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

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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 opportunity in the field of cardiovascular medicine. This consensus review brings together experts from around the world to outline the criteria for identifying plaque vulnerability, suggest strategies for risk assessment, and identify potential targets for therapeutic intervention.
Vulnerable (Thrombogenic) Blood

Serum Markers of Atherosclerosis and Inflammation

Serum markers may predict a patient’s risk of acute cardiovascular complications (Table 1). C-reactive protein (CRP) is an independent risk factor and a powerful predictor of future coronary events in the asymptomatic population and in patients with stable and unstable disease. Although CRP is a nonspecific marker of systemic inflammation, it activates endothelium and accumulates in the plaque, suggesting an important role in plaque inflammation.

Circulating interleukin-6 levels, which are elevated in patients with acute coronary syndromes, also predict the risk of future coronary events in such patients. Recently, investigators have shown that high plasma concentrations of soluble CD40 ligand may indicate an increased vascular risk in apparently healthy women. Likewise, Hwang et al showed in a large population-based sample of individuals that circulating levels of soluble intracellular adhesion molecule were predictive of future acute coronary events.

Markers of systemic inflammation, such as soluble adhesion molecules, circulating bacterial endotoxin, soluble human heat-shock protein 60, and antibodies to mycobacterial heat-shock protein 65, may predict an increased risk of atherosclerosis. Pregnancy-associated plasma protein A (PAPP-A) is present in unstable plaques, and its circulating levels are elevated in patients with acute coronary syndromes. Increased serum levels of PAPP-A may reflect instability of atherosclerotic plaques.

With major advances in high-throughput genomics and proteomics research, future studies will undoubtedly identify new risk and protective factors and biomarkers that can be used for screening purposes. A recent study suggested an association between several genetic polymorphisms and clinical outcomes, some of which can be possibly related to plaque, blood, and myocardial vulnerability. The tools and knowledge base made possible by the Human Genome Project allow the field to move beyond one or a few single-nucleotide polymorphisms in a priori candidate genes. Genome-wide linkage analyses have been

### TABLE 1. Serological Markers of Vulnerability (Reflecting Metabolic and Immune Disorders)

- Abnormal lipoprotein profile (eg, high LDL, low HDL, abnormal LDL and HDL size density, lipoprotein [x], etc)
- Nonspecific markers of inflammation (eg, hsCRP, CD40L, ICAM-1, VCAM-1, P-selectin, leukocytosis, and other serological markers related to the immune system; these markers may not be specific for atherosclerosis or plaque inflammation)
- Serum markers of metabolic syndrome (eg, diabetes or hypertriglyceridemia)
- Specific markers of immune activation (eg, anti-LDL antibody, anti-HSP antibody)
- Markers of lipid peroxidation (eg, ox-LDL and ox-HDL)
- Homocysteine
- PAPP-A
- Circulating apoptosis marker(s) (eg, Fas/Fas ligand, not specific to plaque)
- ADMA/DDAH
- Circulating nonesterified fatty acids (eg, NEFA)

hsCRP indicates high-sensitivity CRP; CD40L, CD40 ligand; ICAM, intracellular adhesion molecule; VCAM, vascular cell adhesion molecule; MMP, matrix metalloproteinases; TIMP, tissue inhibitors of MMPs; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HSP, heat shock protein; ADMA, asymmetric dimethylarginine; ADMA, dimethylarginine dimethylaminohydrolase; and NEFA, nonesterified fatty acids.
TABLE 2. Blood Markers of Vulnerability (Reflecting Hypercoagulability)

- Markers of blood hypercoagulability (eg, fibrinogen, D-dimer, and factor V Leiden)
- Increased platelet activation and aggregation (eg, gene polymorphisms of platelet glycoproteins Iib/IIIa, Ia/IIa, and Iib/IX)
- Increased coagulation factors (eg, clotting of factors V, VII, and VIII; von Willebrand factor; and factor XIII)
- Decreased anticoagulation factors (eg, proteins S and C, thrombomodulin, and antithrombin III)
- Decreased endogenous fibrinolysis activity (eg, reduced t-PA, increased PAI-1, certain PAI-1 polymorphisms)
- Prothrombin mutation (eg, G20210A)
- Other thrombogenic factors (eg, antidiiodiopin antibodies, thrombosis, sickle cell disease, polycythemia, diabetes mellitus, hypercholesterolemia, hyperhomocysteinemia)
- Increased viscosity
- Transient hypercoagulability (eg, smoking, dehydration, infection, adrenergic surge, cocaine, estrogens, postprandial, etc)

1-PA indicates tissue plasminogen activator; PAI, type 1 plasminogen activator inhibitor.

Carried out for coronary artery calcification,13 and genomewide association studies for myocardial infarction are already a reality.14 Further studies are needed to address the relationship between single-nucleotide polymorphisms in components of each of the plaque, blood, and myocardial vulnerabilities and future outcomes (acute coronary syndromes and sudden cardiac death). However, ongoing proteomic research on serum samples of vulnerable patients collected from prospective studies before the onset of symptoms is most promising.

