Review Article

Fractional flow reserve computed tomography in the evaluation of coronary artery disease

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Abstract: Amongst patients with suspected obstructive coronary artery disease (CAD), less than a third of patients have obstructive disease on invasive coronary angiography (ICA) and fewer still have flow-limiting obstructive disease as determined by invasive fractional flow reserve (FFR). FFR is a powerful tool in guiding revascularization of flow-limiting lesions which in turn improves clinical outcome in those with haemodynamically significant obstructive disease. However FFR is infrequently performed due to the cost, time and patient discomfort the procedure entails. Further advances in non-invasive imaging has allowed FFR to be derived non-invasively by applying computational fluid dynamic (CFD) modeling to the coronary computed tomography angiography (CCTA) dataset without the need to induce hyperemia or modify the standard CCTA acquisition protocol. FFR derived from CCTA has been shown to have excellent correlation with invasive FFR and remains diagnostically robust in presence of reduced signal-to-noise ratio (SNR), coronary calcification and motion artifact. More recently, new data have emerged evaluating the clinical impact of fractional flow reserve computed tomography (FFRCT) on the assessment and management of patients with stable chest pain. One such study is the Prospective LongitudinAl trial of FFRCT: Outcome and Resource IMpacts (PLATFORM) study which showed an improved patient selection for ICA using CCTA-FFRCT approach by increasing the likelihood of identifying obstructive CAD at ICA amongst those intended for invasive testing. CCTA-FFRCT may therefore serve as efficacious gatekeeper to ICA that enriches the ICA population. The utility of FFRCT has also helped deepened our understanding of CAD. Through CFD modeling, it is now recognized that there are mechanistic forces of wall shear stress (WSS) and axial plaque force acting on coronary plaques. This has created further interest in exploring the possible interplay between these mechanistic forces on the development of coronary plaque and vulnerability of these plaques to rupture.

Keywords: Myocardial fractional flow reserve (FFR); coronary artery disease (CAD); coronary angiography

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Introduction

Conventional invasive coronary angiography (ICA) remains the gold standard in the evaluation of coronary artery disease (CAD) in symptomatic patients (1). However the invasive nature of the procedure renders ICA to be less then desirable as the first-line investigation particularly when two-third of patients with suspected stable angina have no obstructive CAD at the time of ICA despite having had prior non-invasive testing (2).

Coronary computed tomography angiography (CCTA) allow direct visualization of the coronary artery and vessel wall in a non-invasive manner with diagnostic performance that is comparable to that of ICA (3-5). Additionally, CCTA has the benefit of assessing the vessel wall for early development of coronary atherosclerosis (6). However, one of the inherent drawbacks of CCTA is the

lack of physiological assessment in the presence of CAD. Although the degree of luminal narrowing is predictive of symptomatology and prognosis, it is now well recognized that an important disconnect exist between the degree of luminal narrowing and coronary flow impairment (7). As flow is the main determinant of myocardial perfusion, symptomatology is more closely related to the coronary blood flow than the degree of luminal narrowing (8). In light of this, the traditional luminography-based approach in revascularization to achieve symptomatic relieve and survival benefit in patients with stable CAD has been brought into question (9,10).

For ICA, although the investigation is invasive, it has the ability to provide both anatomical and if needed, lesion-specific hemodynamic data by way of invasive fractional flow reserve (FFR). FFR is the mean pressure immediately distal to a stenosis divided by the mean aortic pressure at peak hyperemia. As pressure is one of the most important drivers of coronary blood flow, FFR has been shown to be a good surrogate marker of myocardial perfusion (11) and FFR value of ≤0.75 correlated well with the presence of inducible myocardial ischemia (12). FFR can therefore provide the important missing link between anatomical stenosis, myocardial ischemia and symptomatology. Furthermore, FFR has been shown to be a powerful tool in driving clinical outcomes (13-15). More recently, instantaneous wave-free ratio (iFR) has emerged as a useful alternative to FFR which does not require adenosine infusion to induce maximal hyperemia and has diagnostic performance that is comparable to FFR (16,17). However, the impacts on decision-making and subsequent clinical outcome are yet to be evaluated (18).

FFR can now be derived non-invasively with fractional flow reserve computed tomography (FFRCT) using computational fluid dynamic (CFD) model. FFRCT has the unique ability in assessing the FFR of all coronary segments simultaneously without the need for coronary instrumentation, adenosine administration or even additional radiation exposure compared to standard CCTA examination.

In this review, we will examine the diagnostic performance of FFRCT in comparison to FFR and how FFRCT could improve the clinical assessment and outcome of patients with stable CAD.

