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REVIEW

Fractional Flow Reserve Measurement by Coronary Computed Tomography Angiography: A Review with Future Directions

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Abstract

Invasive fractional flow reserve (FFR) measurement is currently the gold standard for coronary intervention. FFR measurement by coronary computed tomography angiography (FFR_{CT}) is a novel and promising imaging technology that permits noninvasive assessment of physiologically significant coronary lesions. FFR_{CT} is capable of combining the anatomic information provided by coronary computed tomography angiography with computational fluid dynamics to compute FFR. To date, several studies have reported the diagnostic performance of FFR_{CT} compared with invasive FFR measurement as the reference standard. Further studies are now being implemented to determine the clinical feasibility and economic implications of FFR_{CT} techniques. This article provides an overview and discusses the available evidence as well as potential future directions of FFR_{CT}.

Keywords: Fractional flow reserve; fractional flow reserve measurement by coronary computed tomography angiography; coronary computed tomography angiography; computational fluid dynamics

Introduction

Fractional flow reserve (FFR) is a robust tool to determine the hemodynamic significance of a coronary lesion and aids in reducing unnecessary coronary intervention and downstream adverse events [1]. Recent advancements in computed tomography (CT) technology have led to the rapid development of coronary CT angiography (CCTA), which can noninvasively detect coronary artery disease (CAD). Despite this, CCTA cannot independently determine the hemodynamic significance of coronary stenosis. However, recent innovations in computational fluid dynamics (CFD) have offered alternatives and enabled the calculation of CCTA-derived FFR from three-dimensional imaging anatomic models. This review provides an overview related to FFR measurement by CCTA (FFR_{CT}) for the noninvasive evaluation of hemodynamically significant coronary stenosis.

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Invasive FFR Measurement

Invasive FFR measurements performed during cardiac catheterization represent the current gold

standard in physiologic assessment of obstructive CAD and facilitate determination of whether a particular coronary stenosis is responsible for causing myocardial ischemia [2]. The FFR measurement is based on the relationship between coronary artery pressure and blood flow, and is defined as the ratio of maximal hyperemic blood flow through a stenotic artery to maximal hyperemic flow in the hypothetical normal coronary artery [3, 4]. An FFR value of 0.80 or less is currently considered the common threshold for revascularization to improve clinical outcomes.

Current guidelines assign a class IA recommendation to advocate FFR for identification of hemodynamically significant coronary lesions in patients with no noninvasive evidence of ischemia [5]. Despite unequivocal evidence from numerous studies supporting the clinical benefit of FFR [6–11], the uptake of the use of FFR has been confined by the invasive nature of the procedure and the additional time and equipment needed for measurement of each vessel during pharmacologic vasodilation.

Noninvasive FFR Measurement

FFR_{CT} is a novel imaging modality for the noninvasive assessment of the hemodynamically significant coronary artery stenosis. FFR_{CT} can precisely localize ischemia-causing coronary stenoses by applying CFD to the CCTA data. The coupling of FFR_{CT} with CCTA provides a one-stop shop for combined anatomic physiologic evaluation, wherein FFR of three coronary vessels can be calculated from typically acquired CCTA images without the need for additional imaging or vasodilators [12].

Mechanism and Principles of FFR_{CT}

FFR_{CT} applies CFD to compute "three-vessel" FFR from previously acquired CCTA image data by using standard acquisition protocols, without the need for additional medication, imaging, or radiation. The scientific basis that determines this technology has been previously well described [12]. In brief, there are three main elements for the computation of CCTA-derived FFR: (1) construction of a three-dimensional patient-specific anatomic model from CCTA data, (2) boundary conditions to define physiologic relationships between variables at the boundaries of the region of interest, and (3) numerical solutions of the governing fluid dynamics using Navier-Stokes equations. Further still, calculation of CCTA-derived FFR usually requires five basic steps: (1) creation of patient-specific anatomic models from CCTA, (2) quantification of the total and vessel-specific baseline coronary artery flow in the hypothetical case where the supplying vessels are normal, (3) determination of the baseline myocardial microcirculatory resistance, (4) quantification of the changes in coronary resistance with hyperemia, and (5) application of CFD methods for calculation of coronary flow, pressure, and velocity at rest and hyperemia. The latter step-by-step methods for calculating CCTA-derived FFR are illustrated in detail in Figure 1 [13]. In addition, Figure 2 demonstrates an example case of CCTA and FFR_{CT}. Commercially available products for calculation of CCTA-derived FFR are available from HeartFlow (Redwood City, CA, US).

