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Coronary CT Angiography-Derived Fractional Flow Reserve

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Abstract
Purpose of Review Coronary CT angiography has been shown to be highly diagnostically accurate as compared with invasive coronary angiography and help clinical decision making that affords improved clinical outcomes. Unfortunately, routine coronary CTA does not allow for the discrimination of the hemodynamic significance of stenosis. Recently, through the integration of computational fluid dynamics, Fractional Flow Reserve CT (FFRct) has been developed which allows for the determination of the hemodynamic significance of specific lesions from a resting coronary CTA without additional imaging, a change in protocol or the administration of adenosine.
Recent Findings FFRct has been validated in three large multicenter trials and has been shown to be the most accurate noninvasive test for lesion-specific ischemia as compared with the invasive gold standard of FFR. Importantly, FFRct has been shown also to be highly clinically useful in both trial and real-world settings affording a reduction in the burden of nonobstructive disease at the time of invasive angiography enabling a significant reduction in cost.
Summary FFRct is a novel technique that for the first time allows for a nonbiased noninvasive three-vessel FFR that compares favorably with the invasive gold standard of lesion-specific ischemia. FFRct is proving helpful not only for the adjudication of lesion-specific ischemia but also to help advance our understanding of mechanisms of risk and myocardial infarction. The clinical role of FFRct is being defined with growing registry and real-world data.

Keywords Coronary CT angiography-derived fractional flow reserve · Coronary CT angiography · Coronary artery disease · Invasive coronary angiography

Introduction

Management of patients present to medical care with chest pain is generally approached with two concerns. Is that a manifestation of underlying coronary artery disease, and if so what is the risk for major adverse event including death. Clinical risk calculators have been introduced to practice to help profile a patient's risk for coronary artery disease. Multiple models were designed using variable parameters, and assessing different outcomes like cardiac death or MI. The Diamond Forrester score used age, sex, and type of chest pain, to calculate probability of significant CAD [1]. The probability is low if below 30 %, intermediate if 30–70 % and high when greater than 70 % [2]. While a robust tool has served the field well for over than three decades, it has been recently shown to be in need of contemporary reappraisal [3•, 4].

The strength of the DF score has been weighing disease likelihood against test accuracy and potential harm to further guide management. Accordingly, noninvasive tools should be sufficiently and cost effectively used before invasive measures are offered only to those who need it.

In patients with stable angina and low pretest probability, no cardiac imaging is recommended and alternative differential for chest pain is considered [5••]. Noninvasive

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cardiac imaging may be considered for prognostic rather than diagnostic assessment of patients with high pretest probability of CAD. Based on their risk and severity of symptoms, patients with high disease probability may directly precede to invasive angiography [5••].

Patients with intermediate pretest CAD likelihood are traditionally sent to stress testing to assess for signs of ischemia induced by exercise or drug [5••]. Stress ECG has been part of the practice since 1920s. As technology evolved, stress echocardiography and myocardial perfusion imagings have been introduced as well, including single photon emission computed tomography (SPECT), which is the most commonly used in US, positron emission tomography (PET), and cardiac magnetic resonance (CMR). These tools are used to assess cardiac ischemia manifesting by regional differences of myocardial perfusion in hyperemia and regional wall motion abnormality.

Numerous reviews and meta-analyses were conducted to assess performance of these functional tests for the diagnosis of coronary disease. In 2008, SPECT diagnosed severe ischemia in only 32 % of 314 patients with >70 % stenosis, in the nuclear sub-study of COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation). While, 40 % of patients in same group had no or mild ischemia according to that particular stress test [6]. In 2012, a multicenter registry results showed that stress testing failed to predict obstructive disease in 621 patients underwent invasive coronary angiography (OR 0.79, 95 % CI 0.56–1.11, p 0.17) [7].

A recent National Cardiovascular Data Registry including a little more than 661 thousand patients who underwent elective coronary angiogram showed that stress imaging added minimal incremental value predicting obstructive coronary stenosis (C index 0.75 vs. 0.74 for clinical evaluation vs. noninvasive testing) [8].