FFR-guided therapy

In symptomatic patients with stable obstructive CAD (defined as stenosis >70%), both COURAGE (9) and BARI-2D (10) trials have shown no survival benefit between percutaneous coronary intervention (PCI) revascularization and optimal medical therapy (OMT) compared to OMT alone over 4.6 and 5 years follow-up respectively. Long-term follow-up out to 15 years of the original COURAGE trial cohort continued to report no survival benefit with PCI over OMT alone (19). However, as FFR versus Angiography for Multivessel Evaluation (FAME) trial had shown, there is an important disconnect between degree of luminal narrowing and its hemodynamic impact. In 65% of lesions with 50–70% stenosis and 24% of lesions with 71–99% stenosis were shown to be not hemodynamic significant (i.e., FFR of >0.80) (7). FFR-guide revascularization of the 1,005 patients with multi-vessel CAD led to a 10.4% reduction in PCI compared to angiography-guided revascularization. At 2 years follow-up, there was a 5% absolute risk reduction (35% relative reduction) in all-cause mortality or non-fatal myocardial infarction (MI) in the FFR-guided group (13). The hemodynamic impairment of a stenosis is therefore a stronger driver of outcome than the degree of luminal narrowing. Furthermore, in the subanalysis of the COURAGE trial later revealed that amongst the patients who had myocardial perfusion imaging, only 32% of patients had moderate to severe ischemia and 40% had no or mild ischemia (20). Therefore the lack of hemodynamic consideration in the original COURAGE and BARI-2D trials may have significantly underestimated the benefit of revascularization in patients with stable CAD.

FAME 2 trial further examined the use of FFR-guided revascularization compared to OMT alone in patients with stable obstructive CAD and FFR ≤0.80 (21). Over 2 years follow-up, the rate for urgent revascularization for MI or electrocardiography (ECG) proven ischemia was halved (3.4% in PCI group *vs.* 7.0% in OMT group, P=0.01) and death or non-fatal MI beyond the first 7 days post randomization was halved (4.6% in PCI group *vs.* 8.0% in the OMT group, P=0.04) in those who had PCI (14). For those with angiographically obstructive but FFR negative (FFR >0.80), the 15 years data from Deferral *vs.* Performance of Percutaneous Coronary Intervention of Functionally Non-Significant Coronary Stenosis (DEFER) trial showed that deferring PCI revascularization in these patients was safe (15). In fact, PCI in these patients led to more frequent MI compared than those without PCI (10.0% *vs.* 2.2%, P=0.003). These trials highlighted the importance of the hemodynamic flow of CAD as driver of outcome beyond the degree of luminal narrowing. Therefore despite the drawbacks of invasive testing, longitudinal randomized controlled data continued to support the use of FFR to allow

for better patient selection in whom revascularization is likely to improve outcome, while saving others from potential harm.

Improvement in angina symptom is also an important consideration in patient-centered care for patients with stable CAD. In the COURAGE trial 88% of patients in the PCI arm and 87% in the OMT arm had angina at baseline (9). One-year following their designated therapy, there was an apparent separation between the two treatment groups with more patients in the PCI group being free of angina than in the OMT group (34% *vs.* 42%). However, the difference was lost at 5-year follow-up (74% *vs.* 72%). When FFR was considered in the treatment plan, FFR-guided PCI led to significant improvement in angina symptoms compared to OMT alone. In FAME 2 trial, 69% of patients were symptomatic of angina at baseline (14). Two years following their designated therapy, fewer patients in the PCI group had angina compared to OMT group which was not otherwise explained by difference in medical therapy (5.9% *vs.* 12.0%, P=0.002).

FFR using computed tomography—concept

FFR derived using CFD modeling of the CCTA dataset (FFRCT) allows a non-invasive measurement of FFR by simulating maximal hyperemia. This technique forgoes the need for adenosine administration or alteration to standard CCTA acquisition protocol. However administration of sublingual nitroglycerin is mandatory as per standard CCTA examination (22).

The science and mathematical modeling needed to derive FFRCT goes far beyond the scope of this review and are discussed in more detail elsewhere (23,24). In brief, FFRCT computation involves three main elements: (I) the extraction and modeling of patient specific geometric models of the aortic root and coronary anatomy; (II) a mathematical based flow model defining the inflow and outflow boundary conditions that governs coronary physiology at rest and maximum hyperemia which include the cardiac output, aortic pressure and microcirculatory resistance; and (III) computation of the coronary flow and pressure by solving the multitude of equations governing fluid dynamic which relates to the conservation of mass and balance of momentum, known as the Navier-Stokes equations.

FFRCT—diagnostic performance

Since the introduction of FFRCT, there have been three prospective multicenter trials evaluating the diagnostic performance of FFRCT using FFR as the reference standard. The results are summarized in *Table 1*.

