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STATE-OF-THE-ART PAPER

Anatomic Versus Physiologic Assessment of Coronary Artery Disease

Role of Coronary Flow Reserve, Fractional Flow Reserve, and Positron Emission Tomography Imaging in Revascularization Decision-Making

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Angiographic severity of coronary artery stenosis has historically been the primary guide to revascularization or medical management of coronary artery disease. However, physiologic severity defined by coronary pressure and/or flow has resurged into clinical prominence as a potential, fundamental change from anatomically to physiologically guided management. This review addresses clinical coronary physiology—pressure and flow—as clinical tools for treating patients. We clarify the basic concepts that hold true for whatever technology measures coronary physiology directly and reliably, here focusing on positron emission tomography and its interplay with intracoronary measurements. (J Am Coll Cardiol 2013;62:1639–53) © 2013 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

CAD = coronary artery disease

CFR = coronary flow reserve

ECG = electrocardiographic/electrocardiography

FFR = fractional flow reserve

PCI = percutaneous intervention

PET = positron emission tomography

MI = myocardial infarction

SPECT = single-photon emission computed tomography

In patients with nonacute coronary artery disease (CAD), the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial indicates that up-front percutaneous coronary intervention (PCI) based on angiographic stenosis severity does not reduce coronary events more than initial medical treatment (1). In contrast, randomized trials of PCI report better outcomes when guided by fractional flow reserve (FFR) than when guided by angiographic severity (2) or when compared to initial medical treatment (3). However, reduced emergent procedures after FFR-guided revascularization compared with medical treatment has been appropriately challenged due to lack of differential deaths or myocardial infarction (MI) or to interventional bias between the 2 groups (4).

Several potential explanations have been proposed for these conflicting views. Revascularization procedures may not alter the natural history of multicentric plaque rupture determined by complex arterial vascular biology. CAD exists diffusely in addition to segmental stenosis, so that localized mechanical intervention may fail to alter long-term disease progression or outcome. Additionally, anatomic severity on coronary angiography may not reflect the physiologic severity that directly determines ischemia, left ventricular function, and prognosis. Even more basically, how should we define ischemia and does revascularization to relieve ischemia reduce coronary events? Should we judge "diagnostic" tests primarily by outcomes in randomized trials using hard endpoints after treatment decisions based on those tests?

The current ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial (NCT01471522) addresses these issues by using noninvasive imaging to identify moderate-to-severe ischemia prior to randomization between initial medical management versus up-front mechanical revascularization guided by FFR. The planned FAME-3 (Fractional Flow Reserve versus Angiography for Multivessel Evaluation-3) trial will compare FFR-guided PCI to coronary artery bypass grafting (CABG) in patients with complex coronary disease – a marriage in concept between FAME and SYNTAX (*SYN*ergy Between PCI With *TAX*US and Cardiac Surgery) trials. However, these ongoing or planned studies utilize existing technologies that have significant limitations. First, single-photon emission computed tomography (SPECT) imaging is limited by attenuation artifact, low depth dependent spatial resolution, and a lack of quantitative myocardial perfusion. Second, measuring FFR requires an invasive coronary angiogram that is complexly influenced by the healthcare reimbursement system. Finally, many patients show a discordant hyperemic pressure gradient (low FFR) but adequate coronary flow capacity above ischemic levels, as reviewed here.

Noninvasive myocardial perfusion imaging by positron emission tomography (PET) combines high spatial resolution (down to secondary or tertiary coronary branches) with quantitative measures of rest and stress myocardial perfusion in absolute units to compute absolute coronary flow reserve (CFR). These quantitative measures have been directly correlated with low-flow thresholds causing ischemia. Quantitative myocardial perfusion by PET has an extensive and technically robust literature, with over 250 papers including almost 15,000 subjects in the past 25 years.

Therefore, we review the physiologic basis for PET perfusion imaging to provide all the essential noninvasive measures of severity that, when integrated with clinical judgment, identify patients for whom revascularization procedures may reduce coronary events. Given the existing diagnostic power of PET in nonrandomized studies and its extensive literature, randomized trials of physiologic PET to guide revascularization are essential to confirm or contravene its use for deciding on invasive procedures

projects. Dr. Bateman has received research grants from Bracco, Philips, GE, SpectrumDynamics, and Astellas; is on advisory boards of Astellas, GE, SpectrumDynamics; receives royalties from ImagenPro/MD/Q; and has ownership of CVIT. Dr. Beanlands is a career investigator supported by the Heart and Stroke Foundation of Ontario; is a tier 1 University of Ottawa Chair in Cardiovascular Research; consults with Jubilant DRAXImage and Lantheus; has received grant funding from a government/industry program (partners: GE Healthcare, Nordion, Lantheus Medical Imaging, DRAXImage); consults for Lantheus Medical Imaging and has received grant funding from Genentech; and has received more than $10,000 for research grants. Dr. Bengel has received research grants from GE Healthcare, Bracco Diagnostics, and Lantheus Medical Imaging; and speaker honoraria from Siemens Medical Solutions. Dr. Cerqueira consults for Astellas Pharma US, Cardinal Health, CoreLab Partners, GE Healthcare, and Lantheus Medical Imaging; is on the speakers bureau for Astellas Pharma US and GE Healthcare; and has received research funding from Perceptive Informatics. Dr. Chow is a consultant for GE Healthcare and TeraRecon. Dr. Di Carli receives research grant support from Toshiba Medical Systems and Gilead. Dr. Dorbala has received research grants from Astellas Pharma and stock holdings from General Electric. Dr. Gewirtz has received financial support from the Wild Family Foundation and FluoroPharma, Inc. Dr. Gropler consults for Molecular Insight Pharmaceuticals and Lantheus Medical Imaging; and has received NIH research funding. Dr. Kaufmann is supported by a fund of the Swiss National Science Foundation and the Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland. University Hospital Zurich holds a research grant with GE Healthcare. Dr. Knuuti is supported by Academy of Finland Centre of Excellence in Molecular Imaging in Cardiovascular and Metabolic Research, Helsinki, Finland; has received grant support from Gilead Inc.; and is a consultant to Lantheus Inc. Dr. Merhige is the medical director of and owns stock in Positron Corporation. Dr. Ruddy has received grant support and honoraria from GE Healthcare and MDS Nordion. Dr. Schwaiger has received research grants from Siemens and Lantheus. Dr. Sdringola has received internal funding from the Weatherhead PET Center for Preventing and Reversing Atherosclerosis. Dr. Williams consults and speaks for Astellas Healthcare, Inc. Dr. Gordon is a consultant for Bracco Diagnostics. Dr. Dilsizian is a consultant for and has received research funding from Molecular Insight Pharmaceuticals. Dr. Narula has received research grants and honoraria from GE Healthcare and Philips Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. William E. Boden, MD, acted as Guest Editor for this article.

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and management of CAD, paralleling the COURAGE, FAME, and ISCHEMIA trials.

Such trials are essential for specific PET technology as well as for answering the more basic clinical question: does revascularization for any level of ischemia reduce coronary events compared to medical treatment? If so, how low can flow go (regardless of the tool) before the benefit of revascularization surpasses the net benefit of medical treatment minus procedural risk of revascularization? In essence, outcomes after revascularization define the utility of PET, or any other gatekeeper test, for deciding on revascularization.

Prevalence, Severity, and Risk

Many if not most adults develop some coronary atherosclerosis starting at early ages evolving to a spectrum of severity from asymptomatic to severe angina to acute coronary syndromes or sudden death (5,6,Online Refs. 1–5). Prevention by risk factor control remains the most effective way of reducing adverse outcomes through healthy lifestyle and medications (5,6,Online Ref. 6). With more advanced or obstructive disease, individual risk increases substantially. In contrast to the COURAGE trial (1) showing no survival benefit for such patients when guided by percent diameter stenosis, physiologic-based revascularization may reduce adverse events compared with anatomic-based revascularization (2,3,Online Refs. 7–10). However, these conclusions have been questioned given that the combined endpoints were driven by reduction in urgent revascularizations subject to interventional bias with no difference in MI or death (4).

Limitation of Current Cardiovascular Paradigm

Stress testing monitors evidence of "ischemia" caused by inadequate coronary blood flow for the stress demand (5,6,Online Ref. 11) with its associated cardiovascular risk (Online Refs. 11–17). Coronary angiography then assesses the anatomic severity as a basis for medical or mechanical treatment (Online Refs. 16,17). This current anatomy-based paradigm does not consistently identify patient groups whose prognosis can be improved by PCI, as demonstrated in several randomized trials (1,Online Refs. 18–21). By comparison, patients selected for PCI guided by FFR may improve prognosis compared to PCI based on angiographic severity (2,3,Online Refs. 7–10). These data suggest the possibility of suboptimal patient selection by anatomic endpoints, rather than a general ineffectiveness of PCI, albeit only a hypothesis being addressed by the ISCHEMIA trial (4).

