

Novel Intravascular Modalities for Assessing Coronary Lesions

New imaging options are making it easier to detect vulnerable plaque.

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Atherosclerotic coronary disease remains a major cause of morbidity and mortality. During the last decades, many histological and angiographic studies have confirmed that most acute coronary events are secondary to vulnerable plaque rupture that arises from a non-flow-limiting coronary stenosis.^{1,2} Therefore, the detection of these nonobstructive rupture-prone plaques could have an important impact on the prevention of cardiac illness. Several novel modalities have recently been developed to examine the vascular wall with improved plaque characterization during coronary catheterization. This article focuses on several intravascular techniques that are being used in clinical practice or in advanced human studies.

LIMITATION OF CONVENTIONAL ANGIOGRAPHY

Angiography remains the main tool for the evaluation of the coronary arteries in clinical practice. The world-wide experience in coronary catheterization and angiography for the detection and assessment of lumen narrowing is very extensive. However, conventional angiography depicts the intricate coronary cross-sectional anatomy as a planar two-dimensional silhouette of the contrast-filled vessel lumen. The “lumenogram” thereby obtained is a relatively poor representation of the coronary anatomy and offers no information on vessel wall structures or a potential remodeling process.³ It does not provide insight into the disease state within the arterial wall and often fails to detect lesions prone to thrombosis. These are major limitations because visualization of the vessel wall and plaque

composition is necessary for the identification and analysis of early lesions and rupture-prone plaques.

VULNERABLE PLAQUES

The term *vulnerable plaque* was coined by Muller et al⁴ to describe thrombosis-prone plaques with a high proba-

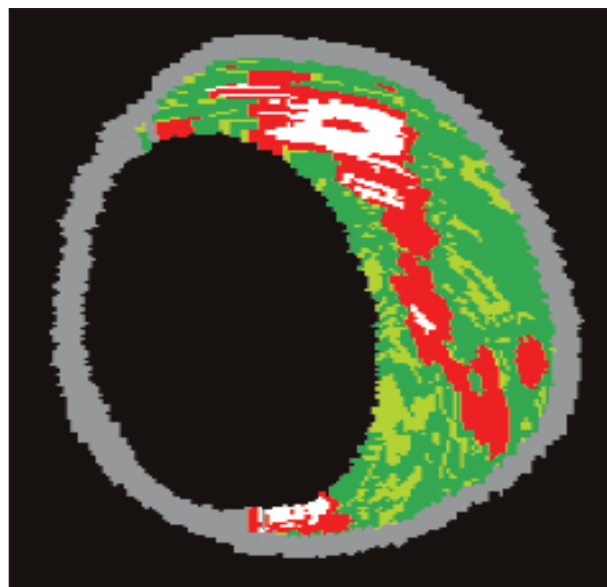


Figure 1. Virtual histology (VH) image of atherosclerotic coronary lesion. The different plaque components are represented by different colors: fibrotic (dark green), fibrofatty (light green), dense calcium (white), and necrotic core (red). Note that this plaque has a significant necrotic core component and that fibrotic tissue is absent between the plaque and vessel lumen in several regions, characteristics of presumable thin-cap fibroatheroma.

bility of rapid progression. Histological examinations by Virmani et al and others identified several characteristics of these high-risk plaques: thin-cap, large lipid core, inflammatory cell infiltrate (thin-cap fibroatheroma), increased proteoglycan content, and calcified nodule.^{5,6} However, clinicians may miss these vessel characteristics using conventional angiographic evaluation of coronary flow-limiting stenoses and thus fail to identify patients at an increased risk for acute coronary syndrome. The ability to detect plaque stability would clearly allow for better prediction of the risk of plaque rupture, which could then be translated to medical actions and interventional therapeutic steps. Therefore, researchers are directing their attention to the detection of regions in the coronary tree that harbor atherosclerotic plaques at risk of tearing or that have a focal erosion that can lead to an intravascular thrombotic state and ultimately to acute myocardial infarction.⁷ Several noninvasive modalities, such as multislice CT, make vessel wall evaluation possible but at a relatively low resolution. Currently, the most accurate methods developed to appreciate vessel wall structures depict intracoronary images.

