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Update on Computed Tomography Myocardial Perfusion Imaging

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Abstract

Purpose of Review—Computed tomography (CT) coronary angiography is a well-validated non-invasive technique for accurate and expedient diagnosis of coronary artery disease (CAD). However, a limitation of coronary CT angiography (CCTA) is its limited capability to identify physiologically significant stenoses, which may eventuate the need for further functional testing. Stress CT myocardial perfusion imaging (CT-MPI) is an emerging technique that has the ability to identify flow-limiting stenoses.

Recent Findings—The combination of CCTA coronary and CT-MPI has transformed the modality from a tool to assess anatomy and morphology to a modality capable of simultaneous assessment of coronary stenoses and their physiologic significance. A growing number of studies have demonstrated the feasibility and diagnostic accuracy of CT-MPI in comparison to a number of reference standard modalities for CAD diagnosis, including single-photon emission CT, cardiovascular magnetic resonance imaging, and invasive coronary angiography with and without fractional flow-reserve testing.

Summary—While there is still a need for consensus regarding acquisition techniques as well as analysis and interpretation of CT-MPI, with further validation, it is likely to become a powerful adjunctive tool to CCTA in the management of patients with suspected coronary disease.

Keywords

Cardiac computed tomography; Myocardial perfusion; Pharmacologic stress testing

Introduction

Coronary CTA has been widely adopted as a non-invasive tool for the evaluation of coronary disease, with excellent prognostic abilities. Given its high negative predictive value, it is now well established as a safe and cost-effective modality to rule out acute coronary syndrome

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for the evaluation of chest pain in a low-to-intermediate probability population [1, 2]. Furthermore, the increase in stenosis severity on coronary CT angiography (CCTA), as well as number of vessels involved, portends a higher risk of adverse cardiovascular events, including all-cause death and non-fatal myocardial infarction [3, 4]. CCTA also offers information regarding the characterization of atherosclerotic plaque severity in addition to features associated with high-risk plaque, such as low attenuation and spotty calcium [5]. While the negative predictive value and sensitivity of CCTA are both estimated above 92 %, the specificity and positive predictive value are lower, pointing to the fact that CCTA can overestimate severity of stenosis. However, there are limitations to image quality that can preclude confident interpretation, such as heavily calcified coronary vessels, implanted stents, coronary bypass grafts, motion artifacts, arrhythmias, and elevated heart rates. Another limitation relates to the fact that while coronary stenoses can be quantitatively assessed, the hemodynamic significance of a particular lesion cannot be easily determined from CCTA alone. Recent studies in invasive angiography have established that the use of fractional flow reserve (FFR) to guide revascularization is associated with a reduced rate of urgent revascularization when compared with anatomical assessment alone [6, 7]. Recently, the application of computational flow dynamics has enabled the calculation of FFR from CCTA data sets. Computed tomography (CT) FFR can be determined without the need for additional radiation and can accurately diagnose flow-limiting stenoses, but analysis is cumbersome and can currently only be performed off-site using costly software [8]. A recent meta-analysis of 609 patients and 1050 vessel showed that when comparing CCTA and CT FFR to the reference standard of invasive FFR, CT-FFR is more accurate in the diagnosis of significant stenoses, with an area under curve (AUC) of 0.89 per patient and 0.88 per vessel, versus an AUC of 0.74 for CCTA [9]. These recent studies highlight the importance of correlating stenosis severity with discernible ischemia, which is now possible in the era of combined CCTA with myocardial perfusion imaging (MPI).

Principles of Myocardial Perfusion Imaging

While a consensus regarding the methodology for quantification of CT-MPI is not yet available, the premise of perfusion imaging relies upon the physiology of downstream effects of a coronary stenosis. In the presence of a stenosis, arteriolar vasodilation augments to preserve blood flow to the distal tissue bed. As the lesion progressively worsens, the compensatory mechanisms to increase blood flow are blunted and perfusion to the myocardium becomes impaired, manifesting as a resting perfusion defect. CT-MPI is able to visualize these abnormalities with the use of iodinated contrast agents, which show similar kinetics to gadolinium-based contrast agents used in cardiovascular magnetic resonance (CMR) first-pass perfusion studies [10]. Iodinated contrast attenuates X-ray photons proportionally to its concentration and does diffuse into the extracellular space over time. Therefore, regions associated with diminished perfusion may appear hypo-attenuated (i.e., darker), due to delayed diffusion of contrast into abnormally perfused myocardium (Fig. 1). CT-MPI can be performed as a resting perfusion study alone or in combination with pharmacologic stress testing as discussed later.

