Need to Test the Arterial Inflammation Hypothesis

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Despite intensive basic and clinical investigation, coronary artery disease remains the principal cause of death and disability in the United States. In recent years, the appreciation of arterial inflammation as an important risk factor has had considerable implications for changing our approach to managing these patients.\(^1\),\(^2\) Arterial inflammation has emerged as central to the progression of atherothrombosis.\(^3\) Of the markers of inflammation, the high-sensitivity C-reactive protein (CRP) is the most studied, with evidence that it may also play a direct pathogenic role in atherosclerotic lesion formation.\(^4\)–\(^11\) In the absence of active infection, measurements of CRP are reasonably reproducible, comparable to measurements of total cholesterol.\(^12\),\(^13\) Additionally, elevated CRP appears to be a more potent risk factor than other mediators of inflammation, such as tumor necrosis factor-\(\alpha\), interleukin-6, or serum amyloid A.\(^4\),\(^14\) A group of pharmacotherapies that are currently available, such as aspirin, statins, angiotensin converting enzyme inhibitors (ACE-I-s), thienopyridines, and peroxisome proliferator-activated receptor (PPAR) agonists have been shown, in addition to their other properties, to reduce CRP and/or arterial inflammation. Although it is clear that elevated CRP denotes increased risk and emerging evidence suggests that there are novel therapies that result in lowering of CRP, the most important unanswered question is whether suppression of inflammation and consequent lowering of CRP will translate into a decrease in clinical events.\(^15\) Surprisingly, despite the importance of the question, the “inflammation hypothesis” of intentional CRP suppression as compared with standard care has not yet been tested. Such a prospective study of patients with established cardiovascular disease and elevated baseline CRP in which incremental pharmacotherapy would be guided by reassessments of the CRP marker could allow formulation of a rational therapeutic strategy instead of an approach of “polypharmacy” for every patient.

**Inflammation as a Risk Factor**

CRP serves as a marker of inflammation and predicts risk of adverse cardiovascular events. Elevated CRP seems to be effective at identifying risk of future ischemic events in patients with acute coronary syndromes. Biasucci et al\(^16\) found patients with a CRP level >0.3 mg/dL had 8.6 times the risk of recurrent ischemic events than patients without this degree of CRP elevation. Interestingly, in this study, 49% of patients had a CRP level >0.3 mg/dL at discharge, indicating just how frequently inflammatory markers are elevated in patients at risk for future ischemia.

In the setting of myocardial infarction (MI), CRP is also an important discriminator of risk, even in patients without residual ischemia or left ventricular dysfunction.\(^17\) The risk stratification allowed by CRP is independent of myocardial necrosis as measured by troponin elevation.\(^18\)–\(^20\) In patients undergoing angiography, elevated CRP is associated with more severe angiographic characteristics, such as thrombotic lesions, highlighting the interconnection between thrombosis and inflammation.\(^21\) Elevated CRP predicts the need for repeat revascularization procedures.\(^22\) Even in chronic stable angina, CRP levels are increased and correlate with outcome.\(^23\),\(^24\) Importantly, CRP provides prognostic information that is at least as strong as that provided by exercise stress testing.\(^25\) The ability of CRP elevation to confer risk is found in patients both with and without angiographic coronary artery disease, with independent and additive effects.\(^5\),\(^26\)

Furthermore, CRP elevation predicts the risk of recurrent stroke, as well as development of symptomatic peripheral arterial disease.\(^27\)–\(^29\) Indeed, CRP seems to be associated with risk even in those who are apparently healthy.\(^30\) Thus, CRP is a potent prognosticator of pan-vascular risk, with an ability to risk-stratify that is complementary to other serological, non-invasive, and invasive tests.

