Identifying and Measuring Severity of Coronary Artery Stenosis
Quantitative Coronary Arteriography and Positron Emission Tomography
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Quantifying severity of coronary artery stenosis is becoming increasingly important for many reasons, including evaluation of interventions such as cholesterol control, stress management, pharmacological agents, percutaneous transluminal coronary angioplasty, thrombolysis, and bypass surgery; clinical decisions on medical versus mechanical treatment of coronary artery stenoses; judgment of adequacy of noninvasive diagnostic techniques; understanding the role of fluid dynamics in localizing atheroma at specific sites of an artery exposed to the same risk factors throughout its length; and in silent coronary artery disease, as the only basis for choosing medical or mechanical intervention to prevent sudden death or acute myocardial infarction.

There are two fundamental ways of describing stenosis severity based on anatomic and physiological approaches. These anatomic and physiological methods are related but provide independent complementary data; each is essential for judging severity and regression or progression or for making clinical decisions and will be briefly reviewed.

Anatomic-Geometric Assessment of Coronary Stenosis Severity

The anatomic-geometric approach uses all of the x-ray-determined geometric dimensions of a stenosis, including percent narrowing, absolute diameter, and length effects. These dimensions are integrated throughout the length of narrowing with fluid dynamic equations to predict stenosis resistance, pressure-flow characteristics of the stenosis, or coronary flow reserve. The anatomic approach is principally an invasive method requiring coronary arteriography because there is no current way of accurately defining stenosis geometry noninvasively.

Visual interpretations of coronary arteriograms are marked by such great interobserver and intraobserver variability that a comparison of arteriograms from different patients or at different times from the same patient are of limited value in assessing severity, changes in severity, or functional significance of coronary artery stenosis. For clinical purposes, percent narrowing is commonly used. However, it is an incomplete approximation of the correct anatomic-geometric method for describing severity because it does not account for other important geometric characteristics of stenoses, such as length, absolute cross-sectional luminal area, shape, multiple lesions in series, or eccentric narrowing that may be worse in one view compared with another. Absolute cross-sectional lumen area has been proposed as a measure of stenosis severity because it correlated with directly measured coronary flow reserve in the left anterior descending coronary artery. However, this association was true only for the left anterior descending artery and did not apply to other coronary arteries for describing stenosis severity. It is not, therefore, an adequate solution.

In contrast with these incomplete approximations of stenosis severity, the validity of quantitative coronary arteriography for predicting the functional pressure-flow characteristics of stenoses has been demonstrated if all the dimensions of the lesion are taken into account, including relative percent narrowing, absolute luminal area, and integrated length effects. Because these multiple dimensions have cumulative hemodynamic effects and interact with each other, they have to be integrated into a single measure of severity for a given stenosis to be practically useful. The most appropriate is flow reserve derived from all geometric dimensions of a stenosis as a standardized, single integrated measure of its severity, reflecting the combined effects of percent narrowing, absolute diameter, and length under 'standardized' hemodynamic conditions. Determination of stenosis flow reserve by this quan-
Arteriography. These methods use pharmacologically dilatory vasomotor tone, and baseline flow levels reflecting metabolic demand. Consequently, for a given fixed stenosis geometry, directly measured coronary flow reserve may vary considerably with acute changes in aortic pressure. Therefore, under acutely changing physiological conditions, directly measured flow reserve may not uniquely describe stenosis severity. In the anatomic-geometric approach of defining stenosis severity, the problem of changing physiological conditions is obviated by assuming standardized values for aortic pressure and normal maximum response to coronary vasodilatory stimuli. These assumed or standardized values are used in equations for determining coronary stenosis flow reserve based on geometric dimensions alone. Accordingly, there is no alteration in stenosis flow reserve because of extraneous physiological variables unrelated to stenosis severity. Therefore, coronary stenosis flow reserve determined by quantitative analysis of stenosis dimensions may not equal directly measured flow reserve in a given patient at a specific time because the physiological variables for the patient may not be the same as those arbitrarily assumed for the standardized geometric analysis. However, stenosis flow reserve based on anatomic geometry with assumed standardized values of aortic pressure and normal flow reserve reflects severity with sufficient precision to make intervention decisions or to compare stenosis severity either between patients or at different times in the same patient because it is independent of varying physiological conditions.

