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Invited Editorial

FFRCT and QFR: Ready to be used in clinical decision making?

Different non-invasive and invasive imaging modalities are currently available for the diagnosis of coronary artery disease (CAD) and subsequent management decisions in symptomatic patients. The choice between modalities is predominantly based on the pre-test likelihood of CAD and clinical context. In recent European, American and United Kingdom (UK) guidelines there has been a move towards more anatomical imaging in the form of non-invasive coronary computed tomography angiography (CTA) with less invasive coronary angiography (ICA). This anatomic approach has the highest sensitivity for CAD and the goal for reducing the rate of ICA within guideline recommendation approaches, particularly in patients with stable symptoms, is driven by the small but significant risk of ICA complications, a higher cost, and the simple fact that in many cases ICA does not result in a change in patient management. However, this anatomy first pathway is limited by a lack of ischemia information.

Invasive fractional flow reserve (FFR) serves as the reference standard of ischemia detection and aids treatment decisions regarding revascularization. A FFR value of ≤0.80 identifies functionally significant lesions where revascularization provides clinical benefit. As FFR is an invasive tool requiring introduction of a pressure wire in the coronary artery, it exhibits a low risk of serious complications and is associated with higher costs. Contemporary practice demonstrates a wide variation of utilization of this reference standard worldwide, which is related to reimbursement issues, health care logistics (some centers performing only invasive ICA), and in some instances perhaps underuse of invasive FFR due to time restrictions or personal preference to conservative “eye-balling” assessment of stenosis. Accordingly, an accurate alternative method to measure FFR without the need for a pressure wire would be potentially useful in clinical decision making.

Image-derived alternatives to FFR enable estimation of coronary blood flow based on three-dimensional reconstruction of angiographic images. Quantitative flow ratio (QFR) is a ‘less invasive’ approach, utilizing ICA images for stenosis measurements and frame count to assess flow, without the introduction of a pressure wire or induction of hyperemia. A completely non-invasive alternative is FFR derived from CTA (FFRCT), which uses deep learning methodology and/or computational fluid dynamic modeling to measure coronary flow.

In this issue of the *Journal of Cardiovascular Computed Tomography*, Kawashima et al. investigated the correlation between FFRCT and QFR in a patient population with a high pre-test likelihood of CAD and advanced CAD. The study was a sub-analysis of data of the international randomized SYNTAX III REVOLUTION trial including acquisition of CTA with FFRCT, and ICA. They demonstrate a high correlation between QFR and FFRCT (R = 0.76; p < 0.001). The Bland-Altman analysis demonstrated minimally lower value for FFRCT with a mean difference of −0.005 but broad range between limits of agreement of 0.116, with discordance between the two measures in 12% of vessels. This good agreement in a population with high disease burden, with 25% of lesions including the left main coronary artery, appears promising. It is consistent with evidence from a previous study by Tanigaki et al. involving a lower-risk population with predominantly single vessel disease and intermediate stenosis, where similar correlations between QFR and FFRCT (R = 0.62; p < 0.001) and agreement on Bland-Altman analysis was observed (mean difference of 0.01 and broad limits of agreement of 0.11).

The two ‘non - less invasive’ tests are only important and clinically useful if the tests:

1. Can be performed on the majority of patients;
2. Are practical and not too costly;
3. Have high diagnostic accuracy against the reference standard (invasive FFR);
4. Have evidence of clinical benefit.

Kawashima et al. report that 12% of patients were excluded because of missing FFRCT data and 21% of vessels due to insufficient image quality of ICA for calculation of QFR leaving a total of 469 (78.7%) vessels in 183 patients included. This is similar to the reported real-world FFRCT rejection rate of 15% and QFR studies per patient rejection rate of 10%. The majority of FFRCT rejections are related to coronary motion, whereas for calculation of QFR a high-quality diagnostic angiogram is required where two angiograms for each vessel must be acquired with an angulation of at least 25°. Whilst not perfect each method thus has promise for the vast majority of patients. This highlights the importance of an excellent image quality of CTA and ICA datasets that are used for computation of FFRCT and QFR, but at the same time may be one of a few sources of error, resulting in suboptimal diagnostic accuracy of the above methods.

