Noninvasive imaging modalities to visualize atherosclerotic plaques

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Abstract: Atherosclerotic cardiovascular disease is becoming a major cause of death in the world due to global epidemic of diabetes and obesity. For the prevention of atherosclerotic cardiovascular disease, it is necessary to detect high-risk atherosclerotic plaques prior to events. Recent technological advances enable to visualize atherosclerotic plaques noninvasively. This ability of noninvasive imaging helps to refine cardiovascular risk assessment in various individuals, select optimal therapeutic strategy and evaluate the efficacy of medical therapies. In this review, we discuss the role of the currently available imaging modalities including computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography. Advantages and disadvantages of each noninvasive imaging modality will be also summarized.

Keywords: Noninvasive imaging; atherosclerotic plaque; computed tomography (CT); magnetic resonance imaging (MRI); positron emission tomography

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Background

Atherosclerotic cardiovascular disease is the leading causes of morbidity and mortality in the Western world (1). As the prevalence of metabolic risk factors increases in a global fashion, cardiovascular disease will be expected to further rise in the future. This underscores the development of better modality to identify atherosclerotic cardiovascular disease and develop effective therapeutic approach.

Atherosclerosis is a chronic progressive disease of the arterial wall. Its underlying pathology is characterized by a chronic inflammatory process and the influx of atherogenic lipids (2-5). Endothelial dysfunction permits subendothelial accumulation of low-density lipoprotein and the recruitment of monocytes and lymphocytes to the artery wall (6,7). This process triggers the production of various pro-inflammatory cytokines from endothelial cells (2-7). Also, highly oxidized LDL particles within vessel wall are uptaken by macrophages, leading to foam-cell formation (8). These atherosclerotic mechanisms have been considered to induce the development and propagation of atherosclerosis, leading to cardiovascular events.

Traditionally, imaging of atherosclerosis has focused on the assessment of luminal narrowing and occlusion. However, the majority of life threatening consequences of atherosclerosis including myocardial infarction result from plaque rupture and acute thrombus formation, and it is now well recognized that plaque composition is closely associated with the vulnerability of these vascular lesions (9,10). Consequently, there are emerging needs for imaging modality that enables the identification of atherosclerotic plaques with high-risk features. Particularly, non-invasive approach would be ideal to detect high-risk patients who require intensive medical therapies.

Recently, considerable advances have been made in imaging techniques for the assessment of these atherosclerotic changes. Various imaging modalities, either noninvasive or invasive, have become available to identify high-risk patients at a relatively early stage and provide the opportunity to evaluate the impact of anti-atherosclerotic medical therapies.

The current review summarizes a range of non-invasive imaging modalities to visualize plaques.



Figure 1 CAC evaluation. (A) Normal coronary artery without any calcification; (B) mild calcification in the left main trunk and the left anterior descending artery; (C) severe calcification involving the left main trunk, the left anterior descending and the left circumflex coronary arteries. CAC, coronary artery calcification.

Computed tomography (CT)

There are two different types of available CT. Electron beam computed tomography (EBCT) is the nonmechanical movement of the X-ray source and multidetector-row computed tomography (MDCT) is performed by the motion of the X-ray source and table, combined with multiple detection to acquire the data in spiral or helical fashion (11). Accumulating evidence suggests the ability of EBCT/MDCT to evaluate coronary artery calcification, atherosclerosis and fractional flow reserve (FFR).

Coronary artery calcification (Figure 1)

Atherosclerotic coronary calcifications are frequently observed at advanced lesions (American Heart Association plaque type Vb) (12) and at high-risk plaque as spotty or speckled pattern. Both EBCT and MDCT are able to accurately quantify coronary artery calcium (CAC). EBCT allows faster imaging by moving the X-ray source-point electronically.

Agatston *et al.* proposed a method to measure CAC by using CAC score (13). In addition to CAC score, a range of measures of coronary artery disease (CAD) including calcium volume score and calcium mass score has been used in other studies (14,15). However, the difference and accuracy in each CAC measure is still on debate. Currently, CAC scoring by Agatston *et al.* still remains the most widely used measure to evaluate the extent of CAC in both epidemiological research and clinical settings (16).

