Physiologic Severity of Diffuse Coronary Artery Disease
Hidden High Risk

K. Lance Gould, MD; Nils P. Johnson, MD, MS

In this issue of Circulation,1 Taqueti and colleagues report cardiovascular outcomes related to both noninvasive, global coronary flow reserve (CFR) and invasive angiographic stenosis severity. Approximately 60% of patients underwent either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) within 90 days of imaging, allowing study of how revascularization modifies outcomes. Because randomized, controlled trials of revascularization for stable coronary artery disease (CAD) have not demonstrated a significant and consistent reduction in mortality or nonfatal myocardial infarction (MI) compared with medical management,2 what possible message does this observational report tell us? The answer incorporates physiological severity as an emerging guide to treatment.

The Context for the Current Paper
Since the first reports of experimental stenosis 40 years ago3,4 developed the concept of CFR, clinical physiological management of coronary lesions has migrated to pressure-derived fractional flow reserve (FFR), essentially a relative severity assessment.5 Over the past 20 years, FFR has evolved from clinical correlations with noninvasive testing6 to 3 large randomized, controlled trials. First, deferral of percutaneous coronary intervention (DEFER) demonstrated no advantage to PCI over medical therapy for lesions with an intact FFR.7 Next, Fractional Flow Reserve versus Angiography For Multivessel Evaluation (FAME) compared angiographic- versus FFR-guided PCI and showed a reduction in composite events when using FFR.8 Finally, FAME 2 randomized low FFR lesions to either medical therapy or immediate PCI.9

A recent meta-analysis of the FFR outcomes literature documented a continuous, inverse relation between the FFR value and risk of subsequent adverse events.10 The analysis also demonstrated a corresponding, continuous, inverse relation between physiological severity assessed with FFR and impact from revascularization, suggesting potentially greater benefit at lower values. Intriguingly, the same analysis also showed adverse events proportional to residual FFR after successful PCI, implying residual risk resulting from remaining diffuse CAD.

Severity of Focal and Diffuse Disease
By intravascular ultrasound, optical coherence tomography, angiography, and pathology, even an intermediate stenosis associates with a substantial global burden of diffuse CAD and progressively high risk of adverse events.11-16 However, these technologies do not quantify diffuse disease in terms of units directly comparable with a focal stenosis. Consequently, the relative severity and associated risk balance between focal stenosis versus diffuse disease cannot be easily compared when making revascularization decisions.

Pressure wire pull-back along the length of a coronary artery may identify a continuous, gradual pressure gradient attributable to diffuse CAD.17 However, the basic equations for FFR do not distinguish between upstream focal and diffuse disease.5 Therefore, FFR cannot directly quantify the diffuse disease actually associated with a focal stenosis.

Randomized revascularization trials have primarily relied on segmental stenosis by angiography or FFR, with no comparable quantification of the underlying diffuse disease. Their failure to demonstrate a significant and consistent reduction in mortality and nonfatal MI may in part reflect the high risk of poorly defined diffuse disease despite elimination of segmental stenosis.

The Current Report
In the current report,1 Di Carli’s group makes 3 important observations on physiological severity of global diffuse disease having major implications for interpreting existing revascularization trials or planning future ones.

First, reduced global CFR<1.6 associates with a steeply increasing risk of adverse events.1,18 When CFR≥2.0, the risk of future adverse events remains low, while intermediate risk exists for CFR between these values.18 Integrating a broad literature, average global CFR equals 4.2 in healthy young volunteers,19 falls to 2.8 in patients with only risk factors,20,21 and decreases further to 2.0 in stable patients with established CAD.20,21 During dipyridamole stress with severe angina and significant ECG ST changes, regional stress defect CFR averages 1.7, a low-flow ischemic threshold.22 Although methodology for measuring absolute flow may be somewhat different among labs, the global CFR of 1.6 reported in the current study indicates very severe diffuse disease associated with a high risk of events arising from multiple potential sites in the coronary tree.

Second, severe anatomic disease as measured by the CAD prognostic index (a weighted score of visual angiographic severity and extent of CAD) associates with low CFR and...
high risk of adverse events. For the group with CFR<1.6, the CAD prognostic index was 37 compared with 32 for CFR ≥ 1.6. However, individual measurements of CFR and anatomic severity correlated poorly, as expected for visual assessment of the angiogram. Nevertheless, low CFR tracked with severe anatomic disease, emphasizing their convergence for extreme diffuse and focal CAD.

More importantly, the physiology–anatomy comparison highlights a fundamental, overlooked detail for comparing severity between diffuse disease and focal stenosis. Quantifying the anatomic severity of cumulative, diffuse disease is difficult, if even possible, especially in terms or units directly comparable with focal stenosis. However, CFR provides a unitless ratio based on absolute stress and rest perfusion (units of flow per supplied mass, cc/min/gm), all of which can be measured regionally and globally. Thus, the physiological severity of diffuse disease and focal stenosis can be directly compared for the whole heart or any coronary arterial distribution, accounting for both size and severity.20,21

Third, the interaction of low global CFR with outcomes as modified by revascularization provides powerful insights into potential criteria for selecting patients for whom revascularization will likely reduce mortality and nonfatal MI. Moreover, it suggests which type of revascularization might be preferred based on the balance of diffuse disease (favoring CABG) versus focal stenosis (favoring PCI).

