

From Vulnerable Plaque to Vulnerable Patient

A Call for New Definitions and Risk Assessment Strategies: Part I

Morteza Naghavi, MD; Peter Libby, MD; Erling Falk, MD, PhD; S. Ward Casscells, MD; Silvio Litovsky, MD; John Rumberger, MD; Juan Jose Badimon, PhD; Christodoulos Stefanadis, MD; Pedro Moreno, MD; Gerard Pasterkamp, MD, PhD; Zahi Fayad, PhD; Peter H. Stone, MD; Sergio Waxman, MD; Paolo Raggi, MD; Mohammad Madjid, MD; Alireza Zarrabi, MD; Allen Burke, MD; Chun Yuan, PhD; Peter J. Fitzgerald, MD, PhD; David S. Siscovick, MD; Chris L. de Korte, PhD; Masanori Aikawa, MD, PhD; K.E. Juhani Airaksinen, MD; Gerd Assmann, MD; Christoph R. Becker, MD; James H. Chesebro, MD; Andrew Farb, MD; Zorina S. Galis, PhD; Chris Jackson, PhD; Ik-Kyung Jang, MD, PhD; Wolfgang Koenig, MD, PhD; Robert A. Lodder, PhD; Keith March, MD, PhD; Jasenka Demirovic, MD, PhD; Mohamad Navab, PhD; Silvia G. Priori, MD, PhD; Mark D. Reikter, PhD; Raymond Bahr, MD; Scott M. Grundy, MD, PhD; Roxana Mehran, MD; Antonio Colombo, MD; Eric Boerwinkle, PhD; Christie Ballantyne, MD; William Insull, Jr, MD; Robert S. Schwartz, MD; Robert Vogel, MD; Patrick W. Serruys, MD, PhD; Goran K. Hansson, MD, PhD; David P. Faxon, MD; Sanjay Kaul, MD; Helmut Drexler, MD; Philip Greenland, MD; James E. Muller, MD; Renu Virmani, MD; Paul M Ridker, MD; Douglas P. Zipes, MD; Prediman K. Shah, MD; James T. Willerson, MD

Abstract—Atherosclerotic cardiovascular disease results in >19 million deaths annually, and coronary heart disease accounts for the majority of this toll. Despite major advances in treatment of coronary heart disease patients, a large number of victims of the disease who are apparently healthy die suddenly without prior symptoms. Available screening and diagnostic methods are insufficient to identify the victims before the event occurs. The recognition of the role of the vulnerable plaque has opened new avenues of

From The Center for Vulnerable Plaque Research, University of Texas—Houston, The Texas Heart Institute, and President Bush Center for Cardiovascular Health, Memorial Hermann Hospital, Houston (M. Naghavi, S.W.C., S.L., M.M., A.Z., J.T.W.); The Leducq Center for Cardiovascular Research, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass (P.L., M.A.); Department of Cardiology and Institute of Experimental Clinical Research, Aarhus University, Aarhus, Denmark (E.F.); Experimental Cardiology Laboratory, Vascular Biology of the University Medical Center in Utrecht, the Netherlands (G.P.); Ohio State University (J.R.); the Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai Medical Center, New York, NY (Z.F.); Cardiac Catheterization Laboratory at the VA Medical Center, University of Kentucky, Lexington (P.M.); Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass (P.H.S.); Division of Cardiology, New England Medical Center, Boston, Mass (S.W.); Department of Medicine, Section of Cardiology, Tulane University School of Medicine, New Orleans, La (P.R.); Department of Cardiovascular Pathology, Armed Forces Institute of Pathology, Washington, DC (A.B., A.F., R.V.); Department of Radiology, University of Washington, Seattle (C.Y.); Stanford University Medical Center Stanford, Calif (P.J.F.); Cardiovascular Health Research Unit, University of Washington, Seattle (D.S.S.); Department of Cardiology, Athens Medical School, Athens, Greece (C.S.); Catheterization Laboratory, Thorax Center, Erasmus University, Rotterdam, the Netherlands (C.L.d.K.); Division of Cardiology, Department of Medicine, University of Turku, Finland (K.E.J.A.); Institute of Arteriosclerosis Research and the Institute of Clinical Chemistry and Laboratory Medicine, Central Laboratory, Hospital of the University of Münster, Munich, Germany (G.A.); Department of Clinical Radiology, University of Münster, Munich, Germany (C.R.B.); Mayo Clinic Medical School, Jacksonville, Fla (J.H.C.); Department of Medicine, Division of Cardiology, Emory University School of Medicine, Atlanta, Ga (Z.S.G.); Bristol Heart Institute, Bristol University, Bristol, United Kingdom (C.J.); Cardiology Division, Massachusetts General Hospital and Harvard Medical School, Boston, Mass (I.-K.J.); Department of Internal Medicine II, Cardiology, University of Ulm, Ulm, Germany (W.K.); University of Kentucky, Lexington, Ky (R.A.L.); R.L. Roudebush VA Medical Center, Indianapolis, Ind (K.M.); School of Public Health, University of Texas—Houston, Houston, Texas (J.D.); Division of Cardiology, University of California Los Angeles, Los Angeles, Calif (M. Navab); Fondazione Salvatore Maugeri, University of Pavia, Pavia, Italy (S.G.P.); Department of Cardiovascular Therapeutics, Pfizer Global Research and Development, Ann Arbor Laboratories, Ann Arbor, Mich (M.D.R.); Paul Dudley White Coronary Care System at St. Agnes HealthCare, Baltimore, Md (R.B.); Center for Human Nutrition, University of Texas Health Science Center, Dallas (S.M.G.); Lenox Hill Hospital, New York, NY (R.M.); Catheterization Laboratories, Ospedale San Raffaele and Emo Centro Cuore Columbus, Milan, Italy (A.C.); Human Genetics Center, Institute of Molecular Medicine, Houston, Tex (E.B.); Department of Medicine, Baylor College of Medicine, Houston, Tex (C.B., W.I.); Minneapolis Heart Institute and Foundation, Minneapolis, Minn (R.S.S.); Division of Cardiology, University of Maryland School of Medicine, Baltimore, Md (R.V.); Karolinska Institute, Center for Molecular Medicine, Karolinska Hospital, Stockholm, Sweden (G.K.H.); Section of Cardiology, University of Chicago, Ill (D.P.F.); Vascular Physiology and Thrombosis Research Laboratory of the Atherosclerosis Research Center, Cedars-Sinai Medical Center, Los Angeles, California (S.K.); Cardiology Department, Hannover University, Hannover, Germany (H.D.); Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Ill (P.G.); UCLA School of Medicine and Cedars-Sinai Medical Center, Los Angeles, Calif (P.K.S.); Massachusetts General Hospital, Harvard Medical School and CIMIT (Center for Integration of Medicine and Innovative Technology), Boston, Mass (J.E.M.); Cardiovascular Division, Division of Preventive Medicine, Brigham and Women's Hospital, Boston, Mass (P.M.R.); and Indiana University School of Medicine, Krannert Institute of Cardiology, Indianapolis (D.P.Z.).

Many of the authors of this work, in addition to their research activities, have served as consultants to and/or employees of pharmaceutical, medical equipment, and other related companies.

