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Multislice computed tomography angiography in the diagnosis of coronary artery disease

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Abstract

Multislice CT angiography represents one of the most exciting technological revolutions in cardiac imaging and it has been increasingly used in the diagnosis of coronary artery disease. Rapid improvements in multislice CT scanners over the last decade have allowed this technique to become a potentially effective alternative to invasive coronary angiography in patients with suspected coronary artery disease. High diagnostic value has been achieved with multislice CT angiography with use of 64- and more slice CT scanners. In addition, multislice CT angiography shows accurate detection and analysis of coronary calcium, characterization of coronary plaques, as well as prediction of the disease progression and major cardiac events. Thus, patients can benefit from multislice CT angiography that provides a rapid and accurate diagnosis while avoiding unnecessary invasive coronary angiography procedures. The aim of this article is present an overview of the clinical applications of multislice CT angiography in coronary artery disease with a focus on the diagnostic accuracy of coronary artery disease; prognostic value of coronary artery disease with regard to the prediction of major cardiac events; detection and quantification of coronary calcium and characterization of coronary plaques. Limitations of multislice CT angiography in coronary artery disease are also briefly discussed, and future directions are highlighted.

1 Introduction

Coronary artery disease (CAD) is the leading cause of death in advanced countries and its prevalence is increasing among developing countries.[1,2] In 2001, CAD was reported to be responsible for 7.3 million deaths and 58 million disability-adjusted life years lost worldwide.[3] According to recent World Health Organization statistics for 2007, cardiovascular deaths account for 33.7% of all deaths worldwide, whereas cancer represents 29.5%, other chronic diseases, injury and communicable diseases contribute to 26.5%, 7%, and 4.6%, respectively.[4] Cardiovascular disease costs more than any other diagnostic group.[1] The total direct and indirect cost of cardiovascular disease and stroke in the United States for 2010 is estimated to be $503.2 billion. In comparison the estimated cost of all cancer and

benign neoplasms was $228 billion in 2008. Due to the current global focus on healthcare utilization, costs, and quality, it is essential to monitor and understand the magnitude of healthcare delivery and costs, as well as the quality of healthcare delivery in relation to the cardiovascular disease.

Traditionally, diagnosis of CAD is performed by invasive coronary angiography which is recognized as the gold standard technique, since it has superior spatial and temporal resolution leading to excellent diagnostic accuracy. However, it is an invasive and expensive procedure associated with a small but distinct procedure-related morbidity (1.5%) and mortality (0.2%).[5] Furthermore, invasive coronary angiography usually requires patients to stay for a short period in the hospital after the examination and this causes discomfort for the patients. Moreover, not all of the invasive angiography examinations are performed for both diagnostic and therapeutic purposes, and some of the invasive angiography examinations are performed only for diagnostic purposes, which is only for verification of the presence and extent of CAD. Thus, a non-invasive technique for imaging and diagnosis of CAD is highly desirable. Over the last decades, non-invasive imaging modalities have undergone rapid developments, such as multislice CT

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(MSCT), magnetic resonance imaging (MRI), radionuclide imaging such as single photon emission computed tomography (SPECT) and positron emission tomography (PET).[6,7] Although promising results have been achieved with cardiac MRI, especially with the technical improvements of MRI scanners such as 3T MRI,[8,9] cardiac MRI has a number of limitations including variable protocols, long scanning time and lack of wide availability. These limitations prevent cardiac MRI from becoming a widely acceptable non-invasive imaging modality in the diagnosis of CAD. Myocardial perfusion imaging with SPECT is a widely established method for non-invasively evaluating the myocardial viability, left ventricular function and coronary artery stenosis.[10,11] PET has been reported to be valuable in the diagnosis of CAD and is more sensitive and specific than SPECT in the detection and localization of coronary stenoses.[12,13] However, these nuclear medicine imaging modalities have an inherent disadvantage of poor anatomical details, thus, providing little information about coronary lumen changes as well as characterization of coronary plaques. SPECT and PET are not recommended as a routine imaging modality for the detection and diagnosis of CAD, despite excellent cardiac functional information can be acquired with these techniques.

