Atherosclerotic Coronary Plaque Development Visualized by In Vivo Coronary Imaging

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In the past decades, coronary imaging has evolved as a valuable adjunct to angiography, providing scientific insights into vascular biology and practical guidance by direct visualization of atherosclerosis and other pathologic conditions within the vessel walls. Especially with intravascular ultrasound (IVUS), the signal is able to penetrate below the luminal surface, so the entire cross-section of an artery, including the complete thickness of the plaque, can be imaged in real-time. On the other hand, optical coherence tomography (OCT) has been offering higher image resolution of both the plaque and the luminal surface. These technologies offer the opportunity to gather diagnostic information about the process of atherosclerosis and to directly observe the effects of various interventions on the plaque and arterial walls. IVUS has proven itself to be a practical and useful tool in the evaluation and optimal guidance of interventional vascular medicine. In this review, we detail the current modalities of coronary imaging and their usefulness in the diagnosis and management of patients with high-risk coronary plaques.

Key Words: Atherosclerosis; Coronary imaging; Intravascular ultrasound; Plaque

The pathophysiology of acute coronary syndrome (ACS) has been clarified histologically, physiologically, and via molecular biology. Pathological studies have revealed that rupture of lipid-rich plaque, followed by thrombus formation, is the main mechanism of acute coronary occlusion in 70–80% of patients with ACS, because the rupture of the thin fibrous cap allows platelets to contact the highly thrombogenic necrotic core (NC). The precursor of the ruptured plaque is a thin-cap fibroatheroma (TCFA). Recent advances in invasive coronary imaging techniques (e.g., intravascular ultrasound [IVUS], optical coherence tomography [OCT], and coronary angioscopy [CAS]) have all shown that rupture-prone plaques have a large NC and a thin fibrous cap. We do not have enough evidence yet about the natural history of atherosclerotic plaques and TCFA. On the other hand, as regards the prevention of cardiovascular (CV) events, stabilization and regression of high-risk plaques are useful imaging surrogate endpoints, and IVUS plaque progression/regression studies have proposed various promising pharmacologic interventions in the past. Currently, interest in systemic and focal inflammation in patients at risk has been refocused because anti-inflammatory intervention (e.g., interleukin 1β antibody) has shown a significant reduction in CV events. In this review article, we will summarize the following: (1) the timeline of atherosclerotic development and characteristics of plaque prone to ACS; (2) the pan-coronary distribution of high-risk plaque in ACS patients; (3) pharmacological interventions aimed at plaque regression/stabilization; and (4) future directions in anti-inflammatory strategies focusing on intraplaque inflammation.

Timeline of Atherosclerotic Development and Effect of Coronary Spasm

Traditionally, pathological classification of coronary atherosclerotic plaques has divided plaques into 6 types and indicated pathways in evolution and progression of human atherosclerotic lesions (Figure 1). As the atherosclerotic stage advances, changes in lesion morphology occur primarily because of increasing accumulation of lipid content from Type I to Type IV. Atheromatous lesions (Types IV and Va) are especially prone to disruption of the lesion surface. Furthermore, Type VI lesions generally have a similar underlying morphology to Type IV or V lesions. Considering the natural history of high-risk plaque (serial change in lesion morphology), the existence of a loop between Types V and VI has been speculated and hypothesized that the loop illustrates the mechanisms underlying plaque progression (increase in intimal thickness) when thrombotic deposits form on their surfaces. This consideration was derived from cross-sectional pathological observations, devoid of imagination. Kubo et al re-examined the natural history study with the use of virtual histology-IVUS (VH-IVUS) and validated the dynamic nature of coronary artery lesion morphology. Lesions were classified based on plaque composition: pathological intimal thickening (PIT);
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had a close and positive relationship with the coronary constrictor response to acetylcholine, which is known to depend on endothelial nitric oxide (NO) activity.

Patients with coronary vasospasm have diffusely thickened fibrous-dominant coronary plaque compared with non-spasm patients (Figure 4).

A decrease in endothelial NO activity may be one of the underlying mechanisms responsible for the intimal thickening in spastic coronary arteries. Also, endothelial injury caused by coronary vasospasm could, in turn, induce coronary vasospasm. Such a vicious cycle may amplify this sequence of events, thereby leading to further progression of intimal hyperplasia and the development of atherosclerosis, suggesting the role of vasospasm in the development of atherosclerosis.