Various studies demonstrated that the amount of coronary calcium detected by CT correlates with atheroma burden of the coronary artery on histology and that CAC is an independent predictor of cardiovascular events (17-19). While the absence of CAC was associated with a very low risk of events (0.5%), in case of intermediate (CAC score 100-400) and high levels (CAC score >400) of CAC, the relative risk of cardiovascular events was 4.3 [95% confidence interval (CI), 3.1-6.1] and 7.2 (95% CI, 5.2-9.9, P<0.0001) in intermediate (CAC score 100-400) and high CAC scores (CAC score >400), respectively compared with low levels of CAC (CAC score =0) (20). In addition, CAC scores added significantly to risk prediction beyond traditional Framingham risk scores, particularly among persons considered to be at intermediate risk. According to these findings, the use of CAC quantification in intermediate risk patients is a Class IIb recommendation by the American Heart Association to improve risk assessment (20).

It was also shown that progression of CAC was associated with multiple risk factors and the increased risk for future cardiovascular events (21-23). This suggests the potential use of serial evaluation of CAC scores to assess the efficacy of novel anti-atherosclerotic therapies for the reduction of cardiovascular events. However, the benefit of slowing progression of CAC under use of anti-atherosclerotic medical therapies has not been demonstrated yet. For instance, statins did not slow the progression of CAC in any randomized controlled trials (24,25).

As such, it remains to be determined to what degree its measurement provides an incremental benefit in risk prediction with clinical use of calcium scoring and whether its use ultimately changes the treatment strategy or outcome for individual patients. The relative failure of intensive lipid lowering strategies to slow progression of coronary calcium scores also suggests that CAC measurement does not have enough ability in the management of coronary atherosclerosis as well as patients. In addition, MDCT is increasingly becoming a major CT imaging modality rather than EBCT because MDCT is capable of evaluating both coronary artery calcification and stenosis. Therefore, EBCT is less likely to play an important role in the clinical settings.

Coronary atherosclerosis

Because of high spatial resolution, MDCT is increasingly becoming a major modality to visualize coronary artery stenosis as well as atherosclerotic plaque morphology. Since the introduction of 4-slice scanners, the technique has developed rapidly and 64-slice and even 320-slice systems are currently available. These new imaging techniques have resulted in improvements in both temporal and spatial resolution, thereby enabling superior image quality (Figure 2). Large numbers of studies reported the improved accuracy in detecting significant coronary artery stenosis, although the strength of this evidence lies more in its negative predictive value rather than ability to precisely quantify the degree of lumen stenosis (26-28). Meta-analyses from 27 studies including 1,740 patients showed that sensitivity, specificity, positive predictive and negative predictive values for native coronary artery stenosis were 86%, 96%, 83%, and 96% by per-segment analysis; 97%, 91%, 93%, and 96% by per-patient analysis (29). This finding highlights the advantage of MDCT to assess coronary artery stenosis. As a consequence, the recent guidelines from the European Society of Cardiology recommends the use of MDCT in patients at low or intermediate pretest probability for CAD in order to avoid unnecessary invasive coronary angiography (30).

MDCT also has the potential to provide information about lesion plaque composition (*Figure 3*). Previous studies showed that MDCT density expressed in hounsfield units corresponds well with echogenicity and plaque composition on intravascular ultrasound (31). This ability of MDCT enables to distinguish non-calcified, mixed and calcified plaques. Recent observational study demonstrated that plaques associated with acute coronary syndrome exhibited distinct plaque features including lower density values, positive remodeling and spotty calcification (32). Additionally, the presence of positive remodeling and lowattenuation plaques on MDCT predicted future acute coronary events (33).

