Review Article

Myocardial ischemia testing with computed tomography: emerging strategies

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Abstract: Although cardiac computed tomography (CT) has high negative predictive value to exclude obstructive coronary artery disease (CAD), particularly in the low to intermediate risk population, it has low specificity in the diagnosis of ischemia-inducing lesions. This inability to predict hemodynamically significant stenosis hampers the ability of CT to be an effective gatekeeper for invasive angiography and to guide appropriate revascularization. Recent advances in CT technology have resulted in the development of multiple techniques to provide hemodynamic information and detect lesion-specific ischemia, namely CT perfusion (CTP), CT-derived fractional flow reserve (CT-FFR) and coronary transluminal attenuation gradient (TAG). In this article, we provide a perspective on these emerging CT techniques in the evaluation of myocardial ischemia.

Keywords: Cardiac computed tomography (CT); myocardial ischemia; CT perfusion (CTP); flow; CT-derived fractional flow reserve (CT-FFR)

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Introduction

Coronary computed tomography angiogram (CCTA) has high accuracy and negative predictive value (NPV) in the evaluation of coronary artery disease (CAD), particularly in the low to intermediate risk population, both in the stable and emergency settings (1-3). In current practice, CTA is used in symptomatic patients in the low-to-intermediate risk category with equivocal stress tests or those unable to perform stress test; however, it can be used as an index test in these patients since studies have shown similar clinical effectiveness to stress testing (4-8). CCAT also provides information on the vessel wall and characteristics of atherosclerotic plaques. CT is however limited in its ability to characterize the hemodynamic significance of a stenotic lesion, with low specificity (39% per-patient, 58% per-vessel) and low positive predictive value (PPV) compared to invasive fractional flow reserve (FFR) (9,10). Knowledge of the functional consequence of an intermediate coronary arterial stenosis is required for further management, including the need for further invasive coronary angiogram (ICA), which is typically provided by stress tests such as exercise stress test, stress echocardiogram, stress perfusion magnetic resonance imaging (MRI) and nuclear medicine techniques [single-photon emission CT (SPECT) and positron emission tomography (PET)]. These tests are not perfect and hence up to 63% of ICA studies end up being unnecessary, with either normal or non-obstructive CAD, in spite of a majority of these patients (up to 84%) having had a prior positive non-invasive imaging test (11,12). Accurate functional information is provided by invasive

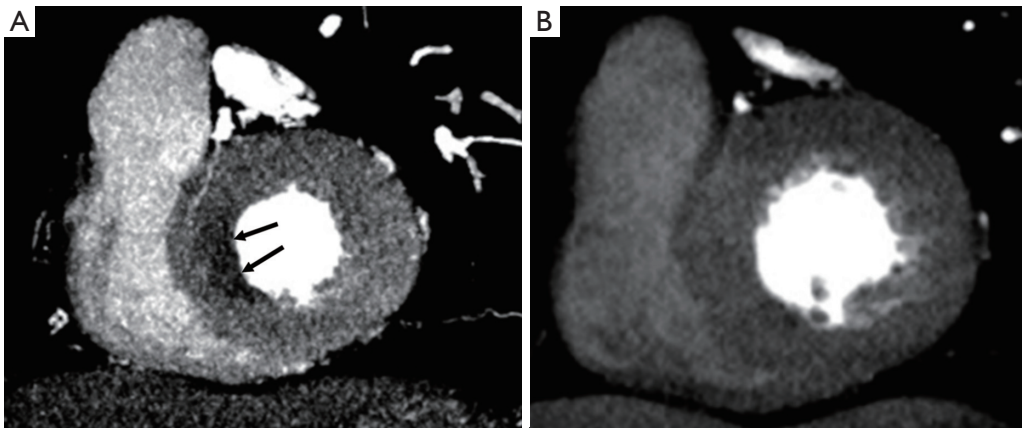

Figure 1 CT perfusion. (A) Short axis stress perfusion CT image obtained at 45% of R-R interval in a patient with chest pain, shows a sub-endocardial perfusion defect in the basal septum (arrows); (B) rest CT perfusion image in the same patient at the same level does not show the defect. These findings are consistent with reversible myocardial ischemia. CT, computed tomography.

FFR during the ICA, and FFR-guided revascularization has shown improved outcomes and lower cost compared to angiographic stenosis-guided revascularization (13,14). However, due to the small but finite risks of cardiac catheterization, it is not appropriate to perform invasive FFR in all patients with suspected CAD.

