Novel clinical applications of state-of-the-art multi-slice computed tomography

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Abstract Recent years have witnessed a rapid development of multi-slice computed tomography (MSCT) technology. The number of detector rows has increased from 4-slices to the current availability of 64-slice and even 320-slice systems. In addition, images are acquired with thinner slices and faster rotation times resulting in substantially improved image quality and diagnostic accuracy. Simultaneously, effective dose reduction acquisition techniques have been developed allowing considerable reduction of the radiation dose. Conceivably, these advancements may allow further expansion of the use of MSCT beyond the visual assessment of the presence or absence of significant coronary artery disease. Indeed, a particular advantage of the technique is that in addition to evaluation of the coronary arteries it also allows assessment of cardiac structures and function. The purpose of the current review is to discuss several novel applications of cardiac MSCT, including stenosis quantification, atherosclerotic plaque imaging and prognostification as well as imaging of left ventricular function, aortic and mitral valve anatomy using state-of-the-art technology.

Keywords Imaging · Computed tomography

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Introduction

Recent years have witnessed a rapid development of multi-slice computed tomography (MSCT) technology. The number of detector rows has increased from 4-slices to the current availability of 64-slice and even 320-slice systems. In addition, images are acquired with thinner slices and faster rotation times resulting in substantially improved image quality and diagnostic accuracy. Simultaneously, effective dose reduction acquisition techniques have been developed allowing considerable reduction of the radiation dose. Conceivably, these advancements may allow further expansion of the use of MSCT beyond the visual assessment of the presence or absence of significant coronary artery disease (CAD). Indeed, a particular advantage of the technique is that in addition to evaluation of the coronary arteries it also allows assessment of cardiac structures and function. The purpose of the current review is to discuss several novel applications of cardiac MSCT, including stenosis quantification, atherosclerotic plaque imaging and prognostication as well as imaging of left ventricular (LV) function, aortic and mitral valve anatomy using state-of-the-art technology.

Developments in imaging of the coronary arteries

Quantification of the degree of stenosis on MSCT

High diagnostic accuracies to detect significant coronary artery stenoses have been reported for MSCT as compared to invasive coronary angiography [1]. Of note, these data are based on visual assessment of the degree of stenosis using in general a cut-off of 50% luminal narrowing or more. In contrast, no validated quantitative approach is currently available which is considered to be a major limitation of the technique. Indeed, the opportunity to obtain a more precise measure of the degree of stenosis, similar to quantitative coronary angiography (QCA), would be highly beneficial in terms of diagnostic accuracy, reproducibility and subsequent therapeutic management decisions. However, the limited temporal and spatial resolution of MSCT as compared to invasive coronary angiography may pose substantial difficulties. Not surprisingly, previous attempts to quantify stenosis of coronary arteries have been disappointing [2, 3]. Leber and colleagues recently evaluated the diagnostic accuracy of stenosis quantification in 59 patients who were underwent both 64-MSCT and invasive coronary angiography [2]. In 55 patients, all coronary artery segments (825 segments, based on a 15 segment model) could be visualized and subsequently quantified on MSCT. Overall, only a moderate correlation ($n = 825$, $r = 0.54$) was observed for diameter stenosis between measurements on MSCT and QCA. In particular, poor diagnostic accuracy of MSCT was observed for distal segments as compared to proximal and mid segments of the coronary arteries. With regard to plaque type, a tendency to overestimate the degree of stenosis in the presence of calcium has been identified. Finally, reproducibility appears to be limited as well [2–4].

To some extent, better correlations may be expected by comparing MSCT to true tomographic atherosclerosis imaging techniques, such as intravascular ultrasound (IVUS). Also, the development of more automated algorithms with less manual interference may substantially improve accuracy and reduce interobserver variability [5, 6]. An example of analysis with automated quantification software developed at our own center is provided in Fig. 1.