The first of these studies was the Diagnosis of Ischemia-Causing Coronary Stenoses by Noninvasive Fractional Flow Reserve Computed from Coronary Computed Tomographic Angiograms (DISCOVER-FLOW) trial which evaluated 159 vessels in 103 patients with suspected or known CAD (25). Compared to CCTA alone using ≥50% to define lesion-specific ischemia, FFRCT had better specificity over CCTA. This translated to a significant reduction in false positive (FP) without compromising the sensitivity of the test. This was true at both per-patient and per-vessel level analysis, although the size of the cohort analysed was not powered for per-patient analysis.

The Diagnostic Accuracy of Fractional Flow Reserve from Anatomic CT Angiography (DeFACTO) study was the first study powered for per-patient analysis (26,28). Although FFRCT continued to show improved sensitivity and specificity, the diagnostic performance of FFRCT fell short of those previously reported and consequently, the study did not reach its primary end-point of diagnostic accuracy of ≥70% in the lower limit of 95% confidence interval (CI). The under-performance of FFRCT in the trial was thought to be predominantly due to the inconsistent and suboptimal adherence to CCTA acquisition protocol, namely beta-blocker and nitroglycerin administration (29).

With improved CFD modeling algorithm and the lessons learned from DeFACTO study, the Analysis of Coronary Blood Flow Using CT Angiography: Next Steps (NXT trial) set out to evaluate the diagnostic performance of FFRCT at per-patient basis and tested the methodology in a setting that is closer to clinical practice by having onsite coronary CCTA interpretation, rather than core laboratory adjudication, and with strict adherence to CCTA acquisition protocol (27,30). Total of 254 patients with stable CAD with 78% experienced angina within the past month across ten participating centers were recruited. FFRCT showed an excellent correlation with measured FFR. The area under the receiver operator curve (AUC) for per-patient analysis was 0.90 (95% CI: 0.87–0.94) and per-vessel analysis was 0.93 (95% CI: 0.91–0.95). Moreover, FFRCT results were highly reproducible at per-vessel interpretation with the limits of agreement between -0.06 and 0.08 and coefficient of variation of 3.3% (95% CI: 1.5–4.3%) (31).

Coronary calcification, motion and noise

The diagnostic performance of FFRCT remained robust

Table 1 Summary of clinical trials evaluating the diagnostic performance of FFRCT

Study	Year	Design	No. of patients (n)	No. of vessels (n)	Non-diagnostic (%)	Analysis	Modality	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
DISCOVER-FLOW trial (25)	2011	Prospective; 4 sites in 3 countries; powered for per-vessel analysis	103	159	0	Per-vessel	FFRCT ≤0.80	87.9	82.2	73.9	92.2	0.90
							CCTA	91.4	39.6	46.5	88.9	0.75
						Per-patient	FFRCT ≤0.80	92.6	81.6	84.7	90.9	0.92
							CCTA	94.4	24.5	58.0	80.0	0.70
DeFACTO trial (26) FFR	2012	Prospective; 17 sites in 5 countries; powered for per-patient analysis	252	407	11	Per-vessel	FFRCT ≤0.80	—	—	—	—	—
							CCTA	—	—	—	—	—
						Per-patient	FFRCT ≤0.80	90	54	67	84%	0.81
							CCTA	84	42	61	72	0.62
NXT trial (27)	2014	Prospective; 10 sites in 9 countries; powered for per-patient analysis	254	484	4.5	Per-vessel	FFRCT ≤0.80	84	86	61	95%	0.93
							CCTA	83	60	33	92	0.79
						Per-patient	FFRCT ≤0.80	86	79	65	93	0.90
							CCTA	94	34	40	92	0.81

NPV, negative predictive value; PPV, positive predictive value; FFRCT, fractional flow reserve computed tomography; AUC, area under the receiver operator curve.

in presence of coronary calcification, motion artefact and reduced signal-to-noise ratio (SNR) where CCTA would glaringly under-perform. In subanalysis of the DISCOVER-FLOW trial, FFRCT had good correlation with invasive FFR despite these challenging scenarios (32). The AUC of FFRCT and CCTA using invasive FFR as the reference standard was 0.99 and 0.79 respectively in setting of motion, 0.90 and 0.73 respectively in setting of reduced SNR and 0.90 and 0.70 respectively in presence of coronary calcification. Similarly, subanalysis of the DeFACTO trial also showed that motion and coronary calcification did not significantly compromised the diagnostic performance of FFRCT (28).