Hence, there is a need for a reliable non-invasive imaging test that can accurately identify lesion-specific ischemia, act as an effective gatekeeper for ICA, reduce unnecessary ICA, and guide appropriate revascularization, all of which will result in improved clinical outcomes and lower costs. Since CT provides good morphological information including the vessel wall, if it is also able to provide functional information, it can potentially become a one-stop shop imaging modality in the evaluation of CAD. Recent advances in CT technology have resulted in the development of multiple techniques to provide hemodynamic information and detect lesion-specific ischemia, namely CT perfusion (CTP), CT-derived FFR (CT-FFR) and coronary transluminal attenuation gradient (TAG). In this article, we provide a perspective on these emerging CT techniques in the evaluation of myocardial ischemia.

CTP

CTP utilizes the iodine uptake of myocardium during the first pass of contrast as a surrogate for myocardial perfusion with ischemia characterized by reversible low myocardial attenuation (hypoperfusion) on stress images, with normal myocardial attenuation on resting images (*Figure 1*). CTP techniques are heterogeneous, either static or dynamic and can be done with either single or dual energy technology. Single-energy scanners can be conventional, wide-detector array/volume scanners or dual-source with high-pitch helical mode and dual-energy scanners can be dual source, rapid kVp switching or dual layer technology. A variety of pharmacological agents can be used for provocative stress, the most common of which include the coronary vasodilators adenosine and regadenoson. A variety of CTP protocols have been described, with rest and stress images obtained in variable order, with or without delayed enhancement for estimation of myocardial scar/fibrosis. Static CTP provides a snapshot of myocardial perfusion in one timeframe, usually 8–16 seconds after peak aortic attenuation. Although this does not provide quantitative information, qualitative or semi-quantitative (transmural perfusion ratio) measurements can be obtained. Qualitative analysis of ischemia depends on relative myocardial hypoattenuation compared to normal attenuation of the adjacent myocardium. Thus, analogous to SPECT myocardial perfusion imaging (MPI), balanced ischemia of all three myocardial territories may be missed (15,16). Dual energy techniques have improved sensitivity and specificity for detecting myocardial perfusion defects by using virtual monoenergetic images and iodine maps which can reduce beam-hardening artifacts (15) and allow quantification of myocardial blood flow. Beam hardening artifacts are caused by polyenergetic nature of the X-ray beam and lead to low attenuation in the myocardium adjacent to dense

contrast in left ventricular (LV) blood pool, especially in the posterobasal wall, mimicking perfusion defect. Virtual monoenergetic images at higher energies (>70 keV) have been shown to have lower beam hardening (17-20). Dynamic CTP images the myocardium several times during the first pass of contrast and generates a time attenuation curve, from which perfusion can be measured using semi-quantitative or fully automated quantitative techniques. However, dynamic CTP is associated with higher radiation exposure, longer breath-hold time, and spatial misregistration compared to static CTP.

CTP has been validated in multiple trials against SPECT, PET, MRI and ICA (*Table 1*). Single-energy static CTP has overall sensitivity of 50–96%, specificity of 68–98%, NPV of 79–98% and PPV of 55–94% (16). Dual-energy static CTP has overall sensitivity of 68–99%, specificity of 72–99%, NPV of 79–98 % and accuracy of 83–97% (16). In a meta-analysis, combined CTA and CTP showed pooled per-vessel sensitivity and specificity of 85% and 93% respectively for diagnosing >50% stenosis with ICA as the gold standard (53). Against the invasive FFR gold standard, a small study of 42 patients in a 320-slice scanner showed that CTP has 84% specificity and 82% PPV on a per-vessel basis in the diagnosis of lesion specific ischemia (33). The combination >50% stenosis on CTA and perfusion defect on CTP is 98% specific for ischemia, while stenosis <50% and normal perfusion on CTP is 100% specific for excluding ischemia (33). Another meta-analysis with invasive FFR as gold standard found that CTP can exclude hemodynamically significant stenosis and serve as an effective gatekeeper for ICA with a per-patient negative likelihood ratio of 0.12, which is comparable to MRI (0.14) and PET (0.14) and superior to SPECT (0.39) and echo (0.42) (54). Further, in a small study on 48 patients from the CORE320 trial who underwent ICA, CTA and either CTP, MRI or SPECT, patient satisfaction was higher when using a strategy of combined CTA + CTP (55).