INTRAVASCULAR ULTRASOUND WITH VIRTUAL HISTOLOGY

During ultrasound imaging, sound wave amplitude reflected from the tissue is converted to electrical amplitude, which in turn, is processed and translated to grayscale colors. The miniaturization of ultrasound transducers and their placement on the tip of the vascular catheter have made intracoronary ultrasound possible. Using intravascular ultrasound (IVUS), clinicians can morphologically differentiate tissues by their level of echogenicity, and they may tomographically evaluate the morphologic characteristics of the pathological vessel wall, namely, regions of vessel enlargement related to positive remodeling, eccentric atherosclerotic plaque, regions with large tears or dissection, ulceration, and less often, the presence of a clot.⁸ Thus, IVUS has become the gold standard for the in vivo real-time evaluation of coronary plaques, including lumen and vessel dimensions. Unfortunately, only limited tissue characterization is possible with conventional IVUS, and seldom can rupture-prone vascular regions be identified reliably and definitively.

To overcome this problem, in recent years, the quality and interpretation of IVUS imaging has been advanced by the addition of spectral analysis of the ultrasound backscatter radiofrequency signals. In this manner, plaque components can be characterized on the basis of tissue characteristics, such as density, compressibility, concentration of various components, and size. This

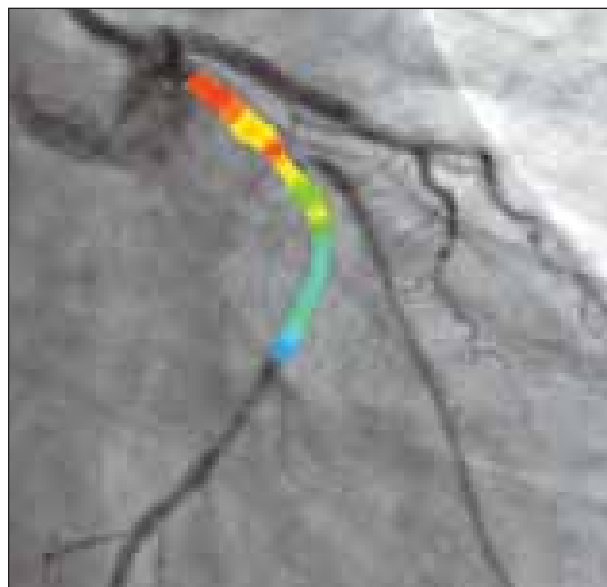


Figure 2. An example of intracoronary palpography-derived imaging of stenotic lesion in the circumflex artery. The amount of displacement of each slice is color-coded. Yellow represents a high strain of approximately 2%, whereas blue represents a low strain level of approximately 0%.

approach, termed *virtual histology* (VH), has been validated by comparing it to ex vivo coronary segment histology. The signals reflected from the artery wall are color-coded to represent the volumetric structure of the atherosclerotic plaque: fibrotic (green), fibrofatty (yellow), necrotic core and inflammatory elements (red), and calcified elements (white) (Figure 1). Nair et al,⁹ in an ex vivo comparison of the VH findings in 52 left anterior descending coronary segments with the histopathological findings (total, 81 slices), found that the accuracy of VH ranged from 80% to 93%, depending on the type of the tissue analyzed. More recent studies revealed even higher accuracy rates.¹⁰ Because the minimal VH resolution is $>150\ \mu\text{m}$, it is not always amenable to direct measurement of atherosclerotic plaque caps, which are thinner than $65\ \mu\text{m}$ in most vulnerable regions.¹¹ Therefore, a substitute method to indirectly localize thin-cap fibroatheromas was developed. Thin-cap fibroatheromas are defined according to VH-based parameters as the presence of a lesion fulfilling all of the following criteria in at least three consecutive cross-sectional areas: necrotic core of 10% or more, an atherosclerotic plaque larger than 40% of the arterial area, and the absence of fibrotic tissue between the atherosclerotic plaque and the vessel lumen.¹² This definition was supported by analyses of arteries with more than 50% stenosis, wherein a higher rate of atherosclerotic

plaques with thin-cap fibroatheromas was documented in patients with acute coronary syndrome than in patients with stable angina.¹² In another study, VH examination of all major coronary vessels was conducted in 40 patients, most presenting with acute coronary syndrome. Sites with atherosclerotic plaques were characterized by a rate of necrotic core (17%) that was higher than sites with minimum lumen area (13%).¹³ VH appears to be a promising plaque-characterization modality, but conclusions regarding its clinical usefulness and predictive value for adverse coronary events await the results of ongoing clinical trials (eg, the PROSPECT study).