In comparison, MSCT angiography allows for excellent visualization of anatomical details of coronary artery and its branches, and is the only imaging modality which has been widely used in the diagnosis of CAD with high diagnostic accuracy being achieved.[14,15] MSCT angiography is a relatively simple procedure that does not require arterial access or hospital admission. After intravenous injection of contrast medium and elective pre-medication, e.g., use of beta-blocker to slow down heart rate in some patients, the entire procedure does not require more than 15 min. Images can be post-processed and reconstructed during different cardiac phases to allow retrospective selection of the phases with the least motion artifacts, while in the meantime to assess ventricular performance. In addition to the detection and diagnosis of coronary artery stenosis, the benefits of MSCT angiography compared to invasive coronary angiography are to quantify and characterize atherosclerotic plaques, provide independent prognostic information for predicting cardiac events and mortality in patients with known or suspected CAD.[16,17] This article reviews the clinical applications of MSCT angiography in cardiac imaging with a focus on the diagnostic accuracy and prognostic value of the MSCT angiography in CAD. MSCT angiography in the detection and quantification of coronary calcium as well as characterization of coronary plaques is also explored. Limitations and future directions of MSCT angiography are highlighted.

2 Multislice CT angiography-technical developments

Imaging of the heart has always been technically challenging due to the heart's continuous movement. Coronary artery has a diameter which ranges from 3 mm to 5 mm in the main segments, and 1 mm to 1.5 mm in the distal segments. A normal heart rate ranges from 60 to 80 beats per minute in a healthy adult. In order to adequately visualize the coronary artery tree with clear demonstration of the normal coronary lumen and detection and quantification of coronary artery stenosis with a minimal 20% change in the coronary diameter, the CT scanners need to provide a spatial resolution of at least 0.5 mm and a temporal resolution of between 200 ms and 250 ms. It is impossible to achieve this goal with a single slice CT scanner as it has limited spatial resolution with 1.0 mm along the longitudinal axis, and inferior temporal resolution which is reflected in the long gantry rotation time (1 s per rotation). Imaging of the heart has moved into the diagnostic era with the introduction of MSCT scanners in 1998, and this represents a significant technical improvement in the CT scanning technique.[18,19]

The early generation of MSCT scanners enables simultaneous acquisition of four slices at a rotation time of 0.5 s, which is four times faster than the traditional single slice CT, providing significant improvement of scan speed and longitudinal resolution.[20,21] Later technical developments such as 64- or more slice CT scanners allow for acquisition of large volume data in a very short time with a rotation time down to 0.165 s, and with high spatial and temporal resolution.[22–24] The developments of MSCT have been widely recognized as revolutionary improvements in the medical imaging field that eventually enable cardiac imaging to be performed with high diagnostic accuracy.

CT angiography has been widely applied to investigate vascular anatomy and diseases, and it has been regarded as one of the most valuable applications in CT imaging. Diagnostic value of CT angiography has been significantly enhanced with use of MSCT techniques, owing to its improved resolution, enabling excellent visualization of both main artery and side branches. MSCT angiography produces angiography-like images non-invasively with high diagnostic accuracy, thus it has replaced invasive angiography in many applications.[7] In particular, MSCT angiography has proved valuable in imaging the coronary artery tree for diagnosis of CAD. Studies have shown that in selected patients, MSCT angiography can be used as a reliable alternative to invasive

coronary angiography.[15,25–27] This is of clinical significance because the number of invasive coronary angiography examinations can be reduced or unnecessary invasive procedures can be avoided based on MSCT angiography findings.

3 Multislice CT angiography in coronary artery disease: coronary calcium scoring

Direct relationships between coronary artery calcification and the presence and to a modest degree, the extent and severity of atherosclerotic CAD have been demonstrated in comparisons based on histology, ultrasound and invasive angiography.[28–30] This correlation of coronary artery calcium (CAC) with the amount of coronary plaque has raised increasing interest in the non-invasive imaging detection and quantification of coronary calcium for diagnosis of CAD and estimation of the disease prognosis. Electron beam CT (EBCT) was the first accurate and sensitive non-invasive imaging technique to quantify CAC.[31] The main limitation of EBCT is its inferior spatial resolution which is between 1.5 mm and 3.0 mm. This restricts its diagnostic value to accurately evaluate the severity of coronary artery disease. EBCT has been replaced with MSCT since 2003 onwards.