A relatively recently introduced tool for CAD imaging is Coronary CTA that assess anatomical characteristics of stenosis rather than its effect on myocardium. The high sensitivity and negative predictive value of CCTA create an excellent test to role out coronary artery disease and avoid unnecessary cardiac catheterization [9, 10]. Yet, identification of hemodynamically significant CAD remains a task beyond the visual anatomic assessment of coronary artery stenosis in CCTA [11].

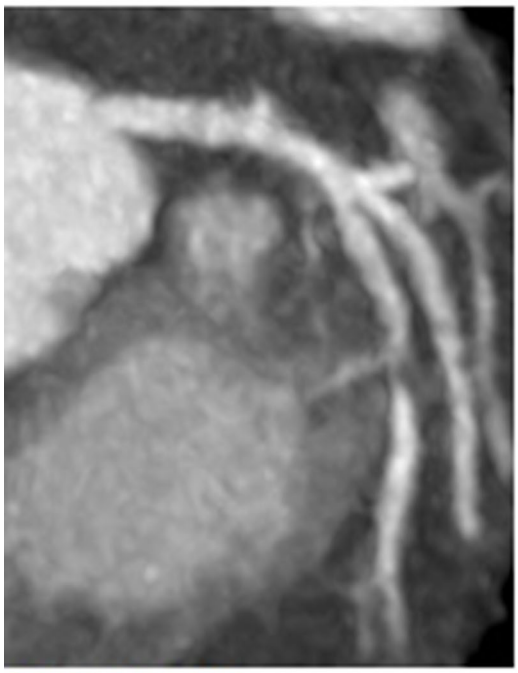
Invasive Evaluation of Lesion-Specific Ischemia with FFR

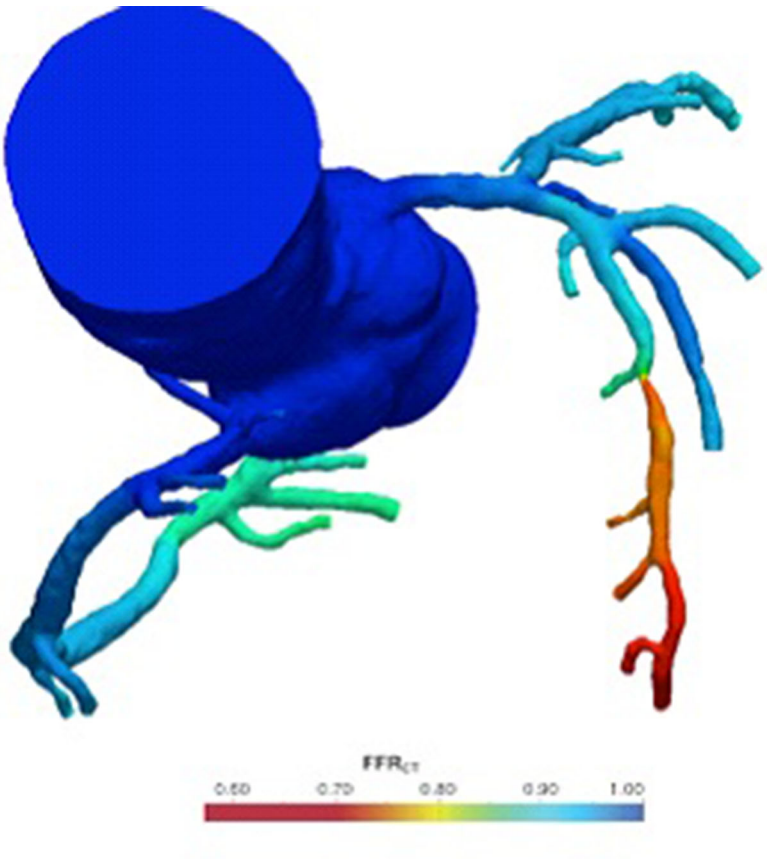
The gold standard for assessment of the hemodynamic significance of coronary stenosis is fractional flow reserve (FFR) preformed at the time of invasive coronary angiography [12]. FFR-guided revascularization in FAME had significantly less incidence of major adverse cardiac events compared to angiography-guided revascularization [13].