Rest Perfusion Imaging

Initial studies of resting CT-MPI were performed as early as the 1970s, but in the last decade, there has been a surge of interest in adapting this approach for routine clinical use [12]. CT resting perfusion imaging has reliably identified the presence of perfusion defects, as detected by resting single-photon emission computed tomography (SPECT) and CMR in patients with and without a history of previous myocardial infarction (MI) [13–15]. It is surmised that the improved spatial resolution of CT-MPI allows for the visualization of small perfusion defects that may go undetected by SPECT, which has a relatively poor spatial resolution. Resting perfusion imaging is advantageous in that it can be performed without additional radiation exposure or contrast administration and is more commonly able to identify resting perfusion defects associated with previous MI and, to a lesser extent, resting ischemia due to hemodynamically significant coronary stenosis. It appears to improve the sensitivity for detection of coronary stenosis >50 % or previous MI when performed as an adjunct to CCTA alone (87 vs. 96 % sensitivity), when compared to invasive coronary angiography as a reference standard [14, 16, 17].

The detection of ischemia may be facilitated by the hemodynamic effects of iodinated contrast and nitroglycerin, which are administered routinely as part of a CCTA, and have been shown to cause a mildly hyperemic state, akin to a vasodilator stress agent; however, because of reduced sensitivity, vasodilator stress CT perfusion imaging is needed to definitively evaluate for ischemia. Additionally, CT perfusion defects appear to underestimate true infarct size as compared to CMR delayed enhancement [16, 18].

Evaluation of resting myocardial perfusion on a standard CCTA image set has the potential to help risk stratify patients presenting with acute chest pain. A recently published subgroup analysis from the Rule Out Myocardial Infarction using Computer Assisted Tomography (ROMICAT I) trial examining resting perfusion in patients with obstructive coronary artery disease (CAD) by CCTA demonstrated that resting CT perfusion abnormalities were an independent predictor of patients with acute coronary syndromes and had a similar discriminatory ability as a combined CCTA-SPECT study [19].

Quantification of Myocardial Perfusion Imaging

A number of quantification methods have been described to assess myocardial perfusion, but qualitative visual assessment is currently the primary mode for clinical assessment of myocardial perfusion (Table 1). Accurate assessment of CT myocardial perfusion images requires the selection of images acquired not only during or shortly after peak myocardial contrast enhancement but also during a quiescent period of the cardiac cycle. Images should also be evaluated after the gray scale has been optimized for visualization of low-attenuation myocardial areas which signify perfusion defects. Rest and stress images are visually examined side by side in multiple anatomic planes (axial, sagittal, and coronal) to confirm the presence of suspected perfusion defects and rule out artifacts [20]. Additionally, a careful survey of images should also be performed to identify whether any relevant artifacts which can cause false-positive diagnoses are present, as discussed later.

Qualitatively, perfusion defects are visually evaluated using the American Heart Association 17-segment model. Perfusion defects can be “scored” as transmural (>50 %) or non-transmural (<50 %), with reversibility graded on a 0 to 3 scale for none, minimal, partial, or complete, respectively [20]. Additional approaches have been proposed with a 0 to 4 scale, where 0 indicates uniform CT attenuation, 1 indicates reduced attenuation of <50 % of the myocardial segment, 2 indicates reduced attenuation involving >50 % of the myocardium, 3 indicates reduced attenuation in 50–75 % of the myocardium, and 4 indicates reduced attenuation in >75 % of the myocardium [21]. Studies have shown good agreement between CT perfusion and SPECT using comparison of visual analysis of perfusion defects, with one study showing comparable sensitivity (79 % for CT versus 80 % SPECT) with a slightly lower specificity (67 % for CT versus 83 % for SPECT) when compared to a reference standard for coronary stenosis of >50 % on invasive coronary angiography [21, 22].

