Noninvasive Coronary Plaque Imaging

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Early identification of high-risk or vulnerable atherosclerotic plaques prone to rupture and performing preemptive therapy prior to catastrophic cardiovascular events are optimal goals of plaque imaging. Despite the advances in imaging modalities to identify vulnerable characteristics, the predictive value of the imaging techniques in the clinical setting is still developing. In this regard, reliable and high-sensitive imaging modalities identifying vulnerable plaque characters that may lead to future cardiovascular events will be useful. In this review article, we describe a current non-invasive plaque imaging technique to identify high-risk coronary plaque features.

Key words: Coronary artery, Plaque imaging, Computed tomography Angiography, Cardiac magnetic resonance, Positron emission tomography

Introduction

Most acute coronary syndrome (ACS) disorders occur as a consequence of atherosclerotic plaque rupture. Since identifying coronary plaques at risk of rupture is yet to be established (Fig. 1), Framingham cardiovascular risk scores based on traditional risk factors have been widely employed for detecting vulnerable patients with a risk of ACS¹⁻⁵. However, this risk score remains imprecise in estimating the risk of ACS on an individual basis. Recent rapid progress in imaging techniques has the potential to not only improve our understanding of the atherosclerotic processes leading to ACS but also provide accurate prognostic stratification and improved patient outcomes. Based on technical advances of imaging modalities, clinical interest has developed for prediction of ACS in patients with coronary artery disease beyond the luminal stenosis assessments. In this regard, invasive coronary plaque imaging has become possible using intravascular ultrasonography (IVUS), optical coherence tomography (OCT), and near-infrared spectroscopy. Each approach provides different complementary information. On the other hand, non-invasive imaging has undergone similar developments. Detailed coronary plaque imaging is now feasible through developments in computed tomography (CT) angiography, cardiovascular magnetic resonance (CMR), and positron emission tomography (PET). In combination, these imaging techniques can provide a multifaceted evaluation of coronary atherosclerosis. In particular, we can directly evaluate not only luminal stenosis but also plaque burden, plaque characteristics, and disease activity that represents inflammation and microcalcification, and visualize high-risk plaque features as atherosclerosis proceeds. Since intravascular imaging modalities have been used to gain important insights but is invasive, indication of these modalities is limited to patients at high risk of coronary artery disease or patients with ACS. For patients with low to moderate risk, non-invasive modalities may be extremely useful to quantitatively monitor plaque progression or regression chronologically and to understand and personalize atherosclerosis therapy.

Coronary Computed Tomography Angiography

CT Calcium Score

Coronary multi-detector computed tomography has the significant advantage of detecting atherosclerosis at early stages before the development of ischemia. The availability of coronary CT with very low radia-
Coronary calcium can also be quantified more accurately with the calcium mass score and the calcium volume score. In the diabetic population, several studies have pointed to the role of CAC in identifying the actual risk of cardiovascular event. CAC has a major role in evaluating a patient's overall cardiovascular risk, therefore, the use of CAC measurements for risk stratification in the diabetic population is warranted and recommended in the guidelines as a class IIa recommendation.

In contrast, a calcium score of zero is a very powerful predictor of event-free survival, and among the asymptomatic population is associated with very low-risk cardiovascular events. But CAC in symptomatic patients in the emergency department beyond coronary computed tomography angiography (CTA) is not used, since patients may have a CAC of zero but may have severe stenosis resulting from a non-calcified plaque by CTA. In the ROMICAT II trial, 473 low to intermediate symptomatic patients were randomized to CAC scanning using CTA. Among 58% of the population with a calcium score of zero, 0.8% developed ACS. Hence, the author concluded that a calcium score of zero does not completely exclude ACS. Although numerous studies support the measurement of the CT calcium score as a tool for risk

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**Fig. 1.** Assessment and treatment of critical coronary stenosis and high-risk or vulnerable atherosclerotic plaques before the development of coronary events

CABG: coronary artery bypass grafting, CTA: computed tomography angiography, ECG: electrocardiogram, PCI: percutaneous coronary intervention, SPECT: single photon emission tomography.
Improving risk prediction, while identifying that lower-density lesions are more vulnerable and high-density lesions represent more stable plaques.

