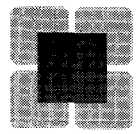

# Physiologic evaluation of coronary flow: the role of positron emission tomography

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■ As the complexity, cost, and risks of cardiac interventions direct attention to careful selection of patients, the ability of diagnostic imaging techniques to provide quantitative documentation of the hemodynamic severity of coronary artery disease will assume greater importance. Among the various techniques currently in use, positron emission tomography yields superior spatial resolution and attenuation correction and has high sensitivity and specificity. The correlation of positron emission tomography results with coronary stenosis severity and the possibility of making quantitative flow measurements using oxygen-15 water suggest that cardiac positron emission tomography may be the best noninvasive approach for diagnostic purposes.

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AS THE COMPLEXITY, COST, and risks of cardiac interventions attract more attention to how patients are selected, the ability of diagnostic imaging to provide optimal physiologic assessment of the severity of coronary artery disease is more important than ever.

In ischemic heart disease, an anatomic approach (coronary arteriography) has traditionally dominated clinical decision-making,[1,2] and the prognostic significance of evaluations of exercise capacity and left ventricular function are recognized.[3,4] But the application of quantitative assessments of coronary artery physiology to clinical practice has been delayed, in part by methodologic difficulties. Numerous approaches to the quantitative assessment of coronary flow have been attempted. This review examines these techniques, with particular attention to positron emission tomography (PET).

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## CORONARY ARTERIOGRAPHY: SHORTCOMINGS

### Anatomic limitations

Even though coronary arteriography is the "gold standard" for determining the presence and severity of coronary artery disease, its ability to fill this role is somewhat limited.[5] Significant interobserver and intraobserver variability occurs, even when experienced observers visually assess high-quality angiograms.[6–8] Factors responsible for this variability include subjective phenomena (level of training, fatigue, bias induced by knowledge of clinical data), the portion of the vessel deemed normal, and lesion geometry. Lesion geometry is particularly important, since most coronary stenoses are eccentric.[9] The correlation between visual assessment of coronary arteriograms and physiologic evaluation of coronary flow is poor.[10]

Quantitative coronary arteriography[11,12] has circumvented some of these technical considerations, with improved correlation with functional parameters.[13,14] These methods characterize the vessel lumen in multiple dimensions at one point in the cardiac cycle, and are calibrated to a known reference measurement. Nevertheless, technical problems remain with this technique, including poor quality angiograms, the obscuring of lesions by overlapping vessels, and end-on viewing of vessels.

The greatest limitation to the routine use of angiography for the physiologic evaluation of coronary disease is inherent in the nature of the angiogram as a "luminogram." Using routine qualitative analysis, segmental narrowing is compared with less narrowed adjacent segments that are presumed to be normal. If the latter areas are actually the site of a concentric stenosis, the degree of segmental narrowing will be underestimated. Comparisons of angiographic interpretation with pathologic findings at autopsy,[15,16] or with intravascular ultrasound,[17] have confirmed this underestimation of lesion severity.

### Physiologic limitations

If it were possible to measure the vessel accurately, classic fluid dynamics would predict the hydrodynamic effects of an obstruction in a normal conduit; however, inherent variability of flow and vessel resistance in the coronary system present problems for the application of fluid dynamic principles.[18] The relationships studied in vitro have not proved consistently applicable in vivo because of difficulties imposed by bifurcations, vessel curvature, and alterations in physiologic conditions,[19] in addition to those of measuring normal vessel diameter and stenosis severity.

Relatively severe stenosis of a coronary artery is required to alter resting blood flow.[20] At rest, resistance at the arteriolar level limits coronary flow until coronary stenosis reaches a critical severity of 80% to 85% of luminal area, corresponding with a diameter reduction of 60% to 80%.[21] At this level, reactive coronary hyperemia, which initially compensates for diminished flow secondary to an obstruction, can no longer maintain flow. Thus, the hemodynamic effect of a coronary stenosis depends on the degree to which vasodilation at the arteriolar level compensates for the increased impedance to flow caused by the stenosis. Due to this coronary autoregulation, there is an inherent dichotomy between coronary anatomy and coronary flow.