Guest editor for this article was Eugene Braunwald, MD, Brigham and Women's Hospital.

This article is Part I of a 2-part article. Part II will appear in the October 14, 2003 issue of *Circulation*.

Correspondence to Morteza Naghavi, MD, Association for Eradication of Heart Attack, 2472 Bolsover, No. 439, Houston, TX 77005. E-mail mn@vp.org

© 2003 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000087480.94275.97

opportunity in the field of cardiovascular medicine. This consensus document concludes the following. (1) Rupture-prone plaques are not the only vulnerable plaques. All types of atherosclerotic plaques with high likelihood of thrombotic complications and rapid progression should be considered as vulnerable plaques. We propose a classification for clinical as well as pathological evaluation of vulnerable plaques. (2) Vulnerable plaques are not the only culprit factors for the development of acute coronary syndromes, myocardial infarction, and sudden cardiac death. Vulnerable blood (prone to thrombosis) and vulnerable myocardium (prone to fatal arrhythmia) play an important role in the outcome. Therefore, the term “vulnerable patient” may be more appropriate and is proposed now for the identification of subjects with high likelihood of developing cardiac events in the near future. (3) A quantitative method for cumulative risk assessment of vulnerable patients needs to be developed that may include variables based on plaque, blood, and myocardial vulnerability. In Part I of this consensus document, we cover the new definition of vulnerable plaque and its relationship with vulnerable patients. Part II of this consensus document focuses on vulnerable blood and vulnerable myocardium and provide an outline of overall risk assessment of vulnerable patients. Parts I and II are meant to provide a general consensus and overviews the new field of vulnerable patient. Recently developed assays (eg, C-reactive protein), imaging techniques (eg, CT and MRI), noninvasive electrophysiological tests (for vulnerable myocardium), and emerging catheters (to localize and characterize vulnerable plaque) in combination with future genomic and proteomic techniques will guide us in the search for vulnerable patients. It will also lead to the development and deployment of new therapies and ultimately to reduce the incidence of acute coronary syndromes and sudden cardiac death. We encourage healthcare policy makers to promote translational research for screening and treatment of vulnerable patients. (*Circulation*. 2003;108:1664-1672.)

Key Words: coronary disease ■ plaque ■ myocardial infarction ■ atherosclerosis ■ death, sudden

Cardiovascular disease has long been the leading cause of death in developed countries, and it is rapidly becoming the number one killer in the developing countries.¹ According to current estimates, 61 800 000 Americans have one or more types of cardiovascular disease.²

Every year, >1 million people in the United States and >19 million others worldwide experience a sudden cardiac event (acute coronary syndromes and/or sudden cardiac death). A large portion of this population has no prior symptom.³ There is considerable demand for diagnosis and treatment of the pathologic conditions that underlie these sudden cardiac events. This consensus document proposes new directions to prevent infarction and sudden cardiac events.⁴

Underlying Causes of Sudden Fatal and Nonfatal Cardiac Events

Figure 1 delineates the underlying causes of acute cardiac events. The first branch point of the tree indicates patients who lack significant atherosclerosis or related myocardial damage, that is, those who have no ischemic heart disease (see The Nonischemic Vulnerable Myocardium). This leaves the patients with atherosclerosis, some of whom also have a hypercoagulable state (see Vulnerable Blood).

The next branch point involves the presence or absence of an occlusive or subocclusive thrombus. A thrombus identifies a culprit plaque that may be ruptured or nonruptured.

Plaque rupture is the most common type of plaque complication, accounting for ≈70% of fatal acute myocardial infarctions and/or sudden coronary deaths (Figure 2). Several retrospective autopsy series and a few cross-sectional clinical studies have suggested that thrombotic coronary death and acute coronary syndromes are caused by the plaque features and associated factors presented in Table 1.⁵⁻⁷ Most techniques for detecting and treating vulnerable plaque are devoted to rupture-prone plaque. This type of plaque has been termed a “thin-cap fibroatheroma.”⁸

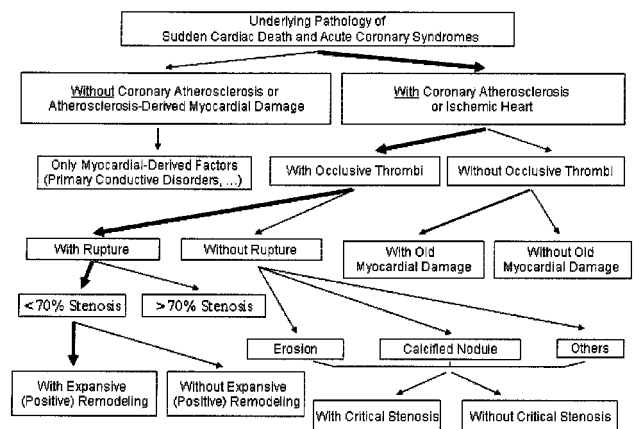


Figure 1. Proposed diagram of the potential underlying pathology of acute coronary syndrome, (ie, unstable angina, acute myocardial infarction and sudden cardiac death).

In some cases, a deep plaque injury cannot be identified despite a careful search. The thrombus appears to be superimposed on a de-endothelialized, but otherwise intact, plaque. This type of superficial plaque injury is called “plaque erosion.”⁹ Other types of culprit plaques also exist (Figure 2). In cases involving nonruptured plaques, plaque erosion or nodular calcification usually accompanies the luminal thrombus.⁵ Other forms of thrombosis in nonruptured plaques may be described in the future. In all cases that involve a superimposed thrombus, the underlying lesion may be stenotic or nonstenotic. However, nonstenotic lesions are far more frequent than stenotic plaques and account for the majority of culprit ruptured plaques.¹⁰

In cases of sudden cardiac death without thrombosis, we hypothesize that coronary spasm, emboli to the distal intramural vasculature, or myocardial damage related to previous injury may account for a terminal arrhythmic episode.

