Coronary plaque imaging by coronary computed tomography angiography

Akira Sato

Akira Sato, Cardiovascular Division, Faculty of Medicine, University of Tsukuba, Ibaraki 305-8577, Japan

Author contributions: Sato A analyzed the data and wrote the paper.

Correspondence to: Akira Sato, MD, Cardiovascular Division, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8577, Japan. asato@md.tsukuba.ac.jp

Telephone: +81-29-8533143 Fax: +81-29-8533143

Received: December 27, 2013 Revised: February 9, 2014
Accepted: April 17, 2014
Published online: May 28, 2014

Abstract

Coronary computed tomography angiography (CTA) has become the useful noninvasive imaging modality alternative to the invasive coronary angiography for detecting coronary artery stenoses in patients with suspected coronary artery disease (CAD). With the development of technical aspects of coronary CTA, clinical practice and research are increasingly shifting toward defining the clinical implication of plaque morphology and patients outcomes by coronary CTA. In this review we discuss the coronary plaque morphology estimated by CTA beyond coronary angiography including the comparison to the currently available other imaging modalities used to examine morphological characteristics of the atherosclerotic plaque. We hope that an integrated, multi-modality imaging approach will become the gold standard for noninvasive evaluation of coronary plaque morphology and outcome data in clinical practice.

Core tip: With the development of technical aspects of coronary computed tomography angiography (CTA), clinical practice and research are increasingly shifting toward defining the clinical implication of plaque morphology and patients outcomes by coronary CTA. In this review we discuss the coronary plaque morphology estimated by CTA beyond coronary angiography including the comparison to the currently available other imaging modalities used to examine morphological characteristics of the atherosclerotic plaque. We hope that an integrated, multi-modality imaging approach will become the gold standard for noninvasive evaluation of coronary plaque morphology and outcome data in clinical practice.

Sato A. Coronary plaque imaging by coronary computed tomography angiography. World J Radiol 2014; 6(5): 148-159 Available from: URL: http://www.wjgnet.com/1949-8470/full/v6/i5/148.htm DOI: http://dx.doi.org/10.4329/wjr.v6.i5.148

INTRODUCTION

For the past decade, invasive coronary angiography (ICA) has been used as the gold standard for the diagnosis of coronary narrowing and clinical decision making for coronary interventions. However, coronary angiography has several limitations, including the substantial interpretation variability of visual estimates and assessment of lesion severity for diffuse atherosclerotic lesions and intermediate-severity lesions[13]. The recent advent of multidetector computed tomography (MDCT) has greatly improved the image quality, and may therefore allow more precise evaluation of coronary stenosis[14]. Multicenter studies have confirmed the accuracy of 64-slice MDCT for directly...
visualizing and detecting coronary artery stenoses in patients with suspected coronary artery disease (CAD)\(^7\)\(^-\)\(^9\). Furthermore, the introduction of 256-slice, 320-detector scanner, and dual-source computed tomography (DSCT) developed to significantly improve faster scan times, wider volume coverage, and high spatial resolution\(^10\). With the improvement of technical aspects of coronary computed tomography angiography (CTA), clinical practice and research are increasingly shifting toward defining the clinical implication of plaque morphology and patients outcomes by coronary CTA (Table 1). In this review, we discuss the coronary plaque morphology estimated by CTA beyond coronary angiography including the comparison to the currently available other imaging modalities used to examine morphological characteristics of the atherosclerotic plaque.

**Coronary plaque imaging**

With the development of MDCT, it is possible not only to detect coronary artery stenosis but also to evaluate coronary plaque quality and quantity such as can be done with intravascular ultrasound (IVUS) and optical coherence tomography (OCT)\(^11\)\(^-\)\(^13\). Leber et al\(^14\) demonstrated that 64-slice CTA-derived measurements showed good correlations with IVUS for lumen and plaque area determinations using individually adapted window settings, although their ability to quantify the grade of a luminal obstruction was limited by the significant trends toward overestimation of the lumen area and underestimation of the plaque area. Our group published that the lumen cross-sectional area (CSA) and percent area stenosis of 32 de novo coronary lesions measured by CTA were closely correlated to those obtained by IVUS (Figure 1); however the lumen CSA measured by CTA was systematically overestimated and percent area stenosis was slightly underestimated\(^15\). Voros et al\(^16\) conducted a meta-analysis to assess the accuracy of coronary CTA against IVUS regarding coronary vessel and plaque sizes, as well as the accuracy of computed tomography (CT) to detect any plaque compared with IVUS. This meta-analysis confirmed that coronary CTA slightly overestimated luminal area, presumably because of partial volume effects that lead to overestimation of the size of very bright structures (such as the contrast-enhanced lumen), whereas plaque area volume, and area stenosis measurements are similar between CT and IVUS. For plaque characterization, it has been shown that CT-derived attenuation values are different in calcified and noncalcified plaques. They also demonstrated that low-density noncalcified plaques, the presumed lipid-rich plaques on CT, correlated best with the sum of necrotic core plus fibro-fatty tissue by IVUS/virtual histology\(^17\). Kashwagi et al\(^18\) revealed that plaque with vascular remodeling and low CT attenuation values had the MDCT morphological features of thin cap fibroatheroma (TCFA) observed by OCT, and a ring-like enhancement observed by MDCT was one important sign of TCFA. Motoyama et al\(^19\) showed that the CT characteristics of plaques associated with acute coronary syndrome (ACS) include positive vascular remodeling, low plaque density, and spotty calcification. Presence of all 3 [i.e., positive remodeling (PR), non-calcified plaque measuring <30 Hounsfield units (HU), and spotty calcification] showed a high positive predictive value, and absence of all 3 showed a high negative predictive value, for the culprit plaques associated with ACS. Coronary CTA is able to successfully characterize ruptured plaques as low-attenuation plaque with PR. However, Ozaki et al\(^20\) demonstrated that CTA fails to characterize lesions at risk of intact fibrous cap-ACS which are often referred to as plaque erosions and responsible for up to one-third of culprit lesions in ACS patients.