Physiologic stenosis severity by either PET or FFR compared to the angiogram as the guide to bypass surgery in a randomized trial has not been reported. However, the well documented variability of visually estimated percent diameter stenosis, common prevalence of diffuse disease, particularly of the reference vessel, multiple stenosis, and heterogeneous remodeling raises a testable hypothesis for potential physiologically guided coronary bypass surgery in addition to anatomic detail for surgical decisions.

Why Physiologic Severity of Coronary Artery Disease?

When integrated with clinical circumstances, regional absolute myocardial perfusion is a fundamental parameter, such as blood pressure, cardiac output, and blood oxygen content. In an extensive literature, cardiac PET measures absolute myocardial perfusion and CFR, as reviewed subsequently. While coronary flow and stenosis pressure gradient are related, which of these physiologic measures predominantly causes ischemia during stress? Are pressure gradient and flow interchangeable to guide procedures, or is 1 predominantly more useful for deciding on revascularization or are both optimal?

Physiologic Versus Anatomic Severity

Stenosis fluid dynamics in experimental models. Anatomic and physiologic measures of stenosis severity have evolved in parallel over the past 40 years. Stenosis dimensions and their pressure/flow effects have been integrated into fluid dynamic equations and validated in experimental models (7–10,Online Refs. 22–31). Based on animal stenosis models, the concept that a 70% diameter narrowing identifies "critical stenosis" reducing coronary flow capacity (7) persists as an anatomic threshold for revascularization. This first experimental observation demonstrated the concept of coronary flow reserve related and alternative to anatomic severity but was not reported as diagnostic criteria for revascularization.

Percent stenosis has a historical record and usefulness as a measure of stenosis severity, also related to physiologic effects as reported by the senior author 40 years ago (7–9). However, the limitations of percent stenosis are also well established, particularly with documentation of diffuse disease, disease of the reference artery or segment, multiple stenosis, heterogeneous remodeling and endothelial dysfunction having complex cumulative effects on coronary flow and pressure not accounted for by a single percent diameter narrowing (11–14,Online Refs. 32–34). Evidence over the intervening years has proven percent diameter stenosis as an inadequate measure of severity for guiding management (11–14,Online Refs. 32–34).

There is a pronounced curvilinear correlation between percent stenosis and CFR for composite data from controlled, idealized experimental stenoses (7–9,Online Refs. 24,27). However, the variability within and among different experiments is large for CFR given a specific anatomic stenosis severity. Similarly anatomic severity varies greatly for given a specific CFR. Therefore, the initial experimental data proved a concept correlating anatomy with function in single experimental stenosis of normal

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animal coronary arteries. However, even for these idealized single experimental stenosis, variation in percent stenosis for each level of reduced flow reserve remains too large for individualized clinical application and was not proposed for guiding management in the original physiologically oriented paper (7).

Therefore, the basic concepts of FFR, CFR, and their interplay are fundamental for clinical application of quantitative myocardial perfusion or of FFR for invasive decisions. Figure 1 shows coronary flow, aortic pressure, and coronary pressure at rest and at hyperemia (9). As flow increases, distal coronary pressure falls due to the increased pressure gradient across a stenosis at elevated flow.

CFR (also called absolute CFR) equals the ratio of maximum stress flow to rest flow for a given arterial distribution with or without a stenosis or diffuse narrowing (7). Relative coronary flow reserve (relative CFR) equals the ratio of maximum stress flow in the diseased artery to maximum flow in the absence of disease in either the same or adjacent arterial distribution (8–10,14–16,Online Ref. 27). FFR as now used clinically equals the ratio of coronary pressure to aortic pressure at pharmacologically induced maximal coronary flow. For a single discrete stenosis in the absence of diffuse disease, the FFR pressure ratio also equals relative CFR by flow or flow velocity measurements (8–10,14–16,Online Ref. 27).

Stenosis fluid dynamics in clinical application. Studies in humans show poor or no correlation between CFR or FFR and percent stenosis by anatomic imaging due to varying degrees of diffuse disease, multiple stenosis and heterogeneous arterial remodeling (11–14,Online Refs. 32–34) not present in the animal models.

Pressure-based FFR was derived as a proxy measure of relative CFR in units of a fraction or decimal of 1.0 (10,15) as in Figure 1. Flow-based CFR is a direct measure of coronary flow capacity. Quantitative perfusion imaging provides absolute perfusion normalized to distal myocardial mass, its regional distribution, absolute and relative CFR. Directly measured CFR by intracoronary techniques predicts coronary events (Online Refs. 8,35), paralleling risk prediction of pressure-derived FFR. Although the 2 physiologic measures of flow and pressure in the coronary arteries are related, they are neither synonymous nor redundant (17–20).

For discrete segmental stenosis in small series of patients, Figure 2 demonstrates that FFR determined invasively from the pressure ratio equals relative CFR measured by PET (15,16). This equivalence of FFR and relative CFR for discrete stenosis was also confirmed experimentally during the experimental derivation and validation of FFR (10).

However, flow-based CFR and pressure-based FFR may not show comparable severity for the same stenosis in

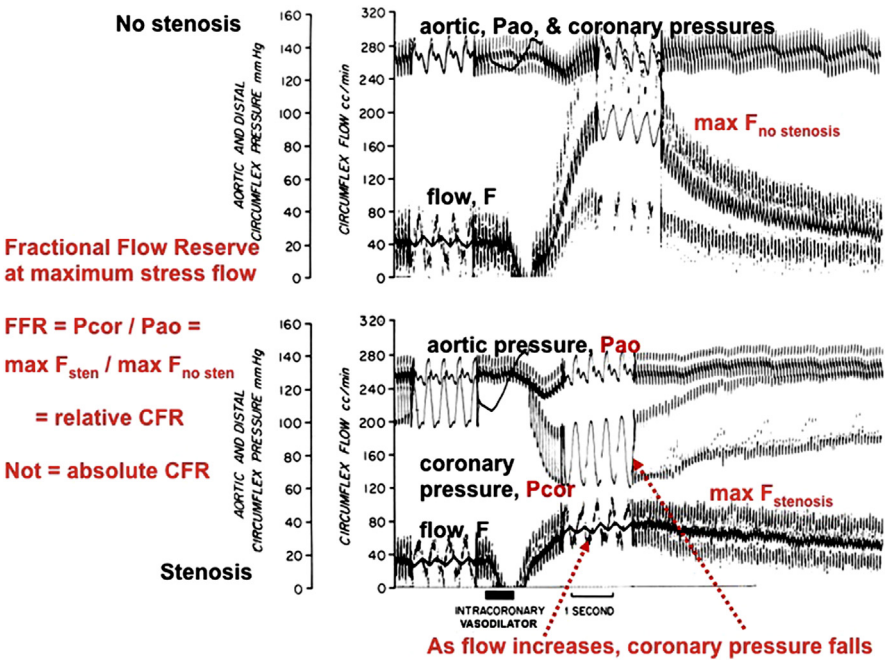

Figure 1 Pressure Flow Tracings, FFR, and CFR

Upper panel shows coronary flow and aortic and coronary pressures without stenosis at rest and during coronary vasodilator stress. Lower panel shows coronary flow and the aortic to coronary pressure gradient with a moderately severe stenosis at rest and during vasodilator stress. Fractional flow reserve (FFR) is the ratio of coronary to aortic pressure at maximum stress flow and therefore reflects relative flow reserve. Absolute coronary flow reserve (CFR) is the ratio of maximum flow to rest flow. Relative CFR is the ratio of maximum stress flow with a stenosis to maximum stress flow without a stenosis comparable to FFR. Adapted with permission from Lipscomb and Gould (9).

