JACC: CARDIOVASCULAR IMAGING VOL. 5, NO. 2, 2012

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC. DOI:10.1016/j.jcmg.2011.09.020

CME

Is Discordance of Coronary Flow Reserve and Fractional Flow Reserve Due to Methodology or Clinically Relevant Coronary Pathophysiology?

Nils P. Johnson, MD, MS, Richard L. Kirkeeide, PhD, K. Lance Gould, MD
Houston, Texas

JACC: CARDIOVASCULAR IMAGING CME

CME Editor: Ragaven Baliga, MD

This article has been selected as this issue's CME activity, available online at http://imaging.onlinejacc.org by selecting the CME tab on the top navigation bar.

Accreditation and Designation Statement

The American College of Cardiology Foundation (ACCF) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The ACCF designates this Journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Method of Participation and Receipt of CME Certificate

To obtain credit for this CME activity, you must:

1. Be an ACC member or *JACC: Cardiovascular Imaging* subscriber
2. Carefully read the CME-designated article available online and in this issue of the journal.
3. Answer the post-test questions. At least 2 out of the 3 questions provided must be answered correctly to obtain CME credit.
4. Complete a brief evaluation.
5. Claim your CME credit and receive your certificate electronically by following the instructions given at the conclusion of the activity.

CME Objective for This Article: At the completion of this article, the reader should be able to: describe the relationship between CFR and FFR as focal stenosis and diffuse disease vary; identify the dominant mechanism of flow alteration given a specific pair of CFR and FFR values; discuss the clinical implications for mechanical revascularization when CFR and FFR are discordant.

CME Editor Disclosure: *JACC: Cardiovascular Imaging* CME Editor Ragaven Baliga, MD, has reported that he has no relationships to disclose.

Author Disclosure: The authors received internal funding from the Weatherhead PET Center for Preventing and Reversing Atherosclerosis. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Medium of Participation: Print (article only); online (article and quiz).

CME Term of Approval:
Issue Date: February 2012
Expiration Date: January 31, 2013

From the Weatherhead PET Center for Preventing and Reversing Atherosclerosis, Division of Cardiology, Department of Medicine, University of Texas Medical School and Memorial Hermann Hospital, Houston, Texas. The authors received internal funding from the Weatherhead PET Center for Preventing and Reversing Atherosclerosis. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received August 1, 2011; revised manuscript received September 12, 2011, accepted September 13, 2011.

JACC: CARDIOVASCULAR IMAGING, VOL. 5, NO. 2, 2012
FEBRUARY 2012:193–202

Is Discordance of Coronary Flow Reserve and Fractional Flow Reserve Due to Methodology or Clinically Relevant Coronary Pathophysiology?

OBJECTIVES The purpose of this study was to determine whether observed discordance between coronary flow reserve (CFR) and fractional flow reserve (FFR) is due to methodology or reflects basic coronary pathophysiology.

BACKGROUND Despite the clinical importance of coronary physiological assessment, relationships between its 2 most common tools, CFR and FFR, remain poorly defined.

METHODS The worst CFR and stress relative uptake were recorded from 1,500 sequential cardiac positron emission tomography cases from our center. From the literature, we assembled all combined, invasive CFR-FFR measurements, including a subset before and after angioplasty. Both datasets were compared with a fluid dynamic model of the coronary circulation predicting relationships between CFR and FFR for variable diffuse and focal narrowing.

RESULTS A modest but significant linear relationship exists between CFR and FFR both invasively ($r = 0.34$, $p < 0.001$) and using positron emission tomography ($r = 0.36$, $p < 0.001$). Most clinical patients undergoing CFR or FFR measurements have diffusely reduced CFR consistent with diffuse atherosclerosis or small-vessel disease. The theoretical model predicts linear relationships between CFR and FFR for progressive stenosis with slopes dependent on diffuse narrowing, matching observed data. Reported changes in CFR and FFR with angioplasty agree with model predictions of removing focal stenosis but leaving diffuse disease. Although CFR-FFR concordance is common, discordance is due to dominant or absent diffuse versus focal disease, reflecting basic pathophysiology.

CONCLUSIONS CFR is linearly related to FFR for progressive stenosis superimposed on diffuse narrowing. The relative contributions of focal and diffuse disease define the slope and values along the linear CFR and FFR relationship. Discordant CFR and FFR values reflect divergent extremes of focal and diffuse disease, not failure of either tool. With such discordance observed by invasive and noninvasive techniques and also fitting fluid dynamic predictions, it reflects clinically relevant basic coronary pathophysiology, not methodology. (J Am Coll Cardiol Img 2012;5:193–202)

Coronary physiology plays an increasingly clinical role in cardiology. Multiple imaging techniques provide routine quantification of absolute flow and myocardial or coronary flow reserve (CFR), from positron emission tomography (PET) to cardiac magnetic resonance, myocardial contrast echocardiography, and contrast computed tomography. Based on randomized clinical trials and strong national/international guidelines, fractional flow reserve (FFR) procedures are growing even as percutaneous coronary intervention (PCI) volume decreases (1).

See page 203

However, 2 different measurements quantify coronary physiology: flow, summarized by CFR, and pressure, summarized by FFR. Although the quadratic relationship between absolute flow and the pressure decrease across a stenosis has been demonstrated in theoretical, animal, and human studies spanning almost 25 years (2–4), the relationship between the common clinical tools of CFR and FFR is not well defined. This void produces clinical uncertainty when an imaging study suggests low CFR but invasive measurement determines normal FFR or vice versa. Additionally, recent publications have sought to determine noninvasive CFR cutoffs using FFR as a reference. However, the gold-standard FFR cutoffs

themselves were originally based on concordance with noninvasive studies (5), thereby revealing logical inconsistency.

