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Quantitative Flow Ratio and Virtual Percutaneous Coronary Intervention for Serial Coronary Stenoses: Attractive Technology, But Still Crawling

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Coronary physiology assessment is an important field in which emerging technologies have been successfully used in facilitating decision-making in interventional cardiology. This started with the advent of coronary wires mounted with pressure sensors to measure pressure distal to the lesion and compare it with aortic pressure. This allowed us to derive fractional flow reserve (FFR) to determine whether a lesion is flow-limiting or not after hyperemic stimulation with adenosine.[1–3]

See Article by Guan et al.

Subsequently, resting pressure indices (also known as nonhyperemic pressure ratio) were derived including instantaneous wave-free ratio,[4,5] diastolic pressure ratio,[6,7] and resting full-cycle ratio.[7,8] It is now well-established that physiology-guided percutaneous coronary intervention (PCI) leads to improved outcomes, guiding treatment in hemodynamically significant lesions and allowing us to safely defer lesions that are functionally nonsignificant (Table). Nevertheless, both instantaneous wave-free ratio and FFR still require an invasive wire-based approach.

More recently, it has now become possible to assess physiology "virtually" with reasonable accuracy, using 3-dimantional reconstruction and computational fluid dynamics based on coronary angiography alone, avoiding the need to instrument the vessel with coronary wires.[9–11] Quantitative flow ratio (QFR) is one of the studied virtual tools to assess coronary flow. In the FAVOR III China (Comparison of Quantitative Flow Ratio Guided and Angiography Guided Percutaneous Intervention in Patients With Coronary Artery Disease) trial, 3825 patients were randomized to QFR-guided PCI or angiography-guided PCI. QFR-guided PCI resulted in improved outcomes with regards to the primary end point of death, myocardial infarction, or unplanned revascularization compared with angiography-guided PCI.[12] Further iterations of QFR, Murray-fractal law-QFR (uQFR), enabled computation of QFR from a single angiographic view.[13]

In this issue of the *Journal of the American Heart Association* (*JAHA*), Guan and colleagues[14] report the results of a prospective study assessing the utility of uQFR to virtually plan PCI. Participants presented with 2 serial lesions that were visually estimated between 30% and 90% in the same epicardial vessel and separated by at least 10mm of an angiographically-looking normal segment. Fifty-four patients with 61 vessels were evaluated

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Table 1. Landmark Clinical Trials Establishing the Role of Coronary Physiology in Interventional Cardiology

Author, study, and population	Intervention	Outcomes
Pijls et al,[1] DEFER, 325 patients with intermediate de novo stenosis	All patients had FFR measured FFR ≤0.75: (n=144) PCI was performed; FFR >0.75 (n=181), patients were randomized to PCI or medical management	5-y event-free survival: 80% vs 73%; P=0.52 (deferral group vs PCI group, respectively)
Tonino et al,[2] FAME, 1005 patients with multivessel CAD planned for PCI	Patients were randomized to angiography-guided or FFR-guided PCI In the FFR group, PCI was performed if FFR was ≤0.80	Death, MI, and repeat revascularization at 1 y: 13.2% vs 18.3%; P=0.02 (FFR-guided PCI vs angiography-guided PCI, respectively)
De Bruyne et al,[3] FAME II, 1220 patients with stable CAD	Patients were randomized to FFR-guided PCI or medical therapy alone In the FFR group, PCI was performed if FFR was ≤0.80	Death, MI, or urgent revascularization at 1 y: 4.3% vs 12.7%; P<0.001 (FFR-guided PCI+medical therapy vs medical therapy alone, respectively)
Gotberg et al,[4] iFR-SWEDEHEART, 2037 patients with stable angina or acute coronary syndrome with planned physiology-guided PCI	Patients were randomized to FFR-guided PCI or iFR-guided PCI	Death, MI, or unplanned revascularization at 1 y: 6.1% vs 6.7%; P=0.53 (FFR vs iFR)
Davies et al,[5] DEFINE-FLAIR, 2492 patients with intermediate coronary stenosis	Patients were randomized to FFR-guided PCI or iFR-guided PCI	Death, MI, or unplanned revascularization at 1 y: 7% vs 6.8%; P=0.83 (FFR vs iFR)

iFR is the only nonhyperemic pressure ratio method evaluated and validated against fractional flow reserve (FFR) on hard clinical end points. CAD indicates coronary artery disease; DEFER, Deferral Versus Performance of Percutaneous Coronary Intervention of Functionally Nonsignificant Coronary Stenosis; DEFINE-FLAIR, Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation; FAME, Fractional Flow Reserve Versus Angiography in Multivessel Evaluation; FAME II, Fractional Flow Reserve Versus Angiography for Multivessel Evaluation II; iFR, instantaneous wave-free ratio; iFR-SWEDEHEART, Instantaneous Wave-Free Ratio Versus Fractional Flow Reserve in Patients With Stable Angina Pectoris or Acute Coronary Syndrome: A Multicenter, Prospective, Randomized Controlled Clinical Trial Based on the Swedish Angiography and Angioplasty Registry; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

in the study. All vessels were assessed by maximal hyperemic FFR, and PCI was performed if FFR was ≤0.80 (44 vessels). PCI was first performed in lesions that were believed to be most hemodynamically significant. Repeat FFR was then performed and PCI to the remaining hemodynamically significant lesion was undertaken whenever residual FFR was ≤0.80 (14 lesions). uQFR was computed at an experienced central academic core laboratory with excellent intraobserver and interobserver variability (±0.03). Predicted uQFR was also calculated after "virtual PCI" of the most significant lesion.

