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Hyperintense plaque identified by magnetic resonance imaging relates to intracoronary thrombus as detected by optical coherence tomography in patients with angina pectoris

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Aims Many investigators have speculated that hyperintense plaques (HIPs) of the carotid artery on non-contrast T1-weighted imaging (T1WI) in magnetic resonance indicate the presence of mural or intraplaque haemorrhage containing methemoglobin. Coronary plaque imaging with T1WI is challenging, and the clinical significance of coronary HIP on T1WI remains unknown. The aim of this study was to compare HIPs on T1WI with coronary plaque morphology assessed by optical coherence tomography (OCT), which allows us to identify not only plaque rupture, but also fibrous cap thickness and intracoronary thrombus *in vivo*, in patients with angina pectoris.

Methods and results Twenty-six lesions from 26 patients with either stable or unstable angina pectoris were examined in this study. All patients underwent T1WI within 24 h before the day on which invasive coronary angiography was performed, and pre-interventional OCT was performed on a native atherosclerotic lesion, considered to be the culprit lesion. Of the 26 lesions studied, 16 (62%) were HIPs and 10 (38%) were non-HIPs. The signal intensity of the coronary plaque to cardiac muscle ratio in HIPs was significantly higher than that in non-HIPs. There were no significant differences in the frequency of lipid-rich plaque, thin-cap fibroatheroma, plaque rupture, and calcification between HIPs and non-HIPs. In contrast, the frequency of thrombus was significantly higher in HIPs than in non-HIPs ($P = 0.004$).

Conclusion This study shows that the HIPs on T1WI in angina patients relate to the presence of intracoronary thrombus as detected by OCT imaging.

Keywords Coronary artery disease • Atherosclerotic plaque • Magnetic resonance imaging • Thrombosis • Optical coherence tomography

Introduction

Despite developments in coronary intervention and effective medications, coronary artery disease is the leading cause of death in the elderly worldwide. However, the majority of these individuals do not develop coronary symptoms before the onset of acute myocardial infarction or sudden cardiac death. Therefore, screening of patients with vulnerable plaque is important for the prevention of the onset of acute cardiovascular events.

Plaque rupture or erosion of the endothelial surface with subsequent thrombus formation is currently recognized as the most important mechanism for acute coronary syndromes.[1,2] Recently,

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magnetic resonance imaging technology has reached a level of spatial resolution that is sufficient for plaque visualization of large and static arteries, such as carotid arteries.[3,4] Moreover, following the introduction of plaque imaging with non-contrast T1-weighted imaging (T1WI), many investigators have speculated that a hyperintense plaque (HIP) on non-contrast T1WI indicates the presence of mural or intraplaque haemorrhage containing methemoglobin.[5,6] However, because of their small dimensions and their continuous motion during data acquisition, the visualization of coronary plaques is challenging,[7–9] and the clinical significance of coronary HIP on T1WI remains unknown. Optical coherence tomography (OCT) is a new intravascular imaging modality with a high resolution of approximately 10–20 μm, which is 10-fold higher than that of intravascular ultrasound (IVUS). This new modality allows us to identify not only plaque rupture, but also fibrous cap thickness and intracoronary thrombus *in vivo*.[10–14] The aim of this study was to compare HIP on T1WI in cardiac magnetic resonance (CMR) with coronary plaque morphology assessed by OCT in patients with angina pectoris.

Methods

Patients

Thirty-nine patients with either stable or unstable angina pectoris, who had not undergone previous percutaneous transluminal coronary intervention (PCI) or coronary artery bypass grafting, were prospectively enrolled in this study between September 2010 and October 2011. Patients eligible for an early invasive strategy according to the ACCF/AHA Guideline (elevated levels of cardiac biomarkers, signs or symptoms of heart failure, and reduced left ventricular function) and those with contraindications to CMR were excluded from the study. All patients underwent CMR within 24 h before the day on which invasive coronary angiography (CAG) and OCT were performed. Of these patients, five patients who did not have significant stenoses after CAG and eight patients who did not undergo OCT examination before PCI were excluded from this analysis (five HIP and eight non-HIP).