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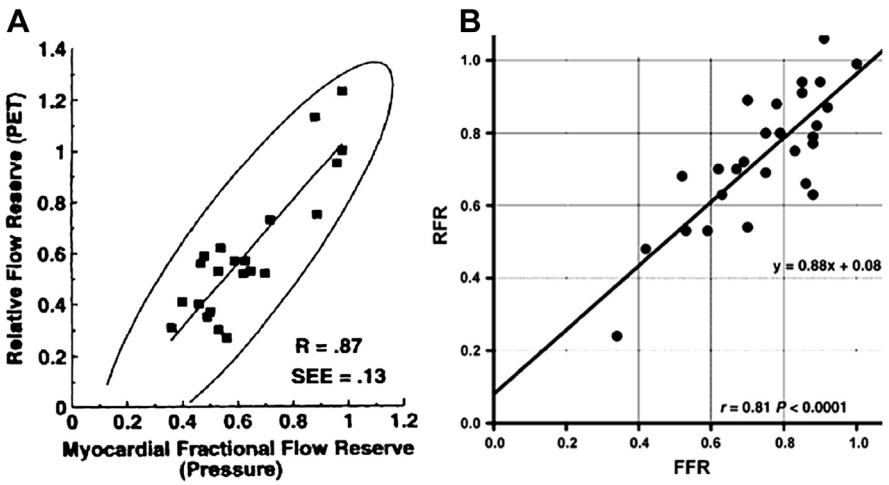

Figure 2 **FFR by Intracoronary Pressure Wire and Relative CFR by PET**

Fractional flow reserve (FFR) measured by intracoronary pressure wire correlated well with relative coronary flow reserve (RFR) derived from absolute coronary flow reserve (CFR) measured by positron emission tomography (PET) in these small groups of patients selected for single coronary stenosis without diffuse narrowing to demonstrate the initial concept of pressure derived relative coronary flow reserve. **Panel A** was adapted with permission from De Bruyne et al. (15). **Panel B** was adapted with permission from Marques et al. (16).

roughly 40% of lesions (17,19). This discordance between FFR and CFR occurs even with purely invasive intracoronary technology using combined pressure-flow velocity wires, thereby reflecting physiology, not methodology (17). Therefore, the discordance arises not from methodological differences of noninvasive versus invasive measurements, but reflects basic physiology that provides additional insights into disease severity of clinical relevance (17).

The discordance between FFR and CFR occurs commonly in 2 types of CAD seen in a larger study population with wider spectrum of disease than the small initial studies of Figure 2. In the first type of CAD, a stenosis causes abnormal FFR but maximum absolute flow and CFR are well above ischemic thresholds due to preserved microvascular function and/or arterial remodeling. In the other type, diffuse narrowing reduces CFR significantly but with only a minimal fall in segmental pressure gradient or FFR for any segment of the artery (17–20,Online Ref. 36). In mixed diffuse and segmental disease common clinically, noninvasive absolute maximal perfusion and CFR together define severity for potential optimal clinical decisions in these complex cases.

For chronic coronary occlusions where classic quadratic pressure/flow dynamics do not apply, myocardial steal during vasodilator stress is an established characteristic of collateralized myocardium wherein stress perfusion falls below resting perfusion (21–23,Online Refs. 37–43). Myocardial steal is caused by falling distal perfusion pressure at the collateral origins caused by high flow in the narrowed feeding artery supplying the collaterals. With exceptionally well-developed collaterals, steal may not be present but only limited CFR. Rarely, collaterals are so well developed as to provide coronary flow capacity comparable to the native arteries with no stress-induced defect.

Are FFR Versus CFR Competitive or Complimentary?

The randomized COURAGE (1) and FAME trials (2,3,Online Refs. 7–10) have had a major influence in moving revascularization decisions from anatomic to physiologic stenosis severity. The optimal binary cutoffs for FFR were originally selected based on prior noninvasive stress testing as indirect clinical indicators of "ischemia". The initially published lowest FFR cutoffs for "ischemia" were around 0.65 for selected single-vessel stenosis (Online Ref. 10) that migrated upward toward 0.80 for patients with diffuse or triple vessel disease (2,3). However, FFR is a pressure-derived relative flow reserve. It is not the same as the more basic, direct measures of maximum absolute stress flow or CFR from which it is derived. Therefore, FFR is not a direct measure of low-flow ischemia, and does not reflect absolute flow or absolute CFR that are the determinants of ischemia (18,19), illustrated experimentally in Figure 3.

Figure 3 shows that myocardial contraction remains preserved with stable flow, regardless of low perfusion pressure with FFR down to 0.43 (24). Therefore, while pressure and flow are related due to homeostatic and fluid dynamic interactions, flow is fundamentally more important than pressure for maintaining myocardial function without ischemia for clinical ranges of distal coronary pressure.

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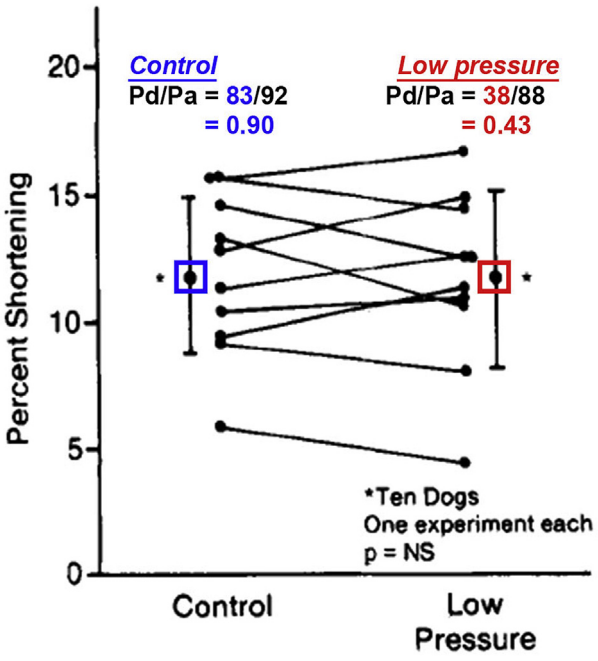

Figure 3 Contractile Function, Coronary Flow, and Coronary Pressure

In an experimental model, left ventricular contractile function measured as percent circumferential shortening remains normal if flow is constant and adequate despite perfusion pressure lowered to 43% of aortic pressure (Pd/Pa = FFR = 0.43). FFR = fractional flow reserve; Pd = distal coronary pressure, Pa = aortic pressure. Adapted from Smalling et al. (24).

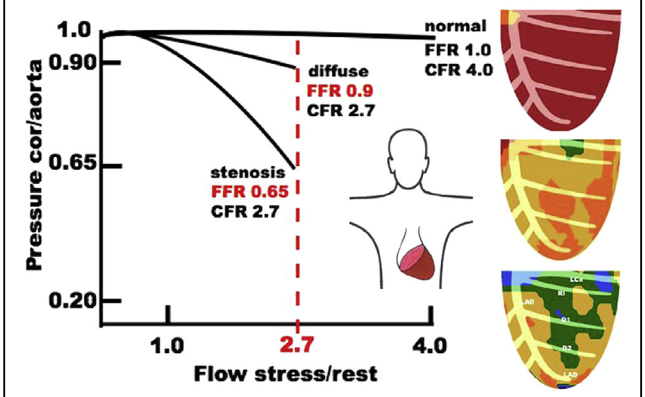

Figure 4 FFR-CFR Discordance With Coronary Stenosis or Diffuse CAD

Coronary pressure as a ratio to aortic pressure is on the vertical axis and coronary flow as a ratio to maximum flow is on the horizontal axis. In the absence of disease, normal FFR is 1.0 and CFR is 4.0. With diffuse disease CFR is reduced but in the absence of localized stenosis FFR is 0.9 indicating no significant segmental pressure gradient. With localized stenosis only and preserved vasodilator capacity, FFR is reduced to 0.65 and CFR is reduced to 2.7, which, however, remains well above ischemic threshold. Thus, for the same adequate CFR well above ischemic threshold, FFR may be above or below current 0.8 criteria for PCI. PET images show corresponding stress perfusion for each of these FFR-CFR discordances (**top:** normal perfusion capacity **[red]** with no coronary artery disease [CAD]; **middle:** mildly reduced perfusion capacity with diffuse CAD **[yellow, orange]**; **bottom:** severely reduced perfusion capacity with segmental stenosis in distribution of a diagonal branch **[dark green]** and diffuse narrowing **[yellow]**). Abbreviations as in Figure 2.

Bridging Invasive FFR and Quantitative PET Perfusion Imaging

Figure 4 illustrates that mild diffuse disease lowers absolute CFR from the 4.2 as seen in young volunteers to 2.7 commonly seen in patients with risk factors over 40 years old (17–19,Online Ref. 44). FFR remains high in the absence of discrete stenosis despite reduced CFR due to diffuse disease in this schematic. In contrast, a discrete stenosis without diffuse or small vessel disease may cause a pressure gradient that lowers FFR to 0.65 but absolute CFR is 2.7, well above ischemic levels due to maintained microvascular function.

