Review Article

Non-invasive functional assessment using computed tomography: When will they be ready for clinical use?

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Abstract: Coronary computed tomography (CT) angiography is a noninvasive and accurate diagnostic tool to detect coronary artery disease (CAD), and is increasingly utilized in clinical practice. However, anatomical information from coronary CT angiography does not always provide accurate insight into whether the stenosis causes clinically significant ischemia. With a concern that widespread use of coronary CT angiography may result in excess referral of patients to invasive coronary angiography and unnecessary revascularization of non-ischemic coronary lesions, novel methods were developed to evaluate both anatomic and functional aspects of coronary stenosis. Several studies suggested that CT assessment of myocardial stress perfusion is feasible and improves the diagnostic accuracy of coronary CT angiography in the detection of hemodynamically significant stenosis. Cardiac CT protocol including both coronary CT angiography and stress/rest myocardial perfusion can simultaneously evaluate anatomical CAD and its physiological consequences. However, significant radiation exposure and a larger volume of iodinated contrast administration are required for additional perfusion imaging. Computational fluid dynamics, as applied to coronary CT angiography, enables prediction of blood flow and pressure in coronary arteries, and calculation of lesion-specific fractional flow reserve (FFR). CT-derived FFR (FFR_{CT}) was reported to have a high diagnostic performance for detection and exclusion of ischemia-causing stenosis. Since the calculation of FFR_{CT} is performed on simulated hyperemia, it does not require modification of typical coronary CT angiography protocols, does not require the administration of additional medication and does not confer any additional radiation. CT myocardial perfusion imaging and CT-derived computed FFR represent significant advances in the field of cardiac CT, with the ability to combine anatomical data from CT angiography together with the physiologic significance of anatomical stenosis. Such non-invasive anatomic-functional testing prior to intervention may improve patient outcomes and reduce costs. Further clinical studies are needed prior to widespread clinical adoption of these diagnostic techniques.

Key Words: Coronary artery disease (CAD); computed tomography (CT); angiography; diagnostic techniques

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Rapid advances in multi-slice computed tomography (CT) imaging technology have facilitated rapidly increasing use of noninvasive coronary artery imaging, with an estimated annual 2.3 million coronary CT angiography examinations in U.S. alone (1). Currently available cardiac CT scanners have the ability to accurately image the entire coronary tree and provide information regarding the coronary lumen and vessel wall for coronary lesions. The diagnostic accuracy of coronary CT angiography for the identification of coronary artery disease (CAD) has been demonstrated in several studies, including recent multicenter trials (2-4). The consistently high sensitivity (94-99%) and negative predictive value (NPV, 97-99%) in individuals without known CAD highlight the ability of coronary CT angiography to detect and exclude obstructive coronary artery stenosis (2,3). Conversely, comparatively low specificity (64-83%) and positive predictive value (PPV, 48-86%) underscore an excessive rate of false-positive coronary CT angiography findings in which diameter stenosis severity is erroneously overestimated. Considering the role of coronary CT angiography as gatekeeper for invasive coronary angiography, these findings have raised concerns that false positive coronary CT angiography findings may precipitate unnecessary referral for invasive angiography and revascularization, resulting in substantial cost to the patient and healthcare system.

Anatomic and functional assessment

The anatomical assessment of a coronary stenosis as determined by coronary CT angiography correlates poorly with the hemodynamic significance of the stenosis (5). In a prospective study of 78 patients undergoing sequential coronary CT angiography, myocardial perfusion single-photon emission CT (SPECT), and invasive coronary angiography, the sensitivity and NPV for coronary CT angiography to detect any perfusion defect was high (94% for both), although the specificity and PPV were only 64% and 63% respectively (6). In a similar study of 79 patients undergoing coronary CT angiography and invasive angiography with fractional flow reserve (FFR) measurements, the sensitivity of coronary CT angiography by visual estimation to detect lesions with functional significance (FFR <0.75) was high (94%), while the specificity to detect such lesion was poor (40%) (5). Nevertheless, these findings did not reflect a failure of coronary CT angiography to accurately assess coronary artery stenosis, since invasive coronary angiography could not improve the diagnostic accuracy to detect myocardial ischemia (5,6). Rather, a high rate of false-positive results is seen by any method of anatomic evaluation, thus questioning the relevance of coronary stenosis detection by anatomic methods for identification of individuals who may most benefit from revascularization. Eventually, patients with obstructive CAD on coronary CT angiography need to be investigated by a subsequent functional test such as stress echocardiography, stress nuclear myocardial perfusion imaging, or magnetic resonance imaging.