FFR is defined as the ratio of maximal hyperemic flow to part of the myocardium in the presence of a stenosis in the supplying epicardial artery to the maximum hyperemic flow to the same myocardial territory in the hypothetical case in which the supplying artery is normal. To perform an invasive FFR calculation, a 0.014-inch pressure sensor tipped guide wire (Pressure Wire, Radi Medical Systems, Uppsala, Sweden) is passed through a guiding catheter, beyond the stenosis being interrogated. Intravenous (IV) adenosine is administered at a dose of 140 μg/kilograms/minute to induce maximal hyperemia. Once hyperemia has been induced, the mean distal coronary pressure (Pd) measured by the pressure wire is divided by the mean aortic pressure (Pa) as measured by the guiding catheter. FFR integrates the influence of collateral vessels [14]. While the impact on prognosis of FFR may be better reflected as a continuous variable recent trials have suggested a value of ≤0.8 can be considered ischemic while a value of >0.8 is considered nonischemic. Importantly, while a binary cutoff is used to help guide revascularization the severity of abnormality of FFR has been shown to convey important prognostic implications [15].

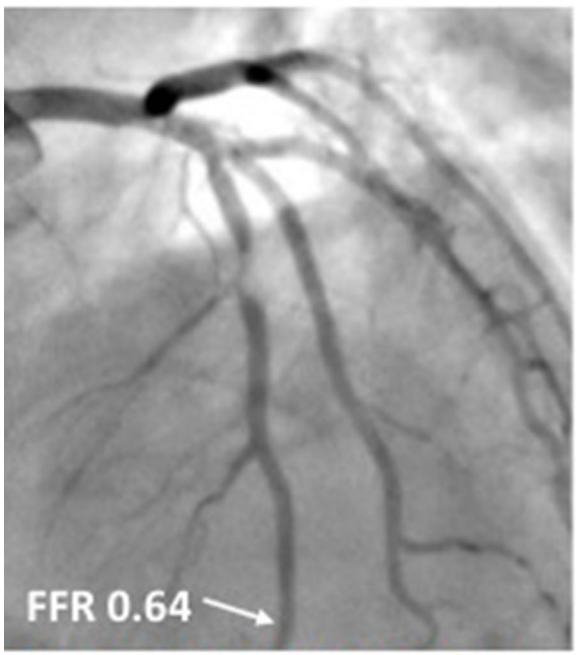
Recently, through the integration of computational fluid dynamics and the application of a number of form function relationships that relate coronary size and myocardial mass, a noninvasive surrogate of FFR has been developed. Importantly, FFR_{CT} is derived from a resting coronary CT angiogram without the administration of a stress agent and without any need for repeat testing or change in CT acquisition protocols.

The science behind the development of FFR_{CT} goes beyond the scope of this review but importantly it is grounded in decades of scientific research and development. Fluid dynamics has been used for some time to solve for pressure and flow in the aerospace and automotive industries but until recently we lacked a robust noninvasive anatomical model for evaluation of the coronary arteries. With the integration of 64 slice MDCT routine imaging of the coronary arteries have become a reality (Fig. 1). This consistent anatomical model improved computational processing capabilities and well established knowledge around the equations that govern fluid flow and pressure a computational FFR can be derived using both higher order and more basic reduced order onsite models [16–18]. Importantly, integrating knowledge from the University of Minnesota from 1990 which has taught us a great deal of the expected response of the coronary arteries to adenosine which can then be modeled in FFR_{CT} calculation obviating the need for adenosine administration [19]. For further detail regarding the science and methodology behind FFR_{CT} calculation, there are a number of recent





CTA 70% LAD stenosis



Angiography > 70% LAD stenosis

Fig. 1 A case of 55-year-old man with atypical chest pain. Patient is a former smoker, has Hypertension and hyperlipidemia. No history of MI, cardiovascular disease, or diabetes mellitus

engineering and more in depth technical reviews that have been recently published.