Thus, 26 lesions from 26 patients, who had angiographically documented narrowing of at least 50% of the luminal diameter of a major coronary artery on CAG, were examined in this study. Pre-interventional OCT images were obtained for all patients with significant stenoses. In all patients, the procedure was performed on a native 'de novo' atherosclerotic lesion considered to be the culprit lesion. Unstable angina pectoris was diagnosed in 20 patients. Unstable angina pectoris was defined either as (i) new onset angina within 2 months after a previous bout; (ii) angina with a progressive crescendo pattern, with the anginal episodes increasing in frequency and/or duration; (iii) angina that occurred at rest; or (iv) angina occurring in the immediate post-infarct period. Stable angina pectoris was diagnosed in another six patients and defined as chest pain typical of cardiac ischaemia on exertion. Oral aspirin (100 mg) and clopidogrel (75 mg) were administered on admission. Moreover, patients with high risk were also treated with intravenous heparin, but no one had received thrombolytic agents.

The following data were collected: age, sex, and presence of risk factors [smoking and hypertension, as defined by the Joint National Committee VII; diabetes mellitus, as defined by the World Health Organization (WHO) Study Group; or hypercholesterolaemia, as defined by the Japan Atherosclerosis Society Guidelines]. The study was approved by the hospital ethics committee, and informed consent was obtained from all patients before the study.

CMR coronary plaque image acquisition

Coronary plaque imaging was performed using a 1.5-T MR imager (Achieva, Philips Medical Systems, Best, the Netherlands) with a 5-element cardiac coil. Nitroglycerin (0.3 mg) was administered sublingually immediately before taking images to obtain high-quality CMR images. First, to obtain detailed anatomic information, free-breathing steady-state free precession whole-heart coronary MR angiographic images were acquired, according to the method described in previous reports.[15,16] Briefly, initial survey images were focused around the heart, and the reference images were then obtained for sensitivity of parallel imaging. Transaxial cine MR images were then acquired using a steady-state free precession sequence with breath-holding (repetition time, 2.2 ms; echo time, 1.1 ms; flip angle, 60°; field of view, 350 × 350 × 10 mm; acquisition matrix, 160 × 160; cardiac phases, 100; SENSE factor, 3.0 in the anteroposterior direction; imaging time, 4.9 s) to determine the trigger delay time when the motion of the right coronary artery is minimum. Patient-specific acquisition windows were set during either the diastolic or systolic phase, depending on the phase of minimal motion of the right coronary artery. Coronary MR angiography was performed while patients were free-breathing by using a three-dimensional segmented steady-state free precession sequence with T2 preparation and radial k-space sampling in the Y–Z plane [repetition time, 3.7 ms; echo time, 1.8 ms; flip angle, 80°; SENSE factor, 2.0; number of excitations, 1; navigator gating window of ±2.0 mm with diaphragm drift correction; field of view, 300 × 255 × 120 mm (rectangular field of view, 85%); acquisition matrix, 240 × 240; reconstruction matrix, 512 × 512 × 160, resulting in an acquired spatial resolution of 1.25 × 1.25 × 1.5 mm reconstructed to 0.6 × 0.6 × 0.75 mm]. Diaphragm drift due to irregular respiration was corrected automatically by the diaphragm drift correction system provided by the MR system. The same value was set for the acquisition window as in the coronary plaque imaging.

Next, coronary plaque images were obtained when patients were breathing freely by using a three-dimensional T1WI inversion-recovery gradient-echo sequence with black-blood condition (inversion time 450 ms), fat-suppressed and radial k-space sampling in the Y–Z plane [repetition time, 4.4 ms; echo time, 2.0 ms; flip angle, 20°; SENSE factor, 2.5; number of excitations, 2; navigator gating window of ±1.5 mm with diaphragm drift correction; field of view, 300 × 240 × 120 mm (rectangular field of view, 80%); acquisition matrix, 224 × 224; reconstruction matrix, 512 × 512 × 140, resulting in an acquired spatial resolution of 1.34 × 1.34 × 1.7 mm reconstructed to 0.6 × 0.6 × 0.85 mm].[5,8,9]