Different Types of Vulnerable Plaque

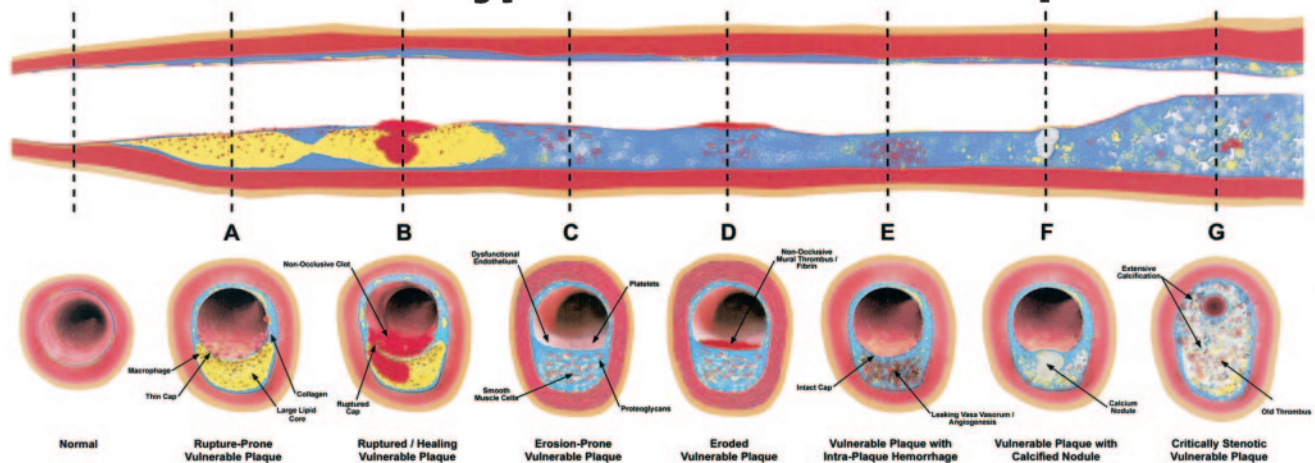


Figure 2. Different types of vulnerable plaque as underlying cause of acute coronary events (ACS) and sudden cardiac death (SCD). A, Rupture-prone plaque with large lipid core and thin fibrous cap infiltrated by macrophages. B, Ruptured plaque with subocclusive thrombus and early organization. C, Erosion-prone plaque with proteoglycan matrix in a smooth muscle cell-rich plaque. D, Eroded plaque with subocclusive thrombus. E, Intraplaque hemorrhage secondary to leaking vasa vasorum. F, Calcific nodule protruding into the vessel lumen. G, Chronically stenotic plaque with severe calcification, old thrombus, and eccentric lumen.

The Challenge of Terminology: Culprit Plaque Versus Vulnerable Plaque

Culprit Plaque, a Retrospective Terminology

Interventional cardiologists and cardiovascular pathologists retrospectively describe the plaque responsible for coronary occlusion and death as a *culprit* plaque, regardless of its histopathologic features. For prospective evaluation, clinicians need a similar term for describing such plaques *before* an event occurs. Plaque rupture was reported sporadically by pathologists in the early 20th century; it became a focus of attention of pioneering scientists in the 1960s (Table 2) and was later documented further by others.^{11–15}

Since the 1970s, scientists have been seeking the mechanisms responsible for converting chronic coronary atherosclerosis to acute coronary artery disease.^{11–15,17} As insights into this process have evolved, the relevant terminology has been continually updated. In the 1980s, Falk¹¹ and Davies and Thomas¹⁵ used “plaque disruption” synonymously with “plaque rupture.” Later, Muller and colleagues^{18,19} used “vulnerable” to describe rupture-prone plaques as the underlying cause of most clinical coronary events. When this functional definition was proposed, the plaque considered responsible for acute coronary events (based on retrospective autopsy studies) had a large lipid pool, a thin cap,

and macrophage-dense inflammation on or beneath its surface (Figure 3).

Over the past several years, “vulnerable plaque” has been used sometimes to denote this concept and at other times to denote the specific histopathologic appearance of the above-described plaque. This dual usage is confusing, particularly as plaques can have other histologic features (see Figure 2) that may also cause acute coronary events.⁵

Vulnerable Plaque, a Future Culprit Plaque

The term “vulnerable” is defined by English dictionaries as “susceptible to injury or susceptible to attack,”²⁰ as in “We are vulnerable both by water and land, without either fleet or army” (Alexander Hamilton). It denotes the likelihood of having an event in the future. The term vulnerable has been used in various reports in the medical literature, all of which describe conditions susceptible to injury. In this regard, the term “vulnerable plaque” is most suitable to define plaques susceptible to complications. An alternative term, “high-risk plaque,” has been recently proposed.¹⁸ The term “high-risk” is often used to describe the

TABLE 1. Underlying Pathologies of “Culprit” Coronary Lesions

Ruptured plaques (≈70%)
Stenotic (≈20%)
Nonstenotic (≈50%)
Nonruptured plaques (≈30%)
Erosion
Calcified nodule
Others/Unknown

*Adapted from Falk and associates,⁶ Davies,⁷ and Virmani and colleagues.⁷

TABLE 2. Descriptions Used by Pioneers for Culprit Plaques^{93,94}

Author	Year	Description Used
Olcott	1931	Plaque rupture
Leary	1934	Rupture of atheromatous abscess
Wartman	1938	Rupture-induced occlusion
Horn	1940	Plaque fissure
Helpert	1957	Plaque erosion
Crawford	1961	Plaque thrombosis
Gore	1963	Plaque ulceration
Byers	1964	Thrombogenic gruel
Chapman	1966	Plaque rupture
Constantinides	1966	Plaque rupture

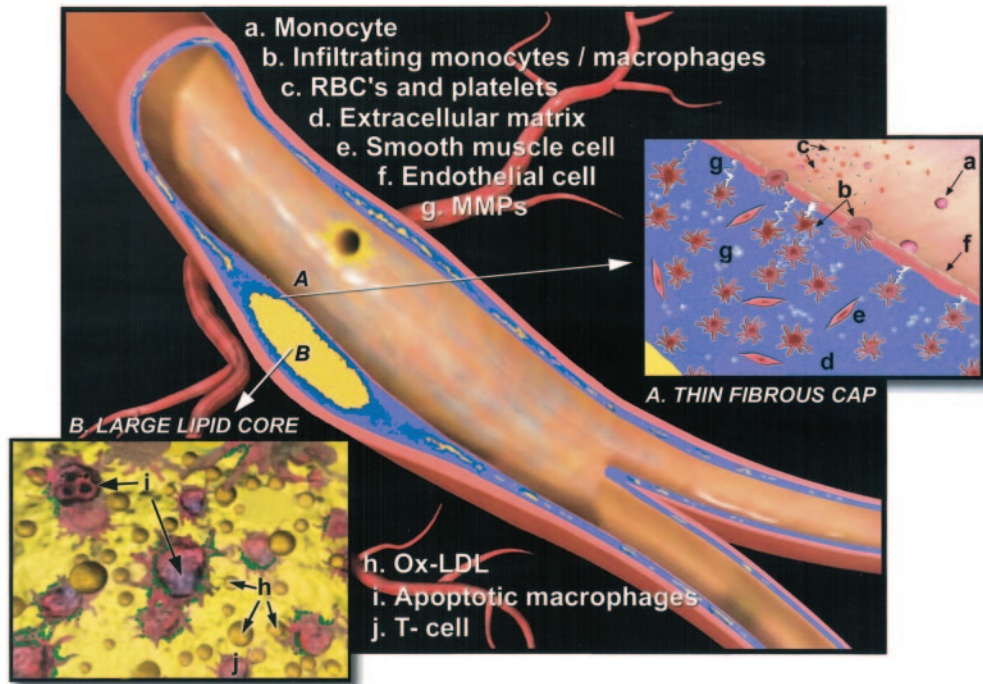


Figure 3. Schematic figure illustrating the most common type of vulnerable plaque characterized by thin fibrous cap, extensive macrophage infiltration, paucity of smooth muscle cells, and large lipid core, without significant luminal narrowing.

high-risk patient groups with acute coronary syndromes. However, our intention is to provide a terminology to identify apparently healthy subjects at risk of future events. Therefore, the term vulnerable seems to be more appropriate. Also, because “vulnerable plaque” has already been widely adopted by investigators and clinicians, we recommend that the existing usage of this term be continued. We advise that the underlying morphological features be described broadly enough to include all dangerous plaques that involve a risk of thrombosis and/or rapid progression.

