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Assessment of Coronary Stenosis Severity and Plaque Characterization with Multislice CT Angiography

By David E. Kandzari, M.D.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Explain the diagnostic accuracy of MSCT coronary angiography for the detection of significant coronary artery disease compared with conventional coronary angiography.
- List the limitations of current MSCT coronary angiography for coronary artery disease screening.
- Discuss the ability of MSCT coronary imaging to assess the components of coronary atherosclerotic plaque.
- Describe ongoing and forthcoming trials with MSCT imaging to refine its role in the detection of coronary stenoses and plaque characterization.

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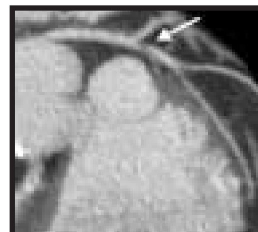
Dr. Kandzari has received grants/research support from General Electric.

Each year in the U.S., approximately one million individuals experience a myocardial infarction, contributing to over 600,000 cardiovascular-related deaths.[1] In more than half of these fatal events, myocardial infarction and sudden cardiac death will be the first and only presenting symptom of coronary artery disease. Considering that the common denominator for nearly all adverse cardiac events is the anatomic presence of coronary artery disease, the need for early identification and treatment of coronary atherosclerosis is paramount.

Against a background of increasing prevalence of coronary artery disease, the practice of clinical cardiovascular medicine has rapidly evolved into a field characterized by dramatic advances in our understanding of the pathophysiology, therapeutic applications, and likely clinical outcomes for patients considered at high risk for initial or subsequent adverse events that include infarction and cardiovascular death. Recent discoveries have identified systemic inflammation as predictive of future adverse outcomes,[2-5] and ongoing trials are examining the utility of novel catheter-based technologies to identify "vulnerable" or unstable atherosclerotic plaque activity.[6-8] The need to identify lesions prone to rupture and clinical sequelae is particularly urgent given that in most instances, atherosclerotic plaque rupture and thrombosis leading to myocardial infarction occur in coronary segments without prior angiographic evidence of significant occlusive disease.[9]



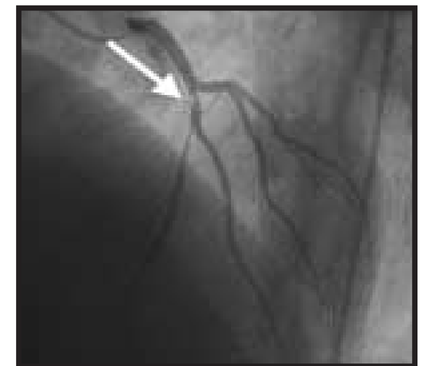


Figure 1. High-grade stenosis (white arrows) in the left anterior descending artery on MSCT (left) and conventional coronary angiography (right).

In many instances, imaging modalities intended to characterize atherosclerotic disease and vessel wall anatomy require invasive measures, including cardiac catheterization and conventional angiography. More than 1.4 million invasive coronary angiographic procedures are performed annually in the U.S.[1] to evaluate the presence of significant (≥50% luminal obstruction) coronary artery stenoses, define coronary anatomy, and help determine

whether coronary revascularization is indicated. Aside from its expense, as an invasive procedure coronary angiography is associated with a morbidity (e.g., stroke, bleeding complications, or cardiac arrhythmias) rate that may be as high as 2% to 3% and with a mortality rate of 0.4%.[10] Accordingly, an accurate, noninvasive assessment of coronary artery plaque composition and stenosis severity would constitute an important advancement in the care of patients with known or suspected ischemic heart disease.

