Moving Beyond Coronary Stenosis
Has the Time Arrived to Address Important Physiological Questions Not Answered by Fractional Flow Reserve Alone?

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Fractional flow reserve (FFR) is an intracoronary pressure-derived index that circumvents many of the limitations of angiography in assessing stenosis severity.1 From a broad perspective, the greatest achievement of the investigators from Aalst, Eindhoven, and Houston who developed FFR was incorporating intracoronary physiology to routine clinical practice. Key elements in FFR success were (1) the simplicity of the technique, (2) the use of a well-defined cutoff (initially 0.75; since the FAME study, 0.80) that facilitated interpretation of the results, and (3) the gathering of evidence in properly designed trials.2 But, above all, the key aspect was the relevance of the question answered by FFR: Does this stenosis requires revascularization?

The latter is an important issue, which largely explains why physiology indices used in the pre-FFR era did not reach clinical application. Leaving aside a few exceptions, the most important studies using Doppler-derived coronary flow reserve (CFR) in the 1990s, such as Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE), DEBATE II, French Randomized Optimal Stenting Trial (FROST), and Doppler Endpoint STenting INternational Investigation (DESTINI) (including in total 1734 patients), explored whether optimization of the results of balloon angioplasty with CFR could reduce restenosis or avoid the use of coronary stenting (the so-called provisional stenting strategy).3,4 A posteriori, it is easy to understand why, despite the positive results of several of these studies, the Doppler guidewire never became indicated for this purpose not a part of the interventionalists toolbox.

On the contrary, the robustness of the question behind FFR (focused on revascularization appropriateness) increased over time, becoming maximal in current scenario, dominated by major doubts on the overall benefit of percutaneous coronary intervention, concerns on percutaneous intervention overindication, and urge for cost-effectiveness in a context of economical crisis. Also in the noninvasive field—and mainly because of the strength of outcome data—FFR has become a standard of reference, and FFR-like indices obtained by applying computational fluid dynamics to multidetector computer angiography compete now with ischemia detection techniques.

Which are the challenges for coronary physiology in FFR era? Without any doubt, the first challenge is to increase its adoption, which remains low in most countries. Simpler adenosine-free indices based on the pressure–flow relationship have been proposed to foster this purpose.5 In addition, a new set of important questions has arrived. After a 50-year stenosis-centered culture of myocardial ischemia, growing evidence indicates that ischemic heart disease is a multilevel condition that affects both the epicardial and the microcirculatory domains of the coronary circulation, as well as the myocardium.6 Postponing the development of tools aiming comprehensive ischemic heart disease diagnosis is no longer tenable; otherwise, it will not be possible to ascertain prognostic implications of multilevel coronary involvement to create awareness of the problem among the cardiovascular community, or to assess the effect of treatments addressing the coronary microcirculation.

Several groups, including ours, have strived in making possible this type of comprehensive assessment by combining FFR and CFR, envisaged as complementary rather than competing techniques.7–9 In this issue of Circulation: Cardiovascular Interventions, van de Hoef et al10 present the results of a research performed in a large cohort of patients investigated with multimodality physiological assessment in whom percutaneous coronary intervention was deferred whenever Doppler-derived CFR and FFR were not concordantly abnormal (using CFR<2.0 and FFR<0.75 as cutoff values). Importantly, the patients included in this cohort were followed up for a long period of time (median, 12 years), providing unique insights on the prognostic relevance of the hemodynamic findings done with FFR and Doppler-derived CFR.

The first important observations made by these researchers refer to the interaction between microcirculatory dysfunction and FFR. By definition, FFR is a stenosis-centered technique that uses the hyperemic translesional pressure ratio as a surrogate of myocardial flow impairment caused specifically by the interrogated stenosis. The rationale behind FFR acknowledges that microcirculatory dysfunction, by impairing myocardial blood flow, modulates FFR values. Yet, since the matter before a coronary stenosis is deciding whether revascularization is appropriate or not, operators have been reassured that issues about concomitant, longstanding microcirculatory

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dysfunction, which would not be solved by stenting, can be left out of the decision-making process.

