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Is FFR_{CT} the answer to our prayers?

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Take Home Messages

- The topic is important because FFRCT will constitute a big investment from UK hospitals.
- This new technology adds to the non-invasive assessment of patients presenting with chest pain.
- Going forward CTCA/FFRCT may be the only modality used for the assessment and management of all risk-categories patients with chest pain.
- My opinion is that more evidence is needed for comparison with existing non-invasive modalities.

Introduction

It is probably one of the most common problems any cardiologist would face in a patient presenting with stable chest pain- does he or she have ischaemic heart disease (IHD)? The initial chest pain pathway (National Institute for Health and Care Excellence -NICE- guidelines 2010) supported CT calcium scoring (with CT coronary angiography- CTCA) for patients with low risk (10-29%), and functional imaging for the intermediate risk group (30-60%).[1] However in 2016 NICE, responding to contemporary health economic pressures for fast and safe patient turnaround, issued guidelines supporting CTCA as the imaging modality of choice for all patients presenting with chest pain, irrespective of their pre-test probability.[2]
This came as a surprise to many cardiologists as it seemingly ignored the fact that CTCA provided information about the anatomy but not the physiology of the disease, that would determine if the patient has IHD responsible for their symptoms. It became evident that both functional and anatomical information is important, but to this purpose the patient would need to undergo two separate non-invasive tests (CTCA and functional imaging) or a single invasive one (coronary angiography with fractional flow reserve- FFR).
FFR_{CT}, a new, computer-based technology that produces functional information from a CTCA derived anatomical model, was introduced in 2010. The technique, approved in the U.S. and Europe, is still evolving and recently led NICE to issue medical technology guidance to support its use in addition to CTCA as a first-line test for patients with chest pain. The idea was that the functional information provided on top of the anatomical details of the coronary artery tree, will act as a gatekeeper and prevent patients with moderate or significant anatomical disease but normal FFR_{CT} values undergoing invasive coronary angiography and intervention. The claimed benefit is promising- saving the NHS a minimum of £9.1million by 2022.[3] In view of the above, UK hospitals are anticipated to increasingly invest on CTCA (and FFR_{CT}), which highlights the importance of understanding the evidence base for this new technology.

How does FFR_{CT} work?

The technology is based on artificial intelligence and deep learning. The clinician sends the CTCA scan to the company (HeartFlow). A personalised digital 3D model of the patient's coronaries is created. Appropriately trained analysts edit the model if required and following application of computational fluid dynamics, blood flow and FFR_{CT} are computed. Within days the clinician receives the final report. As the patient database increases and the algorithms are trained on more data, the produced models become more accurate.

Indications for use of FFR_{CT}

The data derived from most studies is relevant to patients with a rather wide intermediate probability 10-90% for coronary artery disease (CAD). This is indeed the population of interest, since pre-test probability <10% is too low to derive any benefit from further testing, whereas >90% is equivalent to targeted therapy and many cardiologists would recommend invasive coronary angiography to exclude prognostic disease.

Diagnostic accuracy

i) Comparison with invasive FFR

The first multicentre trial assessing the diagnostic accuracy of FFR_{CT} was the DeFACTO study that used invasive FFR as the gold standard for diagnosis of IHD and identified that a strategy using CTCA combined with FFR_{CT} had a diagnostic accuracy of 73%, sensitivity of 90% and negative predictive value of 84%, but low specificity (54%) and positive predictive value (67%). The addition of FFR_{CT} to standard CTCA improved the test sensitivity, but was of no help in filtering the false positives cases, which is the main challenge in anatomical imaging.[4]

