Fractional Flow Reserve Measurement by Computed Tomography: An Alternative to the Stress Test

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Abstract

Recent advances in computed tomographic technology have contributed towards improving coronary computed tomography angiography (CCTA) in determining the severity of coronary artery disease anatomically. Although the viability of CCTA has most often been confined to anatomical assessment, recent development has enabled evaluation of the haemodynamic significance of coronary artery disease. In light of this, CCTA-derived fractional flow reserve (FFR_{CT}), a novel imaging modality, now permits the physiological assessment of coronary artery disease. To date, several studies have documented the diagnostic performance of FFR_{CT}, and more trials are being performed that will further substantiate this technique. The present paper provides an overview and discussion of the available evidence for FFR_{CT} in the clinical setting as well as potential future directions of FFR_{CT}.

Keywords

Coronary computed tomography angiography, coronary artery disease, fractional flow reserve, stress imaging test

Disclosure: JKM has served as a consultant or on the medical advisory boards for GE Healthcare, HeartFlow Inc, and Arineta Ltd; and has received research support from GE Healthcare. JHL, BóH, DH, AR and FL have no conflicts of interest to declare.

Acknowledgements: This study was supported by the National Institutes of Health (Bethesda, Maryland) under award numbers R01 HL111141 and R01 HL118019. This study was also funded, in part, by a generous donation from the Dalio Institute of Cardiovascular Imaging (New York, NY) and the Michael Wolk Foundation (New York, NY).

Received: 18 December 2015 **Accepted:** 31 May 2016 **Citation:** *Interventional Cardiology Review*, 2016;**11**(2):105–9 DOI: 10.15420/icr.2016:1:2

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Coronary computed tomography angiography (CCTA) is a non-invasive tool capable of directly visualising the coronary anatomy with high sensitivity and negative predictive value (NPV) for coronary artery disease (CAD) compared to invasive coronary angiography (ICA).^{1,2} Recent innovations in computed tomography (CT) technology have led to the rapid development of CCTA and its selection as an anatomic alternative to stress imaging.³ Despite this, CCTA alone cannot independently determine the haemodynamic significance of coronary stenosis, as compared with stress imaging, due to the low specificity for identifying coronary stenoses that induce ischaemia.⁴ This emphasises the unpredictable relationship between stenosis severity and ischaemia, which may provoke the need for unnecessary ICA in patients who do not have ischaemia.⁵ For instance, patients undergoing CCTA with an intermediate lesion requiring ischaemia evaluation may have layers of additional testing, such as stress echocardiography, myocardial perfusion imaging by single-photon emission computed tomography, positron emission tomography or cardiac magnetic resonance image.⁶

Fractional flow reserve (FFR), defined as the ratio of maximum flow in a stenotic artery to maximum blood flow if the same artery were normal, is an invasive technique to determine lesion-specific ischaemia and can assist in guiding coronary revascularisation.^{7,8} Notably, in the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trial, the use of FFR to guide coronary intervention compared with ICA guidance resulted in a 33 % reduction in major adverse cardiac

events.⁹ Recent advances in computational fluid dynamics enable the calculation of CCTA-derived FFR (FFR_{CT}) from three-dimensional imaging anatomic models. Foremost, FFR_{CT} reflects a novel imaging modality with the ability to determine the haemodynamic significance of CAD without additional radiation exposure or contrast injection beyond the initial CCTA (see *Figure 1*). This review provides an overview of current evidence describing the appropriate use of FFR_{CT} in the clinical setting, along with a discussion of the potential future directions of FFR_{CT}.

Clinical Usefulness of FFR

FFR has been utilised to assess physiological function at the time of ICA in the cardiac catheterisation laboratory. The former procedure provides a reliable physiological index for determining whether coronary stenosis may cause ischaemia by measuring flow with a coronary guidewire before and after a visualised stenosis during maximal hyperaemia.¹⁰ A common definition of FFR is the maximal blood flow to the myocardium in the presence of a stenosis in the supplying coronary artery divided by the theoretical normal maximal flow in the same distribution.⁷ In current guidelines, an FFR value ≤ 0.80 is widely considered the threshold for revascularisation.