FFR_{CT}: The Data

To date there have been three prospective multicenter trials that have assessed the diagnostic accuracy of the commercially available FFR_{CT} with invasive FFR as the gold standard: DISCOVER-FLOW, DeFACTO, and NXT [16, 17, 20]. All three trials used the FFR and FFR_{CT} value of $\leq$0.80 to denote ischemia and a CCTA stenosis >50 % as the threshold for obstructive disease. Each of these trials used the most contemporary version available of a proprietary software algorithm (Heartflow; Redwood City, CA) at the time to calculate FFR_{CT}. In total with all the 3 trials combined 609 patients were enrolled and 1050 vessels analyzed (Table 1) [16, 17, 20].

DISCOVER-FLOW

DISCOVER-FLOW was the first of these trials to be published. The trial recruited 103 patients, and a total of 159 vessels were evaluated. CTA examinations were assessed to determine whether image quality was adequate for FFR_{CT} analysis. The diagnostic performance of FFR_{CT} in DISCOVER-FLOW remains the highest among all of the trials to date. This likely reflects some degree of optimization of image quality through patient selection as well as the manual nature of these early analyses. The per vessel accuracy of FFR_{CT} was superior to that of CCTA for the determination of ischemia (87.4 vs. 61.2 %). This was driven by a greater than threefold increase in the specificity (81.6 vs. 24.5 %). Similarly, the positive predictive value (84.7 vs. 58 %) and negative predictive value (90.9 vs. 80 %) for FFR_{CT} were also superior to CCTA on a per patient basis. This was achieved with a negligible reduction in sensitivity (92.6 vs. 94.4 %) [20].

DEFACTO

The cohort in DISCOVER-FLOW was too small to assess the diagnostic performance of FFR_{CT} on a per patient basis. As a result, the next trial to be published was DEFACTO which involved 252 patients with 408 vessels being interrogated. While no preselection of scans, any CT not deemed interpretable by the CTA core lab (11 %) was excluded from FFR_{CT} analysis. The accuracy of FFR_{CT} was once again superior to that of CCTA 73 (95 % CI 67–78 %) vs. 64 % (95 % CI 58–70 %). However, DEFACTO did not meet the prespecified primary endpoint

Table 1 FFR_{CT} diagnostic accuracy trials

Study	*N* Vessels	Design	Statistical power calculation	Inclusion criteria	Exclusion criteria[a]	Analysis	Acc (%)	Sn (%)	Sp (%)	PPV (%)	NPV (%)	AUC
DISCOVER-FLOW	103	4 Centers prospective	Per-vessel basis	Suspected or known CAD CCTA > 50 % stenosis + Clinically indicated ICA with FFR	CABG. Contraindication to beta blockers, nitroglycerin or adenosine.	Per vessel	84.3	87.9	82.2	73.9	92.2	0.9
	159					Per patient	87.4	92.6	81.6	84.7	90.9	0.92
DeFACTO	252	17 Center prospective	Per-patient basis	Suspected CAD. Clinically indicated CCTA + non urgent ICA with FFR No event in between	CABG, prior coronary stent. Contraindication to adenosine BMI > 35 kg/m^2	Per patient	73	90	54	67	84	0.81
	408											
NXT	254	10 Centers prospective	Per-patient basis	Suspected or known CAD	CABG, prior PCI. Contraindication to B-blocker, nitroglycerin, and adenosine. BMI > 35 kg/m^2	Per vessel	86	84	86	61	95	0.93
	484					Per Patient	81	86	79	65	93	0.9

Acc accuracy, *Sn* sensitivity, *Sp* specificity, *PPV* positive predictive value, *NPV* negative predictive value, *AUC* area under curve

[a] Table includes only main exclusion criteria

of a diagnostic accuracy of ≥70 % for the lower 95 % CI [16]. There are many possible explanations as to why this may have been the case including the fact that this was the first semiautomated FFR_{CT} study. In addition, while best practice for CTA scans acquisition recommends beta-blockade and nitrate therapy, they were commonly not administered. A subanalysis demonstrated superior performance of FFR_{CT} in patients who underwent CCTA using current best practice protocol recommendations [21].

NXT

The most contemporary of the diagnostic accuracy trials is Heart Flow NXT. The study population was 251 patients, with 484 vessels interrogated [17]. This version of the software had improved segmentation, refined physiologic models, and increased automation.

