A Quick Test Predicts Acute Coronary Events
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A 57-year-old retired critical care nurse was seen in the emergency department of a local hospital with classic signs and symptoms of angina pectoris. The patient had a 4-year history of diabetes mellitus type II, controlled with a low-carbohydrate, weight-reducing diet and a 10-year history of essential hypertension, controlled with an angiotensin-converting enzyme inhibitor (ACEi) and a β-blocker. An excessive hyperlipidemia was treated with a statin on an above-average dose, plus ezetemide, a lipid-lowering compound that selectively inhibits the intestinal absorption of cholesterol. Blood lipids were maintained at therapeutic levels, (eg, total cholesterol, 4.34 mmol/L [168 mg/dL]; triglycerides, 1.41 mmol/L [125 mg/dL]; low-density lipoprotein [LDL], 1.94 mmol/L [75 mg/dL]; and high-density lipoprotein [HDL], 1.71 mmol/L [66 mg/dL]). In the past 18 months, she had infrequent and predictable angina with effort, 1 or 2 attacks per month; however, in the past week the frequency of her angina had increased and in the past 2 days she had experienced 4 to 5 attacks of angina daily unrelated to effort, but the angina responded promptly to sublingual nitroglycerine 0.4 mg. An electrocardiogram (ECG) obtained in the emergency department during a pain-free interval revealed no acute changes and was unchanged compared with a routine ECG obtained 6 weeks before. The high-sensitivity C-reactive protein (hs-CRP) level was within the normal range. Additional history revealed that her husband had died 2 weeks earlier following an automobile accident. The change in the pattern of angina occurred after his death. The interpretation of the change in angina was that there was an increase in oxygen demands due to emotional stress, rather than an increase in plaque vulnerability and a greater degree of plaque inflammation. This interpretation was supported by the report of a normal hs-CRP level. The patient, a retired critical care nurse, understood the increase in oxygen demands and the adverse cardiac reactions that can result from emotional stress; she responded to an increased dose of her β-blocker and became symptom-free without any other intervention. Emotional stress can be a dominant influence on the severity and frequency of angina. The natural history of angina is characterized by episodic variations in frequency and intensity of symptoms that may be due to enhanced plaque pathology, but can also coincide with periods of emotional stress without implications of an adverse change in plaque pathology.1

QUESTIONS

1. Which of the following are properties of endothelium?
   a. maintains hemodynamic homeostasis
   b. senses vascular milieu
   c. consists of a single cell lining all blood vessels
   d. releases prostacycline
   e. has paracrine function
   f. all of the above

2. Dysfunctional endothelium potentiates atherogenesis.
   a. True
   b. False

3. Endothelial dysfunction is reversible.
   a. True
   b. False

4. Endothelial function is usually evaluated in which vascular bed?
   a. cerebral
   b. peripheral
   c. coronary
   d. microvascular
5. Coronary plaque rupture in acute cardiovascular (CV) events is influenced by which of these factors?
   a. shear stress
   b. plaque size
   c. plaque composition
   
6. Which of the following markers is easily measured and the most reliable indicator of impending acute coronary events?
   a. serum homocysteine level
   b. hs-CRP level
   c. interleukin-6 (IL-6) level
   d. plaque temperature

ANSWERS

1. f. all of the above

The endothelium is a single-cell layer that lines the internal surface of all blood and lymph vessels, heart, and serous body cavities. As the source of key surface-related activities, the intimal endothelium is in a strategic anatomic location to sense systemic and local stimuli that affect changes in hemodynamic forces and vascular smooth muscle. The endothelium regulates vascular homeostasis by releasing hormones with paracrine and autocrine functions that influence vasoactivity (Table 1). Endothelium-derived factors include nitric oxide (NO), adenosine, prostacyclin, thromboxane A₂, and endothelin. These influence vascular tone, platelet activity, and coagulation and can potentiate long-term vascular inflammation and smooth muscle cell migration and proliferation (Table 2). Thromboxane A₂ is a vasoconstrictor and promotes platelet adhesion favoring thrombosis: aspirin blocks thromboxane A₂ and promotes prostacyclin. When unopposed by thromboxane A₂, prostacyclin functions as a vasodilator and reduces platelet stickiness. Endothelin is the most powerful vasoconstrictor. The overall effects of the endothelium-derived factors are to maintain normal vascular tone and blood viscosity, and to minimize inflammatory and proliferative responses. NO is the key endothelium-derived relaxing factor; NO determines basal smooth muscle vascular tone and reactivity and opposes the potent endothelium-derived constricting factors, angiotensin II and endothelin. NO inhibits platelet and leukocyte activation and prevents proliferation of smooth muscle cells.