Numerous studies have confirmed the clinical benefit of utilising FFR in clinical practice.^{9,11–15} Revascularisation in the coronary arteries with a measured FFR of ≤ 0.80 was associated with improved prognosis, including a reduction in death rates, non-fatal myocardial infarction and urgent revascularisation when compared with ICA-

Figure 1: Example Case of Coronary Computed Tomography Angiography (CCTA)

A 69-year-old Caucasian man with exertional angina underwent CCTA. (A) Multiplanar reformat of CCTA demonstrates a severe stenosis in the proximal left anterior descending artery (LAD)*, a moderate stenosis in the middle of the LAD, and a moderate to severe stenosis in the proximal of the left circumflex artery (LCx) without specific lesion in the right coronary artery (RCA). (B) The coronary computed tomography angiography-derived fractional flow reserve (FFR_{CT}) values of the LAD, LCx and RCA are 0.74, 0.66 and 0.91, respectively (normal >0.8). Values of the LAD and LCx indicate significant ischaemia.

guided revascularisation alone or optimal medical therapy alone.^{16,17} Further still, Pijs et al. demonstrated in the DEFER trial that 5-year outcomes, and even 15-year outcomes, following deferral of percutaneous coronary intervention in the vessel of an intermediate coronary stenosis based on FFRs of ≥ 0.75 demonstrated excellent prognoses.^{11,18} In light of previous findings, current guidelines advocate a FFR-guided revascularisation strategy as a Class IA recommendation for identifying haemodynamically-relevant coronary lesions in stable patients, especially when non-invasive testing evidence of ischaemia is not available.¹⁹

Diagnostic and Clinical Performance of FFR_{CT}

To date, three prospective multicentre trials, namely the Diagnosis of Ischemia-Causing Stenoses Obtained via Non-invasive Fractional Flow Reserve (DISCOVER-FLOW),²⁰ Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (DeFACTO)²¹ and analysis of Coronary Blood Flow Using CT Angiography: Next Steps (NXT)²² studies, have evaluated the diagnostic performance of FFR_{CT} compared with invasive FFR as a reference standard. These studies are summarised in Table 1.

The DISCOVER-FLOW study was the first multicentre trial that assessed the diagnostic performance of FFR_{CT} against ICA and invasive FFR. It included 103 patients with 159 measured coronary vessels from four

sites in the United States, Europe and Asia.²⁰ Anatomical obstruction was defined as a CCTA with stenosis $\geq 50\%$, and either FFR ≤ 0.80 or FFR_{CT} ≤ 0.80 was defined as ischaemia. In this study, both FFR_{CT} and FFR correlated well on a per-vessel analysis according to Spearman's rank correlation, reporting a coefficient of 0.72 ($p < 0.001$). Further, utilising FFR_{CT} on a per-vessel analysis revealed a diagnostic accuracy of 84.3 %, sensitivity of 87.9 %, specificity of 82.2 %, positive predictive value (PPV) of 73.9 %, and NPV of 92.2 %. The results did not differ materially on a per-patient analysis. Conversely, the accuracy, specificity and PPV were 58.5 %, 39.6 % and 46.5 %, respectively, based on a per-vessel analysis of CCTA; while a per-patient analysis demonstrated an accuracy of 61.2 %, specificity of 24.5 % and PPV of 58.0 %, respectively, according to CCTA. The area under the receiver operating characteristic curve (AUC) was 0.90 for FFR_{CT}, which was superior to CCTA, which had an AUC of 0.75 ($p = 0.001$), indicating a significant improvement in the discrimination of ischaemia.

The DeFACTO trial included 252 patients across 17 centres in five countries with the measurement of 407 coronary vessels. It was conducted to determine the accuracy of FFR_{CT} in comparison with invasive FFR as a gold standard for the diagnosis of haemodynamically-significant coronary stenosis.²¹ On a per-patient analysis, FFR_{CT} was superior in detecting ischaemia when compared with CCTA according to diagnostic accuracy (73 versus 64 %), sensitivity (90 versus 84 %), specificity (54 versus 42 %), PPV (67 versus 61 %) and NPV (84 versus 72 %), respectively. In a patient-based analysis restricted to those presenting with intermediate stenosis (i.e. 30–70 % stenosis), sensitivity was significantly higher for FFR_{CT} than for CCTA (82 versus 37 %), without a change in specificity. In addition, FFR_{CT} displayed superior discrimination for ischaemia based on a per-patient as well as per-vessel analysis when compared with CCTA, with improved AUCs (0.81 versus 0.68 and 0.81 versus 0.75, respectively; $p < 0.001$ for all). Though DeFACTO was unable to meet its pre-specified primary outcome, which was a per-patient diagnostic accuracy lower bound 95 % confidence interval no worse than 70 %, the utilisation of non-invasive FFR_{CT} plus CT among stable patients demonstrated improved diagnostic accuracy as well as discrimination in comparison with CT alone for the diagnosis of haemodynamically-significant CAD.²³