The introduction of DSCT marked another technological improvement of MDCT in cardiac imaging, as the temporal resolution was further increased from 165 ms to 83 ms, thus eliminating the need to control the heart rate during the scan by use of β-blockers. Studies comparing

### Table 1
Respective pros and cons of multi-detector computed tomography and coronary angiogram for analysis of coronary artery disease

| Pros                                      | Cons                                                                 |
|-------------------------------------------|----------------------------------------------------------------------|
| MDCT It can be performed with short examination times, and is generally available and easily performed It is a noninvasive character, and contributes important information of plaque morphology and characterization in the arterial wall Calcium score | Study population was limited to selected patients chosen for good CTA image quality with absence of motion artifacts or severe calcification Quantitative measurement of plaque morphology is slightly limited |
| Serial MDCT plaque imaging                | Radiation exposure, which is currently between 9 and 1 mSv for a retrospectively gated MDCT coronary angiogram Contrast medium is used |
| Degree of luminal stenosis can be measured by QCA | It is an invasive character, and contributes no plaque morphologic information Substantial interpretation variability of visual estimates and assessment of lesion severity for diffuse atherosclerotic lesions and intermediate-severity lesions |
| Gold standard for the diagnosis of coronary narrowing and clinical decision making for coronary interventions | Catheterization costs are expensive. Contrast medium is used |

MDCT: Multi-detector computed tomography; CTA: Computed tomography angiography; CAG: Coronary angiogram; QCA: Quantitative coronary angiography.
DSCT with single-source CT demonstrated that DSCT maintains high diagnostic accuracy in the diagnostic examination of a wide range of patient subsets, e.g., patients with higher and even irregular heart rates\(^2\). Westwood et al\(^{[21]}\) showed the systematic review of the accuracy of dual-source cardiac CT for detection of arterial stenosis in some or all difficult to image patients. The pooled, per-patient estimates of sensitivity were 97.7% (95%CI: 88.0%, 99.9%) and 97.7% (95%CI: 93.2%, 99.3%) for patients with arrhythmias and high heart rates, respectively. The corresponding pooled estimates of specificity were 81.7% (95%CI: 71.6%, 89.4%) and 86.3% (95%CI: 80.2%, 90.7%), respectively. In patients with high coronary calcium scores, previous bypass grafts, or obesity, only per-segment or per-artery data were available. Sensitivity estimates remained high (> 90% in all but one study), and specificities ranged from 79.1% to 100%. We showed the table summarizing various studies reporting analysis of coronary plaque by MDCT (Table 2).

**Non-culprit coronary plaques imaging**

Approximately 6% of PCI patients will have clinical plaque progression requiring non-target lesion percutaneous coronary intervention (PCI) by 1 year, and greater CAD burden confers a significantly higher risk for clinical plaque progression\(^2\). The prospect study showed that on multivariate analysis, nonculprit lesions associated with recurrent events were more likely than those not associated with recurrent events to be characterized by a plaque burden of 70% or greater (HR = 5.03; 95%CI: 2.51-10.11; \(P < 0.001\)) or a minimal luminal area of 4.0 mm\(^2\) or less (HR = 3.21; 95%CI: 1.61-6.42; \(P = 0.001\)) or to be classified on the basis of radiofrequency intravascular ultrasonography as thin-cap fibroatheromas (HR = 3.35; 95%CI: 1.77-6.36; \(P < 0.001\))\(^\text{[23]}\). Our group showed that the number of coronary plaques in non-culprit lesions on CTA images was more significantly observed in acute myocardial infarction (AMI) patients than in stable angina pectoris patients with normal myocardial perfusion imaging (MPI)\(^\text{[24]}\). Specifically, non-calcified, mixed, and vulnerable plaques were more significantly observed in AMI patients than in SAP patients (Figure 2). Leber et al\(^{[25]}\) found that non-calcified plaques contribute to a higher degree to the total plaque burden in AMI than in SAP. In addition, 64-slice CTA enabled the visualization of lipid cores and spotty calcifications that are frequently associated with plaque ruptures\(^\text{[14]}\). We suggested that all three major coronary arteries in patients with AMI were extensively diseased and have multiple vulnerable plaques that could potentially cause another occurrence of ACS, although the natural course of vulnerable plaque development and disruption has not yet been clearly established\(^\text{[24]}\). Recent studies have demonstrated that metabolic syndrome was associated with an increasing risk of cardiovascular disease\(^\text{[26]}\). Furthermore, IVUS study has shown that metabolic syndrome is associated with lipid-rich plaques that contribute to the increasing risk of plaque vulnerability\(^\text{[27]}\). Within the AMI group, the number of PR and low attenuation plaque was significantly higher in patients with metabolic syndrome than in those without the syndrome. This finding might explain the mechanism of metabolic syndrome contributing to the increased risk of cardiovascular events\(^\text{[28]}\). We showed the table comparing various imaging for analysis of coronary vulnerable plaque (Table 3).

**Coronary plaque characteristics on MDCT and slow-flow phenomenon/cardiac troponin T elevation**

Cardiac biomarker troponin T (cTnT) is sensitive and specific for detection of myocardial damage. Porto et al\(^{[36]}\)
Calcification

In multivariate analysis, significant predictors of events were the presence of CAD, obstructive 16, 64-detector n-delining index

Lipid-rich plaque by a signal-poor region with a diffuse 10.00% May 28, 2014

Major findings

CTA fails to characterize lesions at risk of intact fibrous cap-ACS which are often referred to as

Intensive yellow plaque, presence of thrombus 64-detector

TCFA on virtual histology IVUS were most prevalent in mixed plaques, suggesting a higher 31.00%

The mean CT attenuation within plaque that corresponded to hyper-echogenic appearance in 1.20 ± 0.18 N/A 64-detector

Low echoic, positive remodeling, spotty calcification 8.1 mm² vs 7.3 mm² (P < 0.03, r = 0.73) and 50.4% vs 41.1% (P < 0.001, r = 0.61), respectively

The mean plaque areas and the percentage of vessel obstruction measured by IVUS and 1.10 ± 0.21 N/A 16-detector

4-detector

The mean plaque areas and the percentage of vessel obstruction measured by IVUS and 1.5 (1.3-1.8) N/A 4-detector

Echo signal attenuation 14-47 HU was found in lipid-rich plaque

By MDCT and post-PCI cardiac biomarker levels (Table 4).

