FFRCT and QFR

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Invited Editorial

FFR_{CT} 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.[1] 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[2] and aids treatment decisions regarding revascularization. A FFR value of $\leq$0.80 identifies functionally significant lesions where revascularization provides clinical benefit.[3] 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 diagnostic 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,[4] without the introduction of a pressure wire or induction of hyperemia. A completely non-invasive alternative is FFR derived from CTA (FFR_{CT}), which uses deep learning methodology and/or computational fluid dynamic modeling to measure coronary flow.[5]

In this issue of *the Journal of Cardiovascular Computed Tomography*, Kawashima, et al. investigated the correlation between FFR_{CT} and QFR in a patient population with a high pre-test likelihood of CAD and advanced CAD.[6] The study was a sub-analysis of data of the international randomized SYNTAX III REVOLUTION trial including acquisition of CTA with FFR_{CT}, and ICA.[7] They demonstrate a high correlation between QFR and FFR_{CT} ($R = 0.76$; $p < 0.001$). The Bland-Altman analysis demonstrated minimally lower value for FFR_{CT} 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,[8] where similar correlations between QFR and FFR_{CT} ($R = 0.62$; $p < 0.001$) 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 FFR_{CT} 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 FFR_{CT} rejection rate of 15%[9] and QFR studies per patient rejection rate of 10%.[4] The majority of FFR_{CT} 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 FFR_{CT} 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.[10] FFR_{CT} currently remains an offsite external application through a third-party vendor, with an analysis time of 4 hours, although fast onsite machine learning analysis is expected to be available in the future.

Several studies have reported the diagnostic accuracy of FFR_{CT} or QFR versus invasive FFR. FFR_{CT} has shown a high diagnostic accuracy,

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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.[11] 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%).[4,10,12,13] Whilst the study by Kawashima et al. is significantly limited by its lack of invasive FFR comparator, it does allow important observations. Calcification was not a predictor of discordance between FFR_{CT} and QFR despite potential concerns related to using CTA 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 FFR_{CT} 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 FFR_{CT} and QFR in diagnostic and treatment algorithms.[7,14] In addition, FFR_{CT} has been included in recent SCCT expert consensus recommendations[15] and the recent U.S. multisocietal chest pain guideline.[16] FFR_{CT} 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 FFR_{CT} value ≥ 0.80 results in a low event rate during follow up to 5 years.[17] A previous meta-analysis of studies on diagnostic accuracy of FFR_{CT} demonstrated that in case of FFR_{CT} of above 0.90 the diagnostic accuracy as compared to a negative invasive FFR was as high as 98%.[19] CTA together with FFR_{CT} could therefore serve as an important gatekeeper to ICA. The imperfect accuracy of FFR_{CT} 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 FFR_{CT} 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.[14]

In conclusion, both FFR_{CT} 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 FFR_{CT} has a high potential to gain a role as gatekeeper for ICA in patients with intermediate degree stenosis on CTA. FFR_{CT} 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.

References

1. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41:407–477.
2. Pijls NH, Van Gelder B, Van der Voort P, et al. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation*. 1995;92:3183–3193.
3. De Bruyne B, Pijls NHJ, Kalesan B, et al. Fractional flow reserve–guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991–1001.
4. Tu S, Westra J, Yang J, et al. Diagnostic accuracy of fast computational approaches to derive fractional flow reserve from diagnostic coronary angiography: the international multicenter FAVOR pilot study. *J Am Coll Cardiol Intv*. 2016;9:2024–2035.
5. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA*. 2012;308:1237–1245.
6. Kawashima H, Kogame N, Ono M, et al. Diagnostic concordance and discordance between angiography-based quantitative flow ratio and fractional flow reserve derived from computed tomography in complex coronary artery disease. *J Cardiovasc Comput Tomogr*. 2022;16:336–342.
7. Collet C, Onuma Y, Andreinil D, et al. Coronary computed tomography angiography for heart team decision-making in multivessel coronary artery disease. *Eur Heart J*. 2018;39:3689–3698.
8. Tanigaki T, Emori H, Kawase Y, et al. QFR versus FFR derived from computed tomography for functional assessment of coronary artery stenosis. *J Am Coll Cardiol Intv*. 2019;12:2050–2059.
9. Curzen N, Nicholas Z, Stuart B, et al. Fractional flow reserve derived from computed tomography coronary angiography in the assessment and management of stable chest pain: the FORECAST randomized trial. *Eur Heart J*. 2021;42(37):3844–3852.
10. Xu B, Tu S, Qiao S, et al. Diagnostic accuracy of angiography-based quantitative flow ratio measurements for online assessment of coronary stenosis. *J Am Coll Cardiol*. 2017;70(25):3077–3087.
11. Driessen RS, Danad I, Stuijfzand W, et al. Comparison of coronary computed tomography angiography, fractional flow reserve, and perfusion imaging for ischemia diagnosis. *J Am Coll Cardiol*. 2019;73(2):161–173, 22.
12. Westra J, Krogsgaard Andersen B, Campo G, et al. Diagnostic performance of in-procedure angiography-derived quantitative flow reserve compared to pressure-derived fractional flow reserve: the FAVOR II Europe-Japan study. *J Am Heart Assoc*. 2018;7(14), e009603.
13. Westra J, Tu S, Winther S, et al. Evaluation of coronary artery stenosis by quantitative flow ratio during invasive coronary angiography: the WIFI II Study (Wire-Free Functional Imaging II). *Circ Cardiovasc Img*. 2018;11, e007107.
14. Xu B, Tu S, Song L, et al. Angiographic quantitative flow ratio-guided coronary intervention (FAVOR III China): a multicentre, randomised, sham-controlled trial. *Lancet*. 2021;398:2149–2159.
15. Narula J, Chandrashekhar Y, Ahmadi A, et al. SCCT 2021 expert consensus document on coronary computed tomographic angiography: a report of the society of cardiovascular computed tomography. *J Cardiovasc Comput Tomogr*. 2021;15:192–217.
16. Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *J Cardiovasc Comput Tomogr*. 2022;16:54–122.
17. Douglas PS, Pontone G, Hlatky MA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFR(CT): outcome and resource impacts study. *Eur Heart J*. 2015;36(47):3359–3367.
18. Fairbairn TA, Nieman K, Akasaka T, et al. Real-world clinical utility and impact on clinical decision-making of coronary computed tomography angiography-derived fractional flow reserve: lessons from the ADVANCE Registry. *Eur Heart J*. 2018;39(41):3701–3711.
19. Cook CM, Petraco R, Shun-Shin MJ, et al. Diagnostic accuracy of computed tomography–derived fractional flow reserve A systematic review. *JAMA Cardiol*. 2017;2(7):803–810.
20. Smit JM, Koning G, van Rosendael AR, et al. Referral of patients for fractional flow reserve using quantitative flow ratio. *Eur Heart J Cardiovas Img*. 2019;20:1231–1238.

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