CMR coronary plaque image analysis

Coronary CMR image analysis was performed by a single experienced cardiologist who was blinded to the plaque information obtained by OCT. If the target lesion was confirmed in the coronary MR angiography, the areas corresponding to the above site in the coronary T1WI CMR image obtained were carefully matched according to the surrounding cardiac and chest wall structures. Finally, the signal intensity of coronary plaque to cardiac muscle ratio (PMR; PMR was defined as the signal intensity of the coronary plaque divided by the signal intensity of the left ventricular muscle near the coronary plaque), as measured by placing a circular region of interest on a standard console of the clinical MR system, was calculated. Areas with PMR >1.0 were defined as HIP, whereas areas with PMR ≤1.0 were defined as non-HIP, according to the method described in a previous report.[8] The interobserver variability for measurement of the PMR performed in a random sample of patients previously was

5.8 ± 3.9% ($R^2 = 0.968$, $P < 0.0001$) and the κ-value for interobserver agreement in categorization of coronary plaque as high or non-high signal intensity was 0.88 (substantial).

OCT image acquisition

OCT imaging was performed before intervention and only after administration of 0.2 mg of intracoronary nitroglycerin. Thrombolysis or thrombectomy was not performed for any patient. The culprit vessel was identified on the basis of clinical, scintigram stress test, and angiographic data. In all SAP patients, the culprit vessel was considered to be the ischaemia-related vessel, which was shown ischaemia by exercise scintigram stress test. The culprit lesion site selected for the analysis was the image slice with the smallest lumen cross-sectional area. A 0.016-inch OCT catheter (ImageWire; LightLab Imaging, Westford, MA, USA) was advanced to the culprit lesion through a 3-F occlusion balloon catheter. In order to remove the blood from the field of view, the occlusion balloon was inflated to 0.6 atm at the proximal site of the culprit lesion, and Lactated Ringer's solution was infused into the coronary artery from the distal tip of the occlusion balloon catheter at 0.5 mL/s. The entire length of the culprit lesion was imaged using an automatic pullback device moving at 1 mm/s, and the OCT image clearly visualized the culprit lesion.

OCT image analysis

OCT image analysis was performed by two experienced observers blinded to the clinical information by using previously established criteria for OCT plaque characterization.[10–14] The presence of lipid, thin-cap fibroatheroma (TCFA), plaque rupture, calcification, and thrombus were evaluated within the 10 mm long culprit lesion segment (5 mm proximal and 5 mm distal to the culprit lesion site), according to the previous reports.[17,18] If there was discordance of diagnosis between the two observers, a consensus diagnosis was obtained using repeated off-line readings. When lipid was present in ≥2 quadrants in any of the images within a plaque, it was considered a lipid-rich plaque. Thin-cap fibroatheromas were defined as a lipid-rich plaque with a fibrous cap thickness measuring ≤65 μm. Plaque rupture was defined as an intimal interruption and cavity formation in the plaque. Calcification was defined as well-delineated, signal-poor regions with sharp borders. Thrombus was identified as an irregular high- or low-backscattering mass protruding into the lumen. Furthermore, thrombus type was classified as red or white thrombus by OCT, according to the previous reports.[12] Red thrombus was defined as high-backscattering protrusions with signal-free shadowing in OCT images. White thrombus was defined as signal-rich, low-backscattering projections in OCT images.

Statistical analyses

Continuous data are presented as mean ± SD. In case the data were normally distributed, the two groups were compared with a two-tailed unpaired Student's *t*-test. Otherwise, a Mann–Whitney *U*-test was used. Categorical variables were compared by two-sided Fisher's exact test. Concordance between investigators was assessed by κ-statistics. By using intracoronary thrombus detected by OCT as a gold standard, we calculated the sensitivities, specificities, and positive and negative predictive values of the HIP lesions on T1WI, according to the standard methods. All calculations were performed using SPSS software (version 11.5, SPSS Inc., Chicago, IL, USA) and *P*-values of <0.05 were considered significant.

