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The value of noninvasive FFR_{CT} in our current approach to the evaluation of coronary artery stenosis

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Abstract

Purpose of review—Contemporary diagnosis and management of stable chest pain symptoms possibly due to coronary ischemia is a frequent clinical challenge that involves a variety of test options, based upon either coronary angiographic (anatomic) or functional imaging. This review will discuss the evolution of coronary computed tomography derived fractional flow reserve (FFR_{CT}) from basic science to a currently clinically approved diagnostic test.

Recent findings—In recent years, FFR measured invasively in the coronary catheterization lab has demonstrated clinical outcome benefit for coronary revascularization decisions. Both coronary angiographic (anatomic) and functional myocardial imaging have been limited by an inability to reliably estimate physiologic significance determined by FFR. However, advances in computational fluid dynamics have led to interest in FFR estimated by coronary angiograms obtained noninvasively through coronary computed tomography angiography.

Summary—Present day use of FFR_{CT} has been mostly limited to research applications due to lack of availability, cost, as well as limited outcomes and cost-effectiveness data. Nevertheless, interest remains in the potential role of FFR_{CT} for coronary revascularization treatment decisions and thus, ongoing and future studies will continue to investigate this technology.

Keywords

Coronary computed tomography angiography; coronary artery disease; fractional flow reserve; myocardial ischemia

Introduction

During the early to mid-2000s, the evaluation of chest pain entered a new era with the emergence and rapid growth in use of multi-detector coronary computed tomography (MDCT) angiography.⁽¹⁾ Diagnostic accuracy studies using modern scanners (at least 64

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MDCT) established a high negative predictive value to rule out coronary stenosis as a cause of ischemic chest pain.(2) Cohort studies further established the prognostic value of normal (no coronary plaque or stenosis) or non-obstructive (<50% diameter stenosis) coronary artery disease (CAD) versus obstructive CAD, and a meta-analysis published in 2011 pooled data from several of these coronary computed tomography angiography (CTA) cohort studies to show the low likelihood of myocardial infarction (MI) or mortality after normal CTA.(3) Furthermore, about one-third of patients were shown to have non-obstructive CAD, which is associated with a small, but significant, increase in absolute event incidence. Finally, patients with obstructive CAD by CTA were shown to have high annualized event rates. While data continued to accumulate in recent years regarding the diagnostic and prognostic value of CTA, advances in scanner technology and image reconstruction have led to marked reductions in estimated effective radiation dose delivered to the patient, such that CTA scans can now be consistently performed at less than 1 mSv(4), a fraction of the radiation exposure from CTA just 10 years ago. Other advances in CTA have included the identification of various plaque features, which are associated with an increased risk of adverse cardiac events,(5) as well as plaque features, which may be associated with ischemia.(6)

Despite these advances and the capabilities of CTA for accurately ruling-out coronary stenosis, the specificity of stenosis by CTA for detecting ischemia has been limited. For example, in the DEFACTO trial the per-patient specificity of CTA for identifying flow-limiting stenosis was 42%.(7) Accordingly, several clinical and experimental techniques have been evaluated with the goal to reduce the false positive rate of CTA while maintaining a high level of sensitivity. One such approach is the introduction of fractional flow reserve estimation using conventional coronary CTA (so-called FFR_{CT}), which will be the subject of this review.

Overview of FFR_{CT} technology and theoretical assumptions

FFR_{CT} technology has been proposed by Dr. Charles Taylor and colleagues and patented in the currently available method marketed by Heartflow, Inc. (Redwood city, CA). FFR_{CT} evaluates coronary anatomy including plaque burden, stenosis, and luminal diameter to model a simulated hyperemic blood flow response from a resting coronary CT angiogram (Table 1) (Figure 1). The physics principles underlying FFR_{CT} fluid dynamics, the so-called Navier-Stokes equations, were first reported in 1822. Subsequently, these equations have been applied to diverse applications in fluid mechanics and engineering ranging from aeronautics to hydraulics. For the purpose of simulating the potential physiologic significance of coronary stenosis, interest in applying fluid dynamics has been studied for decades, first with invasive angiography and later with coronary CTA. However, current methods involve iteratively solving thousands of mathematical equations to simulate hyperemia, the processing time for which has only recently become practical with improvements in computer processor speed and memory.

