Review: Current Perspective

From Vulnerable Plaque to Vulnerable Patient
A Call for New Definitions and Risk Assessment Strategies: Part I

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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

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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 describin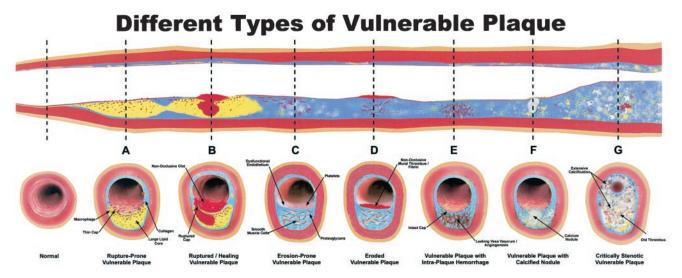g such plaques *before* an event occurs. Plaque rupture was reported sporadically by pathologists in the early 20th century; it became a focus of attention of pioneering scientists in the 1960s (Table 2) and was later documented further by others.[11–15]

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, Falk[11] and Davies and Thomas[15] 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]

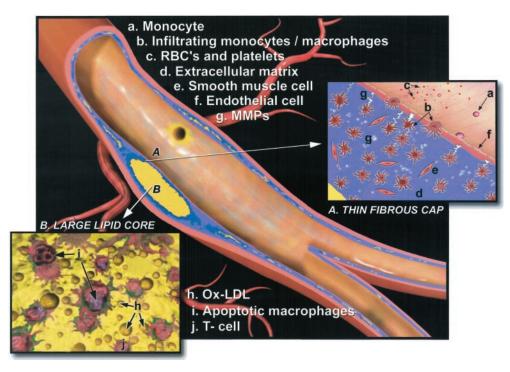| Author	Year	Description Used
Olcott	1931	Plaque rupture
Leary	1934	Rupture of atheromatous abscess
Wartman	1938	Rupture-induced occlusion
Horn	1940	Plaque fissure
Helpern	1957	Plaque erosion
Crawford	1961	Plaque thrombosis
Gore	1963	Plaque ulceration
Byers	1964	Thrombogenic gruel
Chapman	1966	Plaque 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 Davies[22] and Burke et al[23] in cardiac autopsy specimens, Goldstein et al[24] in angiography studies, Nissen[25] and Rioufol et al[26] with intravascular ultrasound, and Buffon et al[27] 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 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]

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

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 ≥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
- 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
- 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, *C. pneumoniae*)

Pan-Arterial
- 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]
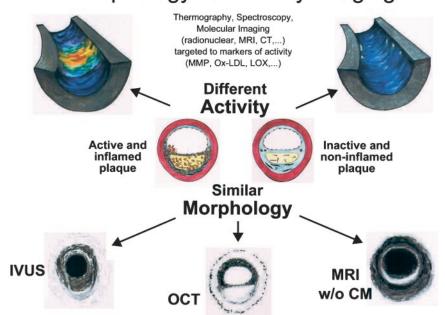
Morphology vs. Activity Imaging

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] fluorode-oxyglucose 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 μm 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] angioscopy,[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 angioscopy with dye[63] 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 thrombo-emboli.[5] Possible intravascular diagnostic techniques include

OCT,[46,47] IVUS, high-resolution IVUS,[49] angioscopy, 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-
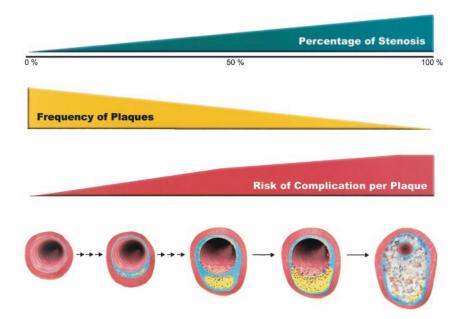
Figure 6. Correlation between frequency of plaques, degree of stenosis, and risk of complication per plaque as a function of plaque progression. Although the average absolute risk of severely stenotic plaques may be higher than the average absolute risk of mildly stenotic plaques, there are more plaques with mild stenoses than plaques with severe stenoses.

clude angioscopy[73] 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 al[82] 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). Autopsy[84] and IVUS studies[85] 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 inflammation[86] 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

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