Diagnostic Performance of FFR_{CT}

Three prospective multicenter trials, comprising more than 600 patients with masked core-laboratory analysis of 1050 vessels, have thus far investigated the diagnostic performance of FFR_{CT} against invasive FFR measurement as the reference standard. These include the Diagnosis of Ischemia-Causing Stenoses Obtained via Noninvasive Fractional Flow Reserve (DISCOVER-FLOW), the Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (DeFACTO), and the Analysis of Coronary Blood Flow Using CT Angiography: Next Steps (NXT). In these trials, FFR_{CT} has proven to be superior to CCTA-determined stenosis alone for diagnosing ischemic lesions when compared with the reference standard, invasive FFR measurement (Table 1) [14–16].

The first trial to assess FFR_{CT} technology against invasive coronary angiography (ICA) and invasive FFR measurement was the DISCOVER-FLOW study, in which FFR_{CT} was performed on 159 coronary vessels in 103 patients who underwent CCTA, ICA, and invasive FFR measurement from four sites in the United States, Europe, and Asia [14]. In this multicenter trial, ischemia was defined as CCTA-derived FFR and FFR of 0.80 or less, whereas

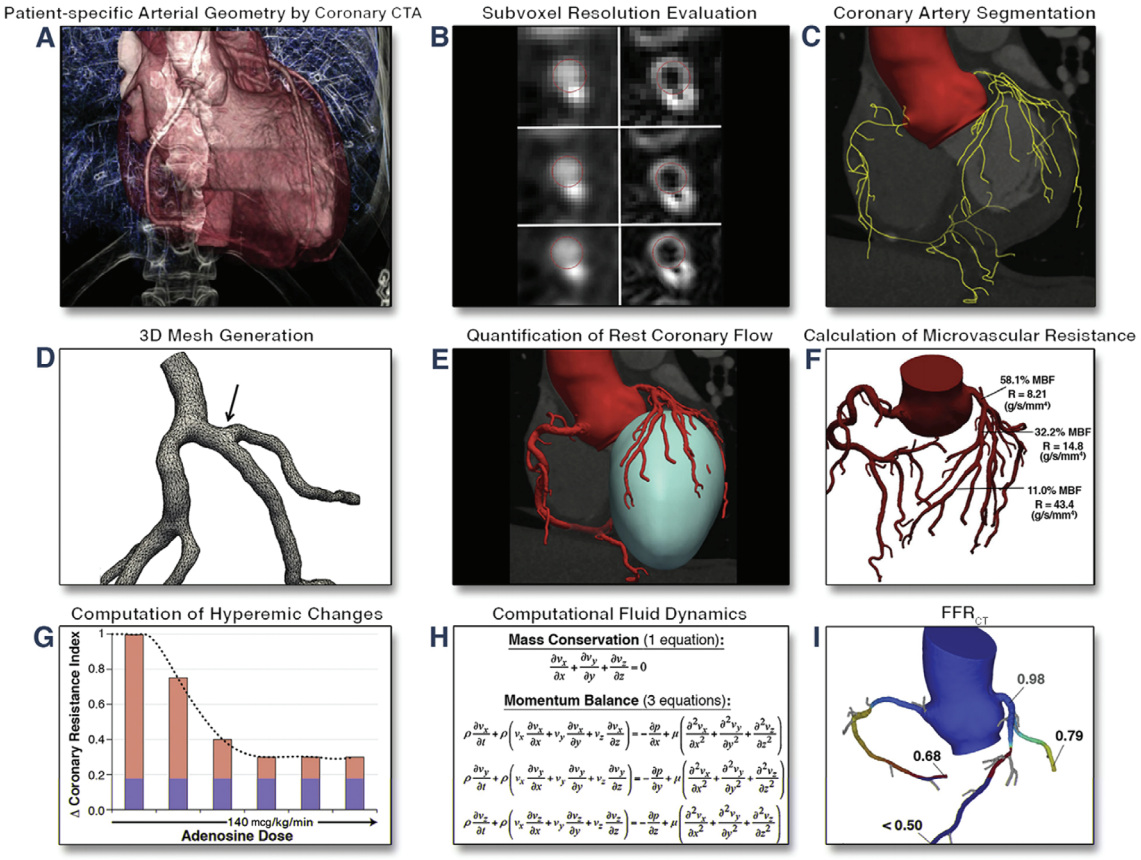

Figure 1 Step-by-Step Method for the Calculation of Fractional Flow Reserve Measured by Coronary Computed Tomography Angiography (FFR_{CT}).
(A) Acquisition of image by coronary computed tomography angiography (CTA). (B) Coronary artery segmentation to second-order and third-order vessels. (C) Application of subvoxel resolution techniques. In this example, a cross-section of a coronary artery shown with image intensity data (B, *left*) and image-gradient data (B, *right*) illustrates typical coronary CTA reconstruction with increasingly improved image resolution (B, *middle* and *bottom*) demonstrating subvoxel resolution techniques. (D) Discretization of mesh elements for calculation