The recent subanalysis of the NXT trial further delineated the impact of coronary calcification on the diagnostic performance of FFRCT by stratifying the diagnostic performance according to the severity of coronary calcification based on Agaston score (AgS) (33). For identifying per-vessel ischemia, CCTA showed a step-wise drop in specificity with increasing coronary calcification severity. Amongst those in the lowest quartile of coronary calcification (AgS 0–0), the specificity was 72%, which dropped to 46% in vessels in the highest quartile (AgS of 121–1,703). Similarly at per-patient basis, the specificity of CCTA dropped from 37% amongst those in the lowest quartile (AgS 0–26) to 19% amongst those at the highest quartile of AgS (AgS 416–3,599) (*Table 2*). In comparison, the diagnostic performance of FFRCT did not suffer dramatically across the ascending quartile of coronary calcification severity at both per-patient and per-vessel basis and continued to show good correlation with invasive FFR in determining the presence of ischemia. The AUC for FFRCT at per-patient and per-vessel in the highest quartile of AgS was 0.86 and 0.91 respectively. Although these results are promising, it should be noted that the number of patients with severe coronary calcification in the NXT trial cohort was small with only 56 patients (22%) having AgS of >400. While interesting and important data, further assessment of the diagnostic utility of FFRCT in the setting of elevated coronary calcium scores is needed, particularly those with AgS greater than 1,000.

On site FFRCT

Due to the complexity of the algorithm, calculation of FFRCT requires analysis from an offsite supercomputer. This is often seen as a barrier to FFRCT integration. A

Table 2 Diagnostic performance of FFRCT at per-patient level analysis—subanalysis of the NXT trial (33)

Diagnostic performance of FFRCT	Q1 [AgS 0–26]			Q2 [AgS 27–147]			Q3 [AgS 148–415]			Q4 [AgS 416–3,599]		
	FFRCT	CCTA alone	P value	FFRCT	CCTA alone	P value	FFRCT	CCTA alone	P value	FFRCT	CCTA alone	P value
Accuracy	85 [73–93]	52 [38–66]	0.0004	83 [71–92]	50 [36–64]	0.0002	83 [70–92]	55 [40–68]	0.0006	74 [60–85]	42 [28–56]	0.0007
Sensitivity	92 [64–100]	100 [75–100]	0.32	77 [46–95]	100 [75–100]	0.66	83 [59–96]	78 [52–94]	0.32	88 [62–98]	94 [70–100]	0.32
Specificity	83 [68–93]	37 [22–53]	0.0001	85 [71–94]	34 [20–51]	<0.0001	83 [66–93]	43 [26–61]	0.0002	68 [50–82]	19 [8–35]	0.0002

FFRCT, fractional flow reserve computed tomography; CCTA, coronary computed tomography angiography; AgS, Agaston score.

reduce-order model, which introduces various assumptions to simplify the CFD algorithm allows for on-site analysis on a standard workstation. In a single centered retrospective study, the reduced-order model performed similarly to the original algorithm in that while sensitivity was maintained (CCTA =81.3%, FFRCT =87.5%), FFRCT significantly improved the specificity of CCTA for lesion-specific ischemia from 37.6% to 65.1% (34). Not surprisingly, however, the reduced-order model did not correlated with measured FFR as well as the original model used in NXT trial (R=0.59 *vs.* 0.82) (27). Nonetheless, reduced-order FFRCT added incremental value to the discriminatory power of CCTA by improving the specificity and thereby reducing FP results. These early results show potential for these reduced-order models to offer simplified workflows despite the limitations associated with onsite processing, such as the limitations of anatomical modeling using advanced sub-voxel analysis made possible via advanced machine learning techniques.

Clinical utility of FFRCT

Prospective LongitudinAl trial of FFRCT: Outcome and Resource IMpacts (PLATFORM) study is the first clinical trial to evaluate the clinical impact of using FFRCT in the clinical management of patients with stable CAD (35). Amongst the 584 symptomatic patients enrolled with intermediate likelihood of obstructive CAD, patients were stratified into two arms: the first strata consisted of patients who were referred for non-invasive testing and were randomized to undergo the planned non-invasive testing or CCTA-FFRCT; the second strata consisted of patients who were referred for invasive testing and were randomized to undergo ICA or CCTA-FFRCT.

Amongst the 380 patients in the second strata who were intended for invasive testing, the use of CCTA-FFRCT led to better patient selection for ICA. Obstructive CAD was found in 88% of patients randomized to CCTA-FFRCT compared to only 27% (P<0.0001) in usual care group (36). This is despite 62% of those in the usual care group having had non-invasive testing prior to their intended ICA. The use of CCTA-FFRCT strategy also led to ICA cancellation in 61% (n=118/193) of patients without subsequent increased risk in death or non-fatal MI (37).

