Update on Inflammatory Markers

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Inflammation is literally a hot topic in preventive cardiology these days, both as an important mechanism for the development of atherosclerosis and as a risk marker. During the past decade, both local and systemic aspects of inflammation have been investigated.[1] Nonspecific systemic markers of inflammation, such as high-sensitivity C-reactive protein (hs-CRP), have been shown to predict cardiovascular risk about as well as cholesterol levels. Patients with high hs-CRP levels appear to benefit the most from lipid lowering in terms of event risk reduction, and several hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have been shown to lower hs-CRP. At the same time, localized inflammation appears to be present in unstable plaques, especially in the shoulder regions, which are most likely to rupture.

At the recent European Society of Cardiology meeting, a high level of interest was certainly present. Several papers confirmed the diagnostic and prognostic values of inflammatory markers. Inflammatory markers were found to provide useful clinical risk assessment in the setting of stable and unstable angina and acute myocardial infarction. Blankenberg and coworkers followed 824 patients with angiographically documented coronary artery disease for a mean of 3.1 years.[2] Patients with elevated CRP (highest quartile versus other 3 quartiles) had 2.5 and 2.9-fold increases in cardiovascular death and cardiovascular events, respectively. Other inflammatory markers also appear to provide prognostic information. Hoffmeister and

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Main Points

- Inflammatory markers were found to provide useful clinical risk assessment.
- Monocyte activation is a feature of plaque destabilization.
- CRP appears to correlate with softer plaques.
- Intracoronary catheters hold promise for directing individual plaque instability

coworkers examined the differences between several inflammatory markers in patients with coronary artery disease and in normal subjects in a 791-subject case-control study.[3] They found that the highest tertile of hs-CRP, fibrinogen, and plasminogen activator inhibitor-1 (PAI-1) predicted odds ratios of about 2 for the presence of coronary disease, and that subjects with the highest levels of all 3 markers have an approximately 3-fold increase in likelihood of disease. Inflammatory markers appear to become abnormal early in life. Melilli and coworkers [delete these 2 words? no coworkers named in ref.] found that the majority of dyslipidemic (<17 years old) studied had elevated CRP levels.[4]

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Unstable Angina

Patti and coworkers compared levels of hs-CRP and of interleukin-1 (IL-1) receptor antagonist, which modulates the production and activity of IL-1, in 375 subjects with stable and unstable coronary disease and atypical angina.[5] Whereas hs-CRP was elevated in the both the stable and the unstable angina subjects compared with those with atypical angina, IL-1 receptor antagonist was elevated only in the unstable coronary disease subjects. This finding provides additional evidence that monocyte activation is a feature of plaque destabilization and underscores the possibility that different inflammatory markers may exist in different stages of coronary heart disease. In contrast to the results of this study, Baglini and coworkers found that CRP [AQ: not hs-CRP? also elsewhere] was elevated in 28 patients undergoing angioplasty for unstable angina compared with levels in 16 patients undergoing angioplasty for stable angina.[6] The elevated CRP appeared to correlate with softer plaques (more prone to rupture) and with thrombosis-associated plaques.

Increased CRP values appear to predict the hospital outcome of patients with unstable angina. Biasucci and coworkers followed 251 patients with unstable angina. An elevated CRP (upper quintile compared with other 4 quintiles) was associated with a 4.2-fold increase in risk ratio for in-hospital complications.[7] Patients without in-hospital complications had mean CRP values of 0.48 mg/dL, vs 2.23 mg/dL for subjects with complications. Temporal changes in inflammatory markers may also provide prognostic information in the setting of unstable angina. Ferreiros and coworkers found that increasing levels of CRP during the initial phase of hospitalization for unstable angina was associated with a 3.6-fold increase in risk ratio for hospital mortality or myocardial infarction.[8] This finding provided additional prognostic value beyond that of ST-segment changes.

Myocardial Infarction

Inflammatory markers may also have predictive value in the setting of acute myocardial infarction. Investigating 154 patients with acute myocardial infarction undergoing thrombolysis, Zairis and coworkers found that subjects with normal CRP on admission were more likely to have TIMI 3 flow, ie, full reperfusion, than patients with elevated CRP, who were more likely to have TIMI 2 flow.[9] The investigators suggest that infarct patients with more intense inflammation are less likely to achieve full reperfusion with thrombolysis. This association appears to translate to patient prognosis. Tomoda and coworkers, in a study of 234 patients with acute myocardial infarction, found that an elevated CRP value (>0.3 mg/dL) was associated with significant increases in coronary reocclusion, target vessel revascularization, and death (16.3% vs 2.2%) and with a trend toward increased reinfarction (2% vs 0.5%).[10] Taken together, these studies confirm a strong, independent value for inflammatory markers in all phases of coronary heart disease.

Therapy

Inflammatory markers have been shown to decrease with lipid lowering by HMG-CoA reductase inhibitors, including pravastatin and simvastatin. Aristegui and coworkers found that atorvastatin also lowers CRP in patients with cardiovascular disease and mixed dyslipidemia but that bezafibrate did not.[11] This finding may partly explain the consistent finding of decreased cardiovascular risk in the HMG-CoA reductase inhibitor trials. In contrast, a recent clinical trial (BIP) of bezafibrate (not available in the USA) in mixed dyslipidemic coronary heart disease patients was neutral.[AQ: ref.?] Interestingly, Jenkins and coworkers found that coronary artery disease patients undergoing elective cardiac catheterization on beta-blockers had lower CRP levels than those not taking beta-blockers.[12] Moderate alcohol intake was also linked to

lower CRP levels in a 1801-subject observation study carried out by Imhof and coworkers.[13] Abstaining and heavy-drinking subjects had higher CRP levels. This association is concordant with the known cardiovascular risk reduction of moderate alcohol intake and raises the question whether some of alcohol's cardioprotective effect may be due to reduced inflammation.

Plaque Temperature

Intracoronary catheters capable of measuring coronary plaque temperature, an index of ongoing inflammation, are currently under development and hold promise for detecting individual plaque instability. Stefanadis and coworkers reported that plaques more than 0.5_C warmer than the surrounding arterial temperature were associated with approximately a 10-fold increase in cardiovascular events over an 18-month follow-up period.[14] Taken together, these recent presentations strongly support an important role ¸stratification, therapeutics, and unstable plaque identification in coronary arter disease. ■

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