of computational fluid dynamics at millions of points in the coronary vascular bed. The tetrahedral vertices are reconstructed in three dimensions and are continuous even at the branch points to accurately calculate FFR_{CT} at these areas commonly affected by plaque. Reduced-order methods that do not use three-dimensional analyses are less accurate at these points. (E) Relationship of the location and size of coronary arteries to the left ventricular mass they subtend. (F) Relationship of coronary vessel caliber and flow and resistance. (G) Demonstration of reduced coronary resistance index at an adenosine dosage of 140 mcg/kg/min. (H) Navier-Stokes equations that govern the fluid dynamics of blood (nonlinear partial differential equations related to mass conservation and momentum balance are solved). (I) Example of a patient-specific FFR_{CT}. MBF, myocardial blood flow.

anatomically obstructive CAD was defined by CCTA with stenosis of 50% or more. The accuracy, sensitivity, and specificity of FFR_{CT} on a per-patient basis was 87% [95% confidence interval (CI) 79–93%], 93% (95% CI 82–98%), and 82% (95% CI 68.0–91.2%) respectively, compared with 61% (95% CI 51–71%), 94% (95% CI 85–99%), and 25% (95% CI 13–39%) for CCTA alone. In a per-vessel-based analysis, FFR_{CT} demonstrated higher accuracy, sensitivity, and specificity for ischemia-causing lesions of 84% (95% CI 78–90%), 88% (95% CI 77–95%), and 82% (95% CI 73–89%) respectively when compared with CCTA-determined stenosis alone, which exhibited accuracy, sensitivity, and specificity of 59% (95% CI 50–66%), 91% (95% CI 81–97%), and 40% (95% CI 30–50%) respectively. Notably, this study encountered its primary end point for detecting a relative improvement in diagnostic accuracy of 25% or more for FFR_{CT}, as compared with CCTA-determined stenosis.

The DeFACTO trial, which is a larger multicenter international study assessing FFR_{CT} against CCTA

