Identification and Treatment of Vulnerable Plaque

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It is now well recognized that the rupture of vulnerable plaque, which consists of an atheromatous plaque core covered by a thin fibrous cap with ongoing inflammation, is a major cause of thrombus formation leading to the development of acute coronary syndrome. Several diagnostic techniques, including vascular imaging and serologic markers, are clinically available or currently under investigation for the detection of vulnerable plaque. A combination of several diagnostic modalities might allow effective screening of individuals at high risk for future cardiovascular events. Plaque stabilization with pharmacologic interventions—statins, ß-blockers, and angiotensin-converting enzyme inhibitors—might effectively prevent the development of acute coronary syndromes caused by plaque disruption.

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Key words: Acute coronary syndromes • Plaque • Intravascular ultrasound • Angioscopy • Optical coherence tomography • Thermography • Spectroscopy

Atherosclerotic cardiovascular disease is the leading cause of death in the United States and in the majority of Western countries. Each year, more than 750,000 people in the United States experience a sudden cardiac event, such as an acute coronary syndrome or sudden cardiac death.[1] Acute coronary syndrome is often associated with thrombus formation within a coronary artery. Over the past decade, it has become recognized that rupture of a vulnerable plaque, which consists of an atheromatous plaque core covered by

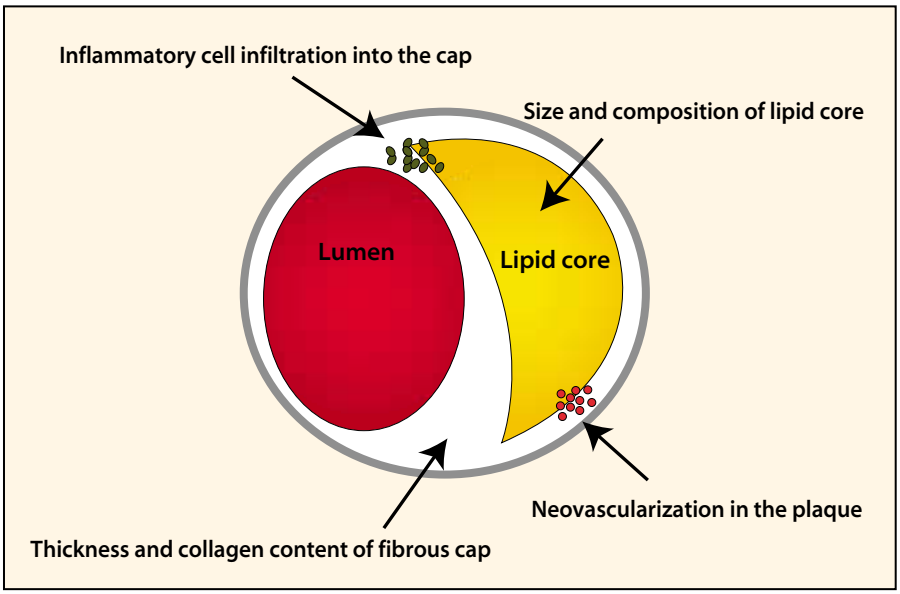

Figure 1. *Schematic diagram of potential morphologic features of vulnerable plaque.*

a thin fibrous cap with ongoing inflammation, is a major cause of thrombus formation leading to acute coronary syndrome. Several autopsy studies have demonstrated that nearly 70% of coronary thrombi occur at sites where the fibrous cap covering an atheromatous plaque has ruptured.[2,3] Coronary thrombi have also been observed overlying nonruptured plaques with superficial endothelial erosion.[4] However, the occurrence of acute cardiac events is often unpredictable because they frequently develop without precedent clinical anginal symptoms. Moreover, although coronary angiography has been the gold standard for diagnosis of coronary artery disease, it provides merely a negative image of internal lumen and lacks the capability to adequately evaluate the vessel wall where an atherosclerotic plaque develops. In fact, previous studies analyzing serial angiograms from patients presenting with acute coronary syndrome have suggested that in nearly two thirds of the culprit lesions, the coronary angiogram obtained weeks or months before the acute event demonstrated only a minor degree of stenosis, usually less than 50% narrowing of the lumen diameter.[5,6] Recently, much research and effort has gone into the characterization and identification of those coronary atherosclerotic plaques that are at high risk of causing an acute coronary syndrome. Accordingly, a variety of potential alternative diagnostic and treatment strategies are under investigation either in clinical or preclinical settings. This article will review current developments in the pathologic understanding of vulnerable plaque, as well as new diagnostic and treatment modalities.