Non-calcified plaques contribute to a higher degree to the total plaque burden in AMI than in SAP patients

More significantly observed in AMI patients than in SAP patients with normal MPI. Non-calcified, mixed, and vulnerable plaques

More significantly observed in AMI patients than in SAP patients with normal MPI. Non-calcified, mixed, and vulnerable plaques

IVUS: Intravascular ultrasound; CT: Computed tomography; MDCT: Multi-detector computed tomography; OCT: Optical coherence tomography; CTA: Computed tomography angiography; HU: Hounsfield units; MPI: Myocardial perfusion imaging; TCFA: Thin-cap fibroatheromas; CAD: Coronary artery disease; LAD: Left anterior descending artery.

Table 2 Various studies reporting analysis of coronary plaque by multi-detector computed tomography

| Ref. | n  | Imaging techniques | Major findings |
|------|----|-------------------|----------------|
| Leber et al[23] | 59 | 64-detector | The mean plaque areas and the percentage of vessel obstruction measured by IVUS and 64-slice CT were 8.1 mm² vs 7.3 mm² (P < 0.03, r = 0.73) and 50.4% vs 41.1% (P < 0.001, r = 0.61), respectively |
| Kashiwagi et al[15] | 105 | 64-detector | Vascular remodeling and low CT attenuation values had the MDCT morphological features of TCFA observed by OCT, and a ring-like enhancement was one important sign of TCFA |
| Leber et al[24] | 46 | 16-detector | The MDCT-derived density measurements within coronary lesions revealed significantly different values for hypoechoic (49 HU ± 22), hyperechoic (91 HU ± 22), and calcified plaques (391 HU ± 156, P < 0.02) |
| Sato et al[25] | 102 | 64-detector | Lumen CSA and percent area stenosis of coronary lesions were closely correlated to those obtained by IVUS, however the lumen CSA measured by CTA was systematically overestimated and percent area stenosis was slightly underestimated |
| Voros et al[26] | 60 | 64-detector | Low-density noncalcified plaques, the presumed lipid-rich plaques on CT, correlated best with the sum of necrotic core plus fibro-fatty tissue by IVUS/virtual histology |
| Motoyama et al[16] | 71 | 16, 64-detector | Presence of positive remodeling, non-calcified plaque < 30 HU, and spotty calcification showed a high positive predictive value for with ACS |
| Ozaki et al[27] | 66 | 16, 64-detector | CTA fails to characterize lesions at risk of intact fibrous cap-ACS which are often referred to as plaque erosions |
| Sato et al[28] | 226 | 64-detector | Number of coronary plaques in non-culprit lesions was more significantly observed in AMI patients than in SAP patients with normal MPI. Non-calcified, mixed, and vulnerable plaques were more significantly observed in AMI patients than in SAP patients |
| Leber et al[29] | 15 | 4-detector | Non-calcified plaques contribute to a higher degree to the total plaque burden in AMI than in SAP patients |
| Schroeder et al[30] | 32 | 16-detector | Mean CT density of 14-47 HU was found in lipid-rich plaque |
| Pohle et al[31] | 100 | 64-detector | The mean CT attenuation within plaque that corresponded to hypo-echogenic appearance was 58 ± 43 HU (n = 176). The mean CT attenuation within plaque that corresponded to hypo-echogenic appearance was 58 ± 43 HU (n = 176, P = 0.001) |
| Pundziute et al[32] | 50 | 64-detector | In multivariate analysis, significant predictors of events were the presence of CAD, obstructive CAD, obstructive CAD in LM/LAD, number of segments with plaques, number of segments with obstructive plaques, and number of segments with mixed plaques |

Table 3 Characteristics of various imaging modalities for analysis of coronary vulnerable plaque

| Modalities | Characteristics of vulnerable plaque |
|------------|-----------------------------------|
| MDCT       | Low-attenuation, positive remodeling, spotty calcification[14] |
|            | Ring-like enhancement[15], napkin-ring sign[16,20] |
| IVUS       | Low echoic, positive remodeling, spotty calcification[14] |
| OCT        | Echo signal attenuation[14] |
| Angioscopy | Lipid-rich plaque by a signal-poor region with a diffuse border[14] |
|            | TCFA [large lipid core and a thin fibrous cap < 65 μm][20] |
|            | Macrophages imaging[14] |

MDCT: Multi-detector computed tomography; IVUS: Intravascular ultrasound; OCT: Optical coherence tomography; TCFA: Thin-cap fibroatheroma.

found that the cause of periprocedural myocardial necrosis after PCI was the impairment of flow in coronary side branches and distal embolization of atherosomatous or thrombotic materials. Therefore, pre-PCI plaque composition may have an impact on myocardial injury/infarction during PCI. However, there are few published data regarding the relation between pre-PCI plaque composition by MDCT and post-PCI cardiac biomarker levels (Table 4).

Table 4 Coronary plaque characteristics on multi-detector computed tomography and slow-flow phenomenon/cardiac troponin T elevation

| Ref. | Minimum CT value (HU) | Positive remodelling index | Calcification appearance | Ring-like appearance |
|------|-----------------------|---------------------------|------------------------|---------------------|
| Uetani et al[33] | 67.0 ± 10.1 | N/A | N/A | 55.60% |
| < 50 | 1.10 ± 0.21 | 37.70% | N/A |
| Watabe et al[34] | 43 (26.5-75.7) | 1.20 ± 0.18 | Spotty (50%) | 31.00% |
| Kodama et al[35] | 23.5 (9.5-40) | 1.5 (1.3-1.8) | CPC (63%) | 100% |

CT: Computed tomography; HU: Hounsfield units; CPC: Circumferential plaque calcification; N/A: Not available.

