Editorial Comment

C-Reactive Protein and Vascular Risk in Stroke Patients: Potential Use for the Future

In the accompanying article, Arenillas and colleagues furnish new evidence that a persistently elevated level of CRP after a first cerebrovascular event (ischemic stroke or TIA) is associated with an increased risk of vascular events (both cerebral and cardiac) in a population of patients with documented intracranial large-artery occlusive disease. The evolving concept of using a high-sensitivity CRP assay as a marker of cerebrovascular risk is enticing, and the message suggested by the results of this study is both provocative and in accord with the increasing body of literature rapidly accumulating in the exciting field of stroke preventive medicine. The theory behind this association is captivating: patients with high-risk lesions may be expected to manifest signs of increased inflammatory activity. Such inflammation appears to occur not only locally (in the affected vessel wall) but also systemically, as suggested by increased circulating levels of CRP. The use of an easily measurable systemic marker of inflammation (such as high-sensitivity CRP) may hold the key for determining which patients with intracranial large-artery occlusive disease are most at risk. In fact, the patients at highest risk manifest evidence of surprisingly widespread inflammatory response. Although the full relation between CRP elevation and cardiovascular risk is not yet completely known, the inflammatory status may be a marker for individuals with an exaggerated inflammatory response that may in turn accelerate atheroma progression and facilitate thrombogenesis.

Studying the effect that a general inflammatory marker, such as CRP, has on cerebrovascular risk prediction is far from a simple task. Methodological problems are inherent in design, implementation, and analysis of any such study. The role of elevated high-sensitivity CRP as a risk marker for cardiovascular diseases, including coronary heart disease, stroke, and peripheral arterial disease, is well established through consistent results from a number of prospective studies. CRP also conveys important prognostic information after stroke, but additional well-designed epidemiological studies are needed to validate the findings. Subjects with ischemic stroke and increased levels of high-sensitivity CRP are candidates for a worse outcome with a variety of adverse events, such as vascular deaths, recurrent strokes, and cardiovascular events. Even in the presence of the results of clinical and neuroradiological outcome predictors, high-sensitivity CRP adds relevant prognostic information. Moreover, persistent elevation of high-sensitivity CRP levels after standard treatment of ischemic stroke according to current strategies, measured at the time of hospital discharge, is predictive of recurrent events. Thus, from the clinical point of view, high-sensitivity CRP testing represents a valuable additional diagnostic tool. The available data suggest the utility of a sample taken at admission, within 12 to 24 hours after stroke onset. However, when samples were also taken at discharge, CRP levels were better predictors of the mid- to long-term prognosis than those at admission. This is probably due to the fact that discharge levels more closely reflect the baseline inflammatory status of the patients and thus their intrinsic risk as a result of inflammatory activity. It is reasonable to assess CRP levels at entry and when possible at discharge; assessment 1 to 3 months later may be useful because it is likely that the highest risk of future events is confined to patients with persistently elevated levels of CRP.

The present torrent of studies of CRP in cardiovascular disease and associated conditions is facilitated by the ready commercial availability of automated CRP assays and of CRP itself as a research reagent. The current enthusiasm over CRP in cardiovascular disease is widely characterized by failure to recognize appropriately the nonspecific nature of the acute-phase response and by lack of critical biological judgment. Hardly a week passes without report of a new potential association between CRP values and some commonly encountered medical condition, physiological state, or vascular risk factor. Examples include cardiac arrhythmias, renal insufficiency, type 2 diabetes mellitus, obstructive sleep apnea, arterial hypertension, obesity, insulin resistance syndrome, estrogen use, frequent physical activity, and moderate alcohol consumption. In contrast, the positive association of CRP values with other classic cardiovascular disease risk factors, such as periodontal disease and smoking, seems more clearly related to local nonarterial inflammation. Furthermore, high-sensitivity CRP assay is far from a perfect test. Quality control and the relevance of experimental design before pathophysiological functions are ascribed are also often ignored. However, it is critically important to recognize that the CRP response is nonspecific and is triggered by many disorders unrelated to cardiovascular disease. Specificity of CRP for inflammation is clearly not infallible, with noninflammatory states such as chronic fatigue, high-protein diet, depression, and aging all associated with increased likelihood of CRP. When CRP is used for assessment of cardiovascular risk, it is therefore essential to clearly estab-
lish true baseline CRP values that are not distorted by either trivial or serious intercurrent pathologies. Not surprisingly, then, these concerns can be raised in regard to the study by Arenillas et al. If the CRP value persistently remains >1.0 mg/dL, indicating the presence of a significant acute-phase response, a single measurement is not sufficient; ≥2 serial samples taken at intervals of ≥1 week should be retested until a stable baseline value is seen. Furthermore, when patients with ischemic stroke are studied, no value should be discharged as too high a priori because after stimulation, CRP levels can increase 1000-fold, and there is evidence that in some patients constitutional hyperresponsiveness may lead to very high CRP levels even in the first hours after stroke and for longer periods.7,8 While adequate data are now available to document an overall increase in relative risk for cardiovascular events in patients with CRP elevation, data are still lacking with respect to absolute risk and the positive predictive value that CRP elevation might have in patients with acute and less acute ischemic stroke. Data are also lacking to show that interventions aimed at reducing CRP levels will lower the risk of subsequent cardiovascular events. Without this information, use of high-sensitivity CRP assay either acutely or as a screening modality will be limited. In particular, routine inclusion of high-sensitivity CRP assay in risk factor profiling of ischemic stroke patients could result in a disproportionate number of patients with false-positive CRP elevations that are unrelated to prediction of future cardiovascular events.27,28 The following guidelines may be reasonable: risk factor assessment with attention to optimizing primary and secondary preventive measures for cardiovascular disease should remain the essential objective of clinicians; interventions aimed at enacting healthy lifestyle changes should benefit all patients; cardiovascular risk may be further reduced by interventions aimed at correcting additional risk factors (ie, enhancing control of diabetes, lipid abnormalities, and blood pressure); and potential preventive measures, such as aspirin, clopidogrel, and angiotensin-converting enzyme inhibitors, should be actively considered and encouraged when appropriate. However, the demonstration that statins are probably effective in the presence of high CRP levels30 and that the efficacy of antiplatelet therapy in secondary prevention appears to be directly related to the level of inflammatory markers31 is already a first response. Finally, inflammation appears an important and common but not a necessary or a sufficient condition, and hence the predictive accuracy of CRP measurement can only be limited, as it is in the case of isolated traditional prognostic factors. Moreover, it is likely that the prevalence of an inflammatory component in acute ischemic stroke may vary according to age, sex, environmental conditions, and different ethnic groups. Variations in baseline plasma CRP of individuals may also reflect differences in CRP responses caused, for example, by genetic differences in the CRP gene yielding high and low responders, with the former being at risk for cardiovascular disease.31 Multicenter, carefully controlled studies in ischemic stroke patients that include information on stroke severity and other important prognostic factors are needed to determine whether CRP evaluation has utility in the secondary prevention of ischemic stroke before its use is recommended in common clinical practice. From this standpoint, CRP measurements should be included according to standardized protocols and reported on appropriate registries together with patient outcome. These registries will provide the presently lacking information and will gradually improve the prognostic information obtainable from CRP measurements according to age, sex, population, clinical variables, and selected clinical end points. Once these data are available, the profile of patients will be drawn; the causes, genetic or acquired, of the hyperresponsiveness can be sought; and new insights will be provided in ischemic stroke medicine.

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References


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