Fractional Flow Reserve in Angiographically Insignificant Stenoses: Unmasking the Lesion or Creating Disease?
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From earliest days of coronary angiography, we have been seeking hemodynamic confirmation of what our eyes tell us in the laboratory. Even before the clinical outcomes for patients undergoing percutaneous transluminal coronary angioplasty were barely known (and certainly before the manufacture of dedicated pressure-sensor guidewires), Grünzig made efforts to measure the transstenotic pressure gradient,1 aware of the limitations of a 2-dimensional image to completely describe the coronary flow dynamics in a diseased vessel.

In intermediate coronary lesions, it can still feel uncomfortable when our eyes “get it wrong.” With randomized trial data supporting that, in such circumstances, fractional flow reserve (FFR) is the better judge of outcomes,2–6 we can at least feel justified in quelling that uncomfortable feeling. But what about situations in which our eyes always get it wrong? Is it plausible that the oculostenotic reflex is so poorly calibrated that it can never be trusted, or are other factors at play that call into question the validity of positive FFR values in the absence of a significant lesion?

FFR: A surrogate measure of coronary flow

In the pre-FFR era, physiological indexes focused on direct measurements of coronary flow to determine the hemodynamic impact of a coronary stenosis.7 However, because of difficulties in obtaining reproducible, high-quality flow signals and the need for post hoc computation and analysis, the use of flow-based or combined pressure- and flow-based indices failed to translate into mainstream clinical practice. In 1993, FFR was uniquely proposed as a pressure-only surrogate measure of flow.8 The rationale was that during maximal pharmacological hyperemia, microvascular resistance was stabilized, and transstenotic changes in pressure became linearly related to changes in flow.

During hyperemia, coronary flow increases. In the presence of a stenosis, the relationship between pressure loss due to a stenosis (shown as ΔP) and flow velocity (shown as V) is related by the equation ΔP=FV²/S, where F is the coefficient of pressure loss due to viscous friction in the stenotic segment and S is the coefficient of pressure loss due to flow separation at the diverging end of the stenosis.9 Consequently, even in the presence of an angiographically insignificant stenosis, if coronary flow velocity increases by a large amount in response to adenosine (a sign of both a healthy microcirculation and, by definition, a non–flow-limiting stenosis), the transstenotic pressure gradient (ΔP) will also increase, and the resultant FFR value will be low (Figure).

This situation reveals an important limitation of the pressure-based FFR technique to provide a complete and accurate surrogate measure of coronary flow. With FFR, the paradox exists in which patients with the mildest stenoses, the healthiest microcirculations, and the greatest increments in coronary flow can still generate low FFR values. Furthermore, because the greatest increments in transstenotic flow occur in vessel locations with the largest amounts of downstream myocardium, these situations occur most frequently in proximal left anterior descending artery or left main stem stenoses.10,11 Such positive FFR values are similar to a young patient with mild aortic stenosis on echocardiographic assessment developing severe aortic stenosis in the same setting with increased flow during exercise. We do not perform aortic valve replacement in such circumstances because we know this measurement is an anomaly caused by a huge increase in flow. So, in the presence of an angiographically insignificant stenosis, does FFR really unmask the lesion or simply create disease? To answer this, we must see past the FFR value and determine whether ischemia itself is truly present. The problem for us as interventionalists is that we have become accustomed to thinking about ischemia in terms of hyperemic transstenotic...
Unmasking the Lesion or Creating Disease?  
Cook and Davies

**Vulnerable Plaque or Vulnerable End Point?**

In this issue of *J AHA*, a subgroup analysis from the 3-Vessel Fractional Flow Reserve for the Assessment of Total Stenosis Burden and its Clinical Impact in Patients With Coronary Artery Disease (3-Vessel FFR-FRIENDS) study provides novel insight into patient outcome data for low-FFR but angiographically insignificant (large hyperemic flow increase) coronary stenoses.

Pressure ratios; however, even quick revision of supply-demand mechanics reminds us that the ischemia results from a reduction in coronary flow, not simply a reduction in coronary pressure. This notion is supported by numerous studies in the literature that proved ischemia detection with FFR fallible to demonstrably high coronary flow situations.

![Figure. The relationship between pressure loss due to a stenosis and coronary flow velocity. Schematic representation of how low fractional flow reserve (FFR) values can be generated by both angiographically severe (small hyperemic flow increase) and angiographically insignificant (large hyperemic flow increase) coronary stenoses.](image)

**Figure.** The relationship between pressure loss due to a stenosis and coronary flow velocity. Schematic representation of how low fractional flow reserve (FFR) values can be generated by both angiographically severe (small hyperemic flow increase) and angiographically insignificant (large hyperemic flow increase) coronary stenoses.

FFR in Angiographically Insignificant Stenoses: Just Because We Can Does Not Mean We Should

As the authors of the study suggest, does the angiographic threshold for FFR measurements need to be lowered? Certainly, the possibility that FFR may identify vulnerable plaque in otherwise unobstructed coronary vessels should be...
investigated; however, perhaps this is best explored with noninvasive FFR modalities. Wiring vessels that you might otherwise potentially have left alone is not a benign process. In the Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction (COMPARE ACUTE) trial, complications (including vessel dissection resulting in death) attributed to FFR measurement in non–infarct-related arteries occurred in 0.2% of the study population.15 Furthermore, FFR computed tomography may provide additive information beyond what the invasive coronary angiogram can offer, given the ability of FFR computed tomography to characterize the plaque itself and not just the lumen. Nevertheless, it is likely any such study would still require an invasive FFR measurement for comparison, given that the accuracy of FFR computed tomography compared with invasive FFR values has recently been called into question.20 Otherwise, we do not support the notion that the angiographic threshold for FFR measurements should be lowered. As already suggested, the findings of the post hoc analysis by Lee et al are difficult to rationalize physiologically. Furthermore, they may reflect nothing more than clinician bias and a vulnerable trial end point. Although it may not be en vogue to say so, it appears that in a small number of situations in the catheter laboratory, we must question FFR and remember the importance of flow, which underpins it.

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References


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