VH-IVUS-derived TCFA (VH-TCFA); thick-capped fibroatheroma (ThCFA); fibrotic plaque; and, fibrocalcific plaque

Figure 1. Classification and timeline of coronary atherosclerotic plaques. (Left) Six patterns of coronary atherosclerotic plaque. The morphology of the intima ranges from adaptive intimal thickening always present in this lesion-prone location to a Type VI lesion in advanced atherosclerotic disease. (Right) Pathways in the evolution and progression of human atherosclerotic lesions. From Type I to Type IV, changes in lesion morphology occur primarily because of increasing accumulation of lipids. The loop between Types V and VI illustrates how lesions increase in thickness when thrombotic deposits form on their surfaces. (Reproduced with permission from Stary HC, et al.31)

Figure 2. Plaque classification by virtual histology-intravascular ultrasound (VH-IVUS). (A) Pathological intimal thickening. (B) VH-IVUS-derived thin-capped fibroatheroma. (C) Thick-capped fibroatheroma. (D) Fibrotic plaque. (E) Fibrocalcific plaque. (Reproduced with permission from Kubo T, et al.32)
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In terms of detection sensitivity of different imaging modalities, plaque rupture and thrombus were more frequently found in acute MI lesions using OCT compared with other invasive imaging techniques. Plaque ruptures were detected in 73% by OCT, in 40% by IVUS, and in 47% by CAS (P=0.021). Thrombi were found in 100% by OCT, 33% by IVUS, and 100% by CAS (P=0.001).

The traditional paradigm is that the mechanism of plaque rupture is equivalent regardless of the clinical presentation of ACS. It is not clear though why some plaque ruptures lead to ST-segment elevation MI (STEMI), whereas others cause non-ST-segment elevation ACS (NSTEACS). Enrolling 158 consecutive ACS patients whose culprit lesions were imaged by pre-intervention IVUS (STEMI=81; NSTEACS=77), our group compared the IVUS and angiographic findings of the culprit lesions, and clinical characteristics. Thrombus was more common in STEMI than in NSTEACS, but the angiographic lesion complexity SYNTAX score was lower in STEMI. In patients with STEMI, culprit lesions were more hypoechoic, and the incidences of plaque rupture, attenuation and “microcalcification” were all significantly higher. Moreover, the maximum areas of the ruptured cavity and the echolucent zone and the arc of microcalcification were

Definition of plaque rupture: the presence of a smooth, erosive or ulcerative surface; the absence of a visible luminal lipin has high sensitivity and specificity for the diagnosis of plaque rupture (96% and 97%, respectively).

Characteristics of Plaque Most Prone to ACS

The most common cause of ACS is rupture of an atherosclerotic lesion containing a large NC and a thin fibrous cap, followed by acute luminal thrombosis. Similar to previous pathological observations, a 3-vessel IVUS trial studied 122 patients with acute myocardial infarction (MI) and 113 with stable angina, and culprit-lesion, infarct-related plaque rupture was more common in patients with acute MI (66%) than in patients with stable angina (27% of target lesions, P<0.001). Plaques prone to rupture (i.e., "vulnerable" plaques) are reported to have the following morphological features by pathological and coronary imaging studies: (1) positive remodeling, (2) thinner fibrous cap: <65 μm at minimum thickness; (3) macrophage infiltration especially in the thin fibrous cap; (4) a large lipid/NC often containing hemorrhage and/or calcification; (5) speckled or diffuse calcification (not enough to increase plaque stability although the absence of any calcium is also rare in rupture-prone plaques); and, (6) abundant intraplaque hemorrhage. Regarding lesion classification according to VH-IVUS, fibroatheromas are defined by the presence of >10% confluent NC. If more than 30 degrees of the NC abuts the lumen in 3 or more consecutive frames, the fibroatheroma is classified as a TCFA.

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Since Rioufol et al reported that most ruptured plaques were at sites remote from the presumed culprit lesion, 15 enthusiasm for a "pan-coronary syndrome" concept of ACS has built up among investigators. In fact, our group significantly greater in STEMI compared with NSTEACS. Quantitative IVUS analysis showed that vessel and plaque area were significantly larger at the site of minimum lumen area (MLA). Morphological features (outward vessel remodeling, plaque buildup and IVUS vulnerability of culprit lesions) seem to relate to the clinical presentation in patients with ACS (Figure 5).