**Physiological-Functional Assessment of Coronary Stenosis Severity**

The physiological-functional approach assesses the effects of a stenosis on resting and maximum coronary flow or myocardial perfusion. It uses the concept of coronary flow reserve, first proposed 14 years ago by Gould and developed into an accepted descriptor of stenosis severity, initially by noninvasive perfusion imaging. Several invasive methods have also been tried, such as coronary sinus thermodilution, Doppler-tipped coronary artery catheters, and digital subtraction angiography. These methods use pharmacologically induced increases in coronary blood flow, most commonly intravenous dipyridamole for noninvasive, and intracoronary papaverine for invasive studies. Controversy about the relative merits of these two drugs is misplaced because one is optimal for invasive (papaverine) and the other is optimal for noninvasive studies (dipyridamole).

Recently, coronary flow reserve has been shown to be equivalent to, interchangeable with, and predicted by the anatomic-geometric analysis of stenosis severity on arteriograms if all stenosis dimensions are accounted for under controlled physiological conditions. Thus, anatomic and physiological analyses are consistent with each other, integrated, and valid theoretically and experimentally. In contrast, percent narrowing or absolute stenosis lumen area alone as a general measure for all arteries and stenoses correlates poorly with the degree of impaired coronary flow reserve.

Directly measured coronary arterial flow reserve (e.g., by flowmeter) is affected not only by stenosis severity but also by physiological characteristics of the vascular system, particularly aortic pressure, coronary vasomotor tone, and baseline flow levels reflecting metabolic demand. Consequently, for a given fixed stenosis geometry, directly measured coronary flow reserve may vary considerably with acute changes in aortic pressure. Therefore, under acutely changing physiological conditions, directly measured flow reserve may not uniquely describe stenosis severity. In the anatomic-geometric approach of defining stenosis severity, the problem of changing physiological conditions is obviated by assuming standardized values for aortic pressure and normal maximum response to coronary vasodilatory stimuli. These assumed or standardized values are used in equations for determining coronary stenosis flow reserve based on geometric dimensions alone. Accordingly, there is no alteration in stenosis flow reserve because of extraneous physiological variables unrelated to stenosis severity. Therefore, coronary stenosis flow reserve determined by quantitative analysis of stenosis dimensions may not equal directly measured flow reserve in a given patient at a specific time because the physiological variables for the patient may not be the same as those arbitrarily assumed for the standardized geometric analysis. However, stenosis flow reserve based on anatomic geometry with assumed standardized values of aortic pressure and normal flow reserve reflects severity with sufficient precision to make intervention decisions or to compare stenosis severity either between patients or at different times in the same patient because it is independent of varying physiological conditions.

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Berman from Cedars Sinai Medical Center, Los Angeles (personal communication) has suggested that the decreasing reported specificity of thallium stress imaging might be because patients with negative studies no longer undergo cardiac catheterization. Therefore, the study population would be biased by the exclusion of normals, thereby reducing the calculation of specificity. However, the study by Schwartz et al.\(^7\) with a sensitivity of 76% and a specificity of 49% was not biased by this selection because all 832 subjects, asymptomatic air force personnel, had coronary arteriograms. Thus, diagnostic accuracy of current exercise thallium imaging, particularly positive predictive accuracy, may be somewhat inadequate in asymptomatic individuals. Although localization of the artery involved is reportedly poor with planar thallium imaging, single photon emission computed tomography has significantly improved the capacity for localizing disease.\(^{25}\) Neither planar nor single photon emission computed tomographic imaging provides quantitative measures of stenosis severity.
Surrogate physiological measurements of stenosis severity use indirect consequences of reduced flow, such as chest pain, electrocardiographic abnormalities, or impaired global or regional left ventricular function during exercise or pacing stress. Commonly, these endpoints are positive only in the presence of fairly severe anatomic narrowing, do not accurately reflect stenosis severity, and may be nonspecific for coronary atherosclerosis. For example, the fall in global left ventricular ejection fraction with exercise stress has limited specificity for diagnosing coronary artery disease with frequent false-positive results. As a general rule, there is an inverse relation between sensitivity and specificity for these indirect methods, thereby limiting their clinical reliability, particularly in asymptomatic patients.