The coronary flow maps by PET imaging during pharmacologic stress show corresponding reduced coronary flow capacity diffusely or as a discrete regional defect in Figure 4 (18). For a given absolute CFR of 2.7 in this example, FFR and therefore relative CFR may be normal or low depending whether diffuse disease or segmental stenosis exists. Thus, discordance may be due to diffuse CAD that lowers coronary flow capacity quantified by PET perfusion imaging without segmental perfusion defects, without corresponding pressure gradient, and therefore with an FFR over 0.8. Alternatively, coronary flow capacity may be preserved above ischemic flow thresholds due to maintained microvascular function and arterial remodeling despite stenosis causing a pressure gradient and FFR <0.8.

An extensive literature documents discordance in 40% of patients between FFR and CFR measured invasively (17). The discordance between absolute CFR and relative CFR has also been documented in 1,500 cases by quantitative PET, exactly paralleling the invasive data. The discordance in about 20% of patients is due to diffuse CAD that lowers absolute CFR without reduced relative CFR, FFR, or a localized pressure gradient. The remaining discordance in 20% of cases is due to adequate absolute CFR despite a stenosis causing reduced relative CFR, and reduced FFR reflecting a localized pressure gradient but with adequate absolute perfusion.

Clinical Implications of Adequate CFR With Low FFR?

For example, a patient with a CFR of 4.0 normally in the absence of diffuse CAD may have a stenosis causing an FFR of 0.8 or a relative CFR of 80%. Reduced relative CFR to 0.8 or 80% of the absolute CFR of 4.0 leaves an absolute CFR of 3.2 ($0.8 \cdot 4.0 = 3.2$) that does not cause ischemia (no angina, no electrocardiographic (ECG) change, no contractile dysfunction, clinically stable). Using

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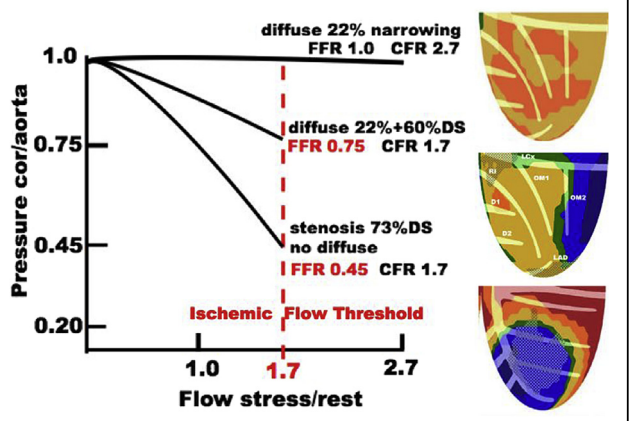

Figure 5 FFR-CFR Discordance Due to Stenosis Plus Diffuse Disease

FFR press Δ = relative CFR ≠ absolute ischemic flow. This schematic has the same coordinates as for Figure 4. Mild diffuse narrowing alone lowers CFR to 2.7 with no segmental pressure gradient (FFR 1.0). Mild diffuse narrowing plus moderate stenosis lower CFR to 1.7 and FFR to 0.75 that are both at ischemic levels whereas the same diffuse or segmental narrowing alone would not reduce CFR or FFR to ischemic levels. In the absence of diffuse narrowing, a severe segmental stenosis is needed to lower CFR to 1.7 with consequent lower FFR of 0.45. Discordance here is the range of FFR from 0.75 to 0.45 reflecting relative CFR for the same reduced absolute CFR of 1.7 due to different relative severity of diffuse and/or segmental narrowing. PET images show corresponding stress perfusion for each of these FFR-CFR discordances (**top:** diffuse narrowing with diffusely reduced perfusion capacity **[yellow, orange]** without localized stenosis; **middle:** diffuse narrowing **[yellow]** plus localized severe stenosis **[blue]**; **bottom**: no diffuse narrowing **[red]** with severe stenosis **[blue]**). Abbreviations as in Figure 2.

relative CFR or FFR of 0.8 as the sole criteria for ischemia includes about 20% of patients with high or adequate CFR well above ischemic low flow threshold who may not need revascularization due to absence of ischemia.

Figure 5 shows the combined effect of mixed diffuse disease and focal stenosis (17–19). Mild diffuse disease lowers absolute CFR to 2.7 as in the prior example. The addition of a moderate discrete stenosis lowers CFR to the ischemic threshold of 1.7 and relative CFR by PET to 0.63 (1.7/2.7 = 0.63) compared to an FFR of 0.75. Therefore, patients whose CFR is better preserved outside of the stenotic territory, for example absolute CFR of 3.8, require a more severe focal stenosis to lower absolute CFR to the ischemic threshold of 1.7, for example an FFR of 0.45 (1.7/3.8 = 0.45). Thus, for disease that lowers absolute CFR to the ischemic threshold, FFR may be 0.65 or 0.45 depending on presence or absence of diffuse disease.

What About FAME?

While important studies of clinical outcomes, the FAME I and II trials (2–4,Online Refs. 7–10) do not link FFR cutoffs directly to specific manifestations of ischemia such as stress-induced angina, ECG changes, or contractile dysfunction at the time of FFR measurement. In the FAME II trial, approximately 80% of patients with low FFR ≤0.80 without initial PCI had no increased myocardial infarction or death over the group with up-front PCI. The well documented 40% discordance between coronary flow reserve and FFR raises an important question about the FAME II trial data. Would adverse outcomes be reduced after PCI based on combined FFR-flow data compared with FFR alone, or compared to medical management alone—a testable hypothesis of clinical importance?

Predicting Physiology From Anatomy

Beginning with initial experimental coronary artery stenosis, angiographic dimensions coupled with fluid dynamic equations matched observed pressure gradients and/or CFR *on average* (7,8,Online Refs. 22–27). The concept of anatomically based stenosis flow reserve presaged more recent approaches to predict FFR using digital subtraction or CT angiogram coupled with computational fluid dynamics (25,Online Refs. 45–49).

These early and recent anatomic predictions of CFR, pressure gradient, or FFR show a reasonable average agreement with experimental observations. However, even under idealized experimental conditions with a single, well-defined experimental stenosis, the scatter is large around the average agreement. This large variability critically limits predictive certainty for individual cases and remains currently unacceptable in the threshold ranges of CFR or FFR used to guide invasive procedures (7,8,25,Online Refs. 22–27). For example, recently reported diagnostic accuracy for CT measured FFR was only 73% compared to directly measured FFR (25).

The variability of anatomically-predicted from directly measured CFR or FFR arises from several basic reasons: 1) All anatomic algorithms rely on assumptions derived from average patient characteristics that, however, commonly do not match with an individual patient; 2) Spatial resolution of the noninvasive angiogram, and some invasive angiograms, remains inadequate for determining flow and pressure endpoints that depend on the arterial radius raised to the fourth power; 3) Potential diffuse disease and heterogeneous arterial remodeling change arterial dimensions such that the original normal size of the coronary artery is not known and cannot be accurately determined from the angiogram; 4) Nonanatomic factors such as endothelial dysfunction, neural-mediated vasomotion, myocardial compression, circulating catecholamines, and flow shear change the relation of coronary flow to anatomy in profoundly unpredictable ways; and 5) Collateral circulation cannot be assessed by anatomically predicted FFR.

Therefore, directly measured flow or pressure remains essential for individually defining physiologic stenosis severity as distinct from theoretically predicted severity derived from anatomy.

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Table 1 Graded Absolute Flow and Coronary Flow Reserve Across Spectrum of Disease (N = 14,962)

Population	n	Rest Flow (cc/min/g)	Stress Flow (cc/min/g)	CFR
Normal controls	3,484	0.82 ± 0.06	2.86 ± 1.29	3.55 ± 1.36
Risk factors only	3,592	0.85 ± 0.08	2.25 ± 1.07	2.80 ± 1.39
Established coronary artery disease	1,650	0.83 ± 0.10	1.71 ± 0.71	2.02 ± 0.70
Mixed (risk factors and/or known coronary artery disease)	4,765	0.97 ± 0.10	1.86 ± 0.58	1.93 ± 0.48
Cardiomyopathy	594	0.73 ± 0.07	1.47 ± 0.56	2.02 ± 0.67
Hypertrophic cardiomyopathy	345	0.90 ± 0.10	1.57 ± 0.33	1.84 ± 0.36
Syndrome X	348	1.06 ± 0.11	2.65 ± 1.31	2.54 ± 1.31
After cardiac transplant	184	1.14 ± 0.18	2.44 ± 1.34	2.29 ± 0.86

N = 14,962 from 252 unique publications. N-13 ammonia = 5,541; O-15 water = 3,161; Rb-82 = 6,175.