PALPOGRAPHY

The prerequisites for vessel tearing are the presence of a vulnerable plaque and exposure of the plaque surface to hemodynamic mechanical forces. Tears occur at regions with low tolerability to shear stress, such as thin-cap fibroatheromas rich in necrotic core. Moreover, the ability of a cap to withstand higher stress is probably more important than its thickness. These findings prompted a search for a feasible method of evaluating the local tissue strain. Ophir et al developed an IVUS-related imaging modality, termed *elastography*.¹⁴ Elastography is based on tissue deformation and manifests as changes in the diameter of the arterial wall layer in response to changes in circumferential pressure. Analyses are performed in the dias-

tolic phase for several cycles, and changes in the diameter of the arterial wall are correlated with blood pressure changes of approximately 5 mm Hg. The image of the radial strain is plotted complementary to the IVUS image. Palpography is based on the same principles as elastography and is easier to interpret. It is performed on 450- μ m-thick slices. The amount of displacement of each slice is color-coded (Figure 2). Several studies of this method showed that strain values differed between fibrous and fatty tissue and that higher strain values were associated with increased macrophage concentration.^{15,16} Therefore, palpography may be used to identify features of vulnerable plaque. The evaluation of the predictive power of palpography compared to the histological findings yielded a sensitivity of 88% and a specificity of 89%.¹⁷ There was a strong correlation between the strain on the caps and the amount of macrophages. In studies on patients, high-strain values (1%–2%) were noted for noncalcified plaques and low strain values (0%–0.2%) for calcified material. Others reported a strong correlation between high-strain spots, clinical symptoms, and inflammation markers. The presence of a high-strain spot surrounded by a low-strain area indicated a high-risk region with high sensitivity and specificity. In recent years, a novel method to acquire strain information on three-dimensional vessel paths has been developed, although further clinical experience is needed to confirm its importance.¹⁸ A prospective study, currently under way, is evaluating the possible association between the distribution of “weak spots” and clinical events.

Optical Coherence Tomography

Optical coherence tomography (OCT), the optical analog of ultrasound, measures the time of reflection of infrared laser light from subsurface tissue. Because the speed of light is too high for electrical measurement, analysis is performed by short-coherence interferometry using a rotating fiberoptic probe. The presence of blood between the catheter and vessel wall causes substantial signal attenuation, so it must be displaced during OCT by saline flushing or balloon. However, these approaches are limited because of the ischemia that results in the territory of the artery. Therefore, imaging of long segments by OCT is currently performed in several stages. Improved technologies are expected to eliminate this disadvantage in the near future.

Similar to IVUS, OCT can supply real-time images of a coronary vessel. Its most important advantage over IVUS is probably its higher resolution (by tenfold) with lower penetration (2 mm vs 5 mm for IVUS) during evaluations of superficial structures (5–20 μ m). Therefore, it is highly suitable for evaluating superficial

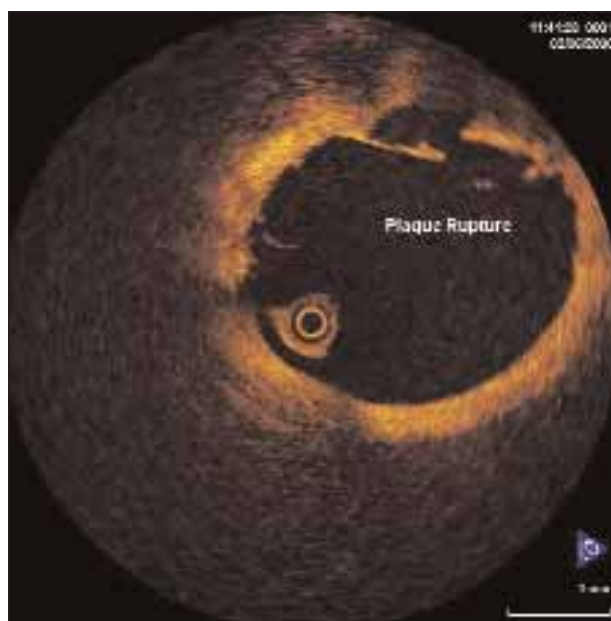


Figure 3. Optical coherence tomography imaging of a “vulnerable” coronary lesion showing thin lesion cap and endothelial tear. Note the high resolution with low penetration of this modality.

