronary obstruction in major proximal coronary vessels of adults and have been carefully validated in extensive animal and clinical studies. Although these catheter systems have a number of laudable features, they have some of the same deficiencies applicable to the suction Doppler (see above). In addition, even with steerable catheters that use a guidewire, several situations cannot be evaluated, including very proximal coronary obstructions, obstructions adjacent to a major bifurcation with a normal branch, and severe diffuse disease. Lastly, because the Doppler catheters require intracoronary coronary cannulation there will always be some risk associated with this approach.

These new Doppler catheters promise to bring sophisticated measurements of coronary reserve in individual coronary vessels to cardiologists practicing at the community level. A reasonably safe effective transient coronary dilator (papaverine) has been characterized for use in man. With the new Doppler catheter and intracoronary papaverine it is possible in many patients to determine the physiologic significance of individual coronary obstructions, the functional capacity of individual bypass grafts, and the need for angioplasty in patients who have a stenosis of indeterminate severity. In addition, it will be possible to examine pharmacologic and physiologic effects of various interventions on the coronary circulation in the presence or absence of disease. Thus, the coronary Doppler catheter promises to be a major addition to the diagnostic armamentarium of the coronary angiographer. Widespread use of this approach should be strongly encouraged.

Positron-emission tomography. In theory, it should be possible to precisely measure regional myocardial perfusion noninvasively with positron-emission tomography. In practice, this goal has not been achieved because the radionuclides available for positron-emission tomography are not ideal and many imaging artifacts continue to plague this approach.

Six radionuclides have been used to measure myocardial perfusion with positron-emission tomography and each of them have achieved some success. Left atrial injection of macroaggregated albumin microspheres labeled with 68Ga and 11C can be used to accurately measure left ventricular perfusion. Although these studies demonstrated the feasibility of assessing left ventricular perfusion with positron-emission tomography, this approach was never intended for clinical use. 13NH3 and 82Rb are tracers that can be injected intravenously and used to measure myocardial perfusion with positron-emission tomography. Under carefully specified conditions, myocardial perfusion can be accurately measured with 13NH3 and 82Rb. These two tracers, however, share two common limitations: their extraction is inversely related to flow, and myocardial uptake is dependent on both perfusion and me-
These disadvantages are largely overcome by $\text{H}_2\text{^{15}O}$ and $\text{¹¹C}$-butanol. Studies with $\text{H}_2\text{^{15}O}$ have demonstrated that extraction is almost independent of flow and myocardial uptake is not significantly altered by changes in metabolism. Measurements of myocardial perfusion with radiolabeled microspheres correlated very closely with perfusion measured simultaneously with intravenous injection of $\text{H}_2\text{^{15}O}$ and positron-emission tomography. Two significant disadvantages of $\text{H}_2\text{^{15}O}$ are that the tracer labels both the myocardium and the blood pool simultaneously and the radionuclide must be produced in an on-site cyclotron. $\text{Rb}^{82}$ can be produced in an inexpensive generator.

In addition to the problems with the tracers for perfusion measurements with positron-emission tomography, studies of this type have been seriously hampered by numerous imaging artifacts. These include limited resolution of the positron cameras (8 mm x 1 cm), cardiac, respiratory, and patient motion, partial voluming, spillover, count rate recovery, and assumptions about left ventricular wall thickness. As a consequence of these problems it is unlikely that right ventricular perfusion or perfusion to the subendocardium of the left ventricle will be measureable with positron-emission tomography in the near future.

Many of the problems noted above are being resolved. For example, the variable extraction of $\text{Rb}^{82}$ can be estimated, gating can be used to limit cardiac and respiratory motion, the resolution of positron cameras continues to improve, and cameras capable of obtaining multiple simultaneous tomographic slices are being introduced. As a consequence of these and other improvements, very encouraging validation studies in animals have been reported, and a few clinical studies, particularly one by Gould's group, show considerable progress. In the clinical studies thus far presented, only relative myocardial flow rates have been reported. In addition, these clinical studies rely on the use of an intravenously administered coronary dilator (dipyridamole) that may not always produce maximal coronary dilation when administered in the conventional dose. The unique capability of positron-emission tomography to measure both perfusion and metabolism and thereby identify areas of perfusion/metabolic mismatch will surely be of clinical value.

Issues related to cost effectiveness of this expensive technique and the potential competition from other imaging technologies will not be resolved for several years. At present, positron-emission tomography is the most promising approach to the noninvasive measurement of left ventricular regional perfusion in patients.

Newer approaches. One of the major deficiencies of all existing techniques for the measurement of myocardial perfusion in patients is the inability to separately assess perfusion in different transmural layers of the left ventricle. This is an enormous disadvantage. Animal studies have shown that alterations in transmural perfusion are of great importance in understanding the regulation of the coronary circulation. This is especially true in the presence of coronary obstructive disease, which is initially manifest as a decrement in subendocardial perfusion. The three new approaches to assessment of myocardial perfusion — ultrastart computed tomography, magnetic resonance imaging, and contrast echocardiography, all share one characteristic, i.e., they can theoretically measure flow in different layers of the left ventricular wall. Although some studies with these newer techniques have been reported, they are all in an early stage of development and each has major problems to overcome. Because measurements of perfusion in different layers of the human myocardium are of paramount importance, both in research and clinical applications, efforts to achieve this goal should be vigorously supported.

Summary. During the past decade, major progress has been made in the evolution of technology directed toward the accurate measurement of regional myocardial perfusion in patients. The deficiencies of some of the other methods (thermodilution and gas clearance) are better appreciated and improved approaches (Doppler catheters, positron-emission tomography, and digital subtraction angiography) have been developed. The new approaches should play a major role in research and for most applications the older methods will gradually be replaced. Efforts to bring these new methods to community hospitals and practicing cardiologists should be stimulated. Doppler catheters, positron-emission tomography, and digital-subtraction angiography are commercially available and Doppler catheters and digital-subtraction angiography could be easily incorporated into routine cardiac catheterization procedures. The Doppler catheter is the most inexpensive and probably the simplest to apply. In our opinion, routine measurements of coronary flow reserve will significantly improve the care of patients with coronary obstructive disease and other diseases that impair myocardial perfusion. If coronary reserve measurements are used frequently, patient selection for coronary angioplasty and bypass surgery will no longer depend entirely on visual assessment of percent diameter stenosis, a very poor criterion in many situations. Also, patients with chest pain syn-
dromes, normal coronary vessels, and impaired coronary reserve will be identified and perhaps some effective treatment for this condition will be devised. On the horizon, a new generation of techniques (magnetic resonance imaging, ultrafast computed tomography, and contrast echocardiography) may permit precise measurement of perfusion in different layers of the left ventricular myocardium without cardiac catheterization.

As the precision of all these new techniques improves and as they become more widely available, additional knowledge concerning the regulation of the coronary circulation in humans will be acquired. In time, this will translate to a significant improvement in the care of patients with diseases affecting myocardial perfusion.

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