The inflammatory etiology of atherosclerosis has prompted a search for biomarkers of inflammation that predict risk for coronary artery disease and its sequelae. Within the acute coronary syndromes (ACS), inflammatory biomarkers may provide independent information regarding pathophysiology, prognosis, and optimal therapeutic strategies. On the basis of the hypothesis that different pathophysiological processes provide nonoverlapping information regarding risk stratification and disease management, this review series addresses biomarkers for each step in the inflammatory process that leads to ACS. Part I reviewed cytokines; this part reviews acute-phase reactants and biomarkers of endothelial cell activation; subsequent parts will address biomarkers of oxidative stress, angiogenesis, extracellular matrix degradation, and platelet activation.

Acute-Phase Reactants
In the acute-phase response, cytokines drive production of acute-phase reactants, defined by >25% change in circulating concentration during an inflammatory response. These markers may also remain elevated chronically because of continuing inflammatory stimuli (Table).

C-Reactive Protein
C-reactive protein (CRP) is a pentraxin acute-phase protein, members of which are evolutionarily conserved in most vertebrates. Hepatocytes and possibly smooth muscle cells and macrophages transcriptionally activate production of CRP in response to inflammatory cytokines, including interleukin-1 and interleukin-6. CRP is a robust clinical marker because of its stability, reproducible results, and ease of assay. Although it was originally proposed as a nonspecific marker of inflammation, several reports suggest that CRP may play a direct pathophysiologi- cal role in the development and progression of atherosclerosis. Proposed mechanisms include induction of endothelial dysfunction, promotion of foam cell formation, inhibition of endothelial progenitor cell survival and differentiation, and activation of complement in atherosclerotic plaque intima and ischemic myocardium.

Patients with ACS have elevations in CRP in association with their presenting symptoms. There appears to be a bimodal CRP response among patients with ACS. In some patients, CRP may remain elevated for up to 3 months, whereas in others, CRP slowly declines during the hospital admission. A correlation exists between troponin elevation and CRP levels, although a significant percentage of patients without troponin elevation have elevated levels of CRP. In patients presenting with acute myocardial infarction (MI), CRP levels correlate with the presence of plaque rupture, as assessed by intravascular ultrasound. The cause of CRP elevations in the absence of overt myocardial necrosis is uncertain but may be related to plaque instability or myocyte necrosis below the limit of detection of standard assays.

An early study examining CRP in ACS found that CRP identified a subset of patients with severe unstable angina at increased risk for death and MI. Studies of CRP elevation and short-term risk after ACS have found that CRP elevation may predict 14-day mortality. A meta-analysis through

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Inflammatory Biomarkers in ACS

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NSTEMI indicates non–ST-elevation MI, CAD, coronary artery disease.

2001 found that elevated CRP at admission in patients with non–ST-elevation MI (NSTEMI) or unstable angina conferred a 1.5-fold increased risk of death or nonfatal MI at 30 days.14

CRP elevations during admission for ACS also predict long-term risk of mortality. Patients with unstable angina and CRP >3 mg/L at discharge are more likely to be readmitted for recurrent cardiovascular instability or MI within 1 year.9 In a prospective study of patients who underwent early invasive therapy for non–ST-elevation ACS (NSTEM ACS), CRP >10 mg/L during admission remained associated with increased risk of death over a mean follow-up of 20 months.15 Similar results were observed in the FRISC (FRagmin during InStability in Coronary artery disease) trial, in which CRP remained an independent predictor of mortality after an average of 30 months.16

Continued elevations in CRP portend increased risk of mortality despite currently available therapeutic strategies for ACS. In the PROVE IT-TIMI 22 (PRavastatin Or atorVastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) trial,17 patients who achieved CRP levels <2 mg/L after treatment with atorvastatin or pravastatin had a decreased rate of death or recurrent MI compared with patients who achieved CRP >2 mg/L; this effect was independent of achieved cholesterol levels. These results validate intensive statin therapy after ACS and suggest that additional interventions targeted at lowering CRP in the post-MI period may provide additive benefit in this high-risk subgroup of patients.

**Serum Amyloid A**

Serum amyloid A (SAA) comprises a group of 3 functionally related apolipoproteins. During the acute-phase response, SAA displaces apolipoprotein (apo) A1 and apoAII from high-density lipoprotein to form larger, denser high-density lipoprotein particles that have diminished ability to catalyze cholesterol esterification and efflux. These particles may subsequently promote foam cell formation.18

During acute MI, SAA levels increase within 24 hours and peak within 3 days after the onset of chest pain.19 A TIMI 11A substudy found that elevated levels of SAA predicted risk of 14-day mortality in patients with unstable angina or NSTEMI but that SAA and CRP provided essentially identical prognostic information.20 Patients with elevated SAA at discharge after hospitalization for ACS are more likely to be readmitted and/or have recurrent angina within 1 year.9 In contrast, measurement of SAA 2 months after MI in the Thrombogenic Factors and Recurrent Coronary Events (THROMBO) Study showed no significant association between SAA and risk of recurrent cardiovascular events over 2 years.21

