Assessment of Cardiac Computed Tomography-Myocardial Perfusion Imaging

– Promise and Challenges –

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Cardiac computed tomography (CT) has evolved rapidly over the last decade into a reliable imaging modality for the non-invasive assessment of coronary artery disease. With the advancement in multi-detector CT technology, there has developed an increasing body of evidence that suggests that the role of cardiac CT can be extended to include functional assessment of the myocardium not only at rest but also during stress. Simultaneous anatomical and functional assessment approaches will have a number of advantages such as evaluation of the transmural extent of myocardial perfusion defects (including small subendocardial perfusion defects), reduced risk associated with multiple sources of radiation, and short image acquisition time. Although initial results hold some promise, CT myocardial perfusion imaging is a modality in the early stages of development and further work and studies are required to define, validate, and optimize this technique. This review will provide an overview of this novel perfusion imaging method, its underlying principles, evolution, limitations and future directions. (*Circ J* 2012; **76**: 544–552)

Key Words: Cardiac computed tomography; Computed tomography coronary angiography; Computed tomography myocardial perfusion imaging; Coronary artery disease; Non-invasive imaging

Coronary artery disease (CAD) is the commonest cause of death in the developed world and is set to emerge as the commonest cause of mortality in developing nations across the world.^{1,2} The profound burden of this disease has led to the development of new therapies and non-invasive detection techniques. Radionuclide myocardial perfusion imaging (MPI), stress echocardiography, computed tomography coronary angiography (CTCA) and cardiac magnetic resonance imaging (CMRI) are the widely used tests for the assessment of diagnosed or suspected CAD. These techniques have established roles in the screening, diagnosis, risk stratification and prognosis of CAD and are often used to guide patient management such as decisions regarding revascularization.

Cardiac CT has evolved rapidly over the last decade into a reliable imaging modality for the non-invasive assessment of CAD. With the advancements in CT technology, CTCA has undergone significant growth over the last decade. The majority of cardiac CT performed presently consists of CTCA, which elucidates coronary anatomy. A number of single and multicenter studies have confirmed the excellent diagnostic accuracy of CTCA for detecting significant CAD compared with invasive coronary angiography (ICA).^{3–8} A high negative predictive value seen in subjects with a low-intermediate risk factor profile effectively rules out significant CAD in those with a normal scan.⁷ Moreover, CTCA has also been shown to

accurately identify patients who may benefit from coronary revascularization similar to ICA.⁹

Although the diagnostic and prognostic value of CTCA is very good, it has certain inherent limitations that restrict its use to certain populations. First, it may have limited value in patients with multiple cardiovascular risk factors because it is often difficult to assess luminal stenosis in the presence of heavily calcification due to blooming and beam hardening artifacts. Such artifacts can result in the overestimation of CAD severity.^{10,11} Another limitation of CTCA is that it provides only anatomic information. Although CT anatomical assessment has prognostic value,^{12–15} CTCA measurements of stenoses do not accurately predict functional significance.¹⁶ Numerous studies have shown that functional information (both at rest and following stress) is essential in guiding clinical management and also long-term prognosis.^{17–19}

In an attempt to overcome these shortcomings, hybrid imaging devices that combine CTCA with functional modalities such as positron emission tomography (PET) and single-photon emission CT (SPECT) were developed. A limitation of multimodality hybrid imaging, however, is the potential exposure of patients to higher doses of radiation and also the need to undergo at least 2 diagnostic examinations, causing inconvenience.²⁰ With the advancement in multi-detector CT (MDCT) technology, however, there is an increasing body of evidence that suggests that the role of cardiac CT can be ex-

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Table. Important CT-MPI Studies