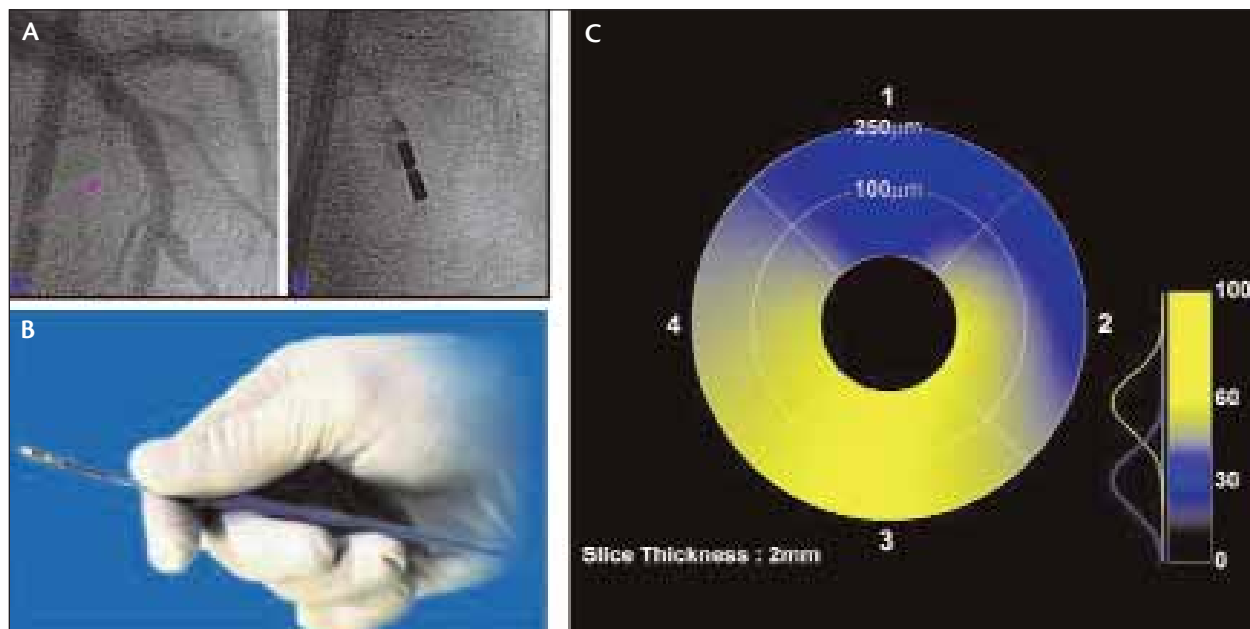


Figure 4. Intravascular magnetic resonance imaging of coronary lesion in the mid-left anterior descending artery. The catheter includes magnetic resonance probe (A). Angiography and catheter insertion (A, B). Color representation of the lipid fraction index where yellow represents high lipid fraction index (C).

tissue near the vessel lumen and diagnosis of thin-cap fibroatheromas (Figure 3). The first clinical studies comparing coronary imaging by OCT and IVUS reported that both methods showed an equal ability to differentiate fibrotic from calcified tissue.^{19,20} However, OCT identified tissue components that were not detectable by ultrasound, including intimal hyperplasia, internal and external elastic lamina, and echolucent regions. OCT also more accurately detected layer tears (70%) than either IVUS (47%) or angioscopy (40%) and better appreciated stent apposition and level of endothelialization.^{19,21} Also, OCT is a much better modality to detect vessel thrombosis compared to IVUS. Jang et al¹⁹ studied 57 patients undergoing coronary angiography and found a very significant association between the presenting clinical event and the prevalence of thin-cap fibroatheroma defined by OCT.