Nakazawa et al[36] reported that patients who experienced transient no-reflow during PCI had lower plaque CT density values in culprit lesions. Uetani et al[33] demonstrated that post-procedural myocardial injury was associated with the volume and fraction of low-attenuation plaques by MDCT. Our group showed that CT attenuation value of < 55 HU was associated with post-PCI cTnT elevation[37]. While in earlier studies, a mean CT density of 14-47 HU was found in lipid-rich plaque[16,20], Pohle et al[31] showed a mean density of 58 HU (median 53) and Leber et al[29] reported that a low CT density value (49 ± 22 HU) is considered to correspond to soft plaque identified on
IVUS. This difference most likely results from the natural course of atherosclerotic plaque or slice thickness and contrast medium concentration that affect plaque density measurements. It will be possible to use our cutoff point of CT attenuation value < 55 HU for prediction of post-PCI cTnT elevation clinically. PR and spotty calcification were also significant predictors of post-PCI cTnT elevation. Furthermore, presence of all 3 CT characteristics (CT attenuation value < 55 HU, remodeling index > 1.05, and spotty calcification) showed a high positive predictive value (PPV) of 94%, and their absence showed a high negative predictive value (NPV) of 90% (Figure 3). Kodama et al demonstrated that CTA-verified circumferential plaque calcification (CPC) with low-attenuation plaque and PR were determinants of slow-flow phenomenon (SF) during PCI. The conditional logistic regression analysis revealed that CPC, plaque density, and dyslipidemia were the predictors of SF, with CPC being the strongest (OR = 79; 95%CI: 8–783, \( P < 0.0001 \)). A previous study exploring potential prognostic predictors of cardiovascular events...
Coronary CTA and nuclear MPI

Stress nuclear MPI using single-photon emission tomography (SPECT) is an established method for assessment of the functional significance of coronary stenosis and delivers valuable information for risk stratification[49,50]. Disagreement between CTA ≥ 50% stenosis and reversible MPI defects is common[47]. CTA and MPI are measuring two different things, vessel patency and perfusion, respectively. Only 50% of obstructed vessels with ≥ 50% luminal narrowing by CTA show abnormal MPI[48]. We previously indicated that 64-slice CTA alone was not always sufficient to assess the functional significance of anatomic stenoses, especially stenoses of intermediate grade (Figure 4). When stenosis severity by CTA was < 60%, ischemia was seldom observed, and when stenosis severity was ≥ 80%, ischemia was common. For intermediate stenosis severity values of 60%-80%, the prevalence of reversible defects was difficult to determine, given CTA’s current spatial resolution[13]. We also demonstrated that combined CTA and stress nuclear MPI provide improved diagnostic accuracy for the noninvasive detection of CAD in comparison with that of 64-slice CTA alone. One hundred thirty symptomatic patients with suspected CAD underwent both 64-slice CTA and stress thallium-201 MPI before ICA. Of 390 arteries in 130 patients, 54 (14%) were nonevaluable by CTA due to severe calcifications, motion artifacts, and poor opacification. All nonevaluable arteries were considered positive. The sensitivity, specificity, PPV and NPV were 95%, 80%, 69%, and 97%, respectively, for CTA alone and 94%, 92%, 85%, 97%, respectively, for CTA with stress nuclear MPI for all nonevaluable arteries on CTA. Per-patient analysis showed a significant increase in specificity and PPV[49]. The results of hybrid SPECT/CTA imaging have provided a marked increase in specificity and PPV to detect hemodynamically significant coronary lesions compared to those of 16-slice CTA alone[40]. Cardiac 3D SPECT/CT fusion imaging has been shown to provide additional information about hemodynamic relevance and facilitates lesion interpretation by allowing exact allocation of perfusion defects to the subtending coronary artery[51]. Pazhenkotill et al[52] demonstrated that the impact of hybrid SPECT/CT imaging in 318 consecutive patients. Referral to revascularization was higher in patients with matched abnormalities (41%), compared with those with unmatched abnormalities (11%) or those with normal studies (9%).

Available clinical experience points toward tailoring the initial diagnostic approach according to the pretest probability of the patient[53]. In low-to-intermediate likelihood patients, CTA may well be the best initial test due to its high NPV; however, in intermediate-to-high probability patients, CTA’s low PPV may result in unnecessary radiation exposure, and stress nuclear MPI might be a better first-line test. In fact, the high diagnostic accuracy of stress nuclear MPI may argue in favor of stress nuclear MPI as the initial test. From the present study, we cannot definitely conclude which is the better first-line test, and we acknowledge that further head-to-head comparisons between the two modalities are required.

Recently, the addition of physiologic measures of coronary flow by fractional flow reserve (FFR) to anatomic-based assessment of stenosis severity by ICA to guide decisions of coronary revascularization improves event-free survival in a manner that is long-lived and cost-effective[54,55]. Ko et al[56] demonstrated that FFR compared with combinations of coronary CTA and CT myocardial perfusion imaging findings in 86 myocardial perfusion territories. The FFR is lowest in patients who have both stenosis ≥ 50% on coronary CTA and myocardial perfusion abnormalities and highest in patients with no significant stenosis and no myocardial perfusion defects. Among patients with discrepant results, FFR correlates better with myocardial perfusion abnormalities then with angiographic stenosis.

Min et al[53] demonstrated that use of noninvasive FFRCT plus CT among stable patients with suspected or known CAD was associated with improved diagnostic accuracy and discrimination in CT alone for the diagnosis of hemodynamically significant CAD when FFR determined at the time of ICA was the reference standard (Figure 5). On a per-patient basis, diagnostic accuracy, sensitivity, specificity, PPV, and NPV of FFRCT plus CT were 73% (95%CI: 67%-78%), 90% (95%CI, 84%-95%), 54% (95%CI: 46%-83%), 67% (95%CI: 60%-74%), and

![Figure 4 Prevalence of reversible defects evaluated by single-photon emission tomography in the study groups defined according to the percentage stenosis obtained by computed tomography angiography[54]. Numbers under the bars represent the number of vessels. *P = 0.018, †P < 0.0001 vs percentage stenosis of 0%-60%.](image-url)
84% (95%CI: 74%-90%), respectively. Compared with obstructive CAD diagnosed by CT alone [area under the receiver operating characteristic curve (AUC), 0.68; 95%CI: 0.62-0.74], FFRCT was associated with improved discrimination (AUC, 0.81; 95%CI: 0.75-0.86; P < 0.001).