Quantifying the amount of CAC with unenhanced CT scan has been widely accepted as a reliable non-invasive technique for screening risk of future cardiac events,[32,33] and is usually quantified by using the Agatston score.[34] The purpose of the scan is to detect and calculate the calcium density, volume or mass. The total coronary calcium is used as a way of predicting and stratifying the risk of CAD. Clinical application of CAC scoring has been supported by evidence showing that absence of calcium reliably excludes obstructive coronary artery stenoses,[35] and that the amount of CAC is a strong predictor for risk assessment of myocardial infarction and sudden cardiac death, independent of conventional coronary risk factors.[36,37] CAC scoring is regarded as a good predictor of major cardiac events and adds incremental prognostic value to risk factors in patients from different risk groups. However, its predictive value is determined by the patients' symptoms. In asymptomatic individuals, it has been reported that a zero CAC is associated with a very low (<1% per year) risk of major cardiac events over the next 3–5 years, whereas in asymptomatic patients with extensive coronary calcification, the major cardiac events have been reported to be increased by up to 11-fold.[38–40] Several large population-based studies have reported that in asymptomatic patients without known CAD, CAC is predictive of future cardiac events above and beyond traditional risk factors.[41–43]

In symptomatic patients, CAC scoring is considered only marginally related to the degree of coronary stenosis, as it is well known that both obstructive and non-obstructive CAD can occur in the absence of calcification.[44,45] Coronary stenoses are frequently found to be non-calcified, and highly calcified plaques are frequently non-obstructive. Thus, the value of a zero or low calcium score in symptomatic patients remains unclear. Studies have shown that zero or low calcium score is present in up to 8.7% of symptomatic patients with obstructive non-calcified plaques.[46,47] Cheng *et al*.[46] reported that low but detectable CAC scores are less reliable in predicting plaque burden due to their association with high overall non-calcified coronary artery plaque. According to these reports, low CAC scores are less valuable in the prediction of prevalence or severity of coronary artery disease caused by the non-calcified coronary plaques.

4 Multislice CT angiography in coronary artery disease: characterization of plaques

Since major adverse cardiac events are caused by plaque rupture, it is important to use imaging methods to detect, quantify and characterize coronary atherosclerotic plaque which enables risk stratification. As calcium comprises only one component of plaque and non-calcified structures, such as a large necrotic core and thin fibrous cap are usually considered to indicate high inclination towards plaque rupture,[48] an increasing interest has seen in the use of medical imaging to visualize and analyze the components of coronary atherosclerotic plaques.

Coronary plaques can be characterized into the following three types based on the CT attenuation[49]: non-calcified plaques are defined as lesions with a radiodensity greater than neighbouring soft tissue but lower density than the contrast-enhanced coronary lumen (Figure 1); calcified plaques indicate lesions with density higher than contrast-enhanced coronary artery lumen (Figure 2); mixed plaques refer to lesions with non-calcified and calcified components (calcium component between 20% and 80%) within a single lesion (Figure 3) or within a segment of the coronary artery (Figure 4).

It is generally believed that lipid-rich plaques have a higher risk of rupture with consequent thrombosis than fibrotic plaques, thus, differentiation of different plaques based on measurements of CT attenuation has attracted attention to researchers. Studies comparing MSCT angiography with intravascular ultrasound (IVUS) demonstrated that MSCT angiography is able to detect variable densities in the coronary atherosclerotic plaques.[50-52] However, a direct comparison between MSCT angiography and IVUS revealed
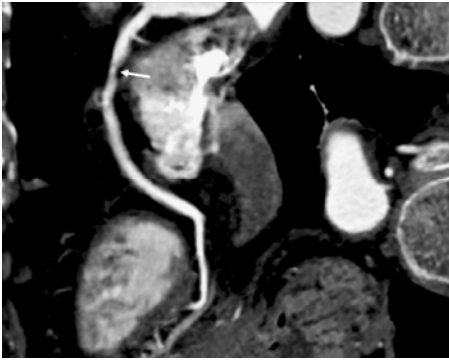
Figure 1. A non-calcified coronary plaque (arrow) is visualized at the proximal segment of right coronary artery on a curved planar reformatted image in a 67-year-old woman presenting with the symptom of chest pain. The plaque results in more than 50% coronary lumen stenosis.

Figure 2. Calcified coronary plaques are shown at the proximal segment of left anterior descending (long arrow) and distal segment of left circumflex (short arrow) branches on a coronal maximum-intensity projection image in a 73-year old man with chest pain and history of hypertension.
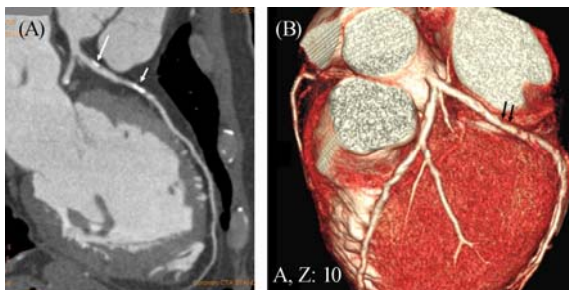

