Quantitative Assessment of Myocardial Perfusion

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Does Coronary Flow Trump Coronary Anatomy?

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Coronary function versus anatomy, flow versus stenosis: which optimizes coronary artery disease (CAD) management? In patients, coronary flow is poorly related to stenosis severity, and revascularization fails to improve mortality over medical treatment in randomized trials. Yet percutaneous intervention (PCI) guided by fractional flow reserve reduces coronary events more than PCI guided by arteriographic stenosis. These paradoxes are explained by the poor relation between coronary flow reserve (CFR) and stenosis severity due to diffuse CAD, with surprising clinical implications. Should the concept of anatomically “critical” coronary stenosis be replaced by the concept of “critical” CFR reduction for managing CAD? (J Am Coll Cardiol Img 2009;2:1009–23) © 2009 by the American College of Cardiology Foundation

Several major paradoxes remain unresolved in the management of coronary artery disease (CAD). The first is that percent stenosis does not predict or reliably relate to maximum flow capacity or coronary flow reserve (CFR) in human CAD. The second is that revascularization procedures to improve coronary blood flow do not reduce coronary events more than intense medical treatment in randomized trials. In contrast to these revascularization trials, percutaneous coronary intervention (PCI) guided by fractional flow reserve (FFR) had significantly fewer follow-up coronary events than PCI based on angiographic percent stenosis. Finally, as an example of the underlying issues, a fixed mild stenosis on a clinical arteriogram may, in some circumstances, markedly reduce maximum coronary flow and flow reserve, reduce FFR, and warrant revascularization despite similar mild stenosis not significantly reducing CFR in precise stenosis of animal models.

These paradoxes are so counterintuitive that they evoke a wide range of explanations, debate, or disregard, all of which have elements of truth but lack cohesive explanation. This analytical review addresses these paradoxes with an explanation leading to a surprising clinical hypothesis: for equal optimal medical management, revascularization to improve coronary flow may reduce coronary events in patients with initial severe reduction in absolute maximum coronary flow or CFR, but not in patients with adequate flow capacity, independent of percent stenosis. In other words, revascularization in patients with low coronary flow capacity may show mortality benefit over revascularization in populations chosen for the revascularization trials based on percent stenosis that is poorly related to coronary flow capacity.

Mild Stenosis Causing Low CFR, Low FFR, Indicating PCI

The following case illustrates these paradoxes. The patient in Figure 1 is a 68-year-old man with hypertension, past smoking, low high-density lipoprotein (HDL) level, and acute...
myocardial infarction 13 years previously, treated with thrombolysis and PCI of the left anterior descending coronary artery (LAD). Seven years after myocardial infarction, rest-dipyridamole positron emission tomography (PET) perfusion imaging showed a mild anterior resting defect with mild stress-induced worsening. Left ventricular function was normal. He gained weight, from 198 to 242 lbs, did not maintain a healthy diet, and did not exercise. His lipid profile during these years showed total cholesterol 118 mg/dl, triglycerides 142 mg/dl, low-density lipoprotein (LDL) 59 mg/dl, HDL 31 mg/dl on simvastatin 5 mg, Niaspan (Abbott Laboratories, Abbott Park, Illinois) 2,000 mg, and fenofibrate 160 mg daily. Although the LDL level was optimal on drug treatment, the low HDL and unhealthy lifestyle remained uncontrolled risk factors for progression.

Routine follow-up PET 6 years after the first PET showed progression with a relative stress-induced defect in the mid-LAD distribution that was 0.65, or only 65% of the activity in adjacent proximal areas of the heart. There was also a severe stress-induced defect in the distribution of a small ramus intermedius or 1st obtuse marginal branch. Computed tomography (CT) done for attenuation correction of PET data showed dense coronary calcification of all coronary arteries. Absolute maximal myocardial perfusion in the mid to distal LAD distribution was markedly reduced to 1.2 cc/min/gm compared with 2.5 to 3.0 cc/min/gm or higher in healthy young volunteers. The CFR in the distal LAD distribution was reduced to 1.8 compared with an average of 3.0 in the rest of the heart proximally and compared with 4.0 in healthy young volunteers.

In view of past myocardial infarction and progressive disease, a coronary arteriogram was done showing concentric 57% mid-LAD stenosis by automated quantitative coronary arteriographic analysis (QCA) and FFR of 0.65 by pressure wire measurements in the aorta and distal to the stenosis. A LAD stent was placed in view of significant progression associated with low CFR, low FFR, low HDL, and uncontrolled lifestyle despite optimal drug treatment. After stent placement, FFR improved to 0.92, indicating improvement but also a residual pressure gradient due to diffuse disease proximal to the stent.

In precise experimental stenosis models with no diffuse disease, a 57% stenosis has little effect on CFR, as shown below in Figure 2A (1). In this patient, absolute perfusion in cc/min/gm showed that the 57% diameter stenosis was superimposed on moderately severe diffuse disease, thereby making the cumulative diffuse and focal disease functionally severe. Relative flow reserve, or flow-derived FFR, expressed as the ratio of absolute CFR of 1.8 in the distal LAD distribution to average CFR of 3.0 in the rest of the heart is 0.6, comparable to the pressure-derived FFR of 0.65 at coronary arteriography.

