Debate: Angiography-derived FFR. The angiographic perspective

A debate: RFF derivada de la angiografía. Perspectiva desde la angiografía

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QUESTION: Compared to the pressure guidewire what possible advantages does coronary angiography-derived fractional flow reserve (FFRangio) have and what is the current clinical evidence?

ANSWER: Guidewire pressure-derived fractional flow reserve (FFR) is the most highly validated physiological index for the analysis of coronary stenoses.[1,2] Despite the large scientific evidence supporting its prognostic impact on the assessment of patients with coronary artery disease and great cost-effective ratio, its use, though on the rise, is still not very popular.[3] And this is so even despite the fact that only one third of the intermediate angiographic lesions considered significant through visual assessment are eventually confirmed as significant at the physiological analysis.[4,5] The main reasons are that performing the FFR requires advancing a guidewire—which is not the best thing to do from the standpoint of maneuverability—through a coronary artery that has some degree of atheromatous disease. Also, to assess hyperemia, it requires the administration of drugs that can have undesirable effects effects.[6]

In order to solve these issues, easier non-hyperemic indices such as the instantaneous wave-free ratio (iFR), the diastolic pressure ratio (dPR), and the resting full-cycle ratio (RFR)[7] have been developed. They all avoid using drugs, but require the advancement of an intracoronary guidewire. FFRangio can be performed using different software, such as the quantitative flow ratio (QFR; Medis, The Netherlands) and others in the pipeline like the 3D-CA (HeartFlow, United States) which provides the same information only with the angiography without having to advance the guidewire or use drugs, which is precisely their main advantage. Similarly, there are different software available to perform this analysis using computed tomography that have already generated evidence;[8] they are based on 3D reconstruction and computational fluid dynamics.[9] They have proved to match the FFR adequately in different contexts[10,11] with a cut-off value of 0.80, an apparently higher accuracy of iFR,[12,13] and an adequate intra- and inter-observer reproducibility in centralized analyses.[14]

The FAVOR pilot study,[15] that gained the CE marking for the QFR software back in 2017, recruited 88 patients with stable coronary artery disease and non-ostial lesions, and proved the good correlation between the QFR and the FFR. Also, it proved that the values of FFRangio in situations of hyperemia (with adenosine [aQFR]) did not increase diagnostic accuracy compared to measurements without hyperemia (only with the administration of contrast [cQFR]), which means that the use of drugs can be avoided. These results have also been confirmed in a recent meta-analysis conducted by Westra et al.[16] that only included prospective registries. It showed he high negative predictive value of FFRangio that would avoid unnecessary delayed procedures.

Q.: Which do you think are the technical limitations of FFRangio?

A.: One in 5 vessels cannot be analyzed accurately with the FFRangio when the study is performed retrospectively, that is, without an optimal angiography based on easy recommendations including 2 projections of the vessel under study with, at least, a 25° difference and a recording at 15 images per second. When performed this way, images can be analyzed more precisely in up to 90% of the vessels. However, the software available is still limited with ostial or bifurcation lesions. Other than the aforementioned, the factor that often slows down a correct analysis is the crossing of vessels in the studied lesion, which explains why when the images are specifically acquired, the possibility of performing the analysis is much higher. As a matter of fact, integrating this type of software online in the catheterization laboratory is essential to obtain FFRangio values and angiographic acquisition simultaneously and correct the latter when inadequate. This is so because with offline analyses the quality of angiography cannot be changed. Another factor that can be misleading and should be taken into consideration is that, although the contour of the vessel is acquired automatically, manual corrections can still be made. To minimize the impact of this subjective factor operators need to have proper training and certification in this technique. Finally, although evidence is scarce on this regard, we should ask ourselves to what extent variations in microcirculation that affect coronary flow (like in the infarct related artery or in stable patients with significant microvascular abnormalities) can also impact the results of the FFRangio analysis. In return, this

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software asseses the entire length of the vessel, not only individual lesions, to decide what part of the vessel should be treated in cases of tandem lesions to be more precise and effective therapeutically speaking (QIMERA-1, NCT04200469).

Q.: Which should be the most appropriate indications for FFRangio with the current state of evidence and which do you think will be its mid-term indications?

A.: From my own perspective, one of the most practical, efficient, and cost-effective uses will be to assess non-culprit lesions in the myocardial infarction setting.[14,17] Although, as I mentioned at the beginning, complete revascularization with pressure guidewire has proven useful in this context, the truth is that when dealing with culprit artery revascularizations the clinical context is often that of an emergency. Therefore, no treatment is administered or physiological assessment of the lesions performed in the remaining vessels. This leads to a second procedure with the resulting risks and costs that, in many cases, can be avoided since FFRangio assessments rules out significance in over 50% of the lesions. Actually, when a second procedure is performed, the most common finding is that, according to the FFR angio, the severity of the stenoses observed in non-culprit arteries often improves compared to the acute phase. As a matter of fact, the QIMERA pilot study[14] confirmed that in patients with cQFR values < 0.82 in non-culprit arteries during the first procedure, the delayed procedure could be avoided without assuming any risks.[14]

Q.: In your opinion, which study or studies would be necessary to bring this technique to the same level as the pressure guide-wire? Do you think this will happen anytime soon?