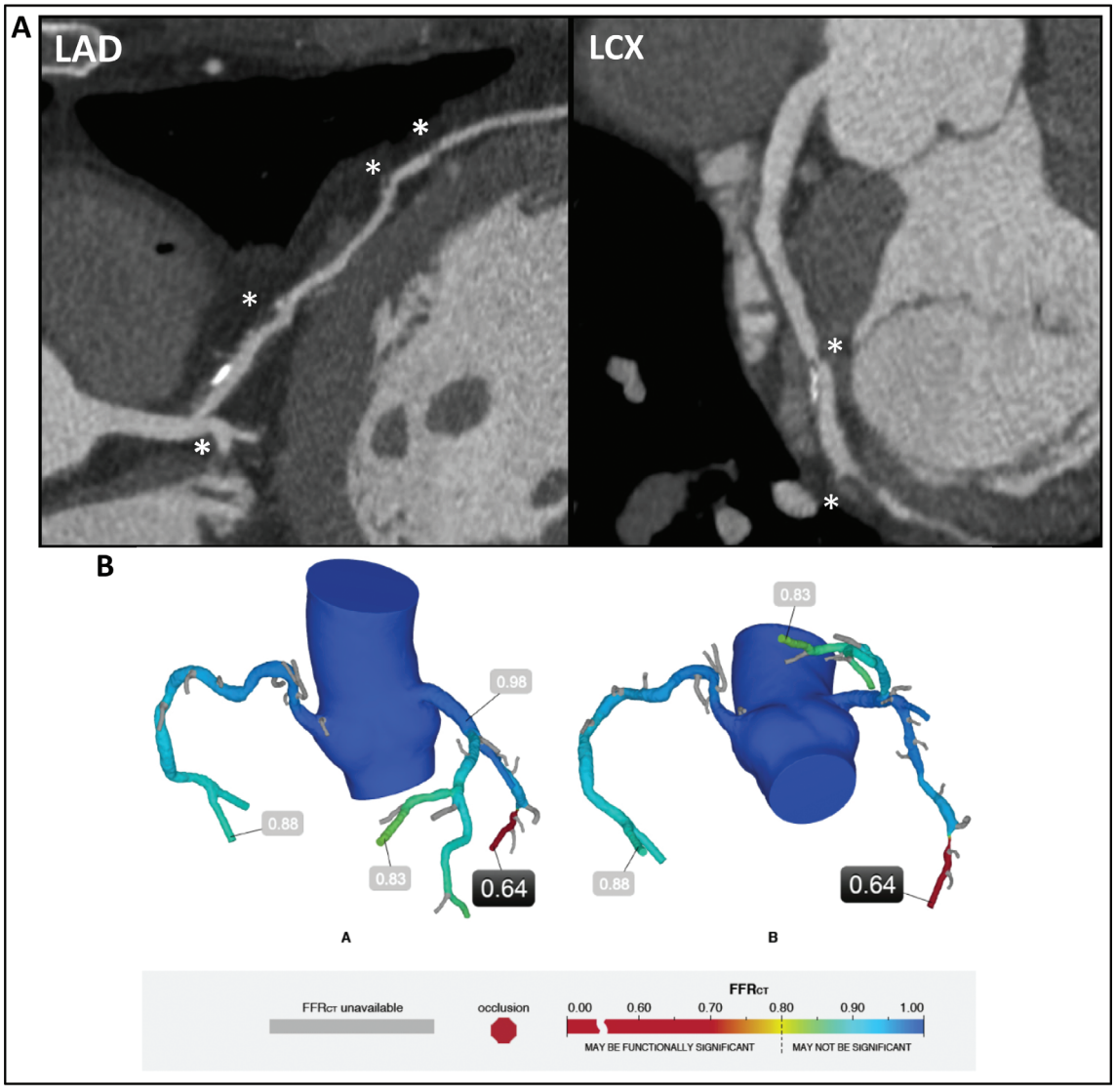

Figure 2 An Example Case of Coronary Computed Tomography Angiography (CCTA) and CCTA-derived Fractional Flow Reserve.
(A) A 75-year-old white man presenting with exertional angina underwent CCTA. Multiplanar reformatting of CCTA data demonstrates moderate stenoses (*asterisk*) in the proximal and mid parts of the left anterior descending (LAD) artery, a severe stenosis in the left circumflex (LCX) artery, and a severe stenosis versus artifact in the distal part of the LCX artery. (B) The fractional flow reserves measured by coronary computed tomography angiography (FFR_{CT}) of the LAD artery, the LCX artery, and the right coronary artery are 0.83, 0.64 and 0.88 respectively (>0.80 is normal). The value for the distal part of the LCX artery indicates significant ischemia.

for diagnostic accuracy of ischemia, was performed on 407 vessels in 252 patients from 17 centers in 5 countries who underwent CCTA, ICA, invasive FFR, and FFR_{CT} [15]. In this study, FFR or CCTA-derived FFR of 0.80 or less was defined as ischemia, whereas a stenosis of 50% or more was defined as obstructive CAD. The investigators reported that the accuracy, sensitivity, and specificity of FFR_{CT} on a per-patient basis were 73% (95% CI 67–78%), 90% (95% CI 84–95%), and 54% (95% CI 46–83%) respectively, compared with 64% (95% CI 58–70%), 84% (95% CI 77–90%), and 42% (95% CI 34–51%) for CCTA alone. The noninferiority end point was not achieved because the per-patient basis diagnostic accuracy of FFR_{CT} plus CCTA did not exceed 70% of the lower bound of the 95% CI.

Most recently, a third validation study, the NXT trial, was performed on 484 vessels in 254 patients from 10 sites in Europe, Australia, and Asia [16]. The investigators used the most recent generation of

Table 1 Diagnostic Performance of Fractional Flow Reserve Measurement by Coronary Computed Tomography Angiography.