INTRAVASCULAR MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging can clearly evaluate arterial wall composition. However, conventional magnetic resonance imaging is impractical for use in the catheterization laboratory because of the large size of the equipment and the need for a large magnetic field (1.5 Tesla). Cardiac and respiratory movements make this application even more problematic. Intravascular magnetic resonance imaging (IVMRI) represents a tech-

nological breakthrough in miniaturizing this modality and abolishing the need for an external magnetic field. To obtain high-resolution IVMRI, researchers designed a self-contained, 8-F catheter, thereby reducing the local magnetic field to 0.2 Tesla, with penetration of approximately 250 μm through the vessel wall at a 60° angle (Figure 4). This made it possible to quantify the different tissue layers, although the atherosclerotic plaque composition could not be differentiated. The catheter is attached to the vessel wall by eccentric balloon inflation at 1.4 atm. In the first catheter prototype, acquisition time was 50 seconds; six acquisitions are required for a full 360° field image. The amount of lipid in the atherosclerotic plaque is quantified (lipid fraction index) on a scale of 0 to 100. This value is clinically important because lipid-rich plaques might be prone to tears. Studies correlating IVMRI findings with pathological examination reported 89% accuracy.²² The first preliminary clinical study of the effectiveness and safety of IVMRI was conducted in 104 patients (88% male; mean age, 65 years) with more than 50% coronary stenosis; 68% had stable angina.²³ Success was achieved in 91 patients (88%). A rare major complication, noted during the first day after procedure, was coronary dissection. During the last year, efforts have been directed at reducing the catheter size and the need for multiple and extended acquisitions. A 6/7-F catheter with two sensors is currently under investigation as a second-gen-

eration device. The widespread use of this novel modality will depend on such technological advancements.

THERMOGRAPHY

Vulnerable atherosclerotic plaques are characterized by a large amount of inflammatory cells. This inflammatory process, especially high metabolism of macrophages, is probably accompanied by local production of heat. Accordingly, studies have shown that comparing the temperature between different segments of the coronary vessel can predict insult to the atherosclerotic plaque and the production of a blood clot.²⁴ Temperature is measured by an intravascular thermometer with an accuracy of .05°C in a selective region measuring 0.5 mm in diameter.²⁵ The viability of this method was supported by reports that patients with acute coronary syndrome showed a greater heterogeneity in coronary vessel temperature than patients with chronic and stable angina (.08±.03°C vs .04±.02°C).²⁶ In addition, these researchers found that plaques with positive remodeling were also characterized by a higher temperature. The ability of intracoronary thermography to detect a plaque tear was recently evaluated in a study of 45 patients with a first anterior myocardial infarction.²⁷ The results showed that in patients with incomplete vascular obstruction, temperature was maximal at a point approximately 2 mm distal to the area of maximal stenosis, whereas in patients with complete obstruction, the mean distance was 8.8 mm. The regions of maximal temperature were highly correlated with the presence of plaque tears identified by ultrasound.

SUMMARY

The early detection of vulnerable atherosclerotic plaque poses a major challenge to clinicians. Conventional angiography is inherently incapable of identifying most high-risk plaques because plaque destabilization does not involve angiographically detectable abnormalities in the vessel wall. Many intravascular modalities with different abilities have been developed to detect different plaque elements. However, currently no single method is clearly superior to the others, and pathological examination remains the gold standard. Prospective studies are needed to confirm the high-risk plaque hypothesis, and randomized trials should evaluate the benefit of treating these lesions either using catheters and/or systemically. Integration of some of the available novel imaging modalities may enable achieving this goal. ■