The CORE320 study compared the combination of CT perfusion (CTP) and coronary artery assessment with SPECT imaging and conventional coronary angiography[58]. Sixteen centers enrolled 381 patients who underwent combined CTA-CTP and SPECT/MPI prior to conventional coronary angiography. The patient-based diagnostic accuracy defined by the AUC of integrated CTA-CTP for detecting or excluding flow-limiting CAD was 0.87 (95%CI: 0.84-0.91). In patients without prior myocardial infarction, the AUC was 0.90 (95%CI, 0.87-0.94) and in patients without prior CAD the AUC for combined CTA-CTP was 0.93 (95%CI: 0.89-0.97). For the combination of a CTA stenosis ≥ 50% stenosis and a CTP perfusion deficit, the sensitivity, specificity, positive predictive, and negative predicative values (95%CI) were 80% (72%-86%), 74% (68%-80%), 65% (58%-72%), and 86% (80%-90%), respectively. For flow-limiting disease defined by ICA-SPECT/MPI, the accuracy of CTA was significantly increased by the addition of CTP at both the patient and vessel levels (Figure 6).

Recent advances in the development of noninvasive imaging techniques have enabled quantification of vessel wall inflammation with 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT). The post hoc analysis in the dal-PLAQUE study demonstrated the possible role of FDG-PET especially in relationship of serum inflammatory biomarkers with plaque inflammation assessed by FDG PET/CT. They showed a positive correlation between baseline serum myeloperoxidase (MPO) and baseline carotid arterial wall (target) to background (blood) of the most diseased segment (TBRmds). This relation remained present at 3-mo follow-up and was independent of traditional risk factors. This study is the first to investigate the relationship between MPO and vessel wall 18F-FDG uptake[59]. Longitudinal studies will be needed to investigate whether vessel wall inflammation measured by 18F-FDG PET/CT is predictive for future cardiovascular events.

**Prognostic value of CTA in symptomatic and asymptomatic individuals**

Currently, the main clinical advantage of CTA appears to be related to its high NPV. The ability to rule out sig-
Figure 6  A complete CORE320 imaging data set for a 64-year-old male without prior history of coronary artery disease with chest pain symptoms. The left anterior descending coronary artery revealed a 96% diameter stenosis by computed tomography angiography (CTA) (row A) and an 85% diameter stenosis by invasive coronary angiography (ICA) (row B). The computed tomography myocardial perfusion (CTP) (row C) study revealed a mild defect in the distal anteroseptal wall, and moderate defects in the basal anteroseptal, the basal anterior, the distal anterior, and apical walls, while the single photon emission computed tomography (SPECT) (row D) study revealed moderate defects in the distal inferoseptal and distal inferolateral walls, and moderate defects in the distal anterolateral and distal anterior walls by CTP, and a moderate defect in the distal anterior wall by SPECT. The right coronary artery revealed a 60% diameter stenosis by CTA, a 77% diameter stenosis by ICA, mild defects in the distal inferoseptal and distal inferolateral walls, and moderate defects in the distal anterolateral and distal anterior walls by CTP, and no myocardial perfusion defects by SPECT.
significant CAD in symptomatic patients with a low pre-test likelihood of disease makes CT a useful tool to diagnose many patients with acute chest pain who are often at a low risk of actually ACS. Recently, several randomized large trials have evaluated clinical value of coronary CTA for chest pain triage in the emergency department. Litt et al demonstrated that among the 908 of 1370 patients with acute chest pain to undergo coronary CTA angiography, 640 could be immediately discharged after negative findings on a CT scan, and none died or had a myocardial infarction within 30 d. As compared with patients receiving traditional care, patients in the coronary CTA group had a higher rate of discharge from the emergency department (49.6% vs 22.7%), a shorter length of stay (median, 18.0 h vs 24.8 h; P < 0.001), and a higher rate of detection of coronary disease (9.0% vs 3.5%). Hoffmann et al demonstrated that among the randomized 1000 low-risk acute chest pain patients in a multicenter trial, 501 patients underwent coronary CTA as a first triage test. After early coronary CTA, as compared with standard evaluation, the mean length of stay in the hospital was reduced by 7.6 h (P < 0.001) and more patients were discharged directly from the emergency department (47% vs 12.9%, P < 0.001). No patient with negative findings on CT experienced AMI, and only 23 MI occurred in the entire patient cohort (plus 52 cases of unstable angina).

The use of coronary CTA has been advocated as a potentially valuable atherosclerotic imaging tool for risk stratification. Several studies have explored the prognostic value of coronary CTA, primarily limited to symptomatic populations. Recent article by Hadamitzky et al add a new data on CCTA that predict both death and myocardial infarction as well as need for subsequent revascularizations out to 5 years. CCTA imaging may be a valuable tool in the assessment of long-term prognosis in patients with suspected CAD. Atherosclerosis imaging such as coronary artery calcium scoring (CACS) or carotid intimal-medial thickness for individuals without chest pain syndrome has been advocated recently for use by professional consensus guidelines. Furthermore, CACS has been demonstrated to improve risk re-stratification above and beyond global risk scores that combine traditional CAD risk factors. However, in a large international multicenter study of individuals without chest pain syndrome, the additional risk-predictive advantage by coronary CTA is not clinically meaningful compared with a risk model based on CACS. At present, the application of coronary CTA for risk assessment of individuals without chest pain syndrome should not be justified.

CONCLUSION

With further improvements in CT technology, coronary CTA become accurate detection of coronary plaques in clinical practice. Assessment of both coronary stenosis and perfusion has great potential application to further advance the evaluation of patients with CAD. In low-to-intermediate likelihood patients, CTA may well be the best initial test due to its high NPV; however, in intermediate-to-high probability patients, CTAs low PPV may result in unnecessary radiation exposure, and stress nuclear MPI might be a better first-line test. The choice of the optimal first line-test remains a question that is not answered in this review. This review underlines the value of a combined assessment of coronary anatomy and myocardial perfusion in patients with CAD, and adds to an increasing body of evidence suggesting an added diagnostic value when combining both modalities. We hope that an integrated, multi-modality imaging approach will become the gold standard for noninvasive evaluation of coronary plaque morphology and outcome data in clinical practice.