Myocardial perfusion imaging with single-photon emission CT (SPECT) and positron emission tomography (PET) are well accepted and widely used to evaluate the functional significance of a CAD since they demonstrate stress-inducible perfusion defects. In appropriately selected patients, nuclear myocardial perfusion imaging has been shown to be an efficient and cost-effective strategy to avoid the use of unnecessary invasive angiography (7). However, normal myocardial perfusion does not exclude the presence of coronary atherosclerosis (8). In addition, due to limited spatial resolution, SPECT is not capable of detecting transmural differences in myocardial perfusion and has limited diagnostic performance in the setting of multivessel disease with balanced ischemia (9). Even with the improvements in spatial resolution, PET still falls short of enabling quantification of transmural extent of myocardial perfusion. Thus, there are strengths and limitations of both the SPECT and PET functional approaches and the anatomic approach of coronary CT angiography.

Alternatively, several recent studies have evaluated the feasibility of hybrid imaging by SPECT-CT or PET-CT, with aims to maximize the advantages of both functional and anatomic imaging methods (10,11). These early studies suggest enhanced diagnostic performance by hybrid imaging, as compared with functional or anatomic imaging alone, for the detection of "functionally significant" CAD. However, these modalities still require two separate imaging technologies, result in additional cost and time and significant increases in the overall radiation dose (10).

Novel technologies for non-invasive functional assessement using cardiac CT

On the basis of these considerations, several methods were developed and suggested to have the ability to combine anatomical data from coronary CT angiography together with the physiological significance during a single examination.

CT myocardial perfusion imaging

One strategy is to combine coronary CT angiography with CT perfusion imaging (*Figure 1*). Experimental work has revealed the feasibility of adenosine-augmented CT myocardial perfusion imaging for the detection of perfusion deficit during first-pass 64-detector CT imaging using a canine model (12). In this study, multidetector CT-based estimates of myocardial perfusion have been validated against microsphere-derived measurement of myocardial blood flow (12). Recently, several clinical trials have shown the feasibility and diagnostic accuracy of adenosine stress CT perfusion imaging for the detection of perfusion