Research studies evaluating accuracy of FFR_{CT} versus invasive FFR

Three large multi-center accuracy studies have evaluated the incremental diagnostic value of FFR_{CT} versus CTA alone using invasive FFR as a reference standard (Table 2). First, the Diagnosis of Ischemia-Causing Coronary Stenoses by Noninvasive Fractional Flow Reserve Computed From Coronary Computed Tomographic Angiograms (DISCOVER-FLOW)(11) study reported that the use of FFR_{CT} in highly selected, routinely acquired CTA datasets in 103 patients (159 vessels) improved the per-vessel accuracy from 59% (sensitivity 91%, specificity 40%) for CTA alone to 84% (sensitivity 88%, specificity 82%) with the addition of FFR_{CT}. Important limitations included the large standard deviation for FFR_{CT}, which was 12%. Thus, the 95% CI for the FFR_{CT} point estimate of 0.8 might range from 0.57 (severe stenosis) to 1.0 (normal flow) when compared to invasive FFR.

Next, the DEFACCTO trial noted an improvement in per-patient accuracy from 64% (sensitivity 84%, specificity 42%) for CTA alone to 73% (sensitivity 90%, specificity 54%) with the addition of FFR_{CT}.(7) In this study, 31 of 285 (11%) CTA studies acquired in experienced centers were reported to be non-evaluable. Like the DISCOVER-FLOW, a similarly imprecise confidence interval was noted in this trial as well.

The third available trial, the so-called Analysis of Coronary Blood Flow Using CT Angiography: Next Steps (NXT)(12) evaluated 310 patients with both CT and FFR_{CT} and achieved the best accuracy and precision of the available prospective studies with an improvement in diagnostic accuracy from 65% (sensitivity 83%, specificity 60%) for CTA alone to 86% (sensitivity 84%, specificity 86%) with the addition of FFR_{CT}. Like in the DEFACCTO study, 47 of 357 (13%) acquired CTA datasets in experienced centers participating in the NXT trial were reported to be non-evaluable. Importantly, the standard deviation improved slightly to ± 0.074 in this study, such that the 95% CI for an FFR_{CT} of 0.8 would range for invasive FFR from 0.66 – 0.94.

In summary, three diagnostic accuracy trials (DISCOVER-FLOW, DEFACCTO, and NXT) have evaluated the currently modest ability of FFR_{CT} to improve specificity of CTA without significantly sacrificing sensitivity. However, the clinical utility for individual patients demonstrated by the accuracy in these trials is currently limited by imprecision as demonstrated by wide limits of agreement with invasive FFR on Bland-Altman analysis.

FFR_{CT} in comparison with alternative technologies

In addition to three clinical trials described above, several single center and smaller size observational studies have been published leading to now 2 systematic review and meta-analyses that summarize the accuracy of FFR_{CT} versus invasive FFR. A recent meta-analysis identified 5 studies with 706 subjects that compared CTA with or without FFR_{CT} to invasive FFR and noted that the specificity of CTA improved from 43% to 72% with the addition of FFR_{CT}.(13) In the same meta-analysis, CT stress myocardial perfusion imaging also improved the specificity from 43% to 77%. A more recent systematic review of the accuracy data for various ischemia tests when compared to invasive FFR as a reference test noted that after pooling data from 609 subjects from the DISCOVER-FLOW, DEFACCTO, and NXT

trials, the low specificity of CTA (39%) could be improved to 78% with the addition of FFR_{CT} .(14) Although not direct comparisons, the specificity of FFR_{CT} was numerically similar to SPECT myocardial perfusion imaging (75%) but lower than stress perfusion MRI (85%).

