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IS FFRCT READY FOR PRIME TIME: HAS NICE BEEN TOO NICE?

Jonathan William Hinton[1], **Nick Curzen**[2]

[1]Department of Cardiology University Hospital Southampton, Southampton-UK

[2]Faculty of Medicine, University of Southampton, Southampton-UK

Address for Correspondence:

Nick Curzen

Faculty of Medicine, University of Southampton, Southampton- UK

Email: jonathan.hinton@uhs.nhs.uk

Date Received: November 08, 2016
Date Revised: February 27, 2017
Date Accepted: March 05, 2017

Contribution

JWH, NC instigated the original idea and guided revisions of the manuscript. Both authors contributed significantly to the submitted manuscript.

Conflict of Interest

Research grants and speaker fee: Heart flow, Boston scientific, Haemonetics.

This article may be cited as: Hinton JW, Curzen N. Is ffrct ready for primetime: has nice been too nice?. Pak Heart J 2017; 50 (02): 57-64.

ABSTRACT

Chest pain is a common presentation with the potential to represent important underlying coronary artery disease. A timely and accurate diagnosis is therefore of paramount importance from both a prognostic perspective and to plan appropriate treatment for relief of symptoms. The current investigative algorithms proposed in major international guidelines recommend either using a test to assess coronary anatomy or a test of ischaemia. Each of these strategies individually does not provide the clinician with the whole picture. We review the potential of a novel technique that provides both anatomical and functional data by using fluid dynamics to analyse the data acquired at the time of CT coronary angiography to calculate the fractional flow reserve non-invasively.

Key Words: FFRCT; coronary artery disease; chest pain

INTRODUCTION

Ischaemic heart disease is amongst the leading causes of death globally.[1] However in both the UK and USA the mortality for ischaemic heart disease has fallen, with around half of this reduction due to better treatment and the other half as a result of risk factor modification, primarily smoking cessation.[2] Indo-Pakistani populations in particular have one of the highest incidences of ischaemic heart disease in the world.[3] Chest pain makes up 1% of all presentations to primary care, of which between 8 and 18% will have a cardiac cause.[4] The timely and accurate diagnosis of coronary artery disease (CAD) is therefore of paramount importance from both a prognostic perspective and to plan appropriate treatment for relief of symptoms. The scale of this problem combined with the consequences of an incorrect diagnosis highlight the importance of having access to a safe, accurate and cost effective diagnostic test to diagnose significant CAD.

DIAGNOSIS OF CORONARY ARTERY DISEASE

There is uncertainty about the optimal algorithm with which to assess patients presenting with chest pain that might represent significant underlying CAD. This is reflected in the variation in advice given by different international guidelines. The European, British and American guidelines all recommend an initial history and risk factor evaluation to exclude the very low risk population. Each society then has different suggestions about the most appropriate further diagnostic tests in higher risk groups. The contention centres around whether the anatomy (most importantly presence of coronary atheroma) or the presence of inducible myocardial ischaemia (IMI) are more useful to guide a diagnosis and subsequent management in patients with different pre-test probabilities of having coronary artery disease.

ANATOMICAL TESTING

Identification of the presence of coronary atheroma and its severity and distribution is extremely useful. The presence of any significant atheroma even when clearly unobstructive, is an indication for the use of disease modifying medical therapy which has been shown to alter the medium to long term course of this disease process. [5] An understanding of the presence of potentially flow-limiting lesions is also important when considering the need for revascularisation. Invasive coronary angiography (ICA) and CT coronary angiography (CTCA) both give detailed information regarding coronary anatomy and the presence of atheromatous disease.

ICA is performed routinely around the world for assessment of potential CAD in patients presenting with chest pain but is associated with a small but significant risk of serious complication, between 0.5 and 2%.[6] Given that the majority of patients referred for ICA are not found to have obstructive coronary artery disease there are a large number of patients undergoing ICA who are put at the risk of the procedure where another test may provide the same reassurance without exposing the patient to undue risk.[7-9] In patients where CAD is found there is increasing evidence that this does not provide an indication for revascularisation unless the lesion is causing myocardial ischaemia. [10-14] This is because the angiographic severity of a lesion does not correlate closely with whether it is causing ischaemia.[10,15,16] It can therefore be difficult to interpret the results of ICA without evidence of IMI.