Study	Year	Model used	Scanner type	Method	Image acquisition phase	Reference	Conclusion
Wolfkiel et al ²⁸	1987	Animal (canine)	Ultrafast CT	Ultrafast CT-MPI	Rest	Microsphere MBF	CT could measure MBF over a limited but clinically relevant range of flows.
Rumberger & Bell ³³	1987	Animal (canine)	Ultrafast CT	EBCT-MPI	Rest	Microsphere MBF	Quantification of regional myocardial perfusion and myocardial flow reserve feasible with CT.
Bell et al ³⁵	1999	Both animal (canine) and human (n=10)	EBCT	EBCT-MPI	Rest	Microsphere MBF	Feasibility of accurate measurements of global and regional myocardial perfusion and perfusion reserve in human demonstrated with CT.
Mahnken et al ³⁹	2006	Animal (porcine)	MDCT (16-detector)	Dynamic CT-MPI	Rest	CMRI	Confirmed potential of MDCT for visual and semi-quantitative assessment of first-pass myocardial perfusion.
George et al ³⁶	2007	Animal (canine)	MDCT (64-detector)	Dynamic CT-MPI	Rest and stress	Microsphere MBF	MBF measurements using CT correlate well with microsphere MBF. (Adenosine used as a stress agent.)
Kurata et al ⁵⁹	2005	Human (n=12)	MDCT (16-detector)	Dynamic CT-MPI	Rest and stress	SPECT	Good agreement between MDCT and MPI for myocardial perfusion.
George et al ⁴¹	2006	Animal (canine)	MDCT	Helical CT-MPI	Rest and stress	Microsphere MBF	Validated semi-quantitative measurements of myocardial perfusion with CT-MPI.
George et al ²¹	2009	Human (n=40)	MDCT (64- and 256-detector)	Helical and dynamic CT-MPI	Rest and stress	SPECT and ICA	Combination of CTCA and CT-MPI can detect atherosclerosis causing perfusion abnormalities.
So et al ⁴⁰	2011	Animal (porcine)	MDCT (64-detector)	Dynamic CT-MPI	Rest	Microsphere MBF and histology	Perfusion measurement of MBF with dynamic CT was accurate and correlated well with histology and microspheres measurements.
Rocha-Filho et al ²⁴	2010	Human (n=35)	Dual source	Dual-energy CT-MPI	Rest and stress	ICA	Combination protocol involving CT-MPI and CTCA feasible with dual-energy technique and improves detection of significant CAD.
Blankstein et al ²²	2009	Human (n=34)	Dual source	Dual-energy CT-MPI	Rest and stress	SPECT	Adenosine CT-MPI predicted perfusion defects comparable to SPECT MPI.
Bastarrika et al ⁴⁶	2010	Human (n=3)	Dual source	Dynamic CT-MPI	Rest and stress	None	Feasibility of addition of adenosine stress dynamic CT perfusion to a cardiac CT protocol consisting of coronary artery calcium, CTCA and delayed acquisition.
Rogers et al ⁴⁷	2010	Human (n=21)	MDCT 320-detector	Processing techniques	Rest	CMR	Minimum intensity projection and thick MPR detect infarcted myocardium with greater definition than thin MPR and maximum intensity projection.
Steigner et al ⁴⁹	2010	Human (n=36)	MDCT 320-detector	Contrast opacification	Rest	N/A	Demonstrated feasibility of measuring contrast opacification gradients in normal coronary arteries.
Chow et al ⁵⁰	2011	Human (n=52)	MDCT 64-detector	Contrast opacification	Rest	ICA	Changes in coronary contrast opacification across coronary stenoses predict abnormal resting coronary blood flow.
Boll et al ⁵⁶	2008	Human (n=50)	MDCT 64-detector	Cardiac phase attenuation	Rest	N/A	Myocardial attenuation on CT-MPI is influenced by cardiac phase and myocardial location.
Nagao et al ⁵⁷	2008	Human (n=34)	MDCT 64-detector	Cardiac phase attenuation	Rest	SPECT	Resting subendocardial hypoperfusion on CT-MPI during systole, and normal perfusion during diastole characterizes ischemic myocardium.
Nagao et al ⁵⁸	2009	Human (n=75)	MDCT 64-detector	Cardiac phase attenuation	Rest	SPECT	CT myocardial imaging at rest demonstrates a characteristic enhancement pattern for ischemia.