A question frequently arises as to whether perfusion imaging by positron emission tomography is too sensitive, detecting coronary artery disease that causes no symptoms. The traditional approach is to use medical or mechanical intervention only for symptoms of ischemia. However, the marker of ischemia then becomes the question. Are chest pain, electrocardiographic change, and contraction changes specific and sensitive indicators of ischemia? As indicated above, they are not always reliable, and they generally indicate advanced anatomic disease. To evaluate functional stenosis severity over the entire range (from mild to severe), maximum perfusion abnormalities reflecting direct fluid dynamic effects of arterial narrowing are necessary, regardless of ischemia. Because finding significant coronary artery narrowing without ischemia now results in significant dietary and/or medical intervention, a way of reliably identifying and following such patients without ischemia endpoints becomes important.

**Optimum Invasive Methods (Cardiac Catheterization)**

Coronary artery flow reserve, defined as maximum flow divided by resting flow, has been directly measured in humans with coronary sinus thermodilution, Doppler-tip catheter, and digital subtraction angiography. These studies have contributed importantly to our understanding of flow reserve and human coronary pathophysiology. However, for clinical purposes, they all require significant alterations in the standard procedures of cardiac catheterization, are affected by physiological conditions other than stenosis severity, and are relatively imprecise, despite being invasive. Therefore, they may not be optimal for defining stenosis severity with adequate precision for clinical decisions in individual patients. They do serve as important investigative tools and add directly measured physiological information to the more accurate and practical anatomic-geometric approach.

Quantitative coronary arteriography requires minor changes in standard catheterization laboratory procedures (i.e., appropriate x-ray views, calibration of the x-ray system, and modest equipment for analysis). It is suitable for either film-based analysis or digital subtraction angiography, thereby making it appropriate for widespread use (see Figure 1). Quantitative coronary arteriography incorporates the traditional measure of severity, percent narrowing, with other important dimensions of absolute lumen area and length derived by automated border recognition and densitometry. These dimensions are integrated into a single number, stenosis flow reserve, that is as precise as the geometric dimensions measured. It is standardized for physiological conditions other than stenosis geometry so that stenoses can be compared between different patients or at different times in the same patient. Therefore, I believe that the optimal invasive approach for defining stenosis severity is quantitative coronary arteriography, taking into account percent narrowing, absolute lumen areas, and length integrated into a single number, stenosis flow reserve. A coronary flow reserve below 2.0–2.5 is usually associated with symptoms, but further research is needed to define the level of flow reserve determined by this method that correlates with subsequent ischemic events in minimally symptomatic or asymptomatic subjects.

**Optimum Noninvasive Methods (Perfusion Imaging)**

Relative maximum myocardial perfusion or regional perfusion reserve can be assessed by radionuclide imaging, echocardiography, nuclear magnetic resonance imaging, or computed tomographic scanning. The well-defined basic principles are a strong stimulus for increasing coronary flow, such as intravenous dipyridamole; a method for monitoring relative regional perfusion changes at high-flow conditions to detect or quantify regional differences attributed to coronary arterial narrowing; and whole heart three-dimensional imaging so that artificial defects are not created or real defects missed because of interplane undersampling or changes in position of the heart in the field.