**Critical Coronary Artery Stenosis and CFR**

Some of the basic concepts here were published before Web- and PDF-based literature and hence are not “widely in mind.” Therefore, original illustrations are used to explain these paradoxes, abetted by the adage that durability supports validity. The concept of “critical” coronary artery stenosis was first documented 35 years ago in animal studies as 85% diameter narrowing, at which resting coronary flow began to fall, and 50% diameter narrowing, at which CFR began to diminish, illustrated in Figure 2A (1). The experimental canine models used external coronary artery constriction with no atherosclerosis or diffuse disease.

Thus, in principle, a 50% to 85% diameter narrowing became the anatomic criterion for classifying severity of stenosis and the basis for revascularization procedures. A single clinical end point of this threshold range evolved as ≥70% diameter stenosis, which remains the anatomic “gold standard” of severity and guide to procedures. Many experimental studies since that time have confirmed the initial observations relating stenosis dimensions of absolute arterial diameter, length, relative stenosis, the pressure-flow characteristics of coronary stenosis, and CFR (2–11).

**Anatomy Versus Flow in Coronary Atherosclerosis**

However, human studies 25 years ago showed no relation between CFR and percent stenosis on arteriogram (Fig. 2B) (12). Recently, this dissociation in patients between anatomic and functional severity was reconfirmed by the poor correlation among quantitative percent stenosis on invasive or CT coronary arteriograms and FFR by pressure wire as a measure of relative CFR (Fig. 3) (13). The FFR is a validated, reproducible measure of relative CFR, derived from pressure measurements in the aorta or proximal and distal to a localized coronary stenosis at maximum pharmacologic arteriolar vasodilation (13–20). Like relative CFR (10), it is expressed as a fraction of 1.0 for no flow-limiting stenosis, decreasing toward 0.1 or 0.2 for very severe stenosis.
In humans, the dissociation of anatomic and functional measures of coronary stenosis severity is due to diffuse atherosclerosis and extent of arterial remodeling. Figure 4A illustrates this simple, but profound, concept that underlies most diagnostic, therapeutic, and interventional management of CAD. However, the broad conceptual and clinical implications of this fact are commonly not recognized in cardiovascular medicine, or at least may not substantially influence its practice.

In Figure 4A for an otherwise normal artery, drawn to scale, an arteriographic 63% diameter constriction mildly reduces CFR to 3.5 from the normal of 4.0 that characterizes young volunteers without risk factors. An arteriographic 87% diameter constriction in a coronary artery reduces CFR to 1.0, i.e., eliminates capacity for increasing flow, in the absence of diffuse disease (1). Now consider a different artery with 38% diameter diffuse narrowing without arterial remodeling and no segmental...
stenosis. This modest, diffuse narrowing along the whole length of the artery has a dramatic fluid dynamic effect, reducing CFR to 1.4 (11). The same diffuse narrowing plus an arteriographic 60% diameter stenosis without remodeling reduces CFR to 1.0, essentially eliminating the capacity for increasing flow.

Anatomy Versus Flow With Coronary Artery Remodeling

Arterial remodeling markedly alters the anatomic-functional measures of severity of both segmental and diffuse disease. With remodeling, despite comparable diffuse disease and arteriographic stenosis, CFR is only mildly reduced to 3.5 in this example. For each of these cases, intravascular ultrasound (IVUS) would measure percent stenosis of the lumen compared with the elastic external membrane of the artery, thereby “seeing” diffuse disease and more severe stenosis not apparent on the arteriogram. However, for diffuse disease with no “normal” segments, IVUS does not measure the extent of remodeling or account for the cumulative effect of narrowing length on flow.

For each of these schematic examples, Figure 4B plots anatomic percent stenosis by arteriogram and by IVUS compared with CFR. It is a scattergram, essentially the same as observed in patients in Figure 2B, explaining why anatomic measures of stenosis, even by precise dimensions of IVUS, fail to correlate with maximum flow or CFR in humans. Depending on the extent of diffuse disease and of remodeling, anatomic measures of stenosis severity by either arteriogram or IVUS do not indicate the functional severity of stenosis or flow capacity despite their role in documenting regression or progression of coronary atherosclerosis. In reality, the coronary arteries in CAD have a heterogeneous mix of all the combinations illustrated in the schematic of Figure 4A in any single artery and/or among all the coronary arteries of any individual, thereby making the relation between percent stenosis by either arteriogram or IVUS and coronary flow capacity even more unpredictable than illustrated by any one of the alternative schemas in Figure 4A.

The challenge to current anatomically driven cardiology is even more profound in view of the documented errors of visually interpreted invasive arteriograms, and inadequacy of even quantitative CT angiography to differentiate among intermediate stenosis of 30% to 75% diameter stenosis (13,21).
Although it is well established in the literature and widely accepted intellectually, cardiologists commonly disbelieve that their “eyeball scale” is so different from actual or objectively measured severity. Figure 5 shows cine views of precisely known dimensions and percent diameter stenosis of a 3-mm model “artery” filled with contrast medium immersed in water with no motion. The 0.5-mm lumen of the 83% stenosis is mottled due to the limited resolution of even the invasive arteriogram. A so-called 90% diameter stenosis of a 3-mm artery will not have a visible lumen on cine, and fluid dynamic analysis requires over 400 mm Hg pressure for forward contrast flow to fill the artery.

**Anatomic Stenosis May Mislead Both for and Against Revascularization Procedures**

In the absence of diffuse disease, the 63% diameter stenosis in Figure 4 would have a CFR of 3.4 as shown in Figure 2A. However, visual reading would likely be of greater severity leading to PCI that is not necessary, given the capacity to increase flow 3 times baseline. However, moderate diffuse disease...
without remodeling and a 60% stenosis would severely reduce CFR to 1.0 and cause ischemia such that PCI might be indicated to improve flow up to the limit imposed by the diffuse disease. On the other hand, severe diffuse disease might limit flow so severely that doing PCI on the stenosis would not improve flow. Only FFR or quantitative PET perfusion imaging can sort out the contribution of the localized stenosis versus the diffuse disease as illustrated in the patient examples below.