## MEASUREMENT OF CORONARY FLOW

### Coronary flow reserve

The use of flow reserve to assess stenosis severity was initially proposed by Gould.[22] Flow reserve is calculated as the ratio of blood flow under maximal vasodilation to normal resting blood flow. This single measure of overall stenosis severity reflects geometric dimensions of length, absolute diameter, percentage of narrowing, and asymmetry. Myocardial flow reserve decreases as coronary pressure falls, and becomes exhausted when coronary pressure reaches the point at which autoregulatory vasodilation is maximal.[23,24]

Various methods have been used to measure coronary flow reserve, and they all use a coronary vasodilator. The most widely used vasodilating agents are papaverine and dipyridamole, although the radiographic contrast agents are also effective at a weaker level.[25] Papaverine (4 to 16 mg in sequential boluses) is the vasodilator of choice for invasive studies, with a reactive hyperemic response of 40 to 50 seconds.[26] Dipyridamole is better suited to noninvasive studies since its hyperemic response is longer.[27] It is normally given in a dose of 0.56 mg/kg over 4 minutes, often followed by hand-grip exercise to maintain systemic blood-pressure.[27] Severely asthmatic patients should not undergo this examination due to the risk of inducible bronchospasm. Side effects of the intravenous vasodilator include flushing (52%), dizziness (7%), arrhythmias (7%), angina pectoris (24%), and, in a few cases, myocardial infarction (1% to 3%).[28] Adenosine[29] is an effective alternative and has the advantage of a more rapid response.

### Coronary sinus thermodilution

Thermodilution is a well-established technique for measuring cardiac output; it is both widely available and inexpensive. With this technique, coronary flow is approximated by measuring flow in the coronary sinus. Although this method has been used to evaluate global coronary flow responses to pharmacologic agents,[28] it is not applicable to the investigation of regional flow. This technique has two main limitations: (1) because the technique is slow, measuring rapid changes in flow is difficult; and (2) catheter whip and respiratory movement can produce radiographic artifacts.[30]

### Gas clearance methods

Gas clearance measurements analogous to those used to assess cardiac output may also be applied to the

determination of coronary flow. Radioactive xenon-133 has been used for this purpose.[31] The technique involves introducing the gas into the circulation, and it requires a multicrystal gamma camera and computer for data acquisition. This method cannot detect differences in perfusion in selected transmural layers of the myocardium; moreover, temporal resolution is limited, so that rapid changes in flow cannot be measured accurately. Xenon-133 is highly soluble in cardiac fat, thereby limiting the number of reliable measurements that can be taken. The effects of myocardial fibrosis, ischemia, or hypertrophy on the partition coefficient of the gas are unknown.

### Direct measurements of volumetric flow

Blood flow velocity may be measured directly with electromagnetic flow probes or Doppler catheters. Although electromagnetic probes have been used intraoperatively on vein grafts, the procedure requires extensive dissection to expose native coronary vessels and is hazardous.

In contrast, intraluminal Doppler techniques are readily performed at the time of coronary arteriography.[32,33] Rapid changes in flow can be measured, and subselective measurements of coronary arterial blood flow velocity may be performed.

### Coronary videodensitometry

Videodensitometry has been applied to acquire physiologic and anatomic data from coronary arteriography.[34] Using this technique, epicardial coronary flow velocity is measured by monitoring radiographic contrast intensity as a function of time at two points in a coronary vessel. Coronary blood flow is then determined as the product of cross-sectional area and flow velocity. The technique is limited by technical problems (corrections for variations in the cardiac and respiratory cycles), coronary vasodilation induced by the contrast agents, and the inability to distinguish regional perfusion inhomogeneities from transmural ones. Moreover, repeating the test under conditions of altered flow gives a commensurate and undesirable increase in dye load.