CMRI, cardiac magnetic resonance imaging; CT, computed tomography; CTCA, computed tomography coronary angiography; EBCT, electron beam computed tomography; ICA, invasive coronary angiography; MBF, myocardial blood flow; MDCT, multi-detector CT; MPI, myocardial perfusion imaging; MPR, multiplanar reconstruction; SPECT, single-photon emission computed tomography.

tended to include functional assessment of the myocardium not only at rest but also during stress.^{21–25} Simultaneous anatomical and functional assessment approaches will have a number of advantages. The superior spatial resolution of cardiac CT would allow evaluation of the transmural extent of myocardial perfusion defects (including small subendocardial perfusion defects), thus potentially making this test more sensitive. Furthermore, it would reduce inconvenience to the patients and risks associated with multiple sources of radiation. Last, due to the relatively short image acquisition time compared to other invasive and non-invasive techniques, cardiac CT has the potential to deal with larger patient volumes and thus will be potentially more cost-effective. Recent studies comparing CTCA to MPI have demonstrated lower follow-up

costs, similar referrals to ICA and revascularization rates, lower false positive rates and no differences in the rates of myocardial or cardiac hospitalizations.^{26,27}

Although initial results hold some promise, CT-MPI is in the early stages of development (**Figure 1**). Further work and studies are required to define, validate, and optimize this technique. This review will provide an overview of this novel perfusion imaging method, its underlying principles, evolution, limitations and future directions.

General Concepts of CT-MPI

First attempts at MPI with CT were carried out in the late 1980s using electron beam CT (EBCT) (**Table**).²⁸ EBCT sys-

Figure 1. Distal septal and apical perfusion defects on (A) rest technetium myocardial perfusion imaging (MPI) (horizontal long axis view) and corresponding perfusion defect on (B) rest computed tomography-MPI (4-chamber view). (C) Computed tomography coronary angiography showing calcified and obstructed proximal left anterior descending coronary artery.

tems, however, have limited spatial and contrast resolution, and have been mostly replaced by current generation MDCT systems. CT-MPI uses iodine-based contrast that attenuates X-rays proportionally to the concentration of iodine in the myocardium.²⁹ This technique relies on first-pass myocardial perfusion following a bolus of contrast injection, which is followed by cardiac imaging to record the transit of the contrast through the vasculature and myocardium. The areas of hypoperfusion are identified by decreased attenuation compared to normal myocardium. Using time-attenuation curves (TACs) obtained from the aorta (or left ventricular blood pool) and myocardium, the myocardial blood flow (MBF) and myocardial blood volume can be assessed. Given that iodinated contrast is a diffusible tracer and its concentration in the extracellular space is known to increase over a period of time, it is crucial to image myocardial perfusion early during the first-pass circulation or apply mathematical models that take into account the extravascular diffusion of tracer.^{30,31} The relationship between CT attenuation number and iodine concentration can be altered by a number of factors such as beam hardening, and motion and reconstruction artifacts. Advances in temporal resolution, beam hardening correction, and reconstruction methods are designed to overcome these problems.³²

CT-MPI can be performed using the following methods: (1) EBCT; (2) dynamic CT-MPI; (3) relative CT-MPI; and (4) dual-energy (DE) CT-MPI.

EBCT-MPI

EBCT uses an electromagnetic field to sweep an electron beam around an immobile tungsten-coated target to generate X-rays. Rumberger et al were the first to demonstrate good correlation between microsphere MBF and EBCT-derived MBF measurements.^{33,34} Later, Bell et al demonstrated feasibility and validity of measurements of global and regional myocardial perfusion and perfusion reserve using EBCT in a canine model and in human volunteers.³⁵ Due to prohibitive cost and limited spatial resolution, however, interest in this CT method of myocardial perfusion assessment has been waning.