**Biomarkers of Endothelial Cell Activation and Leukocyte Adhesion**

Endothelial cells provide the barrier between circulation and the extracellular space; endothelial activation and endothelial cell–leukocyte interactions are therefore a necessary prerequisite for initiation of inflammatory processes that predispose to ACS. Plasma-derived soluble forms of the immunoglobulin family members intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), as well as soluble forms of E-selectin, have been studied as possible biomarkers in ACS. In addition, levels of von Willebrand factor (vWF) may reflect endothelial cell activation acutely during ACS.
von Willebrand Factor

vWF is a multimeric glycoprotein stored in preformed endothelial Weibel-Palade bodies and platelet α-granules that activates platelets and mediates clot formation via association with factor VIII. In humans, the majority of serum vWF appears to be of endothelial origin.22

In patients with ACS, vWF levels are elevated at admission, peak within 24 hours, and return to baseline within 3 days.23 In an Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-wave Coronary Events (ESSENCE) trial substudy, the magnitude of vWF increase (ΔvWF) over the first 48 hours in patients with NSTEMI was an independent predictor of the composite end point of death, MI, recurrent angina, or revascularization at 14 and 30 days.24 In a study of 153 consecutive patients presenting with ST-elevation MI (STEMI), ΔvWF over the first 24 hours was an independent predictor of mortality at 30 days.23 In an ENTIRE-TIMI 23 (ENoxaparin and Tenecteplase with or without glycoprotein IIb/IIIa Inhibitor as REperfusion strategy in ST-elevation MI–Thrombolysis In Myocardial Infarction) substudy of patients undergoing fibrinolysis for STEMI, in- cartridges of patients undergoing fibrinolysis for STEMI, in- cartridges of patients undergoing fibrinolysis for STEMI, in-

SICAM-1

Soluble ICAM-1 is a transmembrane immunoglobulin superfamily protein expressed by endothelial cells, leukocytes, fibroblasts, smooth muscle cells, cardiomyocytes, and many other noncardiac cell types.26 ICAM-1 is expressed at basal levels on endothelial cells and is upregulated in response to inflammatory stimuli; the increased ICAM-1 expression promotes leukocyte adhesion and arrest.

A soluble form of ICAM-1 (sICAM-1) is released into the circulation, probably owing to shedding and the action of neutrophil elastase and matrix metalloproteinases on membrane-bound ICAM-1. sICAM-1 levels are elevated within 10 hours of chest pain onset in ACS and remain elevated above control levels for months.27

A prospective study of 119 patients presenting with chest pain suggestive for ACS failed to reveal any association between sICAM-1 and the risk of a serious cardiac event during hospital admission.28 Although sICAM-1 remains a robust predictor of cardiovascular disease incidence, larger prospective studies will be necessary for the study of secondary prevention. On the basis of studies in the acute setting, it does not currently appear that sICAM-1 has immediate use in risk stratification of patients with ACS.

Soluble VCAM-1

VCAM-1 is a transmembrane immunoglobulin superfamily protein expressed by activated endothelial cells and smooth muscle cells. VCAM-1 binds to VLA-4, an integrin expressed by monocytes, lymphocytes, and eosinophils; this interaction promotes firm cell–cell adhesion and eventual transmigration of inflammatory cells.29

Like ICAM-1, transmembrane VCAM-1 is cleaved to a soluble form (sVCAM-1). Patients with ACS have higher circulating levels of sVCAM-1 relative to healthy patients or patients with stable angina. Patients with in-hospital adverse coronary events are more likely to have higher admission levels of sVCAM-1; this association is independent of CRP.30 In a prospective study of patients with NSTE MI, sVCAM-1 levels were significantly higher at presentation in patients who had a major adverse cardiovascular event at 6 months.31

These initial studies suggest that sVCAM-1 may be a useful marker to predict medium- to long-term risk in patients with ACS. More prospective studies in the acute setting will be necessary before sVCAM-1 can be validated as a marker of in-hospital risk.

Soluble E-Selectin

E-selectin is an endothelial cell–specific selectin that stabilizes leukocyte-endothelial cell interactions by promoting cell-cell adhesion. E-selectin is not expressed on quiescent endothelial cells but is upregulated over the course of hours in response to inflammatory stimuli. Like ICAM-1 and VCAM-1, E-selectin is cleaved to a soluble form (sE-selectin) that may be a surrogate marker for the extent of microcirculatory endothelial cell activation.

Studies have conflicted on measurements of sE-selectin in ACS, with some studies suggesting an association between E-selectin levels and ACS, whereas others found no relationship.32 The major utility of sE-selectin and other markers of endothelial cell activation may be in predicting risk of developing coronary artery disease and risk of death in patients with stable coronary artery disease, rather than as a risk stratification marker in ACS.32

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References


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