**Anatomy Versus FFR: Clinical Outcomes**

For deciding revascularization procedures, the clinical advantage of functional measures of stenosis severity as opposed to anatomic measures is well established. In patients with greater than 50% diameter stenosis visually on invasive coronary arteriogram, those randomized to FFR-guided PCI for FFR <0.8 had fewer PCI procedures and better clinical outcomes than patients randomized to PCI based on visual judgments of arteriographic severity (Fig. 6A) (13,17–19). Furthermore, in many randomized trials of patients with stable CAD and stenosis arteriographically suitable for revascularization, those undergoing revascularization procedures had no benefit on mortality or coronary events over medical management, illustrated for PCI in the most recent of these trials in Figure 6B (22). At the 2- to 5-year follow-up, there was also no difference in angina between the PCI and medically treated groups.

These studies indicate that anatomic measures of coronary stenosis are suboptimal guides to the management of CAD from every viewpoint—physiology, technology, clinical management, outcomes, risks, and costs—yet remain the central guide to current cardiovascular practice. Based on current data, FFR is the invasive definitive physiologic gold standard for assessing stenosis severity as the basis for revascularization procedures that reduces unnecessary procedures, with better clinical outcomes than revascularization decisions based on anatomic severity. Quantitative PET perfusion imaging is the noninvasive definitive gold standard for assessing physiologic stenosis severity by absolute maximal myocardial perfusion in cc/min/g and CFR.

**Fixed Anatomic Viewpoint?**

What explains this anatomic focus of cardiologic practice against substantial opposing scientific data? Invasive cardiologists provide a verbatim answer as follows: “Although cardiologists might believe they are benefiting their stable patients with CAD by performing PCI, this belief appears to be based on emotional and psychological factors rather than on evidence of clinical benefit.” “The only thing that would really change is if there had been an imaging study—and it would have changed it, not by how you responded to the catheterization, but by not doing the catheterization at all” (23).

This conclusion by an invasive cardiologist from a peer-reviewed published survey on use of PCI in stable CAD may help explain why FFR is seldom measured at coronary arteriography prior to PCI in the U.S. despite hard data on its benefits as the basis for these procedures. The same anatomic viewpoint may also help explain why, despite guidelines of the American College of Cardiology recommending stress testing before PCI, only 45% of patients undergoing elective PCI for stable CAD have a prior stress test, with great geographic variation in the U.S. (24). The literature shows the following facts: 1) systematic visual overestimation of stenosis severity compared with objective quantitative coronary arteriographic analysis; 2) in the U.S., 55% of
elective PCI procedures do not have a prior stress test despite guidelines of the American College of Cardiology; 3) revascularization procedures have no benefit over medical treatment for coronary events or mortality in randomized trials; and 4) FFR is not widely used in the U.S. as a basis for doing PCI or not despite randomized trials on its efficacy for selecting patients for PCI.

Emphasizing these facts does not imply that cardiologists are making conscious decisions to do procedures that are recognized as unnecessary. Rather, the implication is that the procedures are done in the intuitive belief that revascularization of anatomic stenosis generally improves coronary flow despite contravening data that remain inadequately explained. This analytical review provides an integrated concept explaining these paradoxes and associated skepticism about the “no added benefit data” that are intuitively contrary to the envisioned benefit of improving coronary flow by revascularization procedures.

The oculoanatomic reflex, invasive technology, and contravening coronary physiology, noninvasive technology, and outcomes of medical treatment, all good medical science, are here to stay but need better integration or balance.

A potential solution to these conflicting viewpoints is outlined in this integrated analysis: measure resting and maximal absolute myocardial perfusion in cc/min/g and CFR as the primary guide to invasive procedures, revascularization, and for following changes in CAD using available technology, maximal pharmacologic treatment, and lifestyle intervention, all of which are already proven effective. If a stenosis does not markedly limit regional myocardial perfusion or CFR, an invasive arteriogram and revascularization procedure will not likely be beneficial. For residual uncertainty about stenosis severity, FFR measured by pressure wire at the time of the coronary arteriogram provides reliable invasive confirmation for proceeding or pulling out without PCI.

### Absolute Myocardial Perfusion in cc/min/g and CFR by PET

Although coronary flow is a major focus of the cardiology profession that justifies procedures based on improving it, few cardiologists quantify myocardial perfusion or measure CFR or have ever measured it, or even understand how to use the information if obtained, here addressed. For several years, this lab has routinely quantified myocardial perfusion in cc/min/g and CFR in all patients undergoing diagnostic cardiac stress perfusion PET using rubidium-82. For this discussion, CFR is used interchangeably with myocardial perfusion reserve. Absolute perfusion is determined using our “simple” method particularly suitable for rubidium-82, validated experimentally with minimal methodologic variability (25,26), and semiautomated for routine clinical application. Attenuation-emission misregistration is routinely checked and corrected for every patient using cine CT attenuation correction that accounts for breathing motion (27–29). Our PET perfusion images are displayed as if looking at 90° quadrants of the heart rotating through 360°, with a superimposed generalized arterial map as in the illustrations below for the various categories of CAD.
Figure 7 illustrates a common clinical problem of assessing coronary calcification. The patient is a 75-year-old man with hypertension, hypercholesterolemia, atypical chest pain, dense coronary calcification with a calcium score $>4,000$, and a coronary CT angiogram reported as the following percent diameter stenosis of the left main 50%, LAD 75% to 80%, left circumflex (LCx) 70% to 80%, and right coronary artery 50%. A coronary arteriogram and bypass surgery were recommended, leading him to request a PET scan and second opinion. His rest-dipyridamole PET perfusion images, Figure 7A, show resting heterogeneity and small, mild-to-moderate, stress-induced perfusion defects in the basal left lateral distribution of a second obtuse marginal (OM2) branch (white arrow) and in the distal inferoapical distribution (white arrow) typical of a LAD wrapping around the apex. Although there are no large severe perfusion defects, “balanced” coronary disease might fail to reveal severe, localized, relative perfusion defects.