Absolute Myocardial Perfusion by PET

While FFR is an invasive pressure-derived relative CFR, noninvasive cardiac PET has been proven experimentally and clinically to measure absolute myocardial perfusion, absolute and relative CFR. Classic relative uptake PET images have powerfully advanced clinical imaging, even without absolute perfusion (22,26–29) due to attenuation correction, high resolution, and quantitative activity recovery. It has the additional advantage of measuring absolute myocardial perfusion, as proven by a substantial literature over the past 25 years, highlighted by recent useful reviews and reports (30–38,Online Refs. 50–81).

Table 1 summarizes the literature on cardiac PET measuring absolute flow in 14,962 adult patients from 15 countries, spanning nearly 25 years from 250 unique publications and using 3 different isotopes (itemized for each paper in the complete table in the Online Appendix) in addition to numerous hardware and software platforms.

Tables 1 to 4 and Online Tables 1 and 2 show variability of flow values as expected for the wide prevalence of subclinical to clinical coronary atherosclerosis, hypertension, diabetes, endothelial dysfunction and multiple factors affecting coronary flow, even for "normal healthy volunteers" in addition to different radionuclides, scanners, imaging protocols, stress agents, and flow models. Therefore, variability may be due to biologic variability or due to test–retest variability (imprecision) of the technology quantified as the coefficient of variation, shown in Table 4 for common measurements made in cardiology.

A systematic approach for interpreting this range of PET flows has to consider and incorporate the following: 1) patient composition from manifest CAD to risk factors only to "normals," keeping in mind that up to 50% of otherwise "healthy" volunteers may have unrecognized risk factors (Online Ref. 44); 2) test–retest variability (imprecision) of quantitative myocardial perfusion; 3) comparison to the variability of other common measurements made in cardiology; 4) narrow lower range of flows causing ischemia to guide procedures because variability at higher flows does not impact these decisions; 5) each PET facility has to establish its own flow values causing ischemia; and 6) definition of "ischemia" has to be comparably defined (some reports define "ischemia" as stress-induced angina and significant ECG changes during dipyridamole stress, whereas others define ischemia by FFR despite absence of angina or ECG changes during adenosine stress).

While there is some imprecision in PET flow, the coefficient of variation for normal PET quantitative perfusion average 14% is within the range for other common cardiac-related measurements from 10% to 29% such as percent diameter stenosis by quantitative angiography, ejection fraction by echocardiographic or gated SPECT imaging, SPECT summed stress scores, serum C-reactive protein, or low-density lipoprotein levels shown in Table 4.

Moreover, the range of PET flows at the threshold of ischemia is much narrower than for higher flows seen in most patients because the variability of flow and CFR in its upper ranges is not critical for revascularization decisions. Other imaging technology may become capable of routinely and accurately measuring quantitative myocardial perfusion in the future. However, for now, no other tool or methodology offers such an extensive track record.

Applying quantitative myocardial perfusion clinically requires an understanding of its range of values, their associated effects on the heart, and the specific therapeutic implications when integrated with clinical circumstances. Just as for FFR or percent stenosis, no test or flow number alone should be used in isolation for clinical decisions but has to be integrated into and interpreted within the clinical circumstances. From this clinical decision making viewpoint, myocardial perfusion falls into 4 broad levels of clinical importance: normal, reduced but not ischemic, ischemic, or infarcted.

Ranges of Coronary Flow Capacity and the Ischemic Threshold

Coronary flows can be categorized into ranges for integrating with clinical information. The highest flow is myocardial perfusion observed in healthy young volunteers with no risk factors (Online Ref. 44). Intermediate flow is less than normal volunteers but adequate and above ischemic

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Table 2 Ischemic Cutoffs of Absolute Stress Flow and CFR

					CFR (No Units)		Stress Flow (cc/min/gm)	
First Author	Citation	n	Isotope	Reference Standard	Cutoff	AUC	Cutoff	AUC
Sambuceti	Am J Cardiol 1993;72:990	33	N-13	Dipyridamole ST depression	1.75	0.59	1.15	0.6
Muzik	J Am Coll Cardiol 1998;31:534	51	N-13	Clinically normal group and cath data	2.74	0.91		
Nesterov	Eur J Nucl Med Mol Imaging 2009;36:1594	48	O-15	Cath %DS >50 (plus FFR in half of cohort)			2.5	
Hajjiri	J Am Coll Cardiol Img 2009;2:751	27	N-13	Cath %DS ≥70	2.0	0.86	1.85	0.90
Kajander	Circulation 2010;122:603	107	O-15	Cath %DS ≥50 or FFR≤0.8			2.5	0.95
Johnson	J Am Coll Cardiol Img 2011;4:990	1,674	Rb-82	PET defect, dipyridamole angina/ST	1.74	0.91	0.91	0.98
Morton	J Am Coll Cardiol 2012;60:1546	41	N-13	Cath %DS ≥70	1.44	0.83	1.48	0.69
Fiechter	J Nucl Med 2012;53:1230	73	N-13	Cath %DS ≥50	2.0	0.92		
Danad	J Nucl Med 2013;54:55	120	O-15	Cath %DS ≥50 (plus FFR in third of cohort)	2.30	0.81	1.86	0.86

AUC = area under the receiver-operating characteristic curve; CFR = coronary flow reserve; %DS = percent diameter stenosis; FFR = fractional flow reserve; ST = ST depression on ECG.

thresholds. The next lowest category of flow occurs at or below ischemic thresholds defined as causing angina and/or ECG changes with segmental stress defects (17–19). The lowest flow category is in myocardial scar.

Normal and reduced but not ischemic. As summarized in Table 1, absolute flow and CFR decrease continuously across the spectrum of CAD, from normal volunteers to risk factors only to established CAD. Given the wide range of flows in asymptomatic people, there is no clear threshold for normal versus abnormal, but instead a graded flow range. Because most people over 40 years old also have some degree of coronary atherosclerosis, the average CFR of 2.7 ± 0.9 largely represents effects of diffuse and small vessel disease. The intermediate level of myocardial perfusion, between normal volunteers and ischemic flows, can be divided into an upper and lower half reflecting degrees of flow-limiting disease above ischemic levels. These intermediate levels above ischemic threshold are rarely associated with symptoms but reflect increasing burden of disease and adverse risk.

Ischemic threshold. Table 2 summarizes the literature on absolute flow and CFR by cardiac PET for various definitions of ischemia. In the largest report in the literature, maximum stress flow of 0.91 cc/min/g and absolute CFR of 1.74 best identified a group with definite ischemia (manifest by a perfusion defect with clinical angina during dipyridamole stress requiring medication reversal of hyperemia and/or significant ECG changes from baseline) (18,19). These ranges provide the basis for the physiologic threshold of severity directly related to ischemia that may potentially guide revascularization procedures when integrated with clinical judgment and tested in a randomized trial.

Myocardial scar. The lowest flow below ischemic perfusion reflects transmural myocardial scar that typically has resting flow of 0.2 cc/min/g or less but also typically increases somewhat with stress flow up to 0.4 cc/min/g and a CFR of up to 2.0 if the parent artery is patent. This very low absolute flow with CFR of 2.0 or higher also exemplifies why both measures are needed for understanding any given clinical circumstance.

Clinically, the most meaningful qualitative reporting of quantitative flows is either "regionally ischemic" or "reduced but adequate or without significant localized regional stress-induced perfusion defects." As reported in the case examples, the relative images are read out first as the primary step toward a revascularization decision that is modified to a final recommendation after interpretive integration with the quantitative flows and clinical circumstances.

Coronary flow map as clinical physiology guide. For the wide range of conditions seen clinically, both absolute hyperemic perfusion and CFR together are essential for defining severity in each highly variable individual. Severe diffuse disease commonly reduces both endpoints but without a regional stress-induced perfusion defect or localized pressure gradient. Maximum flow alone may be at the ischemic level but with low resting flow, as seen with beta

Table 3 Prognostic Value of Quantitative Perfusion

First Author	Citation	n	Isotope	Follow-Up	Events	Adjusted Predictor	Hazard Ratio (95% CI)
Herzog	J Am Coll Cardiol 2009;54:150	229	N-13	5.4 yrs	33%	CFR <2	1.60 (1.00–2.57)
Ziadi	J Am Coll Cardiol 2011;58:740	677	Rb-82	1.1 yrs	4%	CFR <2	2.4 (1.4–4.4)
Murthy	Circulation 2011;124:2215	2,783	Rb-82	1.4 yrs	10%	CFR tertiles	5.6 (2.5–12.4)
Fukushima	J Nucl Med 2011;52:726	275	Rb-82	1 yr	15%	CFR <2.11	2.93 (1.30–6.65)

CI = confidence interval; CPT = cold pressor test.