The NXT trial used stricter quality criteria for CTCA (GTN spray in all patients and concordance with image acquisition guidelines), which meant a significant proportion of patients (13%) were excluded from the study. In this study FFR_{CT} achieved better accuracy 81% and specificity 79%, similar sensitivity 86% and negative predictive value 93%, but still low positive predictive value 65% compared to the DeFACTO study. In patients with Agatston score >400, FFR_{CT} improved the specificity significantly from 23% to 69% compared to CTCA.[5] In a sub-analysis of the NXT trial patients were divided into groups according to the Agatston score. There was no difference in the sensitivity, specificity and diagnostic accuracy of FFR_{CT} across the different groups, and FFR_{CT} performed significantly better compared to CTCA even in highly calcified coronary lesions.[6]

The use of FFR_{CT} has also been assessed in high-risk patients with predominantly stable angina and complex CAD (left main stem or 3-vessel disease) in the recently

published Syntax III Revolution trial. Two heart teams were randomised to decide between coronary artery bypass grafting and percutaneous coronary intervention based on patient's clinical information and coronary anatomy (Syntax score- SS), assessed either by invasive coronary angiography or CTCA. FFR_{CT} analysis was available in 88% of patients. Although the agreement on the anatomical SS between invasive angiography and CTCA was only moderate (likely due to the inherent overestimation of calcified lesions by CTCA), the final agreement on the revascularisation plan was good when clinical information and functional assessment (FFR_{CT}) of the stenotic lesions were added.[7]

ii) Comparison with non-invasive functional imaging

There are no studies as yet directly comparing the diagnostic accuracy of FFR_{CT} with other non-invasive modalities (SPECT, stress echocardiography and cardiac MRI). However, the number of invasive angiographies, revascularisations and MACE (death, non-fatal myocardial infarction and hospitalisation with urgent revascularisation) between a CTCA with FFR_{CT} versus the usual non-invasive strategy (CTCA alone, SPECT, stress echocardiography and cardiac MRI) were compared in the PLATFORM study. In a low-intermediate risk population (pre-test probability approximately 50%) there was no difference in MACE or the number of invasive catheterisations with non-obstructive disease between the two strategies.[8]

Radiation dose

The radiation dose is the same with the standard CTCA as there isn't a requirement for additional images. A minimum of a 64-slice scanner is necessary for the FFR_{CT} analysis. Due to the significant progress in the scanner technology and the ability to image the heart in a single heartbeat, the effective dose of the CTCA is currently lower than conventional angiography (5mSv versus 10mSv respectively) confirming the increasing safety of the test.[7] However in the PLATFORM study where FFR_{CT} was used as an adjunct to a pre-planned invasive or non-invasive strategy to investigate chest pain, the addition of FFR_{CT} in those already undergoing a non-invasive diagnostic strategy resulted in a significant increase in radiation exposure, albeit of comparable magnitude to that received with invasive angiography.[8]

Cost

The Heartflow analysis costs £700 per test on the top of the CTCA cost (£122). Although the cost of invasive angiography with FFR or intervention exceeds that of FFR_{CT} (coronary angiography £1,685 and PCI £2,865), other non-invasive tests are significantly cheaper- the cost of a stress echocardiogram is £271, SPECT £367 and MRI perfusion scan £515.[3]
When compared to an invasive diagnostic strategy, FFR_{CT} results in a significant cost saving, however it is associated with higher costs when compared to a single non-invasive test (CTCA without FFR_{CT}, stress echocardiography, MRI or SPECT) as shown

in the 90-days and 1-year analysis of the PLATFORM study. The difference in cost in both cases was derived from the difference in number of invasive procedures and the subsequent medical care (dual antiplatelet therapy, statin).[9,10]

Discussion

The use of CTCA in patients with chest pain may answer the question for presence of CAD but not for associated ischaemia, and therefore the correlation of the CAD finding with the patient's presentation is weak. The arrival of FFR_{CT} is promising and introduces a non-invasive method of combined anatomical and functional assessment. The radiation exposure is the same as conventional CTCA, and technological advance is progressively improving this.

