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EDITORIAL COMMENT

Quantitative Flow Ratio-Guided Revascularization

Equally Effective Between the Sexes*

Christopher C.Y. Wong, MBBS, PhD,[a,b] Andy S.C. Yong, MBBS, PhD[a]

The discrepancy in severity between visual and functional evaluation of a stenosis has long been recognized as one of the fundamental limitations of coronary angiography. Lesion-specific factors such as location, length, eccentricity, and shape are all subtleties that influence visual-functional mismatch and cannot be easily discerned with an "eyeball" of the 2-dimensional angiogram,[1] which remains the modus operandi for assessing stenosis severity in most catheterization laboratories around the world.

Fractional flow reserve (FFR) is the ratio of maximal myocardial blood flow in the presence of an epicardial stenosis to maximal myocardial blood flow in a disease-free vessel, reflecting the fraction of normal myocardial flow subtended by the interrogated vessel.[2] It is obtained by advancing a guidewire outfitted with a pressure sensor distal to a coronary lesion to measure distal coronary and aortic pressure under maximal hyperemia, a period when perfusion pressure becomes proportional to flow due to constant and minimal microvascular resistance.[3] FFR is highly sensitive and specific at detecting myocardial ischemia,[4] and randomized controlled studies have shown FFR to be superior to angiography in guiding percutaneous coronary intervention (PCI).[5-7] A possible explanation for the improved outcomes with FFR guidance is its ability to identify high-risk lesions that exhibit pathological wall shear stress patterns independent of stenosis severity.[8] However, despite the unequivocal benefits of FFR-guided PCI, its use remains limited in the real world.[9,10] Commonly cited barriers include costs, increased procedure time, patient discomfort secondary to pharmacological induction of hyperemia, and importantly, the potential risk of coronary dissection, which has been estimated to occur at a rate of 0.3% to 0.5%.[11]

Quantitative flow ratio (QFR) is an angiography-based estimation of FFR that circumvents many of these obstacles by obviating the need for insertion of an intracoronary guidewire and induction of pharmacological hyperemia. QFR is computed by applying the principles of computational fluid dynamics in 3-dimensional quantitative coronary angiography-based reconstructions.[12] Studies of QFR have demonstrated good correlation and agreement with FFR, as well as good diagnostic accuracy for identifying myocardial ischemia when compared with FFR as the gold standard.[12-14] In the FAVOR III China (Comparison of Quantitative Flow Ratio Guided and Angiography Guided Percutaneous Intervention in Patients with Coronary Artery Disease) study, patients randomized to QFR-guided PCI had significantly better outcomes compared with the angiography-guided PCI group, driven by lower rates of myocardial infarction (MI) and revascularization.[15] These results compare favorably with those seen in the FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) study,[6] and reinforces the notion that physiology-guided PCI results in superior outcomes compared with angiography-guided PCI, irrespective of the method used.

In this issue of *JACC: Asia*, Chen et al[16] publish a prespecified subgroup analysis of the FAVOR III China study, focusing on sex-specific differences in

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From the [a]Department of Cardiology, Concord Repatriation General Hospital, Concord, New South Wales, Australia; and the [b]Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California, USA.

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outcomes between QFR- and angiography-guided PCI. The study cohort consisted of 2,652 men and 1,107 women, with the primary endpoint being a composite of all-cause death, MI, or ischemia-driven revascularization at 2 years. QFR-guided PCI led to a significant reduction in the primary endpoint compared with angiography-guided PCI in both males (8.7% vs 12.4%; HR: 0.69; 95% CI: 0.54-0.87) and females (8.0% vs 12.7%; HR: 0.62, 95% CI: 0.42-0.90), with no interaction between the sexes ($P = 0.61$). The benefits of QFR-guided PCI persisted in both sexes even after exclusion of periprocedural MI. Interestingly, a significant interaction between treatment effect and sex was found for the secondary endpoint of spontaneous MI, which occurred less often in females undergoing QFR-guided PCI (HR: 0.14 vs 0.58; P for interaction = 0.04).

The authors should be commended for providing detailed sex-specific analyses for an emerging technique in the field of coronary physiology, as there are known distinctions between the sexes with respect to FFR. A previous subgroup analysis of the FAME study found that FFR values were consistently higher in females compared with males that had similar angiographic stenosis severity, and that the proportion of functionally significant stenoses (FFR ≤0.80) was significant lower in females with intermediate lesions compared with males.[17] There are 2 potential explanations for this sex-specific phenomenon. First, females undergoing PCI are usually older and more likely to have comorbidities such as hypertension and diabetes, leading to a higher prevalence of concomitant microvascular dysfunction. The presence of microvascular dysfunction limits the degree of hyperemic flow and results in a higher FFR compared with patients that have normal microvascular function and similar stenosis severity. Second, females are more likely to have smaller myocardial mass and myocardial perfusion territory, which leads to lower absolute coronary flow. Under these circumstances, a comparatively more severe stenosis is necessary to induce myocardial ischemia.