The data from the Amsterdam group put an end to any peace-of-mind generated by this attitude, showing that the outcome of patients with FFR≥0.80 and impaired myocardial blood supply (low-CFR) is unacceptably high when compared with those with preserved CFR. The most immediate question that comes to mind is whether these patients could be similar to those that developed major cardiac events or persistence of angina after being allocated to the deferral revascularization study arm (on the grounds of FFR ≥0.75 or >0.80)\(^1\) in FFR trials. It is beyond the scope of this editorial comment to discuss whether, on the grounds of the microcirculatory resistances reported by van de Hoef et al.,\(^10\) such CFR impairment obeys just to microcirculatory disease or also to diffuse atheromatous involvement,\(^8\) which influences patient outcome.\(^12\) In any case, the take-home message is that this hemodynamic pattern cannot be obtained with FFR alone, and that while revascularization is not currently indicated, physicians involved in the management of the patient should become aware that coronary hemodynamic are abnormal, and that this has been associated to a worse outcome. We can only provide tentative answers on how to proceed; for the time being, the diagnosis of abnormal hemodynamic in patients with stenosis and FFR<0.80 should be followed up by optimization of secondary prevention, anti-ischemic treatment, and close patient follow-up.\(^9\) Future studies will demonstrate whether this attitude, born of more comprehensive physiological information, contributes to improve outcome in patients with multilevel coronary involvement.

The second set of observations refers to the alternative discordant FFR/CFR group, namely vessels with FFR≤0.80 and CFR>2.0. The rationale of FFR implies that the hyperemic trans-stenotic pressure ratio reliably identifies ischemia-generating stenoses, irrespective of the magnitude of coronary flow. However, investigators measuring both FFR and coronary flow have been puzzled by the fact that a substantial number of stenoses have abnormal FFR, despite preserved CFR and low microcirculatory resistances\(^7,9\) (both suggestive of preserved blood supply and absence of microcirculatory dysfunction). The most plausible explanation for this paradox is that, under certain conditions, an FFR below the diagnostic cutoff may reflect the existence of high coronary flow and not of a significantly flow-limiting stenosis. In other words, being FFR a surrogate of coronary flow, the documentation of a nonpathological value of a flow-based index, such as CFR, should raise the concern that such cases are FFR false-positives, and that therefore revascularization might be deferred. This attitude is supported by the long-term outcome of these patients in the present study during the first 3 years of follow-up because the major adverse cardiac events rate was relatively low. Interestingly, there is a long-term catch up of events in this FFR/CFR discordant group. Because a less pronounced phenomenon also occurred over time in the reference group (that in which both FFR and CFR were concordantly normal), the authors interpret this finding as a result of atherosclerosis progression.

How to read the study of van de Hoef et al.?\(^10\) On one hand, the hemodynamic findings are consistent with observations performed by other groups using different methodologies (positron emission tomography, FFR, and thermodilution-derived CFR).\(^9,13\) This provides strong support to the feasibility of performing multilevel physiological interrogation of the coronary circulation with FFR and CFR. On the other, the documentation of differentiated outcomes by their combination is of great importance and suggests that the invasive diagnosis of ischemic heart disease can be still potentially improved beyond FFR. The demonstrated benefit of FFR when compared with angiography should not impede revisiting its diagnostic efficiency in settings, such as the FFR<0.80/CFR>2.0 subgroup discussed above. This is important because the extremely high diagnostic accuracy reported in initial FFR validation was derived from a small number of patients selected with stringent inclusion and exclusion criteria.\(^14\) Finally, in translating the findings of van de Hoef et al.\(^10\) to current practice, it is also important to remember the retrospective, nonrandomized design of the study, and the differences with contemporary secondary prevention and optimal medical treatment.

As cardiologists, we are now exposed to a double tension: to simplify physiology as FFR has done, to foster its adoption and, thus, to translate patients the benefits demonstrated in FFR studies and, on the contrary, to face the complexity of ischemic heart disease, which involves not only the epicardial but also the microcirculatory domains of the coronary circulation and the myocardium. The article of van de Hoef et al.\(^10\) serves in this way as a reminder of the limits of simplicity and parsimony in medical sciences.

Disclosures
Dr Escaned has served as speaker at educational events organized by St Jude Medical and Volcano Corporation (amount category: modest). The other author reports no conflicts.

References


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