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Table 4 Test–Retest Variability of Common Cardiovascular Measurements

Test–Retest Measurement	Coefficient of Variation
PET flow cc/min/gm	14%
Angiogram % DS	17%
LDL cholesterol	9.5%
ECHO EF	15%
SPECT EF	17%
SPECT SSS	29%
C-reactive protein	46%

See Online Table 1 for primary source data and references.

DS = diameter stenosis; ECHO = echocardiogram; EF = ejection fraction; LDL = low-density lipoprotein; PET = positron emission tomography; SSS = summed stress score; SPECT = single-photon emission computed tomography.

blockade, such that CFR exceeds 2.0 or even 3.0 with no signs or symptoms of ischemia.

Alternatively, resting flow may be very high due to high resting pressure-rate product or anxiety thereby reducing CFR but with adequate or high absolute flow capacity (19). Rest flows over 1 cc/min/g are commonly due to mildly elevated heart rate or blood pressure, female gender, medications (e.g., minoxidil), and/or anxiety or other factors increasing resting flow demands (Online Ref. 44).

The term "coronary flow capacity" integrates both maximum stress flow and CFR because at least 2 of the 3 flow endpoints (rest flow, stress flow in absolute units, and their ratio CFR) are needed to define severity completely as noted previously (18,19). Figure 6 illustrates a coronary flow capacity map. Each pixel of the heart map of absolute CFR and stress flow is plotted on a graph color coded for the above ranges of flows: high flow of normal volunteers (red), intermediate flows divided into an upper (orange) and lower half (yellow), mixed signs of ischemia as either angina or ECG changes with dipyridamole stress but not both (green), definite ischemic threshold or below (blue or purple) associated with ischemic flow level, or transmural scar (black). Each color-coded pixel is then mapped back to the heart image for a distinct regional map of coronary flow capacity and size overlayed with the typical arterial distributions (Online Ref. 79).

Coronary flow map: clinical application. A substantial, contiguous area of myocardium with ischemic coronary flow capacity may indicate invasive revascularization after integration with clinical circumstances. Small, distal, or completely global reductions in coronary flow capacity usually indicate medical therapy due to absence of a focal epicardial artery stenosis. However, if sizable and associated with refractory symptoms, intermediate reductions in flow capacity may merit a coronary angiogram with confirming FFR as a further guide to intervention as illustrated subsequently. Severely reduced coronary flow capacity throughout the heart with no regional localized defect is nearly always due to severe diffuse CAD, small vessel disease or failure of pharmacologic stress. Equally balanced and critical epicardial stenoses in all vessels that reduce perfusion uniformly to ischemic thresholds throughout the heart are clinically rare (see Online Appendix).

Figure 7 illustrates coronary flow capacity maps in 1 view for 12 different cases representing the range of diffuse or localized perfusion defects above and below the ischemic threshold. Those to the left of the threshold have common abnormalities that are too mild or too small to warrant mechanical intervention. Those to the right of the threshold warrant an angiogram and FFR if clinically indicated.

Relative Uptake PET Perfusion Images

The unique aspects of myocardial perfusion imaging by PET are attenuation correction, uniform depth independent resolution, and quantitative activity recovery. Myocardial distribution of activity is scaled relative to the highest activity of the left ventricle in units of percent. The good resolution and attenuation correction provide essential localization, size, and relative severity of perfusion defects (Online Ref. 79) as guides for assisting clinical management even without quantitative perfusion. This sharp visualization by PET remains important for revascularization decisions particularly for complex cases after bypass surgery or multiple stents with recurrent symptoms where the culprit lesion superimposed on diffuse disease is otherwise unclear.

Figure 8 illustrates detailed localization, size and severity of multiple complex defects in secondary and tertiary arterial branches (Online Ref. 80). In this case with remote coronary bypass surgery, the stress images show small severe defects in the distribution of the first (OM1), second (OM2) obtuse marginal, and first diagonal branches (D1). Diffuse disease of the left anterior descending is indicated by the longitudinal base-to-apex perfusion gradient. Adequate perfusion in the ramus intermedius distribution but not at its origin indicates a patent bypass graft to the ramus intermedius. Relatively good perfusion in the distribution of the right coronary artery and the first septal perforator rules against physiologically significant flow limiting stenosis of the right or left main coronary arteries. All these findings were confirmed by angiogram.

The first step in the decision tree with perfusion imaging is defining location, size, and severity of defects on the relative images. As reported over the past 25 years from the senior author's clinical cardiac PET consult service (29,39), relative images with large, severe, defects at 60% to 70% of maximum activity in a proximal to mid ventricular arterial distribution involving >10% to 15% of the left ventricle warrant a coronary angiogram if consistent with clinical circumstances.

However, because the best or highest relative activity may have reduced absolute flow capacity due to stenosis or diffuse disease, the relative images may not show the extent and severity of diffuse disease or combined diffuse and segmental disease. Therefore, absolute myocardial perfusion and CFR are needed for separating effects of segmental and diffuse disease severity by quantitative flow for comparison to

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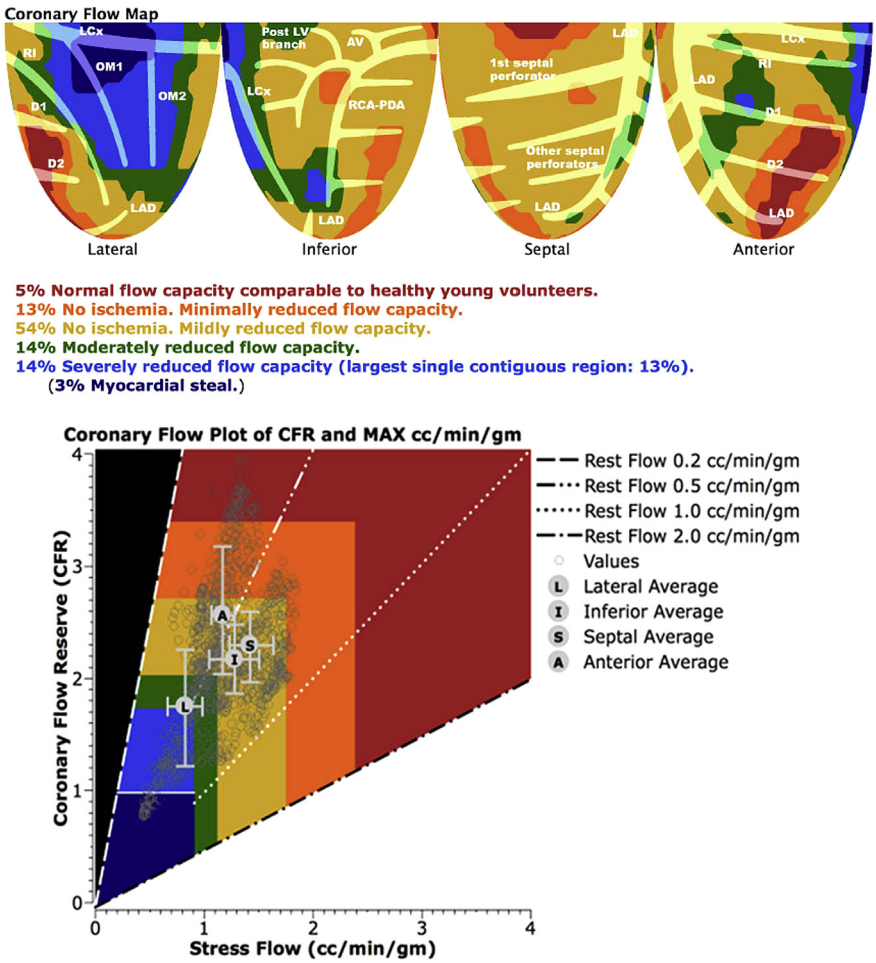

Figure 6 Coronary Flow Capacity Map in 4 Quadrants With Schematic Overlay of Coronary Arteries

Maximum stress perfusion in cc/min/g and absolute coronary flow reserve (CFR) for each pixel of the cardiac image are plotted on the scatter gram and color coded for the range of values from normal healthy young volunteers to low flow ischemic threshold values. Each color-coded pixel is projected back to its original location on the cardiac image thereby producing the 4-quadrant map of coronary flow capacity. This flow capacity map therefore integrates stress perfusion in cc/min/g, CFR and clinically relevant flow capacity ranges accounting for all resting and stress conditions. The color codes for the upper 4 panel maps and the lower graph are defined in the colored mid-figure text. These color codes are the same as for Figures 2, 4, and 5. AV = atrioventricular nodal artery; D = diagonal branch; LAD = left anterior descending artery; LCx = left circumflex artery; LV = left ventricular; OM = obtuse marginal branch; PDA = posterior descending artery; RCA = right coronary artery; RI = ramus intermedius.

thresholds of ischemia for borderline severity or balanced disease.