However, Figure 7B shows good absolute myocardial perfusion and CFR. The maximal perfusion with dipyridamole stress averaged 2.9 cc/min/g for the whole heart, and CFR averaged 3.7, comparable to 4.0 for young healthy volunteers. The septal distribution has a CFR of 4.1, indicating no significant left main stenosis since myocardial perfusion can increase 4 times baseline, comparable to young healthy volunteers. In the LCx distribution, CFR is 3.7, and in the LAD distribution, CFR is 3.4, consistent with mild narrowing. In the small, mild-to-moderate, basal-lateral, and distal inferoapical relative stress-induced defects, maximum absolute perfusion is 1.8 cc/min/g and CFR is 2.7. Even in these small “worst” regions, maximum perfusion is quite good, far above ischemic levels, with flow increasing during stress to 270% of baseline flows. The regions of resting flow heterogeneity that improve with dipyridamole stress are associated with coronary atherosclerosis (30).

The quantitative PET findings explain why this patient can do hard physical exertion without angina, including heavy weight lifting that caused some nonexertional musculoskeletal pain, but not angina. He has diffuse, severe, calcific, nonobstructive coronary atherosclerosis, but does not have clinically significant flow-limiting stenosis that requires invasive coronary arteriogram or revascularization. The reported stenosis severity on CT angiogram is not accurate and fails to indicate coronary flow capacity. The CT spatial resolution is not adequate for determining severity (21) that was overestimated, as also documented for invasive arteriograms. Even with precise high-resolution stenosis measurements, anatomic severity is not reli-
ably related to maximal perfusion or CFR due to diffuse disease and varying degrees of arterial remodeling, as shown in Figure 4A.

Figure 8 illustrates what absolute myocardial perfusion and CFR “tell” us in 3 different patients with severe CAD. Except for the single resting baseline inferior views shown for each patient, all other quadrant views of resting relative uptake images (lateral, anterior, and septal quadrants) were normal for all 3 patients. (B) For each of the same 3 patients, CFR throughout the left ventricle is shown. Average CFR for the whole heart and average quadrant values are shown for each quadrant. Abbreviations as in Figure 1.

![Figure 8. Quantitative PET for Assessing Severe Stenosis](image)

**A** PET relative perfusion images in 3 different patients with severe coronary artery disease. Except for the single resting baseline inferior views shown for each patient, all other quadrant views of resting relative uptake images (lateral, anterior, and septal quadrants) were normal for all 3 patients. **B** For each of the same 3 patients, CFR throughout the left ventricle is shown. Average CFR for the whole heart and average quadrant values are shown for each quadrant. Abbreviations as in Figure 1.

For Patient #3, CFR ranges from 2.5 to 4.4 in proximal LCx and proximal LAD distributions, tapering to 1.5 to 2.0 in mid to distal arterial distributions. This longitudinal base-to-apex gradient or tapering of CFR is characteristic of diffuse narrowing (31,32). An obtuse marginal branch supplies part of the mid inferolateral region with a CFR of 3.0. The CFR of 0.9 in basal inferior and inferolateral distributions indicates myocardial steal associated with collaterals to viable myocardium beyond an occluded PDA and occluded distal LCx. As part of our clinical studies of absolute myocardial perfusion, all 3 patients had coronary arteriograms that confirmed these findings. Patient #1 needed no revascularization procedure as indicated by quantitative PET. For Patient #2, arteriogram showed diffuse and segmental disease for which he refused bypass surgery for 2 years, but with progressive angina, then had successful bypass. Patient #3 did not show anatomy suitable for revascularization due to severe diffuse disease, with collateralized occluded arteries as predicted by PET, but became asymptomatic on vigorous lifestyle and medical treatment.

Figure 9 illustrates what absolute myocardial perfusion and CFR tell us for 3 different patients with positive single-photon emission computed tomography (SPECT) stress tests and/or chest pain who sought a second opinion after recommendation for an invasive procedure. Again, only the resting...
worst relative perfusion views are shown, other resting views being normal and not shown as redundant. The stress relative perfusion images in Figure 9A are all similar with only mild-to-moderate, small, scattered stress-induced perfusion defects. However, perfusion in cc/min/g during dipyridamole stress for each of these patients in Figure 9B also reveals dramatically diverse extent of CAD. Patient A has good CFR of 3.5 throughout the left ventricle and does not need any procedures since the SPECT abnormality was an attenuation artifact. Patient B shows diffuse, uniform, moderate reduction of CFR with no significant regional stress-induced defects, consistent with diffuse small-vessel disease associated with diffuse coronary calcification and hypertension in this asymptomatic patient for which an arteriogram is not indicated. On the relative uptake images of Figure 9A, Patient C has the most severe localized basal inferior and inferoseptal defect of these 3 patients, but has remarkable CFR, averaging 5.0 throughout the left ventricle. In the moderately severe relative stress-induced defects of the relative PET images in Figure 9A, CFR is adequate at 2.9, and an arteriogram is not indicated since myocardial perfusion can increase by nearly 3 times baseline flow in the worst regional relative stress-induced defect.