Coagulation/Anticoagulation System

The importance of the coagulation/fibrinolytic system is highlighted by several autopsy studies that have shown a high prevalence of old plaque disruptions without infarctions. Therefore, an active fibrinolytic system may be able to prevent luminal thrombosis in some cases of plaque disruption.27,28

A transient shift in the coagulation and anticoagulation balance is likely to be an important factor in plaque-blood interaction, resulting in an acute event. “Triggers” such as exercise and smoking, which are associated with catecholamine release, may increase the risk of plaque thrombosis.29 Similarly, metabolic factors, such as postprandial metabolic changes, are associated with increased blood coagulability.30 Likewise, estrogen replacement therapy can lead to a hypercoagulable state.31

Finally, plasma viscosity, as well as fibrinogen and white blood cell counts, is positively associated with CHD events as shown by Koenig et al.32 Furthermore, Junker et al33 showed a positive relationship between plasma viscosity and the severity of coronary heart disease (CHD).

Vulnerable Myocardium

Ischemic Vulnerable Myocardium Without Prior Atherosclerosis-Derived Myocardial Damage

Abrupt occlusion of a coronary artery is a common cause of sudden death. It often leads to acute myocardial infarction or exacerbation of chest pain.34,35 Extensive studies in experimental animals and increasing clinical evidence indicate that autonomic nervous activity has a significant role in modifying the clinical outcome with coronary occlusion.30,36,37 Susceptibility of the myocardium to acute ischemia was reviewed by Airaksinen,38 who emphasized the key role of autonomic tone in the outcome after plaque rupture. Sympathetic hyperactivity favors the genesis of life-threatening ventricular tachyarrhythmias, whereas vagal activation exerts an antifibrillatory effect. Strong afferent stimuli from the mechanism of action responsible for the increased thrombotic complications associated with the presence of these cardiovascular risk factors.21 Acute coronary syndromes are associated with proinflammatory and prothrombotic conditions that involve a prolonged increase in the levels of fibrinogen, CRP, and plasminogen activator inhibitor.22,23

A number of blood abnormalities, including antithrombin III deficiency, protein C or S deficiency, and resistance to activated protein C (also known as factor V Leiden), have been implicated as causes of venous thrombosis. The risk of arterial thrombosis is only modestly increased in these conditions, but these abnormalities are thought to interact with traditional risk factors for arterial thrombosis.

Venous and arterial thromboses are prominent features of the antiphospholipid syndrome.24,25 The main antibodies of this syndrome are the anticoagulant antibody, the lupus anticoagulant, and the IgG antibodies against prothrombin and β2-glycoprotein.24,25

In the nephrotic syndrome, proteinuria results in abnormal concentration and activity of coagulation factors. Moreover, the associated hypoalbuminemia, thrombosis, and hypercholesterolemia may induce arterial and venous thrombosis.26

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Some platelet polymorphisms, such as glycoprotein IIIa P1(A2),17 Ib α gene-5T/C Kozak,18 high factor V and factor VII clotting,19 have been reported as independent risk factors for myocardial infarction. Reiner et al20 recently reviewed the associations of known and potential genetic susceptibility markers for intermediate hemostatic phenotypes with arterial thrombosis.

Other conditions that lead to a hypercoagulable state are diabetes mellitus, hypercholesterolemia, and cigarette smoking. High levels of circulating tissue factor may be the
Ischemic myocardium may impair the arterial baroreflex and lead to hemodynamic instability.39 There seems to be a wide interindividual variation in the type and severity of autonomic reactions during the early phase of abrupt coronary occlusion, a critical period for out-of-hospital cardiac arrest. The pre-existing severity of a coronary stenosis, adaptation or preconditioning to myocardial ischemia, habitual physical exercise, β-blockade, and gender seem to affect autonomic reactions and the risk of fatal ventricular arrhythmias.38,40,41 Recent studies have documented a hereditary component for autonomic function, and genetic factors may also modify the clinical presentation of acute coronary occlusion.42,43 Table 3 depicts conditions and markers associated with myocardial vulnerability.

Ischemic Vulnerable Myocardium With Prior Atherosclerosis-Derived Myocardial Damage (Chronic Myocardial Damage)

Any type of atherosclerosis-related myocardial injury, such as ischemia, an old or new myocardial infarction, inflammation, and/or fibrosis, potentially increases the patient’s vulnerability to arrhythmia and sudden death. In the past few decades, a number of diagnostic methods have been developed for imaging cardiac ischemia and for assessing the risk of developing a life-threatening cardiac arrhythmia. In patients with a history of ischemic heart disease, ischemic cardiomyopathy is the ultimate form of myocardial damage. With the advent of new, effective treatments for hypertension and more efficient management of acute myocardial infarction, deaths resulting from stroke and acute myocardial infarction have steadily decreased.44 More patients are now surviving acute events, but some develop heart failure or ischemic cardiomyopathy later with the potential for fatal arrhythmias. It is also important to remember that in a significant number of patients, sudden cardiac death is the first manifestation of underlying heart disease, and it is still responsible for >450 000 deaths annually in the United States.

