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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), Grüntzig 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 $\Delta P = FV + SV^2$, 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

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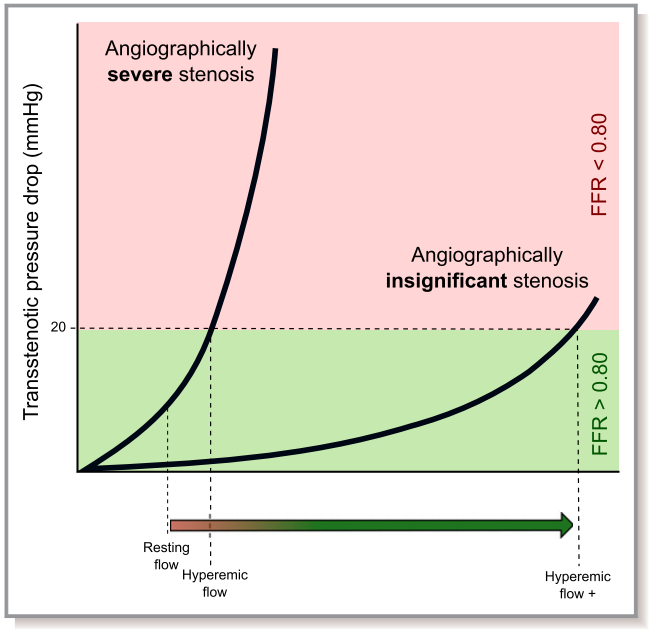

Figure. The relationship between pressure loss due to a stenosis and coronary flow velocity. Schematic representation of how low fractional flow reserve (FFR) values can be generated by both angiographically severe (small hyperemic flow increase) and angiographically insignificant (large hyperemic flow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

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.[12–17]

Vulnerable Plaque or Vulnerable End Point?

In this issue of *JAHA*, 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 lesions.[18] The majority of the findings by Lee et al are consistent with much of what we already know about FFR, namely, that low-FFR values can be generated in even mild stenoses and that these situations arise most frequently in left main stem and proximal left anterior descending artery lesions. In this patient population, however, in which a low-FFR value may have previously been rationalized away as an indirect sign of high flow and a healthy microcirculation, the (comparatively) unfavorable major adverse cardiac event (MACE) outcomes reported by Lee et al potentially imply an altogether different prognosis. The finding that, at 2-year follow-up, deferred angiographically insignificant stenosis with low FFR showed significantly higher event rates than those with high FFR (3.3% versus 1.2%; hazard ratio: 3.371; 95% confidence interval, 1.346–8.442; P=0.009) is very interesting, not least because it appears at odds with the oculostenotic reflex, the physiological mechanisms outlined above, and previous studies.[12–17]

Before proceeding to interpret the meaning of the findings on MACE, a number of observations should be highlighted. First, the authors are correct to stress that the study design does not reflect current guideline practice for the physiological assessment of coronary stenoses. The 3-Vessel FFR-FRIENDS study, from which this data set is drawn, mandated FFR measurement in all major epicardial coronary arteries regardless of angiographic severity. Second, the overall MACE rate in this cohort is low. To put it into context, the 1-year MACE rate for deferred FFR lesions in angiographically intermediate stenoses was 4.1% for the combined DEFINE-FLAIR[5] and iFR-SWEDEHEART[6] studies and 8.0% from DEFER.[4] Indeed, in the present study, MACE attributable to hard clinical end points (cardiac death and vessel-related myocardial infarction) occurred in just 1.1% of the low-FFR group and 0.7% of the high-FFR group.

With these considerations in mind, how do we explain the higher MACE in low-FFR angiographically insignificant lesions? Two potential explanations exist. The first explanation is that in quantifying the transstenotic pressure ratio during pharmacological hyperemia, FFR is somehow also capable of identifying vulnerable plaque. Were this to be true, this synergistic feature of FFR would go far beyond the hopes of even the most optimistic proponents of the coronary physiological technique. The second explanation is that the MACE findings are attributable not to the identification of vulnerable plaque but rather to the inclusion of a vulnerable end point.

The overall MACE rate in this study was driven primarily by so-called ischemia-driven revascularization. Because the definition of ischemia-driven revascularization included “a positive invasive physiologic test” result, this major contributing factor to the overall MACE rate was a de facto foregone conclusion. Compounded by the lack of blinding to the knowledge of previously low FFR value, bias may have occurred, leading to ischemia-driven revascularization events.

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.[19] 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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