These observations indicate the wide availability of MDCT in the clinical setting. For instance, as MDCT is useful for screening coronary artery stenosis, unnecessary invasive coronary angiography could be avoided. Highrisk features of atherosclerotic plaques on MDCT enable to apply more intensive medical therapies to prevent future events. As such, MDCT seems to be easily applicable to manage patients with suspected or established CAD.

Several important limitations of MDCT should be considered. Firstly, severe calcification limits lumen assessment due to blooming artifacts. In case of severely calcified lesions, MDCT can yield false positive results. Secondly, the technique is associated with radiation exposure, although significant dose reductions have been achieved with recent advances in scanner hardware and acquisition protocols. In addition, the resolution of MDCT to monitor plaque composition is inferior compared to invasive intravascular imaging techniques. Further improvement in plaque characterization is expected with the development of dual-energy MDCT or dedicated contrast agents.

Fractional flow reserve (FFR)

FFR is an invasive physiological index that can be measured during intracoronary administration of acetylcholine to assess the functional significance of coronary artery stenosis (34). Recently, technological innovation allows to calculate coronary flow and pressure based on anatomic MDCT image data without hyperemia, thereby measuring FFR noninvasively (35,36). Several studies demonstrated the feasibility and diagnostic performance of FFR evaluation on MDCT (FFR_{CT}) (37-41). Recent multicenter international study investigated the ability of FFR_{CT} for diagnosis of ischemia compared to an invasive FFR measurement in 252 stable patients with suspected or known CAD (37). In this study, diagnostic accuracy, sensitivity, specificity, positive and negative predictive values of FFR_{CT} plus MDCT were 73% (95% CI, 67-78%), 90% (95% CI, 84-95%), 54% (95% CI, 46-83%), 67% (95% CI, 60-74%), and 84% (95% CI, 74–90%), respectively. In addition, FFR_{CT} was associated with better evaluation of ischemia compared to



Figure 2 Visualization of coronary arteries by 64-slice MDCT. (A) Volume rendering technique demonstrates stenosis of right coronary artery; (B) left coronary artery does not have any significant stenosis; (C,D) maximum-intensity projection of the same arteries also visualizes severe stenosis within the right coronary artery, whereas there is no coronary artery stenosis in the left descending artery; (E,F) corresponding images by invasive coronary angiography. MDCT, multi-detector-row computed tomography. Reprinted from (26), with permission from Elsevier.

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Figure 3 Assessment of plaque characteristics by MDCT. (A) Mild stenosis (white box) is observed in the proximal left descending artery; (B) this segment shows positive remodeling (yellow dot line); (C) cross-sectional image in the segment with positive remodeling; (D) substantial plaque burden is observed. White line, lumen area; white dashed line, vessel wall area. MDCT, multi-detector-row computed tomography.

CT alone (area under the receiver operating characteristic curve, 0.81; 95% CI, 0.75–0.86 vs. 0.68; 95% CI, 0.62–0.74, P<0.001) (37). Meta-analyses from 5 studies including 706 patients and 1,165 vessels showed that sensitivity and specificity were 83% (95% CI, 79–87%) and 78% (95% CI, 75–81%) by per-segment analysis; 90% (95% CI, 79–87%), and 72% (95% CI, 67–76%) by per-patient analysis, respectively (38). The area under the curve was 0.94 at the per-patient level and 0.91 at the per-vessel level (38).

These observations indicate FFR_{CT} as a potential noninvasive toll to assess the presence of ischemia. However, several potential limitations should be considered. The diagnostic performance of FFR_{CT} is impaired by CT imaging artifacts including misalignment, motion, beam hardening from coronary calcification, and increased image noise. Physiologic conditions may affect assumed parameters such as fluid density and viscosity on FFR_{CT} . As viscosity is assumed from hematocrit/hemoglobin concentration, patients with severe anemia would exhibit reduced viscosity, potentially leading to the inaccurate calculation of FFR_{CT} . Further investigation is required to elucidate the ability of FFR_{CT} for the management of patients with CAD.

Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA)

High-resolution MRI and MRA emerged as the versatile non-invasive *in vivo* imaging modality for coronary artery stenosis and plaque characterization.