The essential question for clinical practice asks whether CFR-FFR discordance occurs because of method or reflects basic coronary pathophysiology useful for making decisions. To answer this question, we made a 3-way comparison of: 1) all reports of combined invasive CFR and FFR measurements in the literature; 2) PET-measured CFR and relative stress defects in 1,500 sequential cases from our center; and 3) results of a theoretical fluid dynamic model of the coronary circulation predicting CFR-FFR relationships with varying focal stenosis and diffuse or small-vessel disease.

METHODS

PET scan acquisition and processing. Scans were done between April 2007 and June 2011 at the Weatherhead PET Center for Preventing and Reversing Atherosclerosis of the University of Texas Medical School at Houston and Memorial Hermann Hospital after receiving written informed consent from the subject and study approval by the institutional review board. Subjects included both young, asymptomatic normal volunteers and clinical patients representing the entire spectrum of cardiac atherosclerotic disease.

Our cardiac PET acquisition and processing protocol with absolute flow quantification is described in previous publications (6,7). In brief, rest and stress perfusion images were acquired using Rb-82 on a hybrid 16-slice PET-computed tomography scanner for attenuation correction, shifted as need for coregistration. Intravenous dipyridamole produced hyperemia before stress imaging. Image processing converted raw, unrotated 3-dimensional data into 2-dimensional topographic maps reflecting left ventricular anatomy.

Peak integrated activity over an approximate 2 × 2-mm circular area in the left atrium or thoracic aorta was determined from transaxial images acquired during the first 2 min after each radiotracer injection. Integrated myocardial activity during the next 5 min was determined from topographic maps of the left ventricle. For each of 64 radial segments at each of 21 short-axis slices, integrated arterial input and integrated myocardial uptake were used to compute absolute myocardial flow using an established model (8) implemented by custom software. The 21 × 64-pixel topographic flow map was smoothed using a 5 × 5-pixel average to suppress noise introduced by the flow model. CFR was computed as the stress-to-rest ratio on a pixel-by-pixel basis.

The worst CFR was recorded, excluding 4 basal slices (due to low counts in the membranous septum) and 2 apical slices (due to potential partial volume errors caused by partial-thickness slices through left ventricular and apical motion). Relative stress uptake at the identical location as the worst CFR was recorded as a noninvasive surrogate for FFR.

Additionally, clinical patients undergoing cardiac PET followed by invasive FFR were identified from review of our clinical records. Invasive FFR was performed using standard equipment and either intravenous or intracoronary adenosine according to operator preference. Selected cases were chosen to illustrate CFR and FFR concordance and discordance.

Literature search for combined invasive CFR-FFR measurements. PubMed was searched for articles measuring combined CFR and FFR invasively. Their references were examined systematically as were review articles, guidelines, and consensus statements on flow reserve for additional relevant citations. Included studies had to measure and report both CFR (typically using intracoronary Doppler but rarely using thermodilution) and FFR simultaneously or sequentially. Those studies that reported CFR and FFR both before and after PCI were noted, as were articles that included scatterplots or tabular values of CFR and FFR. For each study, the mean and SD of both indexes were recorded. Individual values were manually extracted from tables and graphs.

ABBREVIATIONS AND ACRONYMS

CFR = coronary flow reserve

FFR = fractional flow reserve

PCI = percutaneous coronary intervention

PET = positron emission tomography

Theoretical model. A basic version of the model, its theoretical and experimental bases, and animal validation was published previously (9). Full details regarding its parameters and calculations can be found in the Online Appendix.

The model consists of a branching network of arterial segments terminating in myocardial beds. Each arterial segment has a given length, variable diffuse narrowing, and a superimposed focal percentage of diameter stenosis. Each myocardial bed consists of a summed vascular length (representing combined arterial and arteriolar vessels) and mass. Model inputs based on the literature include normal resting flow, normal CFR, arterial lengths, and myocardial mass. Normal vessel area and diameter in each segment are determined from its distal myocardial mass using experimental data in humans. Summed distal vessel length and myocardial mass adhere to the observed linear relationship.

The Poiseuille equation calculates viscous pressure loss along each segment. A quadratic relationship determines the pressure decrease across a focal stenosis based on its flow. In the absence of diffuse or focal disease, each myocardial bed lowers its resistance until normal CFR has been achieved. Flow to each myocardial bed is altered iteratively in the presence of diffuse and/or focal disease until all beds reach their minimum resistance. Flow in each arterial segment preserves conservation of mass through the model network.

Statistical methods. Statistical analyses were performed using R version 2.13.1 (10). Summary values for the literature used number of patients as a weighting factor. Continuous variables are summarized as mean ± SD. The association between paired, continuous variables is summarized using both the Pearson (r) and Spearman (ρ) correlation coefficients, although 95% confidence intervals (CI) could not be computed for Spearman correlation coefficients due to ties. Applicable tests were 2-tailed, and $p < 0.05$ was considered statistically significant.

RESULTS

Combined CFR-FFR Measurements. Figure 1A displays all available combined invasive CFR and FFR values in the literature, constituting 438 cases (11–17). Figure 1B displays the worst CFR by PET with corresponding stress relative uptake for 1,500 sequential cases from our center. A significant but modest correlation exists between invasive CFR and FFR as a whole ($r = 0.34$ [95% CI: 0.26 to 0.42], $p < 0.001$; $\rho = 0.28$, $p < 0.001$). Similarly, a significant but modest correlation exists between CFR by PET and stress relative uptake as a whole ($r = 0.36$ [95% CI: 0.32 to 0.40], $p < 0.001$; $\rho = 0.30$, $p < 0.001$).

Literature and clinical FFR-CFR measurements. Table 1 summarizes all the invasive literature for combined CFR and FFR measurements, both in the vessel of clinical interest and in reference or nonischemic vessels (11,12,17–36). As the normal range for noninvasive CFR is >4 in young, asymptomatic volunteers (6), the lower portion of Table 1 demonstrates that all studies examined subjects who had either small-vessel disease or at least mild diffuse disease, even in normal reference vessels.