At 1-year follow-up, no difference was seen in major adverse cardiovascular event (MACE) and rate of coronary revascularization between CCTA-FFRCT and usual care strategies amongst patients intended for non-invasive

or invasive testing (37). However, due to the lower-risk patient cohort and therefore low event rates, the study was grossly underpowered for these clinical end-points. A larger sample size with longer follow up was deemed necessary to further evaluate the merits of FFRCT-guided therapy. The Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care (ADVANCE) study aimed to address these issues is currently underway with the intended recruitment size of 5,000 patients with 1–3 years anticipated follow-up data (Registered clinical trial: NCT02499679).

The cost-effectiveness of FFRCT in the diagnostic pathway was also evaluated in the PLATFORM trial. The analysis at 90 days showed that amongst those intended for invasive testing, CCTA-FFRCT strategy resulted in a 32% cost reduction per-patient compared to usual care (USD 7,343 *vs.* 10,734, P<0.0001) which was primarily driven by less frequent referral for invasive testing in the CCTA-FFRCT group (38). At 1-year follow-up, CCTA/FFRCT strategy continued to demonstrate a 33% cost saving over usual care amongst those intended for invasive testing (USD 8,127 *vs.* 12,145, P<0.0001) (37). For the strata of patients intended for non-invasive testing, although CCTA/FFRCT strategy resulted in slightly more ICA (18% *vs.* 12%) and more revascularization (10% *vs.* 5%), the net per-patient cost was not significantly different between the two groups at 90 days (USD 2,679 *vs.* 2,137, P=0.26) (38) and at 1 year (USD 3,049 *vs.* 2,579, P=0.82) (37). When FFRCT was assigned a cost weight equal to CCTA, however, the cost was significantly higher in the CCTA-FFRCT group compared to usual care group in those intended for non-invasive testing. Therefore selective use of CCTA-FFRCT in those intended for ICA resulted in cost saving but not in those intended for non-invasive testing.

Real world clinical experiences with FFRCT

The first real world experience data incorporating use of CCTA-FFRCT in the diagnostic pathway of symptomatic patients has recently been published (39). In a single-centered study evaluating 1,248 patients, CCTA was performed in 1,173 patients (94%) in whom 16% were referred for FFRCT and 7% were referred directly to ICA based on the CCTA result. The decision for sending for FFRCT was primarily base on the coronary anatomy of 1 or 2 intermediate stenosis defined as 30–70% luminal narrowing. Those with <30% stenosis had no further investigation and 31% of these patients were started on lipid-modifying therapy, aspirin and/or anti-anginal therapy. Myocardial perfusion imaging was performed in 4% of patients due inconclusive CCTA.

Amongst those sent for FFRCT, 98% were diagnostic and 31% were FFRCT positive (defined as FFRCT ≤0.80). FFRCT correctly classified 73% of patient and 70% of vessels as adjudicated by FFR. Amongst those with FFRCT positive and underwent ICA, only 45% received revascularization, inferring a high FP rate at the 0.80 threshold of FFRCT (*Figure 1*). Using the FFRCT cut-off value of 0.75, the number of patients who received revascularization increased to 70%. It is however, unclear what the consequence of using a less conservative FFRCT value of ≤0.75 has on clinical outcome and reflects the uncertainty in those with FFR of 0.75–0.80. Accordingly the author recommended 3 months follow-up to evaluate for symptoms. Amongst the 69% of patients with FFRCT >0.80 in whom ICA was deferred no adverse cardiac event was observed during 12 months follow-up.

The single-center study therefore illustrated the feasibility of incorporating the use of FFRCT to further improve patient selection to ICA and safely deferring invasive testing for those with FFRCT >0.80. Although both PLATFORM and Nørgaard *et al*. have provided insight into the clinical utility of CCTA-FFRCT strategy in evaluating symptomatic patients with stable CAD, more data are needed to understand its impact on long term clinical outcomes.

FFRCT and myocardial perfusion imaging

In an era filled with multitude of non-invasive imaging for symptomatic patients with suspected CAD, FFRCT represent another investigative modality, which attempts to find a niche in the diagnostic pathway. For lesion specific ischemia, single photon emission computed tomography (SPECT) is commonly used in conjunction with anatomical findings to determine the significance of a lesion non-invasively. Other modalities include stress echocardiography, stress cardiac magnetic resonance imaging (sCMR), positron emission tomography (PET) and more recently myocardial perfusion CT (CTP). There is however, little guidance as to which is the modality of choice and how FFRCT perform in comparison to these other modalities. To-date there has been limited data making direct comparison between FFRCT and these other modalities. In a recent meta-analysis by Danad *et al.* attempted to address this issue by analyzing the diagnostic