Dynamic CT-MPI

Current state-of-the-art MDCT scanners provide an isotropic

spatial resolution of 0.4 mm and temporal resolution as low as 68–83 ms. Over the last 10 years, the number of detector arrays has increased from 4 to 320, with increasing volume coverage per gantry rotation and reduction in time needed to image the entire heart. MDCT systems can image in a dynamic mode, in which sequential images are obtained over a period of time to record the kinetics of iodinated contrast in the arterial blood pool and myocardium.³⁶ During image acquisition the scanner table can either remain stationary, or a shuttle mode with alternating table positions can be used.³⁷ One of the main advantages of dynamic CT-MPI is the ability to create TACs that can be used to calculate absolute quantitative MBF.³⁸

Mahnken et al performed first-pass CT-MPI using a 16-detector CT in a porcine model of acute left anterior descending coronary artery occlusion and non-reperfused myocardial infarction. Using several parameters derived from TACs, they compared infarcted and normal myocardium and demonstrated significant differences in the maximum attenuation density, time to maximum attenuation density, and upslopes of the myocardial TACs.³⁹ Furthermore, they showed that the area at risk as evident on gross pathology (in triphenyltetrazolium chloride-stained specimens) corresponded well to hypoperfused areas noted on CT-MPI.³⁹ So et al, in a porcine model of acute myocardial infarction, performed quantitative myocardial perfusion and showed that perfusion measurement of MBF with dynamic CT was accurate and correlated well with histology and microsphere measurements.⁴⁰ George et al, using a 64-detector CT in a canine ischemia model, performed CT-MPI during adenosine infusion. They found strong correlations between the ratio of myocardial upslope and left ventricular upslope and microsphere-derived MBF.³⁶

Initial studies using this method were done with 64-detector scanners, which provided limited cardiac coverage in the z-axis. Also, the majority of research was performed using retrospective electrocardiogram (ECG)-gated protocols. Widespread use of this technique was thus limited due to high radiation delivered to the patients during multiple and continuous X-ray exposures. With the availability of scanners providing full heart coverage (320-detector CT) and prospective ECG-triggered protocols, however, dynamic CT-MPI is becoming increasingly attractive. The multi-center, international trial of 320-dynamic volume CT-MPI (CORE 320) is underway and will assess the accuracy of this technique

(NCT00934037).

Relative CT-MPI

With the invention of slip-ring technology, a continuous gantry rotation around the patient while advancing the table was made feasible. CT using slip technology is known as helical scanning and has the temporal resolution to image the moving heart. CT-MPI using helical scanners is performed in either retrospective ECG-gating/helical mode or in prospective ECG-triggering/step-and-shoot mode.

During helical CT-MPI, the scanner table moves the patient through the rotating gantry at a set rate and image data are acquired. In this method the images are acquired only over a short period of time during the upslope or peak of the contrast bolus. This results in imaging of different parts of the heart during the relative peak of coronary arterial contrast enhancement. Therefore, TACs cannot be constructed and also absolute quantification of MBF is not possible. Other semiquantitative and qualitative metrics of myocardial perfusion can be calculated, however, and by using dynamic bolus-tracking data to quantify the arterial input function, an estimate of myocardial perfusion can be obtained.^{22,41,42}

Helical CT-MPI has been used to assess relative perfusion in animal models and in humans. In a canine ischemia model, George et al used this approach during adenosine infusion to image the upslope of the contrast enhancement curve.⁴¹ They found significant qualitative and quantitative differences between attenuation densities of stenosed and non-stenosed territories. The authors replicated the study in humans using adenosine stress 64- and 256-row detector CTCA and CT-MPI. In the human study, they calculated the transmural perfusion ratio (subendocardial attenuation/subepicardial attenuation), which had a significant inverse linear correlation ($r=-0.63$, $P=0.001$) with percent diameter stenosis on quantitative ICA. Furthermore, the combination of CT-MPI and CTCA was 86% sensitive and 92% specific for identifying patients with atherosclerosis causing perfusion abnormalities when compared with the combination of ICA and SPECT-MPI as the gold standard.²¹

DE CT-MPI

The introduction of dual-source CT (DSCT), with 2 X-ray tubes and detector arrays mounted in the same gantry 90° apart, has improved the temporal resolution to 83 ms (and 75 ms in the case of recently introduced second-generation DSCT), and thus facilitated reduction in artifacts during vasodilator stress.⁴³ In addition, DSCT can also be used for DE CT, in which 1 X-ray tube emits a high-energy spectrum (180 kVp) and the other tube a low-energy spectrum (80 kVp) during a single scan. Body tissues and iodinated contrast display unique absorption characteristics when penetrated with X-rays of different energy spectra.⁴⁴ During DE CT-MPI, in addition to the usual attenuation values, additional information that facilitates more specific tissue characterization and mapping of the iodine distribution (in the blood and myocardium) is achieved albeit at the cost of temporal resolution (reduced to 165 ms). For DE CT-MPI, separate reconstructions are required for high- and low-voltage data and are followed by DE post-processing, in which images are merged and superimposed on iodine maps. More recently, single-source CT has been introduced, which has the ability to perform DE CT.