The figures in the current study1 showed that the high risk from global CFR<1.6 only reduced with CABG but not with PCI. Moreover, global CFR≥1.6 had substantially lower risk not modified by either PCI or CABG. These observations raise the hypothesis that the risk associated with severe diffuse disease may override any potential benefit of PCI on focal stenosis. They also suggest that the risk of focal stenosis remains substantially less than for global CFR≥1.6 such that revascularization of the stenosis has no benefit for reducing hard end points.

The failure of existing randomized trials to consistently and significantly reduce mortality and nonfatal MI may be attributable in part to selecting patients with focal disease of insufficient severity to incur high enough risk for benefit from revascularization. Alternatively, patients may have had coexisting high risk from diffuse disease that neutralized the potential benefit from eliminating stenosis. Although data are suggestive rather than definitive, it establishes interactions among the physiological severity of diffuse disease, focal stenosis, and outcomes after revascularization.

The Flaws
What does the current study1 lack that may move it from suggestive clues to definitive knowledge? Most scientific studies have flaws incurring challenges to its veracity. For good studies as here, the essential clues from the data remain valid while detailing the flaws adds further knowledge toward a better next step without the same faults.

First, regional absolute flow and CFR reflecting severity of focal stenosis in addition to global CFR is not reported as we routinely do for every patient as a cardiology-PET consultation.21 Without regional CFR, the crucial contribution of diffuse disease versus focal stenosis, their relative risks, and potential modification by PCI or CABG cannot be analyzed. Second, comparative CFR and quantitative perfusion from young healthy volunteers is not reported. If healthy, young volunteers have CFR of 2.0 to 2.5 in this laboratory, instead of 3.6 to 4.2 as reported in an extensive literature,19,21 then the low global CFR reflects in part poor methodology instead of just coronary pathophysiology.

Third, combining death, MI, and heart failure as the composite outcome of the study improves statistics by increasing events but obfuscates interpretation. As such, it mixes the mechanisms and temporal course of 2 different cardiac syndromes: sudden events related to abrupt coronary occlusion versus chronic heart failure related to old infarction, left ventricular function, and hormonal complexities. Although there may be overlap in some patients, these 2 different syndromes also involve different medical management and interventional procedures.

Finally, patients proceeding to PCI or CABG had to survive until the procedure (immortal time bias), which itself did not count as an end point. Although appropriate for some kinds of studies, for randomized trials of mechanical interventions these exclusions may not be appropriate or may even be misleading. For example in FAME 2, benchmark analysis beginning 1 week after PCI removed procedure-related MI to show reduced MI and mortality compared with the deferred group. However, if outcomes were counted from time of randomization to include procedure-related MI, then FAME 2 showed no statistically significant difference by the traditional nonbenchmark analysis. Additionally, all patients in the immediate PCI group underwent revascularization, but it did not count as an event.21

What Is the Next Step?
The randomized trial remains the definitive test for revascularization procedures to reduce mortality and nonfatal MI. Based on an analytic review of the literature and crucial observational studies like the current report, future trials will have to include in their design several components and criteria for patient selection not found in existing trials.

Physiological severity of both diffuse disease and focal stenosis must be quantified for stratifying randomized interventions and/or their analysis. Patients selected for randomization need to be only those with more severe disease than “intermediate stenosis”; rather, trials must enrich lesions with regional or global CFR of 1.5 to 1.7, or at least <2.0 by validated measurements. For such patients invasive FFR will almost always be ≤0.65.

An essential lesson emerges from this discussion: severity thresholds for binary interventional decisions to reduce death or nonfatal MI require thoughtful integration of complex, interacting, continuous physiological measures of coronary function. Instead of focusing only on the eye-catching focal stenosis, we must accept the heart’s continuum and nuance, rather than the simple binary behavior that we might prefer.

Disclosures
Dr Gould has received internal funding from the Weatherhead PET Center for Preventing and Reversing Atherosclerosis. He is also the 510(k) applicant for cfrQuant approved by the FDA. He has arranged that all his royalties permanently go to a University of
Texas scholarship fund. The University of Texas has a commercial non-exclusive agreement with Positron Corporation to distribute and market cfrQuant in exchange for royalties. However, he retains the ability to distribute cost-free versions to selected collaborators for research. Additionally, Dr Gould has signed a nonfinancial, mutual nondisclosure agreement with Volcano Corporation and St. Jude Medical (makers of invasive pressure and flow sensors) to discuss coronary physiology projects. Dr Johnson has received internal funding from the Weatherhead PET Center for Preventing and Reversing Atherosclerosis. He has signed nonfinancial, nondisclosure agreements with St. Jude Medical and Volcano Corporation to discuss coronary physiology projects. Dr Johnson has signed nonfinancial, nondisclosure agreements from the Weatherhead PET Center for Preventing and Reversing coronary physiology projects. Dr Johnson has received internal funding from the Weatherhead PET Center for Preventing and Reversing coronary physiology projects, and has received significant institutional research support from both companies.

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