Pathohistologic Insight into Vulnerable Plaque

The risk of plaque rupture is related to two factors: the intrinsic individual plaque character that influences vulnerability and an extrinsic force triggering plaque disruption.[7] In past pathohistologic studies, atherosclerotic plaque prone to rupture was demonstrated to possess several unique structural characteristics (Figure 1). In general, atherosclerotic plaque at high risk for rupture contains large lipid pool(s) covered with a thin fibrous cap with ongoing inflammation and neovascularity.[8,9]

Plaque Characteristics Affecting Its Vulnerability

In a previous postmortem study examining morphometric features of atherosclerotic plaque from 17 infarct-related arteries, Gertz and Roberts[8] demonstrated an approximately 30% lipid component in the 39 segments of atheromatous plaque rupture, compared with only 5% lipid component found in the 229 segments without plaque rupture. In addition, the lipid components might affect the stability of the core. Large amounts of cholesteryl ester might soften the lipid core, whereas cholesterol crystals increase the stiffness of plaque.[10] Another important aspect of an atheromatous core is its thrombogenicity. In fact, a lipid-rich core has been suggested as the most powerful thrombogenic plaque type because it contains macrophages that produce tissue factor, as well as thrombogenic lipid forms, such as lipoprotein(a).[11,12] Thus, when exposed to blood, plaque with large amounts of lipid core can be at high risk of encouraging thrombus formation to potentially occlude the vessel.[13,14]

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Stability of the fibrous cap is another important factor in determining plaque vulnerability. Thickness and collagen content are crucial determinants of whether the fibrous cap can maintain its structural integrity. The intact fibrous cap usually includes more collagen and smooth muscle cells, which synthesize collagen in the plaque.[15,16] Thinning of the fibrous cap, generally considered to be a precursor of plaque rupture, is often seen at the shoulders of the lesion and is particularly associated with eccentric plaque formation. It has been suggested that circumferential stress is greater at the shoulders of lesions and increases critically when cap thickness is less than approximately 150 μm.[10,15] Richardson and colleagues[17] examined 85 histologic sections of culprit lesions obtained from 85 patients who had died from coronary thrombi and found that 71 lesions (84%) had a lipid pool within the ruptured plaque. Furthermore, the lipid pool was eccentric in 67 of 71 lesions, with 42 lesions with eccentric lipid pool (63% of 67 lesions with eccentric plaque and 59% of 71 lesions with plaque rupture) rupturing at the junction of the fibrous cap with the adjacent normal intima (shoulder of the lesion). Interestingly, infiltration of lipid-filled foam cells was observed in 28 lesions with plaque rupture at the lesion shoulder (67% of 42 lesions) as well as in the 25 lesions with plaque rupture at the nonlesion shoulder (86% of 29 lesions).

These observations indicate that ongoing inflammation also plays an important role in the weakening of the fibrous cap. One postmortem study of 20 thrombosed coronary artery segments demonstrated an infiltration of inflammatory cells, predominantly by macrophages and T lymphocytes, at the site of plaque rupture or erosion, regardless of the plaque component.[18] In the same study, immunohistochemical examination also revealed the activation of these inflammatory cells, indicating ongoing disease activity. At the cellular level, these activated inflammatory cells synthesize certain cytokines and matrix-degrading proteins, which results in weakening of the fibrous cap framework of the plaque.[19] For instance, activated T cells produce interferon (IFN)-γ, which inhibits collagen synthesis and smooth muscle cell proliferation at the fibrous cap. IFN-γ also activates macrophages and macrophage-derived foam cells, which produce matrix-degrading metalloproteinases, leading to breakdown of the fibrous cap matrix.[19,20] Plaques prone to rupture show depletion in the numbers of smooth muscle cells in the plaque cap. Indeed, an inverse relationship between increased numbers of inflammatory cells and reduced numbers of smooth muscle cells exists and seems to be related to strain characteristics, which promote rupture.[21,22]

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Finally, atherosclerotic plaques often show increased adventitial and intimal neovascularization, particularly at the culprit lesion of an acute coronary syndrome.[9,23] Increased vascularity might provide a source for recruitment of inflammatory cells into the plaque. Rupture of the thin-walled fragile microvessel in the plaque might lead to hemorrhage, causing secondary plaque expansion or rupture[22,24,25] and plaque growth.[26]