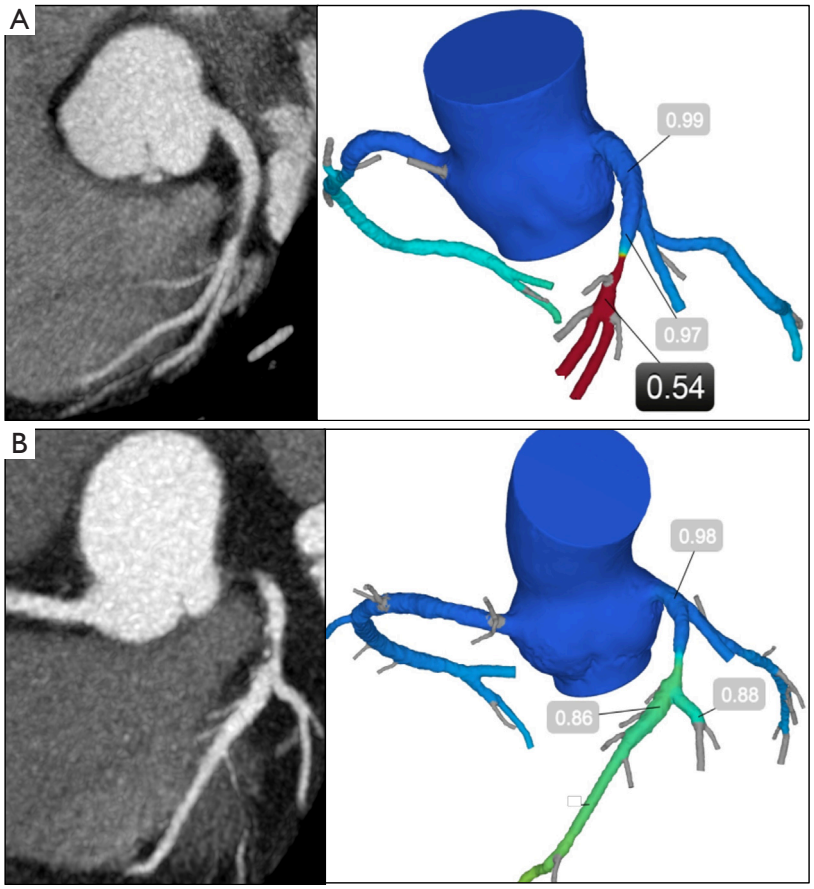

Figure 1 Intermediate lesions with (A) positive flow reserve computed tomography (FFRCT) and (B) negative FFRCT.

performance of these individual modalities using invasive FFR as the reference standard (40). sCMR had the highest diagnostic accuracy in identifying lesion-specific ischemia [sensitivity 91% (range, 84–95%); specificity 85% (range, 79–89%)], followed by FFRCT [sensitivity 83% (range, 78–87%); specificity 78% (range, 78–81%)], which outperformed SPECT [sensitivity 57% (range, 49–64%); specificity 75% (range 69–80%)]. Unfortunately, there was insufficient data on the diagnostic accuracy of other modalities in identifying lesion-specific ischemia.

Coronary plaque and fractional flow reverse interplay

The discordance between severity of luminal narrowing and the functional impairment of obstructive CAD remains poorly understood (*Figure 2*). Furthermore, little is known as to the clinical significance of tapering FFR to ≤0.80 in distal vessels without focal area of stenosis. Although the length of lesion, size of the reference vessel and presence of collaterals may in part explain some of these discrepancies, many are left unexplained.

Coronary plaque with adverse plaque characteristics (APC) of positive remodelling (PR), low attenuation plaque (LAP) and increased plaque burden are associated with future acute coronary syndrome (ACS) (41-43). More recently, there is increasing evidence illustrating the predictive nature of APC in identifying lesion-specific ischemia. In a study involving 58 patients with angiographically determined intermediate stenosis (30–69%), the aggregate plaque volume (APV) was shown to be predictive of lesion-specific ischemia (44). The AUC in presence of high APV was 0.85 compared to 0.68 for degree of luminal stenosis alone. Exploring this concept further, the subanalysis of the NXT trial included 484 vessels interrogated by CCTA, FFRCT and FFR and found that lesions with LAP had a 4-fold relative increased risk of lesion-specific ischemia independent of the degree