All of the above methods suffer from the failure of their “signal” or output information to increase in proportion to flow at the high flows necessary for noninvasive diagnostic imaging of myocardial perfusion. For fast computed tomography, intravenously injected perfusion tracers produce an input function that has a time duration greater than coronary transit time, thereby causing the output signal to plateau as myocardial perfusion increases. Because this problem is a basic one regardless of the type of tracer, it also limits echocardiographic measurements of perfusion after intravenous injection of microbubbles. Because nuclear magnetic resonance signal intensity decreases markedly as flow velocity rises, the signal from such images enhanced by gadolinium also plateaus as coronary flow rises. It is, therefore, unsatisfactory for diagnostic perfusion imaging at high flows. Radionuclide uptake also
fails to increase proportionately as flow increases because of falling myocardial extraction at high flows. When this problem is combined with the limitations of planar imaging or single proton emission computed tomography because of depth-dependent resolution and lack of attenuation correction, the resulting images do not accurately reflect regional maximum perfusion. Consequently, they are not quantitative, which probably explains their suboptimal diagnostic accuracy.

Myocardial uptake of positron radiotracers for perfusion imaging also fails to increase proportionately with flow. However, image reconstruction techniques in positron emission tomography are better than those in single proton emission computed tomography because of coincidence counting and attenuation correction. Although limited by falling extraction of radiotracer at high flows, the signal from positron emission tomography for following relative maximum perfusion is significantly better than other imaging modalities. It has sufficient quantitative capacity to be of reliable clinical value. With positron emission tomography, the perfusion information is reasonably quantitative, and the sensitivity and specificity is high. Figure 2 shows an example of rest-dipyridamole perfusion images obtained with 13N ammonia of a patient with three-vessel coronary disease. Three-vessel disease is readily identified as is relative severity. Significant resting collateral flow is shown by an absolute fall in activity on the dipyridamole image compared with the rest image reflecting myocardial steal. Based on data like that shown in this example, I believe the optimal noninvasive method for identifying and assessing severity of coronary artery stenosis is positron emission tomography. When used with dipyridamole stress testing, it is sufficiently quantitative to show lack of regional flow increase or a flow decrease (marked impairment of flow reserve) and can be used to identify candidates for coronary angiographic study to determine their potential suitability for mechanical treatment.

Current Problems and Future Directions

There are some basic conceptual and practical problems with positron imaging and quantitative coronary arteriography. As currently conceived, quantitative coronary arteriography addresses the severity of discrete segments of an artery. It does not account for diffuse coronary artery disease. However, the methodology now applied to discrete stenoses can theoretically be integrated along the length of the artery to determine flow reserve of the entire artery rather than discrete segments. This problem is more than just one of applied technology because it requires solutions to the biological problem of predicting what normal coronary arterial lumen area would be for a given coronary vascular bed size in the absence of diffuse disease. Several solutions look promising in this important area of research.

The current most basic problem of positron perfusion imaging is the decreasing uptake of perfusion radiotracers at high flows. To avoid this error, a first-pass model has been developed for measuring myocardial perfusion independent of extraction fraction of radiotracer. Although investigations with beta detectors used directly on the myocardium of experimental animals have been successful, the implementation of the first-pass model with positron imaging may not be feasible. The primary limitation, as for fast computed tomography, is attributed to broadening of the intravenous bolus of radiotracer by passage through the lungs so that the arterial input function is longer in duration than the transit time through the coronary vascular bed, thereby invalidating the basic assumptions of the model. Other perfusion models also fail to yield perfusion values that increase in proportion to flow for the same reason. Accordingly, at present, relative distribution of myocardial radiotracer uptake, equivalent to flow multiplied by extraction fraction, is imaged and quantified as the endpoint of perfusion imaging.