Although no large-scale outcomes data exist for CTP, similar data from SPECT-MPI show that MPI can increase continuous net reclassification index (NRI) by 49.4%, reclassifying 66.5% as lower risk and 32.8% at higher risk of death or non-fatal myocardial infarction (MI) (56). A recent study with dynamic CTP showed that the presence and number of perfusion defects were associated with higher risk of major adverse cardiac events (MACE), which is incremental over clinical risk factors and obstructive coronary stenosis in CTA (57). Adding CTP to CTA results in 5-fold reduction in downstream ICA and revascularization with a low 12-month MACE rate (58). CTP with dual-energy has also shown to be more cost-effective than SPECT, with an incremental cost-effective ratio (ICER) $3,191 per quality-adjusted life year (QALY) compared to $3,357 per QALY for SPECT (59).

However, CTP is not widely available in all CT centers, and requires advanced skills in performance, post-processing and interpretation. CTP is also associated with higher radiation exposure, larger volume of iodine contrast and higher costs when compared to CTA alone. Radiation exposure estimates range from 4.5 to 9 mSv for static CTP techniques, which remain lower than traditional SPECT MPI protocols (60).

CT-FFR

CT-FFR is a non-invasive technique of estimating FFR across a coronary stenosis using anatomic data from cardiac CT without any protocol change or additional contrast/radiation. It is based on computational fluid dynamics modelling of cardiac CT data using advanced post-processing and 3D Navier-Stokes equations to solve for flow and pressure measurements across the coronary vascular bed. Currently, CT-FFR relies on a series of mathematical assumptions including the relationship between resting myocardial blood flow and mass, the relationship between microvascular resistance and epicardial coronary size, and a predictable coronary response to adenosine. Such assumptions may limit the accuracy of CT-FFR in certain patient populations (e.g., unstable angina). Hyperemic state is simulated by reducing microvascular resistance by a factor of 0.21. Currently, the most commonly used platform is the *HeartFlow*, in which data is transferred off-site for advanced post-processing, although there are on-site vendor-based hybrid platforms (e.g., Siemens) which use machine learning, reduced-order models in non-stenotic regions and pressure drop models in stenotic regions (61,62). CT-FFR <0.8 is used as a cut-off for a functionally significant stenosis (*Figure 2*). In many centers, CT-FFR data is usually requested retrospectively if moderate luminal stenosis is detected on CTA, to evaluate if the lesion is hemodynamically significant. Interestingly, FFR has been shown to be abnormal in 16.6% of patients with <50% stenosis [ischemia without stenosis (IWOS)], normal in 33% of patients with >70% stenosis [stenosis without ischemia (SWOI)] and abnormal in only 50% of patients with moderate (50–70%) stenosis, suggesting CT-FFR may be appropriate for interrogating a wider spectrum of coronary lesions (63,64). In the case of tandem

Table 1 Diagnostic performance of CT perfusion in various studies

Studies	Acquisition	Energy	Reference standard	Level	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Kurata *et al.* (21)	Static	Single	ICA	Vessel	90	79	NA	NA
George *et al.* (22)	Static	Single	SPECT	Vessel	50	89	55	87
Blankstein *et al.* (23)	Static	Single	SPECT	Vessel	84	80	71	90
Cury (24)	Static	Single	SPECT	Patient	94	78	89	87
George *et al.* (25)	Static	Single	SPECT, ICA	Patient	86	92	92	85
Cury *et al.* (26)	Static	Single	SPECT, ICA	Vessel	88	79	67	93
Rochitte *et al.* (27)	Static	Single	SPECT, ICA	Patient	80	74	65	86
Nasis *et al.* (28)	Static	Single	SPECT, ICA	Vessel	94	98	94	98
Osawa *et al.* (29)	Static	Single	ICA	Vessel	85	94	79	96
Kachenoura *et al.* (30)	Static	Single	ICA	Patient	96	68	88	87
Rocha-Filho *et al.* (31)	Static	Single	ICA	Vessel	91	91	86	83
Bettencourt *et al.* (32)	Static	Single	Invasive FFR	Patient	89	83	80	90
Ko *et al.* (33)	Static	Single	Invasive FFR	Vessel	76	84	82	79
Feuchtner *et al.* (34)	Static	Single	MRI	Vessel	96	88	93	94
Weininger *et al.* (35)	Dynamic	Single	SPECT	Segment	84	92	88	92
	Dynamic	Single	MRI	Segment	86	98	94	96
Ho *et al.* (36)	Dynamic	Single	SPECT, ICA	Segment	83	78	79	82
Wang *et al.* (37)	Dynamic	Single	SPECT, ICA	Segment	85	92	55	98
Greif *et al.* (38)	Dynamic	Single	Invasive FFR	Vessel	95	74	48	98
Rossi *et al.* (39)	Dynamic	Single	Invasive FFR	Vessel	88	90	77	95
Huber *et al.* (40)	Dynamic	Single	Invasive FFR	Vessel	76	100	100	90
Bamberg *et al.* (41)	Dynamic	Single	Invasive FFR	Vessel	93	87	75	97
	Dynamic	Single	MRI	Vessel	100	75	92	100
Bastarrika *et al.* (42)	Dynamic	Single	MRI	Segment	86	98	94	96
Meinel *et al.* (43)	Static	Dual	SPECT	Segment	99	97	92	100
Ruzsics *et al.* (44)	Static	Dual	SPECT	Segment	92	93	83	97
Carrascosa *et al.* (45)	Static	Dual	SPECT	Segment	74	95	–	–
Kido *et al.* (46)	Static	Dual	ICA	Vessel (CTP + CTA)	67	92	84	82
De Cecco *et al.* (47)	Static	Dual	ICA, SPECT	Patient	95	50	NA	NA
Wang *et al.* (48)	Static	Dual	SPECT, ICA	Segment	89	98	87	98
Ko *et al.* (49)	Static	Dual	ICA	Vessel	89	74	80	85
Ko *et al.* (50)	Static	Dual	MRI, ICA	Vessel	42	83	59	70
Kim *et al.* (51)	Static	Dual	MRI	Segment	77	94	53	98
Ko *et al.* (52)	Static	Dual	MRI	Segment	89	78	74	91