CTCA has the benefit of providing anatomical data without the risk of ICA and with steadily reducing radiation doses. The PROMISE study demonstrated the comparability of outcomes when CTCA was used to assess patients presenting with chest pain compared with functional imaging.[9] CTCA was however associated with 50% more referrals for ICA and a higher revascularisation rate but with no associated difference in outcome data.[9] This lack of outcome difference despite increased revascularisation may well be explained by the fact that there was rarely evidence of ischaemia driving revascularisation in the CTCA group. That said, this study and the SCOT HEART study both demonstrate the diagnostic value of CTCA.[17] As a result of this data the National Institute for Health and Care Excellence (NICE) have recently updated their guidelines to use CTCA as the first line test in the majority of patients presenting with stable chest pain.[18] The potential weakness of this strategy is that it does not provide evidence of IMI.

FUNCTIONAL TESTING

Testing for IMI provides a physiological assessment of the impact of any coronary disease: specifically whether it is causing significant limitation to myocardial perfusion. The presence and relative portion of myocardium that has IMI is closely associated with the risk of acute myocardial infarction (AMI) in the near term and also acts as a guide to those patients most likely to benefit in terms of symptoms and prognosis from revascularisation.[11,14,19] The three main functional tests available are stress echo, stress cardiac MRI and myocardial perfusion scanning. The availability of each of these often depends on local expertise and equipment. Each of these functional tests has certain limitations associated with it. A negative test of IMI is clearly reassuring but as it only tests for IMI there will be a portion of patients who have non-obstructive CAD who are falsely reassured. This is of particular importance given that disease-modifying strategies including medical therapy and life style changes provide a considerable prognostic benefit in the patient with non-obstructive CAD. Therefore a negative test of IMI is potentially a missed opportunity to intervene at an early stage in patients with non-obstructive coronary artery disease. Further, confirmation of IMI provides a clear mandate for revascularisation as a symptomatically and

prognostically beneficial intervention.[20]

HOW CAN WE HAVE BOTH CORONARY ANATOMY AND PHYSIOLOGY?

The ideal screening test for patients presenting with new onset chest pain would have the ability to assess for both the presence and distribution of CAD combined with an assessment of IMI. This would allow for accurate reassurance, directed optimal medical therapy and appropriate ischaemia-guided, lesion-specific revascularisation. Given the number of patients presenting to services with chest pain this ideal test would also need to be accessible, cost effective and safe.

It is of course possible to perform both a test of anatomy and IMI separately but this clearly is associated with significant resource implications and is less convenient for both the patient and the healthcare provider. ICA is commonly combined with pressure wire assessment to ascertain the fractional flow reserve (FFR) which is a measure of the relative restriction in blood flow caused by a lesion during maximal hyperaemia. This gives both an anatomical and functional assessment of CAD. This invasive strategy is well supported by literature with both FAME and DEFER demonstrating that PCI to a lesion that is angiographically severe but pressure wire negative is associated with a worse outcome than optimal medical therapy.[15,21] FAME 2 supported the subsequent logic that PCI to a pressure wire positive lesion is associated with better outcomes.[10] This is reinforced by both the RIPCORD study and a recent meta analysis demonstrating that the availability of pressure wire results at ICA changed the management plan in 22% - 48% of patients who had presented with chest pain.[16,22] This mismatch between visual assessment of an angiographic lesion severity and functional significance of the lesion at pressure wire reinforces the need for a test that can provide both anatomical and functional data.