Alternatively, the anatomic assessment from the CTA could be combined with a physiological evaluation, such as exercise treadmill test, stress echocardiography, or stress myocardial perfusion imaging using nuclear imaging, or cardiac MRI. Indeed, for many patients who may have borderline stenosis by CTA, combining the anatomic information with a simple exercise stress test may provide sufficient information to diagnose prognostically important ischemia and guide patient management.(15) Although untested prospectively, registry data(16) of patients who underwent both exercise test and CTA, suggests that combining data from CTA and ETT offers improved risk stratification. Furthermore, the value of CTA + functional testing was also recently demonstrated in the SCOT-HEART trial, where exercise treadmill testing was performed in ~85% of patients. (15) Other solutions to improve the specificity of CTA (e.g., intracoronary transluminal attenuation gradient, TAG),(17) have been limited by low reliability and variable test accuracy when compared with FFR.

Cost-effectiveness

The impact of FFR_{CT} on costs has been evaluated in the recently published PLATFORM study.(18, 19) This study was an observational comparison of the use of FFR_{CT} among patients referred either to ICA or non-invasive testing. FFR_{CT} resulted in increased cost but improved subjective quality of life scores among those evaluated by noninvasive testing, in comparison to a 32% reduction in cost but no change in quality of life scores among those with planned non-invasive testing. This was associated with a 61% reduction in ICA for those in the planned invasive arm of the study. However, there was no comparison of CTA alone among such patients, which by high sensitivity would have likely served a similar gatekeeper role. While this study represents an important step forward to comparative cost effectiveness research for FFR_{CT} , it was limited by the nonrandomized design and lack of comparison of FFR_{CT} to CTA alone or to CTA + functional testing.(20, 21)

Ongoing studies and potential novel applications

Interest in FFR_{CT} continues to grow, although with guarded optimism given the current challenges to work flow, small sample size of accuracy data, lack of extensive real-world experience, and absence of any prospective comparative cost-effectiveness study comparing FFR_{CT} to CTA alone or CTA+ETT. Likely reflecting these limitations, a search of clinicaltrials.gov for “ FFR_{CT} ” demonstrates few publicly registered actively enrolling studies as of Aug 1, 2016 (Table 3).

Current studies have applied, and future studies will continue to pursue the potential of an interesting emerging application of FFR_{CT} , which is so-called “virtual stenting.” This process involves estimating the benefit of PCI by modeling the new FFR_{CT} after improvements in epicardial luminal diameter post-PCI. Of course, PCI in practice does not

always result in perfect arterial re-canalization and may be complicated by incomplete stent apposition, dissection, jailed side-branches or injury to the downstream microvasculature or even procedural myocardial infarction from embolized plaque. Thus, although modeled PCI will never completely predict the final result, use of FFR_{CT} has been suggested as a useful strategy to select the most stenotic lesion upon which to intervene or to prioritize stent placement when multiple lesions exist. One such study demonstrated that a pre-PCI FFR_{CT} of 0.70 ± 0.15 improved to a modeled post-PCI FFR_{CT} of 0.88 ± 0.05 in comparison to pre-PCI FFR of 0.70 ± 0.14 that improved to 0.90 ± 0.05 post-PCI.(22) Pre-PCI bias comparing invasive FFR to FFR_{CT} was 0.006 (95% LOA -0.27 to 0.28) and post-PCI bias 0.024 (95% LOA -0.08 to 0.13), indicating a small bias although with wide limits of agreement. This and other proof of concept studies have generated interest in the use of FFR_{CT} to further counsel patients about the potential benefits of PCI for stable ischemic heart disease.

Additionally, the proprietary FFR_{CT} patented by Heartflow will compete with other computational techniques, such as automated plaque quantification software (Autoplaq) undergoing research evaluation at Cedars Sinai, which also has demonstrated potential for estimation of invasive FFR.(23) Another area of growing interest involves the use of “machine learning” methods, that estimate FFR-CT by comparing new images to large databases of previously evaluated CTA, with the advantage of estimating an FFR-CT for the new study with a high correlation to physics based computation but at a fraction of the computation time.(24) Also, methods of estimating FFR from ICA have been investigated, although with less appeal than CTA due to being invasive (while using simulation to avoid stress agents such as adenosine that are otherwise used for FFR).