What Does Myocardial Perfusion Quantified in cc/min/g and CFR Tell Us Clinically?

These examples show that absolute myocardial perfusion and CFR reveal insights into the coronary circulation that far surpass even high-quality, artifact-free, relative PET perfusion images. Clinically interpreting or “reading” absolute perfusion and CFR is substantially different from interpreting relative uptake PET or SPECT images, and more complex, here summarized based on my experience in the first 1,000 cases:

1. The numbers in cc/min/gm and CFR values are the critical end points that can be scaled by a color bar, but colors are only a visual aid to “seeing” the critical absolute numbers.
2. Classifying absolute perfusion and CFR as normal or abnormal for a given patient is nearly meaningless clinically because many people over 40 to 50 years of age have some nonobstructive coronary atherosclerosis or some other cause of reduced CFR compared with healthy young volunteers. Therefore, the essence of clinically interpreting absolute perfusion and CFR is “how bad” CFR or absolute maximal flow is, not whether they are “normal” or not. Clinical interpretation of the severity of impaired perfusion is the essential guide to invasive procedures, not the binary normal–abnormal categorization now used for relative perfusion images in which relative defects require arteriographic assessment or confirmation. Thus, the guide to invasive procedures is to “read the worst quadrant values of maximum flow and CFR” of the left ventricle corresponding to each major coronary artery.
3. Both maximum absolute perfusion in cc/min/gm and/or CFR are separately and independently important for clinical purposes. Rest-
ing perfusion may be increased at higher heart rates or blood pressure, thereby reducing CFR despite high maximum perfusion values. The argument of CFR or maximum absolute perfusion as “better” than the other fails to recognize the complexity of coronary physiology in which either may be important depending on resting perfusion and diffuse disease as addressed in the next section.

4. Regional maximal stress-induced perfusion in cc/min/g, coronary flow reserve, and relative perfusion images are all necessary for complete understanding of segmental and diffuse CAD as the basis for invasive procedures. Diffusely reduced maximum perfusion or CFR with no focal worse stress-induced defect indicates diffuse disease without sufficient additional localized stenosis that revascularization would benefit. With both diffusely reduced absolute maximum perfusion or CFR and regional worse defects, the relative importance and potential value of revascularization is judged from the regional absolute maximal cc/min/gm and of the regional values versus other areas.

5. In our experience, the threshold for clinically significant flow-limiting stenosis that might justify an invasive procedure requires an absolute maximum perfusion below 1.0 to 1.2 cc/min/g after dipyridamole stress and/or CFR of 1.5 to 1.7 or lower and a corresponding regional stress-induced abnormality on relative perfusion images, or other regions with substantially better absolute perfusion/CFR, indicating severe segmental disease in addition to whatever diffuse narrowing is present. These limits are subject to modification with more data and experience, probably toward lower flows as the threshold for intervention. Of course, all quantification needs to be viewed from a clinical perspective, including symptoms, response to medical treatment, comorbidities, physiologic—clinical judgment, and ongoing evolving data on management of CAD.

6. Myocardial steal associated with collateralization beyond an occluded coronary artery is valuable clinical information that can be assessed only by measuring absolute perfusion and CFR. A CFR of >1.0 indicates a fall in perfusion during stress to below resting levels, or myocardial steal. Although the term steal is widely used, it is a misnomer in a sense because blood is not pulled from one myocardial region into another region. Rather, during dipyridamole-induced high flow, the pressure drop along a diseased artery supplying the collaterals decreases the perfusion pressure at the collateral source, thereby decreasing collateral flow.

7. Absolute perfusion and CFR provide essential physiologic information about isolated stenosis severity, multiple stenosis, diffuse CAD, or combined multiple stenosis and diffuse disease that characterizes most CAD. If the coronary arteriogram is truly normal without stenosis and without diffusely small arteries, then absolute perfusion and CFR may also quantify small-vessel disease.

Which Is Best: Maximum Myocardial Perfusion in cc/min/g or CFR?

In many patients, maximum myocardial perfusion may be severely reduced to the 1.0 to 1.2 cc/min/gm range. However, with beta-blockade and good risk factor control, heart rate of 45 to 50 beats/min, and systolic blood pressure of 100 to 110 mm Hg, the resting myocardial perfusion is commonly as low as 0.4 cc/min/g with CFR of 2.5 to 3.0 and no exertional angina. Therefore, continued medical management is a valid option to revascularization since the coronary arteries retain the capacity for increasing flow to meet increased demand within this overall lower reset demand—supply balance. However, if the resting perfusion were 0.8 to 0.9 cc/min/g with the same maximum perfusion of 1.0 to 1.2 cc/min/g, as in a diabetic patient who does not feel cardiac pain, then CFR is profoundly impaired and revascularization is indicated.

