Guest Editorial

Controversies in Fractional Flow Reserve

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Abstract

Fractional flow reserve (FFR) has been identified as the optimal diagnostic tool to identify significant coronary lesion. However, current evidence does not support this role. The optimal diagnostic strategy should give highly sensitive and specific results with lowest cost and accomplishing this task has been made more difficult in the era following the COURAGE trial.

Keywords

Fractional flow reserve, diagnostic tool, COURAGE trial

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As coronary angiography is of limited value in defining the functional significance of a stenosis, the timely article by Balanescu in this issue of *European Cardiology Review* rationally proposes to integrate the anatomic information with a functional assessment, either by measuring coronary flow reserve (CFR) or intracoronary artery pressure with fractional flow reserve (FFR). CFR measurements depend on the status of the microcirculation, as well as on the severity of the lesion in the epicardial vessel.¹ Nowadays, FFR is considered to be the 'gold standard' for invasive assessment of stenosis haemodynamic impact and a useful tool for decision-making in coronary revascularisation. FFR is calculated as the ratio of distal coronary pressure to aortic pressure measured during maximal hyperaemia. A normal value for FFR is 1.0, regardless of the microcirculation status; stenoses with an FFR >0.80 are rarely associated with exercise-induced ischaemia. This provides guidance for the clinician in situations when it is not clear if a lesion of intermediate angiographic severity is the cause of ischaemia. The use of FFR was upgraded to a Class IA classification in multivessel percutaneous coronary intervention (PCI) in the European Society of Cardiology (ESC) guidelines on coronary revascularisation.² At present, FFR is recommended as for use where noninvasive stress imaging is contraindicated, discordant, nondiagnostic or unavailable in stable ischaemic heart disease. In these conditions, FFR should be used to assess the functional significance of intermediate coronary stenosis (50–70 %) and more severe stenoses (< 90 %).³

There are, however, major pathophysiological, practical and prognostic limitations to the extensive use of FFR in the cardiac catheterisation laboratory.

- FFR determines the physiological significance of coronary stenosis, but fails to identify what is present upstream, within and downstream the stenosis, such as vulnerable blood, vulnerable plaque, coronary

vasomotion or anatomic or dynamic microcirculation dysfunction. All of these variables can determine myocardial ischaemia and catastrophic cardiovascular events, yet are ignored by a merely stenocentric approach.⁴

- The second limitation relates to the additional cost (~US\$1000)⁵ and radiation exposure (~5 mSv, corresponding to 250 chest X-rays, in addition to the 7 mSv of a coronary angiography) associated with FFR performed in the catheterisation laboratory.⁶
- Findings on the prognostic impact of FFR are limited.^{7,8} Its impact is greater than that of assessment of coronary stenosis, but smaller than that of CFR. Concordance between FFR and CFR is low; in more than 25 % of patients, FFR and CFR do not point in the same diagnostic direction. Whereas a combination of abnormal CFR/normal FFR values is indicative of microvascular disease, a normal CFR/abnormal FFR combination has been shown to be associated with a good prognosis.⁹

At present, a stenocentric approach to ischaemic heart disease is not supported by convincing data. Randomised trials, such as Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) 1⁷ and FAME 2,⁸ which are often quoted to promote the use of FFR to guide revascularisation, are conspicuously lacking for CFR; those that have been completed only show, at best, some benefit for weak and soft endpoints.

Evidences are considerably weaker when hard endpoints are considered. In the FAME 1 trial, the entire difference in MI rate was attributable to events occurring during the first few days after randomisation (i.e. at the time of the initial revascularisation procedure).⁹ The difference in adverse events is entirely explained by fewer revascularisation procedures occurring in the FFR-guided

arm compared with the angiography arm. In the FAME 2 trial, patient selection was based on clinical presentation of stable angina pectoris.⁴ One-third of included patients had no 'significant' (FFR <0.80) stenosis at angiography. This observation strongly challenges the association between stable angina and significant stenosis.⁴ The FAME 2 trial was prematurely interrupted due to excess benefit in the PCI arm. However, an unbiased evaluation of the data reveals that hard events, including death and non-fatal MI, occurred at a similar frequency across the three patient groups (no significant stenosis, significant stenosis on medical therapy and significant stenosis on medical therapy plus PCI),⁴ thus supporting a speculation of futility for FFR-guided PCI.

In a head-to-head assessment, coronary flow velocity reserve (a prognostically efficient surrogate of CFR) showed greater prognostic value compared with FFR, thus indicating a greater importance of coronary flow than coronary pressure for prognosis.¹⁰ It is tempting to shift the focus of diagnostic evaluation upstream to the cardiac catheterisation laboratories, where in the stress echocardiography laboratory information can be obtained on regional wall motion, coronary flow velocity reserve,¹¹ left ventricular contractility (with simple assessment of elastance reserve), patient symptoms, ECG changes and extravascular lung water (with B-lines during stress).^{12,13} More variables than merely coronary stenosis are involved in the determination of myocardial ischaemia, and our diagnostic protocols should be changed accordingly.⁴

So, is there no room left in 2016 for FFR in the management of ischaemic patients? The main benefit of FFR, as consistently shown in many studies, is to avoid useless procedures. The second contribution of FFR studies is reassurance that deferring elective procedures does not expose patients to excess risk. Thus, according to current guidelines on coronary revascularisation (ESC 2013 guidance), revascularisation should be considered if a patient has intolerable angina despite optimal medical therapy.² Under these circumstances, when patients present with an intermediate lesion in the culprit vessel, FFR may help in deciding if it is worth treating. This recommendation is consistent with the observations that no prospective randomised trial or metaanalysis has shown a mortality/morbidity benefit following elective revascularisation procedures, and that FFR was not useful in predicting adverse events in one of the initial validation studies.¹⁴

In conclusion, FFR can identify a 'haemodynamically significant' stenosis, but this does not imply that the stenosis causes myocardial ischaemia. It has been conclusively demonstrated that the majority of patients with ischaemic heart disease do not have a significant stenosis and conversely, that the majority of patients with a significant stenosis do not have ischaemic heart disease. Therefore, any technique aimed at diagnosing myocardial ischaemia that focuses on the atherosclerotic obstructions and does not consider the role of functional mechanisms, microvascular dysfunction, platelet dysfunction, etc, is bound to be disappointing and misleading, including FFR. ■

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