The DeFACTO and NXT trial have shown that the sensitivity and specificity of the technique is improving as the software improves, and as expected is very much reliant on the quality of the CTCA scan performed. Similarly the inherent relatively low positive predictive value of the technique can be improved when stricter quality criteria are followed, even when applied to a lower prevalence population (the proportion of patients with FFR ≤0.80 in the DeFACTO study was 52% and the NXT trial 32% but the positive predictive value was similar in both, likely due to the difference in the CTCA quality).[4,5]

When compared to CTCA, FFR_{CT} adds to the diagnostic accuracy of the test and can be particularly helpful in cases with raised Agatston score where the specificity of CTCA is low. As the role of CTCA expands to a higher risk population, with more coronary calcification, FFR_{CT} will play an important role in reducing the relatively high false positive rate. Furthermore FFR_{CT} has the potential to be the only modality used in the evaluation of a high-risk population, and not only provide the diagnosis but also guide the revascularisation strategy. A randomised controlled trial (CABG Revolution) is currently designed to test the above.

Therefore a CTCA/FFR_{CT} diagnostic pathway compares sufficiently with an invasive strategy in terms of outcomes, cost efficiency and possibly influence on decision-making. The associated cost savings led NICE to publish guidelines favouring CTCA/FFR_{CT} as first line approach. However there is no data showing superiority of FFR_{CT} either in terms of outcomes or cost-efficiency with other non-invasive modalities. Both PROMISE and SCOT-HEART have suggested there is no difference in outcomes between a CTCA and a functional imaging strategy.[11,12] It remains unclear if the latter also applies to FFR_{CT} and what the relevant cost implications would be.

Conclusions

The diagnostic accuracy of FFR_{CT} (performed in addition to CTCA) has improved rapidly over the last decade and its role is expanding beyond the diagnosis of CAD in the low-intermediate risk population to the assessment of high-risk patients. Although it demonstrates promising results when compared to invasive coronary angiography, a clear benefit over other non-invasive strategies has not been established and further studies are required.

References

1. National Institute of Health and Care Excellence. Chest pain of recent onset. Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. *NICE CG95*, (2010).
2. National Institute for Health and Care Excellence. Chest pain of recent onset: assessment and diagnosis. *NICE CG95*, (2016).
3. National Institute for Health and Care Excellence. HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography. Medical technologies guidance. *NICE MTG 32*, (2017).
4. Min JK, Leipsic J, Pencina MJ *et al.* Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA*, 308(12), 1237-1245 (2012).
5. Nørgaard BL, Leipsic J, Gaur S *et al.* Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *J Am Coll Cardiol*, 63(12), 1145-1155 (2014).
6. Nørgaard BL, Gaur S, Leipsic J *et al.* Influence of Coronary Calcification on the Diagnostic Performance of CT Angiography Derived FFR in Coronary Artery Disease: A Substudy of the NXT Trial. *JACC Cardiovasc Imaging*, 8(9), 1045-1055 (2015).
7. Collet C, Onuma Y, Andreini D *et al.* Coronary computed tomography angiography for heart team decision-making in multivessel coronary artery disease. *Eur Heart J*, 39(41), 3689-3698 (2018).
8. 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*, 36(47), 3359-3367 (2015).
9. Hlatky MA, De Bruyne B, Pontone G *et al.* Quality-of-Life and Economic Outcomes of Assessing Fractional Flow Reserve With Computed Tomography Angiography: PLATFORM. *J Am Coll Cardiol*, 66(21), 2315-2323 (2015).
10. Douglas PS, De Bruyne B, Pontone G *et al.* 1-Year Outcomes of FFRCT-Guided Care in Patients With Suspected Coronary Disease: The PLATFORM Study. *J Am Coll Cardiol*, 68(5), 435-445 (2016).
11. Douglas PS, Hoffmann U, Patel MR *et al.* Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med*, 372(14), 1291-1300 (2015).
12. SCOT-HEART investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet*, 385(9985), 2383-2391 (2015).