To provide a uniform language to help standardize the terminology, we recommend “vulnerable plaque” to identify all thrombosis-prone plaques and plaques with a high probability of undergoing rapid progression, thus becoming culprit plaques (Table 3). A proposed histopathologic classification for different types of vulnerable plaque is presented in Figure 2. A list of proposed major and minor criteria for defining vulnerable plaques, based on autopsy studies (culprit plaques), is presented in Table 4.

A large number of vulnerable plaques are relatively uncalcified, relatively nonstenotic, and similar to type IV atherosclerotic lesions described in the American Heart Association classifica-

tion.²¹ However, as depicted in Figure 3, different types of vulnerable plaque exist. Although Table 1 shows the relative distribution of ruptured and nonruptured culprit plaques, the exact prevalence of each type of vulnerable plaque is unknown and can only be determined in prospective studies.

Pan-Coronary Vulnerability

Several investigators have noted the presence of more than one vulnerable plaque in patients at risk of cardiovascular events. Mann and Davies²² and Burke et al²³ in cardiac autopsy specimens, Goldstein et al²⁴ in angiography studies, Nissen²⁵ and Rioufol et al²⁶ with intravascular ultrasound, and Buffon et al²⁷ measuring neutrophil myeloperoxidase found multiple rupture-prone or ruptured plaques in a wide range of cardiovascular patient populations. A most recent series of publications on

TABLE 4. Criteria for Defining Vulnerable Plaque, Based on the Study of Culprit Plaques

Major criteria	
• Active inflammation (monocyte/macrophage and sometimes T-cell infiltration)	
• Thin cap with large lipid core	
• Endothelial denudation with superficial platelet aggregation	
• Fissured plaque	
• Stenosis >90%	
Minor criteria	
• Superficial calcified nodule	
• Glistening yellow	
• Intraplaque hemorrhage	
• Endothelial dysfunction	
• Outward (positive) remodeling	

TABLE 3. Interchangeable Terms Used to Denote Vulnerable Plaque

Acceptable But Not Recommended	Unacceptable*
High-risk plaque	Soft plaque
Dangerous plaque	Noncalcified plaque
Unstable plaque	AHA type IV plaque

AHA indicates American Heart Association.
 *The term vulnerable plaque refers to all plaques at risk for thrombosis or rapid progression to become culprit lesions. A vulnerable plaque is *not necessarily* a soft plaque, a noncalcified plaque, an AHA type IV plaque, or a nonstenotic plaque.^{8,21}



Figure 4. The risk of a vulnerable patient is affected by vulnerable plaque and/or vulnerable blood and/or vulnerable myocardium. A comprehensive assessment must consider all of the above.

vulnerability reiterated the importance of going beyond a vulnerable plaque and called for evaluating the total arterial tree as a whole.^{28–30}

Silent-Plaque Rupture

Thrombotic complications that arise from rupture or fissure (small rupture) of a vulnerable plaque may be clinically silent yet contribute to the natural history of plaque progression and ultimately luminal stenosis.^{31,32}

Beyond the Atherosclerotic Plaque

It is important to identify patients in whom disruption of a vulnerable plaque is likely to result in a clinical event. In these patients, other factors beyond plaque (ie, thrombogenic blood and electrical instability of myocardium) are responsible for the final outcome (Figure 4). We propose that such patients be referred to as “vulnerable patients.” In fact, plaques with similar characteristics may have different clinical presentations because of blood coagulability (vulnerable blood) or myocardial susceptibility to develop fatal arrhythmia (vulnerable myocardium). The latter may depend on a current or previous ischemic condition and/or a nonischemic electrophysiological abnormality.

Definition of a Cardiovascular Vulnerable Patient

The term “cardiovascular vulnerable patient” is proposed to define subjects susceptible to an acute coronary syndrome or sudden cardiac death based on plaque, blood, or myocardial vulnerability (for example, 1-year risk $\geq 5\%$). Extensive efforts are needed to quantify an individual’s risk of an event according to each component of vulnerability (plaque, blood, and myocardium). Such a comprehensive risk-stratification tool capable of predicting acute coronary syndromes as well as sudden cardiac death would be very useful for preventive cardiology (Figure 4).

TABLE 5. Markers of Vulnerability at the Plaque/Artery Level

Plaque	
Morphology/Structure	<ul style="list-style-type: none"> • Plaque cap thickness • Plaque lipid core size • Plaque stenosis (luminal narrowing) • Remodeling (expansive vs constrictive remodeling) • Color (yellow, glistening yellow, red, etc) • Collagen content versus lipid content, mechanical stability (stiffness and elasticity) • Calcification burden and pattern (nodule vs scattered, superficial vs deep, etc) • Shear stress (flow pattern throughout the coronary artery)
Activity/Function	<ul style="list-style-type: none"> • Plaque inflammation (macrophage density, rate of monocyte infiltration and density of activated T cell) • Endothelial denudation or dysfunction (local NO production, anti-/procoagulation properties of the endothelium) • Plaque oxidative stress • Superficial platelet aggregation and fibrin deposition (residual mural thrombus) • Rate of apoptosis (apoptosis protein markers, coronary microsatellite, etc) • Angiogenesis, leaking vasa vasorum, and intraplaque hemorrhage • Matrix-digesting enzyme activity in the cap (MMPs 2, 3, 9, etc) • Certain microbial antigens (eg, HSP60, <i>C. pneumoniae</i>)
Pan-Arterial	
	<ul style="list-style-type: none"> • Transcoronary gradient of serum markers of vulnerability • Total coronary calcium burden • Total coronary vasoreactivity (endothelial function) • Total arterial burden of plaque including peripheral (eg, carotid IMT)

MMP indicates matrix metalloproteinase; NO, nitric oxide; and IMT, intima medial thickness.

Diagnosis of Vulnerable Plaque/Artery

A number of issues have hampered establishment of ideal criteria for defining vulnerable plaque: (1) the current body of evidence is largely based on cross-sectional and retrospective studies of culprit plaques; (2) robust prospective outcome studies based on plaque characterization have not been done (due to the lack of a reproducible, validated diagnostic technique); and (3) a lack of a representative animal model of plaque rupture and acute coronary syndrome/sudden death.

On the basis of retrospective evidence, we propose that the criteria listed in Tables 4 and 5 be used to define a vulnerable plaque. The sensitivity, specificity, and overall predictive value of each potential diagnostic technique need to be assessed before entering clinical practice.