Table 2 summarizes studies reporting invasive CFR and FFR before and after PCI, which are diagrammed in Figure 2 (18,19,21–24,26,27,32). The slope between paired measurements and movement toward an FFR of 1 after PCI supports the theoretical model prediction that PCI abolishes the focal stenosis but not the background diffuse and small-vessel disease, indicated by the different slopes of the CFR-FFR relationships.

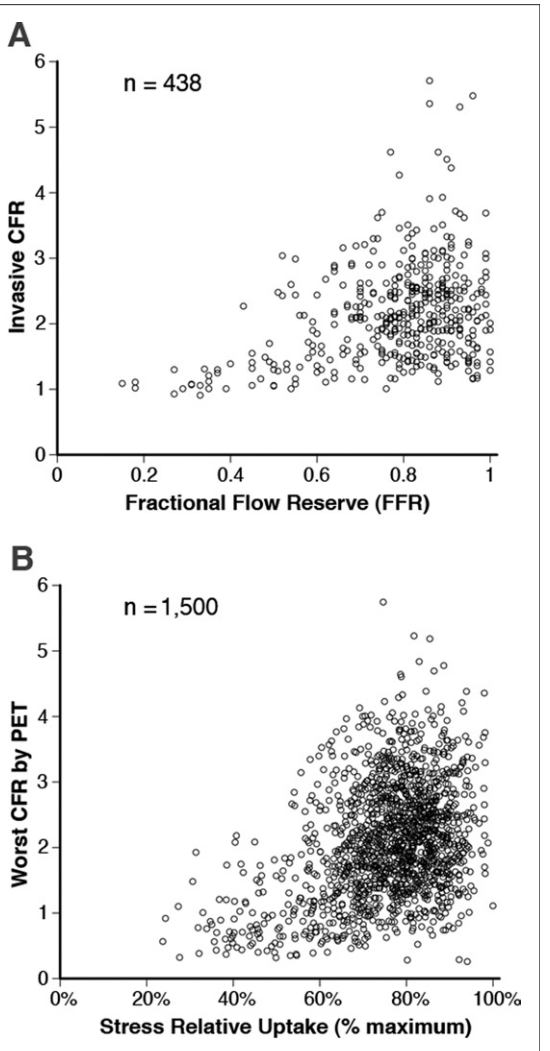

Figure 1. Scatterplot of All CFR and Fractional Flow Reserve Values

(A) Invasive measurements of individual coronary flow reserve (CFR) and fractional flow reserve values in 438 patients from the literature. Data extracted from Figure 3 of Tron (11), Table 2 of Baumgart (12), Figure 1A of Meuwissen et al. (13), Figure 3 of Werner et al. (14), Figure 2 of Fearon (15), Figure 1 of Werner (16), and Table 3 of Meuwissen et al. (17). **(B)** Positron emission tomography (PET) measurements of individual worst CFR and corresponding stress relative uptake in 1,500 sequential cases from our center.

Theoretical model. As detailed in the Online Appendix, the theoretical model examined varying degrees of diffuse disease and a single, superimposed, focal stenosis in the proximal left anterior descending artery. A direct linear relationship

existed between the 2 metrics as the focal stenosis varied. The slope of the CFR-FFR line related inversely to diffuse disease. The maximum CFR in the model was set at 4.2 based on previous studies (6), so that there were no CFR values above the CFR-FFR regression line without diffuse disease. As pressure decreases directly with flow due to viscous loss, a small but nonzero pressure gradient existed along any conductance vessel, even without any diffuse or segmental narrowing. Values below the CFR-FFR line could be observed in any CFR-FFR combination and reflected the simultaneous effects of focal, diffuse, and small-vessel disease.

The model results divide the CFR-FFR scatterplot into 6 regions, as conceptualized in Figure 3. The upper left half of the scatterplot (in white) could only contain data from patients with reference CFR above the average normal value. The lower right wedge (in gray) contains points with reduced CFR but minimal pressure loss along the epicardial conduit vessels, identifying cases with isolated small-vessel disease. For conceptual purposes, the remaining region can be divided into 4 quadrants by typical cutoff values of an FFR of 0.8 and a CFR of 2, while recognizing that these thresholds are not physiologically abrupt in practice. The 2 quadrants with discordant CFR and FFR represent contrasting contributions of focal disease (dominant when FFR decreases more than CFR) and diffuse or small-vessel disease (dominant when CFR decreases more than FFR). Myocardial or coronary steal occurs when CFR is <1, which is rarely measured invasively because the majority of these cases occur with total or subtotal occlusions that render wire placement difficult.

Figure 4 shows representative clinical examples from each CFR-FFR combination of concordant or discordant, adequate or reduced flow capacity. Applying typical binary cutoffs of a CFR of 2.0 and an FFR of 0.8 (5) to the invasive data in Figure 1A, 165 of cases (38%) are concordant and adequate, 98 (22%) are concordant but reduced, 85 (19%) are discordant with dominant focal disease, and 90 (21%) are discordant with dominant diffuse disease. Similarly, applying binary cutoffs of a CFR of 2.0 and stress relative uptake of 80% to the PET data in Figure 1B, 388 of cases (26%) are concordant and adequate, 476 (32%) are concordant but reduced, 386 (26%) are discordant with dominant focal disease, and 250 (17%) are discordant with dominant diffuse disease.