### Limitations of coronary flow testing

The invasive nature of these coronary flow tests restricts their use to the time of coronary arteriography and is an important limitation at serial follow-up (which may be needed to assess restenosis after angioplasty or to examine disease regression with medical therapy). Also, flow reserve in normal patients varies from 3.7 to 8.2 (average 5.0 ± 0.6). This wide range limits the ability of these tests to discriminate normal from abnormal responses. In diseased states, coronary flow reserve is even more variable and may be difficult to assess in diffuse coronary artery disease.[24] Moreover, test results may be altered by changes in loading conditions[35] and in patients with left ventricular hypertrophy.[36]

## MYOCARDIAL PERFUSION IMAGING

Techniques for examining myocardial perfusion are generally noninvasive. They can be readily repeated serially and can be performed under normal hemodynamic conditions rather than during cardiac catheterization. The various methods have three characteristics in common: use of a stimulus (eg, intravenous dipyridamole) for increasing coronary blood flow, perfusion tracers, and tomographic imaging.

### Contrast echocardiography

Myocardial contrast echocardiography provides information on coronary flow reserve and the size of coronary perfusion beds.[37–39] However, despite promising work relating to the transpulmonary passage of contrast agents,[40] systemic administration of contrast medium does not provide adequate definition of myocardial perfusion. Therefore, the technique is limited to situations where sonicated medium may be injected into the left ventricle, aortic root, or coronary arteries. Other technical drawbacks include difficulties imposed by shielding by intense contrast, and the inability to measure absolute flow.

### Single-photon emission computed tomography

The myocardial uptake of several potassium analogues (eg, thallium-201) correlates with regional perfusion.[41] Single-photon emission computed tomography has enhanced the role of perfusion scintigraphy as a noninvasive index of regional myocardial perfusion.[42] However, the clinical use of thallium-201 as a perfusion tracer has important limitations, including the delayed redistribution phenomenon[43] and soft tissue attenuation resulting from the low energy of thallium emissions.

These limitations may be ameliorated by the use of technetium-99m isonitriles.[44] The shorter half-life of technetium permits the performance of a true resting scan that can be compared with the image acquired during maximum coronary vasodilation. Relying on a redistribution scan by thallium imaging for this pur-

pose can introduce confusion in distinguishing ischemia from scar.

The limitations imposed by the low-energy photon emissions of thallium-201 have been improved by the use of technetium-99m; however, images using the latter agent are still prone to attenuation and scatter artifacts. Indeed, none of the conventional nuclear techniques can provide absolute data on coronary flow because of considerations relating to photon attenuation, scatter, and nonlinearity of tracer uptake at high flows.[45]

## POSITRON EMISSION TOMOGRAPHY

Positron emission techniques for assessing myocardial perfusion utilize tracer kinetic principles corresponding to the those that govern the single-photon approaches, but they employ different instrumentation and radiopharmaceuticals and yield superior spatial resolution and attenuation correction.

### Principles of imaging

Positrons are positively charged electron-like particles. When emitted by a disintegrating nucleus, they typically travel only a few millimeters before colliding with an electron. The collision produces two annihilation photons, and the energy loss of this reaction is 511 keV per photon. The photons are released at approximately 180 degrees to each other, and their simultaneous arrival at detectors on opposite sides of the patient activates a coincidence circuit that registers the occurrence of an annihilation event in that field (scatter and random photons activate a single detector and do not register an event). The resulting data are filtered, and images are formed by back-projection.[46]

### Perfusion tracers

PET commonly uses three tracers to define coronary flow: rubidium-82, nitrogen-13 ammonia, and oxygen-15 water. These agents have differing strengths with respect to various aspects of PET imaging.