Results

Table 1 shows the baseline clinical characteristics and angiographic findings in patients with HIP and non-HIP. Of 26 lesions from 26 patients, 16 (62%) had HIP lesions and 10 (38%) had non-HIP lesions. The PMR in HIP lesions was significantly higher than that in non-HIP lesions. There were no significant differences in patient clinical characteristics and angiographic findings between HIP and non-HIP lesions.

The relationship between HIP/non-HIP on T1WI and plaque morphology assessed by OCT is shown in *Table 2*. There were

Table 1 Clinical characteristics and angiographic findings

	HIP ($n = 16$)	Non-HIP ($n = 10$)	*P*-value
PMR	1.85 ± 0.89	0.76 ± 0.15	0.0001
Age (years)	70 ± 11	65 ± 10	0.261
Male	12 (75%)	4 (40%)	0.109
Diagnosis			0.644
SAP	3 (19%)	3 (30%)	
UAP	13 (81%)	7 (70%)	
Hypertension	11 (69%)	7 (70%)	0.999
Hypercholesterolaemia	10 (63%)	7 (70%)	0.999
Diabetes mellitus	6 (38%)	3 (30%)	0.999
Smoking	6 (38%)	2 (20%)	0.420
Culprit vessel			
LAD	9 (56%)	8 (80%)	
LCx	0 (0%)	0 (0%)	
RCA	7 (44%)	2 (20%)	
Percent diameter stenosis	75 ± 7	74 ± 10	0.698

Values are mean ± SD or *n* (percentage).
HIP, hyperintense plaque; PMR, signal intensity of coronary plaque to cardiac muscle ratio; SAP, stable angina pectoris; UAP, unstable angina pectoris; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery.

Table 2 OCT findings in hyperintense and non-hyperintense plaque

	HIP ($n = 16$)	Non-HIP ($n = 10$)	*P*-value
Lipid-rich plaque	12 (75%)	5 (50%)	0.234
TCFA	6 (38%)	2 (20%)	0.420
Plaque rupture	7 (44%)	3 (30%)	0.683
Calcification	9 (56%)	7 (70%)	0.683
Thrombus	12 (75%)	1 (10%)	0.004
Red thrombus	7 (58%)	0 (0%)	
White thrombus	5 (42%)	1 (100%)	

Values are *n* (percentage).
OCT, optical coherence tomography; HIP, hyperintense plaque; TCFA, thin-cap fibroatheroma (lipid, ≥2 quadrants and fibrous cap thickness, ≤65 μm).

