Atherosclerotic Plaque Characterization by Multidetector Row Computed Tomography Angiography

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Multidetector row computed tomography angiography (MDCTA) is seen as a potential alternative to current imaging methods for the assessment of vessel anatomy and atherosclerotic plaque composition/morphology in a great variety of arterial beds. Recent advances represented by the increase in gantry speed to <500 ms per rotation and in the number of detector rows from 4 to 64, in addition to the decrease in slice thickness to submillimetric levels, brought significant improvement in diagnostic accuracy by coronary MDCTA. In general, it has a good correlation with both intravascular ultrasound (IVUS) and histopathology for discrimination between soft, intermediate, and calcified plaques. Plaque area and volume tend to be underestimated by 12-detector row MDCTA and overestimated by 16-detector row MDCTA, but the number of patients studied so far is relatively small. However, it seems that 64-detector row MDCTA can measure plaque area and volume with greater accuracy. Plaque remodeling is overestimated in small vessels by 12-detector row MDCTA, whereas 16- and 64-detector row MDCTA show a good correlation with IVUS. Although still under development, the potential of MDCTA to characterize atherosclerotic plaque composition as well as to precisely determine plaque area, volume, and remodeling in the future is quite promising. (J Am Coll Cardiol 2006;47:C40–7) © 2006 by the American College of Cardiology Foundation

Multidetector row computed tomography angiography (MDCTA) recently emerged as a potential alternative to current imaging methods for the assessment of vessel anatomy and atherosclerotic plaque morphology in numerous arterial beds, such as the aorta (1), the coronary arteries (2–27), the carotids (28), and the main peripheral arteries (29). In this review, we will mainly describe the ability of MDCTA to characterize atherosclerotic plaque composition and morphology within the coronary arteries.

EVOLUTION OF MDCTA

The increase in gantry speed to <500 ms per rotation (19,20) and in the number of detector rows from 4 to 64 (25–27), as well as the decrease in slice thickness to submillimetric levels (23,24), brought significant improvement in diagnostic accuracy by coronary MDCTA (Table 1).

Motion still causes most image artifacts currently found during coronary 16-detector row MDCTA (16). An increased number of detector rows allows image acquisition to occur during shorter breath-hold intervals and through a decreased number of heartbeats, potentially decreasing the frequency of motion artifacts. Our initial clinical experience with both 400/32 × 0.5– (24) and 400/64 × 0.5-MDCTA (Cordeiro et al., unpublished data, May 2005; Fig. 1) apparently confirms this assumption. However, the most important components of temporal resolution are in fact gantry rotation speed and special image reconstruction algorithms, whereas spatial resolution is basically dependent on slice thickness during image acquisition. Unfortunately, owing to implementation of different methodologies, the studies shown in Table 1 cannot be directly compared. Nevertheless, the evolution represented by the progressive increase in gantry rotation speed and implementation of dedicated image reconstruction algorithms, as well as by the decrease in slice thickness that was lately achieved by modern MDCTA systems, can be illustrated by the fact that initial studies performed with 500/4 × 1.0-MDCTA and using a half-scan reconstruction algorithm (temporal resolution of 250 ms) had to exclude up to 32% of the coronary segments because of image artifacts (5). On the other hand, a more recent study (30) performed by 370/16 × 0.75-MDCTA and also using a half-scan reconstruction algorithm (temporal resolution of 185 ms) excluded only 7% of the segments. Likewise, Dewey et al. (23), by using 500/16 × 0.5-MDCTA and a multisegment reconstruction algorithm (temporal resolution of up to 62.5 ms), had to exclude only 2% of the segments. However, Raff et al. (27) more recently excluded 12% of the segments while using 330/64 × 0.6-MDCTA, but this could have been influenced by the apparent enrollment of a larger number of patients with high coronary artery calcium (CAC) scores (26% of individuals with an Agatston score >400) in this particular study.
Calcified vessels still represent a strong limitation to most MDCTA systems. Hoffmann et al. (17) attributed to calcification 94% (18 of 19) of their false positive results for detection of ≥50% coronary stenoses in native arteries by 420/16 × 0.75-MDCTA. However, we recently obtained a sensitivity of 76%, a specificity of 94%, and a diagnostic accuracy of 91% for detection of ≥50% stenoses in native coronary arteries of patients with advanced coronary artery disease (CAD) and high calcium scores (63% of the patients had Agatston scores >400) by 400/32 × 0.5-MDCTA (24). Such good results even in this challenging subgroup of patients might have also been influenced by the new automated approach implemented for the analyses (31).