Major Criteria

The following are proposed as major criteria for detection of a vulnerable plaque. The presence of one or a combination of these factors may warrant higher risk of plaque complication. Techniques for detection of vulnerable plaque based on these criteria are briefly summarized here. A detailed discussion of advantages and disadvantages are reviewed elsewhere.³³

Morphology vs. Activity Imaging

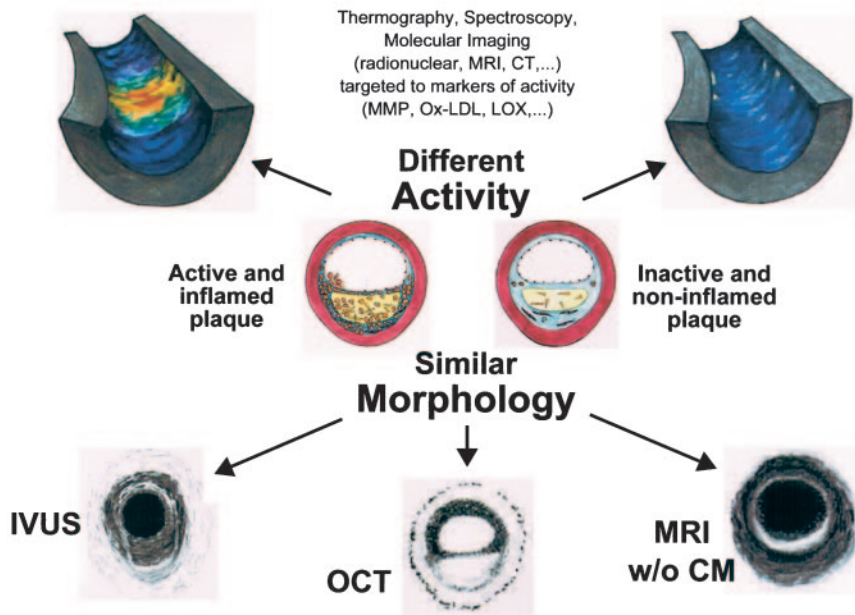


Figure 5. Plaques with nearly similar morphology in terms of lipid core and fibrous cap (middle panel) may look similar with diagnostic imaging aimed at morphology only (bottom panel). However, they might look very different using diagnostic methods capable of detecting activity and physiology of the plaques. The top left plaque is hot (as evidenced in a thermography image), whereas the top right plaque is inactive and detected relatively as a cool plaque.

1. Active Inflammation

Plaques with active inflammation may be identified by extensive macrophage accumulation.¹³ Possible intravascular diagnostic techniques^{34,35} include thermography (measurement of plaque temperature),^{36,37} contrast-enhanced (CE) MRI,^{38,39} fluorodeoxyglucose positron emission tomography,^{33,40} and immunoscintigraphy.⁴¹ It has recently been shown that optical coherence tomography reflects the macrophage content of the fibrous cap.⁴² Noninvasive options include MRI with superparamagnetic iron oxide^{35,36} and gadolinium fluorine compounds.^{43–45}

2. A Thin Cap With a Large Lipid Core

These plaques have a cap thickness of $<100 \mu\text{m}$ and a lipid core accounting for $>40\%$ of the plaque's total volume.⁸ Possible intravascular diagnostic techniques include optical coherence tomography (OCT),^{46,47} intravascular ultrasonography (IVUS),⁴⁸ high-resolution IVUS,⁴⁹ elastography (palpography),^{50,51} MRI,⁵² angiography,⁵³ near infrared (NIR) spectroscopy,^{54–56} and radio-frequency IVUS analysis.^{57,58} The only noninvasive options are presently MRI and possibly CT.^{34,35,59–62}

3. Endothelial Denudation with Superficial Platelet Aggregation

These plaques are characterized by superficial erosion and platelet aggregation or fibrin deposition.⁵ Possible intravascular diagnostic techniques include angiography with dye⁶³ and matrix-targeted/fibrin-targeted immune scintigraphy and OCT.^{46,47} Noninvasive options include fibrin/matrix-targeted contrast enhanced MRI,⁶⁴ platelet/fibrin-targeted single photon emission computed tomography,⁴¹ and MRI.⁵²

4. Fissured/Injured Plaque

Plaques with a fissured cap (most of them involving a recent rupture) that did not result in occlusive thrombi may be prone to subsequent thrombosis, entailing occlusive thrombi or thromboemboli.⁵ Possible intravascular diagnostic techniques include

OCT,^{46,47} IVUS, high-resolution IVUS,⁴⁹ angiography, and MRI.^{34,35} A noninvasive option is fibrin-targeted CE-MRI.^{64,65}

5. Severe Stenosis

On the surface of plaques with severe stenosis, shear stress imposes a significant risk of thrombosis and sudden occlusion. Therefore, a stenotic plaque may be a vulnerable plaque regardless of ischemia. Moreover, a stenotic plaque may indicate the presence of many nonstenotic or less stenotic plaques that can be vulnerable to rupture and thrombosis^{24,66} (Figure 5). The current standard technique is invasive x-ray angiography.³² Noninvasive options include multislice CT,^{67,68} magnetic resonance angiography with or without a contrast agent, and electron-beam tomography angiography.^{59,69–71}

Minor Criteria

For techniques that focus on the plaque level, minor criteria include the following features.

1. Superficial Calcified Nodules

These plaques have a calcified nodule within, or very close to, their cap, and this structure protrudes through and can rupture the cap. This event may or may not be associated with severe coronary calcification and a high calcium score.⁵ Possible intravascular diagnostic techniques include OCT,^{46,47} IVUS and elastography (palpography).⁴⁸ Noninvasive options include electron-beam CT,⁷² multisection spiral CT,⁷³ and MRI.^{34,35}

2. Yellow Color (on Angioscopy)

Yellow plaques, particularly glistening ones, may indicate a large lipid core and thin fibrous cap, suggesting a high risk of rupture. However, because plaques in different stages can be yellow and because not all lipid-laden plaques are destined to rupture or undergo thrombosis, this criterion may lack sufficient specificity.^{53,74} Possible intravascular diagnostic techniques in-

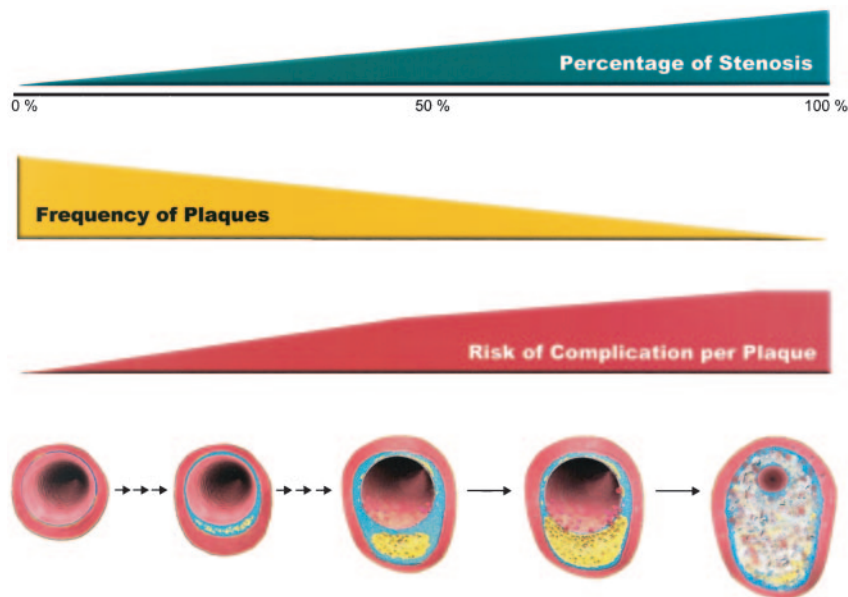


Figure 6. Correlation between frequency of plaques, degree of stenosis, and risk of complication per plaque as a function of plaque progression. Although the average absolute risk of severely stenotic plaques may be higher than the average absolute risk of mildly stenotic plaques, there are more plaques with mild stenoses than plaques with severe stenoses.

clude angioscopy⁷³ and transcatheter colorimetry.⁷⁵ No diagnostic method has yet been developed for noninvasive angioscopy.