Extrinsic Factors Triggering Plaque Disruption

The vessel wall is constantly exposed to the stress generated by a variety of mechanical and hemodynamic forces that might trigger plaque rupture. From the luminal side, the vessel wall constantly receives circumferential stress that increases with higher blood pressure and larger lumen diameter and decreases with thinner wall thickness.[27] In diseased arteries with luminal irregularities and heterogeneous plaque components, distribution of circumferential stress might be uneven along the lumen wall, which creates a focal point with critically higher circumferential stress. Computer modeling studies have demonstrated that higher circumferential stress tends to occur near the shoulders of the plaque, specifically at lesions containing a lipid pool of eccentric shape.[17] Another study, which examined 12 histologic specimens from culprit lesions causing plaque rupture in fatal myocardial infarctions, further demonstrated that most of the plaque ruptures (10 of 12, 83%) occurred at sites close to the point with high circumferential stress, including seven

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(58%) at the point with maximum circumferential stress.[28]

Several anatomic and physiologic conditions might have an impact on the process of plaque rupture. Pulsatile fluctuations of blood pressure and cardiac motion might cause repetitive stretching, bending, and flexing that impose chronic stress on the vessel wall, leading to plaque fatigue, weakening of the fibrous cap, and abrupt plaque rupture.[29] Stresses resulting from shear force over the plaque surface, turbulence, and coronary vasospasm also might serve to destabilize the plaque.[28] Furthermore, increases in arterial pressure during states of emotional stress, physical exertion, or a sudden surge in sympathetic activity might cause an abrupt change of hemodynamic status and accentuation of circumferential stress at certain points along the lumen wall, triggering plaque rupture.[30,31]

Plaque Erosion and Coronary Thrombus

Plaques with superficial endothelial erosion might be associated with coronary thrombi, even without evidence of plaque rupture.[4,32] These conditions are particularly associated with young victims of sudden death, smokers, and women. Unlike ruptured plaque, eroded plaque is rich in proteoglycans and smooth muscle cells, without a superficial lipid core and with less evidence of inflammation. Although the precise mechanisms of thrombosis in this scenario are unknown, alteration of the systemic thrombogenic state enhanced by several conditions, including platelet agreeability, increased circulating tissue factor levels, and a depressed fibrinolytic state, might trigger this condition.[24]

Table 1
Emerging Diagnostic Techniques for the Detection of Vulnerable Plaque

Imaging technique	Resolution	Inflammation	Current status
Invasive			
Intravascular ultrasound	~100–150 µm	(–)	CS/CA
Angioscopy	UK	(–)	CS/CA*
Optical coherence tomography	10 µm	(+)	CS
Intravascular thermography	0.5 mm	(+)	CS
Spectroscopy	NA	(+)	PCS
Intravascular MRI	160 µm	(+)	PCS
Noninvasive			
MRI	300 µm	UK	CS/CA
Spiral CT	>500 µm	(–)	CS/CA
Serum markers	NA	(+)	CS/CA

CS, clinical studies; CA, clinically approved for commercial use; UK, unknown; CA*, clinically approved commercial use in Japan; PCS, preclinical studies; NA, not applicable; MRI, magnetic resonance imaging; CT, computed tomography. Adapted, with modification, from MacNeill et al.[49]

Identification of Vulnerable Plaque

Because angiography provides only a contrast-filled luminal silhouette, it tends to underestimate the severity of coronary atherosclerosis. Accordingly, the development of novel imaging techniques has become one of the most important research areas in the field of vulnerable plaque and has enabled vessel wall visualization and characterization of plaque components. Because emerging evidence suggests inflammation as a crucial factor for the development and disruption of vulnerable plaque, serum inflammation markers have been investigated as a potential modality for screening individuals at high risk for developing future cardiac events. These diagnostic modalities are summarized in Table 1.

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Invasive Approaches

Intravascular Ultrasound. Intravascular ultrasound (IVUS) provides tomographic visualization of vessel wall structures in vivo and allows more precise assessments of lumen narrowing and vessel remodeling. In the setting of an acute coronary syndrome, IVUS can visualize culprit lesion morphology (eg, presence of plaque rupture and thrombus) that has been suggested by histologic observation (Figure 2). Several retrospective IVUS studies have demonstrated outward (positive) remodeling, also known as the *compensatory enlargement* of a vessel, as one of the characteristic features of culprit lesions in acute coronary syndrome.[23,33,34] This observation has been confirmed by a recent IVUS study that followed patients in a prospective manner.[35] In this study, Yamagishi and colleagues reported