Contrast-Enhanced CTA

Coronary CTA has become a widely adopted technique due to its high diagnostic accuracy and comprehensive evaluation of the coronary plaque burden. In clinical settings, coronary CTA is mainly used in symptomatic subjects at moderate risk according to the Appropriate Use Criteria. In a meta-analysis with 64-detector row scanners, per-patient sensitivity was 99%, specificity 89%, positive predictive value was 93%, and negative predictive value was almost 100%. Coronary CTA can characterize not only stratification, CAC scans to reflect treatment effects are inconclusive. A chronological change in calcium scores did not predict cardiovascular events after adjusting for the baseline calcium score. The prospective randomized Beyond Endorsed Lipid Lowering With EBT Scanning Trial compared the use of atorvastatin 80 mg with pravastatin 40 mg and found no significant difference in the progression of coronary calcium volume after one year (15.1% and 14.3%, respectively). IVUS studies showed that calcified plaques are less likely to be influenced by medical therapies. Thus, a calcium score does not seem to be useful in assessing plaque regression. A recent study using the Multi-Ethnic Study of Atherosclerosis demonstrated that density of calcium is inversely correlated with cardiovascular events. This strengthened the predictive power of the CAC score fourfold, improving risk prediction, while identifying that lower-density lesions are more vulnerable and high-density lesions represent more stable plaques.

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ing and low-attenuation plaques, were associated with the subsequent development of ACS. In this study, the percentage of patients with these two features who subsequently developed ACS was 22.2%, compared with only 3.7% of patients with only one feature and 0.5% of patients with neither positive remodeling nor low-attenuation plaques. More recently, the same authors reported that in 3,158 patients with a mean follow-up of 3.4 ± 2.4 years, CTA-derived high-risk plaques characterized by positive remodeling with low attenuation were an independent predictor of ACS. Moreover, in a subgroup of 449 patients who underwent serial CTA, plaque progression was an independent predictor of ACS. The napkin-ring sign (a ring of high attenuation around a coronary plaque) (Fig. 3), positive remodeling, a low HU plaque, and spotty calcification were associated with ACS independently of stenosis in an analysis of the ROMICAT II trial. Morphological high-risk CT plaque features may also be an indicator of a myocardial injury during percutaneous coronary intervention (PCI). CTA-verified low-attenuation plaques, positive remodeling, and spotty calcification but also plaque components (calcified, partially calcified, or non-calcified) and arterial positive remodeling. Several studies have reported the correlation between coronary CTA plaque features and plaque burden with IVUS. In a meta-analysis, coronary CTA had a good diagnostic accuracy to detect coronary plaques compared with the gold standard IVUS, with an area under the curve for the receiver operating characteristics analysis of 0.94, a sensitivity of 90%, and a specificity of 92%. Hoffman et al. reported that a significantly larger plaque area and positive remodeling were found in culprit lesions of patients with ACS, compared with patients with stable CAD. Positive remodeling has been recognized as a surrogate marker of plaque vulnerability. In a landmark study, Motoyama et al. found that culprit lesions of patients with ACS more frequently had positive remodeling, low-attenuation plaque (< 30 HU), and spotty calcifications. Extending these results, they conducted a large prospective trial including 1,059 patients, and demonstrated that CTA-derived high-risk plaques, including positive remodeling and low-attenuation plaques, were associated with the subsequent development of ACS. In this study, the percentage of patients with these two features who subsequently developed ACS was 22.2%, compared with only 3.7% of patients with only one feature and 0.5% of patients with neither positive remodeling nor low-attenuation plaques. More recently, the same authors reported that in 3,158 patients with a mean follow-up of 3.4 ± 2.4 years, CTA-derived high-risk plaques characterized by positive remodeling with low attenuation were an independent predictor of ACS. Moreover, in a subgroup of 449 patients who underwent serial CTA, plaque progression was an independent predictor of ACS. The napkin-ring sign (a ring of high attenuation around a coronary plaque) (Fig. 3), positive remodeling, a low HU plaque, and spotty calcification were associated with ACS independently of stenosis in an analysis of the ROMICAT II trial. Morphological high-risk CT plaque features may also be an indicator of a myocardial injury during percutaneous coronary intervention (PCI). CTA-verified low-attenuation plaques, positive remodeling, and spotty calcification.
Coronary CTA plaque characteristics\(^33,\,44\) . Moreover, inter-observer variability in the assessment of several plaques as a surrogate of vulnerable plaques that can prevent the detailed assessment of several features associated with vulnerable plaques, as is the case of the evaluation of a thin fibrous cap (< 65 µm)\(^30\) (Table 2). This spatial resolution is significantly worse than that of IVUS (150–250 µm) or OCT (10–15 µm)\(^41\). Another limitation of coronary CTA plaque characterization is related to the fact that coronary plaque attenuation values are significantly modified by differences in lumen contrast densities, as has been demonstrated both ex vivo and in vivo\(^42,\,43\) . This is a very critical issue, because lumen contrast can be influenced by different injection speeds and doses of the contrast agent, scanning protocols, and heart rate; these confounders make it difficult to establish thresholds of CT value for the definition of low-attenuation plaques as a surrogate of vulnerable plaques that can be widely adopted. Therefore, the reproducibility of coronary CTA plaque measurements is not adequate, while many previous studies have reported significant inter-observer variability in the assessment of several coronary CTA plaque characteristics\(^33,\,44\) . Moreover, these coronary CTA plaque measurements also depend on motion artifact, vessel size, and degree of calcification. In the future, improvements in spatial resolution and the development of calcification extraction techniques would contribute in overcoming these limitations.

