Reconciling Poststenotic Pressure With Hyperemic Flow
Comparing Coronary Flow Reserve, Instantaneous Wave-Free Ratio, and Fractional Flow Reserve

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Vigorous controversy continues in the coronary physiological community about how a basal index of stenosis severity can compete effectively with a hyperemic index and challenges conventional wisdom and our understanding of what is a true ischemic response that can be quantitated in the catheterization laboratory. Moreover, the controversy is fueled by the absence of an easily obtainable ischemic standard against which various physiological indices of hemodynamic lesion significance can be compared and has led to numerous studies using a noninvasive or surrogate physiological measurement, such as hyperemic stenosis resistance, or as in the current study, coronary flow reserve (CFR, hyperemic/basal flow velocity ratio) to demonstrate the strengths and weaknesses among the proposed pressure-only indices.

In this issue of Circulation: Cardiovascular Interventions, Petraco et al report their pressure and flow velocity data acquired with sensor angioplasty guide wires across 216 coronary stenoses in 186 patients in the catheterization laboratory. Using CFR as a standard, the basal instantaneous wave-free pressure ratio (iFRbasal) had stronger correlation than fractional flow reserve (FFR) to CFR (correlation coefficient, r=0.68 versus 0.50; P<0.001) and higher agreement (receiver operator curveauc=0.82 versus 0.72; P<0.001) and higher agreement (receiver operator curveauc was 0.82 versus 0.72; P<0.001 for CFR <2.0). Of note, the hyperemic iFR performed worse than the iFRbasal (the receiver operator curveauc was 0.74; P<0.001 versus iFRbasal) but similar to FFR. In keeping with the function of a severe stenoses, flow rates across stenoses with FFR <0.75 were reduced and similar for both iFR and FFR (22 versus 26 cm/s; P=ns) in contrast to flow rates for nonsignificant stenoses (ie, FFR >0.75), where flow was higher for the hyperemic index (as it should be) when compared with the iFRbasal (42 versus 26 cm/s; P<0.001). Before attempting to reconcile how a basal state pressure index correlated better than a hyperemic pressure index with a hyperemic flow measurement, some background review is needed.

A hemodynamically significant stenosis blunts hyperemic flow, and if severe, decreases resting flow and markedly reduces or even abolishes CFR and at the same time produces translesional pressure loss (ie, a gradient) increasing in magnitude from that seen at resting flow along the specific curvilinear pressure–flow (P–V) relationship. The P–V curve is determined by the stenosis’ unique morphological characteristics and the capacity of the subtended myocardial bed to increase flow. Despite landmark observations of Dr Gould, CFR in man is unreliable for lesion assessment because of the unknown status of the myocardial microcirculation, which may be affected by pathophysiologic conditions (such as hypertrophy or diabetes mellitus) and result in an abnormal value, despite having no significant epicardial vessel obstruction.

Compared with CFR, translesional pressure measurements more accurately determine the ischemic flow-limiting potential of a stenosis. By applying the fundamental assumption that coronary pressure distal to a stenosis is linearly related to the blood flow when measured at minimal and constant vascular resistance, Pijls et al established a pressure-derived estimate of the percentage of normal coronary blood flow expected in a stenotic artery, designated as FFR. FFR, the ratio of poststenotic:aortic mean pressure at maximal pharmacologically induced hyperemia, correlated strongly to noninvasive clinically used tests for ischemia. The standard of reference was the conversion of a positive to negative ischemic test after relief of the stenosis, with 3 different ischemic tests performed in each subject. This daunting standard of reference coupled to numerous clinical outcome studies formed the basis for FFR to become an in-laboratory standard itself and become strongly recommended for lesion assessment in the United States and European interventional cardiology guidelines.