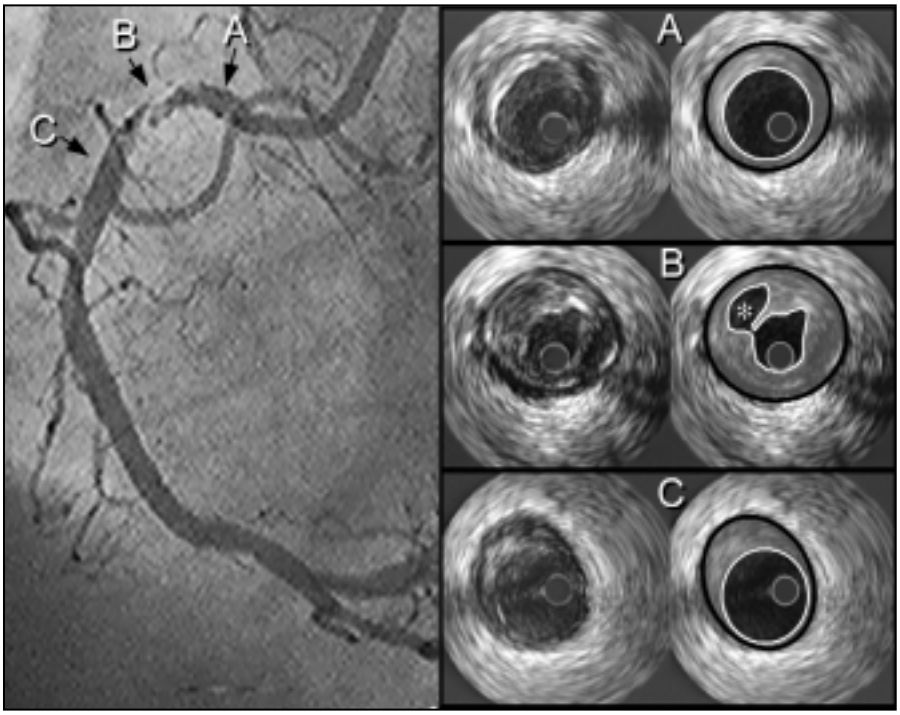

Figure 2. *Representative case of ruptured plaque in patients presenting with unstable angina pectoris.* **Left:** *Right coronary angiography showing severe stenosis with irregular lumen border at proximal segment.* **Right:** *Cross-sectional intravascular ultrasound (IVUS) images. (A) Proximal reference segment, (B) culprit segment, and (C) distal reference segment. In the annotated IVUS panels (right side, A–C), the outer black circle indicates the external elastic lamina (EEM), and the inner white circle indicates the lumen. The EEM area (black circle) is larger in the culprit segment compared with the proximal and distal reference segments, which suggests outward remodeling in the culprit lesion segment. The asterisk in the culprit segment indicates ruptured lipid core.*

that angiographically nonsignificant lesions that subsequently precipitated an acute coronary syndrome had larger eccentric plaques compared with those without subsequent event development. Furthermore, outward remodeling was observed in 60% of the lesions that developed acute coronary syndrome. Moreover, recent pathologic studies of peripheral and coronary arteries have also indicated the close link between positive vessel remodeling and histopathologic characteristics of plaque vulnerability, such as size of the lipid-rich core and the degree of plaque inflammation.[36–38]

Although conventional IVUS is an effective technique for producing structural tomographic images of the arterial wall, its currently limited image resolution (approximately 100–150 μm) makes difficult the accurate identification of plaque components, such as a lipid core and fibrofatty atheroma, both of which can be expressed as the same grayscale imaging. Accordingly, several alternative IVUS approaches in which radiofrequency signals are used (IVUS-RF) are currently under development to more precisely identify plaque composition.

IVUS-RF analysis provides objective indices of tissue characterization and thus has the potential to improve the evaluation of plaque components, such as a lipid core. One ex vivo study has indicated that an analysis of pertinent statistical parameters of the IVUS-RF envelope can identify a lipid core of atheromatous plaque with greater sensitivity and specificity when compared with conventional IVUS tomographic imaging.[39] Recently, in vivo application of the integrated backscatter of IVUS-RF has been investigated, and one study demonstrated that a color-coded mapping of atheromatous plaque based on the different backscatter signals among the tissue types (virtual histology) might facilitate the precise evaluation of plaque components.[40]

With IVUS-RF signals acquired at different intravascular pressures, *intravascular elastography* can measure tissue strain, which reflects a mechanical property of the structure and composition of the vessel wall. In vitro experiments with postmortem coronary artery specimens have shown this modality to be feasible for tissue characterization of fibrous tissue, fibrofatty tissue, and fatty tissue by comparing the measured strain in each tissue type. IVUS elastography might also identify vulnerable plaque according to its own definition of vulnerability, that is, the region with the highest strain at the lumen surface with adjacent low-strain region. With this definition, IVUS elastography detected histologically vulnerable plaque with 88% sensitivity and 89% specificity in vitro.[22] Although IVUS elastography might serve as a useful complementary tool to conventional IVUS, further in vivo study will be necessary to confirm these preliminary results

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ex vivo. In addition, ultrasound-related artifacts, such as acoustic shadowing caused by superficial calcium, might limit detailed characterization of vessel wall composition.