In contrast to FFR, QFR is heavily influenced by vessel geometry and utilizes frame count at rest to estimate hyperemic flow, which reduces the role the coronary microcirculation plays in its measurement.[12] Accordingly, there were no significant differences in QFR values between males and females with similar stenosis severity in this study.[16] Although QFR guidance may have theoretically resulted in more females undergoing PCI than if FFR were performed, the consistent benefits seen in both sexes and lack of interaction should reassure clinicians that QFR-guided PCI remains valid and superior to angiography-guided PCI regardless of sex. The results from this study adds to the evidence supporting the use of QFR to guide revascularization. With continual improvement in image acquisition, ease of use, and integration of QFR into the standard catheterization laboratory workflow, we foresee a future in which physiology-guided PCI becomes the norm, rather than the exception, in clinical practice.

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ADDRESS FOR CORRESPONDENCE: Dr Andy S.C. Yong, Concord Repatriation General Hospital, University of Sydney, Cardiology, Level 3 West Concord Hospital, Hospital Road, Concord, New South Wales 2139, Australia. E-mail: andy.yong@sydney.edu.au.

REFERENCES

1. Park SJ, Kang SJ, Ahn JM, et al. Visual-functional mismatch between coronary angiography and fractional flow reserve. *J Am Coll Cardiol Intv*. 2012;5:1029–1036.

2. 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.

3. Ihdayhid AR, Yong A, Harper R, et al. A practical guide for fractional flow reserve guided revascularisation. *Heart Lung Circ*. 2018;27:406–419.

4. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med*. 1996;334:1703–1708.

5. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol*. 2007;49:2105–2111.

6. 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.

7. 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.

8. Wong CCY, Javadzadegan A, Ada C, et al. Fractional flow reserve and instantaneous wave-free ratio predict pathological wall shear stress in coronary arteries: implications for understanding the pathophysiological impact of functionally significant coronary stenoses. *J Am Heart Assoc*. 2022:e023502.

9. Desai NR, Bradley SM, Parzynski CS, et al. Appropriate use criteria for coronary revascularization and trends in utilization, patient selection, and appropriateness of percutaneous coronary intervention. *JAMA*. 2015;314:2045–2053.

10. Wong CCY, Ng ACC, Ada C, et al. A real-world comparison of outcomes between fractional flow reserve-guided versus angiography-guided percutaneous coronary intervention. *PLoS One*. 2021;16:e0259662.

11. Ahmed N, Layland J, Carrick D, et al. Safety of guidewire-based measurement of fractional flow reserve and the index of microvascular resistance using intravenous adenosine in patients with acute or recent myocardial infarction. *Int J Cardiol*. 2016;202:305–310.

12. Tu S, Westra J, Yang J, et al. Diagnostic accuracy of fast computational approaches to derive fractional flow reserve from diagnostic coronary angiography: the international multicenter FAVOR pilot study. *J Am Coll Cardiol Intv*. 2016;9:2024–2035.

13. Xu B, Tu S, Qiao S, et al. Diagnostic accuracy of angiography-based quantitative flow ratio measurements for online assessment of coronary stenosis. *J Am Coll Cardiol*. 2017;70:3077–3087.

14. Westra J, Andersen BK, Campo G, et al. Diagnostic performance of in-procedure angiography-derived quantitative flow reserve compared to pressure-derived fractional flow reserve: the FAVOR II Europe-Japan study. *J Am Heart Assoc*. 2018;7:e009603.

15. Xu B, Tu S, Song L, et al. Angiographic quantitative flow ratio-guided coronary intervention (FAVOR III China): a multicentre, randomised, sham-controlled trial. *Lancet*. 2021;398:2149–2159.

16. Chen Y, Gao L, Vogel B, et al. Sex differences in clinical outcomes associated with quantitative flow ratio-guided percutaneous coronary intervention. *JACC: Asia*. 2024;4:201–212.

17. Kim HS, Tonino PA, De Bruyne B, et al. The impact of sex differences on fractional flow reserve-guided percutaneous coronary intervention: a FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) substudy. *J Am Coll Cardiol Intv*. 2012;5:1037–1042.

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