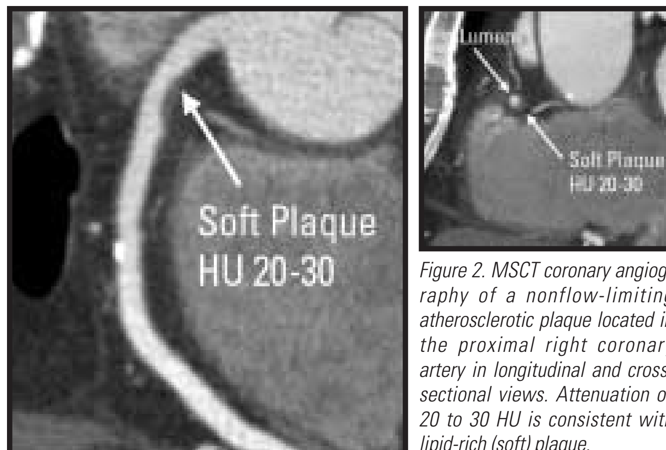


Figure 2. MSCT coronary angiography of a nonflow-limiting atherosclerotic plaque located in the proximal right coronary artery in longitudinal and cross-sectional views. Attenuation of 20 to 30 HU is consistent with lipid-rich (soft) plaque.

Over the past five years, the introduction of contrast-enhanced coronary artery imaging with multislice CT has represented a revolutionary advancement from conventional electron-beam technology, enabling high spatial and temporal resolution and coordination of gated cardiac imaging with the electrocardiogram and cardiac cycle. In many instances, the sensitivity and specificity of MSCT angiography to visualize significant coronary artery lesions may be comparable to cardiac catheterization (Figure 1). Unlike invasive coronary angiography, however, coronary CT angiography may not only identify luminal narrowing, but also provide insight into atherosclerotic plaque composition. In many instances, CT angiography may enable the characterization of vascular lesions even when disease is not visually apparent by conventional catheter-based angiography. The purpose of this review is to examine the results of recent trials with coronary CT angiography designed to characterize atherosclerotic plaque and disease severity and present future directions for clinical investigation.

PATHOPHYSIOLOGY OF UNSTABLE ATHEROSCLEROTIC PLAQUE

Although investigations to characterize and predict “vulnerable,” or unstable, atherosclerotic plaque activity are ongoing,[7-9] a common histologic feature is a thin fibrous cap overlying a lipid-rich core and a dense inflammatory cell infiltrate.[11] In many instances, deep wall injury may not be apparent on catheter-based angiography, and lesions underlying thrombus may be stenotic or nonstenotic, although nonstenotic lesions are much more common and are more frequently identified in culprit ruptured lesions. Accumulation of lipid-laden macrophages (“foam cells”), lymphocytes, matrix metalloproteinases, oxygen radicals, and even erythrocyte membranes[12] contributes to the eventual destabilization and fissuring of the plaque, leading to thrombus deposition and platelet aggregation. Plaque rupture is the most common type of atherosclerotic plaque complication, responsible for approximately 70% of all fatal acute myocardial infarctions and/or sudden cardiac deaths. However, the subsequent clinical presentation is ultimately determined by whether the thrombotic mass is occlusive, partially occlusive, or nonobstructive, and is influenced by collateral flow, baseline left ventricular function, the amount of jeopardized myocardium, diabetes, and other factors. As a result, patients may experience severe angina with electrocardiographic ST-segment elevation, non-ST-elevated myocardial infarction, or unstable angina without elevated cardiac markers.

Coronary calcification is also a common finding with atherosclerosis and may reflect total plaque burden. While the extent of calcification determined by the calcium score may predict future cardiovascular events,[13,14] distribution of calcification is often heterogeneous, and it is noncalcified lesions that have been associated with acute coronary syndromes.[15,16] Thus, the ability to precisely assess coronary atherosclerotic burden, differentiate calcified from noncalcified (“soft”) plaques, and quantify disease progression is essential to the development of novel technologies for coronary artery imaging.