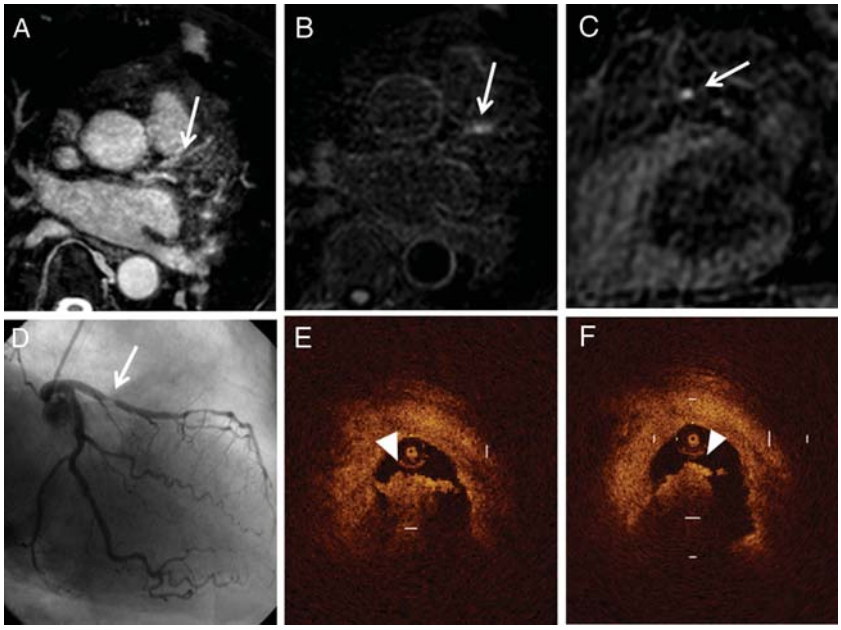

Figure 1 A representative case of HIP lesion on T1WI compared with plaque morphology on OCT. (*A*) Whole-heart coronary MR angiography shows severe coronary stenosis (indicated by arrow) in the proximal left anterior descending coronary artery (LAD). (*B* and *C*) Coronary T1WI CMR images (B: horizontal, C: sagittal). The area corresponding to the stenotic lesion shows hyperintensity (indicated by arrow). (*D*) CAG shows severe coronary stenosis (indicated by arrow) in the proximal LAD. (*E* and *F*) Images (E) and (F) show intracoronary thrombus (indicated by arrowhead) that was detected by OCT in the proximal (E) and mid (F) sites of the culprit lesion.

no significant differences in the frequency of lipid-rich plaque, TCFA, plaque rupture, and calcification between HIP and non-HIP lesions. In contrast, the frequency of thrombus was significantly higher in HIP lesions than in non-HIP lesions ($P = 0.004$). Thrombus on OCT was observed in 12 (75%) of the 16 lesions with HIP as opposed to 1 (10%) of the 10 lesions with non-HIP. Among 12 HIP lesions with thrombus, 7 had a red thrombus and 5 had a white thrombus. In contrast, one non-HIP lesion with thrombus had a white thrombus. Hyperintense plaque on T1WI as an indicator of intracoronary thrombus on OCT had a sensitivity of 92%, specificity of 69%, positive predictive value of 75%, and negative predictive value of 90%. Regarding OCT plaque characterization, interobserver agreement measured as a κ-statistic for TCFA ($\kappa = 0.77$), plaque rupture ($\kappa = 0.89$), calcification ($\kappa = 0.88$), and thrombus ($\kappa = 0.89$) was substantial. In contrast, interobserver agreement showed slightly lower concordance for lipid-rich plaques ($\kappa = 0.62$). A representative case of HIP lesion on T1WI compared with plaque morphology on OCT is shown in *Figure 1*. Whole-heart coronary MR angiography and CAG show severe coronary stenosis in the proximal left anterior descending coronary artery. The area corresponding to the stenotic lesion shows hyperintensity on T1WI. Intracoronary thrombus was detected by OCT in the culprit lesion. Furthermore, *Figure 2* shows one case of both HIP and non-HIP lesions within a single patient, although one lesion in the right coronary artery was not included in the overall statistical analysis. In this case, the HIP lesion in the left anterior descending coronary artery contained thrombus as well as TCFA and plaque rupture, and the other non-HIP lesion in the right coronary artery did not show those plaque morphologies.

Discussion

To the best of our knowledge, this is the first study to show that HIP on T1WI is directly associated with intracoronary thrombus detected by OCT imaging in patients with angina pectoris.

While coronary wall imaging by CMR is challenging due to the small size of coronary arteries and cardiac/respiratory motion, it has been applied in patients using breath-hold or free-breathing techniques. The introduction of plaque imaging with black-blood non-contrast T1WI has especially encouraged researchers in this field. There have been a few CMR studies of coronary plaque vulnerability compared with IVUS, multislice computed tomography (MSCT), or invasive CAG. Kawasaki *et al.*[8] reported that typical coronary HIP on T1WI was associated with a high frequency of ultrasound attenuation and positive remodelling, remarkably low CT density, and a high incidence of transient slow-flow phenomena by using both MSCT and IVUS. These features seem to represent vulnerable plaques. However, in their study, the presence of plaque rupture and thrombus was not assessed, because current IVUS technology does not allow a definitive distinction among some plaque morphologies, such as lipid core, thrombus, and plaque rupture. More recently, Jansen *et al.*[9] showed that HIP on T1WI identified intracoronary thrombus as detected by invasive CAG in patients with acute myocardial infarction. The diagnosis of thrombus by CAG is generally made on the basis of presumptive