REFERENCES

1. White CW, Wright CB, Doty DB, Hiratzka LF, Eastham CL, Harrison DG, Marcus ML. Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? N Engl J Med 1984; 310: 819-824 [PMID: 6700670 DOI: 10.1056/NEJM198403293101304]

2. Marcus ML, Harrison DG, White CW, McPherson DD, Wilson RF, Kerber RE. Assessing the physiologic significance of coronary obstructions in patients: importance of diffuse undetected atherosclerosis. Prog Cardiovasc Dis 1988; 31: 39-56 [PMID: 3293119 DOI: 10.1016/0033-0628(88)90109-2]

3. Vogel RA. Assessing stenosis significance by coronary arteriography: are the best variables good enough? J Am Coll Cardiol 1988; 12: 692-693 [PMID: 3408227 DOI: 10.1016/0735-1097(88)80058-5]

4. Ropers D, Baum U, Pohle K, Anders K, Ulzheimer S, Ohnesorge B, Schlundt C, Bautz W, Daniel WG, Achenbach S. Detection of coronary artery stenoses with thin-slice multidetector row spiral computed tomography and multiphasic reconstruction. Circulation 2003; 107: 664-666 [PMID: 12578863 DOI: 10.1161/01.CIR.0000055738.31551.A9]

5. Achenbach S, Ropers D, Hoffmann U, MacNeill B, Baum U, Pohle K, Brady TJ, Pomerantz E, Ludwig J, Flachskampf FA, Wicky S, Jang IK, Daniel WG. Assessment of coronary remodeling in stenotic and nonstenotic coronary atherosclerotic lesions by multidetector spiral computed tomography. J Am Coll Cardiol 2004; 43: 842-847 [DOI: 10.1016/j.jacc.2003.09.053]

6. Raff GL, Gallagher MJ, O’Neill WW, Goldstein JA. Diagnostic accuracy of noninvasive coronary angiography using 64-slice spiral computed tomography. J Am Coll Cardiol 2005; 46: 552-557 [PMID: 16053973 DOI: 10.1016/j.jacc.2005.05.056]

7. Hamon M, Biondi-Zoccai GG, Malagutti P, Agostoni P, Morrello R, Valgimigli M, Hamon M. Diagnostic performance of multislice spiral computed tomography of coronary arteries as compared with conventional invasive coronary angiography: a meta-analysis. J Am Coll Cardiol 2006; 48: 1896-1910 [PMID: 17084268 DOI: 10.1016/j.jacc.2006.08.026]

8. Vanhoeacker PK, Heijenbrok-Kal MH, Van Heste R, Decramer I, Van Hoe LR, Wijns W, Hunink MG. Diagnostic performance of multidetector CT angiography for assessment of coronary artery disease: meta-analysis. Radiology 2007; 244: 419-428 [PMID: 17641365 DOI: 10.1148/ radiol.2442061218]

9. Budoff MJ, Dowd D, Jollis JG, Gitter M, Sutherland J, Halamert E, Scherer M, Bellinger R, Martin A, Benton R, Delago A, Min JK. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Inva-
voir and angiography. *Eur Heart J* 2011; 32: 2814-2823 [PMID: 21794555 DOI: 10.1093/europace/euhr189]

20 Sun Z, Ng KH. Coronary computed tomography angiography in coronary artery disease. *World J Cardiol* 2011; 3: 503-510 [PMID: 21945752 DOI: 10.4103/0976-1353.83303]

21 Westwood ME, Raatz HD, Misso K, Burgers L, Redekop K, Lhachimi SK, Armstrong N, Kleijnen J. Systematic review of the accuracy of dual-source cardiac CT for detection of arterial stenosis in difficult to image patient groups. *Radiology* 2013; 267: 387-395 [PMID: 23392425 DOI: 10.1148/radiol.13121136]

22 Glaser AD, Selzer F, Faxon DP, Laskey WK, Cohen HA, Slater J, Detre KM, Wilensky RL. Clinical progression of incidental, asymptomatic lesions discovered during culprit vessel coronary intervention. *Circulation* 2005; 111: 143-149 [PMID: 15623544 DOI: 10.1161/01.CIR.0000150335.01285.12]

23 Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea M, de Leval MR, Stone PH. The napkin-ring sign: a clinical and imaging marker of vulnerable coronary plaques. *Nat Rev Cardiol* 2009; 6: 699-710 [PMID: 19851549 DOI: 10.1038/nrcardio.2009.172]

24 Leber AW, Kneze A, von Ziegler F, Becker A, Nikolaou K, Paul S, Wintersperger B, Reiser M, Becker CR, Steinbeck G, Boekstegers P. Quantification of obstructive and nonobstructive coronary lesions by 64-slice computed tomography: a comparative study with quantitative coronary angiography and intravascular ultrasound. *J Am Coll Cardiol* 2005; 46: 147-154 [PMID: 15992649 DOI: 10.1016/j.jcc.2005.03.071]

25 Kashiwagi M, Tanaka A, Kihata H, Tsujikawa H, Kataiwa H, Komukai K, Tanimoto T, Takakura K, Sako T, Hiraoka K, Nakamura N, Mizukoshi M, Imanishi T, Akasaka T. Feasibility of noninvasive assessment of thin-cap fibroatheroma by multidetector computed tomography. *JACC Cardiovascular Imaging* 2009; 2: 1412-1419 [PMID: 20883077 DOI: 10.1016/j.jcmg.2009.09.012]

26 Leber AW, Kneze A, Becker A, Becker C, von Ziegler F, Nikolaou K, Rist C, Reiser M, White C, Steinbeck G, Boekstegers P. Accuracy of multidetector spiral computed tomography in identifying and differentiation the composition of coronary atherosclerotic plaques: a comparative study with intracoronary ultrasound. *J Am Coll Cardiol* 2004; 43: 1241-1247 [DOI: 10.1016/j.jcc.2003.10.059]