Another reason for considering CFR as well as maximum perfusion alone is technical, related to the methodology of determining absolute perfusion. Determining the arterial input function of the radionuclide may be somewhat difficult. If the imaged arterial input were lower than the real value, the absolute perfusion would be too high and would underestimate flow restriction both regionally and throughout the heart at rest and stress, thereby underestimating disease severity. However, to some extent, partially, the stress—rest ratio or CFR would be somewhat less affected by a systematic error in arterial input. Therefore, a low regional CFR with a big severe relative defect, with ECG changes or exertional angina, but maximum absolute perfusion of 2.5 to 3.0 cc/min/g, would make one suspect an error in the arterial input function. Hence, CFR may provide confirming information important for major decisions about people’s lives. Finally, CFR based on absolute perfusion provides some comparison to other measures of severity.
such as the relative uptake images and invasive FFR determined from pressure measurements as confirming data.

**FFR, Relative CFR, Absolute CFR, and Perfusion Images**

Pressure-derived FFR is equivalent to relative CFR, i.e., the ratio of maximum flow in the stenotic artery to maximum flow of the same nonstenotic artery (13–20) expressed as a fraction of 1. FFR derived from pressures just proximal and distal to a specific stenosis does not account for and is not affected by diffuse disease. However, FFR derived from pressures in the aorta and just distal to the stenosis reflects the combined effects of both the stenosis and diffuse disease proximal to the stenosis.

Rephrasing the same paradox above gives an additional insight into the diffuse disease issue. In healthy young volunteers, CFR is typically 4.0 or higher by quantitative PET in our lab. An FFR of 0.75 or lower has been associated with clinical ischemia and indication for PCI. However, 0.75 times a normal CFR of 4.0 indicates a remaining flow reserve of 3.0 that never causes ischemia in our experience and is higher than many asymptomatic people over 40 years of age without known CAD. Therefore, why does an FFR threshold of 0.75 indicate ischemia in clinical trials of its use? The answer to this version of the paradox is the same: diffuse disease in addition to whatever stenosis is on the arteriogram. The FFR studies were done on populations at risk for CAD due to risk factors and high prevalence of diffuse disease. Consequently, their absolute CFR is not 4.0, but averages 2.0 to 2.5 in our experience, so that the FFR threshold of 0.75 corresponds to an absolute CFR of 0.75 times 2.2, or 1.7, which is approximately what we observe in untreated patients with mild exertional angina.

Relative perfusion images (standard radionuclide uptake images) also show relative perfusion defects in the stenotic region compared with an adjacent region expressed as a ratio or fraction of 1, similar to pressure FFR and relative CFR determined from absolute perfusion. However, if the adjacent artery supplying the adjacent myocardial region is also stenotic, the relative defect severity on relative perfusion images is reduced, whereas pressure FFR and relative CFR by absolute perfusion in 1 coronary artery do not depend on the status of the adjacent coronary artery.

**Technical Issues in Quantitative Cardiac PET Perfusion Imaging**

Standard cardiac PET-CT protocols and software are associated with misregistration errors causing significant artifactual abnormalities in 20% to 40% of patients (27–29). Therefore, we developed software for cine CT attenuation correction by acquiring continuous low-dose CT scans during 2 breathing cycles that better matches emission data without added radiation exposure (28,29). In principle, a 3-rod rotating transmission system for attenuation correction would minimize misregistration problems of PET-CT, reduce radiation dose, cost less, and be comparably fast.

For radionuclides with complex kinetics, adequate curve fitting of mathematical low models requires frequent brief images that are count poor with high noise and limited clinical value. The kinetic model for rubidium-82, a potassium analog, is “simple” since cellular trapping of potassium and rubidium is nonlinearly proportional to flow with no exiting from the myocardial cell during imaging. As validated in Figure 10, the “simple” rubidium flow model accounts for flow–dependent extraction (25,26,33) with a single 2-min arterial input image and a single 5-min myocardial uptake image, thereby providing high-quality, high-count, low-noise images from which absolute perfusion is simply and reproducibly determined for routine semiautomated clinical imaging. N-13 ammonia has also proven to be an excellent quantitative clinical radionuclide.

**Clinical Impact of Quantitative Myocardial PET Perfusion Imaging**

The PET-guided management of coronary atherosclerosis integrated with intense lifestyle and vigorous pharmacologic treatment reduce coronary events and invasive procedures by 80% over 5-year follow-up (Fig. 11)(34). Serial changes in PET perfusion images, illustrated in Figure 12A, show response to treatment, predict outcomes, and provide insights into progression/regression of the worst baseline stenosis as well as new lesions, or prevention of new lesions, at follow-up (34,35), illustrated in Figure 12B. The left ventricular quadrant with the maximal change from baseline to follow-up PET, for either better or worse, was different from the baseline worst quadrant in 77% of 409 patients in this 5-year study; the maximum change quadrant coincided with the worst baseline quadrant in only 23% of patients (35). This observation indicates that for most patients, the greatest
perfusion changes over 5-year follow-up were seen in regions other than the baseline worst quadrant corresponding to the most severe stenosis, again an anatomic–functional dichotomy.

The economic impact of PET-guided management in clinical practice has also been demonstrated with reduced invasive procedures, lowered overall costs, and good outcomes compared with the standard anatomic diagnostic treatment paradigm (36). Although providing powerful clinical insights, quantitative cardiac PET perfusion imaging requires substantial care, commitment, specific PET training, knowledge of the technology and of coronary physiology, and physiologically oriented clinical judgment. The physiologic data are sufficiently complex to need integration into clinical decisions by a thought process beyond binary anatomic categorization of “critical” coronary artery stenosis driving current cardiovascular practice.