**Pathogenic Role of Inflammation**

Recent work suggests that CRP may also play a direct pathogenic role in atherosclerotic lesion formation. Uptake of CRP-opsonized native LDL-cholesterol by macrophages seems to contribute to foam cell formation.\(^7\) The presence of a CRP-receptor on monocytes may aid in monocyte recruitment into the arterial wall.\(^11\) CRP can stimulate macrophages to produce the very prothrombotic tissue factor, providing yet another connection between the coagulation and inflammatory pathways.\(^31\),\(^32\) Additionally, CRP can activate complement in atherosclerotic plaques, potentially leading to plaque instability.\(^9\) CRP has also been shown to induce expression of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), and E-selectin on human coronary endothelial cells.\(^6\) In fact, CRP has the ability to sensitize endothelial cells to destruction by cytotoxic CD4\(^+\) T cells.\(^33\) Elevation of CRP is also associated with endothelial dysfunction and the progression of atherosclerosis.\(^8\) Furthermore, CRP has also
been implicated in enhanced vasoreactivity in unstable plaques. Therefore, through several interrelated pathways, CRP may exert deleterious effects on the vascular system.

Potentially, risk conferred by arterial inflammation will become a unifying hypothesis for the excess risk associated with a variety of disease states, such as obesity, the metabolic syndrome, diabetes mellitus, and renal dysfunction. An abundance of adipocytes found in the obese individual may lead to increased production of interleukin-6 and downstream production of CRP. Weight loss has been shown to decrease CRP significantly in obese postmenopausal women. Interestingly, postmenopausal hormone replacement therapy has been shown to elevate levels of CRP, despite having beneficial effects on LDL-cholesterol levels, perhaps explaining in part the negative results of the randomized trials of hormone replacement therapy for secondary prevention. Advanced glycation end products found in diabetes or uremia may bind to their receptor and lead to production of CRP. Indeed, elevated levels of baseline CRP predict the development of diabetes in the future, independent of body mass index. Thus, multiple disease states may ultimately lead to CRP expression and consequent plaque progression and destabilization, and it may be that these systemic states are more relevant to inflammatory risk than are local processes, such as an individual unstable plaque.

The combined evidence of predictive power for a variety of cardiovascular outcomes and of direct pathological involvement suggests that purposeful lowering of CRP levels could have a major impact on preventing ischemic events. If so, it would be logical to use not only a static measurement of CRP to risk stratify and allocate therapy initially, but also to follow CRP levels to gauge therapeutic effectiveness. Indeed, chronic CRP elevation increases risk of death or MI by 40% over the risk associated with CRP elevation only at the time of an ischemic event, supporting this hypothesis. Despite the wealth of data that shows inflammation raises subsequent risk, however, it is currently unknown how to best treat a patient with elevated markers of inflammation.

**Effect of Medical Therapy on Inflammation**

There has been an appropriate push to practice evidence-based medicine in the United States. Multiple clinical trials have demonstrated the individual benefit of antiplatelet therapy, statins, ACE inhibitors, and PPAR agonists in reducing adverse events in specific cardiovascular disease states. The incremental utility of these agents, however, has not been adequately tested, with reluctance by industry to fund this type of research. Instead, the focus by pharmaceutical companies has been on demonstrating as large a benefit as possible in as wide a range of patients as is practical with one particular agent, with no regard to cost or interaction of multiple therapies. Thus, the need to combine in a rational manner multiple proven agents arises.

Aspirin has a longstanding track record as an effective antiplatelet agent across a broad range of vascular disease states. Its properties as an antiinflammatory agent have long been appreciated in the rheumatological literature, though typically at a high dose. In a subset of apparently healthy men in the Physicians’ Health Study, in patients within the highest quartile of CRP elevation, the benefit of 325 mg of aspirin was most significant, with a 55.7% reduction in MI. Perhaps an elevated CRP would demarcate those patients most likely to benefit from primary prevention with aspirin. Indeed, in patients with coronary artery disease, aspirin also seems to reduce levels of CRP, as well as other inflammatory markers.