3. Intraplaque Hemorrhage

Extravasation of red blood cells, or iron accumulation in plaque, may represent plaque instability.⁷⁶ Possible intravascular diagnostic techniques include NIR spectroscopy,^{54,55} tissue Doppler methods,⁷⁷ and intravascular MRI. A noninvasive option is MRI.^{34,35,61}

4. Endothelial Dysfunction

Impaired endothelial vasodilator function occurs in a variety of acute and chronic disease states. Patients with cardiovascular risk factors have endothelial dysfunction. Endothelial dysfunction predicts CHD and stroke.^{89,95} Vulnerable plaques have sites of active inflammation and oxidative stress and are likely to be associated with impaired endothelial function. Possible diagnostic techniques are endothelium-dependent coronary artery dilatation (intravascular)⁷⁸ and measurement of flow-mediated dilatation by brachial artery ultrasonography and other emerging techniques (noninvasive).⁷⁹

5. Expansive (Positive) Remodeling

Many of the nonstenotic lesions undergo “expansive,” “positive,” or “outward” remodeling, namely compensatory enlargement before impinging significantly on the vascular lumen. This phenomenon was considered as positive remodeling because the luminal area was not affected and stenosis was the only measure of risk. However, with the emphasis on plaque rupture in nonstenotic lesions, the so-called positive remodeling may not be truly positive and beneficial. Several studies have suggested that such remodeling is a potential surrogate marker of plaque vulnerability.^{80,81} In these studies, intravascular ultrasound was used to evaluate remodeling in coronary arteries. A recent study by Kim et al⁸² introduced a noninvasive method for detection of expansive remodeling in coronary arteries by MRI. CT might also provide a noninvasive method for studying arterial remodeling.

Few of the above techniques have been tested in clinical trials showing ability to predict events. MRI and CT-based approaches are being developed. These technologies and strategies must also be evaluated with regard to their cost effectiveness.

Functional Versus Structural Assessment

A growing body of evidence indicates that different types of vulnerable plaque with various histopathology and biology exist. To evaluate plaque vulnerability, it is evident that a combined approach capable of evaluating structural characteristics (morphology) as well as functional properties (activity) of plaque may be more informative and may provide higher predictive value than a single approach. For instance, a combination of IVUS or OCT with thermography^{80,83} may provide more diagnostic value than each of these techniques alone. Such an arrangement can be useful for both intravascular as well as noninvasive diagnostic methods (Figure 6). Autopsy⁸⁴ and IVUS studies⁸⁵ have shown that atherosclerotic lesions are frequently found in young and asymptomatic individuals. It is unclear what percentage of these lesions present morphologies of rupture-prone vulnerable plaques. Moreover, chronic inflammation⁸⁶ and macrophage/foam cell formation are an intrinsic part of the natural history of atherosclerosis. These data suggest that screening only based on plaque morphology and/or chronic markers of inflammation may not provide satisfactory predictive value for detection of vulnerable patients.

Pan-Arterial Approach

Diagnostic and therapeutic methods may focus on the total burden of coronary artery disease.²⁷ The coronary Calcium Score is a good example of using CT for this purpose.⁷² The total burden of calcified atherosclerotic plaques in all coronary arteries is identified by ultrafast CT. Extensive efforts are underway to improve image quality, signal processing, and interpretation of detailed components of coronary arteries that lend hope of a new calcium scoring and risk stratification technique based on CT information.⁸⁷ Like systemic indexes of inflammation (eg, high sensitive CRP), endothelial dysfunction

as measured by impaired flow-mediated vasodilation in the brachial artery can aid in the detection of pan-arterial vulnerability and may serve as a screening tool.^{88,89}

Another emerging technique is the measurement of the transcoronary gradient (difference in concentration between coronary ostium and coronary sinus or between proximal and distal segments of each coronary segment) of various factors, including cytokines,⁹⁰ adhesion molecules,⁹¹ temperature, etc.

It will be important in the future to identify plaques that are on a trajectory of evolution toward a vulnerable state, to find out how long they will stay vulnerable, and to be able to target interventions to those plaques most likely to develop thrombosis. Similarly, factors that protect plaques from becoming vulnerable also need to be identified. It is likely that local hemodynamic factors and 3-dimensional morphology may provide insight regarding the temporal course of an evolving plaque.

New studies are unraveling the role of the adventitia and periadventitial connective and adipose tissue in vulnerability of atherosclerotic plaques.⁹² Further studies are needed to define the importance of these findings in the detection and treatment of vulnerable plaques.

Acknowledgments

We are indebted to Valentin Fuster, MD, and Salim Yusuf, MD, for their insightful reviews and thoughtful comments.