Recently, Bruining and coworkers reported their observations using automated coronary plaque measurements on MSCT angiography in comparison to IVUS in 48 patients [5]. Interestingly, the authors demonstrated that automated lumen detection on MSCT angiographic examinations was superior to manual assessment of vessel contours with good reproducibility. Nevertheless, automated quantification of MSCT systematically underestimated coronary plaque, in line with previous investigations. Accordingly, although the potential of automated quantification of stenosis is evident, further developments remain needed before these algorithms can be used in daily clinical practice. In addition, one needs to realize that although assessment of significant stenosis as compared to invasive coronary angiography may improve by the availability of quantitative algorithms, prediction of ischemia will remain limited. Indeed, several studies comparing MSCT coronary angiography with functional testing revealed a large discrepancy between techniques [7, 8]. In line with previous comparisons with invasive coronary angiography, many significant
stenoses on MSCT did not result in ischemia on functional testing. Moreover, Meijboom et al. recently demonstrated that even quantitative assessment resulted in poor correlation with intracoronary fractional flow reserve, confirming that anatomical assessment cannot predict the hemodynamic significance of a coronary stenosis [9]. Accordingly, further evaluation with functional testing remains essential for angiographically intermediate lesions prior to referral for invasive coronary angiography and revascularization.

Plaque imaging with MSCT

An emerging feature of MSCT that receives increasing interest is its capability to non-invasively visualize atherosclerosis, as illustrated in Fig. 2. Despite the development of dedicated risk assessment tools, a large number of patients without any prior symptoms experience acute myocardial infarction or even sudden death [10]. These unexpected adverse cardiac events emphasize the significance of detection of underlying coronary atherosclerosis. Moreover, it appears that not only plaque severity in terms of percentage stenosis but also plaque composition is an important determinant of acute coronary events. Plaques with a large necrotic core and thin fibrous cap (identified by histology) appear to be more vulnerable to rupture and can be a substrate for atherothrombotic events [11]. Until recently, evaluation of potentially vulnerable lesions was only possible by using invasive modalities such as IVUS, elastography and optical coherence tomography. However, recent studies have demonstrated the potential of MSCT to evaluate differences in atherosclerotic plaque burden and composition non-invasively [12–14]. Indeed, an important advantage of the technique, as compared to invasive coronary angiography, is that it visualizes not only luminal narrowing but also atherosclerotic plaque content. Consequently, extensive effort is currently undertaken to determine in more detail what observed differences in plaque morphology on MSCT represent.
Briefly, three different plaques types can be distinguished by MSCT; non-calcified plaque, mixed plaque and calcified plaque. Calcified lesions appear as bright white dense structures, mixed plaques consist of non-calcified and calcified elements within the same plaque and non-calcified plaques have lower density compared with the contrast-enhanced vessel lumen but without any visible calcification. Comparisons with IVUS have shown that using differences in attenuation values MSCT may indeed reliably differentiate plaque configurations [14]. In a recent study, mean MSCT density of calcified plaque was 516 ± 198 Hounsfield Units (HU), while the mean density measured within non-calcified plaques and mixed plaques was 11 ± 12 and 78 ± 21 HU, respectively [15]. Further differentiation of non-calcified plaque however may be difficult. Pohle and colleagues demonstrated significant differences between “lipid rich” (mean density of 58 ± 43 HU) and “fibrous” plaque (mean of 121 ± 34 HU), although the overlap of attenuation values between individual lesions was substantial [16]. Additionally, external factors such as the amount of contrast, body mass index and cardiac output also highly influence attenuation values. As a result, detailed characterization of non-calcified plaque as stable or vulnerable is currently not feasible based on MSCT density measurements alone. Pundziute and colleagues recently compared plaque composition to virtual histology IVUS (VH IVUS) and reported a good correlation between plaque characteristics on MSCT and relative plaque component on VH IVUS [17]. Nevertheless, still small percentages of calcium were observed in lesions deemed to be non-calcified on MSCT. Conversely, in plaques appearing as completely calcified, fibrotic or fibro-fatty tissue is frequently identified on VH IVUS as well. Possibly, initial differentiation into calcified or non-calcified may therefore be more reliable. Based on their appearance, lesions containing calcium may then be further differentiated into large calcification or spotty calcifications, as recently suggested [18]. Interestingly, features of thin capped fibroatheroma (suggesting vulnerability) were most frequently observed in lesions classified as mixed on MSCT. Additionally, Lin and colleagues investigated the relationship of anatomical MSCT variables including plaque composition and extent with functional ischemia on SPECT [19]. The authors observed that mixed plaques were an independent predictor of severely abnormal SPECT studies. These observations suggest that the observation of multiple mixed plaques may possibly confer a higher risk of adverse cardiac events. Moreover, also in retrospective studies comparing plaque morphology on MSCT between patients presenting with acute coronary syndromes

