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EDITORIAL COMMENT

Where Do We Go With Abnormal Flow?*

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Coronary pressure measurements have played an integral role during percutaneous intervention (PCI) since the first procedure was performed in 1977 by Grüntzig et al,[1] at which time they noted a significant reduction in the pressure gradient across the coronary lesion after successful treatment with angioplasty. In the same decade, pioneering animal experiments by Gould et al[2] demonstrated that resting coronary flow was reduced only when an epicardial coronary stenosis reached more than 85% narrowing, after exhausting autoregulation by the microvasculature, whereas maximal coronary flow began to decrease when the luminal stenosis reached 40%. Since then, the field of coronary physiology has vacillated between using coronary flow and using pressure. Coronary flow reserve (CFR), defined as the ratio of maximal coronary flow to resting coronary flow in a given perfusion territory, first gained traction when it was found to be useful in deferring PCI of intermediate lesions and assessing angioplasty results.[3,4] However, the clinical applications of CFR were limited by its inability to separate the epicardial and microcirculatory compartments of the coronary tree, the lack of a normal reference value, and decreased reproducibility given its reliance on resting flow.[5]

Conversely, fractional flow reserve (FFR), which measures the translesional pressure gradient at maximal hyperemia, is a highly specific and reproducible test for assessing the ischemic potential of an epicardial stenosis.[6] FFR has become the gold standard test for identifying epicardial lesions that are responsible for symptoms of myocardial ischemia and are more likely to cause future cardiac events, on the strength of multiple randomized controlled trials showing improved patient outcomes with FFR-guided PCI.[7,8] The desire to avoid induction of hyperemia and further simplify the FFR measurement process led to the subsequent development of the nonhyperemic pressure ratios (NHPRs), of which the instantaneous wave-free ratio (iFR) is the best validated.[9,10] However, discordance between FFR and NHPRs can occur, particularly in focal lesions that subtend a large myocardial territory, as a result of the exponentially higher hyperemic flow across these stenoses, as well as in patients with altered resting flow secondary to conditions such as age and tachycardia.[11,12] Although FFR and NHPRs have replaced CFR for assessing epicardial coronary disease on the basis of a large amount of data, including a recent study finding increased events when deferring revascularization of lesions with a low FFR and normal CFR,[13] given the strong prognostic capability of CFR, particularly in patients with nonobstructive (FFR-negative) epicardial disease, there remains interest in the coronary physiology community for incorporating both pressure and flow measurements.

With this historical context in mind, we read with interest the study published by Yang et al[14] in this issue of *JACC: Asia*. Yang et al[14] performed a retrospective analysis of an international multicenter registry, in which FFR and the ratio of resting distal coronary pressure (Pd) to resting proximal pressure (Pa) were measured with a pressure wire, whereas resting and hyperemic flow were measured with either an intracoronary Doppler technique or a bolus thermodilution technique, in 1,971 vessels from 1,505 patients whose PCI was deferred. Because no normal reference values or clinically relevant cutoffs exist for resting or hyperemic flow-derived parameters (hereafter simplified as flow), Yang et al[14] performed a post hoc analysis to identify the optimal cutoff values for predicting the primary endpoint of target vessel failure—a composite of cardiac death, target vessel myocardial infarction, or clinically driven revascularization, for both resting and hyperemic flow. Yang

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et al[14] found that abnormal pressure or flow, whether at rest or during hyperemia, was associated with an increased risk of target vessel failure at 5-year follow-up. Using vessels with normal pressure and flow as the reference, the addition of each abnormality in flow or pressure worsened outcomes proportionally, with the highest rate of target vessel failure seen in vessels that had abnormal flow and pressure both at rest and during hyperemia. Finally, vessels with normal FFR but abnormal Pd/Pa and resting flow had significantly worse outcomes, as did vessels with normal Pd/Pa but abnormal FFR and hyperemic flow. Yang et al[14] concluded that adding flow measurements improved risk stratification beyond pressure alone and may help guide appropriate treatment strategies for patients with coronary artery disease.