One strength of this trial was the adherence to best practice guidelines for image quality optimization with the administration of beta-blockers for heart rates >60 beats per minute and nitrates being mandatory. Additionally, scan parameters were optimized for body size. In light of this adherence of best practice, only 13 % of scans were excluded due to poor image quality. Unlike the prior two trials, CCTA analysis was performed by the local investigators instead of a core laboratory [16, 20]. In addition unlike its two predecessors, the NXT trial had a large number (90 %) of patients with intermediate stenosis. The superiority of FFR_{CT} compared to FFR across all measures of diagnostic performance with a significant increase in accuracy (81 vs. 53 %) resulting from improved specificity from 34 to 79 %. Interestingly, FFR_{CT} allowed for a 68 % reclassification of false positive results to true negative results thereby helping address one of the historical limitations of CCTA. This was achieved despite a high median Agatston score of 302. A statistically significant improvement in the per patient AUC for detection of ischemia was seen for FFR_{CT} compared to CCTA (0.9 vs. 0.81) [17].

ONSITE FFR_{CT}

To date, all multicenter validation trials of FFRCT have assessed higher order modeling that require parallel supercomputing offsite. To accommodate these computational requirements, de-identified DICOM data are sent offsite to Heart flow for analysis. Recently, three single-center retrospective studies had been conducted, aiming to validate an onsite FFR_{CT} using new reduced order CFD algorithm (Table 2). Noninvasive CT based FFR has been shown to be consistently derived in less than one hour from standard coronary CT angiograms performed at the site [18, 22, 23].

The most recent study had the largest sample size of 189 vessel in 106 patient, and showed a moderate to good agreement between FFR_{CT} and invasive FFR ($R = 0.59$) [18].

Furthermore, FFR_{CT} diagnostic characteristics were superior to CCTA (sensitivity 87 vs. 81 %), (specificity 65 vs. 38 %), (Positive predictive values 65 vs. 49 %) (Negative predictive value 88 vs. 73 %) (Accuracy 75 vs. 56 %) [18].

The other two studies showed good agreement as well ($R = 0.7$) [22, 23]. Both of these additional trials have shown that the real incremental benefit of FFRCT is the significant improvement in the specificity over CTA-based stenosis alone as compared with the invasive gold standard of FFR.

These results are very promising but need to be taken in the context of the study designs. All three publications to date have been retrospective and single center in nature with high disease prevalence resulting in a sampling bias. Nonetheless, they offer real promise and serve the call for future prospective multicenter diagnostic accuracy studies to be performed validating the diagnostic performance of onsite FFRCT [18, 22, 23].

PLATFORM

By 2014, the diagnostic performance of FFRCT was well established; however, the potential clinical utility of FFRCT had not been studied. Recently, the Prospective Longitudinal Trial of FFR_{CT}: Outcome and Resource Impacts (PLATFORM) was published. PLATFORM was a multicenter prospective trial designed to compare the outcome of FFR_{CT} guided care to standard care including MACE, vascular complications, quality of life, cost, and effective radiation dose. A total of 580 patients enrolled in 2 arms with intermediate risk of coronary artery disease referred to usual clinical practice for noninvasive or invasive testing. Patients were enrolled in 2 nonoverlapping arms and were further divided into those who received the initially planned test and those who underwent FFR_{CT} instead and managed accordingly. The primary aim of the study was to assess the rate of nonobstructive disease at the time of invasive coronary angiography in the FFR_{CT} guided arm as compared to those subjects who underwent invasive coronary angiography in the invasive arm on the basis of the standard of care.