Given that there is good data that supports the validity of using pressure wire at the time of ICA it could be suggested that this strategy is the optimal way of assessing patients presenting with chest pain, particularly as this then allows the option for PCI at the same sitting. On the other hand it is important to consider that there are a number of problems with adopting this approach. ICA with pressure wire is associated with a small but important risk of serious complication and therefore exposing all the patients who need a further test to evaluate their chest pain would be inappropriate. There is also an important access issue given that there are a limited number of operators able to perform pressure wire assessment. Given the large number of ICAs performed, a significant proportion of ICA are performed by non-interventional cardiologists. If the new standard was to perform pressure wire assessment in all ICAs then these would need to be performed by interventional cardiologists. This is likely to overwhelm resources. Furthermore, despite the persuasive and extensive body of randomised trial data supporting FFR use the uptake of this technology in routine clinical practice remains surprisingly low.

As discussed, the combination of ICA and pressure wire is not the ideal solution for logistical, cost and risk issues, so there is a clear place in routine practice for a non-invasive test that combines both anatomical data and functional data. The combination of CTCA with a functional assessment therefore would seem to be the most obvious candidate. A novel technique of applying computational fluid dynamics to the data acquired at the time of CTCA allows calculation of the FFR non-invasively (FFR_{CT}).[23-25] This development has exciting potential.

THE TEST

FFR_{CT} can be performed on standard CTCA datasets (64 slice or higher) without the need for additional images or changes to the imaging protocol and allows lesion-specific assessment of FFR (see image).[25] The CTCA data set is sent to the central processing centre in the United States where an analyst creates three-dimensional models including flow characteristics.[26] This information is then relayed to the supervising clinician within 24 hours.

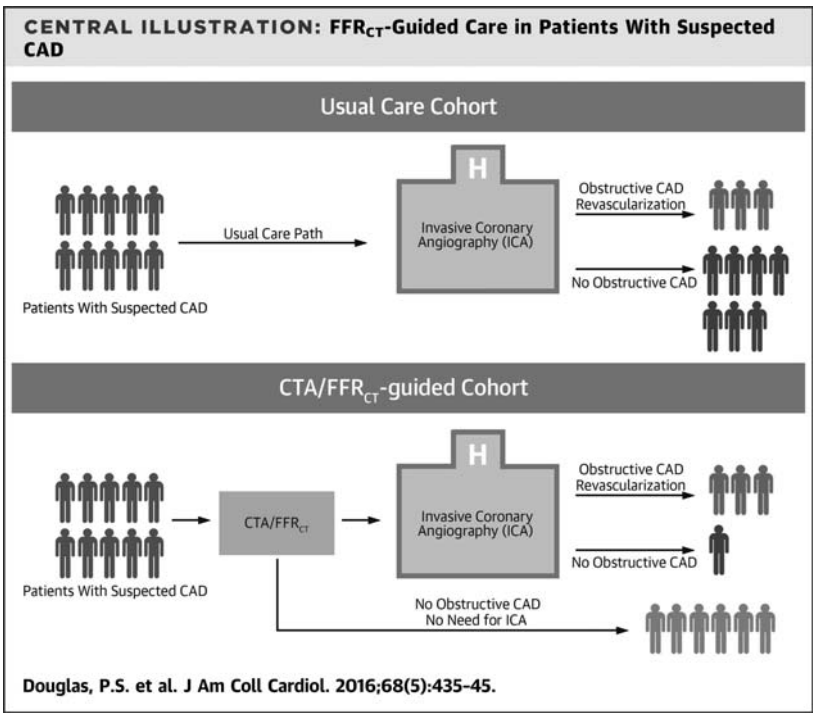
Two recent validation studies involving over 350 patients in total demonstrated significantly improved accuracy in the assessment of CAD with FFR_{CT} compared with CTCA alone, using ICA with FFR as the reference.[23,25] There was good correlation between FFR_{CT} and FFR at ICA (using a threshold of <0.8 at ICA) in both studies, although there was a tendency to underestimation of the FFR from FFR_{CT}.[23,25] However the area under the receiver operator curve was 0.9 in both studies compared with CTCA of 0.81 ($p=0.0008$) in NXT and 0.75 ($p=0.001$) in DISCOVER-FLOW with an invasive FFR of $\leq$ 0.8 as the reference.[23,25] Table 1 demonstrates the improved accuracy, specificity and positive predictive value of FFR_{CT} compared with CTCA from both studies. Importantly the negative predictive values were not significantly different, which is reassuring as this was one of the strengths of CTCA. It is noteworthy that in the NXT study, 13% of patients were deemed to have a CTCA that was not suitable for FFR_{CT} due to image quality.[23] It is likely that this portion will reduce with improvements in both the FFR_{CT} technology and in CT scanners.[23]