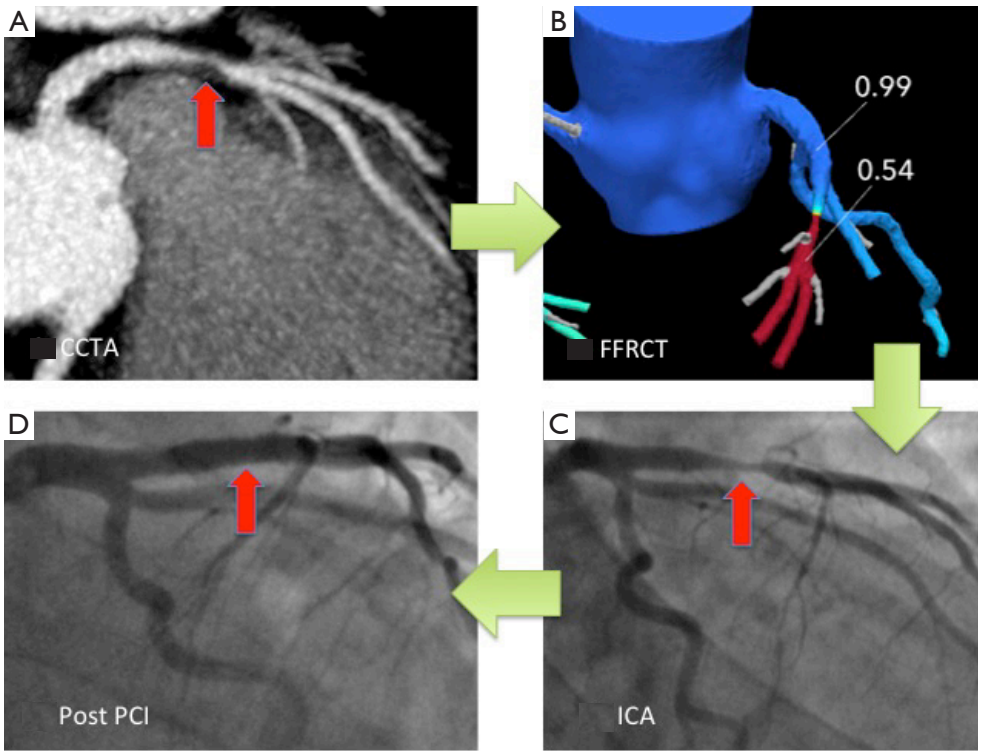

Figure 2 Case example of the clinical utility of flow reserve computed tomography (FFRCT). A 57 years old man with typical stable angina, underwent computed tomography angiography (CCTA) (A) and high grade stenosis identified in the left anterior descending (LAD) artery. CCTA dataset was sent for FFRCT analysis (B) and determined that the lesion was functionally significant. Invasive coronary angiography (ICA) confirmed severe proximal LAD stenosis (C) and the lesion was stented (D).

of luminal narrowing (45). The combination of LAP and FFRCT improved the AUC for lesion-specific ischemia from 0.79 for CCTA alone to 0.93. Total plaque volume using an absolute value of ≥195 mm^3 in this study was, however, not predictive of lesion-specific ischemia.

Building on this finding, recent prospective trial with 252 patients recruited across 5 countries further evaluated the 4 APC of LAP, APV, PR and spotty calcification (SC) and their predictive value in identifying lesion-specific ischemia (46). Ischemia-causing lesions were found to be more likely to have increased APV, PR, LAP and SC compared to those without ischemia. With each additional APC, there was an incremental increase in the likelihood of lesion-specific ischemia and with ≥2 APC, there was a 20-fold increased likelihood of lesion-specific ischemia. When APC were evaluated according to severity of stenosis, PR was highly predictive for lesion-specific ischemia in lesions with <50% and ≥50% stenosis (OR 10.5 and 3.6 respectively), whereas LAP and APV were only predictive in lesions with ≥50% (OR 2.5 and 1.8 respectively). SC was not predictive regardless of the degree of luminal stenosis. It has therefore been proposed that the presence of LAP and PR—the 2-feature-positive plaque (2FPP), causes impaired vasodilatory capacity of the vascular wall which is further exasperated by local inflammatory state induced by the presence of lipid necrotic core and thereby causing flow restriction (47).

Therefore beyond luminal narrowing, APC may explain the discordance between severity of luminal stenosis and impairment of FFR. The combination of these 3 parameters may help us understand and improve prediction of future adverse cardiovascular events and by doing so more aggressive preventative measures could be taken.