Conclusions

Based on an extensive literature, the concept of anatomically “critical” coronary stenosis should be replaced by the concept of “critical” reduction of flow capacity initially by noninvasive quantitative PET perfusion imaging as the optimal guide for decisions on invasive procedures, for medical management, and for following changes in coronary atherosclerosis before clinical events, with invasive pressure-derived FFR as needed for any remaining uncertainty about stenosis severity. Randomized trials of revascularization procedures in patients selected for severe reduction in maximum absolute myocardial perfusion and CFR as compared with patients selected for revascularization based on percent stenosis, which is poorly related to CFR, might finally fulfill the intuitive expectation that improving coronary blood flow benefits clinical outcomes. Given the prevalent overestimation of stenosis severity on arteriogram, the anatomic severity neces-

![Figure 10. Experimental Verification of Rubidium-82 for Measuring Myocardial Perfusion](image)

(A) Initial validation of absolute myocardial perfusion using rubidium-82 measured by epicardial radiation detectors compared with microspheres. Reproduced, with permission, from Goldstein et al. (33). (B) Validation of CFR measured by PET imaging of rubidium-82 using the “simple flow model” compared with the more complex complete compartmental modeling, both having comparable correlation with CFR measured by flow meter. Reproduced, with permission, from Yoshida et al. (25). Abbreviations as in Figure 1.

![Figure 11. 5-Year Survival for PET-Guided Maximal Medical Management](image)

Cumulative events over 5-year follow-up after PET-guided management with maximal intense combined lifestyle–pharmacologic treatment compared with moderate standard lipid drug treatment and casual (poor) community practice as a nonrandomized pilot trial in 409 patients with coronary atherosclerosis. Any event includes death, nonfatal myocardial infarction, coronary bypass surgery, PCI, or stroke. Adapted, with permission, from Sdringola et al. (34). CABG = coronary artery bypass graft; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; TC = total cholesterol; TG = triglyceride; other abbreviations as in Figures 1 and 6.
sary to substantially maximal myocardial perfusion or CFR, and extent of diffuse disease, patient selection based on quantitative PET perfusion imaging would also likely reduce the numbers of procedures by optimal patient selection.

**Figure 12. PET for Following Changes in CAD**

(A) Single views of stress PET relative perfusion images at baseline and follow-up of 2 different patients, illustrating progression and regression of coronary artery stenosis in the single view with a perfusion abnormality, other normal views not shown as redundant. (B) Schematic of stress PET images at baseline compared with follow-up PET in various quadrant pairings. Reproduced, with permission, from Sdringola et al. (35). Abbreviations as in Figures 1 and 3.

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Key Words: quantitative myocardial perfusion • quantitative cardiac PET • coronary flow • coronary stenosis • CAD.
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Coronary Flow Reserve and Pharmacologic Stress Perfusion Imaging

Beginnings and Evolution

K. Lance Gould, MD

Houston, Texas

Coronary Flow Reserve

Pharmacologic stress for myocardial perfusion imaging fell out of my first experiment measuring coronary flow during progressive stenosis in 1972, published in 1974 (1). The arteriogram and flowmeter dramatically showed the 3 fundamental physiological concepts underlying all stress myocardial perfusion imaging. The first was the concept of coronary flow reserve as a physiological measure of stenosis severity separately from anatomical or dimensional severity and shown in Figure 1. The second was the correlation of this physiological coronary function with arteriographic stenosis dimensions and demonstration of critical stenosis that lowers resting flow. The third was pharmacologic arteriolar vasodilation as the stressor for stimulating maximal coronary flow that, in these early studies, was contrast media.

Human Coronary Physiology

The relevance of the initial animal studies to humans was an open question then. Human coronary physiology and stenosis fluid dynamics were not well known. To test the concept of coronary flow reserve and pharmacologic stress imaging in humans, we injected intracoronary macroaggregated albumin labeled with technetium 99 (Tc-MAA) during the hyperemia immediately after intracoronary contrast media for coronary arteriography. Planar images of hyperemic Tc-MAA in patients with coronary artery stenosis showed corresponding regional perfusion defects, confirming the concepts of coronary flow reserve and pharmacologic stress imaging in coronary artery disease (CAD) (2).

Pharmacologic Stress: Dipyridamole

With the basic concepts established, an alternative to intracoronary contrast media was needed, with some literature suggesting intravenous dipyridamole as a possibility (3,4). It was the basis for a series of integrated experimental and human studies entitled “Noninvasive Assessment of Coronary Stenoses by Myocardial Imaging During Coronary Vasodilation: Part I Through Part VIII,” published in the American Journal of Cardiology (5–12) under the creative editorship of Simon Dack.

The first 3 parts of this series addressed dipyridamole perfusion imaging, including the first human dipyridamole perfusion study, done on myself, using thallium-201 at the start of the clinical cases. However, these initial studies also revealed the limitations of planar imaging compared to direct flow measurements for assessing stenosis severity. The fourth study showed the power of experimental postmortem imaging of short-axis sections of the heart after dipyridamole hyperemia and intravenous thallium-201, leading to positron emis-
sion tomography (PET) and the remaining reports of the series (9,10,12,13).

**PET**

In an intense 3-week collaboration with Heinrich Schelbert, I flew a group of chronically instrumented animals to the University of California at Los Angeles for the first study of dipyridamole PET perfusion imaging. It showed dipyridamole-induced myocardial perfusion defects for 47% diameter coronary stenosis, with the severity of the defects proportional to quantitative arteriographic severity. As the last experiment finished, the scanner went down with a blown power supply. An all-night data analysis and writing session made the deadline and won the von Hevesy Prize for research in 1978 (9).