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1. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol*. 1988;12:56-62.
2. Little WC, Constantinescu M, Applegate RJ, et al. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation*. 1988;78(Pt 1):1157-1166.
3. Topol EJ, Nissen SE. Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. *Circulation*. 1995;92:2333-2342.
4. Muller JE, Abela GS, Nesto RW, et al. Triggers, acute risk factors and vulnerable plaques: the lexicon of a new frontier. *J Am Coll Cardiol*. 1994;23:809-813.
5. Virmani R, Kolodgie FD, Burke AP, et al. Atherosclerotic plaque progression and vulnerability to rupture: angiogenesis as a source of intraplatelet hemorrhage. *Arterioscler Thromb Vasc Biol*. 2005;25:2054-2061.
6. Kolodgie FD, Virmani R, Burke AP, et al. Pathologic assessment of the vulnerable human coronary plaque. *Heart*. 2004;90:1385-1391.
7. Thom T, Haase N, Rosamond W, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2006;113:e85-e151.
8. Nissen SE, Yock P. Intravascular ultrasound: novel pathophysiological insights and current clinical applications. *Circulation*. 2001;103:604-616.
9. Nair A, Kuban BD, Tuzcu EM, et al. Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. *Circulation*. 2002;106:2200-2206.
10. Nasu K, Tsuchikane E, Katoh O, et al. Accuracy of in vivo coronary plaque morphology assessment: a validation study of in vivo virtual histology compared with in vitro histopathology. *J Am Coll Cardiol*. 2006;47:2405-2412.
11. Burke AP, Farb A, Malcom GT, et al. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med*. 1997;336:1276-1282.
12. Rodriguez-Granillo GA, Garcia-Garcia HM, Mc Fadden EP, et al. In vivo intravascular ultrasound-derived thin-cap fibroatheroma detection using ultrasound radiofrequency data analysis. *J Am Coll Cardiol*. 2005;46:2038-2042.
13. Rodriguez-Granillo GA, Garcia-Garcia HM, Valgimigli M, et al. Global characterization of coronary plaque rupture phenotype using three-vessel intravascular ultrasound radiofrequency data analysis. *Eur Heart J*. 2006;27:1921-1927.
14. Ophir J, Céspedes I, Ponnekanti H, et al. Elastography: a quantitative method for imaging the elasticity of biological tissues. *Ultrason Imaging*. 1991;13:111-134.
15. de Korte CL, Pasterkamp G, van der Steen AF, et al. Characterization of plaque components with intravascular ultrasound elastography in human femoral and coronary arteries in vitro. *Circulation*. 2000;102:617-623.
16. Lee RT, Richardson SG, Loree HM, et al. Prediction of mechanical properties of human atherosclerotic tissue by high-frequency intravascular ultrasound imaging. An in vitro study. *Arterioscler Thromb*. 1992;12:1-5.
17. Schaar JA, De Korte CL, Mastik F, et al. Characterizing vulnerable plaque features with intravascular elastography. *Circulation*. 2003;108:2636-2641.
18. Schaar JA, Regar E, Mastik F, et al. Incidence of high-strain patterns in human coronary arteries: assessment with three-dimensional intravascular palpography and correlation with clinical presentation. *Circulation*. 2004;109:2716-2719.
19. Jang IK, Bouma BE, Kang DH, et al. Visualization of coronary atherosclerotic plaques in patients using optical coherence tomography: comparison with intravascular ultrasound. *J Am Coll Cardiol*. 2002;39:604-609.
20. Patwari P, Weissman NJ, Boppart SA, et al. Assessment of coronary plaque with optical coherence tomography and high-frequency ultrasound. *Am J Cardiol*. 2000;85:641-644.
21. Matsumoto D, Shite J, Shinko T, et al. Neointimal coverage of sirolimus-eluting stents at 6-month follow-up: evaluated by optical coherence tomography. *Eur Heart J*. 2007;28:961-967.
22. Schneiderman J, Wilensky RL, Weiss A, et al. Diagnosis of thin-cap fibroatheromas by a self-contained intravascular magnetic resonance imaging probe in ex vivo human aortas and in situ coronary arteries. *J Am Coll Cardiol*. 2005;45:1961-1969.
23. Leon MB, et al. Intravascular MRI: First report from the multicenter Topimage study. Presented at the annual Transcatheter Cardiovascular Therapeutics meeting (TCT). Washington, DC, 2007.
24. Stone PH, Coskun AU, Kinlay S, et al. Effect of endothelial shear stress on the progression of coronary artery disease, vascular remodeling, and in-stent restenosis in humans: in vivo 6-month follow up study. *Circulation*. 2003;108:438-444.
25. MacNeill BD, Lowe HC, Takano M, et al. Intravascular modalities for detection of vulnerable plaque: current status. *Arterioscler Thromb Vasc Biol*. 2003;23:1333-1342.
26. Toutouzas K, Synetos A, Stefanadi E, et al. Correlation between morphologic characteristics and local temperature differences in culprit lesions of patients with symptomatic coronary artery disease. *J Am Coll Cardiol*. 2007;49:2264-2271.
27. Takumi T, Lee S, Hamasaki S, et al. Limitation of angiography to identify the culprit plaque in acute myocardial infarction with coronary total occlusion utility of coronary plaque temperature measurement to identify the culprit plaque. *J Am Coll Cardiol*. 2007;50:2197-2203.