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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

The Evolving Future of Instantaneous Wave-Free Ratio and Fractional Flow Reserve

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ABSTRACT

In this review, the authors reflect upon the role of coronary physiology in the modern management of coronary artery disease. They critically appraise the scientific background of the instantaneous wave-free ratio (iFR) and fractional flow reserve (FFR), from early experimental studies to validation studies against indexes of ischemia, to clinical trials assessing outcome. At this important juncture for the field, the authors make predictions for the future of physiological stenosis assessment, outlining developments for both iFR and FFR in new clinical domains beyond the confines of stable angina. With a focus on the evolving future of iFR and FFR, the authors describe how physiological assessment with iFR may advance its application from simply justifying to guiding revascularization. (J Am Coll Cardiol 2017;70:1379–402)

Since the introduction of fractional flow reserve (FFR) more than 20 years ago (1), physiology-guided revascularization has become an established practice in the modern, evidence-based management of patients with coronary artery disease. The central premise of coronary physiology is that it permits identification of myocardial ischemia on a per-vessel basis, measurable at the time of clinical decision making. This aids the selection of stenoses (and therefore patients) likely to benefit from revascularization.

FFR carries a Class 1a recommendation for guiding revascularization in angiographically intermediate coronary stenoses in patients with stable angina (Table 1) (2,3). However, despite this, uptake of FFR in coronary catheter laboratories worldwide has remained low (Figure 1). Potential reasons for the low adoption rate of coronary physiology despite demonstrated clinical benefit of its use may include time consumption to perform FFR measurements, costs associated with adenosine, or in certain countries, no availability of adenosine, patient-related discomfort, contraindications, or lack of reimbursement. Recently, there has been renewed interest and development in the field of coronary physiology, driven by the introduction of a new, nonhyperemic

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

AUC = area under the curve

CABG = coronary artery bypass grafting

CFR = coronary flow reserve

CI = confidence interval

FFR = fractional flow reserve

FFRmyo = myocardial fractional flow reserve

HR = hazard ratio

HSR = hyperemic stenosis resistance

iFR = instantaneous wave-free ratio

MACE = major adverse cardiac events

MI = myocardial infarction

OMT = optimal medical therapy

PCI = percutaneous coronary intervention

PET = positron emission tomography

STEMI = ST-segment elevation myocardial infarction

WFP = wave-free period

WIA = wave intensity analysis

pressure-based index of stenosis severity: the instantaneous wave-free ratio (iFR) (4).

Five years after its initial introduction, 2 large, prospective, randomized trials have concordantly reported noninferiority of iFR when compared with FFR for guiding revascularization (5,6). More importantly, the data yielded from these studies have provided a marked expansion of the patient outcome data available for coronary physiology as a whole. At this important juncture for the field, we pause to critically review how far the techniques and scientific testing for physiological stenosis assessment have progressed, and look forward to the techniques and applications that will define the future of coronary physiology. Specifically, we address the evolving future of iFR and FFR for physiological stenosis assessment.

CORONARY PHYSIOLOGY IN THE PRE-FFR ERA

The purpose-built pressure wires currently used to make coronary physiology measurements are the result of years of development and miniaturization of pressure sensor technology. However, in the pioneering procedures of Andreas Grüntzig in the late 1970s, such high-fidelity equipment was not available. Nevertheless, the importance of quantifying the hemodynamic impact of a coronary stenosis (and the resultant response to balloon angioplasty) led Grüntzig et al. (7) to measure and report the trans-stenotic pressure gradient through the fluid-filled guiding catheter. However, owing to the significant impediment to antegrade flow imposed by the catheters themselves, trans-stenotic pressure recordings failed to gain acceptance after it was demonstrated that the measurement was not always reliable (8).

In the early 1990s, as intracoronary pressure and flow velocity sensor-tipped guidewires became sufficiently miniaturized, a host of additional coronary physiology measurements were proposed (**Table 2**) (9). Furthermore, the notion of performing measurements during hyperemia emerged. In the early days of coronary physiology, efforts to quantify the hemodynamic impact of a stenosis focused mainly upon the measurement of coronary flow, rather than pressure. Instead, the pressure component of combined coronary pressure and flow indexes were considered merely supportive of why flow may not increase or increase abnormally in response to an impaired distal hyperemic response (9).

FFR: INTRODUCTION AND EXPERIMENTAL VALIDATION

In 1993, Pijls et al. (1) published work on FFR. Unlike preceding approaches to coronary physiological assessment, FFR specifically sought to determine coronary flow assessment by using pressure-only-based assessments during hyperemia. By expanding upon the earlier work of Gould (10), who had described the coronary circulation as an electrical circuit of variable serial resistances, with the stenosis of the epicardial artery being one component, Pijls applied Ohm's Law ($V = IR$, where V is the voltage difference, I is the current, and R is the resistance) to rationalize that when coronary resistance was stable and minimal (as occurred during maximal arterial dilation) (11,12), a direct relation between coronary pressure and flow could be presumed.

FFR is defined as the ratio of the pressure distal to a stenosis (Pd) relative to the pressure proximal to the stenosis (Pa) during hyperemia induced by a vasodilating agent. Accordingly, an FFR value of 0.80 represents a 20% pressure loss across the stenosis. This theory was tested experimentally in 5 anesthetized dogs in whom pressure-derived FFR was compared with Doppler-derived fractional coronary artery flow reserve in surgically dissected, balloon-ligated proximal circumflex arteries during intracoronary administration of papaverine (1). Despite the inherent differences between human and animal models, in these early experiments, Pijls et al. (1) demonstrated that FFR could theoretically be used under idealized experimental conditions to determine the flow-limiting potential of a coronary artery stenosis. Although the calculated values of FFR correlated closely with those directly measured by a Doppler velocity meter, replotting the data as a Bland-Altman plot shows that the pressure- and flow-derived FFR values are less tightly associated, as may be suggested by the correlations (**Figure 2**).

Nowadays, only a simplified version of FFR is used clinically, whereby the right atrial pressure measurement is omitted. However, the description of FFR to individually quantify myocardial (FFRmyo), coronary, and collateral components of the coronary circulation (**Table 3**) helped validate the concept and engender continued research in humans.

FFR: FROM THE ANIMAL TO THE HUMAN MODEL

Early studies of FFR in the human model focused on establishing FFR cutoff values for the detection of inducible ischemia, defined by a variety of