From a practical performance aspect QFR assessment can be performed on site, with the available software and training computation of the result takes on average 4.4 ± 2.5 minutes. FFRCT currently remains an offsite external application through a third-party vendor, with an analysis time of 4 minutes, although fast onsite machine learning analysis is expected to be available in the future.

Several studies have reported the diagnostic accuracy of FFRCT or QFR versus invasive FFR. FFRCT has shown a high diagnostic accuracy,
sensitivity, and specificity on a per-vessel basis (87%, 90%, and 86%) with slightly lower accuracy with lower specificity on a per-patient basis (78%, 96%, and 63%) from the latest iterations of analysis software.13 The accuracy of QFR has been investigated in four validation studies including 84 to 328 vessels with similarly high sensitivity (74–95%) and specificity (86–92%).1,6,13,15 While the study by Kawashima et al. is significantly limited by its lack of invasive FFR comparator, it does allow important observations. Calculation was not a predictor of discordance between FFRCT and QFR despite potential concerns related to using CTA data.20 FAVOR III China results, recently published, are a first step in this high-risk 3VD population. This may relate to the exclusion of some high calcium burden in the 12% rejected patients, definition of calcification (>50% of cross sectional area of the lesion containing calcium on CTA and not calcium score per vessel or angiographically present opacifications), but overall it is encouraging, although needs further investigation.

The population and disease burden investigated are important. Left main CAD or ostial disease was frequently an exclusion criterion in QFR studies, and there has been little evidence related to this from FFRCT data. Therefore, a study where 25% of the population have LM disease and on average 2.6 vessels with >50% stenosis per patient, which demonstrates feasibility and good agreement suggests a potentially broader applicability in the future.

As the diagnostic accuracy of both methods seems promising, there are increasing studies including FFRCT and QFR in diagnostic and treatment algorithms.1,4 In addition, FFRCT has been included in recent SCCT expert consensus recommendations6 and the recent U.S. multisocietal chest pain guideline.16 FFRCT has reached this milestone through its clinical utility studies such as PLATFORM, ADVANCE and FORECAST.9,17,18 Furthermore, ICA deferral in case of an FFRCT value of ≥0.90 had an invasive FFR of above 0.80 but lacked outcome follow up to 5 years.17 A previous meta-analysis of studies on diagnostic accuracy of FFRCT demonstrated that in case of FFRCT of above 0.90 the diagnostic accuracy as compared to a negative invasive FFR was as high as 96%.19 CTA together with FFRCT could therefore serve as an important gatekeeper to ICA. The imperfect accuracy of FFRCT must be kept in mind and verification with wire-based FFR should be considered in case of doubt, or failure of optimal medical therapy, especially if FFRCT value is between 0.70 and 0.80.19 A major limitation for QFR, demonstrated by its exclusion from international guidelines, has been the lack of evidence related to clinical outcomes beyond its diagnostic accuracy. A previous study demonstrated that for a QFR value of 0.86 or above only 5% of coronary arteries had an invasive FFR of under 0.80, whereas for a QFR value of <0.77 only 8% of coronary arteries had an invasive FFR of above 0.80 but lacked outcome data.20 FAVOR III China results, recently published, are a first step in this process and certainly show that in patients undergoing PCI a QFR approach results in fewer myocardial infarcts and revascularization at one year compared to an ICA only approach.1,4

In conclusion, both FFRCT and QFR are promising alternatives to wire-based FFR. Clinicians still refer patients for ICA too often and the rate of ICA without significant coronary lesions should be further reduced. Non-invasive CTA and FFRCT has a high potential to gain a role as gatekeeper for ICA in patients with intermediate degree stenosis on CTA. FFRCT has yet to be proven to be able to provide sufficient diagnostic accuracy for decision making on (type of) revascularization. When ICA is performed, QFR has the potential to gain an important role in hemodynamic assessment of lesion severity, and in this way expand availability of functional coronary lesion assessment for treatment decisions. Further improvements in the accuracy of QFR are necessary with evidence from clinical outcome and utility studies before widespread introduction into clinical practice.

Declaration of competing interest

Timothy A. Fairbairn is a mentor at Heartflow.