Clinical Significance of Non-invasive Magnetic Resonance Imaging to Identify High-risk Coronary Plaques as Potential Biomarkers for Preemptive Medicine

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Identification of high-risk coronary plaques is important for management of patients with coronary artery disease (CAD) to prevent future cardiovascular events including death, heart failure, and fatal myocardial infarction. Many studies have described the characteristics of coronary plaques and their clinical outcomes, based on invasive intravascular coronary imaging. Recent technical advancements in multi-slice computed tomography, positron emission tomography, and magnetic resonance imaging (MRI) provide methods for less invasive detection of high-risk coronary atherosclerosis. Our research has focused on understanding the development of coronary atherosclerosis and its clinical outcomes using non-contrast T1-weighted MRI (T1WI), which is non-invasive and does not require the use of ionizing radiation or iodide contrast medium. We have shown that coronary high-intensity plaques (HIPs) detected by non-contrast T1WI are associated with high clinical risk, and therefore might have potential applications in monitoring pharmacological interventions and advancing preemptive medicine in CAD patients. However, the histopathological and molecular mechanisms underlying coronary HIPs remain undetermined. Future studies using a combination of multi-modality images and molecular analysis may facilitate an improved understanding of the molecular dynamics of coronary HIPs.

KEY WORDS: coronary atherosclerosis, magnetic resonance imaging, preemptive medicine

Cardiovascular diseases (CVDs) account for > 17 million deaths globally each year (30% of all deaths), and the number is expected to grow to 23.6 million by 2030. Among CVDs, coronary artery disease (CAD) is the most prevalent. In around 50% of cases, sudden cardiac death (SCD) is the first manifestation of heart disease, and CAD underlies 80% of SCDs. A substantial number of patients suffer sudden death, and others experience lethal complications following acute coronary syndrome (ACS), e.g., cardiac rupture. Therefore, primary prevention of CVD is important in these patients.

Intravascular ultrasound (IVUS) can identify high-risk coronary plaques, and therefore has prognostic value. However, because this technique is invasive, IVUS and optical coherence tomography (OCT) usually take place during percutaneous coronary intervention (PCI). To evaluate coronary atherosclerosis for primary or secondary prevention, a less invasive method of imaging is desirable. Coronary computed tomography (CT) can identify plaque characteristics based on findings of CT value, calcification, and vessel remodeling. Motoyama and colleagues showed that patients with positive vessel remodeling and low-attenuation plaques revealed by CT angiography are at higher risk of future coronary events than patients whose lesions lack these characteristics. However, because CT requires both ionizing radiation exposure and iodide contrast medium, it is considered to be unsuitable for coronary artery screening in the general population. Coronary positron emission tomography (PET) is also a useful technique, but it is only available in a limited number of institutions, and its methodology and clinical significance (including prognostic impact) have not been completely determined. Consequently, there is still a need for a less invasive method of CVD detection prior to clinical events.

Magnetic resonance imaging (MRI) is a promising technology for clinical application because multi-contrast images obtained by multiple sequences can differentiate plaque components based on their biophysical and biochemical parameters. Moreover, MRI does not utilize ionizing radiation, even in the absence of contrast medium, and can be repeated sequentially over time. In this review, we will discuss the potential of MRI for screening and managing coronary atherosclerosis.

I. Magnetic resonance imaging for atherosclerotic plaques

Atherosclerotic plaque characterization by MRI is based on the signal intensity and morphologic appearance of plaques in multiple contrast weightings. MRI detects electromagnetic signals at radio wavelengths emitted by protons in a strong magnetic field. In clinical practice, MRI mainly visualizes signals from...
The presence of HIPs in the contralateral carotid artery, detected by MPRAGE, was also associated with cerebral ischemic events in one-third of patients. A prospective observational study showed that the presence of carotid HIPs even in patients with moderate stenosis was associated with future cerebrovascular events during a median of 38 months of follow-up.

Saam and colleagues reported the clinical importance of carotid IPH detected in T1-weighted fat-suppression images. Their systematic review showed that the prevalence of carotid HIPs is 49%, the presence of HIPs is associated with ~6-fold higher risk for cerebrovascular events, and the annual event rate in patients with carotid HIPs is 17.7% (vs. 2.4% in those without carotid HIPs). In addition, Noguchi and colleagues showed that the presence of HIPs in the carotid artery, detected by MPRAGE, is related to an increased incidence of coronary events in patients with clinically stable coronary artery disease during a mean of 38 months of follow-up. Taken together, these results indicate that non-contrast T1-weighted imaging (T1WI) is a non-invasive method with important clinical applications for evaluation of whole-body atherosclerosis and screen-
To clarify the clinical significance of coronary HIPs detected by non-contrast T1WI as biomarkers, we sought to examine 1) whether coronary MRI can predict future cardiac events and identify the periprocedural risk during percutaneous coronary intervention (PCI), and 2) whether coronary MRI can evaluate plaque characteristics or monitor their changes.