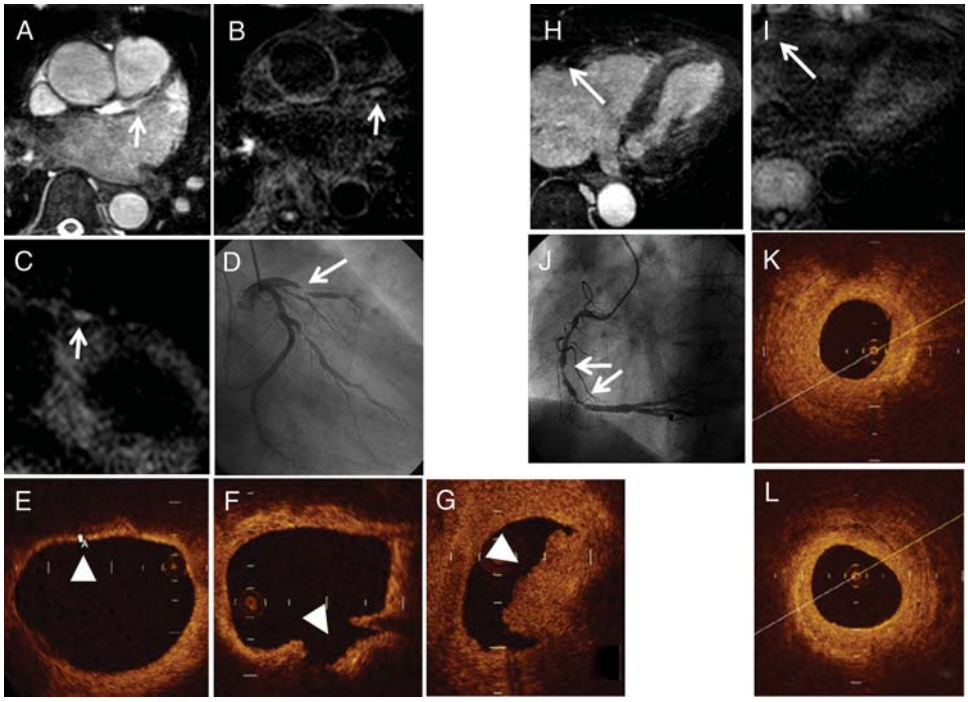

Figure 2 A case of both HIP and non-HIP lesions in a single patient. (*A* and *H*) Whole-heart coronary MR angiographic images show severe coronary stenoses (indicated by arrow) in the proximal LAD (*A*), and mid right coronary artery (RCA) (H). (*B*, *C*, *I*) Coronary T1WI CMR images. The area corresponding to the LAD lesion shows hyperintensity [indicated by arrow in B (horizontal) and C (coronal), and the other area corresponding to the RCA lesion shows non-hyperintensity (indicated by arrow in *I*)]. (*D* and *J*) CAG showing severe coronary stenoses (indicated by arrow) in the proximal LAD (D) and, the mid and distal RCA (J). (*E*–*G*) Images (E) to (G) show the OCT images in the LAD lesion. Thin-cap fibroatheroma (E), plaque rupture (F), and intracoronary thrombus (G) (indicated by arrowhead) were observed in the corresponding lesion with HIP. Images (*K*) (mid RCA) and (*L*) (distal RCA) show the OCT images in the RCA lesions. Thrombus was not found in the corresponding lesions with non-HIP.

evidence; therefore, they would also have underestimated intracoronary thrombus. Intravascular OCT, on the other hand, was recently developed as a high-resolution imaging device for plaque characterization that provides additional morphological information beyond that of IVUS images.[10–14] Several studies have already shown that OCT allows the identification of not only plaque rupture, but also TCFA and intracoronary thrombus *in vivo* more frequently compared with IVUS and angioscopy.[10–14] By using this technology, we have shown that the factor associated with HIP lesions on T1WI was intracoronary thrombus. The predictive power of HIP on T1WI in the detection of intracoronary thrombus on OCT was considerably substantial. However, four false-positive cases were observed in lesions with HIP. There was a time-lag of $\leq$24 h between CMR and OCT procedures in this study. The possibility cannot be excluded that intracoronary thrombus had disappeared during the time-lag. Nevertheless, our present findings add more detailed information on HIP lesions by CMR to the previous data by using IVUS or CAG. In the present study, the relation between HIP on T1WI and lipid-rich plaque, TCFA, or plaque rupture was not found. Further studies with more cases will be needed to confirm the present results.