Figure 3. A mixed coronary plaque (long arrow in A) is present within a lesion at the proximal segment of left anterior descending artery as shown on a curved planar reformatted image in a 55-year-old man with symptoms of chest discomfort and epigastric pain. A calcified plaque is also noticed at the mid-segment of the same left coronary artery (short arrow in A). Three-dimensional (3D) volume rendering demonstrates significant stenosis in the left anterior descending due to the calcified plaque (arrows in B).
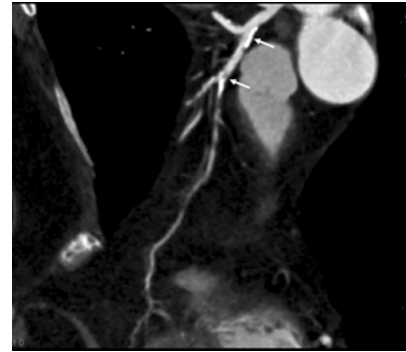

Figure 4. Curved planar reformatted image shows mixed coronary plaques (arrows) at the proximal segment of left anterior descending in a 67-year-old female with atypical chest pain, diabetes and hypertension.

general overestimation on MSCT for quantitative measurements of plaque areas and thickness.[53,54] Moreover, MSCT angiography fails to detect unstable plaques, thus differentiation of lipid-rich content from fibrous content with MSCT remaining challenging due to overlap in the attenuation values of lipid and fibrous tissue.[55]

5 Multislice CT angiography in coronary artery disease: diagnostic value

Diagnostic value of MSCT angiography in CAD has been significantly enhanced with the developments of MSCT scanners over the last decade. Early studies with use of 4- and 16-slice CT showed moderate diagnostic accuracy in the diagnosis of CAD due to technical limitations.[14] Image quality of coronary artery visualization was impaired and suboptimal in a number of cases with 4-slice CT as the unassessable coronary segments could be as high as more than 20%.[14] With 16-slice CT, thinner detector rows increased the spatial resolution and further shortened the total scan time. Therefore, image quality in 64-slice CT angiography has become more consistent with the reported sensitivities and specificities ranging from 83% to 98% and 96% to 98%, respectively.[56–58] Further increased diagnostic accuracy was achieved with 64-slice CT due to improved spatial and temporal resolution, thus leading to shorter examination times. Several meta-analyses of 64-slice CT studies in the diagnosis of CAD reported that the sensitivities were more than 90% and specificities more than 96% in most of the studies.[15,25–27] Heart rate control with use of beta-blockers is necessary in single source 64-slice CT as image quality is affected by motion artifacts in patients with heart rates more than 65 beats per minute. This limitation has been overcome with the introduction of dual-source CT as the temporal resolution was shortened

from 165 ms to 75 ms, thus heart rate dependence was eliminated. Studies performed with dual-source CT demonstrated high diagnostic accuracy for diagnosis of CAD, and most importantly the image quality is independent of heart rate (Figure 5).[59–61] In particular, MSCT angiography has demonstrated a very high negative predictive value (more than 95%), indicating that it can be used as a reliable technique to exclude patients suspected of CAD, thereby reducing the need for invasive coronary angiography.

Expansion of MSCT systems from a prototype 64-slice to a 256-slice or 320-slice system has allowed for acquisition of whole-heart coverage in one gantry rotation with a slice thickness of 0.5 mm.[23,24,62–64] A maximum 4 cm (64×0.625 mm) longitudinal coverage can be achieved with 64-slice CT in one heart beat, thus, 3–5 heart beats are normally required to cover the entire heart volume with 64-slice CT scanners. In contrast, a 12.8-cm (256×0.5 mm) and 16-cm (320×0.5 mm) of craniocaudal coverage can be achieved with 256- and 320-slice CT in a single heart beat, with excellent image quality and demonstration of the entire coronary arteries (Figure 6). Very high diagnostic accuracy has been reported with 320-slice CT angiography for detection of significant coronary stenosis across all coronary segments, regardless of size, cardiac rhythm or image quality.[62,63] Furthermore, 320-slice CT enables visualization of coronary artery and its segments with sufficient image quality in patents with atrial fibrillation.[64] 320-slice CT represents a promising technical improvement of MSCT angiography in cardiac imaging, although further studies based on large cohorts from multicenters are needed to confirm its diagnostic value.