Nonischemic Vulnerable Myocardium

A smaller subset of patients experience fatal arrhythmia as a result of diseases other than coronary atherosclerosis. The various forms of cardiomyopathy (dilated, hypertrophic, restrictive, and right ventricular) account for most noncoronary cardiac deaths. Other underlying pathological processes include valvular heart disease, such as aortic stenosis and primary electrical disturbances (long-QT syndromes, Brugada syndrome, Wolff-Parkinson-White syndrome, sinus and atrioventricular conduction disturbances, catecholaminergic polymorphic ventricular tachycardia, T-wave alternans, drug-induced torsades de pointes). Commotio cordis from chest trauma. Less common pathological conditions include anomalous origin of a coronary artery, myocarditis, and myocardial bridging (Table 3). Circulating nonesterified fatty acids are another risk factor
for sudden death in middle-aged men, as is elevated serum concentration of CRP; serum measurements may help screening for vulnerable myocardium.45

Recently, the Task Force on Sudden Cardiac Death, organized by the European Society of Cardiology, issued a report that includes detailed diagnostic and therapeutic recommendations for a large number of cardiomyopathic conditions capable of causing sudden cardiac death.46

Table 4 provides electrophysiological diagnostic criteria and techniques for detection of myocardial vulnerability.

**Risk Assessment for Vulnerable Patients**

**Traditional Risk Assessment Strategies**

Despite extensive studies and development of several risk prediction models, traditional CHD risk factors fail to predict development of CHD in a large group of cases (25%47 to 50%3,48,49). Risk prediction models developed on the basis of data from long-term population-based follow-up studies may not be able to predict short-term risks for individual persons. The recent report by Ridker et al,3 who noted a greater impact of an inflammatory marker such as serum CRP than LDL levels, is of interest. Several risk factor assessment models (eg, Framingham,50 Sheffield,51,52 New Zealand,53,54 Canadian,55 British,56 European,57 Dundee,58 Munster [PROCAM],59 and MONICA60) have been developed. However, all of them are based on the traditional risk factors known to contribute to the chronic development of atherosclerosis. Addition of emerging risk factors, particularly those indicative of the activity of the disease (ie, plaque inflammation), may allow individualized risk assessments to be made.

The traditional risk assessment has been shown to predict long-term outcome in large populations. However, they fall short in predicting near-future events particularly in individual clinical practice. For example, a high Framingham Risk Score, although capable of forecasting an adverse cardiovascular event in 10 years, clearly falls short in accurately predicting events in individual patients and cannot provide a clear clinical route for cardiologists to identify and treat, to prevent near future victims of acute coronary syndromes and sudden death. The same is true for...
coronary evaluations using electrocardiography, myocardial perfusion tests, and coronary angiography. A positive test for coronary stenosis or reversible perfusion defect (ischemia), although considered as a major risk factor, must be coupled in the future with emerging methods of risk assessment for detection of vulnerable patients to predict more accurately the near-future outcome and prognosis. Those who have no indication of coronary stenosis or myocardial ischemia and who may even lack traditional risk factors may benefit from the techniques now under development that evaluate plaque biology and inflammation.

New Risk Assessment Strategies

We propose a Cumulative Vulnerability Index based on the following:

- Vulnerable plaque/artery
- Vulnerable blood (prone to thrombosis)
- Vulnerable myocardium (prone to life-threatening arrhythmia)

This proposal is by no means intended to disregard the predictive value of traditional risk assessment strategies that have been proven in predicting long-term outcome but instead to strengthen their value in providing higher accuracy, especially for near-term outcomes.

Atherosclerosis is a diffuse and multisystem, chronic inflammatory disorder involving vascular, metabolic, and immune systems with various local and systemic manifestations. Therefore, it is essential to assess total vulnerability burden and not just search for a single, unstable coronary plaque. A composite risk score (eg, a vulnerability index), that comprises the total burden of atherosclerosis and vulnerable plaque in the coronaries (and aorta and carotid, femoral, etc, arteries), and that includes blood and myocardial vulnerability factors, should be a more accurate method of risk stratification. Such a vulnerability index would indicate the likelihood that a patient with certain factors would have a clinical event in the coming year. Use of the state-of-the-art bioinformatics tools such as neural networks may provide a cost-effective, stepwise approach designed to further stratify risk and provide reliable diagnosis and pathways for monitoring therapy. Obviously, these goals are hard to achieve with today’s tools. However, it is well within our reach, if academia and industry in the field of cardiovascular medicine undertake a coordinated effort to embark on developing new screening and diagnostic techniques to identify vulnerable patients (Figure).

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References


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