COMPARATIVE TRIALS

Faster gantry speeds, multislice acquisition scanners, and enhanced image reconstruction algorithms have markedly improved the spatial and temporal resolution of noninvasive coronary angiography. Exploring the potential for MSCT angiography to improve diagnostic performance and enable complete visualization of clinically important coronary segments, several recent modest-sized trials have compared the accuracy of MSCT imaging with invasive coronary angiography to identify significant (≥50% luminal obstruction) coronary artery disease (see table). Collectively, these trials

TABLE 1. COMPARATIVE TRIALS OF 16-ROW MSCT AND CONVENTIONAL CORONARY ANGIOGRAPHY

Trial	Number of patients	Sensitivity (%)	Specificity (%)	Negative predictive value (%)
Nieman et al, *Circulation* 2002	59	95	86	97
Mollet et al, *JACC* 2004	128	92	95	98
Mollet et al, *JACC* 2005	51	95	98	99
Martuscelli et al, *EHJ* 2004	64	89	98	98
Ropers et al, *Circulation* 2003	77	92	93	97
Kuettner et al, *JACC* 2005	72	82	98	97
Kuettner et al, *JACC* 2004	66	37	99	92
Kuettner et al, *JACC* 2004	60	72	97	97
Hoffmann et al, *Circulation* 2004	33	63	96	96

have demonstrated favorable sensitivity and specificity for MSCT coronary angiography with high negative predictive value.[17-25]

In the most recent study, 51 patients with stable angina or atypical chest pain scheduled to undergo diagnostic cardiac catheterization were studied with 16-row MSCT angiography.[25] Patients with prescan heart rates ≥70 beats/min received treatment with an oral beta blocker, and the mean scan time was 18.9 ± 1 seconds. All patients with angiographically normal coronary arteries or with significant lesions were correctly identified. Overall, the sensitivity, specificity, and negative predictive value for the detection of significant lesions on a segment-based analysis were 95%, 98%, and 99%, respectively.

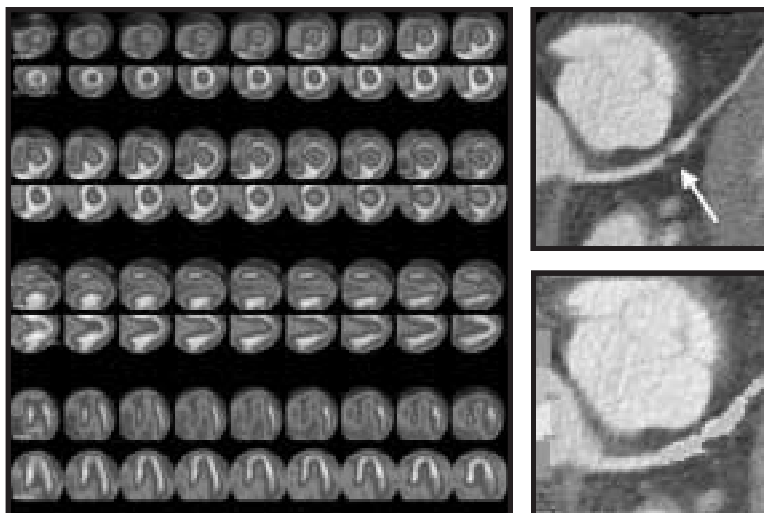


Figure 3. Simultaneous MSCT coronary angiography and PET imaging for myocardial ischemia. MSCT angiography identified a severe stenosis of the proximal left anterior descending artery (white arrow) with lipid and fibrous components determined by plaque characterization software (bottom right). PET imaging (left) confirmed the functional significance of the stenosis, revealing adenosine-induced ischemia of the left ventricular anterior, apical, and septal wall segments (Provided by Dr. Salvador Borges-Neto, Duke Medical Center)