Fig. 2 Evaluation of atherosclerotic plaque with MSCT. a A curved multiplanar reconstruction of the right coronary artery (RCA), obtained by 320-slice MSCT without evidence of atherosclerosis. In contrast, the curved multiplanar reconstruction (320-slice MSCT) of the RCA in b shows the presence of diffuse atherosclerosis (arrows). Note that both non-calcified and calcified tissue can be identified.
and stable CAD, relative more non-calcified and mixed plaques have been identified in the former patients [20–23]. However, no robust prospective data are currently available to support this thesis.

At present, it is important to realize that the inferior resolution of MSCT as compared to invasive plaque imaging techniques remains an important limitation. Nevertheless, novel approaches are currently under investigation including dual-energy source MSCT and dedicated contrast agents for improvement in plaque characterization [24, 25]. In addition, sophisticated algorithms to accurately determine plaque volume are under development. Potentially, these algorithms in combination with assessment of plaque component may allow MSCT to play a role in the monitoring of the efficacy of anti-atherosclerotic interventions [26, 27]. Accordingly, knowledge of CS may refine traditional risk stratification and thus guide therapeutic decisions by shifting patients to either a higher or lower risk category. As a consequence, particularly patients deemed at intermediate risk based on traditional risk assessment may benefit from this technique.

Preliminary investigations using MSCT coronary angiography have suggested that this technique may also provide prognostic information [31, 32]. Pundziute et al. assessed the prognostic value of 16- or 64-slice MSCT in a cohort of 100 patients with known or suspected CAD [31]. During a follow-up period of 1 year MSCT was shown to predict the occurrence of events independent of baseline risk factors. In a larger study by Min et al., 1,127 patients undergoing 16-slice MSCT were evaluated during a follow-up period of 2 years [32]. As illustrated in Fig. 3, event rates for all-cause mortality ranged between 0.3% for patients with none or mild atherosclerosis (stenosis $<50\%$) on MSCT to 15% in patients with mild to moderate left main disease.

Several studies have addressed the incremental prognostic value of anatomic imaging when used in addition to myocardial perfusion imaging (MPI). In the studies by Ramakrishna et al. and Anand et al., respectively 835 and 510 patients were enrolled who underwent both CS and MPI [33, 34]. The combination of these techniques resulted in a synergistic prediction of cardiovascular events. Rozanski and colleagues assessed the combined use of CS and MPI in a large cohort of 1,153 asymptomatic patients [35]. Interestingly, in patients with normal myocardial perfusion on MPI ($n = 1,089$), the observation of a high CS was not associated with an increased risk for cardiac death and myocardial infarction during a mean follow-up of $32 \pm 16$ months. In contrast, Schenker et al. recently observed in symptomatic patients that the risk of all-cause mortality and myocardial infarction increased with increasing CS, both in patients with normal and in patients with abnormal perfusion on MPI [36]. Similarly, van Werkhoven et al. recently demonstrated that the information on plaque burden and composition obtained by MSCT coronary angiography had incremental prognostic value over MPI [37]. Accordingly,
the precise relative prognostic values of anatomical and functional techniques remain not fully defined at present and may highly depend on the patient population that is studied. Although their combination may enhance risk stratification, one should realize that it is at the cost of increased radiation burden. Further research is required to identify those patients that may substantially benefit from comprehensive anatomical and functional assessment. However, recent innovations in MSCT technology and acquisition protocols, such as prospective ECG-triggering, have resulted in substantial dose reduction without loss of image quality [38]. Moreover, Herzog et al. recently demonstrated that also the high diagnostic accuracy and high negative predictive value of the technique in particular, were maintained at an average radiation dose as low as 2.1 ± 0.7 mSv (range: 1.0–3.3) [39]. Importantly these recent developments are currently also being implemented in hybrid systems and recent data have confirmed the feasibility of low dose (<10 mSv) hybrid PET/CT and even SPECT/CT [40, 41].