More recently the multicentre PLATFORM study recruited 584 patients with new onset chest pain and prospectively assigned them to either standard care or FFR_{CT}. The primary end point was the proportion of ICA performed within 90 days where no obstructive CAD was found (obstructive CAD was defined as either $\geq$50% luminal stenosis or FFR $\leq$0.8). In patients in whom ICA was deemed standard care, no obstructive coronary artery disease was found in 12% in the FFR_{CT} arm and 73% in the usual care arm ($p<0.0001$) with a

Table 1: Comparison of Diagnostic Performance Per Patient of CT_{FFR} with CTCA in Both the NXT and DISCOVER-FLOW Studies

	NXT		DISCOVER-FLOW	
	CT_{FFR}	CTCA	CT_{FFR}	CTCA
Accuracy	81	53	87	61
Sensitivity	86	94	92	94
Specificity	65	40	82	25
Positive predictive value	65	40	85	58
Negative predictive value	93	82	91	80

Figure 1: Graphical Representation on the Impact of FFR_{CT} on the Assessment of Patients Presenting with New Onset Chest Pain (Reproduced with Permission from 27)



similar cumulative radiation exposure.[27] Specifically when the results of FFR_{CT} were known ICA was deemed unnecessary in 61%.[27] Further, despite significantly less ICA, there was no price to pay in terms of increased clinical event rates in the FFR_{CT} group in whom ICA was deferred.[27] There was no difference in the finding of obstructive coronary artery disease in patients where planned functional non-invasive testing was performed compared with CT_{FFR}.[27] It has been suggested that this demonstrates that CT_{FFR} is not advantageous compared with functional non-invasive testing.[28] On the other hand, as previously discussed a negative test of IMI does not mean that there is no CAD, whereas FFR_{CT} will also give data about non-obstructive CAD which provides an opportunity to intervene with disease modifying medical therapy and lifestyle modification. The study concluded that FFR_{CT} was a safe and feasible alternative to ICA and was associated with a significantly lower rate of subsequent ICA showing no obstructive CAD.[27] As demonstrated in previous studies the PLATFORM study also found a small but important proportion of CTCA datasets (10%) where the image quality was inadequate to calculate CT_{FFR}.[27]

The PLATFORM group also had a pre-specified one year

follow up to assess the impact on quality of life (QOL), clinical outcomes and economic impact of FFR_{CT} compared with standard care alone. Major adverse cardiac events were infrequent, with no difference in the groups. [29] The costs within the planned invasive stratum were 33% lower with FFR_{CT} compared with standard care ($8,127 vs $12,145, $p<0.0001$). [29] In the planned non-invasive stratum there was no significant difference in the costs ($3,049 vs $2,579 $p=0.82$) (Figure 2). [29] The QOL indices improved across all groups and were similar in patients in the usual care groups