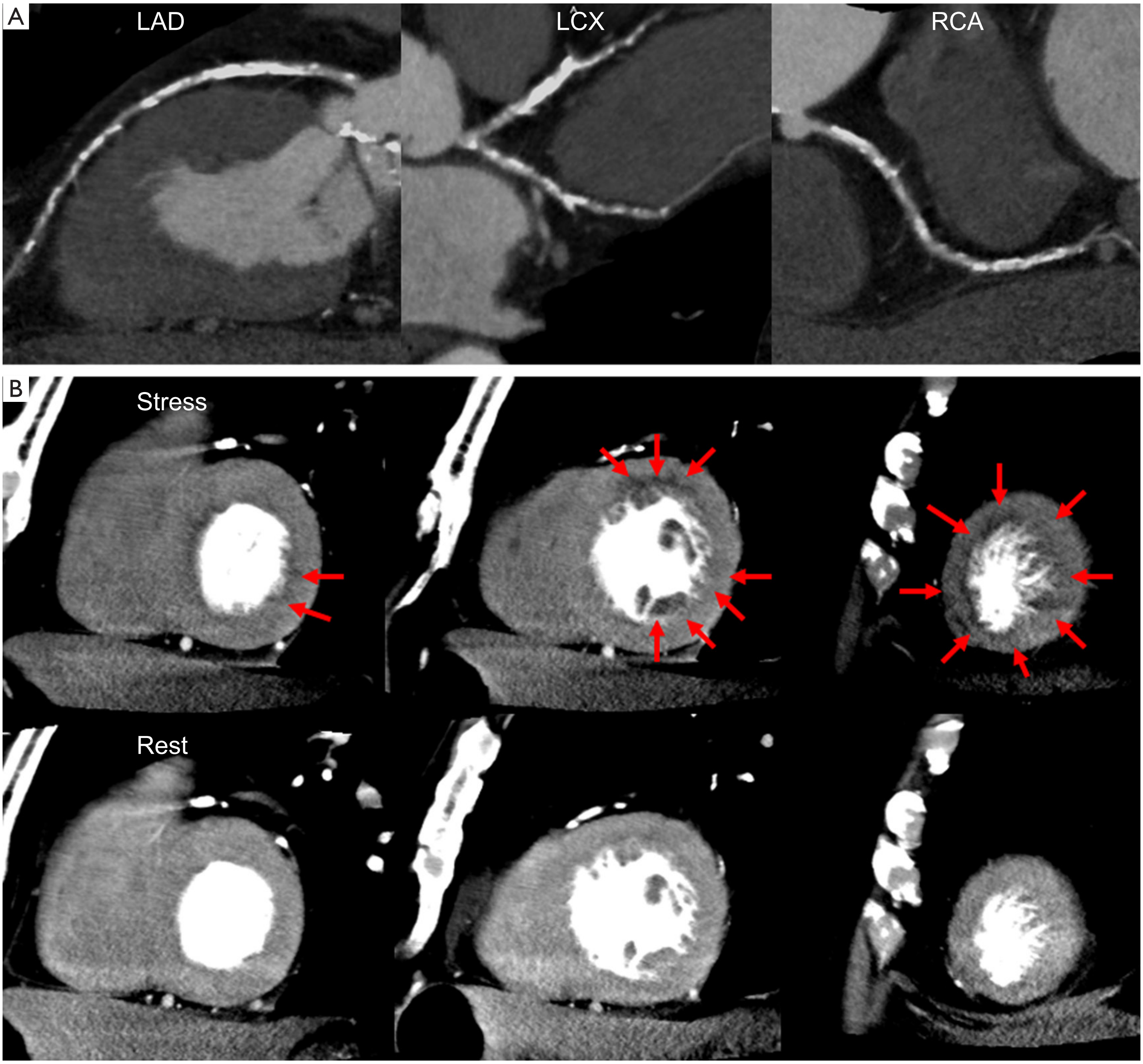

Figure 1 A case of unevaluable coronary artery stenoses by coronary computed tomography (CT) angiography due to heavy calcification, but ischemia by CT myocardial perfusion imaging. A: Coronary arteries were not assessable due to heavy calcification by coronary CT angiography; B: However, stress CT myocardial perfusion imaging showed ischemia (red arrows) suggesting flow-limiting stenoses of left anterior descending artery, left circumflex artery and right coronary artery (Images were provided by Dr. Hajime Sakuma and Dr. Kakuya Kitagawa, from Mie University Hospital, Japan.)

abnormalities, which is comparable to those of SPECT (13-15). George *et al.*, studied 40 patients with abnormal SPECT perfusion imaging who underwent adenosine stress CT perfusion and coronary CT angiography (14). In a subset of 27 patients who underwent invasive coronary angiography, CT perfusion imaging, when combined with coronary CT angiography, accurately predicted coronary stenosis causing perfusion deficits as compared to the combination of quantitative coronary angiography and SPECT as a reference standard with sensitivity, specificity,

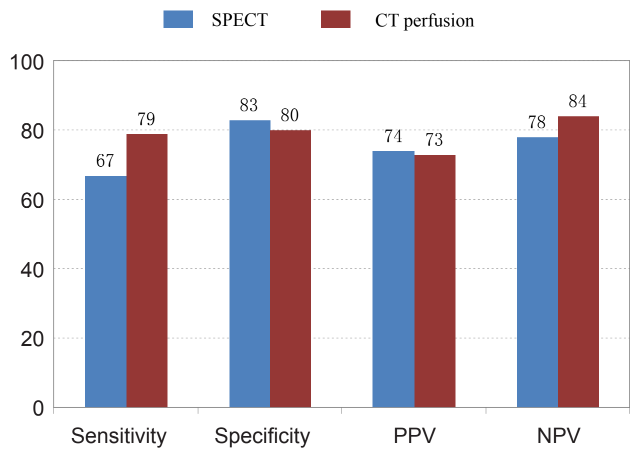

Figure 2 Diagnostic accuracy of CT perfusion and SPECT for the detection of stenosis ≥50% on a per-vessel basis (15)