Recently, in hopes of increasing the low clinical adoption of in-laboratory physiological lesion assessment, Sen et al reported the use of a hyperemia-free basal pressure index, the iFR, which is the resting distal coronary/aortic pressure ratio during the diastolic wave-free period of the cardiac cycle. The use of the wave-free period purportedly satisfied a condition wherein flow and pressure were presumed to be linearly related as was assumed for the FFR derivation. Despite the fact that hyperemia further reduces the wave-free period resistance as shown in this study, several clinical trials demonstrate approximately an 80% concordance to FFR, suggesting that iFR (or simple P/P) has the potential to reduce the use of pharmacological hyperemia for lesion assessment in some settings. As done for FFR, outcome studies of iFR for percutaneous coronary intervention guidance are required.
Why should the CFR correlate better with a resting (iFR, $P_d/P_a$) than hyperemic pressure ratio (FFR, iFRa)? The detailed results attempt to direct us to an answer. The mean CFR for iFR < or >0.90 was 1.7 and 2.5, respectively. For FFR < or >0.80, the CFR cut point is not provided but there are values scattered on both sides of 2.0. In lesions with low iFR (<0.90) and corresponding FFR >0.80, the CFR was <2.0; and conversely in 28 lesions (4%) where iFR was >0.90 with low FFR (<0.75), CFR was >2.5. Does this mean that for patients with FFR <0.80 with CFR >2.5 that this is a lesion not associated with ischemia? Perhaps this individual requires a CFR >3.0 or 4.0 to satisfy myocardial oxygen demand beyond this stenosis. Although these same contradictory responses were shown more than a decade ago by the coauthors, clinical significance of a stenosis, which has a high CFR with low FFR, still remains unknown.

Does the stronger CFR/iFR relationship further elevate iFR as an index capable of detecting flow-limiting CAD? Continuing uncertainty about the ability of iFR to separate a mild from severe lesions remains from this study especially because the standard of CFR cannot be relied on to determine the status of an intermediate lesion. Petraco et al demonstrate that a CFR <2.0 may have an FFR < or >0.75, just as it may have an iFR < or >0.90.

As noted for FFR, hyperemia produced worse agreement with iFR than with iFR$_{bas}$. It is true that pharmacological hyperemia introduces some degree of measurement variance. Among patients with normal or near-normal coronary arteries, adenosine produces different levels of hyperemia depending on the individual's microvascular responsiveness. Another consideration in the disparity between CFR/FFR is the role of diffuse subangiographic epicardial atherosclerosis with or without an impaired coronary microvasculature. As carefully noted by Johnson et al, CFR is linearly related to FFR for progressive stenosis superimposed on diffuse disease with different contributions from each variable (focal versus diffuse narrowing) defining the slope of the CFR/FFR relationship. Discordant CFR/FFR values reflect extremes of focal and diffuse disease, not failure of either technique. The net translesional hemodynamic effect of a discrete stenosis may not be fully appreciated unless the conduit and microcirculatory resistance is reduced to its true minimum, a condition that is not expected to occur with iFR for intermediate lesions, as shown here by iFRa.

As expected with complex concepts and measurements made in patients during cardiac catheterization, there are limitations and strengths, if not contentious discussion points. For all studies using CFR as a standard, an important caveat must be heeded. Recall that the same CFR values can be produced from markedly different absolute hyperemic and basal flow velocity results. Small changes in either absolute flow value will have a large effect on the CFR ratio. For example, a low basal flow of 5 cm/s with hyperemic flow of 15 cm/s produces a CFR of 3.0 at onetime and later in the same patient when the basal flow increases, perhaps because of tachycardia to 10 cm/s, the CFR now becomes 1.5. With that in mind, it is of interest that Petraco et al would like us to infer that iFR should also reflect similar clinical long-term outcomes as CFR, a worthy objective but one that does not give me more confidence in appreciating the ischemic potential of a given stenosis.

Petraco et al have produced another stimulating physiological study exploring the relationship between basal and hyperemic pressure indices, coupling their findings to CFR as a reflection of the microcirculatory influence on poststenotic pressure. From this work, we learned that for the extremes of stenosis severity (minimal or severe), there is complete concordance of both iFR and FFR; that hyperemia produces a spread of the correspondence of pressure to flow (CFR); that for the severe stenosis, iFR and FFR have similar resting and hyperemic flow values; and finally that there are discordant values wherein the physiological and clinical meaning of a high CFR/low FFR remains unknown.

For those important angiographic lesions of questionable clinical significance, which pressure-flow index is right? The knowledge that iFR performs more like CFR with its inherent limitations for lesion assessment than FFR should still give one great pause. From a well-grounded fundamental physiological principle tested by a rigorous ischemic standard and a decade of well-performed clinical outcome studies, at this time I trust FFR more than iFR and much more than CFR for lesion assessment. Although we continue to explore whether there are resting physiological measurements that will precisely define the ischemic potential of a stenosis and clinical outcomes, we must carefully consider the limitations of each methodology (CFR/iFR/FFR) and apply the most accurate as possible to reduce our uncertainty in percutaneous coronary intervention decision making.

**Disclosures**

Dr Kern is a consultant to St Jude Medical and Volcano Therapeutics, manufacturers of the pressure-wire and intravascular ultrasound imaging catheters.

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