Most recently, the prospective multicentre NXT trial evaluated the diagnostic performance of FFR_{CT} in 254 patients, with 484 vessels being studied.²² On a per-patient analysis, diagnostic accuracy, specificity and PPV were markedly higher for FFR_{CT} (81 %, 79 % and 65 %, respectively) versus CCTA (53 %, 34 % and 40 %, respectively) ($p < 0.001$, for all). Similarly, on a per-vessel analysis the accuracy, specificity and PPV were 86 %, 86 % and 61 %, respectively, for FFR_{CT} compared with CCTA (65 %, 60 % and 33 %, respectively) ($p < 0.001$, for all), without disparity in sensitivity (84 versus 83 %). In the same study, a subgroup analysis among patients with intermediate stenosis severity (i.e. 30–70 % stenosis) demonstrated that FFR_{CT} was superior to CCTA on a per-patient level, with better accuracy (80 versus 51 %), specificity (79 versus 32 %) and PPV (63 versus 37 %) ($p < 0.001$, for all) observed. Moreover, the AUCs for FFR_{CT} on a per-patient and per-vessel basis were 0.90 and 0.93 versus 0.81 and 0.79 for CCTA, respectively ($p < 0.001$ for all), indicating superior discrimination for ischaemia on the background of FFR_{CT}. In summary, findings from the NXT multicentre trial support the contention that adding FFR_{CT} to CCTA might provide a more comprehensive anatomical and physiological assessment of CAD.

Table 1: Summary of Diagnostic Accuracy Studies of Coronary Computed Tomography Angiography-derived Fractional Flow Reserve

Study	Authors (year)	N (sites)	Vessel Size for Inclusion (mm)	Reference Standard (fraction flow reserve)	Diagnostic Performance (%)							
					Per-patient Analysis				Per-vessel Analysis			
					Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
DISCOVER-FLOW ²⁰	Koo et al. (2011)	103 (4)	≥2.0	≤0.80	93	81	85	91	88	82	74	92
DeFACTO ²¹	Min et al. (2012)	252 (17)	≥1.5	≤0.80	90	54	67	84	83	78	–	–
NXT ²²	Nørgaard et al. (2014)	251 (10)	≥2.0	≤0.80	86	79	65	93	84	86	61	95

DISCOVER-FLOW = Diagnosis of Ischemia-Causing Stenoses Obtained Via Non-invasive Fractional FLOW Reserve; DeFACTO = Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography; NXT = Analysis of Coronary Blood Flow Using CT Angiography: Next Steps; PPV = positive predictive value; NPV = negative predictive value.

In previous studies, CT datasets were transferred so software applications could be run, and consequently hours of processing were required before the results were returned to the physician. To this end, recent studies have explored on-site prototype algorithms to compute FFR from CCTA, which in turn may enable a more efficient patient flow and reduce analysing time to within 1 hour.^{24–26} Among these studies, De Geer et al. demonstrated that the sensitivity, specificity, NPV, PPV and accuracy of FFR_{CT} for detecting significant stenosis (FFR≤0.80) were 0.83, 0.76, 0.93, 0.56 and 0.78, respectively, on a per-lesion basis, and displayed a Spearman rank correlation coefficient of 0.77 (p<0.001).²⁶ Although still in its infancy, these investigators have strongly emphasised that this software permits on-site assessment of FFR_{CT} within clinically-practical time frames, and may therefore have the necessary potential to be performed in a clinical setting.