There are semiquantitative methods for the evaluation of myocardial perfusion, but the application of these methods depends upon the acquisition type (static versus dynamic). One such method is designed to detect myocardial ischemia and uses a transmural perfusion ratio (TPR), which is calculated by determining the ratio of subendocardial to subepicardial attenuation. This approach capitalizes on the fact that, in ischemia, there is a relatively greater decrease in perfusion to the subendocardium when compared to the subepicardium. A TPR of <0.99, considered the threshold for abnormal, has a sensitivity of 74 % and specificity of 66 % for hemodynamically significant lesions in combination with CCTA but was outperformed by visual assessment and CCTA in one study [23]. Another CT-derived myocardial perfusion index has been proposed as a method to normalize myocardial attenuation to the left ventricular (LV) cavity, with the myocardium divided into segments, and the subendocardial attenuation (in HU) divided by LV cavity attenuation resulting in a segmental perfusion index value [14].

Studies have shown that efforts to express myocardial blood flow in quantitative measures may offer advantages in the discrimination of multivessel and severe CAD when compared to other approaches described above [24]. Fully quantitative methods for determination of absolute myocardial blood flow (MBF) in milliliter per minute per gram are feasible and require the calculation of time attenuation curves in the blood pool and the myocardium over a number of consecutive cardiac cycles during the first pass of iodine contrast. Dynamic CT perfusion imaging, which is discussed later, is theoretically the ideal technique to allow for MBF quantification as it inherently acquires a series of images over time [25]. Two computational analyses borrowed from the MRI and PET literature for the assessment of MBF are deconvolution and upslope analyses [26]. Deconvolution methods rely on a mathematical solution of a two-compartment model with blood and tissue attenuation curves. Upslope analysis relies on time attenuation curves to derive variables reflecting blood flow, such as time to peak, peak enhancement, and attenuation upslope in a myocardial region of interest, normalized by the same indices measured in the blood pool. Ischemia is suggested by diminished upslope values or an elevated time to peak value, both reflecting slower wash-in, compared to normally perfused myocardium. Another quantitative method described in the literature uses a three-dimensional analysis of myocardial perfusion, by measuring attenuation in volumetric myocardial segments, which is normalized to the LV cavity and compared to a histogram of a reference normal myocardial segment (Fig. 2). The

extent of segmental hypoenhanced voxels in a myocardial segment reflects the relative volume of perfusion defect, and the defect severity is estimated by the difference in the positions of peaks of the attenuation histogram of the segment of interest and the reference segment. Together, these indices are used to estimate an overall defect volume and severity, the combination of which demonstrated good agreement with SPECT MPI for rest CT-MPI, with improved detection for CAD noted with the addition of stress CT-MPI [11, 27]. Despite the number of available methods for quantification of myocardial blood volume and/or blood flow, there is no clear benefit of using one method over another.

CT perfusion may help improve the discriminatory ability of CCTA in clinical scenarios, which might otherwise limit the diagnostic utility of the modality. Coronary arteries with stented segments can hinder the diagnostic ability of CCTA due to metal artifact, but the CORE320 study demonstrated that a combined CCTA-CT-MPI protocol improved the identification of lesions warranting revascularization on invasive angiography, with an improved AUC of 0.82 when compared to an AUC of 0.64 for CCTA alone [28]. Another study in lesions with severe calcification (defined as an Agatston score >400) found an incremental improvement in the discrimination index in patients with CT-MPI in addition to CCTA, pointing to the helpful role of CT-MPI in determination of myocardial ischemia, when significant coronary calcification precludes evaluation of the coronary lumen [29].

Stress Perfusion Imaging

While the detection of resting perfusion defects is clinically valuable, it has limited sensitivity, and thus, ischemic myocardium may go undetected. This is where vasodilator stress CT and its subsequent hyperemic state prove a great clinical benefit, as it capitalizes on the physiologic consequences of significant coronary disease. Indeed, vasodilator stress CT perfusion imaging outperforms CCTA alone in the detection of ischemic regions found on SPECT [30, 31].