PPV, and NPV of 86%, 92%, 92%, and 85%, respectively. In comparison to SPECT, CT has improved spatial resolution and is expected to be better at detecting small areas of ischemia or infarction. Importantly, in this study, CT perfusion imaging detected transmural differences in myocardial perfusion that can be accurately quantified as the transmural perfusion ratio (subendocardial/subepicardial attenuation density), and these differences were inversely related to the percentage of diameter stenosis measured at quantitative angiography (14). Furthermore, CT perfusion could offer improved accuracy for detecting multivessel disease because actual rather than relative blood flow patterns are assessed, thus avoiding false negatives that can occur in the setting of balanced myocardial ischemia.

Blankstein *et al*. reported the diagnostic accuracy of adenosine stress CT perfusion for the identification of hemodynamically significant stenosis as compared with that of SPECT (15). The study included 34 patients who underwent SPECT and invasive coronary angiography. On a per-vessel basis, CT perfusion alone had a sensitivity of 79% and a specificity of 80% for the detection of stenosis ≥50%, while those for SPECT perfusion imaging were 67% and 83%, respectively (*Figure 2*). For the detection of vessels with ≥50% stenosis with a corresponding SPECT perfusion abnormality, CT perfusion had a sensitivity of 93% and a specificity of 74%. In this study, the comprehensive cardiac CT protocol included coronary CT angiography, as well as stress perfusion, rest perfusion, and delayed-enhancement imaging, with an average radiation dose of 12.7 mSv. An important advantage of CT perfusion imaging is the ability to simultaneously visualize both anatomical CAD and its physiological consequences. However, there are several limitations that are pertinent to CT perfusion imaging. First, although the radiation exposure of comprehensive cardiac CT examination was equivalent to that of SPECT (15), it is still high. Second, in comparison to conventional coronary CT angiography, a larger volume of iodinated contrast is required as both rest and stress images are acquired. Third, CT perfusion imaging performed during adenosine infusion increases heart rate and thus the likelihood of artifactual reduction in CT attenuation densities caused by heart motion, partial volume effects, and beam-hardening artifiacts, which can be mistaken for myocardial perfusion deficits. Finally, CT perfusion imaging does not provide lesion-specific ischemia data and cannot distinguish between diffuse disease and stenoses which may be targets for revascularization. Newer scanners with wide-area coverage (such as 256-slice and 320-detector row CT scanners) permit single axial image acquisition of the heart in a single heartbeat and have several potential advantages in CT perfusion imaging. Whether simultaneous imaging of all myocardial segments renders different diagnostic performance as compared with sequential imaging of the heart remains unknown. However, shorter scanning time, with elimination of redundant radiation from helical oversampling or overlapping of sequential axial acquisitions, translates to lower than expected radiation dose, and will allow imaging at the higher heart rate commonly experienced during adenosine infusion.

CT-derived computed FFR (FFR_{CT})

Fractional flow reserve (FFR), defined as the ratio of maximal blood flow in a stenotic artery to maximal flow if the artery were normal, serves as an index of the physiologic importance of coronary artery stenosis. In the FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) study, of 1,005 patients with multivessel CAD, those that underwent FFR-guided revascularization, as compared to patients undergoing angiogram-guided revascularization, experienced lower rates of adverse events with fewer coronary stents and lower healthcare costs (16,17). However, measurement of FFR requires invasive cardiac catheterization, an expensive coronary pressure wire and intravenous or intracoronary adenosine infusion.