We commend Yang et al[14] for their in-depth analysis on the prognostic impact of resting and hyperemic flow, which has greatly advanced our understanding of the individual contributions of the 2 components of CFR. However, there are considerations of the data that should be kept in mind. First, a clear threshold for "normal" resting flow does not exist in a vacuum and requires clinical context because lower resting flow is not always "normal." In patients with relatively unobstructed epicardial coronary arteries seen in this study (mean diameter stenosis, 47%; FFR, 0.88), elevated resting flow arising from conditions that increase baseline myocardial demand, such as tachycardia, hypertension, and left ventricular hypertrophy, may have contributed to the poor clinical outcomes and be deemed "abnormal." Conversely, in the presence of severe epicardial coronary stenoses (not included in this study), resting flow can be decreased but should clearly not be defined as "normal." Therefore, the results demonstrated in this study may not be generalizable to a broader group of patients with more severe coronary artery disease. Second, vessels with normal FFR but abnormal Pd/Pa and resting flow are not equivalent to vessels with normal Pd/Pa but abnormal FFR and hyperemic flow. The former situation arises from elevated resting flow, which approximates hyperemic flow and leads to a lower Pd/Pa in a lesion that is not sufficiently severe to cause a positive FFR result. Conversely, the latter situation arises in a lesion that is severe enough to cause a positive FFR result in the presence of reduced hyperemic flow either from the lesion itself or from concomitant microvascular dysfunction. Although both lesions are associated with poor outcomes, the latter group is more likely to benefit from revascularization.

It is now increasingly evident that measuring flow adds incremental prognostic information compared with pressure alone. The next challenge lies in incorporating flow data to current treatment strategies. The DEFINE-FLOW (Distal Evaluation of Functional Performance With Intravascular Sensors to Assess the Narrowing Effect-Combined Pressure and Doppler Flow Velocity Measurements) study has already demonstrated that normal CFR should not be used to defer PCI for a lesion with abnormal FFR[13]; similarly, it would be unrealistic to expect improved outcomes from performing PCI in patients with normal FFR and Pd/Pa but elevated resting flow. The answer may lie in targeting the underlying pathophysiology for elevated resting and/or low hyperemic flow with medical therapies such as β-blockers and angiotensin-converting enzyme inhibitors.[15,16] We look forward to future studies demonstrating the benefit of treating abnormal resting or hyperemic flow; until then, we believe that the addition of flow measurements to pressure measurements may improve prognostication but should not guide revascularization decisions.

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REFERENCES

1. Grüntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med*. 1979;301:61–68.

2. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. *Am J Cardiol*. 1974;33:87–94.

3. Di Mario C, Moses JW, Anderson TJ, et al. Randomized comparison of elective stent implantation and coronary balloon angioplasty guided by online quantitative angiography and intracoronary Doppler. DESTINI Study Group (Doppler Endpoint STenting INternational Investigation). *Circulation*. 2000;102:2938–2944.

4. Chamuleau SA, Tio RA, de Cock CC, et al. Prognostic value of coronary blood flow velocity and myocardial perfusion in intermediate coronary

narrowings and multivessel disease. *J Am Coll Cardiol*. 2002;39:852–858.

5. Fearon WF, Kobayashi Y. Invasive assessment of the coronary microvasculature: the index of microcirculatory resistance. *Circ Cardiovasc Interv*. 2017;10(12):e005361.

6. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation*. 1993;87:1354–1367.

7. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213–224.

8. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991–1001.

9. Götberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N Engl J Med*. 2017;376:1813–1823.

10. Davies JE, Sen S, Dehbi HM, et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. *N Engl J Med*. 2017;376:1824–1834.

11. Kobayashi Y, Johnson NP, Berry C, et al. The influence of lesion location on the diagnostic accuracy of adenosine-free coronary pressure wire measurements. *J Am Coll Cardiol Intv*. 2016;9:2390–2399.

12. Dérimay F, Johnson NP, Zimmermann FM, et al. Predictive factors of discordance between the instantaneous wave-free ratio and fractional flow reserve. *Catheter Cardiovasc Interv*. 2019;94:356–363.

13. Johnson NP, Matsuo H, Nakayama M, et al. Combined pressure and flow measurements to guide treatment of coronary stenoses. *J Am Coll Cardiol Intv*. 2021;14:1904–1913.

14. Yang S, Hwang D, Lee JM, et al. Prognostic implications of individual and combinations of resting and hyperemic coronary pressure and flow parameters. *JACC Asia*. 2023;3(6):878–880.

15. Pauly DF, Johnson BD, Anderson RD, et al. In women with symptoms of cardiac ischemia, nonobstructive coronary arteries, and microvascular dysfunction, angiotensin-converting enzyme inhibition is associated with improved microvascular function: a double-blind randomized study from the National Heart, Lung and Blood Institute Women's Ischemia Syndrome Evaluation (WISE). *Am Heart J*. 2011;162:678–684.

16. Billinger M, Seiler C, Fleisch M, Eberli FR, Meier B, Hess OM. Do beta-adrenergic blocking agents increase coronary flow reserve? *J Am Coll Cardiol*. 2001;38:1866–1871.

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