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EDITORIAL COMMENT

Coronary pressure (sometimes) lies...

A pressão coronária (às vezes) mente...

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''Coronary pressure never lies.''[1] This was what we were told 10 years ago, just a few months before the publication of the seminal FAME trial,[2] arguably one of the most important physiology trials ever published and surely the one that had the biggest impact on daily practice and revascularization guidelines. It clearly demonstrated the superiority of fractional flow reserve (FFR) over the common practice of visual estimation of stenosis severity by angiography to guide percutaneous coronary intervention of coronary lesions. Also, at some point during the learning process of FFR measurement, the dogma was also implanted that ''neither blood flow nor trans-stenotic pressure gradient at rest can determine whether a stenosis in a coronary artery will limit myocardial perfusion under conditions of increasing demand. Only when hyperemia is induced and coronary flow reserve is measured can a relationship between stenosis severity and the presence of ischemia be demonstrated.''[3]

For this reason, research examining other pressure indices, such as resting Pd/Pa[4] or contrast-induced low-intensity hyperemia,[5] was paid little attention for many years. Still, it must be admitted that the idea was attractive from a practical standpoint: all one needed to do was to push a pressure wire through the lesion, induce hyperemia with adenosine and calculate FFR. If it was over 0.80, operators could be confident that coronary revascularization could be safely postponed every time; on the other hand, they could be sure that ischemia was present in all cases when it was 0.80 or less, and proceed with treatment. Even if Pd/Pa was completely normal or a very high contrast FFR reading was obtained, we were told that there should be no doubt concerning the indication for revascularization as long as adenosine FFR was below 0.80. FFR thrived for years (even if possibly not as much as it should have) in this black vs. white scenario, one that we, as physicians, would love to have for all medical conditions: being able to make the right decision for each and every patient based on a simple yes-or-no measurement.

End of story? No: iFR enters the picture. In their first major paper, the ADVISE study, published in 2012,[6] the group headed by Justin Davies (Imperial College, London, UK) challenged the dogma of mandatory hyperemia and proposed a new index – the instantaneous wave-free ratio (iFR) – as an alternative to hyperemic adenosine FFR. Measurement of iFR is based on the concept of the diastolic wave-free period, during which coronary resistance remains low and stable. This enables the pressure gradient measured during this interval to be used as a surrogate for coronary flow, in

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exactly the same way as FFR, according to its underlying theory, but without the need to induce hyperemia.[6] After the publication of the ADVISE study, a long and interesting discussion ensued between classical FFR 'believers'[7–9] and the newcomer iFR investigators.[10,11] Several papers were published in major cardiology journals on both sides arguing the relative merits of each of the pressure indices. From a clinical perspective – probably the most important – this discussion was settled in 2017 with the presentation at the American College of Cardiology annual meeting (and simultaneous publication in the *New England Journal of Medicine*) of two major randomized trials: DEFINE-FLAIR[12] and iFR-SWEDEHEART.[13] These two trials, which recruited a combined total of over 4500 patients, clearly demonstrated that iFR (with a cut-off set at 0.89) was as good as FFR for guiding revascularization decisions.

However, the introduction of iFR as an invasive assessment tool had another important consequence: there were patients and lesions in which the results of iFR and FFR would not be concordant. In some, iFR would be >0.89 (suggesting absence of inducible ischemia), but FFR would be $\leq$0.80 (suggesting it was present), and also, although less often, the opposite (iFR<0.89 and FFR>0.80). Why was this important? Because it clearly highlighted the obvious question some of us had had from the beginning: could FFR sometimes lie? In fact, this is exactly what has been observed when using resting full-cycle Pd/Pa and contrast FFR together with adenosine FFR.[14]

In the current issue of the *Journal*, Menezes et al.[15] describe their experience with more than 150 patients assessed by both FFR and iFR. Not surprisingly, they found a similar pattern. In a proportion of cases (13%), iFR and FFR did not agree, even when using different cut-offs in a hybrid strategy, in which iFR is positive or negative when below or above the gray area of 0.86-0.93, respectively.

The underlying mechanisms and the implications of this apparent disagreement between iFR and FFR have been the subject of intense debate. In a recent analysis of the IDEAL study[16] – the largest registry to date in which both pressure and flow velocity were measured at rest and during hyperemia – Cook et al. suggested that disagreement would be a reflection of baseline flow and microvascular resistance and their response to adenosine. According to the authors, iFR would be a better indicator of coronary flow (and flow reserve), and discordance with FFR would be the consequence of both false positive (probably due to excessive increase in coronary flow or to excessive decrease in microcirculatory resistance, both induced by adenosine) and false negative FFR (for example, due to inadequate hyperemia).

Notwithstanding this interesting theoretical discussion, the clinical relevance of these discordant FFR/iFR patterns appears to be less than expected. As showed in a recent Korean study, deferred lesions with discordant results (both FFR+/iFR- and FFR-/iFR+) had a similar prognosis to lesions with negative results in both tests, and only deferring lesions with concordant positive FFR and iFR was associated with a worse prognosis.[17]

Yet, despite the clinical evidence from the two above-mentioned randomized clinical trials, iFR is still not widely accepted in the interventional cardiology community. There is skepticism concerning the use of a resting index, since it challenges the fundamentals underlying both vasodilator non-invasive stress testing and FFR.[18] Additionally, the two iFR trials have been criticized for including less severe patients and lesions (the mean FFR was 0.83, compared to 0.71 in the FAME trial).[18] Also, evidence for iFR is still relatively scarce in specific settings such as complex patients and acute coronary syndromes. However, being easier to measure, iFR is particularly appealing in these situations, particularly in patients with ST-elevation myocardial infarction and multivessel disease. In these patients, the use of iFR to assess non-culprit lesions in the acute phase has recently been analyzed,[19] and a major international randomized trial comparing acute iFR-guided full functional revascularization with deferred stress cardiac magnetic resonance imaging – iMODERN (iFR Guided Multi-vessel Revascularization During Percutaneous Coronary Intervention for Acute Myocardial Infarction; ClinicalTrials.gov identifier NCT03298659) – is ongoing and has just started enrolling patients. Portuguese investigators contributed significantly to the trial design and several Portuguese centers will participate actively in the study.

But is iFR the last cookie in the jar? Likely no. Other resting indices are currently being developed. Most of them rely on the fact that it is apparently not necessary to measure the pressure gradient strictly within the wave-free period, as iFR does: measurements performed using several different time intervals in diastole showed similar results to iFR using the Volcano system.[20] Thus, it is only to be expected that other companies may use this concept to create their own 'diastolic flow reserve' indices. Determination of the largest resting pressure gradient across the full cardiac cycle (regardless of its location) is another approach currently being evaluated. Portuguese investigators lead the first-in-man international prospective study to test this technology, PREDICT (Performance of a New REsting Pressure Index During Invasive Angiography Compared To Adenosine Hyperemic FFR; ClinicalTrials.gov identifier NCT03237169). Results will soon be available.

We have definitely moved forward from the 2008 statement that ''Coronary pressure never lies''. However, there is undoubtedly still much more to learn in coronary physiology, especially about microvascular function. Having Portuguese centers involved in this field of research is very important and surely a goal that is worth pursuing.

Conflicts of interest

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