Table 1. Summary of Literature With Combined Invasive CFR and FFR Measurements

First Author (Ref. #)	n	FFR	Invasive CFR
Vessel of clinical interest			
Pijls et al. (18)	50	0.53 ± 0.16	1.47 ± 0.52
Kolyva et al. (19)	11	0.53 ± 0.14	1.48 ± 0.46
Seiler et al. (20)	50	0.53 ± 0.28	1.7 ± 0.7
Beleslin et al. (21)	33	0.56 ± 0.14	1.4 ± 0.3
Leung et al. (22)	18	0.57 ± 0.19	1.8 ± 0.6
Verhoeff et al. (23)	24	0.59 ± 0.16	1.70 ± 0.57
Ogawa et al. (24)	34	0.61 ± 0.06	1.13 ± 0.27
Meuwissen et al. (25)	151	0.62 ± 0.18	1.76 ± 0.68
Siebes et al. (26)	14	0.62 ± 0.16	1.80 ± 0.64
Roy et al. (27)	32	0.62	2.3 ± 0.1
Barbato et al. (28)	59	0.66 ± 0.16	1.7 ± 0.6
Tron et al. (11)	62	0.67 ± 0.20	1.9 ± 0.6
Abe et al. (29)	24	0.68 ± 0.13	1.83 ± 0.78
de Bruyne et al. (30)	13	0.70 ± 0.17	1.76 ± 0.54
Chamuleau et al. (31)	127	0.75 ± 0.18	2.21 ± 0.76
Kini et al. (32)	72	0.77 ± 0.03	1.43 ± 0.28
Wexberg et al. (33)	26	0.79 ± 0.12	2.48 ± 1.40
Kirschbaum et al. (34)	50	0.80 ± 0.14	2.1 ± 0.8
Baumgart et al. (12)	21	0.81 ± 0.15	2.1 ± 0.5
Meuwissen et al. (17)	170	0.84 ± 0.07	2.56 ± 0.55
Marques et al. (35)	77	0.85 ± 0.12	2.6 ± 0.8
Weighted average	1,118	0.70 ± 0.11	1.98 ± 0.61
Reference or nonischemic vessel			
Meuwissen et al. (25)	151	0.82 ± 0.11	2.50 ± 0.72
Pijls et al. (18)	50	0.87 ± 0.08	2.64 ± 0.59
Abe et al. (29)	22	0.87 ± 0.05	3.14 ± 0.85
Ng et al. (36)	15	0.88 ± 0.06	2.8 ± 1.0
Barbato et al. (28)	59	0.89 ± 0.08	2.4 ± 1.0
Ogawa et al. (24)	164	0.92 ± 0.08	2.55 ± 0.29
Verhoeff et al. (23)	24	0.96 ± 0.04	2.76 ± 0.73
Siebes et al. (26)	14	0.97 ± 0.03	2.8 ± 0.74
Weighted average	495	0.88 ± 0.08	2.57 ± 0.61

Values are n or mean ± SD.
CFR = coronary flow reserve; FFR = fractional flow reserve.

DISCUSSION

Our results demonstrate that the discordance between CFR and FFR arises from basic coronary pathophysiology. Such discordance occurs with both invasive and noninvasive techniques consistent with theoretical fluid dynamic predictions and, therefore, is not due to methodology. The relative contributions of focal, diffuse, and small-vessel disease define the relationship between CFR and FFR for a specific case. For observed simultaneous CFR and FFR measurements, Figure 3 enables qualitative physiological categorization into each of the concordant, discordant, and dominant stenosis or dominant diffuse disease groups. Our theoretical

Table 2. Summary of Literature With Both Invasive CFR and FFR Before and After Angioplasty

		FFR		Invasive CFR	
First Author (Ref. #)	n	Before	After	Before	After
Pijls et al. (18)	33	0.53 ± 0.16	0.89 ± 0.07	1.47 ± 0.52	2.40 ± 0.44
Kolyva et al. (19)	11	0.53 ± 0.14	0.93 ± 0.05	1.48 ± 0.46	2.84 ± 0.69
Beleslin et al. (21)	33	0.56 ± 0.14	0.91 ± 0.06	1.4 ± 0.3	2.6 ± 0.7
Leung et al. (22)	18	0.57 ± 0.19	0.92 ± 0.06	1.8 ± 0.6	3.0 ± 0.8
Verhoeff et al. (23)	24	0.59 ± 0.16	0.89 ± 0.10	1.70 ± 0.57	2.84 ± 0.64
Ogawa et al. (24)	7	0.62 ± 0.04	0.91 ± 0.08	1.09 ± 0.21	2.41 ± 0.24
Siebes et al. (26)	15	0.62 ± 0.16	0.85 ± 0.11	1.80 ± 0.64	2.86 ± 0.59
Roy et al. (27)	31	0.62	0.89	2.3 ± 0.1	3.6 ± 0.3
Kini et al. (32)	36*	0.76 ± 0.02	0.99 ± 0.01	1.49 ± 0.25	2.44 ± 0.67
Kini et al. (32)	36†	0.77 ± 0.03	0.97 ± 0.03	1.36 ± 0.31	1.89 ± 0.30

Values are n or mean ± SD. *Without diabetes. †With diabetes.
Abbreviations as in Table 1.

fluid dynamic model makes predictions consistent with clinical data shown in Figures 1 and 2. As PCI changes only the focal stenosis, the comparable slopes in Figure 2 for pre- and post-PCI measurements also fit predictions of the theoretical model for residual diffuse disease.