Developments in imaging of cardiac structures and function

LV function assessment using MSCT

LV function serves as a valuable prognostic and diagnostic marker in patients with CAD [42, 43] and can be evaluated with MSCT. Depending on the MSCT acquisition technique, retrospective reconstruction of cardiac images in any tomographic plane throughout the cardiac cycle is possible. To assess global LV function, 10 or 20 cine-loops are in general obtained by reconstructing thick slices (2 mm) in the short-axis orientation throughout the R–R interval (in steps of 5 or 10%). Subsequently, end-systolic and -diastolic phases are determined by selecting the smallest and largest cross-sectional LV cavity areas. Specialized software is used for semi-manual or since more recently fully automatic delineation of the endocardial borders of the appropriate phases [44]. Based on the Simpson method, end-diastolic and -systolic volumes are subsequently derived and the LV ejection fraction (LVEF) is calculated. More recently also dedicated volumetric algorithms have become available. These algorithms use the high contrast between the LV cavity and myocardium to derive LV volumes following manual or automated definition of the mitral valve plane and LV axis.

The feasibility of LV function evaluation with MSCT has been investigated extensively. Numerous studies have shown good agreement for the assessment of global LV function between MSCT and 2D-echocardiography [45, 46]. Good agreement was demonstrated for LVEF by Wu et al., as determined by 64-slice MSCT and 2D-echocardiography in 63 patients (r = 0.87, P < 0.001) [47]. In addition, excellent correlations have also been observed between measurements obtained by MSCT and magnetic resonance imaging (MRI), which is regarded as the gold standard for non-invasive quantification of LV function [48–50]. Moreover, Yamamuro et al. showed that measurements between MSCT and MRI were more closely related than
measurements between 2D-echocardiography and MRI, suggesting that MSCT may be even more accurate than 2D-echocardiography in the evaluation of LV function [51]. This may be explained by the fact that, while echocardiography relies on a geometrical assumption of two-dimensional images, MSCT uses true three-dimensional endocardial border definition.

In addition to global LV function assessment, MSCT allows evaluation of regional wall motion by displaying the images in cine-loop. Previously, Henneman et al. showed excellent agreement for regional wall motion between 64-slice MSCT and 2D-echocardiography, with 96% of segments scored identically on both modalities (kappa = 0.73) [52]. Mahnken et al. assessed regional wall motion using 16-slice MSCT in comparison to cardiac MRI. In line with other investigations, the investigators observed a good agreement between the two modalities, with 86% of segments scored identically (k = 0.79) [53].

It is important to realize that with previous standard MSCT acquisition protocols, LV function measurements could be obtained retrospectively from the same data set acquired for coronary angiography. Thus, LV function could be assessed without the need for additional acquisitions. Recently, prospective ECG gating protocols have been introduced. With these protocols, data are acquired during a small part of the cardiac cycle. As a result, radiation dose is substantially reduced but assessment of LV function is no longer possible. Of note, when ECG pulsing or dose-modulation is applied, LV function can still be reliably assessed despite the increased noise during systole. Nevertheless, the radiation dose associated with this approach remains higher as compared to when data are acquired prospectively only during diastole. Therefore, the necessity for LV function analysis should be carefully considered for each individual patient.

Imaging of pulmonary vein anatomy with MSCT

In addition to assessment of CAD, the role of MSCT within catheter ablation procedures has increased substantially. An increasing number of patients presents with atrial fibrillation and is subsequently referred for treatment by means of catheter ablation. Since the aim of this procedure is to electronically isolate the pulmonary veins, detailed knowledge of left atrial and pulmonary vein anatomy both prior and during the procedure is important. Previous studies have demonstrated that among patients with atrial fibrillation, a considerable variation in pulmonary vein anatomy, including the presence of a common ostium of the pulmonary veins or the presence of additional pulmonary veins, exists [54]. These anatomical variations can be easily recognized on MSCT with higher accuracy as compared to other techniques [55]. In addition, knowledge of variations in anatomy and size of related structures such as atrial appendage, roof and septum is important and may facilitate the catheter ablation procedure [56]. Moreover, close proximity of surrounding structures such as the esophagus and the coronary arteries can be identified with MSCT beforehand. Based on this information, the individual ablation strategy may be adapted to avoid complications such as atrioesophageal fistula and coronary artery injury.