Analysis type	Study							
	Off-site			On-site				
	Koo et al. [14] (DISCOVER-FLOW, 2011)	Min et al. [15] (DEFACTO, 2012)	Nørgaard et al. [16] (NXT, 2014)	Renker et al. [17] (2014)	Coenen et al. [18] (2015)	De Geer et al. [19] (2015)	Kruk et al. [20] (2016)	Ko et al. [21] (2016)
Per-patient basis								
Number	103	252	254	53	–	21	90	–
Sensitivity (%)*	93 (82–98)	90 (84–95)	86 (77–92)	94 (70–99)	–	83	76	–
Specificity (%)*	82 (68–91)	54 (46–83)	79 (72–84)	84 (68–94)	–	80	71	–
PPV (%)*	85 (73–93)	67 (60–74)	65 (56–74)	71 (48–89)	–	63	69	–
NPV (%)*	91 (78–98)	84 (74–90)	93 (87–96)	97 (84–99)	–	93	78	–
Accuracy (%)*	87 (79–93)	73 (67–78)	81 (76–85)	–	–	81	73	–
AUC	0.92	0.81	0.90	0.91	–	–	–	–
Per-vessel/per-lesion basis								
Number	159	407	484	67†	189†	23†	96†	56
Sensitivity (%)*	88 (77–95)	83 (76–88)	84 (75–89)	85 (62–97)	88 (78–94)	83	76	78 (52–93)
Specificity (%)*	82 (73–89)	78 (73–88)	86 (82–89)	85 (72–94)	65 (55–74)	76	72	87 (71–95)
PPV (%)*	74 (62–84)	–	61 (53–69)	71 (49–87)	65 (55–74)	56	67	74 (49–90)
NPV (%)*	92 (85–97)	–	95 (93–97)	93 (81–98)	88 (79–94)	93	80	89 (74–96)
Accuracy (%)*	84 (78–90)	–	86 (83–89)	–	75 (68–81)	78	74	84
AUC	0.90	–	0.93	0.92	0.83	–	0.84	0.88

Fractional flow reserve of 0.80 or less is defined as lesion ischemia. Off-site analysis was performed by HeartFlow software, whereas on-site analysis was performed by research-type prototype fractional flow reserve measurement by coronary computed tomography angiography with a local workstation–based computational fluid dynamics algorithm.

AUC, area under the curve; DeFACTO, Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography; DISCOVER-VP, Diagnosis of Ischemia-Causing Stenoses Obtained via Noninvasive Fractional Flow Reserve; NXT, Analysis of Coronary Blood Flow Using CT Angiography: Next Steps; NPV, negative predictive value; PPV, positive predictive value.

*The 95% confidence interval is given in parentheses.

†Per-lesion basis.

FFR_{CT} analysis software (version 1.4) at HeartFlow with enhanced image quality and substantial refinements in physiologic models and image-processing methods. In this prospective international study of 254 patients (484 vessels) undergoing clinically indicated ICA because of suspected CAD, obstructive stenosis on CCTA was defined as a greater than 50% lumen reduction, while ischemia was defined as CCTA-derived FFR and FFR of 0.80 or less. The per-patient diagnostic accuracy, sensitivity, and specificity for FFR_{CT} were 81, 86, and 79% respectively versus 53% (P<0.001), 94% (P=0.058), and 34% (P<0.001)% for CCTA for identifying myocardial ischemia. Correspondingly, on a per-vessel basis, the diagnostic accuracy, sensitivity, and specificity were 86, 84, and 86% respectively for FFR_{CT} against 65% (P<0.001), 83% (P=0.91), and 60% (P<0.001) for CCTA. Compared with the DeFACTO trial, the improved diagnostic power in the NXT trial likely reflects enhanced processing as well as increased focus on CCTA image quality, especially regarding heart rate control and nitroglycerin use [12, 22]. Accordingly, this trial revealed the high diagnostic performance of FFR_{CT} as compared with invasive FFR measurement in identifying patients with hemodynamically significant obstructions with high sensitivity as well as high specificity.