III. Clinical significance of coronary HIPs detected by non-contrast T1WI as biomarkers

To investigate the prognostic impact of coronary HIPs, we examined 568 patients with suspected or known coronary artery disease (CAD), who were initially screened by CT angiography (CTA) and subsequently underwent 1.5-T MRI examinations to evaluate coronary plaques. During a median of 55 months of follow-up, 55 coronary events were observed. To quantitate plaques, the plaque to myocardium signal intensity ratio (PMR) was calculated in each case of coronary atherosclerosis (Fig. 3). PMR was higher in patients with coronary events than in those without coronary events (with: 1.49; without: 0.94; P < 0.001). Based on receiver operating characteristic (ROC) curve analysis, the optimal PMR cutoff value for predicting cardiac events was 1.40, and the area under the ROC curve was 0.83. Multivariate analysis revealed that PMR ≥ 1.4 and proven CAD (defined as 1) history of myocardial infarction (MI) or PCI, 2) ischemia-proven
Plaque to Myocardium signal intensity Ratio = PMR
= Signal intensity of coronary plaque: 211 / Signal intensity of nearby left ventricular myocardium: 63
= 3.45

Fig. 3  Quantification method for coronary plaques detected by non-contrast T1-weighted imaging.
Plaque to myocardium signal intensity ratio (PMR) is defined as the signal intensity of the coronary plaque (red circle) divided by that of the nearby left ventricular myocardium (pink circle), measured using a freehand region of interest on a standard console of the clinical MR system. We use left ventricular myocardium located the same distance from the surface coil as the plaque to determine plaque signal intensity. RCA: right coronary artery. Ao: ascending aorta. RV: right ventricle. LV: left ventricle.

Angina pectoris or silent myocardial ischemia diagnosed by stress myocardial scintigraphy, or 3) coronary arteriography–proven coronary artery stenosis ≥ 50% were both significant independent prognostic factors. According to the PMR cut-off value and the presence or absence of proven CAD, Kaplan–Meier analysis revealed that patients with PMR ≥ 1.4 had significantly more cardiac events than those with PMR < 1.4, irrespective of proven CAD status (Fig. 4). The results of that study indicate that non-contrast T1W1 has the potential to detect high-risk coronary plaques and predict future coronary events.

To investigate the clinical applications of non-contrast T1WI during PCI, we also examined the relationship between MRI findings of coronary HIPs and periprocedural myocardial injuries (pMI), defined as an increase in serum cardiac troponin T (cTnT) levels more than 5 times the upper limit of normal (0.07 ng/ml) 24 h after PCI, following elective PCI in patients with stable CAD.26 During PCI, 5–30% of patients experience pMI, which is associated with long-term adverse outcomes and immediate adverse events.27 Between October 2012 and March 2014, 57 CAD patients underwent 3T MRI before PCI, and pMI was observed in 15 of them (26%). Median PMR at the PCI site was higher in patients with pMI than in those without it (pMI patients: 1.3 [1.1–2.0] ; non-pMI patients: 1.0 [0.8–1.2] ; P < 0.014). ROC curve analysis revealed that the optimal PMR cut-off value for predicting pMI was 1.3, and the area under the ROC curve was 0.71. The same examination was performed by another group, who reported that the optimal cutoff value for predicting pMI in 1.5 T non-contrast T1WI was 1.4.27 Taken together, these observation suggest that MRI could have clinical applications for identifying high-risk coronary plaques, even in PCI patients.

We further examined the effect of statin on coronary plaques by non-contrast T1WI. Statin treatment leads to plaque stabilization, ameliorates the progression of native coronary and graft atherosclerosis, and reduces the incidence of subsequent cardiac events.28, 29 Therefore, we hypothesized that statin treatment would affect coronary HIPs detected on non-contrast T1WI and change PMR. The AQUAMARINE pilot study was a prospective, open-label, propensity score–matched study examining the effect of 12 months of pitavastatin therapy for coronary atherosclerosis, evaluated by non-contrast T1WI.30 Between June 2009 and December 2011, 48 patients with CAD who were screened with CTA followed by MRI using non-contrast T1WI were enrolled as the intensive statin group; they received 4 mg/day...
pitavastatin to achieve an LDL-cholesterol (LDL-C) level < 80 mg/dl. CTA and MRI were repeatedly performed 12 months after pitavastatin treatment. For ethical reasons, 48 propensity score–matched patients with CAD not receiving statin treatment, who underwent CTA followed by MRI at baseline and 12 months between 2008 and 2009, were enrolled as a historical control group. In the statin-treated patients, the signal intensities of coronary plaques on T1WI were reduced, whereas in the no-statin control patients, plaque signal intensity was elevated (intensive statin group: -18.9% ; control group: +19.2% ; P<0.001). These effects were especially enhanced at coronary plaques with PMR ≥ 1.4, and the change in PMR was associated with changes in serum LDL-C levels, C-reactive protein levels, percentage of total atheroma volume, and percentage of low-attenuation plaque volume measured by CTA. This study demonstrated that coronary MRI on non-contrast T1WI has the potential to evaluate and monitor coronary plaque characteristics during pharmacological interventions. Little is known about the mechanisms underlying the reduction in signal intensity of coronary HIPs after statin treatments. Carotid IPH was less frequent in patients on statins before endarterectomy, and the use of statins before a transient ischemic attack or stroke is negatively associated with the presence of IPH.