Unfortunately, contrary to what seemed to be logical in this new scenario of higher temporal resolution and shorter scanning time, effective radiation doses have actually increased from 8.0 to 11.0 mSv with 500/4 × 1.0-MDCTA (4) to 11.8 to 16.3 mSv with 375/16 × 0.75-MDCTA (20), and lately to 8.0 to 18.0 mSv with 330/64 × 0.6-MDCTA (27). It is true that radiation doses might vary depending on the measurement tools, the MDCTA system’s manufacturer, and the coronary imaging protocol used. However, it seems that thinner slice collimations lately achieved by modern MDCTA scanners represent the

<table>
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<th>Table 1. Studies Comparing Coronary MDCTA With Conventional Invasive Angiography on a Per-Segment Basis</th>
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<td><strong>Patients (n)</strong></td>
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<td>Nieman et al. (3)</td>
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<td>Knez et al. (4)</td>
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<td>Achenbach et al. (5)</td>
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<td>Sato et al. (10)</td>
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<td>Maruyama et al. (11)</td>
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<td>Matsuo et al. (12)</td>
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<td>Nieman et al. (13)</td>
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<td>Ropers et al. (14)</td>
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<td>Kuetterer et al. (15)</td>
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<td>Mollet et al. (16)</td>
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<td>Hoffmann et al. (17)</td>
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<td>Hoffmann et al. (18)</td>
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<td>Kuetterer et al. (19)</td>
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<td>Mollet et al. (20)</td>
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<td>Achenbach et al. (21)</td>
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<td>Martuscelli et al. (22)</td>
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<td>Dewey et al. (23)</td>
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<td>Cordeiro et al. (24)</td>
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<td>Leschka et al. (25)</td>
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<td>Leber et al. (26)</td>
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<td>Raff et al. (27)</td>
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*Reader 1. †Reader 2.

MDCTA = multidetector row computed tomography angiography.
The major reason for the observed higher radiation doses, followed by the smaller increase also caused by the wider X-ray cone beams required to cover a greater number of detector rows.

**CALCIUM MEASUREMENTS BY MDCTA**

A high correlation was already described between CAC and the overall magnitude of atherosclerotic plaque burden in the coronary arteries (32). In addition, CAC was also related to prognosis in symptomatic and asymptomatic individuals, providing predictive power above that obtained by established CAD risk factors (33).

The major impact of electron-beam computed tomography angiography (EBCTA) was the quantification of CAC (34). Multidetector row computed tomography angiography was lately shown to be comparable to EBCTA in estimating the magnitude of CAC (35) (Fig. 2). Despite previous reports that raised questions about the reproducibility of the traditional CAC score (36), Detrano et al. (37) recently demonstrated in 3,551 individuals studied by EBCTA and 3,190 scanned by MDCTA from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort study (38) that calcium volumes and interpolated volume scores are slightly more reproducible than Agatston scores (34) (mean relative differences of 18.3, 18.3, and 20.1, respectively; p < 0.01). Although this small difference reached statistical significance, it is not clinically relevant. These authors also showed that EBCTA and MDCTA have equivalent reproducibility for measuring CAC, with a mean absolute difference between scores for two scans of 15.8 for EBCTA and of 16.9 for MDCTA (p = NS).

Sequential CAC measurements were already successfully used to estimate the extent to which the volume of atherosclerotic plaque decreased, stabilized, or increased as a consequence of treatment with statins (39). However, Arad et al. (40) suggested in a recent study of asymptomatic and low-risk individuals receiving a relatively low dose of atorvastatin that CAC monitoring might have little value for assessing atherosclerosis progression in this particular subset of individuals. Additionally, in view of the heterogeneity of calcified plaques within a subject, it was recently proposed that individual plaque analysis might be preferable to global calcium measurements as a way to evaluate progression/regression of atherosclerosis in serial studies such as those involving lipid-lowering or anti-inflammatory agents (41).