Computational fluid dynamics, as applied to coronary CT angiography images, represents a novel non-invasive method that quantitates coronary blood flow, flow velocity

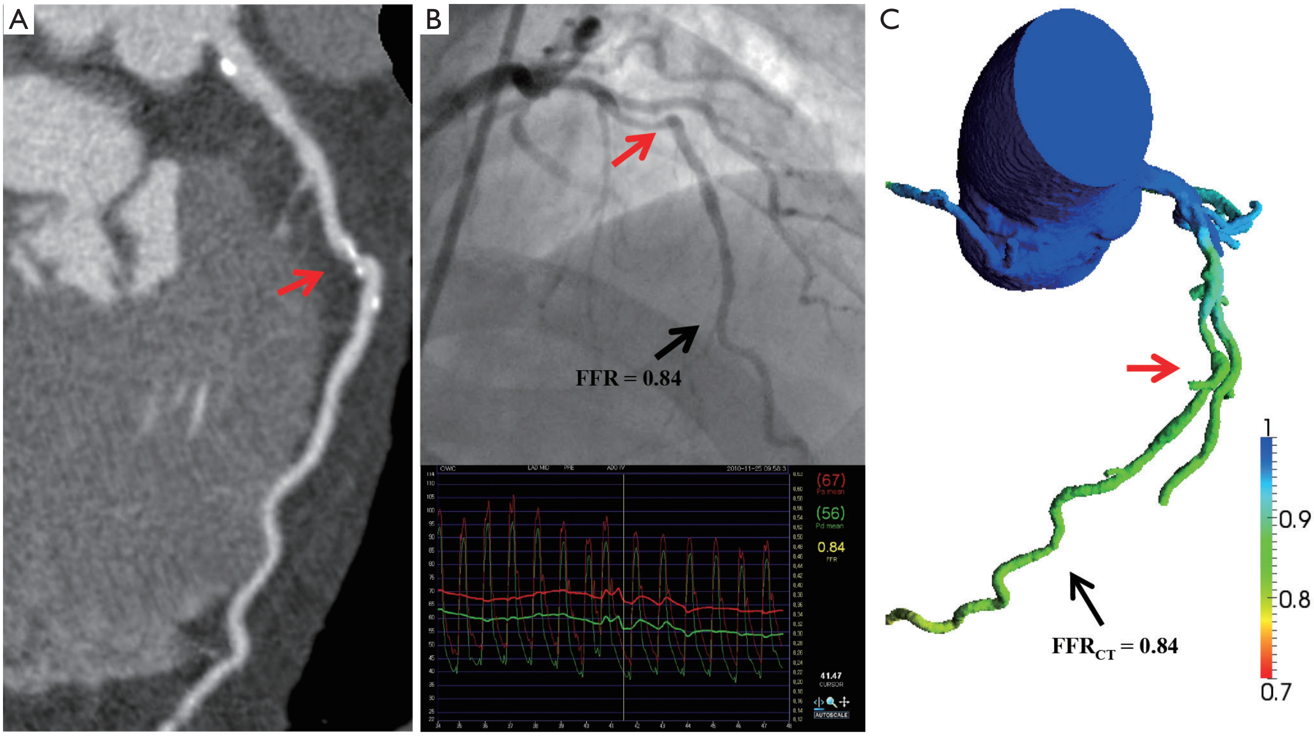

Figure 3 A case of significant stenosis by anatomical assessment, but insignificant stenosis by physiologic assessment. A: Coronary computed tomography angiography detected obstructive (≥50%) stenosis (red arrow) in the mid left anterior descending artery; B: Although invasive coronary angiography also showed obstructive stenosis (red arrow) in the mid left anterior descending artery, invasively measured fractional flow reserve (FFR) of 0.84 demonstrates no ischemia of left anterior descending artery. Similarly; C: Computation of FFR from coronary computed tomographic angiography data (FFR_{CT}) with a value of 0.84 demonstrates no ischemia in the left anterior descending artery