**Stenosis Pressure-Flow Characteristics**

In retrospect, at this point a very important issue slipped by me because of my intense focus on stenosis. My pressure-flow data with quantitative arteriographic dimension of stenosis fit classic quadratic equations described in the fluid dynamic literature (14) at resting conditions. At maximum flow, the data failed to fit the same equations that worked at rest. This discrepancy was deeply disturbing for 1 year because it called into question everything done before—data quality, the physiological and fluid dynamic concepts—nightmares of failure. Finally, I realized that the data at maximum hyperemic flow fit the classic fluid dynamic equations only if the stenosis dimensions were worse than at baseline resting flow conditions.

**Flow-Mediated Vasodilation**

How could the stenosis at maximum hyperemic flow be worse with a fixed rigid mechanical constriction on the coronary artery? The answer was on the arteriograms done with pressure flow data, shown in Figure 2. At maximum hyperemic flow, the normal coronary artery on each side of the stenosis dilated substantially so that the percent stenosis was worse, thereby explaining more severe pressure flow characteristics during hyperemia compared to resting baseline conditions, as published in 1978 (15).

This first demonstration of flow-mediated epicardial coronary vasodilation was interesting because the mechanism was unknown. However, having tied together the concepts of coronary flow reserve, pharmacologic stress, and the pressure–flow–anatomy relations of coronary artery stenosis, I headed for the University of Texas at Houston as Chief of Cardiology to establish the first dedicated clinical cardiac PET center, and failed to pursue those mechanisms. In 1980, Furchgott (16) re-
ported the mechanism of flow-mediated coronary vasodilation as endothelial acetylcholine.

**Clinical Cardiac PET**

In Texas, my PET technical team, under the direction of Nizar Mullani, Ross Hartz, and David Bristow, designed and built the first multiring PET scanner for imaging the entire heart in 1 acquisition without indexed repositioning for each tomographic slice. As this scanner was completed, before the cyclotron building was finished, we did the first large clinical trial of generator-produced rubidium-82 compared with quantitative coronary arteriography (12,13).

Dipyridamole PET perfusion imaging was also identifying early asymptomatic CAD, raising the difficult issue of management not found in traditional paradigms of cardiovascular medicine at the time. However, cardiac PET perfusion imaging was incorporated into a trial of extremely low-fat, complete intravenous alimentation in patients with inoperable CAD. Dipyridamole PET showed smaller stress-induced perfusion defects immediately after 90 days of low-fat intravenous alimentation compared with baseline PET before treatment or with PET at 60 days after treatment was ended (17). We hypothesized that this short-term improvement in myocardial perfusion was caused by improved endothelial function, later confirmed by others.

The Lifestyle Heart Trial (18) confirmed improved myocardial perfusion by PET imaging in CAD patients after 1 year on a low-fat diet; PET imaging further confirmed improved myocardial perfusion in association with and predictive of reduced coronary events after 5 years of combined vigorous lifestyle and lipid-lowering drugs (19,20). Additional experimental studies defined relative and absolute coronary flow reserve as the physiological basis for quantitative PET perfusion imaging (21).

**The Weatherhead PET Center for Preventing and Reversing Atherosclerosis**

The technology has evolved to PET-computed tomography (CT) that has strengths but also significant complexities and potential errors not widely recognized or resolved (22). Having developed solutions to these problems, the Weatherhead PET Center for Preventing and Reversing Atherosclerosis now routinely uses PET for identifying early or advanced CAD, for assessing its physiological severity as the basis for invasive procedures or not, for following up changes in severity, and for improving patient adherence. Quantitative PET perfusion images show the entire range of absolute flows and coronary flow reserves of each artery down to small branches with single or multiple stenosis, diffuse disease, and/or myocardial steal indicating collateralization, illustrated in Figure 3. Here, PET imaging has become integral to and inseparable from management of CAD—integrated diagnosis, treatment, and procedural guide (23–25).
Figure 3. PET of Myocardial Perfusion

(A) Orientation of views. Adapted with permission from Sdringola et al. (20). (B) Myocardial uptake of rubidium-82 at rest and during dipyridamole stress showing relative myocardial perfusion reserve according to the color bar scale, ranging from maximum (white) in steps down to next highest (red), intermediate normal (yellow), intermediate low (green), low (blue), and lowest (black). The superimposed generic arterial map based on 1,000 PET-arteriogram correlations shows the precision of coronary arterial distributions by PET. In the lowest panel, values for absolute coronary flow reserve based on absolute myocardial perfusion in ml/min/g range from normal of 4.1 to intermediate low of 2.2 to 0.9, indicating myocardial steal characterizing collateralized occluded coronary arteries. In this example, the PET scans indicate severe diffuse disease of the left anterior descending, the left circumflex, and the distal posterior descending coronary arteries with collateralized occluded diagonal and obtuse marginal branches without myocardial scar on resting images, confirmed by coronary arteriogram. PET = positron emission tomography.
Assessing myocardial perfusion has evolved from initial concepts shown by flowmeter in experimental models to integration with detailed stenosis geometry to complex endothelial function to routine measurements of absolute myocardial flow and flow reserve of every artery and branch of the coronary tree as a guide to management of CAD.

The Future

Cardiovascular medicine and procedures are largely involved with coronary blood flow directly or indirectly. However, few people measure or understand it in humans. Artifact-free, quantitative perfusion images, absolute myocardial flow in milliliters per minute per gram, and coronary flow reserve open profound new windows into the heart with awaiting discoveries and clinical applications.

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