References

1. Yusuf S, Reddy S, Ounpuu S, et al. Global burden of cardiovascular diseases, I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation*. 2001;104:2746–2753.
2. American Heart Association. *2002 Heart and Stroke Statistical Update*. Dallas, Tex: American Heart Association; 2002.
3. Myerburg RJ, Interian A Jr, Mitrani RM, et al. Frequency of sudden cardiac death and profiles of risk. *Am J Cardiol*. 1997;80:10F–19F.
4. Zipes DP, Wellens HJ. Sudden cardiac death. *Circulation*. 1998;98:2334–2351.
5. Virmani R, Kolodgie FD, Burke AP, et al. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*. 2000;20:1262–1275.
6. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation*. 1995;92:657–671.
7. Davies MJ. A macro and micro view of coronary vascular insult in ischemic heart disease. *Circulation*. 1990;82 (suppl II):II-38–II-46.
8. Kolodgie FD, Burke AP, Farb A, et al. The thin-cap fibroatheroma: a type of vulnerable plaque: the major precursor lesion to acute coronary syndromes. *Curr Opin Cardiol*. 2001;16:285–292.
9. Farb A, Burke AP, Tang AL, et al. Coronary plaque erosion without rupture into a lipid core: a frequent cause of coronary thrombosis in sudden coronary death. *Circulation*. 1996;93:1354–1363.
10. 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.
11. Falk E. Plaque rupture with severe pre-existing stenosis precipitating coronary thrombosis: characteristics of coronary atherosclerotic plaques underlying fatal occlusive thrombi. *Br Heart J*. 1983;50:127–134.
12. Friedman M, Van den Bovenkamp GJ. Role of thrombus in plaque formation in the human diseased coronary artery. *Br J Exp Pathol*. 1966;47:550–557.
13. Constantinides P. Pathogenesis of cerebral artery thrombosis in man. *Arch Pathol*. 1967;83:422–428.
14. Chapman I. Relationships of recent coronary artery occlusion and acute myocardial infarction. *J Mt Sinai Hosp N Y*. 1968;35:149–154.
15. Davies MJ, Thomas AC. Plaque fissuring: the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. *Br Heart J*. 1985;53:363–373.
16. Deleted in proof.
17. Willerson JT, Campbell WB, Winniford MD, et al. Conversion from chronic to acute coronary artery disease: speculation regarding mechanisms. *Am J Cardiol*. 1984;54:1349–1354.
18. Muller J, Tofler G, Stone P. Circadian variation and triggers of onset of acute cardiovascular disease. *Circulation*. 1989;79:733–743.
19. 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.
20. Vulnerable. In: *Merriam-Webster's Collegiate Dictionary & Thesaurus*. 11th ed (e-book). Springfield, Mass: Merriam-Webster, Inc; 2003.
21. Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis: a report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation*. 1995;92:1355–1374.
22. Mann J, Davies MJ. Mechanisms of progression in native coronary artery disease: role of healed plaque disruption. *Heart*. 1999;82:265–268.
23. 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.
24. Goldstein JA, Demetriou D, Grines CL, et al. Multiple complex coronary plaques in patients with acute myocardial infarction. *N Engl J Med*. 2000;343:915–922.
25. Nissen SE. Who is at risk for atherosclerotic disease? Lessons from intravascular ultrasound. *Am J Med*. 2002;112(suppl 8A):27S–33S.
26. Rioufol G, Finet G, Ginon I, et al. Multiple atherosclerotic plaque rupture in acute coronary syndrome. *Circulation*. 2002;106:804–808.
27. Buffon A, Biasucci LM, Liuzzo G, et al. Widespread coronary inflammation in unstable angina. *N Engl J Med*. 2002;347:5–12.
28. Casscells W, Naghavi M, Willerson JT. Vulnerable atherosclerotic plaque: a multifocal disease. *Circulation*. 2003;107:2072–2075.
29. Maseri A, Fuster V. Is there a vulnerable plaque? *Circulation*. 2003;107:2068–2071.
30. Kereiakes DJ. The emperor's clothes: in search of the vulnerable plaque. *Circulation*. 2003;107:2076–2077.
31. Davies MJ. Pathology of arterial thrombosis. *Br Med Bull*. 1994;50:789–802.
32. Burke AP, Kolodgie FD, Farb A, et al. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. *Circulation*. 2001;103:934–940.
33. Vallabhajosula S, Fuster V. Atherosclerosis: imaging techniques and the evolving role of nuclear medicine. *J Nucl Med*. 1997;38:1788–1796.
34. Fayad ZA, Fuster V. Clinical imaging of the high-risk or vulnerable atherosclerotic plaque. *Circ Res*. 2001;89:305–316.
35. Naghavi M, Madjid M, Khan MR, et al. New developments in the detection of vulnerable plaque. *Curr Atheroscler Rep*. 2001;3:125–135.
36. Stefanadis C, Diamantopoulos L, Vlachopoulos C, et al. Thermal heterogeneity within human atherosclerotic coronary arteries detected in vivo: a new method of detection by application of a special thermography catheter. *Circulation*. 1999;99:1965–1971.
37. Stefanadis C, Toutouzas K, Tsiamis E, et al. Thermal heterogeneity in stable human coronary atherosclerotic plaques is underestimated in vivo: the “cooling effect” of blood flow. *J Am Coll Cardiol*. 2003;41:403–408.
38. Schmitz SA, Coupland SE, Gust R, et al. Superparamagnetic iron oxide-enhanced MRI of atherosclerotic plaques in Watanabe heritable hyperlipidemic rabbits. *Invest Radiol*. 2000;35:460–471.
39. Ruehm SG, Corot C, Vogt P, et al. Magnetic resonance imaging of atherosclerotic plaque with ultrasmall superparamagnetic particles of iron oxide in hyperlipidemic rabbits. *Circulation*. 2001;103:415–422.
40. Lederman RJ, Raylman RR, Fisher SJ, et al. Detection of atherosclerosis using a novel positron-sensitive probe and 18-fluorodeoxyglucose (FDG). *Nucl Med Commun*. 2001;22:747–753.
41. Ciavolella M, Tavolaro R, Taurino M, et al. Immunoscintigraphy of atherosclerotic uncomplicated lesions in vivo with a monoclonal antibody against D-dimers of insoluble fibrin. *Atherosclerosis*. 1999;143:171–175.
42. Tearney GJ, Yabushita H, Houser SL, et al. Quantification of macrophage content in atherosclerotic plaques by optical coherence tomography. *Circulation*. 2003;107:113–119.
43. Krinsky GA, Freedberg R, Lee VS, et al. Innominate artery atheroma: a lesion seen with gadolinium-enhanced MR angiography and often missed by transeophageal echocardiography. *Clin Imaging*. 2001;25:251–257.
44. Bonk RT, Schmiedl UP, Yuan C, et al. Time-of-flight MR angiography with Gd-DTPA hexamethylene diamine co-polymer blood pool contrast agent: comparison of enhanced MRA and conventional angiography for arterial stenosis induced in rabbits. *J Magn Reson Imaging*. 2000;11:638–646.
45. Yuan C, Kerwin WS, Ferguson MS, et al. Contrast-enhanced high resolution MRI for atherosclerotic carotid artery tissue characterization. *J Magn Reson Imaging*. 2002;15:62–67.