and pressure in the major epicardial coronary arteries. Simulation of maximum hyperemic coronary blood flow, such as occurs with adenosine infusion, allows calculation of fractional flow reserve and determination of lesion-specific FFR (*Figure 3*) (18-20). The feasibility and diagnostic performance of CT-derived computed FFR (FFR_{CT}) were evaluated in the study entitled Diagnosis of Ischemia-Causing Stenoses Obtained Via Non-invasive Fractional Flow Reserve (DISCOVER FLOW), conducted at 5 hospitals internationally, which prospectively enrolled 103 patients (159 lesions) who had undergone coronary CT angiography (21). In this study, all patients also underwent invasive angiography with FFR, with lesion-specific ischemia defined as an FFR ≤0.80. Computed FFR_{CT} values were found to have a very high degree of correlation with invasively measured FFR. As expected, coronary CT angiography alone showed high sensitivity of 91% and NPV of 89%, but comparatively low specificity of 40% and PPV of 47% for the identification of lesion-specific ischemia. By comparison, FFR_{CT} produced sensitivity of 88% and NPV of 92%, similar to those of coronary CT angiography, but much higher specificity of 82% and PPV of 74%, resulting overall accuracy increased by 25% (*Figure 4*). While the result is encouraging, the data regarding the clinical value of FFR_{CT} are still limited and further study in a larger number of patients as well as comparison to other noninvasive and invaisive studies is needed. A larger, prospective multicenter clinical trial, the DeFACTO study (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography) is similarly designed to determine the diagnostic performance of FFR_{CT} for the non-invasive assessment of lesion-specific ischemia using measured FFR as the reference standard (22). This multi-national 17 center, 285 patients study has completed patient enrollment and results are expected in the near future.

FFR_{CT} is a unique technology for the physiologic assessment of ischemia by cardiac CT. Although adenosine stress CT myocardial perfusion imaging also has the

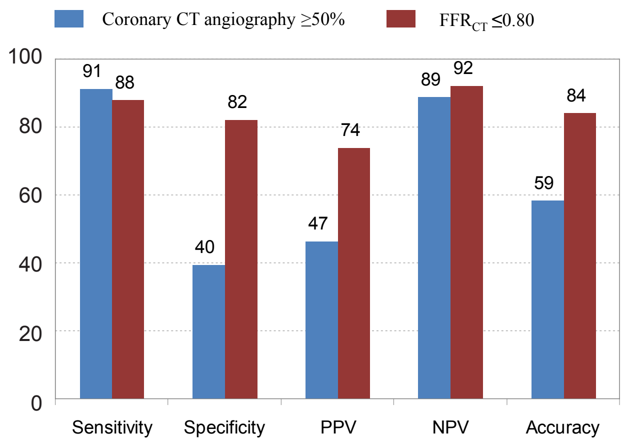

Figure 4 Diagnostic accuracy of coronary CT angiography and FFRCT for the detection of lesion specific ischemia, defined as FFR ≤0.80, on a per-vessel basis (21)

potential to assess the hemodynamic significance of an anatomic lesion, FFR_{CT} may offer several advantages over stress perfusion methods. First, FFR_{CT} technology is based on the physiologic models and the calculation of FFR_{CT} does not require modification of typical coronary CT angiography protocols, does not require the administration of additional medication including adenosine, and does not confer any additional radiation. Further given its index of epicardial stenosis-related ischemia, FFR_{CT} allows the precise pinpointing of lesions that cause functional reduction in blood flow and may thus enhance specificity of lesion detection over stress testing for which perfusion deficits may occur due to epicardial coronary stenosis, microcirculatory dysfunction or both. The calculation of FFR_{CT} requires uploading the CT scan DICOM image dataset to HeartFlow, Inc servers for image analysis, geometric modeling and supercomputer computation. This process currently takes several hours per exam. Iterative improvements in automation are expected reduce processing time in the near future.

Conclusions

Criticisms of coronary CT angiography have focused on the inability of coronary CT angiography to assess the "functional" significance of an identified coronary stenosis. CT myocardial perfusion imaging and CT-derived computed FFR represent significant advances in the field of cardiac CT, with ability to combine anatomical data from CT angiography together with the physiologic information. These noninvasive 'all-in-one' technologies may reduce unnecessary invasive coronary angiography and revascularization procedures. However, data on the clinical value and cost-effectiveness of these technologies is still limited. While non-invasive anatomic-functional testing prior to cardiac catheterization and intervention have the potential to significantly improve patient outcomes and reduce costs, further studies with appropriate and larger patient cohorts are needed prior to widespread clinical adoption of these diagnostic techniques.

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