Published in 2014, the multicenter CORE320 study tested a combined CCTA/CT-MPI strategy in 381 patients with suspected CAD and compared to SPECT, with invasive angiography showing a >50 % stenosis as the reference standard [32••]. In the study protocol, CCTA was performed first, with CT MPI to follow using a 320-multidetector CT. The combined CCTA-CT-MPI strategy clearly outperformed SPECT, with a per-patient and per-vessel AUC of 0.89 vs. 0.69 and 0.79 and 0.66, respectively. Interestingly, the accuracy of testing was improved with combined CCTA + CT-MPI overall (79 % versus 73 % for CCTA alone), even in patients without a history of previous MI or CAD [33]. Furthermore, the sensitivity of CT-MPI was consistently greater than that of SPECT, including in multivessel and left main disease, where the concept of “balanced ischemia” may impair the ability of SPECT to highlight diminished perfusion reserve [34]. Additional studies comparing vasodilator CT stress testing to CMR perfusion with and without invasive angiography have demonstrated comparable specificity and negative predictive value in intermediate-to-high-risk patients, with estimates of CCTA-CT-MPI sensitivity of 89–100 % and negative predictive value of 90–100 % [30, 35]. Table 2 highlights the available CT stress perfusion studies to date in comparison to reference modalities of SPECT, CMR perfusion, coronary angiography, and CT-FFR. Additionally, studies have shown that the

addition of CT-MPI to CCTA improves the assessment of indeterminate lesions, improving upon the specificity of CCTA and appropriately reclassifying stenosis severity, particularly for lesions with significant flow limitation by FFR (<0.8) or stenosis severity ($>50\%$) on coronary angiography [52, 53].

Delayed Enhancement Imaging

Cardiac CT has been shown to be a useful tool in evaluating MI, with older infarcts often associated with lower attenuation, subendocardial fat, wall thinning, and LV dilation, with good concordance and similar infarct sizing compared to CMR [10, 54]. A delayed enhancement (DE) image can be obtained by repeat imaging 6–10 min following contrast-enhanced image acquisition. It does not require the administration of additional contrast and may aid in the detection and differentiation of MI. Abnormal regions can be seen with DE imaging due to lingering of iodinated contrast in infarcted myocardium, when compared to normal regions, resulting in increased concentration of contrast. DE imaging also appears to more accurately identify infarct size than myocardial hypoenhancement during first pass of contrast, which can be underappreciated on rest perfusion imaging alone. Importantly, the presence of DE on CT may portend a higher risk of adverse cardiac events [55, 56]. However, one study suggested that the addition of DE imaging did not improve the accuracy of CT-MPI overall in an intermediate-to-high probability population, pointing to the fact that more research is needed in this area to validate the widespread adoption of DE imaging. This is especially important because the acquisition of DE images is associated with a higher radiation dose when added to standard CT-MPI protocols [39].

Image Acquisition

Static Versus Dynamic Imaging

Static CT-MPI images of the myocardium are able to visualize myocardial distribution as a surrogate of blood flow to the myocardial microvasculature, and acquires images at a single moment times to the peak contrast bolus. Static CT-MPI can be performed as a rest study in conjunction with a CCTA, or as a stress study, but due to the single time frames inherent to static imaging, only qualitative or semiquantitative methods for assessment of MBF can be used with this acquisition technique. Additionally, it may be more prone to missing perfusion defects given the need to time image acquisition with the coinciding peak of arterial contrast transit, even with the help of automated bolus tracking, or the lingering effects of iodinated contrast or vasodilators in the MBF [57].

By comparison, dynamic imaging generates time attenuation curves by acquiring a series of images over multiple cardiac cycles, allowing for the measurement of MBF in milliliters per minute per gram [57]. Technically, dynamic imaging can be performed using a “shuttle” mode, in which the table quickly alternates between two set positions while ECG-gated images are being acquired, to allow for full coverage of the heart during the upslope phase of the contrast first pass. Another strategy is the use of wide-detector CT scanners, which afford greater coverage of the left ventricle with a single gantry rotation, allowing a shorter breath hold and less slab artifact [58]. While numerous reports have demonstrated the feasibility of dynamic stress CT-MPI when compared to SPECT, CMR, and invasive FFR,

these are limited to single-center studies, and standardization of protocols has not yet been achieved [30, 31, 36, 45, 50, 58]. One small study comparing dynamic CT-MPI with cardiac MRI demonstrated the ability to differentiate infarcted tissue from ischemia due to the calculation of MBF and myocardial blood volume [18]. However, due to the need for imaging over a series of cardiac cycles, there is a significantly higher dose of radiation associated with this technique and longer breath holds are required for image acquisition, both of which remain an obstacle to widespread clinical use.