6　Multislice CT angiography in coronary artery disease: prognostic value

The anatomy-based approach is a well established method for risk stratification of patients as demonstrated by invasive coronary angiography, which clearly delineates the severity and extent of significant coronary stenosis. High risk coronary anatomy (three-vessel CAD, stenosis of left
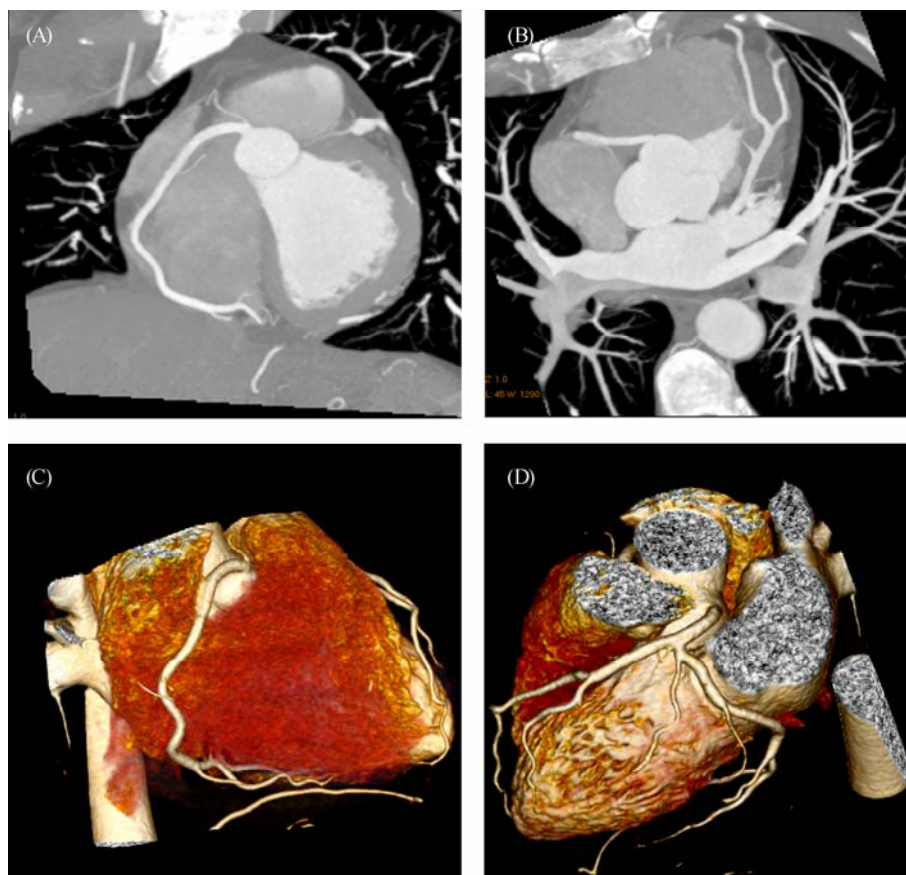

Figure 5.　Coronal maximum-intensity projection images acquired with a dual-source 64-slice CT angiography shows normal right (A) and left coronary artery branches (B) in a 47-year-old man with atypical chest pain. 3D volume rendering images (C and D) demonstrate right and left coronary arteries with excellent visualization of the main coronary and side branches.
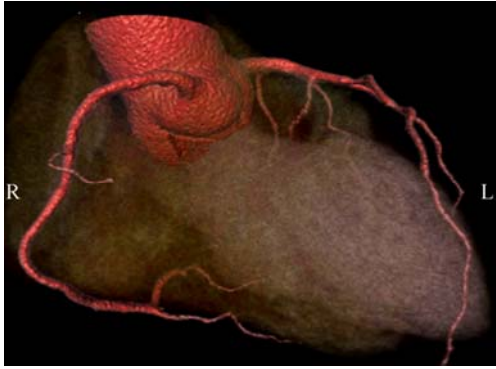
Figure 6. 3D volume rendering of the coronary arteries and side branches are clearly demonstrated with use of 320-slice CT angiography in a 58-year-old man presenting with chest pain. Volumetric data are acquired within a single heart beat with excellent image quality.

main coronary artery) is directly related to poorer outcome,[65–67] while normal coronary artery is associated with an excellent prognosis. [68] Despite many reports showing the prognostic value of coronary calcifications detected on non-enhanced CT scans, it is not until very recently that the prognostic value of MSCT angiography has been made clear.