Extensive effort is currently invested in the integration of the MSCT images with the electrophysiological data in order to have accurate electro-anatomical images available on-line during the catheter ablation procedure. Several studies have indicated that fusion of these data is indeed feasible with only minor registration errors (ranging from 1.6 to 2.1 mm on average) [57]. Moreover, preliminary data indicate that integrated use of MSCT during the catheter ablation procedure may substantial reduce procedural and importantly also fluoroscopy times [58]. In a recent study, Kistler et al. observed a significant reduction in average fluoroscopy time from 62 ± 26 min using only the electrophysiological images to 49 ± 27 min when integrated electro-anatomical images were available [58]. Also, an improvement in procedural success was observed.

Thus, detailed anatomical information obtained by MSCT may be helpful to facilitate catheter ablation procedures and may have the potential to improve procedural success as well reducing complications. However, thus far only small studies are available and larger, randomized trials are needed to confirm that integrated use of MSCT will eventually improve outcome after catheter ablation.

Imaging of mitral and aortic valve anatomy with MSCT

Although echocardiography remains the cornerstone in the evaluation of valvular heart disease, recent data
have demonstrated the feasibility of MSCT to accurately study mitral and aortic valve anatomy and function [59–64]. By using multiphase data sets obtained during ECG gating, the leaflet or cusp motion can be evaluated in cine loop. For this purpose, ten image data sets are usually reconstructed at each 10% of the R–R interval similar as described for the assessment of LV function. For mitral valve evaluation, perpendicular planes images of the valve are preferred, whereas for aortic valve study the cross-sectional image plane perpendicular to the valve cusps illustrates precisely the morphology of the valve (Fig. 4).

The opportunity to non-invasively visualize valvular anatomy and surrounding structures may be of particular interest in the setting of percutaneous valve repair or replacement (PVR) techniques. These techniques have been recently introduced as an alternative therapy for those patients ineligible for surgery due to high perioperative risk, elderly age or comorbidity [65–67]. Although transesophageal echocardiography along with fluoroscopy will remain the most important imaging techniques to guide PVR procedures, several technical aspects related to these procedures require an exact, detailed depiction of the valvular anatomy and morphology to reach the highest procedural success. In this new clinical field, three-dimensional high-resolution imaging with MSCT may be of great value.

Particularly, before performing a coronary sinus annuloplasty, one of the current percutaneous approaches for mitral valve repair, an exact study of the anatomical relation between the mitral annulus and the coronary sinus is required. The feasibility of this percutaneous procedure depends on the distance between the coronary sinus and the mitral annulus, but also, on the anatomical relation of these two structures with the course of the left circumflex coronary artery (LCx). The left atrial enlargement and the mitral annular dilatation usually observed in patients with severe mitral regurgitation result in an abnormal separation between the coronary sinus and the mitral annulus. In those clinical scenarios, the implantation of the device through the coronary sinus results in inefficient remodeling of the mitral annulus and unsuccessful procedure. So far, two studies have investigated the anatomical relation between the coronary sinus, the mitral annulus and the LCx using MSCT. Choudre et al. studied 14 patients with mitral valve prolapse.