Coronary artery stenosis

Coronary MRA assess the proximal and mid portion of

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coronary arteries, especially left anterior descending and right coronary artery. By contrast, the image quality of left circumflex is diminished due to an increased distance from the cardiac coil. In general, the possible imaged length for left anterior descending artery is 50 mm, for right coronary artery is 80mm and for left circumflex artery is 40 mm (42-49). Previous studies showed an excellent agreement between the proximal segments of coronary on MRA and invasive angiography (50).

As mentioned above, MDCT allows to evaluate coronary artery stenosis accurately. One recent meta-analysis showed that MDCT was more accurate than MRA for the assessment of significant coronary artery stenosis (51). However, in a recent multicenter study, whole-heart magnetic resonance (MR) at 1.5T detected significant CAD with high sensitivity (88%), moderate specificity (72%) and a negative predictive value of 88%, showing the acceptable ability of this technique to exclude the presence of significant CAD (52). Interestingly in particular, this negative predictive value is similar to that in the CORE-64 MDCT multicenter study (53). Moreover, in another study, there was no significant difference in the detection of CAD between 3T MRI and 64-slice MDCT (54). MRA might have the acceptable ability to assess coronary artery narrowing compared to MDCT.

It should be noted that MRA imaging takes more time compared to MDCT and some patients can not tolerate, whereas advantage of MRA is to visualize coronary arteries without any contrast medium. Therefore, MDCT seems to be more applicable non-invasive imaging tool in the clinical settings and MRA is good for patients with kidney disease.

Plaque composition

MRI is able to differentiate plaque components on the basis of biophysical and biochemical parameters, such as chemical composition, water content, physical state, molecular motion, or diffusion (55). Specifically, recent improvements in MR techniques such as multicontrast MR, generated by T1- and T2-weighted, proton-density-weighted, and time-of-flight imaging have been shown to help to characterize fibrocellular, lipid-rich, and calcified regions of atherosclerotic coronary plaques (56-59).

One imaging study investigated the ability of highresolution, black-blood MR to assess coronary wall thickness (60). In 13 subjects including 8 normal subjects and 5 patients with CAD, the coronary artery wall was clearly seen in all patients and had distinct MR signal characteristics of surrounding tissue. In brief, the average coronary wall thickness for each cross-sectional image was $0.75\pm0.1~7$ mm in the normal subject, whereas it was 4.38 ± 0.71 mm in patients with localized atherosclerotic lesions. The difference in these wall thicknesses was statistically significant (P<0.0001).

The feasibility of contrast-enhanced cardiac MRI for vessel wall imaging has been shown to characterize fibrous plaque tissue and neovascularization in patients with advanced carotid artery stenosis (61,62). In preliminary data analyzing patients with stable CAD, contrastenhanced cardiac MRI visualized different types of plaque composition in major coronary arteries compared with MDCT (63). In addition, this imaging has been demonstrated to image inflammatory tissue signal changes in patients with carotid artery stenosis (64-66), giant cell arteritis (67) or Takayasu's arteritis (68). In 10 patients with acute myocardial infarction, serial contrast-enhanced cardiac MRI imaging identified changes in spatial extent and intensity of coronary contrast enhancement (*Figure 4*) (69).

Recent studies demonstrated that the visualization of plaque instability by using non-contrast T1WI MRI imaging. Kawasaki *et al.* reported that the presence of coronary high-intensity plaques detected by non-contrast T1WI is associated with positive coronary remodeling, low density on MDCT, and ultrasound attenuation (*Figure 5*) (70). Based on this finding, Noguchi *et al.* investigated the predictive ability of high-intensity signals within coronary plaques on non-contrast T1-Weighted MRI in cardiovascular events in 568 patients with suspected or known CAD (71). In this study, plaque-to-myocardium signal intensity ratio >1.4 was significantly associated with an increased risk of future coronary events.