Angioscopy. Intracoronary angioscopy allows direct visualization of the plaque surface and can be a useful tool to assess plaque characteristics by evaluating color and morphologic features of the plaque surface, including tears, ulcerations, and fissures, as well as to identify the presence of thrombus. Generally, angioscopic xanthomatous yellow plaques indicate a high concentration of cholesterol-laden crystals seen through a thin fibrous cap and are considered to be associated with the development of acute coronary syndrome, whereas white plaques have a thick fibrous cap and thus are considered stable.[41] Yellow plaques are also observed in all 3 major coronary arteries, which suggests that the development of these plaques prone to acute coronary syndrome is a pan-coronary process.[42]

Limitations of current angioscopic systems include the need to create a blood-free field, either by occlusion of proximal vessels or continuous saline flushing, both of which might cause complications. Also, interpretation of plaque color is subjective, and the development of a computed diagnosis technique might be required to enable objective and standardized interpretation.

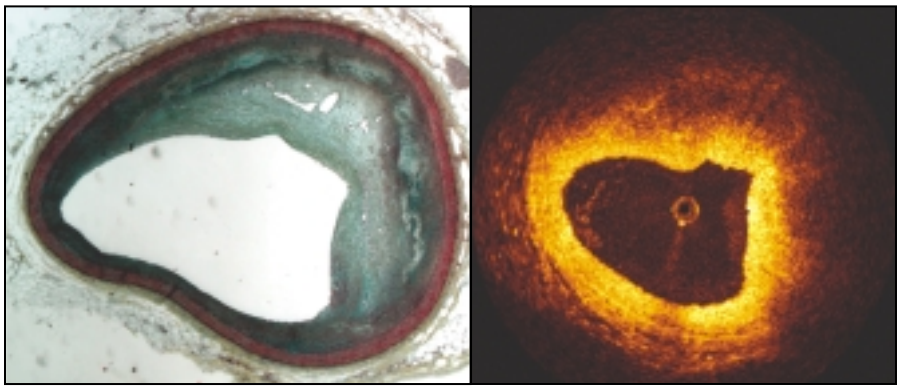

Figure 3. *Representative optical coherence tomographic image of vulnerable plaque in human coronary artery, showing a large lipid core covered by a thin fibrous cap. Image courtesy of Light Lab (Boston, MA).*

Optical Coherence Tomography. Intravascular optical coherence tomography (OCT) is a new imaging technique that uses optical echoes of an infrared light source directed at the vessel wall to create high-resolution, tomographic images of a vessel (Figure 3). The resolution of OCT ranges from 2 mm to 10 mm and allows superior depiction of the thin fibrous caps responsible for plaque vulnerability, as well as improved visualization of plaque components, such as regions of lipid-rich plaque, compared with IVUS.[43] In fact, OCT characteristics of various plaque types have been demonstrated to correlate well with ex vivo histologic characteristics, yielding a sensitivity and specificity of 92% and 94%, respectively, for lipid-rich plaque; 95% and 100% for fibrocalcific plaque; and 87% and 97% for fibrous plaque.[44] Furthermore, a recent postmortem study examining 26 lipid-rich atherosclerotic arterial segments demonstrated a significant positive correlation between OCT signal and histologic quantification of macrophages within the fibrous cap, as identified by the area positive for CD-68 staining, which indicates the ability of this technology to quantify macrophage infiltration within the fibrous cap.[45]

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Current limitations of OCT are related to features of a light-based energy source, including poor tissue penetration and blood interference. Therefore, like angioscopy, this modality requires saline injection with or without proximal vessel balloon occlusion to displace blood to avoid reduction of image quality. However, although the current penetration depth is limited to approximately 2 mm, this depth is sufficient to assess plaque vulnerability because it is predominantly characterized by the morphology of the luminal surface.