### Table 2. Comparison of Plaque Imaging Modalities

|                          | CTA       | MRI       | OCT       | IVUS      |
|--------------------------|-----------|-----------|-----------|-----------|
| Spatial resolution (µm)  | 400-600   | 500-1,000 | 10-15     | 150-250   |
| Penetration depth (mm)   | not applicable | not applicable | 2         | 5-8       |
| Specific features        | Radiation | No radiation | Invasive | Invasive |
| Lipid pool               | Good      | Good      | Good      | Fair      |
| Calcium                  | Excellent | Fair      | Excellent | Fair      |
| Fibrous cap              | Poor      | Fair      | Excellent | Excellent |
| Thrombus                 | Poor      | Good      | Good      | Fair      |

MRI of Atherosclerosis

Atherosclerotic plaque characterization by MRI is based on the signal intensity and morphological appearance of the plaque on multiple contrast weightings such as T1-weighted (T1W), T2-weighted (T2W), and proton density-weighted (PDW). MRI depicts electromagnetic signals with radiofrequency from protons in a strong magnetic field. In clinical practice, MR mainly visualizes signals from protons in free water, triglycerides, and free fatty acids. Macromolecules such as proteins and cholesterol crystals do not contribute to conventional MR signals, because they have a very short T2. Since atherosclerotic plaques contain only a small amount of triglycerides, their MR images mainly visualize free water. Since calcification does not contain free water and triglycerides, densely calcified tissue appears as dark regions on MRI. On the other hand, MRI cannot identify sparsely calcified tissue because it detects signals from water protons in other tissues, and sparse calcification is masked by the partial volume effect. With MRI, signals from atherosclerotic plaques vary according to the free water concentration or proton density and relaxation time (T1 and T2). MRI can characterize plaque components such as fibrous tissue, hemorrhagic tissue, and dense calcification\(^45,\,46\) . Since the advantage of carotid plaque imaging using MRI lies in the combination of multicontrast images, both bright-blood imaging (e.g., time-of-flight [TOF] magnetic reso-
imaging using a spin echo black-blood technique in humans. MR coronary plaque imaging was performed with breath holding in order to minimize respiratory motion. This technique was subsequently improved by Botnar et al., allowing for high-resolution coronary plaque imaging while breathing freely. To alleviate the need for breath holding, the black-blood fast-spin echo method has been combined with a real-time navigator for respiratory gating and real-time slice-position correction.