Recently, the Prospective Longitudinal Trial of FFR_{CT}: Outcome and Resource Impacts (PLATFORM) trial compared a FFR_{CT}-guided diagnostic strategy (n=297) with usual care (n=287) in 584 patients with new-onset chest pain and intermediate risk of CAD.²⁷ Usual care was stratified by planned ICA or planned non-invasive testing prior to enrollment. In the planned ICA stratum (FFR_{CT}-guided, n=193; usual care, n=187), ICA was cancelled in 61 % after receiving coronary CTA/FFR_{CT} results, because the rate of non-obstructive CAD by ICA was 12.4 % (n=24) in the coronary CTA/FFR_{CT} arm versus 73.3 % (n=137) in the usual care arm (p<0.001), with similar cumulative radiation exposure and 90 days clinical event rates. This result was similar after applying propensity score matching for 148 patients in each group (e.g. 12 % for CTA/FFR_{CT} versus 72 % for usual care, P<0.001). In the planned non-invasive testing stratum (FFR_{CT}-guided, n=104; usual care, n=100), the rate of non-obstructive CAD by ICA was comparable in both arms (12.5 versus 6.0 %; p=0.95). Overall, there was no significant difference in revascularisation in subjects allocated to CTA/FFR_{CT} compared to usual care in either the planned non-invasive or planned invasive testing arms (p=0.29 and 0.58, respectively). The PLATFORM trial suggests that FFR_{CT} may be a useful and safe gatekeeper to ICA, particularly for reducing the likelihood of normal ICA when used as an alternative diagnostic tool to guide care in patients with planned invasive catheterisation.

Principal Components for Determining FFR_{CT}

The scientific principles for determining FFR_{CT} are described in detail elsewhere.²⁸ In brief, FFR_{CT} utilises a computational fluid

dynamics approach to determine the FFR of three vessels from typically-obtained CCTA images without additional imaging, changes of image acquisition protocols, additional medication or radiation exposure.²⁸ The computational fluid dynamics method enables the quantification of fluid pressure and velocity based on laws of mass conservation and momentum balance, while also solving the equations of human blood flow when applied to CCTA.

Details regarding the steps involved in the calculation of FFR_{CT} have been outlined previously,²³ and are briefly described as follows: 1) the acquisition of CCTA and creation of patient-specific anatomical models; 2) the quantification of total and vessel-specific coronary flow; 3) the calculation of baseline microvascular resistance; 4) the computation of hyperaemic changes in coronary artery resistance; and 5) the application of computational fluid dynamics to calculate coronary flow, pressure and velocity during the stages of rest and hyperaemia. While it can take approximately 8 hours to calculate the results of FFR_{CT}, the majority of FFR_{CT} measurements can generally be calculated within a few hours, and it is anticipated that more advanced techniques in the field of FFR_{CT} will eventually induce a substantial reduction in calculation time.

Further Study of FFR_{CT}

At present, studies related to FFR_{CT} have mostly focused on its diagnostic performance for the determination of ischaemia, and comparisons of FFR_{CT} with other stress imaging tests have not yet been implemented. To this end, several prospective multicentre clinical trials are currently on-going for the purpose of exploring the utility of FFR_{CT} against other more established myocardial perfusion imaging procedures (see Table 2). The upcoming Computed Tomographic Evaluation of Atherosclerotic Determinants of Myocardial Ischemia (CREDENCE) trial aims to evaluate the direct comparison of coronary CTA plus FFR_{CT} with MPI by SPECT or PET (NCT02173275). Moreover, two other multicenter trials, the Dual Energy CT for Ischemia Determination Compared to “Gold Standard” Non-Invasive and Invasive Techniques (DECIDE-Gold)²⁹ and the comparison between stress cardiac computed tomography PERfusion versus Fractional flow rEServe measured by Computed Tomography angiography In the evaluation of suspected cORoNary artery disease (PERFECTION),³⁰ aim to assess the diagnostic power of FFR_{CT} as compared with single/dual-energy CT perfusion stress imaging testing. The results of these trials will undoubtedly spark further interest in the clinical utility of FFR_{CT}.

Table 2: On-going Prospective Multicentre Trials for Coronary Computed Tomography Angiography-derived Fractional Flow Reserve (FFR_{CT})

Study	N	Study Objectives
CREDENCE	618	Assessment of coronary computed tomography angiography plus FFR _{CT} versus myocardial perfusion imaging by single-photon emission computed tomography or positron emission tomography
PERFECTION ³⁰	300	Assessment of FFR _{CT} versus rest/stress single-energy computed tomography perfusion imaging
DECIDE-Gold ²⁹	156	Assessment of FFR _{CT} versus rest/stress dual-energy computed tomography perfusion imaging

CREDENCE = Computed tomographic Evaluation of atherosclerotic dEterminants of myocardial isChemia; DECIDE-Gold = Dual Energy CT for Ischemia Determination Compared to 'Gold standard' non-invasive and invasive techniques; PERFECTION = comparison between stress cardiac computed tomography Perfusion Versus Fractional Flow Reserve Measured by Computed Tomography Angiography in the Evaluation of Suspected Coronary Artery Disease.