Figure 2: One year Costs by Stratum and Evaluation Strategy

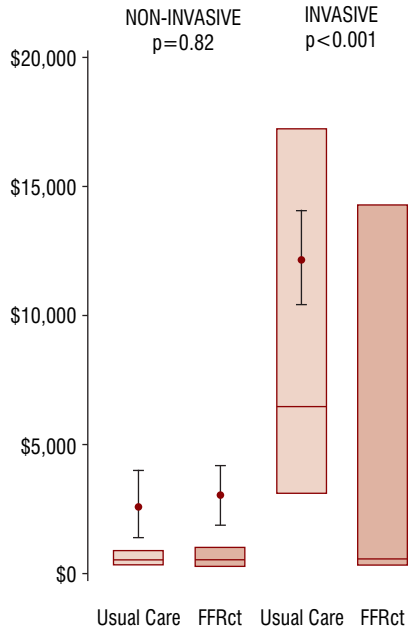
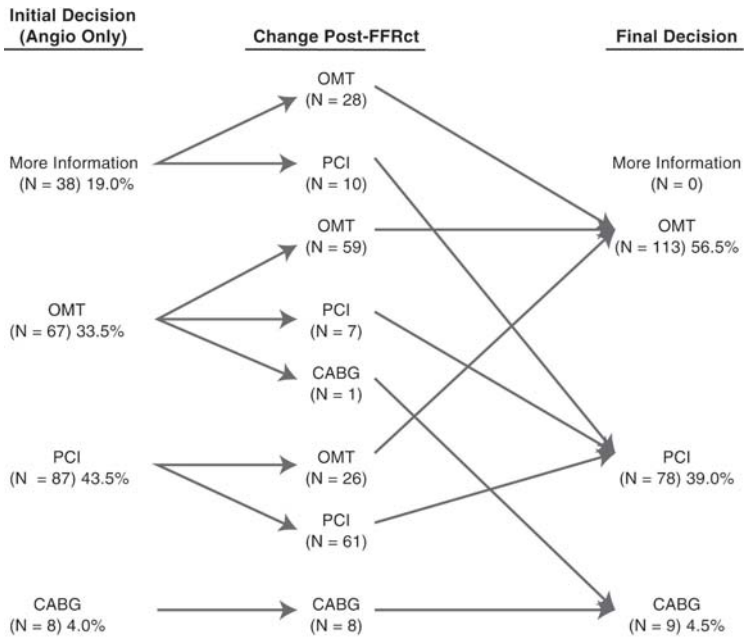


Figure 3: Breakdown of Management Allocations by CTCA Data Alone and after FFRCT Data Available (reproduced with permission from 30)



and the FFR_{CT} groups . This one year follow up adds more encouraging data to support the role of FFR_{CT} as being a safe, accurate, cost effective investigation in patients presenting with stable chest pain.

In the FFR_{CT} RIPCORD, Curzen et al assessed the effect of knowing the FFR_{CT} data on top of CTCA alone on lesion interpretation and subsequent management in 200 cases from the NXT cohort. [30] There was a change in the allocated management category in 36% of cases (Figure 3). This difference was due to discordance between CTCA and FFR_{CT} derived assessments of lesion severity. These data are entirely consistent with the difference in estimates of lesion severity and consequent management when invasive FFR is added to angiographic data alone, including the original RIPCORD study. [16]

TIME FOR FFRCT FOR ALL PATIENTS WITH STABLE CHEST PAIN

Whilst the concept and early data are suggestive that FFR_{CT} could be a default test in patients presenting with new onset chest pain, further evidence are required before this dramatic shift in the investigative algorithm should become the routine in both clinical practice and international guidelines. This concept is due to be tested in the upcoming randomised FORECAST trial in the UK. [31] There are also a number of practical barriers to consider before this technique can become the routine investigation. Whilst CT scanners are common, access to the subspecialist equipment, techniques and expertise required for CTCA can be limited. However, NICE has recently revised its CG95 guidance on management of patients with recent onset chest pain. [18] In this new guideline, the majority of patients will be committed to CTCA as the dominant test. This guideline guarantees that a fundamental alteration in the infrastructure for such patients will be required throughout the UK, with the introduction of new CT scanners and experts to report the CTCA. At the same time, NICE has recently produced a Technology evaluation of FFR_{CT} and has recommended that it represents an option for assessment of such patients. [26] However, a NICE guideline to recommend FFR_{CT} will require randomised trial data, such as those that will be made available in the FORECAST trial. By the time that this trial reports its results, the UK infrastructure will have changed substantially.

CONCLUSION

Given the importance of ischaemia in the decision making about revascularisation, and the value of disease-modifying medication on the prognosis of patients with coronary atheroma, a screening test of patients presenting with chest pain the provides anatomy and physiology non-invasively would be of substantial clinical value. The observational data available suggest the FFR_{CT} may well represent a leading candidate for this role, although randomised trial data are now required.

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