Fig. 4 Assessment of the anatomy of cardiac valves with MSCT. a A sagittal plane of the left-side valves with severe calcification of both the aortic and mitral annulus (arrows). The cross-sectional plane of the mitral annulus (b) demonstrates the extent of calcification spreading towards the left ventricular outflow tract (LVOT). Mixomatous mitral valve can be also imaged by MSCT, showing thickened mitral leaflets (c, arrows). The cross-sectional plane of the aortic valve demonstrates the anatomy of the valve (tricuspid/bicuspid) and the extent of calcification (d).
who were scanned with 16- or 40-MSCT, and observed that the distance between the coronary sinus and the mitral annulus increased proportionally with the mitral annular dilatation in the posterolateral location [68]. Furthermore, in 80% of the patients the LCx crossed between the coronary sinus and the mitral annulus, indicating the risk of impingement of the epicardial artery and the subsequent myocardial infarction. These findings were confirmed by Tops and coworkers, who compared observations with 64-slice MSCT in 15 patients with severe mitral regurgitation to 90 patients without [69]. The authors observed a course of the coronary sinus located superiorly to the mitral annulus in the majority of the patients (95%), with an increasing distance in patients with severe mitral regurgitation as compared to patients without. In addition, the LCx was located between the coronary sinus and the mitral annulus in 68% of the patients. Accordingly, MSCT may become an important imaging technique to select potential candidates for percutaneous mitral valve repair.

Similarly, percutaneous aortic valve replacement has emerged as a potential alternative approach in the treatment of patients with severe symptomatic aortic stenosis [70–73]. To assure a high procedural success-rate, an optimal selection of the potential candidates is necessary. For this purpose, an exact aortic annulus sizing and a detailed anatomical description of the aortic root and the surrounding structures, including the coronary ostia, are crucial to avoid complications such as the presence of significant paravalvular aortic regurgitation or coronary occlusion by a bulky leaflet after device deployment. In addition, knowledge of the amount of calcification and the morphology of the aortic valve (tricuspid or bicuspid) is also highly relevant. Indeed, excessive calcification of the valve or a bicuspid morphology may result in misdeployment of the device and higher risk of complications (paravalvular leakage or

**Fig. 5** Assessment of the aortic valve prior to and after PVR with MSCT. Before percutaneous aortic valve replacement, the distance between the aortic annulus and the left and right coronary ostia may be of great value in order to estimate the risk of coronary ostium occlusion by a bulky leaflet (a and b). After prosthesis implantation, the optimal deployment of the device and the patency of the coronary ostia can be assessed by MSCT (c and d).
prosthesis embolization) [74, 75]. Accordingly preoperative knowledge of these aspects obtained by MSCT may influence the choice of valvular prosthesis type as well as valve replacement strategy. The feasibility of MSCT in this regard was recently investigated by Tops et al., who performed an extensive assessment of the aortic root anatomy using 64-MSCT in 169 patients, including 19 patients with aortic stenosis [76]. The main findings of this study included an oval-shape of the aortic annulus, with larger diameter in the coronal images (26.7 ± 3.9 mm) than in the sagittal images (24.2 ± 3 mm). In addition, a variable height of the coronary ostia (Fig. 5) was observed with the length of the left coronary leaflet exceeding the distance between the annulus and the left coronary ostium in 49% of patients. Accordingly the authors concluded that MSCT may indeed provide detailed and clinically relevant information on the shape of the aortic annulus as well as its relation with the ostia of the coronary arteries. Potentially, MSCT may also be of value in assessing prosthesis deployment and positioning after the procedure (Fig. 5). Prospective studies should address whether assessment with MSCT may indeed improve selection of potential candidates for PVR procedures and improve procedural success and outcome.

Summary and conclusions

During the past few years MSCT has rapidly developed into a versatile non-invasive imaging modality. While imaging of the coronary arteries to determine or rule out the presence of CAD will remain one of the main indications, additional information on plaque severity and composition can be obtained. Potentially this particular feature may provide clinically relevant information with regard to risk stratification. Notably, imaging with MSCT is not restricted to the coronary arteries as the entire heart is visualized high resolution. Accordingly, comprehensive cardiac assessment is possible and as a result, the technique has a high potential for several other cardiac applications, including guidance of interventional procedures such as catheter ablation in atrial fibrillation or PVR in valvular heart disease. Importantly, the improvements in image quality and accuracy have been paralleled by simultaneous effective dose reduction, broadening acceptance of this promising imaging modality. Nevertheless, as the technique is relatively new, only limited data are currently available. Large prospective studies are needed to validate these novel applications of MSCT for use in daily clinical practice.

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