In spite of such encouraging results with coronary CT angiography, some limitations do exist before the modality can be adopted as a routine screening method for all patients. In previous trials, for example, the incidence of coronary segments that have been described as unevaluable due to motion artifact, calcification, and low contrast-to-noise ratio has ranged from 6% to 16%. In particular, calcification frequently contributes to an overestimation of stenosis severity, and motion artifact and contrast-related image deterioration are the major reasons for false-negative findings. In a study by Mollet et al, although sensitivity in the detection of significant coronary lesions increased with greater vessel calcification (87% for noncalcified lesions versus 98% for heavily calcified lesions), specificity declined considerably, from 98% for noncalcified lesions to 85% for lesions with extensive calcification.[23] In a similar trial, Kuettner et al described an overall sensitivity of 72% and specificity of 97% for 58 patients undergoing MSCT coronary angiography.[22] However, when the analysis was restricted to patients having an Agatston calcium score <1000 (n = 45), both sensitivity and specificity increased to 98%.

Coronary calcification may also limit the role of MSCT in individuals perceived to be at high risk for coronary artery disease or among patients with angiographically proven disease. Among 66 patients with coronary artery disease established by conventional angiography, MSCT correctly identified only 39 of 105 lesions (sensitivity 37%, specificity 99%).[21] Artifacts due to elevated heart rates or severe coronary calcification were the most frequent causes of poor diagnostic visualization of coronary segments. Specifically, "blooming artifact," which results from beam hardening effects of vascular calcium, compromises the interpretation of diseased segments. Assessment of luminal obstruction may also be compromised in small-caliber vessels in which visualization is at the limits of spatial resolution with current technology. Because coronary calcification so limited assessment, these investigators[21] concluded that when the total calcium burden exceeds an Agatston score equivalent of 335, referral for conventional coronary angiography should instead be considered.

Finally, patients with pacemakers or defibrillators, atrial fibrillation, elevated serum creatinine, and coronary bypass grafts or stents have also been routinely excluded from enrollment in comparative trials, and experience with MSCT coronary angiography in such patients is therefore limited. However, trials examining coronary stent and bypass graft patency are ongoing. In a preliminary study of 22 patients with 65 coronary stents, the sensitivity and specificity of MSCT to identify in-stent restenosis were 78% and 100%.[26] Small stents and stents with thicker struts were the most common reasons for the inability to assess coronary stent segments.

CORONARY PLAQUE CHARACTERIZATION

In addition to assessment of luminal obstruction, MSCT also permits characterization of the lipid, fibrous, and calcific components of coronary atherosclerotic plaque that may not be visually apparent by conventional coronary angiography. For example, MSCT may enable detection of nonsignificant coronary soft plaques responsible for acute myocardial infarction by providing information on plaque volume, eccentricity, and density.[27] More complete characterization of atherosclerosis is particularly relevant since the extent of calcification detected by electron-beam CT may represent only one-fifth of the entire atherosclerotic plaque burden.[28] Variable composition of vascular lesions may be differentiated according to the relative Hounsfield unit densities of calcified versus soft plaque (Figure 2). In general, window levels measured to differentiate plaque composition are: thrombus = 0 to 15 HU; lipid = 15 to 30 HU; fibrous tissue = 30 to 75 HU; and calcium = 130 to 500 HU. Based on encouraging results from preliminary MSCT studies of carotid and coronary plaque, this imaging modality may be considered the leading technology for the rapid and noninvasive assessment of atherosclerotic disease.

At present, the comparator for coronary plaque density determined by MSCT remains lesion echogenicity by intravascular ultrasound.[29,30] Among 37 patients who underwent both coronary IVUS and MSCT angiography, 58 evaluable vessels were divided into 3-mm segments and compared with IVUS findings.[29] Density measurements determined by MSCT differed significantly according to plaque composition: hypoechoic plaque was 49 ± 22 HU, hyperechoic was 91 ± 22 HU, and calcified plaque was 391 ± 156 HU ($p < 0.02$).

MSCT correctly classified hypoechoic ("soft") plaque in 78% of segments, hyperechoic plaque (fibrous tissue) in 78% of segments, and calcified plaque in 92% of segments. Assessment of noncalcified segments was limited by smaller plaque and vessel size.