Interestingly, Table 1 shows that FFR has only been applied clinically in populations with reduced CFR. This "disease-enriched" population preselected by clinical evidence of significant coronary artery disease explains the success of the FFR cutoff of 0.75 to 0.8 for guiding PCI, but also warns against its indicating ischemia in patients without diffuse disease, explained as follows. Relative CFR (dividing the observed CFR in the diseased artery by the CFR in a normal reference artery) approximates FFR because their relationship is linear (37), as seen in our model. Assuming CFR in a normal artery to be approximately 4.0 (6), an FFR or relative CFR of 0.8 would imply an observed CFR of $4.0 \times 0.8 = 3.2$ in the diseased artery. However, a CFR of 3.2 is sufficient to avoid ischemia (5). Why, then, does an FFR cutoff of 0.8 identify ischemia? Table 1 gives the answer: CFR in the reference artery is not 4.0 but rather 2.5 due to diffuse disease present in most patients with clinically significant segmental disease. Therefore, $2.5 \times 0.8 = 2.0$, which is approximately the CFR threshold for ischemia (5). FFR thresholds of 0.7 to 0.8 "work" because they have been applied in populations with sufficient diffuse disease to lower the reference CFR. Conversely, measuring FFR in a population with a higher reference CFR would require lower FFR cutoffs for ischemia compared with functional tests and/or imaging, as in the earliest FFR reports described subsequently.

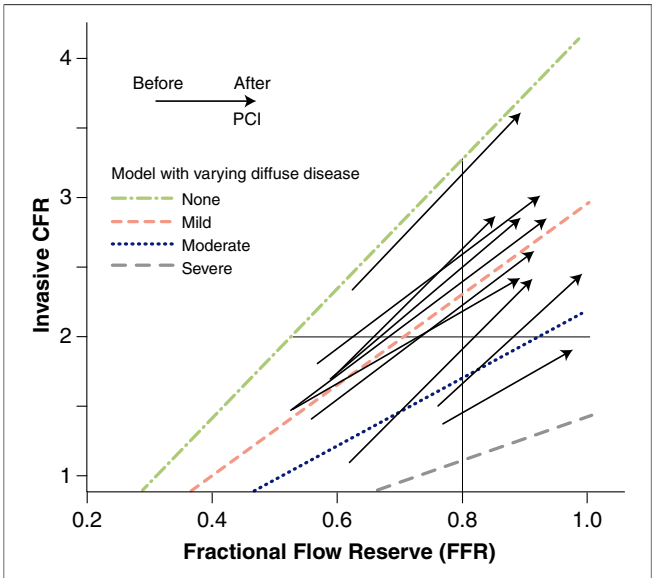

Figure 2. Literature Data of Invasive CFR and FFR Before and After PCI

Average coronary flow reserve (CFR) and fractional flow reserve (FFR) values before and after percutaneous coronary intervention (PCI), as reported in Table 2. **Background lines** represent the theoretical model predictions for varying degrees of diffuse disease. Experimental slopes and movement toward a fractional flow reserve of 1 after treatment agree with the model within error. PCI reduces focal disease but does not alter diffuse or small-vessel disease.

In the absence of significant diffuse disease, normal CFR matches normal FFR. However, FFR may be reduced with preserved CFR when diffuse disease is minimal. FFR may be adequate (nonischemic) with reduced CFR when diffuse disease is severe. Therefore, "mismatch" or "discordance" between CFR and FFR does not imply a failure of either tool clinically. Instead, it imparts information on the presence and relative

balance of diffuse versus focal atherosclerotic disease or small-vessel disease.

Our results highlight the key role of diffuse disease in causing discordant CFR-FFR, as seen in Table 1. A single measurement of FFR cannot determine whether pressure has decreased due to a localized stenosis or the cumulative effects of diffuse atherosclerosis. Only performing a distal-to-proximal pull-back along the entire length of the artery can distinguish diffuse narrowing from local stenosis. However, reduction in CFR with near unity FFR in the distal artery (approximately <5 mm Hg pressure loss) signals pure small-vessel disease. Therefore, small-vessel disease offers a coexisting or alternative explanation to diffuse disease for the reduced CFR in Table 1. In our fluid dynamic model, decreasing the normal reference CFR limit (Online Appendix) also predicts the effects of small-vessel disease separately from diffuse disease that matches clinical observations.

The FFR thresholds of 0.75 to 0.8 were derived originally by comparison with noninvasive functional tests (5). These earliest reports selected patients with greater focal than diffuse disease in an attempt to avoid the known complexities of quantifying diffuse disease. In these settings, the optimal cutoffs were lower, averaging an FFR of 0.66 (38,39), suggesting that the optimal threshold varies given the relative balance of diffuse and focal atherosclerosis. Indeed, the theoretical model confirms this observation with an FFR near 0.65 for a focal 65% diameter stenosis and no diffuse disease (Online Appendix).

Comparison with existing literature. Several studies examined combined invasive CFR and FFR, as detailed in Tables 1 and 2 and Figure 1A. To our knowledge, only 1 study has graphed combined noninvasive CFR with invasive FFR values (40), which found 12% discordance using myocardial contrast echocardiography to measure flow in the left anterior descending artery in 50 patients. The prevalence of concordance and discordance between CFR and FFR appears similar between the invasive literature and our PET data, but vary somewhat with the mix of focal, diffuse, and small-vessel disease as detailed earlier.

Our results clarify a disagreement in the literature on the correlation coefficient between CFR and FFR. For example, 1 paper reported no significant correlation ($r = 0.03$, $p = 0.87$) (14), whereas another found a significant moderate correlation ($r = 0.60$, $p < 0.001$) (13). When all the data are aggregated, as in Figure 1, a significant but modest correlation exists. However, individual studies may sample small cohorts with different extents of diffuse and/or small-vessel disease. The scatter in Figure 1 near the intersection of an FFR of 0.8 and CFR of 2 may incorrectly suggest a lack of association between the variables. However, over their entire range for all the data in the aggregate, CFR and FFR are physiologically related to each other, as detailed in Figure 3.