Even though the occurrence of coronary calcification is a well established marker of atherosclerosis, its absence does not rule out the existence of atherosclerotic plaques. In a study involving nearly 200 patients, Nikolaou et al. (42) demonstrated that 15% of those without CAC were ultimately found to harbor noncalcified plaques. Since the majority of vulnerable plaques are poor in calcium deposits (43) and therefore could be missed during such screenings, it is

**Figure 1.** Coronary 400/32 × 0.5-multidetector row computed tomography angiography (MDCTA) demonstrating a significant stenosis in proximal left anterior descending (red arrow), confirmed by quantitative coronary angiography as being equivalent to 85%. The same curved multiplanar reformatted image also shows a nonsignificant lesion in proximal right coronary artery (green arrow).

**Figure 2.** (Left) Axial multidetector row computed tomographic (CT) image in a 55-year-old man shows calcium in left anterior descending. Agatston score was 318.6. (Right) Axial electron beam CT image obtained 18 days previously in the same subject. Agatston score was 234.1. Reproduced, with permission, from Stanford et al. (35).
unlikely that CAC surveillance alone would favorably impact the prevention of a future acute coronary syndrome (ACS).

**PLAQUE COMPOSITION BY MDCTA**

There is striking heterogeneity among atherosclerotic lesions (Fig. 3), and human coronary plaques often consist of noncalcified tissue (44). A few studies were conducted in an attempt to relate specific computed tomography (CT) densities with different atherosclerotic plaque components (Table 2). Initial reports in patients showed that even 500/4 × 1.0-MDCTA could achieve some differentiation between soft and calcified plaques both in vivo (45,46) and ex vivo (47), with findings confirmed by intravascular ultrasound (IVUS) in the former and by histopathology in the latter. European investigators were able to confirm in two small series that overall CT densities steadily increased as coronary plaques were classified as soft, intermediate, and calcified in humans (45,46). Even in the acute setting, 500/4 × 1.0-MDCTA was able to provide important in vivo information on human plaque density (48).

To our knowledge, the only coronary plaque imaging study published to date using 500/8 × 1.25-MDCTA was conducted by Komatsu et al. (49). In their study, involving 45 patients with ACS and using IVUS as the gold standard, these authors demonstrated sensitivities of 92%, 87%, and 89% for detection of soft, intermediate, and calcified plaques, respectively. Diagnostic accuracy of 420/12 × 1.0-MDCTA for discrimination between calcified and noncalcified plaques was considered high, whereas interobserver variability was considered low in a study of 14 patients whose left coronary systems alone were compared to IVUS (50). Two small, in vivo human studies, now comparing 420/12 × 0.75-MDCTA with IVUS, also showed high sensitivities (94% to 95%) and specificities (92% to 94%) for detection of calcified plaques (51,52). However, Achenbach et al. (51) pointed out that sensitivity for detection of exclusively noncalcified plaques dropped to 53% in their study involving only 22 individuals. In the other study, Leber et al. (52) obtained similar results while analyzing 37 patients. Sensitivity for identification of calcified plaques was 95%, whereas for detection of noncalcified plaques it went down to 78%. More recently, Viles-Gonzalez et al. (53) imaged in vivo atherosclerotic abdominal aortas from six rabbits by 420/12 × 0.75-MDCTA. These authors reported difficulties in differentiating between fibrous-rich and lipid-rich plaques, even though they demonstrated that these two types of lesions actually had significantly different attenuation properties by CT (Table 2).

Twenty-two patients with ACS and nonsignificant coronary stenoses by conventional angiography were studied by Caussin et al. (54) using 420/16 × 0.75-MDCTA. These authors showed a high diagnostic accuracy for detection of vulnerable lesions when compared to IVUS, even though IVUS does not represent the definitive gold standard for vulnerable plaque characterization (55). However, Schroeder et al. (56), also using 420/16 × 0.75-MDCTA to image ex vivo nine specimens of human popliteal arteries from amputated limbs of patients with severe atherosclerotic disease, concluded that its diagnostic accuracy to further subclassify noncalcified plaques as lipid-rich or fibrotic was low even under ex vivo conditions.