Virtual stenting

With patient specific complex geometric modeling of the coronary tree as part of the FFRCT analysis, virtual stenting of coronary lesion to examine the hemodynamic effect of revascularization is now possible. After the initially

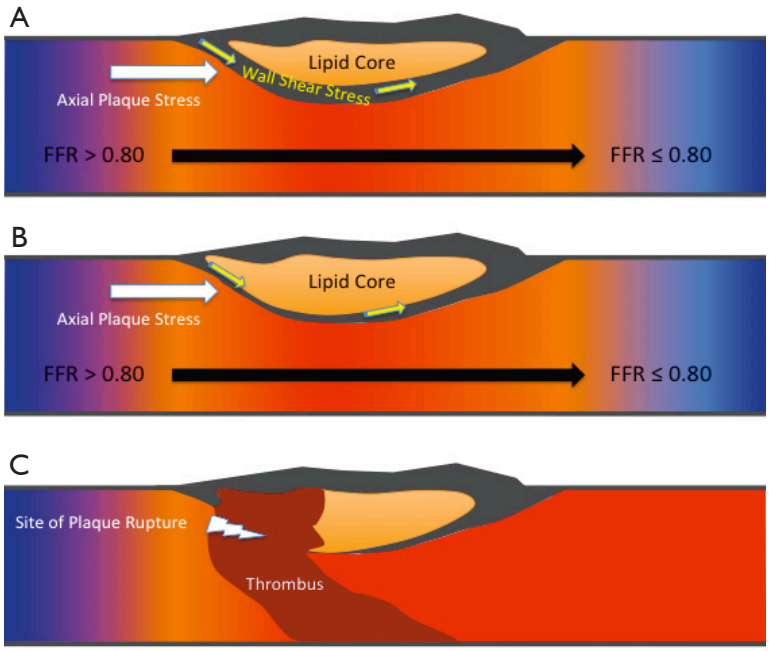

Figure 3 Adverse plaque characteristics and hemodynamic interplay. (A) Intermediate lesion with thick fibrous cap and lipid-rich core experience axial plaque stress and increased wall shear stress (WSS) associated with hemodynamic impairment; (B) regression of fibrous cap to thin fibrous cap and increase lipid content (49); (C) disruption of the thin fibrous cap from persistent external hemodynamic stress resulting in plaque result and acute coronary syndrome (ACS) (50).

modelling of patient-specific coronary geometry including lesion stenosis to derive baseline FFRCT value, the coronary model is modified to reflect restoration of lumen diameter via virtual stenting. FFRCT is then recalculated to account for the luminal change and thereby allowing the assessment of the hemodynamic impact of revascularization. In a prospective feasibility study involving 44 patients with predominantly single coronary lesion, FFRCT pre- and post-coronary stenting values had good correlation to FFR values measured invasively (48). Although larger cohort is needed to validate the use of this technology, the implications of this is wide and include determining which lesion requires revascularization, whether the lesion is amendable to PCI and allow the examination of the hemodynamic effect post-intervention, particularly on tandem lesions.

Extending the horizon beyond FFRCT: wall shear stress (WSS) and axial plaque forces

Beyond the ability to derive FFRCT, assessing the shear stress of plaque lesions and quantifying the biomechanical forces are also within reach of the technology. WSS is the tangential force exerted on per unit area of the luminal surface and axial plaque stress (APS) is the axial component of stress acting upon the lesion (49) (*Figure 3A*). Where APS is closely related to the absolute pressure on the surface of the plaque, WSS is closely related to the coronary flow and pressure gradient across the lesion. Importantly, APS is orders of magnitude greater than the forces associated with shear. The relative impact that each of these distinct forces has on the risk of plaque rupture and subsequent ACS is the subject of ongoing investigation. The presence of increased WSS has been shown to be 20 times more likely to be associated with plaque that exhibit APC, particularly LAP and PR (50). Previous experimental study showed that over 6 months, those with WSS had progression of coronary plaque with necrotic core, dense calcium and regression of fibrous tissue—features associated with high risk of plaque rupture (*Figure 3B*). Yet it is unclear what the underlying relationship is between WSS and adverse plaque. It is possible that coronary plaque develops and alters the coronary geometry, leading to alteration of flow dynamic. The external hemodynamic force eventually led to disruption of the fibrous cap resulting in plaque rupture at the site with the highest APS (*Figure 3C*) (51,52). It remains

unclear however, the mechanism which initiated the plaque deposition in the first instance.

Conclusions

FFRCT has been shown to be an excellent diagnostic tool which adds incremental value to CCTA by improving the specificity of assessing for ischemia at both per-patient and per-vessel basis. Initial results from the PLATFORM trial suggested that a CCTA-FFRCT strategy could offer an opportunity in reducing the number of patients being referred to catheterization laboratory with non-obstructive coronary artery disease. Furthermore those with FFRCT >0.80 has been consistently shown to have excellent medium-term follow up and deferring revascularization in these patients were safe. Ongoing real world registry data from ADVANCE will undoubtedly prove invaluable in further understanding what role FFRCT will play and how to best use it to optimize the clinical outcomes of the patients we serve.

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Footnote

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