Inflammatory Biomarkers in Acute Coronary Syndromes
Part I: Introduction and Cytokines
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Acute coronary syndromes (ACS) are multifactorial and occur in response to inflammation, plaque rupture and subsequent thrombosis, progressive mechanical obstruction, and dynamic obstruction. Patients with ACS span a large spectrum of risk that progresses from unstable angina (UA) to non–ST-elevation myocardial infarction (NSTEMI) to ST-elevation myocardial infarction (STEMI). ECG findings and markers of myocyte necrosis are used to define the type of ACS and guide reperfusion strategy in ST-elevation myocardial infarction. For patients with non–ST-elevation (NSTE) ACS, however, a large degree of uncertainty remains regarding long-term risk and optimal secondary prevention for the individual patient. Increasingly, biomarkers are being used as tools to identify subgroups of patients with ACS who are at increased risk for subsequent cardiovascular events.

Among potential biomarkers, much interest has focused on biomarkers of inflammation. The process that leads to eventual plaque erosion or rupture involves a number of inflammatory mechanisms, including endothelial dysfunction, leukocyte migration, extracellular matrix degradation, and platelet activation (Figure). The optimal inflammatory biomarker would provide a method for quantitating cardiovascular-specific inflammation, thereby predicting the risk of recurrent atherothrombosis and its clinical sequelae. Because they address a separate aspect of ACS pathophysiology, biomarkers of inflammation may provide unique information to the clinician separate from that provided by biomarkers of myocyte necrosis and hemodynamic stress.

The present review series summarizes our current understanding of inflammatory biomarkers and is based on their presumed pathophysiological role in ACS and the clinical evidence that supports their prognostic importance. The discussion is organized from early to late inflammatory mediators of plaque disruption; in reality, these processes are intertwined and simultaneous (Figure). Part I focuses on cytokines, part II on acute-phase reactants and biomarkers of endothelial cell activation, part III on biomarkers of oxidative stress and angiogenic factors, and part IV on matrix metalloproteinases and biomarkers of platelet activation.

Cytokines
Cytokines are pleiotropic proteins that regulate leukocyte activity. In the acute-phase response, cytokines such as interleukin (IL)-1 and IL-6 drive production of reactant proteins, including C-reactive protein (CRP). IL-6 and monocyte chemoattractant protein-1 (MCP-1) are the major cytokines that are implicated clinically as biomarkers in ACS (Table). A number of other cytokines with possible clinical application are also discussed briefly.

Interleukin-6
IL-6 is a ubiquitous cytokine, the presence of which is crucial for leukocyte and endothelial cell activation. IL-6 also promotes production of hepatic acute-phase reactants, including CRP. IL-6 is expressed at the shoulder region of atherosclerotic plaques and may increase plaque instability by driving expression of matrix metalloproteinases, MCP-1, and tumor necrosis factor (TNF)-α.

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Patients with ACS have increased circulating levels of IL-6 compared with those patients who have stable angina. Among patients with unstable angina, an increase in IL-6 levels that occurred 48 hours after admission compared with the admission value was associated with the combined end point of death, myocardial infarction (MI), or refractory angina. In the FRISC-II (Fragmin and/or early Revascularization during InStability in Coronary artery disease) study, elevated IL-6 (≥5 ng/L) was associated with higher 6- and 12-month mortality and was additive to and independent of cardiac troponin T status. Elevated IL-6 levels also identified a subgroup of patients who derived the greatest mortality benefit from an early invasive strategy. These results suggest that an elevated level of IL-6 may identify patients with a more severe index event, who would therefore benefit from more aggressive treatment. Currently, however, the large circadian variations in IL-6 levels and lack of confirmatory studies limit the applications of IL-6 as a biomarker in ACS.

Monocyte Chemoattractant Protein-1

MCP-1 is a chemokine that activates mononuclear phagocytes by promoting leukocyte–endothelium binding and migration to sites of inflammation. Consistent with a pathophysiological role in ACS, inhibition of MCP-1 signaling in a mouse model of MI improved survival at 4 weeks and also improved left ventricular function. In the OPUS (Orbofiban in Patients with Unstable coronary Syndromes)-TIMI 16 trial, an MCP-1 level >238 pg/mL was associated with an increased risk of death or MI after 10 months, even after adjustment for traditional risk factors. Measurement of MCP-1 in the coronary sinus blood of patients with unstable angina demonstrated an association between MCP-1 levels and the extent of coronary atherosclerosis as assessed by the coronary angiogram. Although levels of MCP-1 may be primarily a surrogate for atherosclerotic burden, MCP-1 remains a promising therapeutic target with a compelling pathophysiological role in atherothrombosis.

Other Cytokines

TNF-α is a proinflammatory cytokine implicated in myocardial dysfunction and remodeling after ACS. In the CARE (Cholesterol And Recurrent Events) trial of patients with a recent...
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NSTE indicates non-ST-segment elevation.

MI, those who experienced a recurrent MI or cardiac death had higher levels of TNF-α at study enrollment than matched controls. Among patients with TNF-α levels >95th percentile of control values, the risk of death or nonfatal MI was 2.7 relative to control cases.

IL-18 promotes expression of interferon-γ, a mediator of plaque progression. Administration of exogenous IL-18 markedly increases lesion size in a mouse model of atherosclerosis. IL-18 mRNA is expressed at high levels in unstable human coronary plaques relative to stable plaques, which suggests that IL-18 also mediates later events in plaque stability and eventual disruption. In a prospective study of patients with unstable angina who were undergoing coronary angiography, patients with IL-18 levels in the fourth quartile (>77.7 pg/mL) had a markedly increased risk of cardiovascular death during long-term follow-up; a similar association was also observed in patients with stable angina.

IL-10 is unusual among proposed ACS biomarkers in that it is anti-inflammatory. In the CAPTURE (c7E3 AntiPlatelet Therapy in Unstable Re-fractory angina) study, patients with elevated IL-10 levels had a decreased risk of death or nonfatal MI. Patients with elevated CRP and elevated IL-10 were at lower risk than were patients with elevated CRP but no elevation in IL-10, which suggests that IL-10 may be protective against pro-inflammatory mediators in ACS.

Other cytokines, such as macrophage inhibitory cytokine-1 and soluble TNF receptors (sTNFR1/sTNFR2), have shown promise in the prediction of coronary heart disease incidence, but these markers require further study for possible application to ACS risk stratification. As the number of cytokines implicated in ACS increases, it will become progressively important to determine not only pathophysiological interrelationships among these markers but also whether these cytokines provide independent prognostic information apart from more established inflammatory biomarkers such as CRP. Furthermore, when clinicians read reports of the predictive value of new markers, it is important to determine whether the investigators have used appropriate cutpoints for the levels of established markers.

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References


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