Clopidogrel is a thienopyridine agent that antagonizes the adenosine diphosphate (ADP) receptor and has been shown to be a more potent anti-thrombotic agent than aspirin. In addition to its effect as an antiplatelet agent, clopidogrel seems to modulate the response to inflammation. Clopidogrel decreases expression of P-selectin, which plays a key role in platelet-neutrophil crosstalk. Clopidogrel has also been shown to decrease the ADP-induced expression of CD40 ligand, a pivotal mediator of platelet interaction with inflammatory cells. For example, CD40 ligand on activated platelets has been shown to interact with endothelial cells, causing them to secrete chemokines and express adhesion molecules, ultimately resulting in the recruitment of leukocytes to the site of vascular injury. Elevated levels of CD40 ligand predict an increased future risk of ischemic events in healthy individuals. Even in stable coronary artery disease, there is an increase in circulating platelet-monocyte aggregates that is further amplified by ADP. By interrupting the platelet–endothelial–monocyte cascade, clopidogrel may have an antiinflammatory benefit beyond just its antiplatelet action. Indeed, clopidogrel does seem to have a heightened treatment effect in patients undergoing percutaneous coronary intervention (PCI) who have elevated levels of CRP. Certainly, the antiplatelet and antiinflammatory activities of clopidogrel (or aspirin) are inextricably linked, with platelet inhibition necessarily disrupting inflammatory pathways, and vice versa.

The hydroxy-methyl glutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) have been shown to reduce ischemic events in numerous at-risk populations with varying degrees of cholesterol elevation. In fact, evidence suggests that direct antiinflammatory effects may be the primary mode of action of these agents. The recently presented Heart Protection Study suggested that there was a benefit even in patients with LDL cholesterol levels under 100 mg/dL, and this appeared to be of similar magnitude to those patients with LDL levels greater than 130 mg/dL. Statins have been proven to reduce CRP levels in several studies. One particular statin reduced median CRP levels by 13.3% (P<0.001); whereas LDL-lowering was found to be dependent on the dose of the statin, the effect on CRP levels was not related to the specific doses studied. The ability of statins to reduce CRP seems to be class-specific and not drug-specific. Statins also seem beneficial in patients undergoing PCI, with the benefit seen predominantly in those with elevated CRP.

ACE-Is have shown unequivocal benefit as vasodilators in patients with left ventricular dysfunction, but recent studies have found benefit in other populations at risk of vascular disease that are out of proportion to the degree of blood pressure lowering. In fact, in a study of patients at risk of vascular disease, the benefit of the ACE-I ramipril was roughly 3 times greater than would be expected from blood pressure reduction alone. These non-blood pressure-related effects are likely mediated at least in part by anti-inflammatory properties. Blood pressure elevation itself,
however, leads to an increase in cytokine levels; thus, lowering of blood pressure by any means may secondarily have an effect on inflammatory markers.61,62 ACE-Is have also been shown to have direct antiinflammatory effects in several studies. For example, the ACE-I quinapril has been shown to decrease expression of nuclear factor-κB, as well as interleukin-8 and monocyte chemotactic protein-1 in a rabbit model of atherosclerosis.63 Other animal models of atherosclerosis and vascular injury have also found a benefit of ACE inhibition.64 Therefore, use of ACE-Is guided by inflammatory markers may provide a way of identifying which patients would benefit from the non-blood pressure-related effects of ACE-Is.

PPAR-α agonists, such as the fibrates, have also been shown to have a beneficial impact on patients with atherosclerotic vascular disease who have suboptimal levels of HDL cholesterol. In a secondary prevention population of patients with low HDL levels, gemfibrozil reduced the rate of MI, stroke, and death.65 The change in HDL levels, however, only partially explained the observed benefits of gemfibrozil.65 Potentially, antiinflammatory effects accounted for part of the benefit seen with this drug as well. Additionally, HDL may itself have antiinflammatory activity, so agents that raise HDL levels may protect against arterial inflammation through this route. In fact, part of the benefit of agents associated with CRP reduction may be due to an interaction with HDL elevation.66 Fenofibrate has been shown to improve vascular reactivity, which correlated with CRP reduction, independent of any effect on lipid parameters.67 Thus, use of fibrates in patients with low HDL and evidence of inflammation might be particularly efficacious.

The PPAR-γ agonists known as thiazolidinediones (TZDs) have been proven to be effective agents in the management of diabetes mellitus. Beyond this role, PPAR-γ agonists have been shown to have antiinflammatory activities.68 For example, PPAR-γ agonists have been shown to inhibit the expression of the cell adhesion molecules VCAM-1 and ICAM-1 in activated endothelial cells, thereby decreasing the ability of monocytes to infiltrate into atherosclerotic plaques.69 Additionally, anti-atherosclerotic properties have been demonstrated, such as the ability to decrease carotid artery intimal-medial thickness.68,70 Recently, the TZD rosiglitazone was shown to lower CRP significantly when compared with placebo; of note, this reduction in CRP was paralleled by a reduction in matrix metalloproteinase-9, which is believed to play a role in plaque rupture.71 Thus, TZDs may have an important antiinflammatory and anti-atherosclerotic role in patients with vascular disease, beyond their role in treating diabetes mellitus.