PPV, positive predictive value; NPV, negative predictive value; ICA, invasive coronary angiogram; SPECT, single-photon emission computed tomography; FFR, fractional flow reserve; MRI, magnetic resonance imaging; CTA, computed tomography angiogram; CTP, CT perfusion; NA, not available.

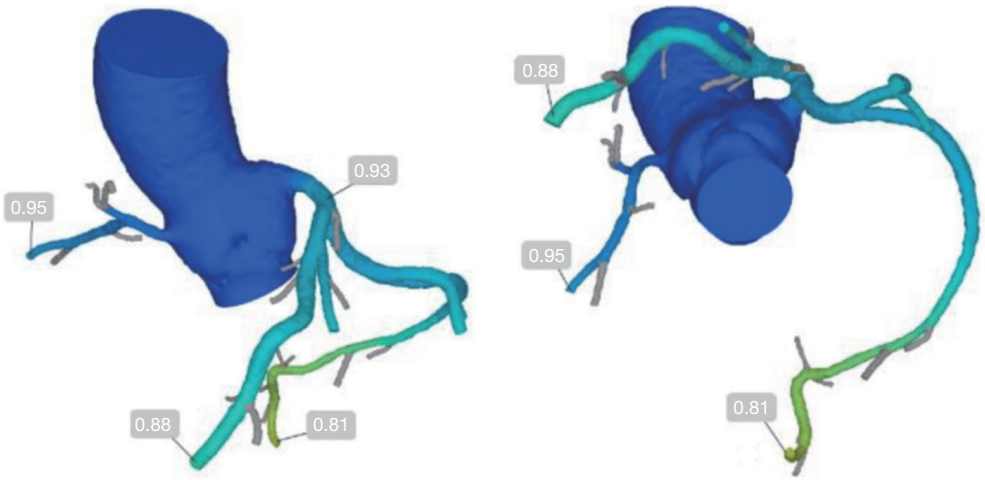

Figure 2 CT fractional flow reserve. CT-FFR values from a patient with acute chest pain and intermediate coronary artery stenosis in CTA were above 0.8, indicating that there is no hemodynamically significant coronary arterial narrowing. CT-FFR, computed tomography-derived fractional flow reserve; CTA, computed tomography angiogram.

lesions, CT-FFR has been shown to guide revascularization by identifying hemodynamically-significant culprit lesion(s) and predict the response to revascularization by placing a virtual stent (65).

Several studies have been performed using CT-FFR with good accuracy (*Table 2*) (61,62,66-72). Trials such as DISCOVER-FLOW, DEFACTO and NXT performed with the HeartFlow platform have shown significantly improved specificity of CT-FFR compared to conventional CTA (82% *vs.* 25%, 54% *vs.* 42%, 79% *vs.* 34%, respectively) for lesion-specific ischemia using invasive FFR as the gold standard, without compromising sensitivity on a per-patient basis (66-68). Studies performed with on-site platforms have also shown improved specificity of CT-FFR over CTA alone (85% *vs.* 32% and 65% *vs.* 38%) (69). A meta-analysis of five studies showed that on a per-patient basis, the pooled specificity of CT-FFR is 70% compared to 35% for conventional CTA, with additional improvements in accuracy (83% *vs.* 55%), PPV (69% *vs.* 51%), NPV (90% *vs.* 83%), and area under the curve (AUC) (0.87 *vs.* 0.74), and comparable sensitivity (89% *vs.* 90%) (71). A meta-analysis of all the seven studies showed pooled estimates of sensitivity, specificity and diagnostic odds ratio for detection of ischemic lesions of 0.89, 0.76 and 26.2, respectively (72). Another meta-analysis of all imaging methods with invasive-FFR as gold standard showed a sensitivity of 90% and specificity of 71% for CT-FFR, compared to 90% and 39% respectively for CTA, with improved specificity generated by coupling CTA and CT-FFR (10).