![Table 1 Glossary of terms](image)

![Table 2 Function of substances derived from endothelial cells](image)

2. a. True

Coronary atherosclerotic disease is a chronic process that often begins in childhood. Acute coronary events occur as a result of rupture of an unstable atheromatous plaque. These sudden events are preceded by prolonged disruption of the normal endothelial regulatory functions. Endothelial dysfunction is the key in the development of atherosclerosis and is enhanced in diabetics, hypertensives, and in hyperlipidemics. Biochemical evidence of endothelial dysfunction can be detected long before angiographic or histologic signs of atherosclerosis.

Endothelial function is a “barometer” of vascular health. Prolonged vascular stress and injury occur as a result of CV risk factors, vascular inflammation,
infection, and environmental or genetic risk factors. The resulting dysfunctional endothelium potentiates the pathophysiology of acute coronary events, that is, vasoconstriction, loss of endothelium-dependent relaxation, leukocyte adherence, platelet activation, oxidation, thrombosis, and vascular inflammation. Finally, dysfunctional endothelium facilitates enzyme production, which promotes the breakdown of the plaque matrix structure. Elevated levels of LDL and low levels of HDL are significant risk factors (Table 3). Oxidized LDL triggers a cascade of pathologic sequences that are vasoconstrictive, inflammatory, and prothrombotic.

3. a. True

Many factors can impair endothelial function (Table 4). Endothelial dysfunction appears at an early stage in the development of atherosclerosis. Pharmacological agents and lifestyle modification can restore endothelial health and function and reduce CV risk. Improving endothelial cell function can retard or prevent the clinical course of coronary artery disease (CAD). Recent trials have shown that normal endothelial dilating function can be restored by a number of strategies; these include administration of statins (which act independently of their lipid-lowering actions), use of endothelin blockers, inhibition of the renin-angiotensin system with the use of ACEi or angiotensin-receptor blockers, the use of antioxidants, folate (via homocysteine reduction) increasing HDL levels, reducing LDL levels, smoking cessation, and regular physical exercise. ACE inhibition also directly increases NO availability.

Table 3 Cardiovascular risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age</td>
<td>Elevated C-reactive protein levels</td>
</tr>
<tr>
<td>Male sex</td>
<td>Male sex</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Elevated brain natriuretic peptide levels</td>
</tr>
<tr>
<td>Elevated low-density</td>
<td>Smoking</td>
</tr>
<tr>
<td>lipoprotein cholesterol levels</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Sedentary lifestyle</td>
<td>Mental stress</td>
</tr>
<tr>
<td>Low high-density lipoprotein</td>
<td>High-fat diet</td>
</tr>
<tr>
<td>cholesterol levels</td>
<td>Hyperhomocysteinemia</td>
</tr>
<tr>
<td></td>
<td>Increased body mass index</td>
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</tbody>
</table>

Table 4 Factors impairing endothelial function

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history</td>
<td>Obesity</td>
</tr>
<tr>
<td>Mental stress</td>
<td>High-fat diet</td>
</tr>
<tr>
<td>Aging</td>
<td>Inactivity</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Hypertension</td>
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<tr>
<td>Smoking</td>
<td>Oxidized low-density lipoprotein cholesterol levels</td>
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<tr>
<td>High low-density lipoprotein</td>
<td>Lipoprotein cholesterol</td>
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<tr>
<td>cholesterol levels</td>
<td>Small density low-density lipoprotein</td>
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<tr>
<td>Low high-density lipoprotein</td>
<td>Hyperhomocysteinemia</td>
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<td>cholesterol levels</td>
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4. b. peripheral
c. coronary

Patients with CAD or CV risk factors are known to have endothelial dysfunction. Endothelial function is evaluated by noting the vasodilating or constricting response of the microvascular and epicardial arteries to various pharmacological agents or physiological stressors. Normal coronary vasodilator response to stress is through the release of NO from the endothelial cells. With the onset of endothelial dysfunction, the availability of NO is reduced and endothelial homeostasis is compromised.