In previous studies, the software application investigated was on the background of an off-site CT-based FFR algorithm, in which the dataset was delivered as a remote service that required the transfer of data, which would subsequently lead to several hours of processing. This method uses three-dimensional modeling with calculation of FFR values throughout the entire coronary vessels. Recently, several studies of an on-site research prototype using local workstation-based CFD algorithms have been developed, which use a simplified one-dimensional analysis using computational FFR (cFFR; Siemens Healthcare). This analysis potentially enables readers to compute cFFR values in selected locations of the coronary tree, which can then be compared with invasive FFR measurements. Among these investigations as shown in Table 1 [17–20], Kruk et al. [20] evaluated 96 lesions belonging to 90 patients, using a workstation-based calculation of cFFR for intermediate stenosis with invasive FFR measurement of 0.80 or less as the gold standard. They reported that the per-patient diagnostic accuracy, sensitivity, and specificity for cFFR were 73, 76, and 71%, compared with 47, 100, and 2% for CCTA. On a per-vessel basis, the diagnostic accuracy, sensitivity, and specificity were 74, 76, and 72% respectively, versus 44, 100, and 2% for CCTA. Unlike these studies using cFFR, an additional study using a reduced-order (one-dimensional) fluid model (CT-FFR; Toshiba Medical Systems) revealed that CT-FFR is reproducible and may accurately detect lesion-specific ischemia [21]. Although these findings are still in the preliminary stages, and require appropriate validation in a multicenter cohort, these studies have underscored the applicability of these software programs, which may allow the on-site evaluation of cFFR in cases as necessary in clinical practice, and within clinically viable time frames.

Diagnostic Performance of FFR_{CT} in Patients with Intermediate Stenosis Severity

Among patients with intermediate stenosis severity (30–70%), differentiating between hemodynamically significant and nonsignificant coronary lesions is often challenging by either noninvasive imaging or ICA alone. Notably, the use of invasive FFR measurement is recommended as a class IIa indication in patients with intermediate lesions with less than 70% stenosis [23], as hemodynamically significant lesions are occasionally detected in these patients [1]. Nonetheless, given the lower prevalence of significant coronary lesions in this patient group when compared with those with severe stenosis in the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study [1], FFR_{CT} would be more beneficial for physiologic assessment of intermediate lesions and can potentially help avoid unnecessary invasive procedures. To this end, the DeFACTO study evaluated the diagnostic performance of FFR_{CT} among patients with intermediate stenosis severity. FFR_{CT} demonstrated a high diagnostic performance, with a greater than two-fold increase in sensitivity over CCTA-determined stenosis alone [82% (95% CI 63–92%) vs. 37% (95% CI 22–56%)], without compromising specificity [66% (95% CI 53–77%) vs. 66% (95% CI 53–77%)]. The diagnostic accuracy of FFR_{CT} versus CCTA was 71% (95% CI 61–80%) and 57% (95%

CI 46–67%) respectively [24]. Further still, the NXT study displayed improved diagnostic power of FFR_{CT} compared with CCTA alone, with accuracy, sensitivity, and specificity of 80% versus 51% (P<0.0001), 85% versus 93% (P=0.058), and 79% versus 32% (P<0.0001) respectively [16].

Diagnostic Performance of FFR_{CT} in Patients with Elevated Coronary Artery Calcium Scores

Heavily calcified plaque with a severely elevated coronary artery calcium (CAC) score can cause blooming artifacts that can interfere with CCTA interpretation of stenosis, and can lead to reduced specificity and lower diagnostic accuracy. Studies have compared the diagnostic accuracy of FFR_{CT} and CCTA for ischemia evaluation in patients with severely elevated CAC scores greater than 400, and have demonstrated that high calcification does not affect FFR_{CT} and it can maintain a high diagnostic accuracy, sensitivity, and specificity [16, 25, 26]. In a subsequent substudy of the NXT trial, among patients with higher levels of coronary calcification, the diagnostic accuracy, sensitivity, and specificity were higher for FFR_{CT} [74% (95% CI 60–85%), 88% (95% CI 62–98%), and 68% (95% CI 50–82%) respectively], as compared with CCTA alone [42% (95% CI 28–56%), 94% (95% CI 70–100%), and 19% (95% CI 8–35%) respectively] [26]. Similar findings with a high diagnostic performance for FFR_{CT} compared with CCTA were observed in a subanalysis of the DeFACTO trial (P>0.05) [25].

