Fractional flow reserve as the reference standard for myocardial perfusion studies: fool’s gold?

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The evidence for the use of cardiovascular magnetic resonance (CMR) as a first-line diagnostic tool in patients with suspected coronary artery disease (CAD) has been solidified by the recent publication of large clinical studies and meta-analyses.1–3 Most of this evidence has been gathered against anatomical angiographic endpoints, despite the well-known fact that luminal stenosis correlates poorly with haemodynamic significance, particularly for coronary stenoses between 30 and 80% of luminal diameter.4,5 Multiple factors, such as entrance effects, friction, and turbulence, can contribute to coronary blood flow resistance and the loss of pressure across a stenosis, and therefore the haemodynamic significance of lesions can be underappreciated by two-dimensional angiographic images, particularly in the setting of eccentric or irregular stenoses.6 In clinical practice, coronary angiography is therefore often complemented by non-invasive imaging tests to determine the functional significance of a borderline stenosis and guide patient management. Recent clinical practice guidelines for revascularization recommend a combination of anatomical and ischaemia testing for most clinical scenarios.7 Invasive pressure-wire-derived fractional flow reserve (FFR) has become a popular alternative for the functional assessment of coronary stenosis that can be performed in the catheter laboratory. FFR is calculated as the ratio of maximal blood flow in a stenotic artery relative to maximal flow in the same artery in the theoretic absence of any stenosis.8–11 In recent years, several studies have shown that FFR-guided percutaneous coronary intervention (PCI) improves health and economic outcomes compared with treatment based on angiography alone.12–17 Carried by these data, FFR has also become the favoured endpoint for myocardial perfusion studies. In this issue of the European Heart Journal - Cardiovascular Imaging, a study by Ebersberger et al. compared perfusion CMR at 3 Tesla (T) to a clinical routine algorithm in which coronary stenoses exceeding 75% on coronary angiography were deemed pathological and FFR-measurements were performed in intermediate lesions (50–75%). Myocardial perfusion CMR yielded a high diagnostic performance for the detection of significant coronary artery stenosis defined in this way, with an impressive area under the curve of 0.93. These results are in accordance with several other recent studies that have shown a high diagnostic performance of perfusion CMR in comparison with FFR.18,19 The authors conclude that 3T myocardial perfusion CMR provides consistently high image quality and an excellent diagnostic performance in patients with suspected or known significant CAD as defined by FFR.

In light of the recent proliferation of papers evaluating imaging tests against FFR as the reference test for ischaemia, it is pertinent to ask the question whether FFR really is the most appropriate endpoint in this context. The prognostic value of FFR is beyond doubt, as FAME, FAME II, and DEFER all demonstrated the benefits of FFR-guided PCI in terms of event reduction (predominantly a reduction in urgent revascularization).12,20,21 However, none of these studies has claimed FFR to be the diagnostic gold-standard of ischaemia testing nor has this ever been shown in other studies. It is often overlooked that FFR was itself originally validated against non-invasive stress tests.9 The fact that FFR is now used as an endpoint for non-invasive imaging studies is somewhat paradoxical and creates questionable circular arguments. Furthermore, the initial validation study compared FFR with three different stress tests including SPECT in a population of only 45 individuals.9 All the subsequent studies comparing the diagnostic performance of FFR to other standard diagnostic methods have also had relatively small populations, and no large-scale comparison of non-invasive and invasive assessment of ischaemia is available. Importantly, a recent meta-analysis of 15 of these studies (n = 976 lesions) showed only modest concordance of FFR with SPECT [random effects sensitivity 75% (95% CI: 66–82); specificity 77% (95% CI: 70–83)], leaving continued uncertainty about the concordance of FFR with non-invasive imaging techniques.22

In addition, FFR has well-documented limitations, for example, in the setting of multiple stenoses in the same vessel, left main stem disease or recent myocardial infarction23 and in the commonly used simplified FFR equation, central venous pressure is not considered and right atrial pressure is rarely measured or accounted for.24 These limitations can lead to discrepancies between invasive and non-invasive assessment of ischaemia.

There are other important conceptual differences between FFR and myocardial perfusion imaging. FFR gives no direct indication of the size of territory at risk or its viability, but both are important indicators of risk that should be considered when deciding a
revascularization strategy. As a vessel-based index, FFR assumes uniform endothelial function either side of the lesion and an intact microcirculation, whereas perfusion imaging assesses contrast delivery through the entire vascular system of the heart. Myocardial ischemia associated with microvascular disease as a result of atherosclerosis, obesity, advancing age, or smoking (which may be present even in the absence of significant epicardial stenosis) will therefore affect myocardial perfusion imaging and FFR differently.25,26

Finally, although several studies have demonstrated significant reduction in angina by FFR-guided revascularization, it is myocardial ischemia and not coronary stenosis that ultimately accounts for anginal symptoms. Myocardial perfusion assessment may therefore be a more appropriate test for suspected angina than FFR. Interestingly, in the FAME II trial, there was no difference in the frequency of angina symptoms in the FFR <0.80 group (mean FFR = 0.68) and the normal FFR negative registry group (9.0 vs. 10.9%; P = 0.64).31

So while FFR is unquestionably a better alternative to lumenerography to guide decisions in the catheterization laboratory, it is far from being an ideal reference standard for ischaemia testing with non-invasive imaging studies. Other invasive indices are being developed, such as the hyperaemic stenosis resistance index, an invasive pressure-, and flow-based index, which is more stenosis specific, and less dependent on an intact microcirculation.27 More recently, measurements entirely independent of adenosine-mediated hyperaemia have also been proposed such as basal stenosis resistance, instantaneous wave-free ratio, and computed tomography-derived FFR,28–30 but whether any of these will emerge as alternative comparators for non-invasive imaging studies is questionable given the additional simplifications made in their calculations.

Meanwhile, imaging tests also continue to evolve, and in particular, adenosine stress perfusion CMR has undergone many technical improvements and several levels of clinical validation over the last decade. 3T systems have been introduced more widely and the higher field strength provides greater signal-to-noise and contrast enhancement, which can be used to improve image quality, spatial resolution, or myocardial coverage. Many of the artefacts initially seen at 3T are being overcome with new-generation systems and recent studies of 3T perfusion CMR like that by Ebersberger et al. show significant promise.31–34 3T perfusion CMR can now be performed with a spatial resolution of under 2 mm or alternatively with complete myocardial coverage (three-dimensional perfusion CMR).35,36 The ongoing MR-INFORM study is expected to provide much needed outcome data for FFR vs. stress perfusion CMR-guided revascularization.37 Quantitative analysis to estimate absolute myocardial blood flow can be performed with positron emission tomography and, increasingly, with CMR, further improving the ability of non-invasive imaging to detect and quantify ischaemia.

Given the high accuracy of non-invasive imaging achievable today, it may be time that established quantitative non-invasive imaging methods themselves rather than invasive parameters serve as the reference for the diagnostic performance of new imaging methods. The field can then move swiftly on to assess their real clinical value in terms of determining patient outcome and prognosis.

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References