The improved specificity of CT-FFR beyond CTA results in conversion of false-positives to true-negatives (68% reclassification in NXT trial) in the intermediate risk group in CTA, which significantly decreases the rate of non-obstructive disease in ICA, thus improving the capabilities of CT as a gatekeeper for ICA, and selecting optimal patients for revascularization. In the RIPCORD study on 200 patients of the NXT trial, interventional cardiologists were asked to make a consensus decision on management [medical *vs.* percutaneous coronary interventions (PCI) *vs.* coronary artery bypass grafting (CABG)] based on the findings of CTA. Later, they were given the CT-FFR data and again asked to give their consensus decision on management. The management plan was changed in 36% of patients, with eventual 30% reduction in PCI, and 18% change of vessel for PCI (33), and overall combined change of 44% (73). Among these patients, 12% were reallocated from optimal medical to PCI, which is similar to that of original RIPCORD study which evaluted ICA and invasive FFR (74). Outcomes of CT-FFR have also been evaluated in few studies. In the PLATFORM trial, CT-FFR obviated need for ICA in 61% patients with chest pain and CAD who would have been referred for ICA based on results of CTA alone. Further, a CT-FFR-guided approach significantly lowered the rate of ICA demonstrating normal or non-obstructive CAD (12% *vs.* 73%) in those intended for ICA (75). A CT- FFR based strategy may also improve quality of life

Table 2 Diagnostic performance of CT-FFR in various studies

Studies	Software	Types	Reference standard	Levels	Accuracy (%)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	AUC
Koo *et al.* (66) (DISCOVER-FLOW)	HeartFlow	Multi-center, prospective	Invasive FFR	Patient	87	93	82	85	91	0.75
Min *et al.* (67) (DEFACTO)	HeartFlow	Multi-center, prospective	Invasive FFR	Patient	73	90	54	67	84	0.80
Nørgaard *et al*. (68) (NXT)	HeartFlow	Multi-center, prospective	Invasive FFR	Patient	81	86	79	65	93	0.90
Kim *et al.* (69)	HearFlow	Multi-center, prospective	Invasive FFR	Patient	77	85	57	83	62	–
Renker *et al.* (61)	Siemens cFFR	Single center, retrospective	Invasive FFR	Patient	NA	94	84	65	93	0.91
Coenen *et al.* (62)	Siemens cFFR	Single center, retrospective	Invasive FFR	Patient	75	88	65	65	88	0.83
De Geer *et al.* (70)	Siemens cFFR	Single center, retrospective	Invasive FFR	Lesion	78	83	76	56	83	NA
Baumann *et al.* (71)	Metaanalysis	Metaanalysis	Invasive FFR	Patient	83	89	70	69	90	0.87
Wu *et al.* (72)	Metaanalysis	Metaanalysis	Invasive FFR	Patient	NA	89	76	NA	NA	NA

AUC, area under the curve; CT-FFR, computed tomography-derived fractional flow reserve; NA, not available.

and lower costs. In a study by Hlatky *et al.*, CT-FFR was associated with 30% lower costs and 12% fewer MACE at 1 year compared to ICA and visual guidance (76). Among patients with CT-FFR >0.8 for whom ICA was deferred, no patients experienced MACE within a 12-month follow-up period, supporting feasibility and safety of CT-FFR in the real world (61,73).