Thermography. From insights obtained by pathologic studies, it is now well recognized that activated macrophages play an important role in the pathogenesis of acute coronary syndromes and cause an intense inflammatory reaction that might enhance plaque vulnerability. Because the inflammatory reaction causes local heat production, measurement of temperature on the plaque surface has been explored as an alternate method of evaluating the degree of local inflammatory reaction. Previous ex vivo studies in which needle thermistors were used have demonstrated thermal heterogeneity in human carotid atherosclerotic plaques and confirmed a positive correlation

between focal temperature increase and degree of histologically detected inflammation.[46] Recently, with catheter-based devices for temperature measurement of the coronary artery wall, several clinical studies have demonstrated larger temperature heterogeneity between the culprit and reference segment in acute coronary syndrome compared with stable angina pectoris.[47,48] Although intravascular thermography is a unique technique that potentially evaluates plaque vulnerability from the bioactive standpoint, there seems to be a significant overlap in temperature heterogeneity between stable and unstable presentations of coronary artery disease. Furthermore, there has been no clear evidence that directly links focal temperature increase of the vessel wall to plaque vulnerability. Combining this device with imaging modalities might provide an attractive synergy of both anatomic and physiologic predictors of plaque vulnerability.[49]

Spectroscopy. By analyzing the emission and absorption of different wavelengths (spectra) of light for various chemical components, spectroscopy allows accurate analysis of the histologic composition of the vessel wall. Currently, 2 approaches using this technique, namely Raman spectroscopy and near-infrared (NIR) spectroscopy, have been under investigation as alternative modalities for detecting vulnerable plaque in ex vivo conditions.[50–53] Compared with IVUS, Raman spectroscopy provides better detection of cholesterol, as observed by histochemistry in the plaque.[51] Also, in a current ex vivo study examining human atherosclerotic plaques, NIR spectroscopy identified the lipid core with 90% sensitivity and 93% specificity.[53] Furthermore, it achieved sensitivities and specificities ranging from 77% to 93% for detection of the fibrous cap and inflammation within the plaque.

Intravascular Magnetic Resonance Imaging. Current conventional noninvasive magnetic resonance imaging (MRI) is capable of characterizing plaque structure on the basis of biophysical and biochemical parameters of superficial vessels, such as the carotid arteries. However, because significant reduction of signal-to-noise ratio occurs as the distance from the external coil and artery increases, similar resolution is difficult to achieve within "deep" vessels, including the coronary arteries. Furthermore, current conventional MRI does not achieve in-plane resolution smaller than 300 μm and is therefore unreliable to detect the thin fibrous cap, which is typically less than 100 μm thick. To overcome these problems, the application of an intravascular imaging coil has been proposed. Recently, ex vivo imaging of human carotid endarterectomy specimens with standard 0.5-T MRI combined with a 5F intravascular MRI coil has demonstrated improved special resolution at 160 μm and indicated the potential to characterize various intraplaque components through a variety of imaging protocol approaches by use of clinically applicable whole-body scanners.[54] Intravascular MRI has the potential to provide high image resolution without exposing the patient to radiation. However, several technical limitations remain to be solved to achieve meaningful clinical application. These limitations include artifacts originating from cardiac motion and flow variation and a prolonged acquisition time.

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Noninvasive Techniques

Computed Tomography. Electron beam computed tomography (EBCT) is a highly sensitive imaging modality used to detect and quantify coronary artery calcium, which occurs exclusively in atherosclerotic arteries and is absent in the normal vessel. At present, calcium quantification with EBCT is applied to screening of selected asymptomatic individuals at high risk for developing clinically significant coronary artery disease as well as for the diagnosis of obstructive coronary artery disease in symptomatic individuals.[55] The presence and extent of coronary calcium seems to correlate with overall atherosclerotic plaque burden and might indirectly suggest an increased frequency of the presence of vulnerable plaque.[52] However, the role of calcification in the biology of vulnerable plaque is unclear, and there is no established consensus regarding the exact impact of calcification on the process or risk of plaque rupture.

Recently, 1 clinical study investigated the ability of contrast-enhanced multidetector spiral CT to detect plaque types in nonstenotic major coronary arteries from 22 select individuals, compared with IVUS-observed[56] plaque types, in a blinded fashion. Although this modality characterized calcified plaque well, with a sensitivity and specificity of more than 90%, detection of exclusively noncalcified plaque was still unreliable, yielding only 53% sensitivity, particularly in the distal part of the vessel.

Magnetic Resonance Imaging. Compared with the invasive techniques and CT, noninvasive MRI has a great advantage to better visualize vessel wall components and evaluate the degree of luminal stenosis. In addition, it can be performed repeatedly over time to evaluate atherosclerosis progression without increased intrinsic risk of complications from invasive techniques or exposure to radiation. Recently, high-resolution MRI has emerged as the potential next-generation noninvasive imaging modality for plaque characterization. In a select patient group, this modality has demonstrated its capability to visualize plaque components in both the carotid and coronary arteries.[57,58] In addition, use of contrast agents, such as gadolinium chelates or superparamagnetic nanoparticles of iron oxide, might enhance plaque components related to its vulnerability, such as neovascularization and macrophage accumulation, and thus facilitate the detection of plaque at high risk of disruption.[59,60] However, further improvements regarding image resolution and intrinsic artifact reduction from respiration and cardiac motion are necessary to bring this novel approach into useful clinical application.