Clinical Utility and Cost-Effectiveness of FFR_{CT} in Clinical Practice

The Prospective Longitudinal Trial of FFR_{CT}: Outcome and Resource Impacts (PLATFORM) has evaluated the clinical utility of FFR_{CT} to help guide clinical decision making among patients with suspected CAD [27]. In this prospective multicenter study, 584 patients with new-onset chest pain and intermediate CAD risk were referred to a standard care strategy (n=287), including a noninvasive test (n=100) or ICA (n=187), versus an FFR_{CT}-guided diagnostic strategy (n=297). The primary end point was the rate of ICA normalcy, defined as ICA findings without significant obstructive CAD, and important secondary end points were related to costs, resource utilization, quality of life, and radiation exposure. Among patients for whom ICA was planned (standard care, n=187; FFR_{CT}-guided strategy, n=193), the study documented that ICA was cancelled in 61% of the latter group after FFR_{CT} had been performed. Subsequently, no significant obstructive CAD was found in 73% of those who received the standard care strategy, while no significant obstructive CAD was found on ICA in only 12% of those who received the FFR_{CT}-guided strategy, with both groups exposed to a similar cumulative radiation dose. Conversely, for those with the planned noninvasive test (standard care, n=100; FFR_{CT}-guided strategy, n=104), there were no significant differences in the rate of no significant obstructive CAD by detected by ICA between the two strategies (6% vs. 13%, P=0.95). Importantly, this study suggests that FFR_{CT} was associated with a significantly lower rate of no obstructive CAD detected by ICA and likely provides a safer alternative to ICA, and may be considered as an alternative diagnostic tool for guiding clinical decision making in patients in whom ICA is planned. Follow-up after 1 year revealed too few major adverse cardiac events to evaluate the safety of the strategy [28]. Larger studies will be needed to evaluate the safety of this promising strategy before its adoption in clinical practice.

More recently, Nørgaard et al. [29] aimed to assess the real-world clinical feasibility of FFR_{CT} for decision making among patients referred for FFR_{CT} testing with suspicion of CAD. They reported that CCTA-derived FFR of 0.80 or less correctly classified 73% of patients and 70% vessels using invasive FFR measurement of 0.80 or less as the reference standard. In contrast, patients with CCTA-derived FFR greater than 0.80 in whom ICA was being deferred did not experience adverse cardiac events during a median follow-up duration of 12 months.

Lately, although FFR_{CT} was commercially approved by the US Food and Drug Administration and received a CE mark in Europe in 2011, the evaluation of the cost-effectiveness of FFR_{CT} has been an important issue in the context of the practical utility of this procedure. To this end, few investigations have evaluated the economic value of FFR_{CT}

over the ICA strategy [30–32]. In a substudy of DISCOVER-FLOW, Hlatky et al. [30] demonstrated that the use of FFR_{CT} in the selection of patients for ICA and percutaneous coronary intervention (PCI) led to 30% lower costs at 1 year ($7674 per patient), when compared with ICA by visual assessment with PCI ($10,702 per patient). Similarly, in the NXT subanalysis study, an ICA-visual strategy showed the highest cost and projected 1-year death to myocardial infarction rate ($10,360 and 2.4%), whereas the strategy of initial CCTA with an FFR_{CT}-guided strategy had a cost of $7222 and a projected 1-year death to myocardial infarction rate of 1.9% [31]. Accordingly, use of the CCTA-FFR_{CT} strategy to select patients for PCI resulted in 30% lower medical costs and a 21% reduction in the death to myocardial infarction rate at 1 year when compared with the usual ICA-visual strategy [31]. More recently, a substudy of 584 patients from PLATFORM by Hlatky et al. [32] determined the effect of the use of FFR_{CT} on cost and quality of life instead of standard care to assess stable patients with symptoms typical of CAD. In the invasive testing stratum, the FFR_{CT} group showed a significant reduction of medical costs compared with the standard care group ($8619 vs. $10,734, P<0.0001), while in the noninvasive testing stratum, the FFR_{CT} group had higher costs compared with the standard care group ($2766 vs. $2137, P=0.02). However, the quality of life greatly improved in the FFR_{CT} strategy group as compared with the standard noninvasive strategy group (i.e., Seattle Angina Questionnaire 19.5 vs. 11.4, P=0.003; EQ-5D 0.08 vs. 0.03, P=0.002; and visual analog scale 4.1 vs. 2.3, P=0.82) [32].

Further Studies Comparing FFR_{CT} with Functional Stress Imaging Modalities

To date, the diagnostic performance of FFR_{CT} for prediction of ischemia has been assessed by many studies by use of invasive FFR measurement as the reference standard. However, studies evaluating the diagnostic performance of FFR_{CT} in comparison with other stress imaging modalities are still lacking. To this end, several prospective multicenter trials are currently ongoing to test FFR_{CT} against other methods of myocardial perfusion imaging. The Computed Tomographic Evaluation of Atherosclerotic Determinants of Myocardial Ischemia (CREDENCE) trial will determine the diagnostic performance of integrated CCTA plus FFR_{CT} compared with integrated myocardial perfusion imaging measures [33]. Further, two other multicenter trials, the Dual Energy CT for Ischemia Determination Compared to "Gold Standard" Non-Invasive and Invasive Techniques (DECIDE-Gold) trial 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) tial will investigate the diagnostic power of FFR_{CT} against single- and dual-energy CT perfusion imaging modalities [34,35]. These studies will provide further insight into the clinical feasibility of FFR_{CT}.