**Figure 4.** Dynamic nature of coronary atherosclerotic plaques. (Left) Effect of coronary vasospasm. Especially in the early stage of atherosclerotic development, coronary vasospasm generates a vicious cycle of endothelial dysfunction, NO synthesis impairment and thickened intimal formation. (Right) Comparison of intimal tissue components between patients with and without coronary spasm. The patients with coronary vasospasm have diffusely thickened fibrous-dominant coronary plaque. NO, nitric oxide. (Reproduced with permission from Tsujita K, et al.)

**Figure 5.** Positive remodeling and plaque vulnerability between STEMI- and NSTEACS-prone vessels. NSTEACS, non-ST-segment elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction. (Reproduced with permission from Takaoka N, et al.)

**Pan-Coronary Distribution of High-Risk Plaque in ACS Patients**

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Because the pathogenesis of ACS is coronary plaque rupture and erosion of the intima followed by thrombus formation and further platelet reaction in the coronary artery, as described before, and because the pan-coronary distribution of high-risk plaques is in ACS patients, the management of coronary risk factors and plaque stabilization/regression are important to improve CV outcomes in ACS patients. Although coronary plaque regression is just one of the morphological parameters detected by different imaging modalities, Dohi et al. demonstrated that plaque regression determined by volumetric IVUS, over a period of 6 months, was associated with a lower rate of CV events among patients with ACS, suggesting that plaque regression could be a surrogate marker of future CV events.

Towards achieving coronary plaque regression, low-density lipoprotein-cholesterol (LDL-C) dependency (“the lower, the better” concept) existed in the statin era. Whether LDL-C dependency towards plaque regression derived from the intensity of the statin therapy (“statin hypothesis”) or from the achieved LDL-C level (“LDL hypothesis”) is unknown, because most studies tested the...
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Additionally, growing evidence supports the concept that ezetimibe or PCSK9 inhibitors are acceptable in those who are unable to reach the target level of LDL-C or who are intolerant to statins after ACS.

It is now expected that the management of lipid-lowering therapy will move into a new era.

Contemporary imaging studies have shed new light on the mechanisms of ACS. In their review article, Crea and Libby propose segmenting coronary artery thrombosis caused by plaque rupture into cases with and without signs of concomitant inflammation. This distinction may have substantial therapeutic implications, because direct anti-inflammatory interventions for atherosclerosis are emerging. Ridker et al accomplished an epoch-making randomized, double-blind trial of canakinumab, a therapeutic monoclonal antibody targeting interleukin-1β (CANTOS trial), and showed that anti-inflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent CV events than placebo, independent of the level of lipid lowering.

Future Directions of Anti-Inflammatory Strategies Focused on Intraplaque Inflammation

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Figure 7. Relationship between achieved low-density lipoprotein-cholesterol (LDL-C) levels and median change in percent atheroma volume in prior intravascular ultrasound (IVUS) trials and the PRECISE-IVUS trial. There has been a close correlation between achieved LDL-C levels and median change in percent atheroma volume in several intravascular ultrasound trials ($r^2=0.926$). Even in the stable angina pectoris cohort of the PRECISE-IVUS trial, the plots are located in range with the preexisting regression line. In contrast, the plot is located far below the line in the atorvastatin/ezetimibe combination arm of the acute coronary syndrome cohort of the PRECISE-IVUS trial, but still in range with the line in the atorvastatin monotherapy arm. REVERSAL, Reversal of Atherosclerosis With Aggressive Lipid-Lowering; ASTEROID, A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; SATURN, Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin. (Reproduced with permission from Tsujita K, et al.)

The 2016 ACC Expert Consensus or European guidelines show the consideration of ezetimibe combined with statins if the LDL-C level has not reached the target level with a high tolerable dose of statins. Treatment with statins is widely accepted as the first-line lipid-lowering therapy, as demonstrated by many trials and meta-analyses. Although there are different concepts between “fire-and-forget” and “target-to-treat,” early and intensive administration of statins consistently contributes to the reduction in CV events after ACS. Additionally, growing evidence supports the concept that ezetimibe or PCSK9 inhibitors are acceptable in those who are unable to reach the target level of LDL-C or who are intolerant to statins after ACS. It is now expected that the management of lipid-lowering therapy will move into a new era.
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substantiated the causal contribution of inflammation to atherosclerotic events. Recent high-resolution OCT imaging can visualize the macrophage accumulation inside the plaque. Next to aggressive lipid-lowering therapy, an anti-inflammatory strategy is a promising option in order to regress/stabilize vulnerable plaques.

Conclusions

We expect that a more mechanistic approach to the categorization of ACS onset will provide a framework for better triage, future tailoring of medications and more efficient, personalized therapy for patients.

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Conflict of Interest Disclosures

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