Integrating FFR and coronary flow reserve into management of CAD

Conceptually, the FFR calculation refers to the ratio of maximal blood flow in a coronary artery distal to a stenosis to the hypothetical maximal blood flow in the same artery in the absence of a stenosis.(25) As such, FFR is an excellent marker of pressure gradients along a coronary artery that, unlike CFR, is not affected by basal levels of blood flow that can vary across patients and even within patients over time. Although FFR and ischemia measurements are correlated, this correlation is not one to one. This is because myocardial ischemia results from a complex interaction between focal epicardial stenosis, diffuse atherosclerosis, and microcirculatory function and remodeling (including obstruction and rarefaction) (Table 1). In contrast, CFR measurements integrate both epicardial and microcirculatory components thereby offering a more precise measure of ischemic burden and clinical risk and, thus, provide potentially complementary information to FFR that may allow better identification of revascularization candidates among patients with stable IHD. Indeed, a global CFR of 1.5 or less by PET associated with a high risk of coronary events, as compared to global CFR over 2.0 carrying relatively lower risk.(26) Preliminary evidence from a relatively small observational study suggests that CABG but not PCI in patients with global CFR of less than 1.6 may modify this high-risk natural history.(27) Conversely, revascularization had no apparent survival benefit among patients with either normal or mildly reduced CFR.(27) Additional evidence from a single center study of 157 patients with stable IHD treated medically offers further insights into the complementary nature of FFR and CFR information in management decisions.(28) Patients with reduced FFR (<0.8)

but normal CFR (>2.0) had comparable low risk of adverse events (death, myocardial infarction, and revascularization) to patients with concordant normal FFR (>0.8) and CFR (>2.0). In contrast, a reduced CFR (<2.0) identified higher risk patients even when FFR was normal. These findings confirm the prognostic value of physiologic flow measurements independent of focal stenosis or its pressure surrogate. Based on these observations, a multicenter, international study is examining the hypothesis that PCI in lesions with $\text{CFR} > 2$ despite $\text{FFR} \geq 0.8$ can be safely deferred and treated with medical therapy alone (DEFINE-FLOW, NCT 02328820).

Conclusion

In summary, FFR_{CT} has the potential to overcome one of the major contemporary limitations of CTA, a low specificity to identify myocardial ischemia. In a pooled analysis, the specificity of CTA of 39% improved to 78% with FFR_{CT} . However, the current clinical use of FFR_{CT} has been limited by challenging workflow (i.e. need to send CTA datasets to the single proprietary vendor), increased cost, and limited outcomes and cost-effectiveness data compared to CTA alone or CTA + functional testing. In spite of these limitations, there is continued and growing interest in the potential clinical value of FFR_{CT} in addition to three actively enrolling publically registered studies.

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Key points

1. Coronary CT angiography has a high sensitivity but low specificity for evaluation of possible coronary ischemia.
2. Several methods have been proposed to improve coronary CTA, one of which is the estimation of invasive FFR from a resting CTA, so-called FFR_{CT}.
3. Accuracy studies demonstrate that FFR_{CT} improves the specificity of CTA to identify flow-limiting stenosis, but with limited precision and need to send data for processing at increased cost.
4. There are no randomized trials currently and thus further data are needed regarding the potential outcomes and cost-effectiveness of management strategies involving FFR_{CT}.
5. Future studies will continue to evaluate advances in the ability to estimate FFR from CT by FFR_{CT} and other technologies.

Figure 1.

Example of FFR_{CT} analysis added to coronary CTA to assess the hemodynamic significance of moderate stenosis. 52-year old male with hypertension and dyslipidemia was referred to coronary CTA for evaluation of exertional chest pressure. Coronary CTA demonstrated a moderate amount of non-calcified plaque associated with positive remodeling (arrow), resulting in moderate (50%–69%) stenosis. FFR_{CT} across the lesion was 0.85 suggesting it is unlikely to be hemodynamically significant. The patient was treated with medical therapies and 7 years later remains asymptomatic and without any cardiac events.

Table 1

Invasive fractional flow reserve versus non-invasive coronary flow reserve versus FFR_{CT}.