The authors found an excellent correlation (r=0.97, P<0.001) and agreement between baseline uQFR and FFR (mean difference: 0.00±0.03) for evaluation of the hemodynamic significance of serial lesions in the target vessel. Discordance between FFR and uQFR was only present in 2 cases where FFR was >0.80 while uQFR was ≤0.80.

The was no difference between ΔμQFR and ΔFFR in the proximal lesion (0.15±0.10 and 0.15±0.10, respectively; P=0.71), with good correlation (r=0.79, P<0.001; mean difference of 0.00±0.06). The same pattern was observed in terms of the difference between ΔμQFR and ΔFFR of the distal lesion (0.13±0.08 and 0.14±0.08, respectively; P=0.56). There was very good correlation between ΔμQFR and ΔFFR (r=0.82, P<0.001; mean difference of 0.00±0.06).

uQFR and FFR were consistent in judging the primary lesion by comparing the gradient through the proximal and distal lesion. However, 1 proximal lesion (4.0%) and 2 distal lesions (10.5%) showed discordance between μQFR and FFR, meaning that the primary lesion was misjudged in 1 in 7 cases.

After stenting the primary lesion, the accuracy of QFR for identifying the hemodynamic significance of the nonprimary lesion was ≈90% (area under the curve, 0.94) and predicted μQFR was higher than residual observed FFR (0.87±0.06 versus 0.83±0.07, P<0.001). Using the same cutoff value of ≤0.80 for the detection of hemodynamically significant stenosis, the predicted uQFR was shown to be 100% specific but only ≈70% sensitive.

The authors are to be congratulated for their efforts to simplify physiology assessment by avoiding wire-based hyperemic methods and further guide PCI optimization using an angiographic, computer-based reconstruction and fluid dynamics algorithm. The concept is attractive as it attempts to remove the "guess work" and apply a physiologic approach to help decision-making. This approach has been shown to alter interventional cardiologists' treatment strategy and potentially affect chosen stent size.[15] However, does this mean that such a strategy is ready for prime time or does it simply represent the early days of an emerging technology? Several caveats need to be taken into consideration.

First, although the QFR-guided PCI strategy is superior to angiography-guided PCI, this has not been

compared with the "gold standard," being FFR-guided PCI for intermediate lesions in a clinical outcome trial. Second, authors included a wide range of stenoses, namely 30% to 90%, while similar studies have looked at more intermediate lesions of at least 50% stenosis. Third, the performance of a QFR-guided PCI strategy has only modest performance in identifying functional significance of the nonprimary lesion once the primary lesion has been treated, with a sensitivity of only 70%, meaning that many unnecessary PCIs would be performed from false-positives. On the other hand, the high observed specificity is certainly because many lesions included in the study were relatively minor stenosis (ie, 30%–50%), which will tend to be negative, therefore accounting for the high specificity values. Fourth, it remains uncertain as to whether physiological assessment of 2 serial borderline stenoses is the best strategy to guide PCI. Intracoronary imaging may be better suited to precisely decide on stent sizing, landing zone, and plaque vulnerability. Fifth, in this study, uQFR was measured in a central core laboratory with minimal intraobserver and interobserver variability. It is yet to be determined how variable this tool will be once introduced to mainstream laboratories. Sixth, target vessel revascularization was previously shown to be higher in patients with residual FFR of <0.90.[16] This may be indicative of undersized stenting, which may account for target vessel failure. Hence, in the presence of serial stenoses, this issue becomes more challenging to judge. Is it an undersized stent causing suboptimal residual FFR or is it a remaining stenosis (ie, geographical miss)? It is well-known that FFR requires several steps to assess serial lesions, including the induction of maximal hyperemia with adenosine after the completion of the first lesion PCI. In this regard, nonhyperemic pressure ratio methods simplify the assessment of multiple lesions using pullback, because individual pressure indexes do not interact with each other.[17,18] Nonetheless, it should be highlighted that the only nonhyperemic pressure ratio method validated against FFR that looked at patient-important clinical outcomes is instantaneous wave-free ratio (Table).[4,5] Notably, the same comment also applies to the paper by Guan and colleagues.[14] Given the lack of clinical outcomes assessment, it substantially limits the knowledge translation into daily clinical practice. Finally, while the adoption of less invasive approaches is welcome, pressure wire-based measurements provide important diagnostic information for the workup of ischemia with nonobstructive coronary arteries (INOCA), providing evidence of impaired coronary microvascular function through impaired coronary flow reserve (<2.0)[19] or abnormal coronary microvascular resistance indices (such as indices index of microcirculatory resistance ≥25). Indeed, coronary microvascular resistance has been associated with 59.1% of the variability when

calculating virtual FFR estimates.[20] Importantly, the diagnostic workup of a patients with coronary artery disease does not merely stop at the decision to stent or not.

In summary, the study by Guan and colleagues[14] is informative and sheds light for further research. Once streamlined, QFR may serve as a useful tool to supplement coronary angiography, but further studies are needed to establish its role in predicting residual FFR following PCI to help procedural planning as well as broadening the role of noninvasive tools to assess microvascular function.

ARTICLE INFORMATION

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