Although both Botnar et al. and Fayad et al. demonstrated that coronary artery walls are significantly thicker in patients with advanced, lumen-encroaching coronary artery disease, Kim et al. recently demonstrated that free-breathing MRI with isotropic resolution can detect increased coronary wall thickness in patients with early coronary artery disease, when the coronary artery lumen size remains normal.

In an effort to develop non-contrast coronary plaque imaging procedures, Maintz et al. and Yeon et al. were the first to describe coronary plaque imaging with non-contrast T1W imaging. Additionally, in 2007 Koga et al. reported the successful 3D non-contrast T1W imaging of a coronary artery.

Coronary Plaque Characterization by MR

MR coronary plaque imaging has been challenging due to the small size of coronary arteries, and cardiac and respiratory motion. These two factors had previously prevented the effective imaging of coronary arteries. In 2003, our group demonstrated that visualization of a coronary intramural hematoma with coronary artery dissection is possible with non-contrast T1W imaging (MPRAGE) on a 1.5T MR system. In a landmark study, Fayad et al. were the first to demonstrate the feasibility of in vivo coronary plaque imaging using a spin echo black-blood technique in humans. MR coronary plaque imaging was performed with breath holding in order to minimize respiratory motion. This technique was subsequently improved by Botnar et al., allowing for high-resolution coronary plaque imaging while breathing freely. To alleviate the need for breath holding, the black-blood fast-spin echo method has been combined with a real-time navigator for respiratory gating and real-time slice-position correction.

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plaque using a commercially available 1.5T MRI system (Fig. 5) and they termed the plaques visualized by non-contrast T1W imaging as a high-intensity plaque (HIP). A comparison of CTA and CMR images of the right coronary artery indicates that a plaque with a low CT density value appears with high intensity on non-contrast T1W imaging. Kawasaki et al. systematically evaluated the components of coronary HIPs with non-contrast T1W imaging with the use of CTA invasive coronary angiography, and IVUS. This cooperative study showed that coronary HIPs are associated with ultrasound attenuation, vascular positive remodeling, low CT density, and a high incidence of slow flow phenomena following PCI. These findings are in good agreement with those from earlier studies using T1W imaging for carotid plaque characterization in the reference of histological studies showing that HIPs correlated with complicated plaques, lipid-rich cores, and intraplaque hemorrhage.

**Non-Contrast T1-Weighted Magnetic Plaque Imaging**

Non-contrast T1-weighted imaging provides important prognostic information. The presence of a HIP in the carotid arteries predicted cardiac events, outperforming carotid intimal medial thickness and traditional cardiovascular risk factors. In the coronary arteries, a case report first described a high-intensity coronary plaque going on to rupture and cause MI. HIPs are quantitatively assessed by a plaque-to-myocardium signal intensity ratio (PMR). Subsequently, a relative large study demonstrated coronary HIPs in 159 of 568 patients with known or suspected CAD. Forty-one of these subjects subsequently went on to have a coronary event, with the presence of a HIP with higher PMR (1.4) acting as an independent predictor on multivariate analysis (hazard ratio: 3.96; 95% confidence interval: 1.92–8.17) (Fig. 6). In addition, Asaumi et al. and Hoshi T. et al. reported that coronary HIPs with high PMR in patients with stable CAD were predictive of periprocedural myocardial injury at the time of PCI. These two recent studies confirmed the results from a study conducted by Kawasaki et al., which indicated the relationship between coronary HIP and the slow-flow phenomenon after PCI. Most recently, Noguchi et al. demonstrated that intensive statin therapy reduces HIPs with high PMR by 19.2% and reduces high-sensitivity C-reactive protein levels. These emerging prognostic data, coupled with the ability to image the entire coronary tree, place non-contrast T1W imaging as perhaps the most promising CMR approach for identifying high-risk coronary atheroma.