However, CT-FFR has several limitations. A recent systematic review found that although the overall accuracy of CT-FFR is 81.9%, high accuracy is observed only at extremes of CT-FFR values. The accuracy is significantly lower in patients with borderline CT-FFR values (i.e., 0.7–0.8) (77). Furthermore, most of the trials examining CT-FFR had a low prevalence of intermediate stenosis (12.8%), implying selection of lower-risk populations who are more likely to benefit from non-invasive imaging compared to invasive FFR (77). Data comparing CT-FFR with other noninvasive tests such as SPECT MPI is limited, with one study showing no additional benefit (75). In addition, CT-FFR has only modest diagnostic performance for the detection of ischemia in non-culprit lesions in patients with recent ST-elevation myocardial infarction (STEMI), likely related to the smaller vessel volume in these patients than stable angina, with the vessel lumen volume relative to myocardial mass affecting the diagnostic performance of CT-FFR (78). Although some earlier studies showed good reproducibility of CT-FFR, this was not evaluated in the trials mentioned above (79). There is also poor numerical matching between CT-FFR and invasive FFR values, calling into question the threshold value of 0.80 used to determine lesion-specific ischemia with CT-FFR (77). Larger multicenter trials with outcomes data in specific patient populations will be required before widespread acceptance of this technology.

The added costs of CT-FFR may also be prohibitive (up to $1,500 per case) (80). However, a Category III CPT code was recently approved for CT-FFR which will allow this technology to be tracked by the American Medical Association beginning in January 2018, an important first step towards widespread coverage and reimbursement (81). Another current limitation of CT-FFR is the processing/turnaround time, often several hours when data is

transferred off-site, further challenging the evaluation of acute chest pain in the emergency room (ER) setting, although on-site solutions are currently available in some centers. High image quality is required, especially without motion and misalignment, which needs good scanners and expertise. Although the algorithm was initially limited in patients with calcium, stents and bypass grafts, a recent study found that the accuracy of CT-FFR in patients with high calcium is superior to that of CT alone (82).

Recent studies have shown that CT-FFR can provide additional information on biomechanical forces acting on plaques, such as plaque stress, plaque strain and radius gradient (83), all of which play roles in plaque initiation and progression (84). These CT-FFR derived biomechanical forces also provide superior information in predicting acute coronary syndrome (ACS) than stenosis and high-risk plaque features (AUC, 0.727 *vs.* 0.675 *vs.* 0.673, respectively) and also provides incremental risk stratification tool (85). Lipid-rich plaques with large necrotic core and positive remodeling have been shown to be associated with FFR <0.8, independent of the degree of luminal narrowing. This has been shown to be an independent predictor of ACS. With positive remodeling, the smooth muscles are stretched and possibly unable to dilate further on administration of vasodilators for invasive FFR measurement (63,64).

TAG

Coronary arterial TAG is relatively simple technique of estimating the hemodynamic significance of coronary stenosis from a routine CTA without additional contrast, radiation, change of protocol or complex post-processing. TAG is the gradient of luminal attenuation in Hounsfield units (HU) along the coronary artery and is usually measured along the coronary artery at 5-mm intervals from the ostium to the point where the arterial dimension decreases to <2 mm^2 (*Figure 3*). TAG is defined as the HU change per 10 mm of coronary artery and defined as linear regression coefficient between the luminal attenuation and length from ostium in mm. In a small study of 54 patients, a cut-off of –15.1 HU/10 mm is considered to be highly accurate, with sensitivity of 77%, specificity of 74%, PPV of 67% and NPV of 86% to predict FFR <0.8 (86). TAG has higher specificity than CT and adding TAG to CTA improves the specificity of CTA to detect functionally significant FFR (83), with improved AUC of 0.88 compared to 0.81 for TAG alone. TAG can be used in patients with unstable angina, which is a limitation of CT-FFR (86). However, this technique ideally requires a volume/wide array scanner, such as a 320-detector scanner so that the entire heart is scanned in one heartbeat. With smaller detector scanners, differences in contrast timing for different segments of the coronary arteries result in artefactual attenuation gradients and misregistration artifacts. TAG studies performed on 64–256 slice scanners did not show significant difference from CTA and were inferior to CT-FFR (87). TAG can be performed both at rest and stress with comparable AUC (0.78 and 0.75), but the image quality of stress TAG was lower along with higher radiation due to two acquisitions (88).