High-resolution MRI has emerged as the potential next-generation noninvasive imaging modality for plaque characterization.

Serum Markers

Traditional risk assessment with established clinical risk factors for coronary artery disease has been shown to predict chronic development of coronary artery disease in large populations. However, it is unclear whether this same risk assessment strategy can reliably predict acute cardiac events occurring in the near future on an individual case basis, particularly in those who have no indication of coronary artery stenosis or myocardial ischemia and who might lack traditional risk factors. From previous investigation of the atherosclerotic disease process, inflammation is now well recognized as a key pathogenic mechanism in the development of atherosclerosis, including plaque vulnerability. Several serum markers, such as C-reactive protein (high sensitivity), serum amyloid A, interleukin-6, and soluble intercellular adhesion molecule 1 have been proposed as potential inflammation markers that might predict future cardiovascular events.[61–64] Although further investigations are needed, combining serum markers and imaging modalities might offer an effective step-up approach to screening high-risk populations for plaque rupture.

Treatment of Vulnerable Plaque

Pharmacologic Approaches

Although the optimal pharmacologic strategy to treat patients with vulnerable plaque has yet to be established, there are several candidate drugs that might improve the stability of plaques vulnerable to future development of acute coronary syndrome. These include ß-blockers, angiotensin-converting enzyme (ACE) inhibitors, standard antiplatelet agents, such as aspirin, and lipid-lowering agents or "statins." Reduction of blood pressure and heart rate by ß-blocker therapy can favorably affect circumferential vessel wall stress and thus prevent plaque disruption, specifically in patients with relatively fast heart rates and left ventricular hypertrophy.[65] ACE inhibitors also lower blood pressure and might stabilize plaque by reducing the synthesis of angiotensin II, which induces inflammation through the synthesis and release of interleukin-6 from macrophages.[66] Also, aspirin, which reduces platelet aggregability, seems to have a greater role in the prevention of future myocardial infarction in individuals with serologic evidence of inflammation.[67]

Among those drug classes mentioned, lipid-lowering therapy with statins is probably most important and has been intensively investigated. In fact, previous large population studies have demonstrated that statin-treatment groups achieved more than 30% reduction of first acute coronary events, compared with groups receiving placebo.[68,69] Recently, the effect of statins in preventing acute cardiac events has been postulated to occur through multiple biological processes that might be related to the modification of lipid metabolism.[70,71] These potential mechanisms include 1) improvement of endothelial function; 2) systemic and focal reduction of inflammation in the atheromatous plaque; and 3) reduction of thrombogenicity and enhanced fibrinolysis. Improvement of endothelial function might favorably enhance vascular tone to

Reduction of blood pressure and heart rate by ß-blocker therapy can favorably affect circumferential vessel wall stress and thus prevent plaque disruption.

increase coronary circulation and might relieve ischemic symptoms. Focal reduction of inflammation in atheromatous plaques can be achieved by the reduction of oxidized low-density lipoprotein (LDL), which induces macrophage proliferation and accumulation of cholesteryl esters in macrophages, as well as by inhibition of lymphocyte growth via multiple pathways, unrelated to cholesterol metabolism. Interestingly, recent studies have indicated that statins reduce systemic inflammatory activity, as measured by reduction of C-reactive protein, without an association with the changes in LDL cholesterol, thus suggesting that the effect of this drug in the reduction of inflammation is independent from its modification of lipid metabolism.[72,73] In cultured cells, statins have also been suggested to possess an antithrombotic effect caused by inhibition of plasminogen activator inhibitor-1 production in human endothelial and smooth muscle cells, as well as by reduction of the expression of potential procoagulant tissue factor in macrophages. These anticoagulant effects of statins might favorably impact thrombosis prevention. Furthermore, the effect of statins on inflammatory reduction and modification of thrombogenicity, both of which are independent of lipid metabolism, might further indicate these drugs' potential to reduce acute coronary events caused by nonruptured plaques. Such cases typically occur at plaques without a lipid core but with erosion and inflammation covered by the thrombus and have been reported in approximately 30% of cases of acute coronary syndrome.[4,32]

Percutaneous coronary intervention with a stent, in combination with glycoprotein IIb/IIIa receptor inhibitors, can be highly effective and has rapidly become the gold standard of treatment.

Finally, with a better understanding of the molecular and genetic mechanisms of plaque vulnerability, new treatment strategies, such as molecular or gene therapies, might be applicable in the near future. Such strategies should include genetic modulation of focal inflammation, lipid metabolism, or endothelial function.