Investigators who have used DSCT to perform CT-MPI use prospective ECG-triggered protocols during rest perfusion

scans or retrospective ECG-gated protocols for rest and stress perfusion scans, with tube current modulation and narrow full-dose pulsing windows targeted at 60–70% of the R-R interval.^{24,45} The X-ray tube settings are decided according to the complexity of scanning protocols and radiation concerns. Blankstein et al used the same settings for both tubes (100–120 kV and 330–370 mA, determined by body mass index), when performing stress and rest CT perfusion scans, in addition to delayed enhanced myocardial viability imaging.²² Schwarz et al used 140 kV for tube A (associated with the larger detector array) and 100 kV for tube B when performing only rest CT perfusion scans in addition to calcium scoring during DE CT-MPI.⁴⁵

DE CT-MPI can be done either using helical or dynamic mode, or using a recently described a novel dynamic “shuttle” mode.⁴⁶ In shuttle mode, the image data are captured during contrast medium infusion at 2 alternating table positions with the table shuttling back and forth between the 2 positions covering the anatomic volume. The authors applied this acquisition technique for detecting differences in perfusion patterns between healthy and diseased myocardium and for quantifying MBF under adenosine stress in 3 patients with CAD.⁴⁶ Perfusion was assessed qualitatively and CT-MPI was found to be 86% sensitive and 98% specific for detection of segmental perfusion defects, with CMRI-derived perfusion considered the gold standard. Furthermore, CT-derived myocardial to LV upslope indices (a semiquantitative measurement) were comparable to similar CMRI-derived measures. MBF measured quantitatively on CT was reduced in hypoperfused areas compared to normal myocardium ($96 \pm 27.9 \text{ ml} \cdot 100 \text{ ml}^{-1} \cdot \text{min}^{-1}$ vs. $122.2 \pm 49.4 \text{ ml} \cdot 100 \text{ ml}^{-1} \cdot \text{min}^{-1}$).

Qualitative CT-MPI

Visual evaluation of the perfusion is complementary to other quantitative and semi-quantitative methods and should be performed in all cases. Like other related modalities (SPECT and PET) used for this purpose, a visual qualitative assessment of MBF alone can be performed to determine presence or absence of perfusion defects. Visual evaluation can also be used to identify artifacts, intramyocardial fat, and other issues that can alter myocardial attenuation and thus identify erroneous MBF measurements on quantitative methods.

Although data are limited at present on qualitative assessment of CT-MPI, this status is likely to change in the near future with improvement in CT technology. Blankstein et al compared stress-induced myocardial perfusion defect on CT and SPECT in 34 patients who later underwent ICA. On a per-vessel basis, CT-MPI provided 79% sensitivity and 80% specificity for detection of stenosis $\geq 50\%$, whereas with SPECT, a sensitivity of 67% and specificity of 83% were obtained. For the detection of vessels with $\geq 50\%$ stenosis with a corresponding SPECT perfusion abnormality, CT-MPI provided a sensitivity of 93% and specificity of 74%.²² To compare different reconstruction techniques, Rogers et al performed 64-slice cardiac CT and CMRI in subjects who were successfully treated with percutaneous coronary intervention for ST-segment myocardial infarction. Delayed enhancement on CMRI was used to identify the location of infarcted myocardium. Contiguous short-axis images of the left ventricular myocardium were created from the CT source images with multiplanar reconstruction (thick and thin), maximum intensity projection and minimum intensity projection. Segments already confirmed to have infarction on CMRI were then evaluated qualitatively and quantitatively on CT. The authors reported that on qualita-

tive analysis, minimum intensity projection and thick multiplanar reconstruction detected infarcted myocardium with greater visibility and definition than thin multiplanar reconstruction and maximum intensity projection ($P < 0.001$).⁴⁷

Recent Advances

Measurement of coronary contrast opacification gradients can provide an indirect estimate of coronary blood flow. Feasibility of coronary contrast opacification gradient measurement has been confirmed in previous studies with 320-detector CT.^{48,49} CT scanners with incomplete cardiac coverage that require multiple cardiac cycles for image acquisition, however, lack temporal uniformity.