Comparison of modalities

An ideal comparison of the efficacy of the above-mentioned modalities will require large, multi-center randomized controlled trials. However, this is lacking and even small-scale comparison studies are limited. Since CT-FFR and CTP are fundamentally different, there is no unifying gold standard invasive test, although invasive FFR is a good surrogate. A small two-center study on 74 patients in which both dynamic CTP and CT-FFR (on-site) were performed on the same patients showed that both the techniques have comparable efficacy (accuracy, 70% both; AUC, 0.78 both; specificity, 68% *vs.* 60%; sensitivity, 73% *vs.* 82%) in the detection of hemodynamically significant stenosis with invasive FFR as gold standard (89). Whereas the combination of CTA and CTP significantly improves the diagnostic performances of either of these two techniques individually (AUC, 0.83 *vs.* 0.78), the combination of CTA and CT-FFR only results in a small, statistically insignificant improvement (AUC, 0.80 *vs.* 0.78) than either of these two techniques individually. A single functional CT variable that integrates data from both CT-MPI and CT-FFR had superior performance than these tests separately (accuracy of 79% *vs.* 70%, individually; AUC, 0.85 *vs.* 0.78, individually), indicating that these tests provide complementary information. A step-wise diagnostic work up of CT-FFR followed by selective use of CTP also had an improved accuracy of 77% than the two tests individually (86). In patients who had CT-FFR values between 0.74 and 0.85 (i.e., intermediate stenosis), the accuracy of CT-FFR alone was 55%, but combined with CTP, the accuracy increased to 77%, indicating improved hemodynamic classification of intermediate stenosis. In addition, the step-wise approach will theoretically avoid CTP in 46% of patients, i.e., 69% of territories (89). Another similar study by Yang *et al.* in

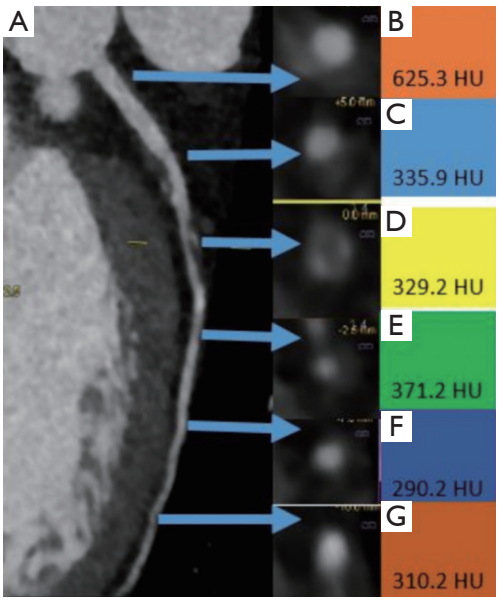

Figure 3 Transluminal attenuation gradient. (A) Left anterior descending coronary artery with non-calcific atherosclerotic plaques; (B-G) axial cross-sectional views at multiple levels are used to measure intraluminal attenuation (HU) at 5-mm intervals. TAG is defined as the HU change per 10 mm of coronary artery and defined as linear regression coefficient between the luminal attenuation and length from ostium in mm. This patient has a TAG of 36, which is considered to be significant. TAG, transluminal attenuation gradient.

72 patients using on-site FFR showed no difference in AUC between CT-FFR and CTP and the diagnostic performance of CTA (AUC, 0.856) was improved by combining it with CT-FFR (AUC, 0.919) or CTP (AUC, 0.913) (90). A meta-analysis showed that CTP and CT-FFR improve the specificity of CCTA for detecting hemodynamically significant stenosis defined by invasive FFR on a per-patient level with pooled specificities of 0.77, 0.72 and 0.43 and PPV of 0.83, 0.70 and 0.56 respectively (91).

A sub-study of NXT study showed that CT-FFR had better correlation with invasive FFR than TAG320, in terms of accuracy (93% *vs.* 78%), sensitivity (92% *vs.* 58%), specificity (79% *vs.* 86%), PPV (65% *vs.* 65%), NPV (96% *vs.* 83%), AUC (0.93 *vs.* 0.72) (87). This is likely due to the differences in principles of each technique. TAG is a surrogate for resting coronary blood flow based on in-vitro observation (87) and is likely influenced by epicardial as well as microvascular resistance; hence, a linear relationship between flow and pressure cannot be assumed (87). This is not the case with FFR, where assumptions are made for conditions of hyperemia and microvascular resistance. The low sensitivity of TAG in this study may be due to algorithmic errors in luminal contouring causing premature cessation of sampling of HU in the distal vessel, which can cause an artefactual overestimation of TAG, leading it to be less negative and hence a lot of false negatives (87). Another study which compared TAG, CTA, CTP, and integrated TAG + CTA+ CTP found that the accuracy of integrated method was superior than either TAG + CTA, or CTP + CTA, with AUC of 0.91, 0.844, 0.845, respectively in detection of FFR-significant stenosis. While CTA predicted FFR-significant stenosis with sensitivity and specificity of 89%, and 65%, respectively, corresponding values for integrated technique were 88% and 83% (92).