These findings suggest the promising ability of MRI in imaging coronary atherosclerosis in the clinical settings. However, most of studies were conducted in relatively small study population. In addition, MRI has several limitations such as cost, length of the examination and inability of the patient to tolerate. Further technological advances are expected to make MRI more applicable modality in the clinical settings.

Positron emission tomography (PET)

Nuclear imaging techniques such as PET can target distinct mediators and regulators involved in the cascade of atherosclerosis.



Figure 4 Contrast-enhanced cardiac MRI of coronary artery. (A) Invasive coronary angiography shows the presence of mild stenosis in the right coronary artery; (B) MRA visualizes the right coronary artery; (C,D) contrast-enhanced cardiac MRI revealed diffuse contrast enhancement (white arrow) in the right coronary artery. MRI, magnetic resonance imaging; MRA, magnetic resonance angiography. Reprinted from (69), with permission from Elsevier.

¹⁸F-FDG (fluorodeoxyglucose) PET

PET imaging with F18-FDG is currently considered to be one of the most promising imaging modalities to visualize plaque inflammation. ¹⁸F-FDG is a radioactively labeled glucose molecule that is readily consumed by the cells showing high metabolic activities (72-74). ¹⁸F-FDG was started to use for imaging of the brain and tumors (75,76). Then, its use has been extended to imaging of atherosclerotic plaque and inflammation. Its effectiveness at diseased lesions harbouring high levels of metabolic activities has been demonstrated in preclinical and clinical studies (77).

Mechanistically, the ability of cells to utilize glucose analog is a key for the adequate uptake of ¹⁸F-FDG for imaging plaque inflammation. The way that ¹⁸F-FDG enters the cells is equivalent to the way glucose does through the glucose transporter (GLUT) protein system. ¹⁸F-FDG becomes phosphorylated to ¹⁸F-FDG-6 phosphate, but it cannot be metabolized further in the glycolytic pathway. Thus, it accumulates in the cells proportionally, enabling its imaging by PET/CT.

For the analysis of signal acquired from ¹⁸F-FDG in PET/CT imaging, the standardized uptake value (SUV) has been used extensively (78-82). The SUV is calculated by dividing the decay-corrected tissue concentration



Figure 5 HIP Measurement on MRI. (A) MDCT identified tight stenosis with positive remodeling in the proximal left descending artery (arrow); (B) a "hyperintense spot" (dashed arrow) was observed at the corresponding segment on CMR; (C) invasive coronary angiography showed severe coronary stenosis in the proximal left descending artery (arrow head); (D) on IVUS imaging, positive remodeling and ultrasound attenuation (arrowheads) were observed. IVUS, intravascular ultrasound; HIP, hyperintense plaque; MDCT, multi-detector-row computed tomography. Reprinted from (70), with permission from Elsevier.

(kilobecquerels per milliliter) by the injected dose of ¹⁸F-FDG per body weight (kilobecquerels per gram) (83). The target to background ratio (TBR) is another quantitative measure for the extent of plaque inflammation. The TBR is calculated by dividing the SUV of the artery of interest by that of the venous blood pool. The maximum and mean values of TBR seem to provide the most reliable results for evaluating atherosclerotic inflammation (84).

Recent study reported feasibility of FDG-PET for coronary artery inflammation imaging by using refined image acquisition methods. Rogers *et al.* underwent cardiac CT angiography and PET imaging with ¹⁸F-FDG after invasive angiography in 25 patients with CAD (*Figure 6*) (85). TBR was greater at culprit lesions in patients with acute coronary syndrome compared to those within lesions of patients with stable CAD. Additionally, TBR correlated with C-reactive protein (r=0.58, P=0.04).

Despite its potential applicability for the evaluation of plaque inflammation, it is still difficult to image coronary artery. In particular, myocardial ¹⁸F-FDG uptake would hinder isolation of signal from the adjacent coronary artery. Coronary motion also influences quality of imaging. Imaging coronary atherosclerosis by FDG-PET still needs more technological advances.

