Editorial Commentary

C-Reactive Protein

Just a Biomarker of Inflammation or a Pathophysiological Player in Myocardial Function and Morphology?

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In response to inflammatory stress, C-reactive protein (CRP) is predominantly secreted from the liver and adipose tissue(s), and an independent relationship exists between different markers of overweight/obesity and elevated high-sensitive (hs) CRP levels (figure).

Higher hsCRP levels predict incident myocardial infarction (MI), stroke, peripheral arterial disease, sudden cardiac death, and all-cause mortality in healthy individuals with no history of cardiovascular disease.1,2 hsCRP at admission predicts inhospital outcome, and hsCRP at discharge predicts 6-month event rate and 30-day mortality (Global Utilization of Strategies To Open occluded arteries [GUSTO] IV) in patients with an acute coronary syndrome. Indeed, adding hsCRP levels to the Global Registry in Acute Coronary Events (GRACE) acute coronary syndrome risk model improves the prediction of 30-day mortality. In patients with non-ST-elevated MI, an increased hsCRP level predicts the death rate even at 20-month follow-up but does not predict stent-related complications.

The question of whether CRP, apart from serving as a biomarker, acts as a causal factor in vascular/coronary artery disease has been addressed in animal models, in which CRP, as a causal factor in vascular/coronary artery disease. However, CRP genotypes and CRP levels do not predict coronary heart disease risk, again arguing against a causal role.

Studies on Endothelial Function

Endothelium-dependent vasodilation is impaired in native CRP-treated apolipoprotein E (ApoE) knockout mice, and this effect is attenuated by inhibition of inducible nitric oxide synthase (NOS), whereas mutated (or monomeric) CRP is ineffective. Mice overexpressing the human CRP gene (CRPtg) also exhibit endothelial dysfunction, associated with reduced nitric oxide (NO) bioavailability; their endothelial NOS is downregulated, and this action of CRP on endothelial NOS is mediated at the level of gene transcription. Along with impaired vasodilation, tissue factor expression is increased in carotid arteries of CRPtg mice, and this effect is mediated through mitogen-activated protein kinase (MAPK) activation and increased reactive oxygen species (ROS) formation. In CRPtg mice, the number of monocyte/platelet aggregates is increased, and similar effects have been reported from human blood incubated with CRP. Clinically, elevated admission CRP correlates to impaired reperfusion in the infarct-related artery myocardial perfusion territory, suggesting extended no-reflow areas.

Thus, elevated CRP impairs endothelial vasodilator function and activates platelets.

Studies on Atherosclerotic Lesions

Continuous infusion of human native CRP in male ApoE knockout mice is not associated with increased atherosclerotic lesion size or local inflammation. In contrast, treatment with native CRP for 8 weeks results in a 4-fold greater aortic plaque area in female ApoE knockout mice. In CRPtg mice, however, results on plaque size vary substantially: plaque size is decreased in ApoE/low-density lipoprotein (LDL) receptor double-knockout mice, unchanged in LDL receptor or ApoE knockout mice, or even increased in ApoE knockout mice. While results in native vessels are equivocal, neointima formation and rate of thrombotic occlusion in injured carotid arteries are exaggerated in CRPtg compared to wild-type mice.

Clinically, the association between hsCRP and intima-media thickness is largely explained by confounding factors such as age, gender, and cardiovascular risk factors, and hsCRP levels are not independently associated with coronary plaque subtypes, plaque calcification, and/or the degree of coronary stenosis.

Thus, elevated CRP is not an independent causal factor in plaque development and composition.

Genetic Studies

Polymorphisms in the CRP gene are associated with marked increases in CRP in humans and thus theoretically are expected to predict an increased risk of ischemic vascular disease. However, CRP genotypes and CRP levels do not predict coronary heart disease risk, again arguing against a causal role.

Microembolization and CRP

Atherosclerotic plaque rupture is the key event in the pathogenesis of acute coronary syndromes, and it also occurs during coronary interventions.3 Atherosclerotic plaque rupture facilitates the embolization of atherosclerotic and thrombotic debris into the coronary microcirculation, resulting in
microinfarcts with a subsequent inflammatory response and an elevation of hsCRP.4

Thus, increased CRP reflects ongoing active vascular processes, leading to plaque rupture, microembolization, microinfarction, and local and systemic inflammation.3

Why Does Increased CRP Then Predict Patient’s Mortality Risk?
Increased baseline left ventricular (LV) mass and abnormal LV geometry confer an increased risk for mortality in patients with hypertension or following high-risk MI. Concentric LV hypertrophy carries the greatest risk of adverse cardiovascular events, including death.

These unequivocal associations bring direct effects of CRP on cardiac function and morphology into the focus.

Cardiac Effects of CRP
The study by Nagai et al,3 published in this issue of Hypertension, demonstrates that CRPtg mice have accelerated pressure overload-induced LV dilatation (verified by echocardiography and atrial natriuretic peptide/brain natriuretic peptide measurements) and hypertrophy (LV weight and cardiomyocyte area), increased rate of cardiomyocyte apoptosis, increased perivascular but not interstitial fibrosis, activated p38 MAPK and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (increased p47phox expression and dihydroethidium staining), and increased inducible but decreased endothelial NOS expression. These results confirm recent data of accelerated adverse LV remodeling in CRPtg mice during continuous angiotensin II infusion6 or post-MI.7

These findings in CRPtg mice extend data from isolated cardiomyocytes, in which CRP increased the interleukin-1β-induced inducible NOS expression and nitrite production and augmented the hypoxia-induced apoptosis through a mitochondrion-dependent pathway. Indeed, increased ROS formation and subsequent MAPK activation contribute to the development and progression of heart failure8 through oxidation of myofilaments and induction of cardiomyocyte apoptosis.8 Several enzymes such as NADPH oxidase, inducible NOS, and mitochondrial respiratory chain complexes contribute to ROS formation.9

In the present study, the plasma hsCRP concentrations of ≥30 mg/L in CRPtg mice are 3 to 10 times higher than the ones observed in patients with stable coronary artery disease or heart failure, but similar to the hsCRP concentrations measured in almost 40% of patients undergoing percutaneous coronary interventions10; the latter patients experience a reduced event-free survival during follow-up.10 Also in endomyocardial biopsies from heart failure patients, CRP levels are increased (up to 10 mg/L), and increased CRP levels correlate with increased LV volume.

However, it remains to be established in future animal experiments whether or not also lower hsCRP concentrations, as seen in patients with stable coronary artery disease, can indeed activate the same signaling cascades and induce LV remodeling. Finally, to prove a cause-effect relationship, strategies to reduce excessive high hsCRP concentrations and their impact on LV remodeling and prognosis need to be investigated both experimentally and clinically.

In conclusion, while CRP serves as a biomarker for active vascular processes, it also exerts direct actions on cardiac function and morphology that may causally contribute to a patient’s prognosis.

Disclosures
None.

References


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