More recently, Leber et al. (26) analyzed by 330/64 × 0.6-MDCTA 59 patients originally scheduled for conventional angiography because of stable angina pectoris. This group was able to perform IVUS in 32 coronary arteries without luminal stenoses >50% on conventional angiography. The comparison between 330/64 × 0.6-MDCTA and IVUS was based either on a site-by-site basis, if single coronary plaques could be easily distinguished, or on a segmental basis, in the case that a distinct plaque involved the entire segment. Overall sensitivity and specificity to detect nonsignificant coronary plaques by 330/64 × 0.6-MDCTA were 84% and 91%, respectively.

**PLAQUE AREA AND VOLUME BY MDCTA**

Because of its ability to image the coronary vessel wall, MDCTA is in theory well-suited for measuring atherosclerotic plaque area and volume within the coronary arteries.

**Table 2. Mean Attenuation Densities of Atherosclerotic Plaques by MDCTA**

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<th>Soft</th>
<th>Intermediate</th>
<th>Calcified</th>
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<td>500/4 × 1.0-MDCTA</td>
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<tr>
<td>Schroeder et al. (45)*</td>
<td>14 ± 26†</td>
<td>91 ± 21</td>
<td>419 ± 194</td>
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<tr>
<td>Schroeder et al. (47)‡</td>
<td>42 ± 22</td>
<td>71 ± 21</td>
<td>715 ± 328</td>
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<tr>
<td>420/12 × 0.75-MDCTA</td>
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<tr>
<td>Leber et al. (52)*</td>
<td>49 ± 22</td>
<td>91 ± 22</td>
<td>391 ± 156</td>
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<tr>
<td>Viles-Gonzalez et al. (53)$</td>
<td>51 ± 25</td>
<td>116 ± 27</td>
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*In vivo human studies (coronary arteries). †CT densities in Hounsfield units (mean ± SD). ‡Ex vivo human study (coronary arteries). $In vivo rabbit study (abdominal aortas). MDCTA = multidetector row computed tomography angiography.
However, an initial study by Achenbach et al. (51) including 22 patients showed that despite a relatively good correlation ($r = 0.8, p < 0.001$) between $420/12 \times 0.75$-MDCTA and IVUS, the former systematically underestimates plaque volume (mean difference = 19 mm$^3$) when compared to IVUS. Reproduced, with permission, from Achenbach et al. (51).

PLAQUE REMODELING BY MDCTA

The increase in cross-sectional vessel size observed during the process of atherosclerotic plaque growth, frequently referred to as plaque remodeling, can be quantified by MDCTA (Fig. 5). This outward expansion of the vessel wall known as “positive remodeling” is responsible for the observed delay in luminal narrowing (58). Positive remodeling is believed to be associated with plaque vulnerability on both histopathological and clinical studies (59,60).

In vivo assessment of plaque remodeling in humans by $420/12 \times 0.75$-MDCTA in comparison to IVUS showed systematic overestimation of cross-sectional areas, especially in vessels with smaller diameters. In a study involving 44 patients with high-quality MDCTA data sets showing atherosclerotic plaques only in proximal coronary artery segments, Achenbach et al. (61) were able to compare $420/12 \times 0.75$-MDCTA with IVUS-derived cross-sectional vessel areas in 13 individuals (26 sites, mean $420/12 \times 0.75$-MDCTA: 20 ± 7 mm$^2$, mean IVUS: 18 ± 8 mm$^2$). The mean absolute difference was 3 ± 3 mm$^2$ (range 0 to 8 mm$^2$) or 16% of the mean value of IVUS and $420/12 \times 0.75$-MDCTA, and the Bland-Altman analysis...