46. 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.
47. Jang I-K, Bouma BE, Kang D-H, 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.
48. Nissen SE. Clinical images from intravascular ultrasound: coronary disease, plaque rupture, and intervention—the inside view. *Am J Cardiol*. 2001;88:16–18.
49. Nissen SE, Yock P. Intravascular ultrasound: novel pathophysiological insights and current clinical applications. *Circulation*. 2001;103:604–616.
50. de Korte CL, Cespedes EI, van der Steen AF, et al. Intravascular ultrasound elastography: assessment and imaging of elastic properties of diseased arteries and vulnerable plaque. *Eur J Ultrasound*. 1998;7:219–224.
51. de Korte CL, Siervogel MJ, Mastik F, et al. Identification of atherosclerotic plaque components with intravascular ultrasound elastography in vivo: a Yucatan pig study. *Circulation*. 2002;105:1627–1630.
52. Corti R, Osende JI, Fuster V, et al. Artery dissection and arterial thrombus aging: the role of noninvasive magnetic resonance imaging. *Circulation*. 2001;103:2420–2421.
53. Takano M, Mizuno K, Okamoto K, et al. Mechanical and structural characteristics of vulnerable plaques: analysis by coronary angiography and intravascular ultrasound. *J Am Coll Cardiol*. 2001;38:99–104.
54. Cassis LA, Lodder RA. Near-IR imaging of atheromas in living arterial tissue. *Anal Chem*. 1993;65:1247–1256.
55. Moreno PR, Lodder RA, Purushothaman KR, et al. Detection of lipid pool, thin fibrous cap, and inflammatory cells in human aortic atherosclerotic plaques by near-infrared spectroscopy. *Circulation*. 2002;105:923–927.
56. Wang J, Geng YJ, Guo B, et al. Near-infrared spectroscopic characterization of human advanced atherosclerotic plaques. *J Am Coll Cardiol*. 2002;39:1305–1313.
57. Jeremias A, Kolz ML, Ikonen TS, et al. Feasibility of in vivo intravascular ultrasound tissue characterization in the detection of early vascular transplant rejection. *Circulation*. 1999;100:2127–2130.
58. Nair A, Kuban BD, Tuzcu EM, et al. Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. *Circulation*. 2002;106:2200–2206.
59. Helft G, Worthley SG, Fuster V, et al. Progression and regression of atherosclerotic lesions: monitoring with serial noninvasive magnetic resonance imaging. *Circulation*. 2002;105:993–998.
60. Hatsukami TS, Ross R, Polissar NL, et al. Visualization of fibrous cap thickness and rupture in human atherosclerotic carotid plaque in vivo with high-resolution magnetic resonance imaging. *Circulation*. 2000;102:959–964.
61. Yuan C, Mitsumori LM, Ferguson MS, et al. In vivo accuracy of multi-spectral magnetic resonance imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human carotid plaques. *Circulation*. 2001;104:2051–2056.
62. Yuan C, Zhang S-X, Polissar NL, et al. Identification of fibrous cap rupture with magnetic resonance imaging is highly associated with recent transient ischemic attack or stroke. *Circulation*. 2002;105:181–185.
63. Uchida Y, Nakamura F, Tomaru T, et al. Prediction of acute coronary syndromes by percutaneous coronary angiography in patients with stable angina. *Am Heart J*. 1995;130:195–203.
64. Flacke S, Fischer S, Scott MJ, et al. Novel MRI contrast agent for molecular imaging of fibrin: implications for detecting vulnerable plaques. *Circulation*. 2001;104:1280–1285.
65. Corti R, Osende JI, Fayad ZA, et al. In vivo noninvasive detection and age definition of arterial thrombus by MRI. *J Am Coll Cardiol*. 2002;39:1366–1373.
66. Asakura M, Ueda Y, Yamaguchi O, et al. Extensive development of vulnerable plaques as a pan-coronary process in patients with myocardial infarction: an angiographic study. *J Am Coll Cardiol*. 2001;37:1284–1288.
67. Nieman K, Oudkerk M, Rensing BJ, et al. Coronary angiography with multi-slice computed tomography. *Lancet*. 2001;357:599–603.
68. Giesler TBU, Ropers D, Ulzheimer S, et al. Noninvasive visualization of coronary arteries using contrast-enhanced multidetector CT: influence of heart rate on image quality and stenosis detection. *AJR Am J Roentgenol*. 2002;179:911–916.
69. Duerinckx AJ. Imaging of coronary artery disease: MR. *J Thorac Imaging*. 2001;16:25–34.
70. Hecht HS. New developments in atherosclerosis imaging: electron beam tomography. *Curr Atheroscler Rep*. 2001;3:417–424.
71. Corti R, Fayad ZA, Fuster V, et al. Effects of lipid-lowering by simvastatin on human atherosclerotic lesions: a longitudinal study by high-resolution, noninvasive magnetic resonance imaging. *Circulation*. 2001;104:249–252.
72. Rumberger JA. Tomographic (plaque) imaging: state of the art. *Am J Cardiol*. 2001;88:66E–69E.
73. Achenbach S, Ropers D, Regenfus M, et al. Noninvasive coronary angiography by magnetic resonance imaging, electron-beam computed tomography, and multislice computed tomography. *Am J Cardiol*. 2001;88:70E–73E.
74. Kodama K, Asakura M, Ueda Y, et al. The role of plaque rupture in the development of acute coronary syndrome evaluated by the coronary angioscope. *Intern Med*. 2000;39:333–335.
75. Lehmann KG, van Suylen RJ, Stibbe J, et al. Composition of human thrombus assessed by quantitative colorimetric angiographic analysis. *Circulation*. 1997;96:3030–3041.
76. Moulton KS. Plaque angiogenesis and atherosclerosis. *Curr Atheroscler Rep*. 2001;3:225–233.
77. Nasu K, Kawamoto A, Sasaki Y, et al. Measurement of vascular tissue blood flow of the atherosclerotic aorta in Watanabe heritable hypercholesterolemic (WHHL) rabbit by using laser Doppler flowmeter-equipped balloon catheter. *Am J Cardiol*. 1999;84:84P.
78. Drexler H, Zeiher AM, Wollschlaeger H, et al. Flow-dependent coronary artery dilatation in humans. *Circulation*. 1989;80:466–474.
79. Vogel RA. Brachial artery ultrasound: a noninvasive tool in the assessment of triglyceride-rich lipoproteins. *Clin Cardiol*. 1999;22:II34–II39.
80. Vamava AM, Mills PG, Davies MJ. Relationship between coronary artery remodeling and plaque vulnerability. *Circulation*. 2002;105:939–943.
81. Smits PC, Pasterkamp G, Quarles van Ufford MA, et al. Coronary artery disease: arterial remodeling and clinical presentation. *Heart*. 1999;82:461–464.
82. Kim WY, Stuber M, Bornert P, et al. Three-dimensional black-blood cardiac magnetic resonance coronary vessel wall imaging detects positive arterial remodeling in patients with nonsignificant coronary artery disease. *Circulation*. 2002;106:296–299.
83. Naghavi M, Madjid M, Gul K, et al. Thermography basket catheter: in vivo measurement of the temperature of atherosclerotic plaques for detection of vulnerable plaques. *Catheter Cardiovasc Interv*. 2003;59:52–59.
84. Wissler RW, Strong JP. Risk factors and progression of atherosclerosis in youth. PDAY Research Group. Pathological Determinants of Atherosclerosis in Youth. *Am J Pathol*. 1998;153:1023–1033.
85. Tuzcu EM, Kapadia SR, Tutar E, et al. High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults: evidence from intravascular ultrasound. *Circulation*. 2001;103:2705–2710.
86. Pasterkamp G, Schoneveld AH, van der Wal AC, et al. Relation of arterial geometry to luminal narrowing and histologic markers for plaque vulnerability: the remodeling paradox. *J Am Coll Cardiol*. 1998;32:655–662.
87. Becker CR, Nikolaou K, Muders M, et al. Ex vivo coronary atherosclerotic plaque characterization with multi-detector-row CT. *Eur Radiol*. 2003;12:12.
88. Vogel RA. Heads and hearts: the endothelial connection. *Circulation*. 2003;107:2766–2768.
89. Targonski PV, Bonetti PO, Pumper GM, et al. Coronary endothelial dysfunction is associated with an increased risk of cerebrovascular events. *Circulation*. 2003;107:2805–2809.
90. Cusack MR, Marber MS, Lambiase PD, et al. Systemic inflammation in unstable angina is the result of myocardial necrosis. *J Am Coll Cardiol*. 2002;39:1917–1923.
91. Yamamoto H, Uemura S, Tomoda Y, et al. Transcardiac gradient of soluble adhesion molecules predicts progression of coronary artery disease. *Int J Cardiol*. 2002;84:249–257.
92. Moreno PR, Purushothaman KR, Fuster V, et al. Intimomedial interface damage and adventitial inflammation is increased beneath disrupted atherosclerosis in the aorta: implications for plaque vulnerability. *Circulation*. 2002;105:2504–2511.
93. Friedman M, Van den Borenkamp G.J. The pathogenesis of a coronary thrombus. *Am J Pathol*. 1966;48:19–44.
94. Friedman M. The pathogenesis of coronary plaques, thromboses, and hemorrhages: an evaluative review. *Circulation*. 1975;52(suppl III):III34–III40.
95. Halcox JP, Schenke WH, Zalos G, et al. Prognostic value of coronary vascular endothelial function. *Circulation*. 2002;106:653–658.