FUTURE DIRECTIONS

In part due to marked heterogeneity in atherosclerotic plaque composition, the development of a noninvasive method that can reliably image coronary stenosis severity, assess disease burden, and characterize plaque composition represents an important advance in our understanding of vascular disease and risk stratification. Although further study is required to evaluate the prognostic impact of density-based characterization of coronary atherosclerosis, advances in CT technology and reconstruction algorithms have positioned MSCT angiography as the most promising noninvasive method for the assessment of significant coronary atherosclerosis. Combined with the enhanced spatial and temporal resolution achieved with newer generation 64-detector row scanners, novel software algorithms may not only enable more accurate assessment of lesion composition but also permit earlier treatment with preventive therapies and assess their effect on disease progression or regression.

In addition to disease screening and prevention, ongoing studies will likely further define the role of MSCT coronary angiography in clinical decision-making. In the Comparison of Noninvasive CT Angiography for Epicardial Coronary Imaging with Catheter-based Angiography (CINEMA) trial comparing MSCT with conventional coronary angiography, the ability to make decisions regarding revascularization and medical therapy following blinded review of both CT and catheterization studies will be independently evaluated. MSCT coronary imaging may also assist in determining the method of revascularization and help predict procedural success.[31] Further, ongoing studies evaluating the combination of MSCT coronary angiography with PET imaging for myocardial ischemia may prove to be the most complete noninvasive assessment of both coronary anatomy and coronary functional significance (Figure 3). While unresolved issues mandate further clinical trials to refine the place of MSCT coronary imaging in routine clinical practice, clinicians can apply the presently available evidence on MSCT imaging not only to enable earlier noninvasive identification of atherosclerotic disease but also to provide treatment to patients at risk for vascular events.