Commonly, relative images are not normal but show only small, mild to moderate, distal or scattered stress-induced perfusion defects that identify coronary atherosclerosis but do not warrant invasive procedures without other overt clinical evidence of severe localized epicardial stenosis. Stress images with only a longitudinal base-to-apex perfusion gradient indicate mild to moderate diffuse CAD without segmental stenosis (Online Refs. 72,73,77,81).

Clinical Reports Including Quantitative Perfusion

Potentially, the most widespread powerful clinical application of cardiac PET perfusion imaging may be selection of the small cohort within the large population of patients with coronary atherosclerosis who might potentially benefit from revascularization due to severe flow limiting stenosis, subject to a randomized trial. Large, severe, regional, stress-induced perfusion defects on relative uptake images with severe flow restriction to below ischemic threshold may justify an angiogram based on high risk associated with large ischemic areas, again subject to clinical judgment and a randomized trial of revascularization.

In the Weatherhead PET Center, rest-stress PET imaging contravenes as unnecessary many invasive procedures that had been recommended before the PET. Consequently, in nonrandomized cohort analysis, cardiac PET reduces subsequent or downstream procedures that lower the overall cost of cardiovascular care (40),

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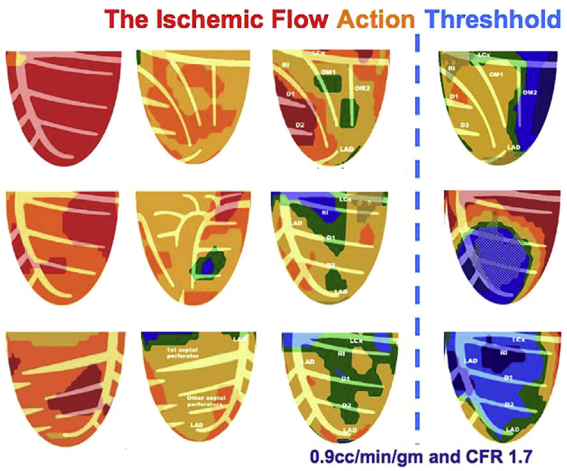

Figure 7 **Coronary Flow Maps and Range of Abnormalities in Coronary Flow Capacity**

A map of coronary flow capacity is shown in single view from 12 different patients with different burden of diffuse or segmental disease and size/severity above or below the low flow threshold causing ischemia. The size and severity of cases to the right of the ischemic threshold (max stress perfusion of 0.9 cc/min/g and CFR of 1.7) indicate potential revascularization as clinically appropriate. Reprinted with permission from Johnson and Gould (19). Abbreviations as in Figure 6.

paralleling cost reduction by FFR (Online Ref. 82), and identifies patients whose survival may be improved by physiologically guided revascularization, subject to randomized trial. PET may also identify some patients with unexpected, clinically "silent" disease manifest by severe large stress defects below ischemic threshold that are not identified by standard clinical evaluation or testing or associated with clinical symptoms.

An example of unexpected disease severity is illustrated in the first case here. Four other cases are in the Online Appendix with their PET reports that include a brief summary, followed by a detailed report including indication, medical history, procedure, interpretation of relative images, interpretation of absolute perfusion and CFR, qualitative coronary calcification, ventricular function, and finally a recommendation for or against invasive procedures integrated with clinical circumstances.

Cases 1 to 5 illustrate the entire spectrum of patients undergoing PET perfusion imaging for revascularization decisions. The coronary flow capacity maps specifically demonstrate the concept of ischemic flow thresholds for revascularization decisions. Case 1 (Fig. 9) illustrates large size and severity of a stress abnormality on relative images and coronary flow capacity map in a patient with severe stenosis and diffuse CAD before and after a stent. Case 2 (Online Fig. 1) shows a large, mild stress abnormality but with coronary flow capacity well above the ischemic threshold confirmed by an FFR of 0.85 at a protocol angiogram with no indication for revascularization. Case 3 (Online Fig. 2) shows a medium sized, moderately severe, stress abnormality due to known occlusion of a collateralized ramus branch that, considered in clinical context, indicated enhanced medical management without further invasive procedures. Case 4 (Online Fig. 3) shows a small sized, moderately severe stress-induced relative abnormality that has excellent coronary flow capacity for which angiography is not indicated. Case 5 (Online Fig. 4) shows minimal localized stress abnormality but severely diffusely reduced absolute stress flow reflecting

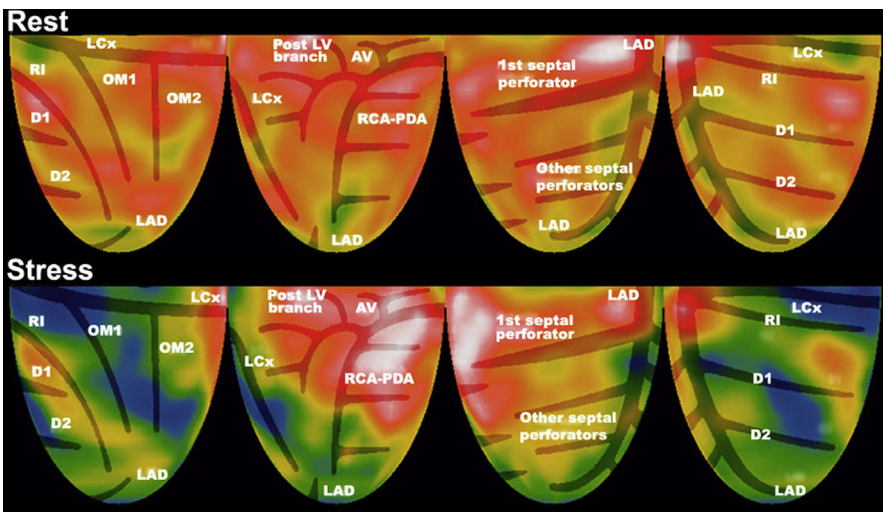

Figure 8 **Relative Images of Rubidium-82 Uptake in Multivessel Disease**

Rest images are in the **upper row** and stress images in the **lower row**. See text for details of perfusion anatomy. Adapted with permission from Gould et al. (Online Ref. 80). Abbreviations as in Figure 6.