The rate of nonobstructive stenosis decreased from 73 to 12 % when triaged by FFR_{CT} in the invasive test cohort. Interestingly, 61 % of the subjects who underwent FFR_{CT} had their planned ICA canceled without and adverse event

Table 2 Onsite FFR_{CT} trials

Authors	*N* Vessel	Study design	Inclusion criteria	Exclusion Criteria[a]	FFR CT calculation and duration	Analysis	Acc (%)	Sn (%)	Sp (%)	PPV (%)	NPV (%)	AUC
Renker et al.	53	Single center retrospective	Clinically indicated Nonemergent CCTA, ICA and FFR	CABG, Prior PCI, severe proximal right, left or bifurcation stenosis. Total occlusion	Siemens cFFR version 1.4 software on standard workstation	Per Lesion	–	85	85	71	93	0.92
	67		Within 3 months	Cardiac event between 2 tests. Reduced LV function	Mean duration = 38 min	Per Patient	–	94	84	71	97	0.91
Baumann et al.	28	Single center retrospective	Clinically indicated CCTA, nonemergent ICA and FFR	Prior MI, CABG or PCI. Severe proximal right, left or bifurcation stenosis. Total occlusion	Siemens cFFR version 1.4 software on standard workstation							
	36		Within 3 months	Reduced myocardial mass	Mean duration = 51.9 min							
Coenen et al.	106	Single center retrospective	Clinically indicated CCTA, ICA & FFR within <50 days	Cardiac event between 2 tests. Calcium score > 2000	Siemens cFFR version 1.4 software on standard workstation	Per Lesion	74.6	87.5	65.1	64.8	87.7	0.83
	189				Time per patient = 5–10 min							

Acc accuracy, *Sn* sensitivity, *Sp* specificity, *PPV* positive predictive value, *NPV* negative predictive value, *AUC* area under curve

[a] Table includes only main exclusion criteria

through 1 year. While there was a significant reduction in the rate of invasive catheterization, the rate of coronary revascularization was similar between the 2 arms (28 vs. 32 %). These findings are reassuring in that they suggest that FFR_{CT} allowed for the identification of those in need of revascularization [24].

In a cost subanalysis, the FFR_{CT} strategy was shown to be associated with significantly lower cost in the invasive arm (32 % less) with a significant improvement in the quality of life compared to the traditional arm. In the noninvasive arm of the study, costs were not significantly different at 90 days despite the higher rates of ICA (18 vs. 12 %) and revascularization (10 vs. 5 %) in the FFRCT cohort [25].

Next Steps

With the recent publication of two large international randomized trials supporting CTA as a suitable first line test for stable chest pain, the use of coronary CT angiography is almost certainly going to increase worldwide [3•, 26]. While CTA has shown to be diagnostically accurate as compared to ICA and even perhaps to be a more effective gatekeeper to the catheterization lab than stress testing, there remains risk with its broad adoption that less experienced readers may drive an increased referral for invasive assessment in the setting of an intermediate coronary disease [27, 28]. It is in these patients that FFR_{CT} may offer the greatest potential benefit allowing the more appropriate selection of patients for invasive assessment not only by increasing the likelihood of obstructive disease at the time of catheterization but also increasing the likelihood of lesion-specific ischemia. In the NXT trial, the accuracy of FFR_{CT} in 30–70 % lesions as compared to FFR was 80 versus 50 % for stenosis alone [17]. As there is little real-world data available, it will be important to confirm the probable benefit of FFR_{CT} through large-scale registries and large single center experiences. To help inform the field, the multicenter registry Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care (ADVANCE) (NCT02499679) was created. It commenced in July 2015 and will finish enrollment in 2021, with the aim of recruiting 5000 patients. As the field of cardiovascular medicine waits on these data, we are already seeing the publication of early clinical experiences with FFR_{CT} from Europe and the US which suggest that in clinical practice FFR_{CT} can enrich the population in the catheterization lab and safely defer ICA in those who have an $FFR_{CT} \geq 0.80$ [29]. While more data are needed it would seem that FFR_{CT} has the potential to disrupt our current management of stable chest pain in patients with both suspected and confirmed coronary artery disease.

Conclusion

FFR_{CT} accuracy has been established in comparison to the gold standard invasive FFR. Current data highlight meaningful promise of FFR_{CT} as a noninvasive tool used in conjunction with coronary CTA to help reduce unnecessary ICA.

Compliance with Ethical Guidelines

Conflict of Interest Nada Sulaiman and Jeanette Soon each declare no potential conflicts of interest. Jonathon Leipsic serves as a consultant of HeartFlow.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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