Temporal uniformity is necessary to determine opacification gradients at a particular point in time, a prerequisite for the gradients to accurately reflect coronary blood flow. Chow et al, however, have shown that by correcting the changes in coronary opacification and normalizing to the descending aorta, even with existing CT scanners with incomplete cardiac coverage, coronary blood flow can be predicted reliably.⁵⁰ Although measurement of resting coronary contrast opacification may not be a sensitive measure of significant stenosis, comparison of changes following pharmacologic stress may clarify the functional importance of the stenosis. With pharmacologic vasodilator stress, greater augmentation of coronary flow would be expected in normal arteries compared with arteries with fixed stenoses. Independent investigators using a similar approach have shown that measurement of contrast gradient across the lumen (ie, transluminal attenuation gradient, defined as the linear regression coefficient between luminal attenuation and axial distance) has the potential to evaluate the degree of coronary stenosis, and also improves classification of stenosis severity in CTCA, especially in severely calcified lesions.⁵¹

Previous work by Goto et al and Iwanaga et al has shown that cardiac contraction influences systolic coronary flow and transmural myocardial perfusion.^{52,53} In addition, ischemia is also known to affect microvascular resistance and the effect is more pronounced in subendocardium in systole compared to subepicardium in diastole. To maintain the capillary patency, the capillary microvessels undergo greater phasic change in microvascular resistance.⁵⁴ Thus, a fall in the capacitance of microvessels during systole is noted due to increase in subendocardial resistance induced by ischemia.⁵⁵ Boll et al and Nagao et al, using MDCT, showed that endocardial intensity in ischemic myocardium was significantly lower than that for non-ischemic myocardium during systole, while no difference was seen during diastole.^{56,57} Subsequently, they evaluated the ability of 64-slice MDCT to detect ischemia at rest and compared this with MPS.⁵⁸ They used a pattern of transient endocardial hypoenhancement during systole and normal enhancement during diastole at rest as the definition of ischemia on CT. They found that this pattern distinguished patients with or without ischemia with a sensitivity of 90%, specificity of 83%, positive predictive value of 86% and negative predictive value of 88%. This method of CT-MPI may have the potential to detect ischemia at rest.

Comparison of CT-MPI With Other Imaging Modalities

A number of investigators have compared the performance of CT-MPI with other imaging modalities. Kurata et al, in 2005, using 16-detector CT, found good agreement (83%) between

stress adenosine CT-MPI and thallium-201 MPS. In that study, however, only 48% of coronary segments were evaluable under stress (compared with 89% at rest, $P < 0.05$), probably due to the limited temporal resolution obtained with available scanners at the time.⁵⁹ Okada et al used DSCT to assess myocardial perfusion following adenosine stress and compared the results with MPS. CT-MPI in their study compared favorably to SPECT for detection and assessment of perfusion defects with good correlations on a per-vessel (rest, $r = 0.66$; stress, $r = 0.56$) and a per-patient level (rest, $r = 0.76$; stress, $r = 0.60$).⁶⁰ George et al, using 64- and 256-detector MDCT, found a per-vessel territory sensitivity, specificity, positive predictive value, and negative predictive value of 75%, 87%, 60%, and 93%, respectively, compared with ICA and SPECT.²¹ In a 36-patient study, Ruzsics et al demonstrated excellent overall sensitivity, specificity, and accuracy of 92%, 93%, and 93% respectively for DE CT-MPI to detect perfusion defects seen on SPECT MPS.⁶¹ The extent and severity of perfusion defects on CT-MPI and SPECT MPS were compared by Tamarrappoo et al using a 5-point scale and a total perfusion deficit score, and they reported good agreement between the modalities.⁶² Kido et al investigated the feasibility of cardiac MDCT for quantitative assessment of MBF using the adenosine triphosphate load technique.⁶³ MBF was successfully measured in their study and the results were validated using MPS and ICA. Finally, a different stress agent (dipyridamole) was used by Cury et al, who confirmed equivalent sensitivity and specificity of CT-MPI to SPECT in the detection of stenosis found on ICA.²³