Previous studies have shown that HIP formation on T1WI scans is due to methemoglobin production in the early stages of thrombus formation. When the thrombus is formed, red blood cells are trapped within a mesh of platelets and fibrin. Kelly *et al.*[19] reported that red blood cells containing methemoglobin produced T1 shortening, the extent of which was in proportion to the level of methemoglobin. This signal persists for several weeks, although the overall period is less than 6 months. The information obtained from the signal might provide data about thrombus characteristics, such as age and volume. At this stage, it is understood that OCT does not allow accurate quantification of thrombus volume, because some intracoronary thrombi produce extensive signal-free shadowing, which makes it impossible (or at least unreliable) to assess thrombus volume. In this patient population, among 12 HIP lesions with thrombus, 7 had a red thrombus and 5 had a white thrombus. In contrast, one non-HIP lesion with thrombus had a white thrombus. Further studies are needed to clarify the relationship between thrombus characteristics and HIP on T1WI.

What is the clinical implication of identifying intracoronary thrombus by non-contrast T1WI in CMR in human atherosclerotic lesions? This method is completely non-invasive and easily repeatable because of lack of ionizing radiation, contrast injections, or a vascular access. From this point of view, T1WI in CMR is best suited for the detection of patients with subclinical vulnerable

plaques. Moreover, there is increasing evidence that atherosclerotic disease is a chronic inflammatory process with the involvement of many arterial segments, including coronary and carotid arteries, despite the fact that a single localized culprit lesion may cause an acute cardiovascular event. T1-weighted imaging in CMR is a promising tool for the detection of multiple vulnerable plaques associated with thrombus. One of the goals of our future studies will be to investigate whether the presence of HIP on T1WI in non-ischaemic-related coronary or carotid arteries is associated with subsequent development of acute cardiovascular events. Finally, if HIP on T1WI can be shown to be limited to a finite time span, its presence could be used to accurately identify recent plaque thrombosis. This information may have several novel clinical implications in the field of coronary intervention, e.g. it can be used to predict slow-flow/no-flow phenomena or the age of the chronic total occlusion. Furthermore, although patients with elevated levels of cardiac biomarkers, signs, or symptoms of heart failure, or ECG changes should be considered for early invasive intervention (early CAG), differential diagnosis and treatment of the remaining patients remain challenging in emergency triage. This non-invasive thrombus-detection technique may be useful for further risk stratification and for obtaining prognostic information in the high-risk group.

Limitations

This study has several limitations. First, coronary thrombectomy was not performed for the identification and examination of intracoronary thrombus. Therefore, there was no evidence based on pathohistological findings. For coronary MR, however, OCT is the generally accepted method and is acknowledged as one of the most reliable tools for assessment of coronary plaque characterization, although this modality is not routinely used in the clinical setting. We consider, therefore, that the quality of both coronary MR and OCT data obtained by this approach is sufficiently high to validate our conclusion. Secondly, patients eligible for an early invasive strategy and without significant stenoses were excluded from this study. Moreover, there were no patients with the culprit lesion in the left circumflex coronary artery. Therefore, our results were limited by selection bias and may not apply to such patients. Thirdly, in the present study, a fixed inversion time (450 ms) was used for black-blood condition. Strictly speaking, however, the patient-specific (heart rate-specific) inversion time should be adjusted to null blood signal. Finally, in the present CMR and OCT analyses, the number of patients examined was very small. This may have limited the statistical power, making all comparisons descriptive.

Conclusions

This study shows that the HIP lesions on T1WI in patients with angina pectoris relate to the presence of intracoronary thrombus as detected by OCT imaging. This non-invasive technology appears to be a promising tool for identifying vulnerable plaques associated with thrombus.

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Conflicts of interest: none declared.

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