Acquisition Protocols

Dual-energy CT (DECT) imaging is based on simultaneous use of two different photon energy levels (typically one high energy ~140 kV and one low energy ~80 kV), relying upon differences in X-ray attenuation between different materials. The relative iodine content within the myocardium, which represents blood volume, can be color-coded to create an iodine map, which can serve as a quantitative surrogate for perfusion. Technically, DECT can be performed with different scanner configurations, with the underlying concept that two different energy spectra are used during the same scan [59]. One configuration involves a dual-source scanner, in which two different X-ray tubes are mounted perpendicularly on the same gantry rotation, with one tube emitting high-energy and the other emitting lower-energy photons. Another DECT configuration involves the use of a single X-ray tube, which can rapidly switch between high- and low-energy photons within milliseconds. A third approach is to use a single-source X-ray tube with alternating high-and low-energy potentials with each gantry rotation [60]. Post-processing of imaging acquired using DECT generates four sets of images: the low-energy image, high-energy image, merged image, and the iodine distribution map. With this wealth of image data, DECT can provide nuanced visualization of tissue characterization that may be particularly useful for the identification of myocardial perfusion defects. In a study of 50 patients undergoing adenosine stress DECT MPI, the sensitivity and specificity were 89 and 78 %, respectively, when compared to CMR perfusion imaging as the reference standard [41]. The diagnostic performance of CCTA is improved with the addition of DECT stress perfusion imaging, with an improvement in AUC from 0.74 to 0.83 [61]. In addition to an improvement in tissue characterization, DECT is also associated with less beam-hardening artifact, which may improve image quality and diagnostic confidence in the diagnosis of perfusion defects [62]. With further technical refinements, DECT may eventually be able to allow plaque characterization and thus help identify lesions with high-risk features, such as presence of a thin fibrous cap or a necrotic lipid-rich core, though studies have shown mixed results for in vivo testing [63, 64].

There is ongoing debate as to the ideal order of CCTA and stress perfusion imaging, in an effort to minimize patient radiation exposure and contrast administration while ensuring a reliably accurate assessment of coronary disease and any concomitant ischemia (Fig. 3). One approach is to embark upon a comprehensive CT evaluation only after an initial CCTA has been performed and interpreted as abnormal, to prevent unnecessary radiation exposure to patients with normal or minimally diseased coronary arteries, as well as avoidance of administration of vasodilators and additional iodinated contrast. Critiques of this approach cite the concern that beta-blockers and nitrates, which are administered prior to CCTA to optimize image quality, may mask ischemia or interfere with the vasodilatory response

required for a good-quality stress test if it is performed later. A strategy which involves the performance of stress perfusion imaging upfront will increase the sensitivity of the test to detect ischemia as discussed previously but commits the individual patient to a longer test with greater radiation exposure. Additionally, early contrast administration may interfere with the ability of rest perfusion to detect infarction via the effects of DE. Furthermore, reports in the CMR literature have suggested that in a population of normal individuals, there were both delays in maximal hyperemia with regadenoson administration, as well as persistent residual regadenoson-induced hyperemia even after administration of aminophylline, which is used as a reversal agent [65]. This suggests that resting perfusion imaging following pharmacologic stress imaging may not represent a true resting perfusion state. There is no widely accepted recommendation regarding the order of imaging, and additional research is needed to determine the optimal workflow for CT perfusion imaging protocols.

Limitations/Areas for Improvement Upon Current Techniques

There are some limitations to note with regard to CT perfusion imaging techniques that will likely be refined as better equipment as well as reconstruction and analysis software become available. Despite these shortcomings, CT-MPI is a feasible modality often preferred by patients due to its fully non-invasive nature and high speed of acquisition [66].

Beam Hardening

Beam hardening is a well-known artifact which occurs when X-ray beams pass through high-density objects, in which lower-energy beams are absorbed, leading to a hypoenhanced region that may appear as a falsely positive perfusion defect. This commonly occurs in the basal inferolateral wall, which is adjacent to the contrast-enhanced descending aorta (Fig. 4). There are a number of reconstruction algorithms that have been described in an effort to correct for beam hardening, but it remains a problematic artifact in CT-MPI imaging [58, 68, 69].

Radiation

Radiation exposure is a necessity of CT imaging, but minimizing exposure to the patient while ensuring an adequate diagnostic performance of perfusion imaging is the focus of ongoing efforts. Many studies have shown equivalent radiation doses with CCTA-CT-MPI and SPECT or coronary angiography, but dynamic imaging techniques or DE imaging is both inevitably associated with additional radiation.