Endothelial-dependent vasodilatation can be assessed in either the coronary or peripheral circulation; however, the most reliable data are obtained with intracoronary measurements during cardiac catheterization. Three days before catheterization, all cardiac medications are discontinued and the endothelial-dependent vasodilating function is evaluated by measuring the changes in coronary artery diameter, resistance, and blood flow, in response to intracoronary infusion of a vasodilator (acetylcholine, sodium nitroprusside, or adenosine). In normal coronary vessels, acetylcholine triggers an NO-mediated vasodilatory response. In contrast, with endothelial dysfunction, the vasodilating effect is blunted or paradoxical vasoconstriction occurs. Noninvasive assessment of coronary endothelial function has been performed with Doppler echocardiography, positive-emission tomography scanning, and phase-contrast magnetic resonance imaging. Assessment of coronary endothelial function is relevant to future CV events and therapy; however, the routine use of cardiac catheterization and the intracoronary infusion of vasoactive agents to assess coronary artery function can increase risks in patients with unstable coronary disease, let alone the constraints of time and cost. Although the brachial and coronary vascular beds are similar in their vulnerability to CV risk factors, their physiological mechanisms and clinical manifestations of atherosclerosis vary. As a consequence, endothelial function is best measured in the coronary arteries. Nevertheless, the routine use of coronary artery catheterization to
assess coronary vasodilator function in potentially unstable coronary patients is not feasible because of the factors previously noted and the availability of a simple blood test that can predict acute coronary events.

5. a. shear stress
   b. plaque size
   c. plaque composition

The clinical manifestations of acute coronary events are precipitated by plaque rupture, which often results in thrombosis and critical occlusion. Coronary plaque stability is determined by plaque composition. Plaques that contain monocytes, phagocytes, a high fat content, and a thin cap are unstable and prone to rupture regardless of size. The incidence of rupture is highest in plaques that are less than 50% stenotic on angiography. Shear stress is a critical factor in plaque rupture when a jetted arterial blood stream forcibly strikes an acute upstream angle of a coronary plaque. Inflammation is a significant component of plaque pathology and an indicator of plaque instability. Inflammation is either a product of plaque pathology or a contributor to plaque pathology or both. Regardless, plaque inflammation and the degree of inflammation are measurable (CRP level) and are important guides in treatment and prognosis.

6. b. hs-CRP level

Several hundred risk factors for CAD have been identified, but only a few evolved as reliable markers worthy of routine screening.\textsuperscript{5,6} The drive to identify new predictors of CV risk is fueled by the lack of sensitivity and specificity of the usual risk factors. Advances in genomics, the cataloging and analysis of all the genes in the human body, and advances in proteonomics, the cataloging of every protein in the human body, will probably help uncover additional markers with greater accuracy.\textsuperscript{7}

Inflammation has an integral role in the origin and complications of CAD.\textsuperscript{2} A feature of inflammation, tissue necrosis, infection, and neoplasia is the increase in circulating levels of plasma proteins, the acute-phase reactants. An example is CRP, which is an abnormal serum globulin formed by the liver (hepatocytes) in response to either inflammation, infection, tissue necrosis, or neoplasia. The abnormal serum globulin is called CRP because it forms a precipitate with the somatic C-polysaccharide of the pneumococcus.\textsuperscript{8,9} CRP levels are low in healthy patients, but increase in response to inflammation. Elevations in CRP levels reflect an increase in production of the proinflammatory substances IL-6 and IL-1. These interleukins are triggered by inflammation, tissue damage, or intercurrent infections.\textsuperscript{10} In addition to being a marker of systemic inflammation, CRP is directly responsible for tissue damage. CRP can activate the complement pathway and neutralize platelet-activating factors.\textsuperscript{7,10} High-sensitivity assays measure minor elevations of CRP that are predictive of acute coronary events.\textsuperscript{7} A study evaluating CRP levels in the emergency department confirmed that hs-CRP levels are elevated in the majority of patients with chest pain who develop an acute myocardial infarction. In this study, a normal hs-CRP level in patients with chest pain negated a diagnosis of an acute coronary event and ruled out the probabilities of an impending acute myocardial infarction. In contrast, elevation of hs-CRP implies an immediate risk of an acute CV event.\textsuperscript{10}

**Summary**

Inflammation of the coronary arterial wall plays a major role in atherosclerosis and ultimately thrombosis by contributing to vascular constriction, spasm, and thrombus formation. Measurement of hs-CRP level is a readily available laboratory blood test that serves as a gauge of coronary plaque inflammation. As a result, hs-CRP has become a very useful biological marker for predicting the risk of acute coronary events and for making decisions regarding treatment. It is important to recognize that lipid-lowering therapy decreases plaque inflammation and slows the progression of calcium buildup in the coronary arteries, which is readily verified by reduction in hs-CRP levels.\textsuperscript{10}

Endothelial dysfunction is a product of plaque inflammation and as such can predict acute CV events. Endothelial function can be assessed during cardiac catheterization by measuring the vasoactive response to pharmacological or physiological stress. However, the routine use of cardiac catheterization to measure drug-induced coronary vasoactivity can have potential adverse effects in patients with unstable coronary disease. Time and costs can also be additional constraints in the routine use of this procedure. Consequently the simple and readily available hs-CRP test is accurate and preferable.

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**REFERENCES**

SELECTED REFERENCES