Perspective

It is indeed an exciting time to be a cardiac imager with at least three emerging CT techniques available for the assessment of myocardial ischemia, thus improving the capabilities of CT and moving it closer to a one-stop-shop providing anatomic and functional assessment of CAD. This combination complements the high NPV of CTA with the high specificity and PPV of functional imaging, providing an optimal strategy for guiding appropriate revascularization

Table 3 illustrates the pros and cons of these CT techniques. While CTP requires at least one additional phase of scan resulting in higher radiation dose and contrast, CT-FFR and TAG do not require any protocol modifications, radiation or contrast. The accuracy of these techniques for the detection of hemodynamically significant ischemia has been established, with more evidence available for CTP and FFR than TAG. Each technique appears to be superior to conventional CTA for detection of lesion-specific ischemia. Some studies have directly compared these techniques, but these are limited with small sample sizes. Large randomized trials will be necessary to evaluate their comparative effectiveness. Due to their fundamentally different principles, CT-FFR, CTP and TAG may be useful in different populations. For example, CTP is likely to be of greater value in the evaluation of heavily calcified lesions and coronary stents (93). CTP has shown higher diagnostic accuracy when combined with CTA in patients with heavy calcium (>400) (94). However, CT-FFR is likely to be more useful than CTP in the evaluation of balanced ischemia, since CTP relies on relative hypoperfusion compared

Table 3 Pros and cons of the different CT techniques of myocardial ischemia

Techniques	Pros	Cons
CT perfusion	Hemodynamic significance of stenosis;	Not widely available;
	Effective reclassification of stenotic lesions;	Advanced skills for performance, post-processing, interpretation;
	More cost-effective than SPECT;	Higher radiation;
	Useful in heavy calcium or stent	Larger volume of iodinated contrast;
		Higher cost than CTA alone;
		Limited in balanced ischemia
CT-FFR	Hemodynamic significance of stenosis;	Accuracy lower in borderline values (0.7 to 0.8);
	Effective gatekeeper for ICA;	Modest performance in non-culprit lesions in recent STEMI;
	Lower cost and improved outcomes compared to ICA and visual guidance;	Added cost;
	Biomechanical information on plaques;	Limited availability;
	Effective in balanced ischemia;	Long post-processing time;
	No additional radiation;	High image quality required with low motion;
	No additional contrast	Limited in calcium, stents and bypass grafts
TAG	Hemodynamic significance of stenosis;	No outcome data yet;
	No additional radiation;	Requires wide array/volume scanner
	No additional contrast;	
	No complex post-processing;	
	No additional cost	

CT-FFR, computed tomography-derived fractional flow reserve; SPECT, single-photon emission computed tomography; CTA, computed tomography angiogram; ICA, invasive coronary angiogram; STEMI, ST-elevation myocardial infarction; TAG, transluminal attenuation gradient.

to normal myocardium. CT-FFR may be more useful in patients with multi-vessel disease or serial lesions, since it can identify specific ischemic lesions that would benefit from revascularization. There have been outcomes data for CTP and FFR, with studies demonstrating that the addition of these techniques to CTA yields a more effective gatekeeper for selecting patients for cardiac catheterization by reducing the number of false positives, particularly in patients with moderate (50–70%) stenosis. This reduces the prevalence of non-obstructive disease in ICA, limiting ICA for revascularization cases, which results in overall optimization of resources and downstream cost savings.

In spite of all this evidence, significant challenges remain in the widespread adoption of these technologies, which are currently limited to select tertiary care centers. Most of these technologies require state-of-the art equipment or software, not accessible for all institutions. CTP requires a good quality scanner and considerable resources have to be invested to establish a dedicated program including advanced protocols and workflow, highly skilled staff, equipment, nursing care and post-processing. Although FFR and TAG do not require additional hardware and can be performed with a routine coronary CTA, CT-FFR performed using HeartFlow requires transfer to off-site center for advanced post-processing and involves additional fee. The on-site reduced order vendor-driven algorithms, are not yet approved and are available only in select institutions. CT-FFR also requires a high-quality CTA with minimal motion. TAG does not require any complex post processing, but it works well only with a wide-array/volume scanner, which is not available in all institutions. With the availability of such possibly competitive technologies which can be performed in different ways in different platforms, it is imperative for the cardiac CT community to take

additional steps to standardize the performance, techniques and interpretation, come up with appropriateness criteria and improve the accessibility of the technique (53).

Conclusions

CT evaluation of myocardial ischemia is now possible with state-of-the-art functional techniques such as CTP, CT-FFR and TAG. Combination of CTA and functional CT provides high negative predictive value as well as high specificity, which enables the accurate detection of ischemia-inducing lesions in patients with intermediate stenosis, and hence select appropriate patients for invasive angiography and revascularization. However, further studies are required for long-term outcomes of these tests and if and how they can replace traditional diagnostic approaches.

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Footnote

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