	Invasive FFR	CFR	FFR_{CT}
Equipment	Invasive coronary pressure wire at peak adenosine hyperemia	Non-invasive by PET* at peak adenosine hyperemia and at rest	Non-invasive by rest CTA
Measures	Ratio of pressure distal to coronary lesion to pressure proximal to coronary lesion	Ratio of Myocardial blood flow at peak hyperemia to resting myocardial blood flow	Computerized image post-processing of routine rest CTA data without hyperemia
Advantages	Clinical gold standard for lesion specific ischemia based upon outcomes data; precise	Non-invasive, integrates epicardial stenosis, microvasculature and collateralization	Non-invasive, does not require pharmacologic stress
Disadvantages	Neglects contribution of microvasculature, risks of anti-coagulation and invasive procedure	No RCT outcomes data	Increased cost, data send out to proprietary processing site slows work-flow, no RCT outcomes data, lack of precision, requires excellent image quality of CTA
Abnormal	<0.8	1.5 – 2.0	<0.8
RCT outcomes	DEFER(8), FAME(9), FAME-2(10)	Ongoing	Ongoing

CFR = coronary flow reserve; CTA = computed tomography angiography; FFR = fractional flow reserve; PET = positron emission tomography; RCT = randomized controlled trial.

* Non-invasive CFR is most validated by PET, but quantification via MRI, SPECT and echocardiography are areas of active research.

Table 2Key studies of FFR_{CT} accuracy validation.

	DISCOVER-FLOW	DEFACTO	NXT
n, patients	103	252	254
n, vessels	159	408	484
Per patient			
CTA vs. FFR Sens, %	94 (85–99)	84 (77–90)	94 (86–97)
CTA vs. FFR Spec, %	25 (13–39)	42 (34–51)	34 (27–41)
CTA vs. FFR Accuracy, %	61 (51–71)	64 (58–70)	53 (47–57)
FFR _{CT} vs. FFR Sens, %	93 (82–98)	90 (84–95)	86 (77–92)
FFR _{CT} vs. FFR Spec, %	82 (68–91)	54 (46–63)	79 (72–84)
FFR _{CT} vs. FFR Accuracy, %	87 (79–93)	73 (67–78)	81 (76–85)
Per vessel			
CTA vs. FFR Sens, %	91 (81–97)	–	83 (74–89)
CTA vs. FFR Spec, %	40 (30–50)	–	60 (56–65)
CTA vs. FFR Accuracy, %	59 (50–66)	–	65 (61–69)
FFR _{CT} vs. FFR Sens, %	88 (77–95)	80 (73–86)	84 (75–89)
FFR _{CT} vs. FFR Spec, %	82 (73–89)	61 (54–67)	86 (82–89)
FFR _{CT} vs. FFR Accuracy, %	84 (78–90)	–	86 (83–89)

Sens: sensitivity; Spec: specificity

Table 3

Key ongoing trials of FFR_{CT} registered publicly on [Clinicaltrials.gov](https://clinicaltrials.gov).

Trial	Status	Anticipated completion	Objective
SYNTAX III	Enrolling	June, 2017	Randomized trial to compare CTA with FFR-CT versus ICA for coronary revascularization planning
CREDENCE	Enrolling	March, 2017	Cohort study evaluating CTA and FFR-CT in comparison with stress testing, ICA and invasive FFR for prediction of ischemia
EMERALD	Not yet enrolling	–	Case control study to retrospectively evaluate CTA and FFR-CT previously performed 1–2 months prior to myocardial infarction
ADVANCE	Enrolling	July, 2021	Observational registry to compare revascularization decisions based upon CTA versus FFR-CT

ADVANCE = Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care; **CREDENCE** = Computed Tomographic Evaluation of Atherosclerotic Determinants of Myocardial Ischemia; **EMERALD** = Exploring the Mechanism of the Plaque Rupture in Acute Myocardial Infarction; **SYNTAX III** = A Randomized Study Investigating the Use of CT Scan and Angiography of the Heart to Help the Doctors Decide Which Method is the Best to Improve Blood Supply to the Heart in Patients With Complex Coronary Artery Disease.