Invasive Approaches

For short-term stabilization of already disrupted and/or thrombotic plaque, percutaneous coronary intervention with a stent, in combination with glycoprotein IIb/IIIa receptor inhibitors, can be highly effective and has rapidly become the gold standard of treatment. Theoretically, stent implantation might seal the intimal tear that occurred at the rupture site and increase luminal dimension to reestablish blood flow and reduce focal mechanical stress of the vessel wall, resulting in a short-term reduction of focal thrombosis.[74] Although in-stent restenosis has been the major limitation for this approach, the emergence of drug-eluting stents might solve this problem. However, further clinical investigation is warranted to examine the effect of this

Main Points

- Intravascular optical coherence tomography (OCT) is a new imaging technique that uses optical echoes of an infrared light source directed at the vessel wall to create high-resolution, tomographic images of a vessel.
- Because the inflammatory reaction causes local heat production, measurement of temperature on the plaque surface has been explored as an alternate method of evaluating the degree of local inflammatory reaction.
- Invasive imaging techniques currently being investigated for the identification of vulnerable plaque include intravascular ultrasound, angioscopy, optical coherence tomography, thermography, spectroscopy, and intravascular magnetic resonance imaging (MRI); noninvasive techniques include computed tomography and high-resolution MRI.
- Several serum markers, such as C-reactive protein, serum amyloid A, interleukin-6, and soluble intercellular adhesion molecule 1 have been proposed as potential inflammation markers that might predict future cardiovascular events.
- Several candidate drugs that might improve the stability of plaques vulnerable to future development of an acute coronary syndrome include ß-blockers, angiotensin-converting enzyme inhibitors, standard antiplatelet agents, such as aspirin, and lipid-lowering agents or "statins."
- For short-term stabilization of already disrupted and/or thrombotic plaque, percutaneous coronary intervention with a stent, in combination with glycoprotein IIb/IIIa receptor inhibitors, can be highly effective and has rapidly become the gold standard of treatment.

novel device in the setting of acute coronary syndrome, particularly when combined with antithrombotic agents, such as glycoprotein IIb/IIIa receptor inhibitors.

Several catheter-based approaches are currently under investigation for the stabilization of vulnerable plaque before its disruption. Cryoplasty simultaneously dilates and cools plaques with the use of an angioplasty balloon inflated with nitrous oxide instead of saline. It is known to induce a significant degree of apoptosis in tissues treated at the ideal temperature and thus has the potential to promote cell senescence, leading to alteration of the thickness of the fibrous cap to varying degrees. Therefore, cryoplasty, performed at a low atmospheric pressure, might favorably modify vulnerable plaque with a trivial effect on surrounding tissue. Although further device development is warranted, this system might have the capability of combining thermal detection methods with a therapeutic platform.

Intravascular sonotherapy is another potential catheter-based approach that might be effective in plaque stabilization. Previous studies with cell cultures have shown that high-energy ultrasound altered cell viability, migration, and adhesion among different cell cultures.[75] This concept might be applicable for plaque stabilization through the alteration of cellular components of the vulnerable plaque.

Last, photodynamic therapy is a unique modality that combines systemic and local approaches to inhibit plaque formation and enables the diagnosis and stabilization of vulnerable plaque. This approach involves the combination of a chemical photosensitizer and visible light at a specific wavelength to selectively illuminate and activate the photosensitizer, thus leading to the production of singlet radical oxygen species, which mediates apoptosis. A previous animal study has demonstrated that motexafin lutetium, a photosensitizer derived from the porphyrin molecule, binds LDL receptors and is transported into macrophage-rich plaque.[76] Futhermore, in the same study, a significant decrease in macrophages and a mild decrease in atheroma were observed without damage to the normal vessel wall in the area of photoactivation.[76] Recently, another clinical study has confirmed the safety of this treatment for use in human coronary artery disease.[77]

Conclusions

Over the past decade, our understanding of the pathophysiology of acute coronary syndrome has dramatically evolved, from the histomorphologic aspect of the culprit plaque to the molecular mechanism of plaque disruption, leading to the conceptual genesis of vulnerable plaque. Although the optimal diagnostic strategy has yet to be established, risk stratification based on the combination of biological markers and imaging modalities might effectively screen high-risk populations for aggressive management, either by pharmacologic or mechanical intervention or a combination of both. To maximize the clinical benefit for patients at high risk for acute coronary syndrome, future development of novel diagnostic and treatment approaches should be based on a more thorough understanding and definition of vulnerable plaque. ■

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