Current Limitations of FFR_{CT}

Despite the recent approval of FFR_{CT} by the US Food and Drug Administration for routine use in patients without known CAD in the clinical setting, there remain several considerations relative to FFR_{CT} that should be emphasised. Foremost, impaired image quality is capable of affecting the susceptibility of FFR_{CT}. This infers that significant motion, beam-hardening from calcified lesions and artefacts from irregular breathing can affect image quality. Moreover, irregular and/or high heart rate, as well as a high body mass index, can further impair the quality of CT images. Further, several important factors are required to determine the accuracy of FFR_{CT}, including the mathematical models related to coronary flow, lumen size, vessel resistance and potential variation in the hyperaemic response.⁶ To date, the extant literature has mostly focused on data from patients with an intermediate risk of CAD in contrast to those with a high pre-test probability for whom performing ICA is typically mandatory in light of the time-consuming process of FFR_{CT}. To this end, although the computation of FFR_{CT} often takes several hours, forthcoming innovative iterations improve this limitation.²³ At present, whether the impact of FFR_{CT} is influenced by symptom typicality remains to be elucidated, and underlines the importance of future studies to examine the connection between FFR_{CT} and symptom typicality. Although previous studies have demonstrated positive results in terms of diagnostic performance, we may add that FFR_{CT} might not reliably reproduce the data obtained when using invasive FFR. To this end, the most recent NXT trial using the latest version of computational fluid dynamics demonstrated a PPV of only 65 % based on per-patient analysis. As such, additional studies are warranted to reliably determine the clinical performance of FFR_{CT} for detecting significant lesion ischaemia. In

addition, the performance of FFR_{CT} is not yet indicated in patients with a prior history of coronary artery bypass surgery or percutaneous coronary intervention with suspected in-stent restenosis. Forthcoming studies will advance our understanding through utilising further FFR_{CT} development, including automated segmentation methods, machine-learning techniques and the refinement of the boundary conditions that underlie the FFR_{CT} technology, thereby hopefully addressing the limitations of this method.²³

Future Directions for FFR_{CT}

Several potential studies should be considered in future research that utilises FFR_{CT}. Beyond improved diagnostic accuracy, FFR_{CT} may enable improved guidance for clinical decision making. Importantly, further studies will assist in determining the role of FFR_{CT} as a gatekeeper to cardiac catheterisation as well as its impact on cost and outcomes, thus building upon the near-term data brought to light by the PLATFORM trial.²⁷ To this end, future studies such as the Assessing Diagnostic Value of Non-invasive FFR_{CT} in Coronary carE (ADVANCE) study will investigate the clinical and economic impact of FFR_{CT} as well as the potential reclassification of subjects with abnormal FFR_{CT} for adverse cardiovascular outcomes.²³ Determining the appropriate risk factors and CT characteristics for performing FFR_{CT} remains a pressing issue for future research to address. Further, studies aimed at evaluating the cost-effectiveness of FFR_{CT} should be considered. Hlatky et al. investigated the initial treatment costs from 96 patients in the DISCOVER-FLOW trial.³¹ In this study, the use of FFR_{CT} for guiding the referral of patients for ICA and percutaneous coronary intervention reduced costs by 30 % (USD7,674 per patient) when compared with the most commonly used ICA/visual strategy (USD10,702 per patient), highlighting the potential value of FFR_{CT} in a clinical setting.

The performance of 'virtual stenting' is an emerging topic in the field of FFR_{CT}. In this regard, the computational modelling required for FFR_{CT} allows for the modification of coronary flow models. Moreover, Kim and colleagues documented a positive correlation between invasive FFR and FFR_{CT} before and after stenting, while displaying a 96 % overall accuracy.³² In that study, the investigators demonstrated the feasibility of virtual coronary stenting of CT-derived computational models, suggesting this technology may prove useful for predicting functional outcomes after coronary revascularisation.

Conclusion

FFR_{CT} is a novel non-invasive technique for determining the haemodynamic significance of coronary artery stenosis. Prospective advances in FFR_{CT} technology will assist in overcoming some of the current considerations associated with FFR_{CT}. On-going prospective studies designed to compare the diagnostic power of FFR_{CT} with other stress imaging tests will also offer clinicians an evidence-based alternative for detecting significant CAD, allowing for appropriate utilisation of FFR_{CT} in the clinic. ■

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