The major attraction of rubidium-82 for clinical cardiac PET is that it may be obtained from a generator, avoiding the need for a cyclotron.[47,48] The short half-life of rubidium allows serially repeated measurements in the same patient, but it also requires rapid data acquisition. Rubidium uptake is proportionate with flow at normal and low flow rates but underestimates very high flow rates. Moreover, the rubidium positron is of high energy and may travel for a significant distance before annihilation, creating some ambiguity regarding the point of origin of the positron.[49]

Nitrogen-13 ammonia[50] is cyclotron-produced. Its half-life of 10 minutes allows its application in exercise stress tests but limits its use with sequential studies. As with rubidium-82, the retention fraction of nitrogen-13 ammonia declines at higher flow rates, and ischemia itself may limit the uptake of tracer. However, nitrogen-13 ammonia has lower positron energy than rubidium-82, with consequent improvement of image quality.

Oxygen-15 water is also cyclotron-produced, although a generator is under investigation. Nearly 100% is extracted by the myocardium, and its uptake is not influenced by ischemia. The half-life of this tracer is 2.2 minutes; this permits the performance of serial studies. The major limitation of oxygen-15 water is its high concentration in blood (including intramyocardial blood volume) and in lung tissue, which complicates measurements of tracer uptake in the myocardium. This blood-pool activity may be measured in a scan of oxygen-15-labeled carbon monoxide.[51] Because of this data manipulation, while these results produce reliable data regarding coronary flow, the image quality may be suboptimal.

### Imaging protocol

The imaging protocol begins with a transmission scan using a gallium-filled plexiglass ring or a rotating positron-emitting source.[52] The resulting image is used to correct for photon attenuation. The resting perfusion scan is followed by administration of vasodilator stress and stress (or hyperemic) imaging. Patient preparation and monitoring for PET is similar to that for thallium imaging: patients must fast and, with dipyridamole stress, must abstain from theophylline or caffeine products for at least 8 hours prior to the test. Electrocardiographic monitoring and blood pressure readings are obtained throughout the scan.

### Efficacy

The results of rubidium-82 PET have been compared with angiographic evidence of coronary disease.[47,53,54] The sensitivity of PET ranged from 93% to 96%, and the specificity ranged from 78% to 100%.

The binary system of sensitivity and specificity does not allow for a continuous spectrum of disease, and percent diameter of stenosis alone is not an optimal standard for quantifying the clinical severity of a lesion. For these reasons, Demer et al[55] compared PET results with "stenosis flow reserve," a measurement cal-

culated from static quantitative arteriographic dimensions. Stenosis (or relative) flow reserve is defined as the maximum flow in the stenotic artery divided by the normal maximum flow in the absence of stenosis. It is independent of hemodynamic conditions, in contrast to coronary flow reserve, which depends on perfusion pressure, coronary venous pressure, arteriolar tone, and the strength of the hyperemic stimulus.

Demer et al found that, of 193 patients, 115 had significant coronary artery disease (stenosis flow reserve >3), 37 had mild disease (stenosis flow reserve of 3 to 4), and the 41 remaining patients had essentially normal coronary arteries (stenosis flow reserve >4). Increasing impairment of stenosis flow reserve correlated with increasing subjective PET defect severity. In addition, for individual patients, the most severe PET score correlated with the calculated stenosis flow reserve of the patient's most severe coronary artery stenosis.

Recent work[56] has examined the accuracy of PET with oxygen-15 water for the definition of coronary flow reserve. Although the results correlate well with angiographic evidence of significant disease, they have yet to be compared with functional angiographic parameters.

## CONCLUSION

Accurate approaches to measuring coronary flow include quantitative angiography or direct measurements (such as intracoronary Doppler). These techniques are applicable at the time of cardiac catheterization; however, they are ill-suited to sequential follow-up. The correlation of PET results with coronary stenosis severity[46] and the possibility of making quantitative flow measurements using oxygen-15 water suggest that cardiac PET may be the best noninvasive approach for diagnostic purposes.

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