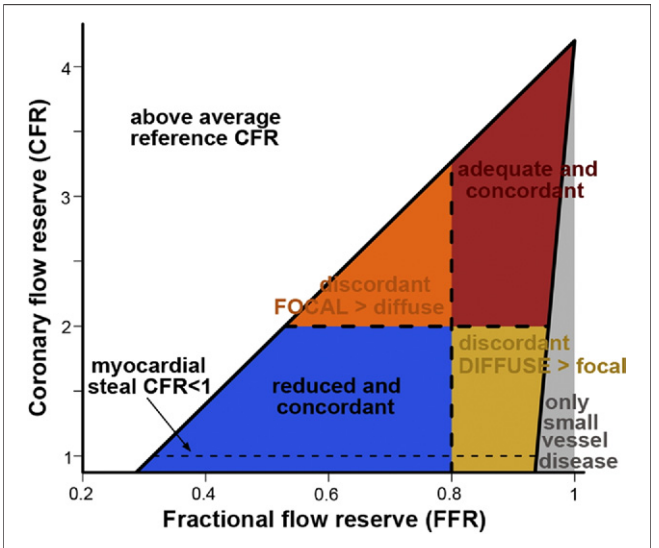

Figure 3. Conceptual Plot of CFR and Fractional Flow Reserve Regions

Six regions can be identified by combined measurement of CFR and FFR. First, the **white area** at the upper left labeled "above average reference CFR" contains patients whose CFR without focal disease is greater than the mean in young healthy volunteers. Second, the **gray area** at the lower right labeled "only small vessel disease" contains patients with reduced CFR but an FFR near 1. Third, the **red quadrant** at the upper right labeled "adequate and concordant" contains patients with an FFR >0.8 and a CFR >2. Fourth, the **blue quadrant** at the lower left labeled "reduced and concordant" contains patients with an FFR <0.8 and a CFR <2. Fifth, the **orange quadrant** at the upper left labeled "discordant FOCAL > diffuse" contains patients with a dominant focal stenosis with an FFR <0.8 but relatively preserved CFR >2. Sixth, the **yellow quadrant** at the lower right labeled "discordant DIFFUSE > focal" contains patients with dominant diffuse disease which reduces CFR <2 but at most mild focal disease which leaves FFR >0.8. Patients with myocardial or coronary steal fall below the dashed line at CFR = 1.

CONCLUSIONS

Our cumulative results explain CFR-FFR concordance and discordance as being due to basic pathophysiology with key clinical implications for understanding and interpreting these physiological measures of coronary artery disease, regardless of method. CFR is linearly related to FFR for progressive stenosis superimposed on diffuse narrowing. The relative contributions of focal and diffuse

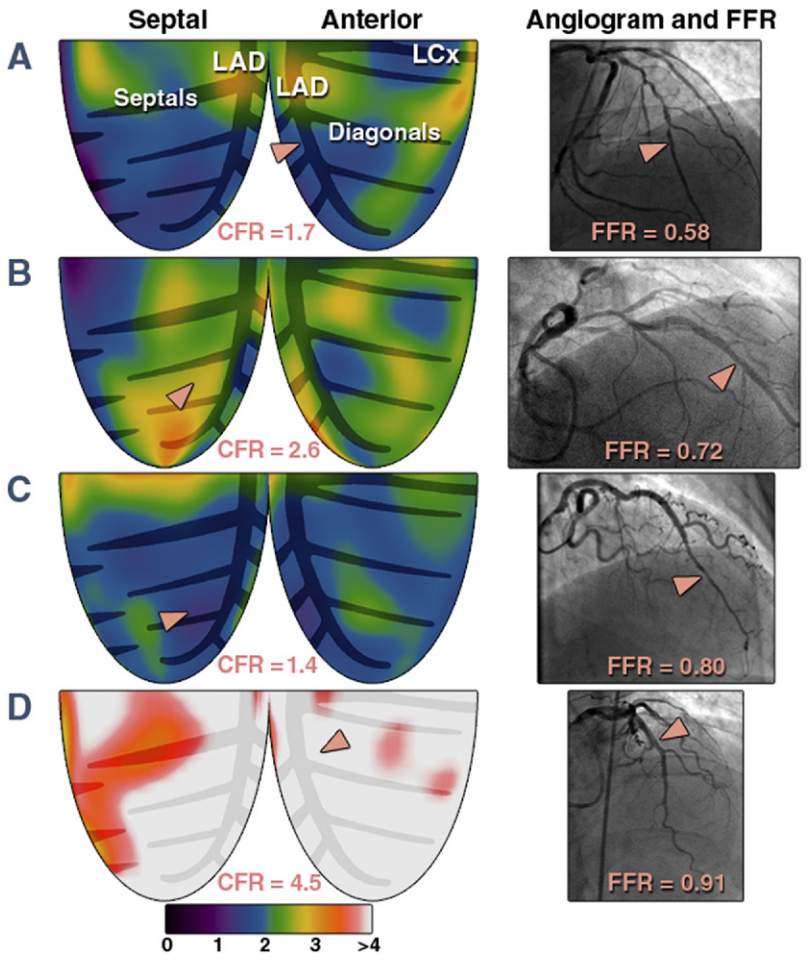

Figure 4. Clinical Cases of Invasive FFR and Noninvasive CFR by PET

As all cases measured FFR in the left anterior descending artery (LAD), only septal and anterior quadrant maps of CFR by positron emission tomography (PET) are shown for publication efficiency along with superimposed, idealized arterial maps. **(A)** A 64-year-old man without previous manifest atherosclerosis but numerous risk factors had no symptoms but was sedentary. A mild relative uptake defect had a CFR of 1.7 with a concordant FFR of 0.58. **(B)** A 52-year-old man with extensive atherosclerosis and previous multivessel stenting who presented after a myocardial infarction. Relative uptake imaging was stable from 7 months previously with a preserved CFR of 2.6 but a decreased FFR of 0.72. **(C)** A 63-year-old woman with a previous myocardial infarction and multivessel stenting who presented with exertional dyspnea. A moderate relative uptake defect had a decreased CFR of 1.4 but a preserved FFR of 0.80 at its nadir. **(D)** A 37-year-old man undergoing evaluation for a coronary fistula using dobutamine stress testing. Both a CFR of 4.5 and an FFR of 0.91 were preserved. LCx = left circumflex artery; other abbreviations as in Figure 1.

disease define the slope and values along the linear CFR and FFR relationship. Discordant CFR and FFR values reflect divergent extremes of focal and diffuse disease, not failure of either tool. With such discordance observed by invasive and noninvasive techniques and also fitting fluid dynamic predictions, it reflects clinically relevant basic coronary pathophysiology, not methodology.