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REFERENCES

1. American Heart Association. 2005 Heart and Stroke Statistics—2005 Update. American Heart Association, Dallas: 2005.
2. Heeschen C, Dimmeler S, Hamm CW, et al (CAPTURE Study Investigators). Soluble CD40 ligand in acute coronary syndromes. N Engl J Med 2003;348(12):1104-1111.
3. Buffon A, Biasucci LM, Liuzzo G, et al. Widespread coronary inflammation in unstable angina. N Engl J Med 2002; 347(1):5-12.
4. Kereiakes DJ. The fire that burns within: C-reactive protein. Circulation 2003;107(3): 373-374.
5. Blankenberg S, Luc G, Ducimetière P, et al (PRIME study group). Interleukin-18 and the risk of coronary heart disease in European men: the Prospective Epidemiological Study of Myocardial Infarction (PRIME). Circulation 2003;108(20):2453-2459.
6. Maehara A, Mintz GS, Bui AB, et al. Morphologic and angiographic features of coronary plaque rupture detected by intravascular ultrasound. J Am Coll Cardiol 2002;40(5):902-910.
7. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation 2003;108(14): 1664-1672.
8. Zarrabi A, Gul K, Willerson JT, et al. Intravascular thermography: a novel approach for detection of vulnerable plaque. Current Opinion in Cardiology 2002;17(6):656-662.
9. Smith SC. Risk-reduction therapy: the challenge to change. Circulation 1996; 93(12):2205-2211.
10. Baim DS, Grossman W. Cardiac catheterization, angiography, and intervention. Baltimore: Williams & Wilkins, 1996.
11. Heistad DD. Unstable coronary artery plaques. N Engl J Med 2003;349(24): 2285-2287.
12. Kolodgie FD, Gold HK, Burke AP, et al. Intraplaque hemorrhage and progression of coronary atheroma. N Engl J Med 2003; 349(24):2316-2325.
13. Wayhs R, Zelinger A, Raggi P. High coronary artery calcium scores pose and extremely elevated risk for hard events. J Am Coll Cardiol 2002;39(2):225-230.
14. O'Malley PG, Taylor AJ, Jackson JL, et al. Prognostic value of coronary electron-beam computed tomography for coronary heart disease events in asymptomatic populations. Am J Cardiol 2000;85(8):945-948.
15. Virmani R, Kolodgie F, Burke AP, et al. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 2000; 20(5):1262-1275.
16. Kragel A, Reddy S, Wittes J, Roberts WC. Morphometric analysis of the composition of atherosclerotic plaques in the four major epicardial coronary arteries in acute myocardial infarction and in sudden coronary death. Circulation 1989;80(6):1747-1756.
17. Nieman K, Cademartiri F, Lemos PA, et al. Reliable noninvasive coronary angiography with fast submillimeter multislice spiral computed tomography. Circulation 2002; 106(16):2051-2054.
18. Ropers D, Baum U, Pohle k, et al. Detection of coronary artery stenoses with thin-slice multi-detector row spiral computed tomography and multiplanar reconstruction. Circulation 2003;107(5):664-666.
19. Martuscelli E, Romagnoli A, D'Eliseo A, et al. Accuracy of thin-slice computed tomography in the detection of coronary stenoses. Eur Heart J 2004;25(12):1043-1048.
20. Hoffmann U, Moselewski F, Cury RC, et al. Predictive value of 16-slice multidetector spiral computed tomography to detect significant obstructive coronary artery disease in patients at high risk for coronary artery disease: patient- versus segment-based analysis. Circulation 2004;110:2638-2643.
21. Kuettner A, Kopp AF, Schroeder S, et al. Diagnostic accuracy of multidetector computed tomography coronary angiography in patients with angiographically proven coronary artery disease. J Am Coll Cardiol 2004;43(5):831-839.
22. Kuettner A, Trabold T, Schroeder S, et al. Noninvasive detection of coronary lesions using 16-detector multislice spiral computed tomography technology. J Am Coll Cardiol 2004;44(6):1230-1237.
23. Mollet NR, Cademartiri F, Nieman k, et al. Multislice spiral computed tomography coronary angiography in patients with stable angina pectoris. J Am Coll Cardiol 2004;43(12):2265-2270.
24. Kuettner A, Beck T, Drosch T, et al. Diagnostic accuracy of noninvasive coronary imaging using 16-detector slice spiral computed tomography with 188 ms temporal resolution. J Am Coll Cardiol 2005;45(1): 123-127.
25. Mollet NR, Cademartiri F, Krestin GP, et al. Improved diagnostic accuracy with 16-row multi-slice computed tomography coronary angiography. J Am Coll Cardiol 2005; 45(1):128-132.
26. Schuijf JD, Bax JJ, Jukema JW, et al. Feasibility of assessment of coronary stent patency using 16-slice computed tomography. Am J Cardiol 2004;94(4):427-430.
27. Caussin C, Ohanessian A, Ghostine S, et al. Characterization of vulnerable nonstenotic plaque with 16-slice computed tomography compared with intravascular ultrasound. Am J Cardiol 2004;94(1):99-104.
28. Rumberger JA, Simons DB, Fitzpatrick LA, et al. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. Circulation 1995;92(8):2157-2162.
29. Leber AW, Knez A, Becker A, et al. Accuracy of multidetector spiral computed tomography in identifying and differentiating the composition of coronary atherosclerotic plaques: a comparative study with intravascular ultrasound. J Am Coll Cardiol 2004;43(7):1241-1247.
30. Achenbach S, Moselewski F, Ropers D, et al. Detection of calcified and noncalcified coronary atherosclerotic plaque by contrast-enhanced, submillimeter multidetector spiral computed tomography: a segment-based comparison with intravascular ultrasound. Circulation 2004;109(1):14-17.
31. Mollet NR, Hoye A, Lemos PA, et al. Value of preprocedure multislice computed tomographic coronary angiography to predict the outcome of percutaneous recanalization of chronic total occlusions. Am J Cardiol 2005;95(2):240-243.

M05JS008AUG • Release: Aug 2005 • Expiration: Aug 2008
Reviews Scheduled: Aug 2006 and Aug 2007

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