The final limitations to the routine use of both quantitative coronary arteriography analysis and positron emission tomography are practical ones. Currently, there is no commercially available cine workstation or digital subtraction angiographic unit with adequate automated border recognition and densitometric algorithms for measuring and integrating all stenosis dimensions of percent narrowing, absolute lumen area, integrated length, and shape into a single practical number, stenosis flow reserve. However, such units should be available within 1–2 years. At present, clinically oriented positron cameras that are capable of true uniform three-dimensional sampling in one scan are commercially available. They are sufficiently sensitive that adequate data can be collected with ultrashort half-life isotopes, such as 82Rb (T1/2, 75 seconds), yet do not saturate at high doses necessary for obtaining adequate numbers of counts in the image during the short period of data collection. The stress drug, intravenous dipyridamole, and an economical, generator-produced positron tracer, 82Rb, are planned for commercial release within 1 year.

Thus, it is important to emphasize that specific, unique measures of stenosis severity are established. They have been well developed theoretically, validated experimentally, and applied extensively in clinical protocols. However, their routine clinical applications will require products scheduled for commercial availability in 1–2 years.

Connection Between Quantitative Coronary Arteriography, Positron Emission Tomography, and Stenosis Severity

Quantitative coronary arteriography accounting for all stenosis dimensions of percent narrowing, absolute lumen area, and length provides a single integrated measure of anatomic geometry with suf-
Figure 2. Positron emission tomography in oblique semilong-axis views as acquired (top), in true short-axis views (middle), and in horizontal and vertical long-axis views (bottom). Rest images are shown in the top two rows with dipyridamole stress images in the bottom two rows of each panel. In the color coding, white is the highest, red next highest, yellow intermediate, green and blue lowest flows. Tomographs are oriented as if looking down from above with the anterior or apex at the top of each image (ANT), the left lateral free wall on the left (LAT), and the muscular septum (SEP) on the right with the atrioventricular ring and/or inferior myocardium at the bottom (POST). In the top left panel, the first slice shows the top of the heart, while the last slice shows the inferior or diaphragmatic myocardium below the left ventricular cavity. In the top right panel, the cuts are arranged from the atrioventricular ring to apex. The open "c" in the basal short-axis views are attributed to the membranous septum. Resting tomographs show a small posterior defect indicating a small myocardial scar. With dipyridamole stress, the septum increases activity appropriately. The anterior and apical myocardiums show a moderate defect. The lateral free wall shows a severe stress defect; the inferior myocardium also shows a severe defect. Tomographic data can be summarized in a polar display as if looking up from below at the apex of the left ventricle located at the center of a bullseye where the outer rim of the bullseye corresponds to the atrioventricular ring. Polar displays on the lower left of bottom left panel show the relative defect on a scale from 0% to 100% with rest being the upper and the stress the lower of the polar maps on the left side of the panel. Right-hand polar map labeled S2/S1 absolute ratio shows the absolute counts of the stress image divided by the rest image displayed on a scale from 0 to 2. Increase in activity is shown by warm colors indicating ratios >1 or an increase in absolute activity reflecting increased perfusion on the dipyridamole image. Blue area indicates an absolute fall in activity reflecting a fall in perfusion during dipyridamole stress consistent with myocardial steal and a large area supplied by collaterals. Lower right polar display labeled S2/S1 percent ratio illustrates the change in the relative distribution of flow at stress normalized to rest (instead of the absolute values). Thus, polar maps demonstrate a small inferior lateral resting defect on the rest study (Study 1), and a severe large stress defect of distal anterior, apical, inferior, and inferior lateral myocardiums on the stress study (Study 2). A large area of viable collateralized myocardium showing myocardial steal is seen in the polar display of S2/S1 absolute ratios. On a visual scale from 0 (no defect) to 5 (severe defect), positron imaging therefore demonstrated three-vessel disease consistent with a moderate left anterior descending coronary artery stenosis, severe left circumflex and right coronary artery stenoses with a small posterior scar, and a large area of myocardium that is collateralized and viable. These findings were confirmed at arteriography.
sufficient accuracy to use for clinical decisions or investigative purposes. It is theoretically well developed, validated experimentally, and has been demonstrated clinically useful. Therefore, it is optimal for defining stenosis severity invasively.