Limitations of FFR_{CT}

An impaired CCTA image quality is a potential limitation that may not only affect the diagnostic performance of FFR_{CT} but may also influence the processing time of FFR_{CT}. Numerous artifacts such as beam hardening from coronary calcification, significant motion, misalignment, and increased image noise are important contributors to impaired image quality. Further, a high body mass index and an irregular or high heart rate can also impair image quality. Adherence to CCTA image acquisition guidelines [36] can help minimize these artifacts and can enhance the image quality, especially by controlling heart rate by use of beta-blockers and dilation of coronary arteries by sublingually administered nitrates. At present, the generalizability of FFR_{CT} to a broader range of patient populations requires further elucidation, as most data are limited to stable patients without inclusion of those with acute coronary syndromes, or a history of coronary artery bypass surgery or PCI with suspected in-stent restenosis [37]. Moreover, the FFR_{CT} processing and calculation in real-world clinical practice requires several hours for computation of CCTA-derived FFR. In this era of rapid technology, semiautomated and automated processes will likely overcome this limitation soon, thereby reducing the FFR_{CT} processing time. In

addition, the diagnostic performance of FFR_{CT} among patients with acute coronary syndrome, PCI, or coronary bypass graft surgery still needs to be explored. In this line, Gaur et al. [38] have recently documented that FFR_{CT} has low diagnostic performance in patients with recent ST-segment elevation myocardial infarction. Accordingly, the clinical feasibility of FFR_{CT} among patients who have experienced recent acute coronary syndromes warrants further studies.

Future Directions and Applications of FFR_{CT}

While the PLATFORM study reported on short-term outcomes, no studies have determined the long-term prognostic utility and the beneficial effect of FFR_{CT}-guided revascularization beyond CCTA findings – most likely because FFR_{CT} was only recently introduced. To this end, Assessing Diagnostic Value of Non-Invasive FFR_{CT} in Coronary Care (ADVANCE) is a prospective multicenter longitudinal registry that will assess the prognostic utility of FFR_{CT}-guided evaluation, and will include the clinical and economic impact of FFR_{CT} as well as the potential reclassification of patients who have abnormal FFR_{CT} findings for adverse outcomes (NCT02499679) [13].

When compared with other noninvasive modalities, FFR_{CT} may potentially have the ability to simulate coronary vessel intervention so as to predict the benefit of revascularization. To this end, the application of "virtual coronary stenting" is an emerging interest in the field of FFR_{CT}. Kim et al. [39] determined the feasibility of FFR_{CT} for virtual stenting, wherein FFR was obtained by CCTA and CFD before and after virtual coronary stenting of the invasively treated coronary lesions. The computational model was modified to perform a virtual coronary intervention to enlarge the area of the target lesion in the coronary vessel according to the proximal and distal reference areas. Kim et al. reported a positive correlation between invasive FFR measurement and FFR_{CT} before and after stenting, with 96% diagnostic accuracy of FFR_{CT} after stenting to predict ischemia (96% specificity, 100% sensitivity, 50% positive predictive value, and 100% negative predictive value). In this pilot study, Kim et al. determined the utility of virtual stenting belonging to CT-derived computational models, thus indicating that this technology may be of value for determining an optimal revascularization plan and strategies before coronary intervention, and might also help reduce related costs by avoiding unnecessary revascularizations [30]. If confirmed by others, this novel technology may offset some of the other unnecessary factors such as additional procedure times, use of harmful contrast material, and unwanted radiation exposure.

Conclusion

As a novel noninvasive technology, FFR_{CT} can determine the physiologic significance of coronary stenosis along with anatomic CCTA image data. This computational analysis of FFR_{CT} can accurately identify coronary lesions that can cause myocardial ischemia. Prospective studies have shown higher diagnostic performance of FFR_{CT} versus CCTA-determined stenosis alone. Undoubtedly, studies are warranted to fit this emerging modality into real-world clinical practice, while accounting for the cost-effectiveness of FFR_{CT}-based strategies to help guide treatment decision making for improving patient care.

Conflict of Interest

James K. Min serves as a consultant to HeartFlow and has received grant support from GE Healthcare. The other authors declare that they have no conflicts of interest.

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