**Evidence for Suppressing Inflammation Before Revascularization**

Elevated CRP before revascularization procedures also worsens a patient’s prognosis. Interestingly, the luminal temperature of coronary arteries correlates closely with the level of CRP, even in patients with stable coronary artery disease.72 Patients with elevations of CRP have a much higher rate of death and MI, but outcomes might conceivably be improved if such patients are “cooled off” with medical therapy before revascularization. In an analysis of patients undergoing angioplasty, Buffon et al.22 found that all intraprocedural and in-hospital complications occurred in patients whose baseline CRP was >0.3 mg/dL. Additionally, at a 1-year follow-up, clinical restenosis occurred significantly more frequently in patients with elevated CRP (63% versus 27%, \( P<0.001 \)). The ability of elevated CRP to predict the risk of death or MI in a PCI population is beyond that of clinical or angiographic parameters.5,23,73,74 Similar to the PCI population, in patients undergoing CABG, CRP levels >0.3 mg/dL predicted increased risk of future ischemia.75 These data provide a logical basis for delaying elective revascularization procedures and “cooling off” patients with medical therapy to lower their state of inflammation. In fact, pretreatment with aspirin has long been appreciated to improve outcomes after angioplasty. It also seems that pretreatment with clopidogrel before the time of angioplasty or stenting decreases the rate of subsequent ischemic events, in both stable and unstable coronary artery disease.51,76,77 There also seems to be a beneficial effect of statin therapy in reducing ischemic events when given before the time of PCI.78,79

**Need for a Clinical Trial**

It is vital that the “inflammation hypothesis” be tested in a large-scale clinical trial, which has the potential to change radically the approach used with patients with cardiovascular disease. Patients with a history of cardiovascular events and an elevated baseline CRP could be randomized to either usual-care or a CRP-guided strategy. All patients would be treated with aspirin at a moderate dose of 81 to 162 mg.41 Patients with an LDL cholesterol level greater than 100 mg/dL would be treated with a statin. ACE-Is would be prescribed to patients with left ventricular dysfunction. Further therapy in the group randomized to the CRP-guided strategy would be based on a prespecified algorithm of tiered therapy and response of CRP levels to initiation of a particular medication (Figure). If CRP levels remain elevated, the next medication in the algorithm would be prescribed. If an added agent had no effect on CRP, then it would be
discontinued. Additionally, patients who are to undergo elective revascularization procedures in the CRP-guided arm would receive stepwise medical therapy to achieve a reduction in repeat measurements of CRP before their procedure. In addition to evaluating the effect of such a strategy on clinical events, creation of a DNA repository on enrolled patients would allow establishment of the relationship between single nucleotide polymorphisms and haplotypes to inflammatory markers and specific drug interactions.

The results of such a trial would validate whether an inflammation-guided strategy of tailored medical therapy can reduce death, MI, and stroke, as well as the need for revascularization and rehospitalization. As such, it could result in a major improvement in public health concomitant with a decrease in health care costs. The results would be applicable to a large cross-section of the population and could be easily implemented by clinicians everywhere.

Practicing clinicians are often skeptical about implementing the results of clinical trials, because it is often unclear if a new drug would have been effective if the patients in the trial had already been on all known optimal therapies. Therefore, an inflammation-directed trial would provide the opportunity for clinicians finally to ask if combinations of drugs really do enhance an individual patient’s care. Thus, a rational approach to stepwise pharmacotherapy and to triage for elective revascularization would potentially be validated. With well over 13 million patients who have known coronary artery disease in the United States alone, the potential impact of this trial on public health would be profound. An enlightened approach to tailoring medications to individual patients through pharmacogenomics may finally be realized. Thus, a trial of inflammation to guide noninvasive and invasive therapy could revolutionize contemporary cardiovascular practice.

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