Positron imaging of the heart with either generator-produced $^{82}\text{Rb}$, cyclotron-produced $^{13}\text{N}$ ammonia, or $^{18}\text{F}$ deoxyglucose is optimal for accurate noninvasive diagnosis of coronary artery disease in symptomatic or asymptomatic patients,$^{8,18,19,45,46}$ for assessing physiological stenosis severity,$^{8,18,47-49}$ for imaging myocardial infarction$^{50-59}$ and determining myocardial viability,$^{61-64}$ for assessing effects of interventions such as thrombolysis$^{56}$ or percutaneous transluminal coronary angioplasty on coronary flow reserve$^{60}$ or of bypass surgery on function and metabolism,$^{64}$ or for following progression or regression of coronary artery disease during risk factor treatment,$^{61}$ and for evaluating collateral function noninvasively.$^{62}$ Positron imaging, therefore, provides a physiological or functional basis for specific therapeutic approaches in the management of heart disease, particularly silent or symptomatic heart disease, that was not previously possible.

Accurate noninvasive physiological (positron emission tomography) and invasive anatomic (quantitative coronary arteriography) definition of stenosis severity are complementary. Together, they provide a complete description of coronary artery narrowing. Each is becoming essential to clinical cardiology for two major reasons. The first reason is that modern cardiovascular medicine has powerful medical or mechanical interventions for coronary artery disease that can heal or harm patients in the face of currently inadequate methods for quantitating stenosis severity. The bases for deciding on complex advanced interventions and for assessing or following their effects are usually fairly subjective or qualitative and have changed little clinically over the last 25 years. These endpoints are primarily chest pain and visual evaluation of arteriograms, assisted by electrocardiographic and thallium imaging; all are of limited independent accuracy, especially in the asymptomatic patient, and are poorly related to stenosis severity.

The second reason for optimal quantitation of stenosis is the growing importance of silent coronary atherosclerosis. Coronary heart disease causes one third to one half of all deaths of people between the ages of 35 and 64 years in the United States. Up to 13% of middle-aged men in the general population have coronary artery disease.$^{63,64}$ Most without symptoms. Consequently, 40–60% of patients with sudden death or myocardial infarction present without previous symptoms.$^{65-68}$ Silent ischemia is increasingly recognized in symptomatic and asymptomatic individuals$^{69,70}$ and may have a less-favorable prognosis when occurring during exercise testing$^{71}$ or in patients with recent unstable angina.$^{72}$ The community model of mass intervention for coronary atherosclerosis has been questioned as optimal compared with the medical model for intervention by risk factor control in specific individuals.$^{73}$ However, even assuming its effectiveness, the medical model of risk factor control is limited by risk factor analysis having a low sensitivity and specificity for identifying individuals with significant coronary artery disease. For example, of 40–55-year-old adult men with high cholesterol and blood pressure, two thirds remain well over the subsequent 25 years.$^{74}$

Therefore, major questions facing cardiologists are how to identify silent coronary artery disease in specific individuals, how to define its severity, how to decide objectively between medical and mechanical interventions, and how to assess the results. Because anginal pectoris correlates relatively poorly with stenosis severity and can be improved if not eliminated in many patients with medical therapy, what endpoints are used for deciding on mechanical intervention? How are the results assessed?

Although we hope to improve mortality and use it as an important endpoint, mortality is a remote, indirect measure of outcome in coronary atherosclerosis, providing no quantitative gradations, no causal interconnections, and no insight into mechanisms in circumstances where they are most needed medically. Based on data outlined here, the answers to these questions may be best provided by quantitative coronary arteriography and positron emission tomography because they offer optimal definition of anatomic and physiological severity of coronary artery stenosis by both noninvasive and invasive means.

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KEY WORDS • coronary artery stenosis • catheterization • positron emission tomography • perfusion imaging
Identifying and measuring severity of coronary artery stenosis. Quantitative coronary arteriography and positron emission tomography.

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Circulation. 1988;78:237-245
doi: 10.1161/01.CIR.78.2.237

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