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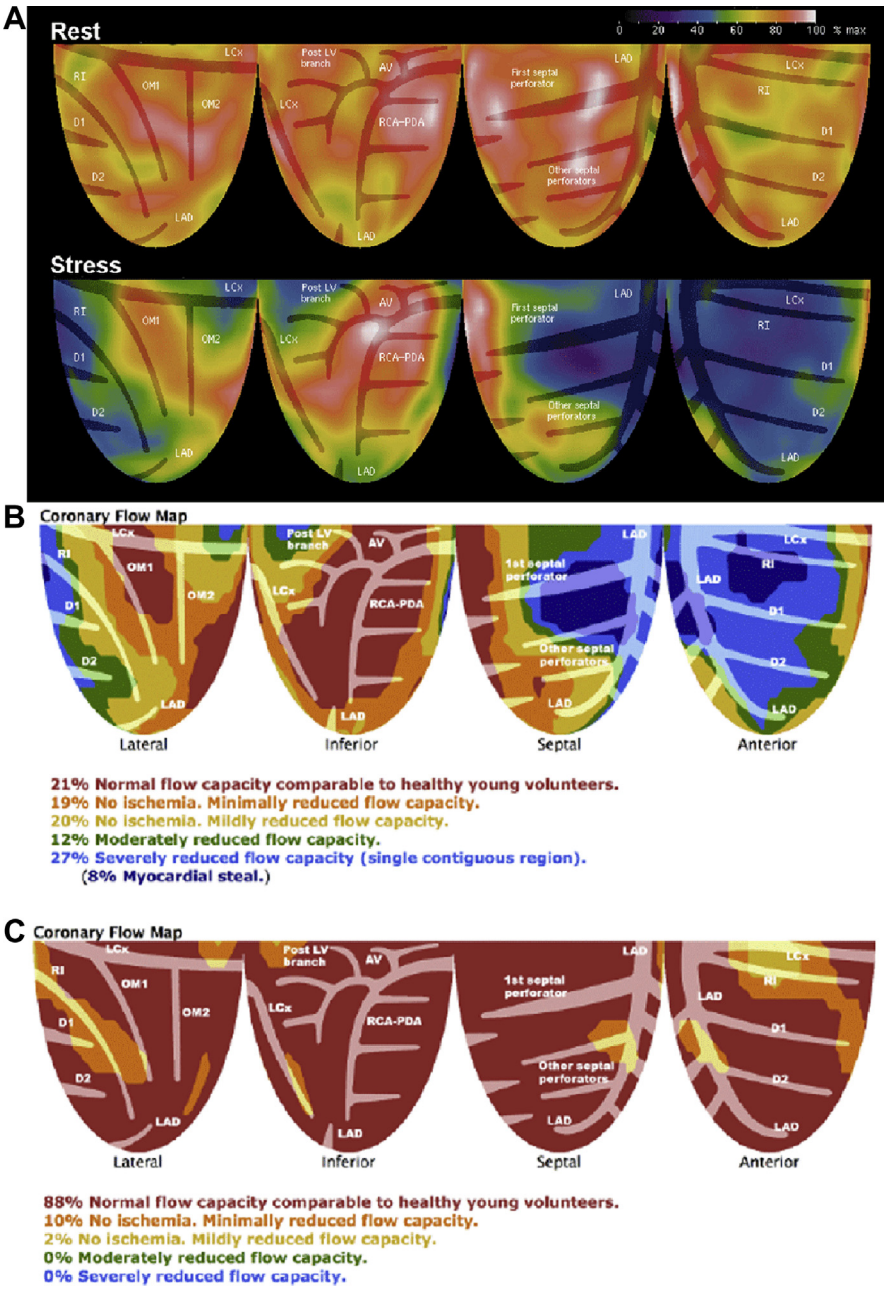

Figure 9 **Case Example and Report**

Case 1 illustrates size and severity of a stress abnormality on relative images **(A)** and coronary flow capacity map **(B)** in a patient with severe stenosis and diffuse coronary artery disease (CAD) before **(B)** and after a stent **(C)**. PET Report for This Case: 66 year-old male with known CAD s/p CABG in 2005 (LIMA-LAD, radial to OM2, SVG-PDA) with new mild exertional angina. Description: Myocardial perfusion imaging was carried out by positron emission tomography (PET) at resting conditions and during dipyridamole stress using rubidium-82. Procedure: There were no complications with the procedure. The patient had angina with 2 mm ST-segment depression on EKG after dipyridamole, resolving after intravenous aminophylline and metoprolol. Baseline blood pressure was 136/78 mm Hg, heart rate 65 beats/min. Findings: Relative Myocardial Perfusion Images: The PET images show the following **(A)**: 1) A large, severe, anterior, septal, apical, and distal lateral stress-induced defect involving 60% of the left ventricle in the distribution of the proximal LAD coronary artery; 2) A small size, severe, basal infero-lateral stress induced defect involving 2% of the left ventricle in the distribution of the distal LCx or LV extension branch of the RCA. Absolute Coronary Flow Reserve & Myocardial Perfusion: For the inferior and mid lateral best perfused areas, absolute myocardial perfusion (cc/min/gm) was 0.64 at resting conditions, 2.44 after dipyridamole stress, and coronary flow reserve 3.86. In the anterior, septal, and apical regions, rest flow is similar but stress flow averages 1.0 and coronary flow reserve 1.5, all below ischemic thresholds **(B)**. The proximal septum has a minimum CFR of 0.46 indicating myocardial steal. Other: 1) The CT scan done for attenuation of PET data shows dense coronary calcification in all coronary arteries. 2) Gated PET perfusion images showed abnormal left ventricular contraction with anterior, apical and septal akinesis but normal rubidium trapping at rest indicating viable stunned myocardium of approximately 60% of the LV. The ejection fraction was 43% at stress with anterior hypokinesis. Conclusions: These findings suggest high-grade stenosis of the proximal LAD, but patent bypass grafts to the PDA and OM2 distributions. Based on the PET scan, coronary angiography with a revascularization procedure is essential due to the size and severity of the stress PET abnormalities. Follow up: At cath, the left main and LAD were stented with subsequent normalization of the threshold map at follow-up **(C)** with stress ejection fraction of 63%.

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severe diffuse CAD without segmental stenosis for which angiography is not likely useful despite severe diffuse CAD.

Because some physicians may not have in-depth knowledge of coronary physiology, quantitative myocardial perfusion, ischemic flow threshold and their clinical relevance, the cardiology PET consultant has to provide an integrated technical, physiologic, and clinical interpretation specific for each individual. Or the PET reader needs to communicate with the primary cardiologist the PET findings in order to integrate with clinical circumstances for optimal, tailored management. While other clinical models may work in different facilities, in the senior author's cardiac PET practice, the imaging findings are integrated with detailed clinical evaluation so that the PET report provides a clear recommendation for or against invasive procedures after integration with clinical circumstances. Invasive cardiologists at this center specifically refer patients for and expect this recommendation to assist their decisions in the cath lab. Some patients also request a specific second opinion on invasive procedures. Without this integrated interpretation, the unique power of PET for patient management is partly lost and PET could become "another test" having very limited impact as reported in the SPARC (Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease) trial for SPECT (Online Ref. 83).

Additional Uses of PET Perfusion Imaging

Prognosis. A growing body of evidence supports the prognostic ability of absolute flow when quantified by cardiac PET (28,Online Refs. 51–54,71,77). Table 3 summarizes the current literature, showing that intact CFR is associated with a favorable prognosis. Mechanistically, a reduced CFR leads to a worse prognosis either through a severe, focal defect and its future risk of plaque rupture with an acute coronary syndrome, or through a global flow reduction that serves as a marker for diffuse disease and overall CAD burden. Importantly, test related prognostic risk scores do not account for the effect of treatment on prognosis (Online Ref. 78). Therefore, prognosis related to all diagnostic imaging becomes somewhat moot in the absence of a controlled randomized intervention trial.

Endothelial dysfunction. PET may be used to assess coronary microvascular endothelial dysfunction noninvasively by perfusion imaging with cold pressor stress, or by resting perfusion heterogeneity that improves with vasodilator stress (Online Refs. 70–78).

Serial imaging. Serial PET perfusion tracks regression or progression (29,40,41,Online Refs. 85–88). However, current data suggest that changes in absolute flow or CFR smaller than about 20% can frequently occur due to measurement or biological variability (Online Ref. 44). Therefore, in the absence of significant clinical indications, only large areas of severe worsening by PET are grounds for considering an angiogram if clinically appropriate.

PET changes are often mixed regionally with the greatest change in areas that were not the worst region at baseline (29), especially with suboptimal risk factor control. In a longitudinal study, 77% of changes on follow-up PET involved areas that were not the most severe defect on the prior PET, indicating the multicentric or diffuse character of CAD and its progression or regression (29).

Study limitations. PET technology is complex, not yet standardized, and the experience from the years of developing centers not yet encapsulated into widely available hardware, software algorithms, or protocols for general use, as reviewed in the Online Appendix. Moreover, the heterogeneity of clinical practice is associated with substantial crossovers that complicate randomized trial design and interpretation. Both of these issues affected the PARR-2 (PET and Recovery Following Revascularization-2) trial (Online Refs. 89,90) and the ongoing randomized Century Health Project of the Weatherhead PET Center For Preventing and Reversing Atherosclerosis at the University of Texas–Houston (Online Ref. 91) (NCT00756379).

Conclusions

In cardiovascular practice, PET perfusion imaging is now technically advanced enough and demonstrated for potential broad use to the extent of other current cardiac imaging as well as reimbursed by Medicare and most third-party insurers. This review outlines the scientific basis for clinical cardiac PET to guide management and revascularization procedures, potentially for optimal outcomes at lower overall downstream costs as suggested in cohort studies (40) but remaining to be proven by randomized trials. The current evidence base now justifies PET perfusion imaging as a powerful clinical tool to advance current cardiovascular practice in guiding revascularization decisions.

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Key Words: coronary flow ■ coronary physiology ■ ischemia ■ PET perfusion imaging ■ revascularization.

APPENDIX

For an expanded Methods, Results, and Discussion, references section, and supplemental figures and tables, please see the online version of this article.

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