Figure 5. Positive remodeling of a non-calcified plaque proximally located in the right coronary artery (yellow arrows) as depicted by $400/16 \times 0.5$-multidetector row computed tomographic angiography. Outward expansion of the arterial wall can be seen in both curved multiplanar reformatted (left) and cross-sectional (right) images.
showed a bias toward larger vessel areas in $420/12 \times 0.75$-MDCTA (mean difference: $1.2 \text{ mm}^2$). Remodeling index was $1.1 \pm 0.3$ in $420/12 \times 0.75$-MDCTA and $1.1 \pm 0.4$ in IVUS ($r^2 = 0.82$, $p = 0.001$).

While studying by $420/16 \times 0.75$-MDCTA 21 patients presenting with ACS, Caussin et al. (54) were able to demonstrate a sensitivity of 100% and a specificity of 90% for detection of positive remodeling in comparison to IVUS.

Fifty-nine patients were recently analyzed by Leber et al. (26), who found that mean luminal cross-sectional area as determined by $330/64 \times 0.6$-MDCTA and IVUS were, respectively, $9.4 \pm 5.1 \text{ mm}^2$ and $8.4 \pm 4.5 \text{ mm}^2$ ($p < 0.01$). The correlation coefficient for these measurements was 0.81.

**COMPREHENSIVE APPROACH TO ATHEROSCLEROSIS AND ISCHEMIA INDUCED MYOCARDIAL INJURY BY MDCTA**

One of the major advantages of MDCTA is the opportunity to provide a more comprehensive approach to the patient with coronary atherosclerosis. In this regard, our group has demonstrated experimentally that it is also possible to assess myocardial viability by $400/32 \times 0.5$-MDCTA after reperfused myocardial infarctions as a byproduct of similar scanning parameters commonly applied for visualization of the coronary anatomy (62). In addition, we were able to show that $400/32 \times 0.5$-MDCTA can also quantify myocardial perfusion during adenosine stress in a dog model of left anterior descending stenosis (63).

Current coronary MDCTA scanning protocols enable accurate measurements of cardiac diameters and volumes, providing reliable assessment of left ventricular functional parameters (64) as well as of noncoronary abnormalities such as pulmonary embolism, lung masses, lymphadenopathies, hiatal hernias, esophageal wall thickening, liver cysts, atelectasis, emphysema, pulmonary infiltrates, and pleural effusions (65). Moreover, with somewhat different scanning protocols, including a broader scan range, and consequently involving higher contrast and radiation doses, it is possible to assess cardiac and noncardiac causes of acute chest pain in stable emergency department patients (66) (Fig. 6).

Recent studies demonstrated that only a small proportion of coronary stents are assessable by 16-detector row systems (67,68). Our initial experience with the new $400/64 \times$
0.5-MDCTA system showed promising results regarding its ability to diagnose in-stent restenosis (Cordeiro et al., unpublished data, May 2005; Fig. 7).

Finally, it is worth underscoring that, because of the systemic nature of atherosclerosis, patients with peripheral artery disease not only present with a high prevalence of atherosclerotic disease in their coronary and cerebral circulation, but also have, irrespective of that, the approximate same relative risk of death from cardiovascular causes as those with a documented history of coronary artery and cerebrovascular disease (69). In such an important subset of patients, 400/32 × 0.5-MDCTA was able to define both the presence and morphology of existing atherosclerotic plaques as well as the existence and/or origin of collateral flow support (Cordeiro et al., unpublished data, May 2005; Fig. 8).

**CONCLUSIONS**

The ability of MDCTA to quantify atherosclerotic plaque burden as coronary calcification is well-established. Although the technique is still under development, its potential to accurately characterize atherosclerotic plaque composition, as well as to precisely determine plaque area, volume, and remodeling in the future, is quite promising. This potential is likely to be fully realized as the technique is further refined by an increased number of detector rows, faster rotating gantries, more sophisticated image reconstruction algorithms, and the ability to acquire even thinner slices. However, even though it might soon be possible to infer with sufficient details about atherosclerotic plaque composition by MDCTA, the prognostic impact of the detection and classification of noncalcified plaques by this method still needs to be prospectively evaluated against that of traditional CAD risk factors and CAC score.

**REFERENCES**