We would like to describe non-contrast T1W coronary plaque imaging techniques. According to our MRI protocols, scans in 1.5 tesla and 3 T MR systems proceed in the following sequence: (1) survey scan, (2) reference scan for use in parallel imaging, (3) cine MRI scan to detect coronary artery motion resulting from the cardiac cycle, (4) MRA to identify the severity and the location of atherosclerotic lesions, and (5)

![Representative non-contrast T1W and CTA of coronary plaque in the distal right coronary artery](image)
patient cooperation. T1W imaging data can be acquired only during diastole in the cardiac cycle. Patients with slower heart rates will produce better images (<75 bpm). Total acquisition time to get whole heart coronary non-contrast T1WI requires 25–40 min.

3D T1W plaque imaging. MRA is routinely used in our protocols because 3D T1W sequences provide low spatial resolution and thereby fail to visualize healthy coronary artery walls, although they can identify pathological plaques. MRA scans are used to locate plaques. Practically, irregular respiratory motions and other patient movements significantly deteriorate image quality. Therefore, for successful imaging it is important to reduce patient anxiety and encourage

Contrast-Enhanced T1-Weighted Imaging
Late gadolinium enhancement has become

Fig. 6. Representative images of high-intensity plaques developing acute coronary syndrome and Kaplan-Meier curves comparing the probability of all coronary events

A: Representative images of a high-intensity plaque (HIP) with a PMR ≥ 1.4 at the proximal site of the right coronary artery (yellow arrowheads, middle panel) corresponding to the intermediate stenosis with positive remodeling on CTA (yellow arrowheads, left panel) developing into acute coronary syndrome detected by CAG (right panel).
B: During a median follow-up period of 55 months, coronary events were observed in 55 out of 568 study patients. Receiver operating characteristic curve analysis identified a PMR of 1.4 as the optimal cutoff for predicting cardiac events. At this value, the sensitivity and specificity for predicting a cardiac event were 69.5% and 82.3%, respectively.
C: Multivariate Cox regression analysis identified the presence of PMR ≥ 1.4 plaques as the significant predictor of coronary events (HR, 3.96; 95% CI, 1.92–8.17; p < 0.001) compared with the history of CAD (HR, 3.56; 95% CI, 1.76–7.20; p < 0.001) and other traditional risk factors.
D: Among the four groups based on the PMR cutoff of 1.4 and the presence of CAD, coronary event-free survival was lowest in the PMR ≥ 1.4 + CAD group, shown in red, and highest in the PMR < 1.4 + no CAD group, shown in orange. Interestingly, the patients with PMR ≥ 1.4 + no CAD, shown in green, had an intermediate level of survival, which was similar to the PMR < 1.4 + CAD group, shown in blue.
CAD: coronary artery disease, CAG: coronary angiography, HIP: high-intensity plaque, HR: hazard ratio, CI: confidence interval, PMR: plaque-to-myocardium signal intensity ratio.

| Multivariate analysis for all coronary events | Hazard Ratio | p value | 95% CI |
|---------------------------------------------|-------------|---------|--------|
| Age                                         | 1.04        | 0.023   | 1.01–1.07 |
| Male gender                                 | 2.61        | 0.071   | 0.92–7.39  |
| HbA1C                                       | 1.04        | 0.018   | 1.03–1.36  |
| History of CAD                              | 3.56        | <0.001  | 1.76–7.20  |
| Presence of PMR ≥1.4                        | 3.96        | <0.001  | 1.92–8.17  |