IV. What are the coronary high-intensity plaques detected by T1WI: plaque components or intravascular thrombi?

As mentioned above, non-contrast T1WI for coronary atherosclerosis can be applied to assessment of clinical risk and used to guide therapeutic intervention in CAD patients. Furthermore, coronary HIPs detected by non-contrast T1WI have the features of high-risk coronary plaques. However, histopathological findings of coronary HIPs remain incompletely determined, although it is known that HIPs in carotid artery plaques are composed of complex plaques with large IPHs.

To compare coronary HIPs and their histological findings, Jansen and colleagues first demonstrated that defects visualized by x-ray coronary angiography, described as coronary thrombi in their study, are depicted as high-intensity signals by non-contrast T1WI in patients with ACS. In their study, intracoronary material was obtained from three patients by coronary thrombectomy, and histological findings revealed fresh thrombi. Ehara and colleagues performed a direct comparison between coronary MRI findings and intravascular optical coherence tomography (OCT) in patients with both stable and unstable angina pectoris. They demonstrated that the prevalence of intraluminal thrombi confirmed by OCT was higher in the coronary HIPs group than in the non-HIPs group, whereas the prevalences of lipid-rich plaques, thin-cap fibroatheromas, plaque rupture, and calcification on OCT were comparable. Moreover, a more recent study by the same group revealed that high-intensity signals on T1WI at the culprit lesion in both stable CAD and ACS patients were associated with clinical presentation, and coronary HIPs were more frequent in ACS patients (ACS patients: 72% ; stable patients: 45%). However, they did not mention the OCT findings, especially in stable CAD patients, because of the limited number of patients enrolled in their study (42 of 100 patients). Therefore, for our comparison of the findings of coronary MR and OCT, we focused on patients with stable CAD eligible for PCI. Our study showed that the prevalence of intracoronary thrombi detected on OCT was comparable between the coronary HIPs group and the non-HIPs group. In addition, we also investigated the histopathological findings of coronary HIPs in stable CAD patients from samples in which coronary embolus from the culprit lesion occurred during PCI. Histological findings of coronary emboli revealed a large amount of necrotic core with over-
Further studies are needed to screen functional target molecules to improve visualization of atherosclerosis.

VI. Unresolved issues of coronary MRI and future perspectives

MRPAGE imaging of coronary atherosclerosis is a promising method for detection of high-risk plaques. However, several problems must be overcome in order to apply non-contrast T1WI as a clinical diagnostic tool.

First, evaluation of coronary plaques by T1WI requires relatively long scan times (15–20 minutes per patient to visualize coronary plaques in the whole heart) and the area of enhancement is associated with the severity of atherosclerosis as detected on coronary CT and quantitative CAG. For a better understanding of the functional and molecular mechanisms of processing atherosclerosis, targeted contrast agents for atherosclerosis will be needed for MRI, as is the case for non-invasive cancer assessments. There are several stages of progression of atherosclerosis. Microarray or proteomics analysis might help us to understand the specific molecules involved in atherosclerosis and to screen candidate proteins for functional targeted probes.

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because health care costs already account for a major fraction of gross domestic product (GDP) in Japan. Therefore, the distinct clinical importance and evidentiary value of coronary MRI should be established in future studies.

Second, the components and mechanisms of coronary HIPs on T1WI remain undetermined, although carotid HIPs are characterized as IPHs derived from tissue methemoglobin.

To resolve this issue, a direct comparison between coronary tissues and MRI findings is necessary. Creating appropriate animal models for vulnerable coronary plaques might also improve our understanding of the molecular mechanism of coronary HIPs, because they would allow repeated examination of in vivo cardiac MRI over a time course. Currently, however, few rodent or other animal models resemble vulnerable plaques in humans.

Third, PET images could be used to visualize molecular metabolism (glucose, calcium, and tissue hypoxia) in pathogenesis of atherosclerosis, as it is in cancer.

In coronary atherosclerosis, "18"F-sodium fluoride (NaF) is a more promising PET tracer for detection of microcalcification than 18"F-fluorodeoxyglucose (FDG), because myocardial cells also uptake 18"F-FDG; consequently, the high background of myocardial 18"F-FDG uptake makes interpretation of signal derived from the coronary arteries problematic, but this is not the case for 18"F-NaF. Combining PET with T1WI might facilitate comprehensive understanding of the molecular metabolism of atherosclerotic lesions, and could be used to evaluate the anatomical details and functional assessments of coronary atherosclerosis detected on T1WI.

VII. Conclusions

Recent findings from our laboratory and others suggest that coronary MRI, especially in T1WI, would have clinical applications as potential biomarkers to identify high-risk patients susceptible to future coronary events, and could be used to advance preemptive medicine by enabling early intervention (Fig. 6).

However, our understanding of the mechanisms of coronary plaque components (i.e., histology and molecular constituents) detected by T1WI remains incomplete. The development of new molecular imaging probes with specific biological functions could add new dimensions to plaque imaging. Further studies are needed to clarify the histopathology and molecular mechanisms of coronary HIPs.

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