27 Sato A, Hiroe M, Tamura M, Ohigashi H, Nozato T, Hikita H, Takahashi A, Aonuma K, Isobe M. Quantitative measures of coronary stenosis severity by 64-Slice CT angiography and relation to physiologic significance of perfusion in non-obese patients: comparison with stress myocardial perfusion imaging. *J Nucl Med* 2008; 49: 564-572 [DOI: 10.2967/jnumed.107.042481]

28 Voros S, Rinehart S, Qian Z, Joshi P, Vazquez G, Fischer C, Belur P, Hulten E, Villines TC. Coronary atherosclerosis imaging by coronary CT angiography: current status, correlation with intravascular interrogation and meta-analysis. *JACC Cardiovascular Imaging* 2011; 4: 557-568 [PMID: 21565743 DOI: 10.1016/j.jcmg.2011.03.006]

29 Voros S, Rinehart S, Qian Z, Vazquez G, Anderson H, Murrieta L, Wilmer C, Carlson H, Taylor K, Ballard W, Kampradiotis D, Kalynych A, Brown C 3rd. Prospective validation of standardized, 3-dimensional, quantitative coronary computed tomographic plaque measurements using radiofrequency backscatter intravascular ultrasound as reference standard in intermediate coronary arterial lesions: results from the ATLANTA (assessment of tissue characteristics, lesion morphology, and hemodynamics by angiography with fractional flow reserve, intravascular ultrasound and virtual histology, and noninvasive computed tomography in atherosclerotic plaques) I study. *JACC Cardiovascular Imaging* 2011; 4: 198-208 [DOI: 10.1016/j.jcmg.2010.10.008]

30 Motoyama S, Kondo T, Sarai M, Sugiuara A, Harigaya H, Sato T, Inoue K, Okumura M, Ishii J, Anno H, Virmani R, Ozaki Y, Hiroe M, Tamura M, Ohigashi H, Nozato T, Hikita H, Takahashi A, Kobayashi Y, Ishii H, Izawa H, Murohara T. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation* 2004; 110: 1245-1250 [PMID: 15326607 DOI: 10.1161/01.CIR.0000140677.20606.0E]

31 Amano T, Matsubara T, Uetani T, Nanki M, Marui N, Kato M, Arai K, Yokoi K, Ando H, Ishii H, Izawa H, Murohara T. Impact of metabolic syndrome on tissue characteristics of angioarcheologically mild to moderate coronary lesion integrated backscatter intravascular ultrasound imaging. *J Am Coll Cardiol* 2007; 49: 1149-1156 [DOI: 10.1016/j.jcc.2006.12.028]

32 Maurich-Horvat P, Schleffl C, Alkadhi H, Nakano M, Ot- suka F, Stolzmann P, Scheffel H, Ferencik M, Kriegel MF, Seifarth H, Virmani R, Hoffmann U. The napkin-ring sign indicates advanced atherosclerotic lesions in coronary CT angiography. *JACC Cardiovascular Imaging* 2012; 5: 1243-1252 [PMID: 22326975 DOI: 10.1016/j.jcmg.2012.03.019]

33 Otsuka S, Nakane K, Aonuma K, Isobe M, Takahashi A, Yoshikawa J, Shimada K, Yoshiyama M. The napkin-ring sign as an indicator of atherosclerotic plaques in patients with acute myocardial infarction. *JACC Cardiovascular Imaging* 2012; 5: 448-457 [PMID: 23498679 DOI: 10.1016/j.jcmg.2012.09.016]

34 DeMaria AN, Narula J, Mahmud E, Tsimikas S. Imaging vulnerable plaque by ultrasound. *J Am Coll Cardiol* 2006; 47: C52-C59 [PMID: 16631508 DOI: 10.1016/j.jacc.2005.11.047]

35 Kimura S, Fukushima T, Totsuka A, Nakano K, Taguchi H, Yoshikawa J, Shimada K, Yoshiyama M. Napkin-ring sign on coronary CT angiography for the prediction of acute coronary syndrome. *JACC Cardiovascular Imaging* 2013; 6: 448-457 [PMID: 23498679 DOI: 10.1016/j.jcmg.2012.09.016]

36 Sato A. Coronary plaque imaging by CT.
Characterization of non-calcified coronary atherosclerotic plaque by multi-detector row CT: comparison to IVUS. Atherosclerosis 2007; 190: 174-180 [PMID: 16494883]

Pundziute G, Schuif JD, Jukema JW, Boersma E, de Roos A, van der Wall EE, Bax JJ. Prognostic value of multislice computed tomography coronary angiography in patients with known or suspected coronary artery disease. J Am Coll Cardiol 2007; 49: 62-70 [PMID: 17207724 DOI: 10.1016/j.jacc.2006.07.070]

Pundziute G, Schuif JD, Jukema JW, Decramer I, Sarno G, Vanhoeppen P, Reiber JH, Schalij MJ, Wijns W, Bax JJ. Head-to-head comparison of coronary plaque evaluation between multislice computed tomography and intravascular ultrasound radiofrequency data analysis. JACC Cardiovasc Imaging 2008; 1: 176-182 [DOI: 10.1016/j.jcmg.2008.01.007]

Hachamovitch R, Berman DS, Shaw LJ, Kiat H, Cohen I, Cabico JA, Friedman J, Diamond GA. Incremental prognostic value of myocardial perfusion SPECT for the prediction of cardiac death: differential stratification for risk of cardiac death and MI. Circulation 1998; 97: 535-543 [DOI: 10.1161/01. CIR.97.6.535]

Hacker M, Jakobs T, Matthias E, Vollmar C, Nikolaou K, Becker C, Knez A, Pfuger T, Reiser M, Hahn K, Tiling R. Comparison of spiral multidetector CT angiography and myocardial perfusion imaging in the noninvasive detection of functionally relevant coronary artery lesions: first clinical experiences. J Nucl Med 2005; 46: 1294-1300 [PMID: 16085585]