Motion Artifact

While CT perfusion focuses on imaging the myocardium rather than the coronary arteries, there are still issues with motion artifact that can impair diagnostic interpretation. There may be clues to differentiate motion from true perfusion defects, such as perfusion defects which lack concordance with a clear coronary territory, or appearance in some and not all phases of the cardiac cycle.

Iterative Reconstruction

The visual interpretation of perfusion defects in CT-MPI is of major clinical importance but can be limited by suboptimal image quality and compromises in signal to noise ratio due to patient body habitus and the desire to minimize radiation exposure to the patient. Iterative reconstruction algorithms have been developed in an effort to reduce image noise in CT and are feasible in animal and human studies, with improved signal to noise and contrast to noise ratios without requiring an increase in radiation to optimize image quality for interpretation when compared to filtered back-projection, a standard algorithm used for image reconstruction (Fig. 5). This new reconstruction strategy is especially promising for CT-MPI imaging, as it offers an effective way to acquire additional images with only minimal radiation exposure, without compromising image quality and diagnostic accuracy [70, 71].

Conclusions

CT-MPI is an emerging modality which has the ability to improve upon the sensitivity and specificity of CCTA, which is already well integrated into clinical practice for the evaluation of patients with suspected coronary disease. A number of studies have established the safety and efficacy of rest and stress CT-MPI, although there are evolving techniques to optimize image acquisition and quality to reduce artifact while minimizing radiation. There is not yet a consensus on a standardized technique or interpretation method for clinical use, evident in the fact that previous studies of CT-MPI have used a variety of algorithms and equipment. It is anticipated that with increased prospective studies, similar to CORE320, combined CCTA-CT-MPI will become a commonplace non-invasive modality to determine the severity and burden of coronary disease and detect underlying ischemia or infarction owed to the presence these lesions.

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Fig. 1. Example of a CT stress perfusion defect. Endocardial hypoattenuation involving the entirety of the septum and anterior wall is present, suggestive of LAD stenosis. Reprinted from [11] by permission of Wolters Kluwer Health, Inc./Journal of Computer Assisted Tomography

Fig. 2.

Semiautomated myocardial segmentation of the left ventricle (*top*) and histograms of X-ray attenuation in normally perfusion segment (at *bottom left*) compared to an abnormally perfused segment (at *bottom right*), with the difference in relative peaks of the curves used to derive a segmental perfusion index. Reprinted from [27] by permission of Springer/European Radiology

Fig. 3.

Proposed algorithms for the performance of rest-stress CT myocardial perfusion imaging

Fig. 4. Example of beam hardening artifact in the typical location of the basal posterolateral wall, which can mimic the presence of a perfusion defect. Reprinted from [67] by permission of Springer/International Journal of Cardiovascular Imaging

Fig. 5. Examples of iterative reconstruction (IR) algorithms applied to CT perfusion imaging. *Panel 1* demonstrates images of a patient with no significant coronary disease. *Panel 2* demonstrates images of a patient found to have a significant [$>50\%$] LAD stenosis, manifest as an anteroseptal perfusion defect. Reprinted from [70] by permission of Elsevier/Journal of Cardiovascular Computed Tomography

Table 1

Quantification methods for myocardial perfusion

Method	Description
17-Segment model	Transmural (>50 %) vs. non-transmural (<50 %); 0 (normal) to 3 (severe) score for reversibility
Transmural perfusion ratio (TPR)	Ratio of subendocardial attenuation to subepicardial attenuation for each segment; TPR <0.99 = abnormal
Upslope analyses	Relies on myocardial time attenuation curves to generate index of myocardial blood flow; peak signal intensity, time-to-peak signal, upslope (signal change over time)
Myocardial segmental perfusion index	Ratio between subendocardial attenuations divided by LV cavity attenuation for 16 myocardial segments
Deconvolution analyses	“Two-compartment” model fit to time attenuation curves representing blood and myocardium and extravascular space, needs entire first-pass data set
3D segmental volumetric perfusion index	Segmental mean attenuation value (normalized to LV cavity) compared to histogram of a normal reference myocardial segment; hypoenhanced voxels in each segment generate a volume of perfusion defect and peak-to-peak difference between attenuation histograms of segment of interest and reference normal segment to generate segmental Qh