Recent studies have confirmed high diagnostic accuracy and superiority of CMRI over SPECT for the diagnosis of CAD.⁶⁴ Although CMRI is being increasingly used for the diagnosis and determination of appropriate management plans for CAD patients, there are very few studies directly comparing CT-MPI to CMRI perfusion defects. Feuchtnet et al found a per-vessel territory sensitivity, specificity, positive predictive value, and negative predictive value of 96%, 88%, 93% and 94%, respectively, for DSCT to detect perfusion defects seen on CMRI.⁶⁵

Stress CT-MPI

Similar to radionuclide MPS, the CT-MPI protocol consists of stress phase acquisition and rest phase acquisition. One important difference, however, is that during rest phase CT-MPI, images are also acquired to evaluate coronary anatomy. Iodinated contrast is infused during both stress and rest acquisitions (60–75 ml for each acquisition). In all the available literature on CT-MPI to date, pharmacological agents (such as adenosine, dipyridamole, or regadenoson) have been used during the stress phase.^{21–23}

Depending on the order of scan acquisition (ie, stress phase first followed by rest phase, or vice versa), there are 2 different ways to perform stress and rest CT-MPI. Iodine-based contrast agents have similar pharmacokinetics to gadolinium-based compounds used in CMRI.⁶⁶ If the interval between the 2 scans is short (<20–30 min), the residual contrast can cross-contaminate the second acquisition. If stress phase images are acquired first and a short scan interval is used to acquire the second set of rest images, contrast from the stress scan would accumulate in an area of previous myocardial necrosis due to the slow wash-out phenomenon and may lead to possible underestimation of myocardial infarction (perfusion defect during the rest scan) and/or the overestimation of myocardial ischemia. Patients with (1) intermediate-high pre-test proba-

Figure 2. Multiple images of the same patient with large distal septal and apical perfusion defect demonstrating how different settings can be used to improve visualization of areas of perfusion defect. Typically perfusion defects are best visualised with the use of thick multiplanar reconstruction (MPR) or minimum intensity projection (MinIP) images with a narrow window and level. (A) Thick MPR (10mm; window [W], 800; level [L], 300); (B) thick MPR (10mm; W, 800; L, 200); (C) thick MPR (10mm; W, 450; L, 150); (D) thick MPR (10mm; W, 100; L, 100); (E) thick MPR (10mm; W, 200; L, 100); (F) thin MPR (1mm; W, 200; L, 100); (G) maximum intensity projection (10mm; W, 200; L, 100); (H) MinIP (10mm; W, 200; L, 100).

bility of CAD; (2) high calcium scores (ie, calcium score >400); (3) known CAD; (4) prior myocardial infarct; or (5) need for simultaneous assessment of a stenotic coronary vessel responsible for ischemia in order to define revascularization options, are those who benefit from having the stress phase of the perfusion done first.

Conversely, in patients in whom the rest scan is performed first with a short inter-scan interval, there is a risk of contrast contamination during the stress scan, which may lead to late contrast enhancement and thus reduce the sensitivity of the test for ischemia detection. This protocol (rest scan first) has better sensitivity to detect infarct if no significant CAD is evident on rest images (on CTCA), in which case the stress component of the scan is not required. Patients with lower pre-test probability of CAD would benefit from this protocol.

Last, a third optional delayed-phase acquisition can be performed in cases in which late contrast enhancement evaluation for myocardial scar is desired. The usefulness and clinical relevance of the delayed phase scan remain to be established. Delayed-phase acquisition is performed approximately 10min after the completion of the second acquisition and no contrast injection is required, because it uses previously injected contrast in the stress and rest phases.