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Presence of PMR ≥1.4
3.96
<0.001
1.92–8.17

n=568

AUC = 0.83

pmiley11

CAG

PMR cut off =1.4
Sensitivity 69.5%
Specificity 82.3%
AUC = 0.83

PMR < 1.4 + no CAD
PMR < 1.4 + CAD
PMR ≥ 1.4 + no CAD
PMR ≥ 1.4 + CAD

p < 0.001 by log-rank test

All coronary events

Months of follow-up
PET

Inflammation plays a pivotal role in the precipitation of acute myocardial infarction, with macrophages secreting matrix metalloproteinases that weaken the fibrous cap, predisposing the plaque to rupture. Angiogenesis is another key process of plaque progression within the necrotic core and commonly observed in vulnerable lesions. The new vessels that develop are immature, leaky, and associated with intraplaque hemorrhage, which in turn can trigger abrupt plaque growth and/or rupture. Thus, both inflammation and angiogenesis represent key vulnerable characteristics and are imaging targets. To date, two PET tracers have been used to evaluate high-risk atherosclerotic plaques: 18F-fluorodeoxyglucose (18F-FDG) and 18F-sodium fluoride (18F-NaF). 18F-FDG is a glucose analog that has been widely used as a marker of vascular inflammation in the carotid arteries on the basis that macrophages use more glucose than surrounding cells. Indeed, increased 18F-FDG uptake shows an association with high-risk anatomical plaque features in carotid arteries. The arterial wall 18F-FDG uptake measurement is highly reproducible and positively correlates with macrophages gene expression. 18F-FDG activity in atherosclerotic plaques was found to be an independent predictor of subsequent cardiovascular events. In addition, statin treatment results in a reduction in 18F-FDG activity in atherosclerotic plaques. 18F-NaF has recently been shown to preferentially bind regions of vascular microcalcification activity beyond the resolution of CT. In contrast to the macroscopic calcium deposits detected by CT that impart stability, microcalcification is consistently associated with high-risk coronary lesions and increased risk of rupture. 18F-NaF uptake in the coronary arteries has been reported in two clinical trials. Increased 18F-NaF uptake could be localized to coronary plaques and identified high-risk patients with increased Framingham risk scores. In a recent study, the use of 18F-FDG and 18F-NaF was investigated in 40 patients with myocardial infarction and 40 patients with stable angina pectoris who underwent invasive coronary angiography. The authors demonstrated that 18F-NaF uptake was significantly localized to the culprit coronary plaques with high-risk features such as a large-lipid core and spotty calcification lesions, while 18F-FDG was not able to discern culprit from non-culprit lesions. Despite significant detection of plaque activity, visualization of 18F-FDG activities in the coronary arteries is still challenging due to spatial resolution (4–5 mm), respiratory and heart motion, and physiological 18F-FDG uptake in the myocardium. In order to suppress physiological myocardial 18F-FDG uptake, low-carbohydrate and high-fat diets have been proposed. PET-CT or PET-MR hybrid imaging may allow for simultaneous evaluation of anatomical and metabolic tissue characteristics. In particular, PET-MR has the potential for evaluating patients with ischemic heart disease by delineating the area at risk by visualizing decreased 18F-FDG uptake. However, MR attenuation correction is still challenging.

Summary

CTA, CMR, and PET have the potential to provide a multiparametric assessment of coronary atherosclerosis, incorporating key information related to plaque burden, high-risk plaque characteristics, and disease activity. Considerable technical challenges remain in reliably translating these techniques into the coronary arteries. However, with ongoing technical advances, non-invasive imaging will play a critical role in identifying patients at high risk for ACS, and in delivering personalized preemptive therapy for coronary artery disease.

Disclosure

There are no conflicts of interest to disclose.

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