Table 2Human studies of diagnostic performance of stress CT-MPI versus other modalities (with $n > 10$)

Author/year	Study population	CT protocol	Reference standard	Per-patient analysis			
				*Per-vessel analysis			
				Sens	Spec	PPV	NPV
Cury (2011) [36]	Abnormal SPECT ($n = 26$)	Stress CT-MPI	SPECT	94	78	89	87
George (2009) [37]	Abnormal SPECT ($n = 40$)	CCTA + stress CT-MPI	SPECT	86	92	92	85
George (2012) [31]	Abnormal SPECT ($n = 50$)	Stress CT-MPI	SPECT	50	89	55	87
So (2012) [38]	Known CAD ($n = 26$)	Dynamic stress CT-MPI	SPECT	95	35	83	67
Bettencourt (2013) [39]	Symptomatic with suspected CAD ($n = 150$)	CCTA + stress CT-MPI	Cardiac perfusion MRI	90	81	80	90
Feuchner (2011) [35]	Intermediate-high risk for CAD ($n = 30$)	Stress CT-MPI	Cardiac perfusion MRI	96*	88*	93*	94*
Kim (2014) [40]	Suspected CAD ($n = 50$)	Dual-energy stress CT-MPI	Cardiac perfusion MRI	94	71	60	96
Ko (2011) [41]	Known CAD by SPECT ($n = 70$)	Dual-energy stress CT-MPI	Cardiac perfusion MRI	89*	78*	74*	91*
Blankstein (2009) [22]	Previous SPECT ($n = 34$)	Dual-source stress CT-MPI	Invasive coronary angiography	92	67	89	75
Ho (2010) [25]	Abnormal SPECT ($n = 35$)	CCTA + dynamic stress CT-MPI	Invasive coronary angiography	83*	78*	79*	82*
Ko (2012) [42]	Known CAD ($n = 45$)	Dual-energy stress CRP	Invasive coronary angiography	89*	74*	80*	85*
Ladeiras-Lopes (2016) [43]	Suspected CAD ($n = 95$)	CCTA + stress CT-MPI	Invasive coronary angiography	67	93	88	78
CORE-320 (2015) [33]	Suspected CAD ($n = 381$)	CCTA + stress CT-MPI	Invasive coronary angiography	78	73	85	64
Nasis (2013) [44]	Abnormal SPECT ($n = 20$)	CCTA + stress CT-MPI	Invasive coronary angiography	94	98	94	98
Reif (2013) [28]	Known CAD with stents ($n = 91$)	CCTA + stress CT-MPI	Invasive coronary angiography	82	88	61	96
Rocha-Filho (2010) [45]	Suspected CAD ($n = 36$)	CCTA + Dual-source stress CT-MPI	Invasive coronary angiography	96	100	100	91
Rochitte (2014) [32••]	Suspected or known CAD ($n = 391$)	Stress CT-MPI	Invasive coronary angiography	80	74	65	76
Yang (2015) [26]	Known coronary disease	Stress CT-MPI	Invasive coronary angiography	89	86	–	–
Bamberg (2011) [46]	Suspected or known CAD ($n = 33$)	CCTA + dynamic stress CT-MPI	Invasive FFR	95*	64*	84*	88*
Greif (2013) [47]	Chest pain symptoms ($n = 65$)	CCTA + stress CT-MPI	Invasive FFR	97	69	76	96
Huber (2013) [48]	Suspected CAD ($n = 32$)	Dynamic stress CT-MPI	Invasive FFR	76*	100*	100*	91*
Ko (2012) [49]	Documented >50 % stenosis ($n = 42$)	CCTA + stress CT-MPI	Invasive FFR	76*	84*	82*	79*
Ko (2012) [23]	Symptomatic patients ($n = 40$)	CCTA + stress CT-MPI	Invasive FFR	74*	66*	56*	81*
Rossi (2014) [50]	Symptomatic with suspected CAD ($n = 80$)	CCTA + dynamic stress CT-MPI	Invasive FFR	88*	90*	77*	95*
Wong (2014) [51]	Symptomatic patients with known or suspected CAD ($n = 75$)	CCTA + stress CT-MPI	Invasive FFR	76	89	78	88