Study limitations. Although a large amount of literature reports event rates based on either CFR or FFR (5), much less is known about prognosis based on combined measurements that provide more precise physiological assessment of severity and causes of ischemia than either separately. One study suggests that discordant measurements in either direction predict an adverse event rate of approximately 20% over 1 year following deferral of mechanical revascularization (17). However, our pathophysiologic analysis suggests that dominant focal disease optimal for PCI might be distinguished from dominant diffuse disease requiring either aggressive medical therapy or conceivably coronary artery bypass grafting. Although small-vessel disease clearly can

impart a worsened prognosis in some cases, its treatment remains medical (41). Thus, combined CFR-FFR assessment has the potential for optimizing individual patient treatment, thereby deserving additional study as a guide to the management of coronary artery disease.

Reprint requests and correspondence: Dr. K. Lance Gould, Weatherhead PET Center for Preventing and Reversing Atherosclerosis, University of Texas Medical School at Houston, 6431 Fannin Street, Room 4.256 MSB, Houston, Texas 77030. *E-mail: K.Lance.Gould@uth.tmc.edu.*

REFERENCES

1. Riley RF, Don CW, Powell W, Maynard C, Dean LS. Trends in coronary revascularization in the United States from 2001 to 2009: recent declines in percutaneous coronary intervention volumes. Circ Cardiovasc Qual Outcomes 2011;4:193–7.
2. Young DF, Cholvin NR, Kirkeeide RL, Roth AC. Hemodynamics of arterial stenoses at elevated flow rates. Circ Res 1977;41:99–107.
3. Gould KL. Pressure-flow characteristics of coronary stenoses in unsedated dogs at rest and during coronary vasodilation. Circ Res 1978;43:242–53.
4. Marques KM, Spruijt HJ, Boer C, Westerhof N, Visser CA, Visser FC. The diastolic flow-pressure gradient relation in coronary stenoses in humans. J Am Coll Cardiol 2002;39:1630–6.
5. Kern MJ, Lerman A, Bech JW, et al., American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology. Physiological assessment of coronary artery disease in the cardiac catheterization laboratory: a scientific statement from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology. Circulation 2006;114:1321–41.
6. Sdringola S, Johnson NP, Kirkeeide RL, Cid E, Gould KL. Impact of unexpected factors on quantitative myocardial perfusion and coronary flow reserve in young, asymptomatic volunteers. J Am Coll Cardiol Img 2011;4:402–12.
7. Johnson NP, Gould KL. Physiological basis for angina and ST-segment change PET-verified thresholds of quantitative stress myocardial perfusion and coronary flow reserve. J Am Coll Cardiol Img 2011;4:990–8.
8. Yoshida K, Mullani N, Gould KL. Coronary flow and flow reserve by PET simplified for clinical applications using rubidium-82 or nitrogen-13-ammonia. J Nucl Med 1996;37:1701–12.
9. Gould KL, Kirkeeide R, Johnson NP. Coronary branch steal: experimental validation and clinical implications of interacting stenosis in branching coronary arteries. Circ Cardiovasc Imaging 2010;3:701–9.
10. R Development Core Team. 2011. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0. Available at: http://www.R-project.org/. Accessed January 4, 2012.
11. Tron C, Donohue TJ, Bach RG, et al. Comparison of pressure-derived fractional flow reserve with poststenotic coronary flow velocity reserve for prediction of stress myocardial perfusion imaging results. Am Heart J 1995;130:723–33.
12. Baumgart D, Haude M, George G, et al. Improved assessment of coronary stenosis severity using the relative flow velocity reserve. Circulation 1998;98:40–6.
13. Meuwissen M, Chamuleau SA, Siebes M, et al. Role of variability in microvascular resistance on fractional flow reserve and coronary blood flow velocity reserve in intermediate coronary lesions. Circulation 2001;103:184–7.
14. Werner GS, Ferrari M, Richartz BM, Gastmann O, Figulla HR. Microvascular dysfunction in chronic total coronary occlusions. Circulation 2001;104:1129–34.
15. Fearon WF, Nakamura M, Lee DP, et al. Simultaneous assessment of fractional and coronary flow reserves in cardiac transplant recipients: Physiologic Investigation for Transplant Arteriopathy (PITA Study). Circulation 2003;108:1605–10.
16. Werner GS, Emig U, Bahrmann P, Ferrari M, Figulla HR. Recovery of impaired microvascular function in collateral dependent myocardium after recanalisation of a chronic total coronary occlusion. Heart 2004;90:1303–10.
17. Meuwissen M, Chamuleau SA, Siebes M, et al. The prognostic value of combined intracoronary pressure and blood flow velocity measurements after deferral of percutaneous coronary intervention. Catheter Cardiovasc Interv 2008;71:291–7.
18. Pils NH, De Bruyne B, Smith L, et al. Coronary thermodilution to assess flow reserve: validation in humans. Circulation 2002;105:2482–6.
19. Kolyva C, Verhoeff BJ, Spaan JA, Piek JJ, Siebes M. Increased diastolic time fraction as beneficial adjunct of alpha1-adrenergic receptor blockade after percutaneous coronary intervention. Am J Physiol Heart Circ Physiol 2008:295:H2054–60.
20. Seiler C, Fleisch M, Billinger M, Meier B. Simultaneous intracoronary velocity- and pressure-derived assessment of adenosine-induced collateral hemodynamics in patients with one- to two-vessel coronary artery disease. J Am Coll Cardiol 1999;34:1985–94.
21. Beleslin B, Ostojic M, Djordjevic-Dikic A, et al. The value of fractional and coronary flow reserve in predicting myocardial recovery in patients with previous myocardial infarction. Eur Heart J 2008;29:2617–24.
22. Leung MC, Meredith IT, Cameron JD. Aortic stiffness affects the coronary blood flow response to percutaneous coronary intervention. Am J Physiol Heart Circ Physiol 2006;290:H624–30.
23. Verhoeff BJ, Siebes M, Meuwissen M, et al. Influence of percutaneous coronary intervention on coronary microvascular resistance index. Circulation 2005:111:76–82.
24. Ogawa J, Ohkubo T, Fukazawa R, et al. Estimation of myocardial hemodynamics before and after intervention in children with Kawasaki disease. J Am Coll Cardiol 2004;43:653–61.
25. Meuwissen M, Siebes M, Chamuleau SA, et al. Hyperemic stenosis resistance index for evaluation of functional coronary lesion severity. Circulation 2002;106:441–6.
26. Siebes M, Verhoeff BJ, Meuwissen M, de Winter RJ, Spaan JA, Piek JJ. Single-wire pressure and flow velocity measurement to quantify coronary stenosis hemodynamics and effects of percutaneous interventions. Circulation 2004;109:796–800.
27. Roy AS, Banerjee RK, Back LH, Back MR, Khoury S, Millard RW. Delineating the guide-wire flow obstruction effect in assessment of fractional flow reserve and coronary flow reserve measurements. Am J Physiol Heart Circ Physiol 2005;289:H392–7.