For analysis, stress, rest, and delayed images are reconstructed at mid-diastole. Standard short-axis, 2-chamber, and 4-chamber views are then created using the axial images created using multiplanar reconstruction. Maximum intensity projections are known to mask perfusion defects and reduce sensitivity. Although minimum intensity projections are preferred so as to bring out subtle perfusion defects, they are also more susceptible to noise and can lead to false positives.⁴⁷ Use of a narrow window width (100–200 HU) centered at an attenuation of around 100HU (window level) is recommended for perfusion analysis (Figure 2).

Challenges of CT-MPI

This technique continues to evolve and has several limitations,

which will be eventually overcome as the CT technology improves. Motion artifacts can be reduced by pre-medicating patients with β -blockers, by using DSCT or using a wide-area detector scanner with the capability to perform segmented reconstruction. By evaluating multiple phases of the cardiac cycle, it is possible to differentiate a true perfusion defect from a motion artifact, because the true perfusion defect will remain stationary and unchanged but the motion artifact may disappear or change in location. Beam-hardening artifacts (selective attenuation of lower-energy beams when passing through high-density objects leading to increased mean energy of the remaining beams) can result in regions of low attenuation, mimicking areas of hypoperfusion. Although these artifacts are triangular in shape and appear to originate from the region of high attenuation next to it, and may not conform to any vascular territories,⁴¹ these artifacts can also be reduced by using myocardial-specific beam-hardening correction algorithms.³²

The impact of widespread use of cardiac CT on health-care utilization and spending on evaluation of suspected CAD is still debatable. Although a study in older patients showed that the use of CTCA led to increased diagnostic tests, invasive cardiac procedures and higher spending on care,⁶⁷ a similar analysis in a cohort of younger patients found a decrease in follow-up costs.²⁶ Indeed, longer-term and broader perspective studies are needed to accurately assess the impact on health-care utilization and spending given that clinical management changes resulting from use of cardiac CT may affect the level of symptoms, quality of life or long-term mortality.

A potential limitation of cardiac CT is the exposure of patients to ionizing radiation. Radiation doses associated with cardiac CT have raised concern. With the adoption of prospective ECG-triggered image acquisition, however, radiation doses have been significantly reduced (2–4 mSv). Most recently, with software and hardware advances, many vendors are now reporting <1-mSv doses. Current dose rates are similar to or less than other competing modalities (technetium-99m SPECT, 9–15 mSv; Thallium-201 SPECT, 16–19 mSv; ICA, 2–11 mSv; rubidium-82 PET, 1–3 mSv).²⁰ Other potential limitations of

cardiac CT are the need for contrast, which may limit its utility in patients with significant renal impairment; and the potential need for β -blockers for patients with uncontrolled heart rates, limiting its applicability in patients with severe reactive airways disease.

Conclusions

Cardiac CT is a unique non-invasive modality that permits rapid anatomical and functional assessment of the heart. Cardiac CT has excellent spatial resolution and has the potential to provide accurate anatomical detail of the coronary arterial and venous systems, valves, myocardium, pericardium and left ventricular function.^{10–16,68} Recent data also indicate that it may also have the ability to assess plaque vulnerability and predict onset of acute coronary syndrome.^{69,70} While the ability of cardiac CT to provide all of the aforementioned information in 1 examination gives it a competitive edge over other related modalities, for it to truly become a one-stop technique for the assessment of CAD, it must also provide reliable and robust information about myocardial perfusion.

The feasibility of CT-MPI has been evaluated both in animal models and in single-center prospective studies. Initial results with newer scanners are promising and comparable diagnostic characteristics to SPECT are reported. Moreover, because the CT-MPI protocol allows for the simultaneous CTCA, it adds to the accuracy of CTCA. With the increasing use of prospective ECG-triggering and newer reconstruction methods, CT-MPI now uses a significantly reduced radiation dose not different to that of traditional rest/stress SPECT-MPI.³⁸ While the aforementioned facts would indicate that this technique has the potential to become the first-choice modality for the assessment of CAD, certain limitations need to be overcome and larger multicenter validation studies in a wider patient population are needed for it to achieve its projected place. More research is needed so that uniform optimal imaging protocols, contrast use, acquisition parameters, reconstruction techniques and post-processing methods can be developed.

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