A.: We will probably need several prospective and controlled studies that compare both tools in different clinical settings: infarctions, stable patients, pre- and post-angioplasties, etc. In this sense, our group simply conducted a prospective comparison among different non-hyperemic tools (RFR and QFR versus FFR)— to be published shortly—proving that there is a better correlation between QFR and FFR. Therefore, these strategies that do not require advancing a coronary guidewire for physiological assessment will probably be widely used. However, other technological achievements still need to be made first.

On the other hand, I don't believe one technique will end up replacing the other in the mid-term. Actually, evidence suggests that a combination of both can be very useful. Thus, with QFR values < 0.75 or > 0.85 it would not make sense to run more physiological tests (avoiding 60% of pressure guidewires). Regarding the gray values in that area a guidewire-based non-hyperemic index may be used, which could reach sensitivity and specificity values of 97%, both consistent with an analysis conducted by our group of over 100 lesions with a 94.5% positive predictive value and a 98.5% negative predictive value. This combined approach would avoid the administration of adenosine to 100% of the patients and minimize the need to advance an intracoronary guidewire. According to the interventional cardiol-ogists surveyed, this is the main setback for the physiological assessment of lesions.[18]

CONFLICTS OF INTEREST

REFERENCES

1. Zimmermann FM, Ferrara A, Johnson NP, et al. Deferral vs. performance of percutaneous coronary intervention of functionally nonsignificant coro-nary stenosis: 15-year follow-up of the DEFER trial. *Eur Heart J*. 2015;36: 3182-3188.

2. Xaplanteris P, Fournier S, Pijls NHJ, et al. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. *N Engl J Med* 2018;379:250-259.

3. Götberg M, Cook CM, Sen S, Nijjer S, Escaned J, Davies JE. The Evolving Future of Instantaneous Wave-Free Ratio and Fractional Flow Reserve. *J Am Coll Cardiol*. 2017;70:1379-402.

4. Lindstaedt M, Spiecker M, Perings C, et al. How good are experienced interventional cardiologists at predicting the functional significance of intermediate or equivocal left main coronary artery stenoses? *Int J Cardiol*. 2007;120:254-261.

5. Tonino PAL, De Bruyne B, Pijls NHJ, et al. Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention. *N Engl J Med*. 2009;360:213-224.

6. 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.

7. Sen S, Escaned J, Malik IS, et al. Development and Validation of a New Adenosine-Independent Index of Stenosis Severity From Coronary Wave–Intensity Analysis. *J Am Coll Cardiol*. 2012;59:1392-1402.

8. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA*. 2012;308:1237-1245.

9. Morris PD, Narracott A, von Tengg-Kobligk H, et al. Computational fluid dynamics modelling in cardiovascular medicine. *Heart*. 2016;102:18-28.

10. Tu S, Barbato E, Köszegi Z, et al. Fractional Flow Reserve Calculation From 3-Dimensional Quantitative Coronary Angiography and TIMI Frame Count. *JACC Cardiovasc Interv*. 2014;7:768-777.

11. Tu S, Lansky A, Barbato E, et al. Diagnostic Accuracy of Fast Computational Approaches to Derive Fractional Flow Reserve From Diagnostic Coronary Angiography. *JACC Cardiovasc Interv*. 2016;9:2024-2035.

12. Emori H, Kubo T, Kameyama T, et al. Quantitative flow ratio and instan-taneous wave-free ratio for the assessment of the functional severity of intermediate coronary artery stenosis. *Coron Artery Dis*. 2018;29:611-617.

13. Asano T, Katagiri Y, Chang CC, et al. Angiography-Derived Fractional Flow Reserve in the SYNTAX II Trial: Feasibility, Diagnostic Performance of Quantitative Flow Ratio, and Clinical Prognostic Value of Functional SYNTAX Score Derived From Quantitative Flow Ratio in Patients With 3-Vessel Disease. *JACC Cardiovasc Interv*. 2019;12:259-270.

14. Cortés C, Rodríguez-Gabella T, Gutiérrez H, et al. *Quantitative Flow Ratio en infarto de miocardio para la evaluación de lesiones en arterias no culpables: estudio piloto QIMERA*. *REC Interv Cardiol*. 2019;1:13-20.

15. Tu S, Westra J, Yang J, et al. Diagnostic Accuracy of Fast Computational Approaches to Derive Fractional Flow Reserve From Diagnostic Coronary Angiography. *JACC Cardiovasc Interv*. 2016;9:2024-2035.

16. Westra J, Tu S, Campo G, et al. Diagnostic performance of quantitative flow ratio in prospectively enrolled patients: An individual patient-data meta-analysis. *Catheter Cardiovasc Interv*. 2019;94:693-701.

17. Sejr-Hansen M, Westra J, Thim T, et al. Quantitative flow ratio for imme-diate assessment of nonculprit lesions in patients with ST-segment elevation myocardial infarction-An iSTEMI substudy. *Catheter Cardiovasc Interv*. 2019;94:686-692.

18. Tebaldi M, Biscaglia S, Fineschi M, et al. Evolving Routine Standards in Invasive Hemodynamic Assessment of Coronary Stenosis. *JACC Cardiovasc Interv*. 2018;11:1482-1491.