Early studies investigating the short to mid-term outcomes of patients undergoing 64-slice CT angiography reported that MSCT angiography is able to provide independent prognostic information for predicting cardiac events and mortality in patients with known or suspected CAD.[69,16] Findings of MSCT angiography based on a single centre experience have been closely associated with the future cardiac events, with 0% or 1% cardiac events being reported in patients with normal cardiac CT or mild coronary artery disease, and up to 30% in patients with one or more vessel obstructive CAD.[70,17] Recently, Abdulla *et al*.[71] conducted a meta-analysis of 10 relatively large studies evaluating the prognostic value of 64-slice CT angiography. The meta-analysis showed that cumulative cardiac event rates over a mean follow-up of 21 mo were 0.5% in patients with normal MSCT angiography, 3.5% in those with non-obstructive CAD and 16% in patients with obstructive CAD by 64-slice CT angiography. Compared to a normal MSCT angiography, non-obstructive CAD was associated with a significant increased risk of major adverse cardiac events, while obstructive CAD was associated with a greatly increased further significant risk. The prediction of excellent prognosis together with the high negative predictive value makes MSCT angiography the appropriate imaging modality to exclude CAD and prognosticate populations with different pre-test likelihoods for CAD.

7 Multislice CT angiography in coronary artery disease: future directions

MSCT angiography is one of the most exciting developments in recent years in the diagnosis of CAD. Although rapidly technical improvements and increased diagnostic accuracy with satisfactory results have been achieved with latest MSCT scanners, invasive coronary angiography still remains the gold standard technique in the diagnosis of CAD as it allows for quantitative assessment of the coronary artery lumen. The spatial resolution of the latest MSCT scanners is 0.5 mm, which is quite close to the 0.2 mm that is available with invasive coronary angiography. Thus detection of coronary wall changes with current MSCT scanners can be achieved with high accuracy. However, the temporal resolution of 75 ms that is available with MSCT angiography is still inferior to the 20 ms with invasive coronary angiography, therefore, aggressive heart rate control is a necessity in most of the MSCT angiography examinations. Further technical developments to improve the gantry rotation speed will enable MSCT angiography applicable to patients with high or irregular heart rates.

There is no doubt that MSCT angiography cannot replace invasive coronary angiography in the diagnosis of CAD in the near future, however, the judicious use of this non-invasive imaging technique could play an important role in the clinical workup and management of patients with suspected CAD. MSCT angiography should be used to aim for more effective risk stratification of patients, allowing identification of those patients who would be most likely to benefit from invasive coronary angiography and reduce the number of invasive procedure in patients who do not have obstructive coronary disease. Studies have shown that a reasonable number of patients with suspected CAD had normal coronary arteries or non-obstructive disease on invasive coronary angiography.[72–74] These reports suggest that many unnecessary invasive angiography examinations were performed in the clinical evaluation of patients with suspected CAD. MSCT angiography is an effective imaging modality of determining which patients should undergo invasive coronary angiography.

It is generally agreed that CT is an imaging modality with high radiation exposure, as it contributes up to 70% radiation dose of all radiological examinations, although it comprises only 15% of all radiological examinations.[75] Radiation-induced malignancy associated with cardiac CT imaging is a major issue which has raised serious concern in the literature. With increasing application of MSCT angiography in the diagnosis of CAD, the research focus has shifted from the previous emphasis on diagnostic value to the current

focus on reduction of radiation dose with acceptable diagnostic images. This is reflected in the increasing publications on dose reduction through applying different dose-saving strategies in MSCT angiography.[76–79] Thus, the responsible use of MSCT angiography is absolutely necessary in terms of justifying and adjusting the MSCT scanning techniques.

8 Summary and conclusion

MSCT angiography represents the most rapidly developed imaging modality in cardiac imaging, with satisfactory results having been achieved in the diagnosis of CAD. MSCT angiography demonstrates high accuracy for detection of coronary calcium, characterization of atherosclerotic plaques and prediction of disease progression. Currently, MSCT angiography cannot be recommended as a reliable alternative to invasive coronary angiography in patients with suspected CAD. MSCT angiography serves as an effective and independent predictor for predicting coronary artery disease progress and major cardiac events. This has significant clinical value because a normal MSCT angiography suggests that patients have normal coronary arteries and can be safely reassured without undergoing further tests or invasive examinations such as invasive coronary angiography.

Radiation associated with MSCT angiography has increased significantly over the last decade and this should draw attention to the clinicians responsible for referring patients for CT examinations. Accurate risk stratification for appropriate selection of MSCT angiography is crucial, and both radiologists and referring physicians (mainly cardiologists) need to work together to develop better selection criteria for patients referred for MSCT angiography.

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