Schuif JD, Wijns W, Jukema JW, Atsma DE, de Roos A, Lamb HJ, Stokkel MP, Dibbits-Schneider P, Decramer I, De Bondt P, van der Wall EE, Vanhoenacker PK, Bax JJ. Relationship between noninvasive coronary angiography with multi-slice computed tomography and myocardial perfusion imaging. J Am Coll Cardiol 2006; 48: 2508-2514 [PMID: 17174190 DOI: 10.1016/j.jacc.2006.05.080]

Sato A, Nozato T, Hikita H, Miyazaki S, Takahashi Y, Kuhwara T, Takahashi A, Hiroe M, Aonuma K. Incremental value of combining 64-slice computed tomography angiography with stress nuclear myocardial perfusion imaging to improve noninvasive detection of coronary artery disease. J Nucl Cardiol 2010; 17: 19-26 [DOI: 10.1016/j.jsc.2009.09.015]

Rispler S, Keidir Z, Gheresin E, Roguin A, Soil A, Dragu R, Litmanovich D, Frenkel A, Aronson D, Engal A, Beyar R, Israel O. Integrated single-photon emission computed tomography computed tomography coronary angiography for the assessment of hemodynamically significant coronary artery lesions. J Am Coll Cardiol 2007; 49: 1059-67 [DOI: 10.1016/j.jacc.2006.10.069]

Gaemperli O, Schuijf JD, Valenta I, Husmann L, Shefel F, Duerst V, Eberli FR, Luscher TF, Kaufmann PA. Cardiac image fusion from stand-alone SPECT and CT: clinical experience. J Nucl Med 2007; 48: 696-703 [PMID: 17475956 DOI: 10.2967/jnumed.106.037606]

Pazhenkotti AP, Nkoulou RN, Ghadri JR, Herzog BA, Küest SM, Hussmann L, Wolfrum M, Goetti R, Buechel RR, Gaemperli O, Luscher TF, Kaufmann PA. Impact of cardiac hybrid single-photon emission computed tomography/computed tomography imaging on choice of treatment strategy in coronary artery disease. Eur Heart J 2011; 32: 2824-2829 [DOI: 10.1093/eurheartj/ehr232]

Meijboon WB, van Mieghem CA, Mollet NR, Pugliese F, Weustink AC, van Pelt N, Cademartini F, Nieman K, Boersma E, de Jaegere P, Krestin GP, de Feyter PJ. 64-slice computed tomography coronary angiography in patients with high intermediate, or low pretest probability of significant coronary artery disease. J Am Coll Cardiol 2007; 50: 1469-1475 [PMID: 17919567]

Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikono F, van’t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, McCarthy PA, Fearon WF, FAME Study Investigators. Fractional flow reserve vs angiography for guiding percutaneous coronary intervention. N Engl J Med 2009; 360: 213-224 [DOI: 10.1056/NEJMoa0807611]
by computed tomography. *J Am Heart J* 2010; 51: 1442-1448 [PMID: 20484566 DOI: 10.1016/j.eahj.2010.01.004]

64 **Min JK**, Shaw LJ, Devereux RB, Okin PM, Weinsaft JW, Russo DJ, Lippolis NJ, Berman DS, Callister TQ. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol* 2007; 50: 1161-1170 [PMID: 17868808 DOI: 10.1016/j.jacc.2007.03.067]

65 **Ostrom MP**, Gopal A, Ahmadi N, Nasir K, Yang E, Kakadiaris I, Flores F, Mao SS, Budoff MJ. Mortality incidence and the severity of coronary atherosclerosis assessed by computed tomography angiography. *J Am Coll Cardiol* 2008; 52: 1335-1343 [PMID: 18929245 DOI: 10.1016/j.jacc.2008.07.027]

66 **Hadamitzky M**, Tübert S, Deseive S, Byrne RA, Martinoff S, Schönig M, Hausleiter J. Prognostic value of coronary computed tomography angiography during 5 years of follow-up in patients with suspected coronary artery disease. *J Am Heart J* 2013; 34: 3277-3285 [PMID: 24067508 DOI: 10.1016/j.jaha.2013.05.001]

67 **Greenland P**, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Flakty MA, Hodgson JM, Kushnir FG, Lauer MS, Shaw LJ, Smith JC, Taylor AJ, Weintraub WS, Wengler NK, Jacobs AK, Anderson JL, Albert N, Buller CE, Creager MA, Ettenger SM, Guyton RA, Halperin JL, Hochman JS, Nishimura R, Ohman EM, Page RL, Stevenson WG, Tarkington LG, Yancy CW. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2010; 56: e50-e103 [DOI: 10.1016/j.jacc.2010.09.001]

68 **Detrano R**, Guerci AD, Carr J, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, O’Leary DH, Tracy R, Watson K, Wong ND, Kronmal RA. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008; 358: 1336-1345 [PMID: 18367736 DOI: 10.1056/NEJMoa072100]

69 **Polonsky TS**, McClelland RL, Jorgensen NW, Bild DE, Burke GL, Guerci AD, Greenland P. Coronary artery calcium score and risk classification for coronary heart disease prediction. *JAMA* 2010; 303: 1610-1616 [PMID: 20424251]

70 **Cho I**, Chang HJ, Sung JM, Pencina MJ, Lin FY, Dunning AM, Achenbach S, Al-Mallah M, Berman DS, Budoff MJ, Callister TQ, Chow BJ, Delago A, Hadamitzky M, Hausleiter J, Maffei E, Cademartiri F, Kaufmann P, Shaw LJ, Raff GL, Chinnaian KM, Villines TC, Cheng V, Nasir K, Gomez M, Min JK. Coronary computed tomographic angiography and risk of all-cause mortality and nonfatal myocardial infarction in subjects without chest pain syndrome from the CONFIRM Registry (coronary CT angiography evaluation for clinical outcomes: an international multicenter registry). *Circulation* 2012; 126: 304-315 [PMID: 22885117 DOI: 10.1161/CIRCULATIONAHA.111.081380]