¹⁸F-NaF (sodium fluoride) PET

Calcification is one of the important components associated with plaque stability instability. NaF is a promising PET imaging agent to visualize plaque calcification, which is



Figure 6 ¹⁸F-FDG (fluorodeoxyglucose) PET imaging of coronary artery. (A) Increased uptake was observed in the left main trunk of patients with ACS (dashed arrow); (B) in a patient with stable CAD, the amount of uptake in the left main trunk was smaller compared to ACS case. ACS, acute coronary syndrome; CAD, coronary artery disease; FDG, fluorodeoxyglucose; PET, positron emission tomography. Reprinted from (85), with permission from Elsevier.



Figure 7 ¹⁸F-NaF (sodium fluoride) PET imaging. Focal ¹⁸F-NaF uptake is observed in the proximal LAD overlying existing coronary calcium. NaF, sodium fluoride; PET, positron emission tomography. Reprinted from (88), with permission from Elsevier.

a marker of active mineralization. In 269 asymptomatic cancer patients, 35% of patients had uptake of NaF within carotid arteries. In addition, NaF significantly correlated with the degree of atherosclerotic calcification on CT imaging (r=0.85, P<0.0001) and traditional cardiovascular risk factors (86). Derlin *et al.* retrospectively reviewed 45 studies using PET/CT in oncology patients (87). In this study, calcified lesions were associated with NaF rather than FDG (77% *vs.* 15%) and the overlap between NaF and FDG signals was minimal, occurring in only 6.5% of

patients. In a study of 119 subjects with or without aortic valve stenosis, NaF uptake was significantly associated with prior cardiovascular events and traditional risk factors. In addition, uptake of NaF was correlated with CAC score (r=0.652, P<0.001) (Figure 7) (88). Of note, patients with high CAC scores >1,000 had no detectable NaF activity. Considering that CAC scores of >1,000 are associated with a markedly elevated cardiovascular risk, NaF might detect earlier-stage calcified lesions. Thus, NaF is a promising agent for plaque calcification and provides new insights into atheroma progression complementary to FDG-PET. On the other hand, several issues remain, including refinement of techniques to control for cardiac and respiratory motion, as well as improvement in spatial resolution. Further studies are needed to establish ¹⁸F-NaF PET-CT will provide a clinically useful technique capable of improving risk stratification, monitoring disease progression and assessing novel anti-atherosclerotic therapies. PET imaging is an expensive study with radiation exposure. Considering these advantaged and disadvantages of ¹⁸F-NaF PET imaging, we have to establish refined imaging method and conduct clinical outcome studies in large study population to elucidate the association between NaF activity within plaques and cardiovascular events.

Conclusions

Various non-invasive imaging modalities allow to evaluate

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Table 1 Comparison of non-invasive imaging modanties to visualize coronary autorosecrosis					
	EBCT	MDCT	MRA	MRI	PET
Calcium detection	+	+	-	_	-
Luminal stenosis	-	++	+	-	-
Plaque area	-	++	-	-	-
Plaque composition	-	++	-	++	+
Radiation	+	+	-	-	+
Contrast use	-	+	-	-	-
Cost	Low	High	High	High	High
Required time for imaging	Short	Short	Long	Long	Medium

Table 1 Comparison of non-invasive imaging modalities to visualize coronary atherosclerosis

EBCT, electron beam computed tomography; MDCT, multi-detector-row computed tomography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PET, positron emission tomography.

both atheroma burden and composition (*Table 1*). This technological advance will enable to identify highrisk subjects prior to the occurrence of cardiovascular events, thereby potentially improving clinical outcomes. Although new imaging modalities will provide us a greater understanding about the mechanism of atherosclerosis, improved spatial resolution will be necessary to accurately evaluate plaque composition and assess the impact of medical therapies. In the future, more clinical trials are needed to demonstrate whether imaging assessment of atherosclerosis will improve treatment strategies and clinical outcomes. We also have to understand and investigate how these modalities can be used more effectively in the development of emerging therapies aimed to prevent cardiovascular disease.

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Footnote

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