28. Barbato E, Aarnoudse W, Aengevaeren WR, et al. Validation of coronary flow reserve measurements by thermodilution in clinical practice. Eur Heart J 2004;25:219–23.
29. Abe M, Tomiyama H, Yoshida H, Doba N. Diastolic fractional flow reserve to assess the functional severity of moderate coronary artery stenoses: comparison with fractional flow reserve and coronary flow velocity reserve. Circulation 2000;102:2365–70.
30. de Bruyne B, Bartunek J, Sys SU, Pijls NH, Heyndrickx GR, Wijns W. Simultaneous coronary pressure and flow velocity measurements in humans. Feasibility, reproducibility, and hemodynamic dependence of coronary flow velocity reserve, hyperemic flow versus pressure slope index, and fractional flow reserve. Circulation 1996; 94:1842–9.
31. Chamuleau SA, Meuwissen M, van Eck-Smit BL, Koch KT, et al. Fractional flow reserve, absolute and relative coronary blood flow velocity reserve in relation to the results of technetium-99m sestamibi single-photon emission computed tomography in patients with two-vessel coronary artery disease. J Am Coll Cardiol 2001;37:1316–22.
32. Kini AS, Kim MC, Moreno PR, Krishnan P, Ivan OC, Sharma SK. Comparison of coronary flow reserve and fractional flow reserve in patients with versus without diabetes mellitus and having elective percutaneous coronary intervention and abciximab therapy (from the PREDICT Trial). Am J Cardiol 2008;101:793–800.
33. Wexberg P, Sperker W, Morgenthaler NG, et al. Inhomogeneous vasomotor effects of moderate selective and non-selective endothelin-receptor blockade in stable coronary artery disease. Heart 2009;95:1258–64.
34. Kirschbaum SW, Springeling T, Rossi A, et al. Comparison of adenosine magnetic resonance perfusion imaging with invasive coronary flow reserve and fractional flow reserve in patients with suspected coronary artery disease. Int J Cardiol 2011;147: 184–6.
35. Marques KM, van Eenige MJ, Spruijt HJ, et al. The diastolic flow velocity-pressure gradient relation and dpv50 to assess the hemodynamic significance of coronary stenoses. Am J Physiol Heart Circ Physiol 2006;291: H2630–5.
36. Ng MK, Yeung AC, Fearon WF. Invasive assessment of the coronary microcirculation: superior reproducibility and less hemodynamic dependence of index of microcirculatory resistance compared with coronary flow reserve. Circulation 2006;113: 2054–61.
37. Gould KL. Does coronary flow trump coronary anatomy? J Am Coll Cardiol Img 2009;2:1009–23.
38. De Bruyne B, Bartunek J, Sys SU, Heyndrickx GR. Relation between myocardial fractional flow reserve calculated from coronary pressure measurements and exercise-induced myocardial ischemia. Circulation 1995;92: 39–46.
39. Bartunek J, Van Schuerbeeck E, de Bruyne B. Comparison of exercise electrocardiography and dobutamine echocardiography with invasively assessed myocardial fractional flow reserve in evaluation of severity of coronary arterial narrowing. Am J Cardiol 1997;79:478–81.
40. Meimoun P, Sayah S, Luycx-Bore A, et al. Comparison between non-invasive coronary flow reserve and fractional flow reserve to assess the functional significance of left anterior descending artery stenosis of intermediate severity. J Am Soc Echocardiogr 2011;24:374–81.
41. Lanza GA, Crea F. Primary coronary microvascular dysfunction: clinical presentation, pathophysiology, and management. Circulation 2010;121: 2317–25.

Key Words: absolute flow quantification ■ coronary flow reserve ■ fractional flow reserve ■ physiology ■ positron emission tomography.

▶APPENDIX

For supplementary material, please see the online version of this article.

To participate in this CME activity by taking the quiz and claiming your CME credit certificate, please go to **http://imaging.onlinejacc.org** and select the CME tab on the top navigation bar.