Inflammation, Blood Pressure, and Stroke: An Opportunity to Target Primary Prevention?

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The weight of evidence supporting a link between the inflammatory response and vascular disease has grown considerably in recent years, driven to a large extent by the development of highly sensitive and standardized assays for the acute phase reactant C-reactive protein (CRP), and has led to the current view of atherosclerosis as a systemic inflammatory disease rather than simply a process of intravascular lipid deposition.\(^1\) Most evidence hitherto has looked at coronary heart disease and in particular has sought to relate inflammatory markers to existing biochemical risk factors, such as cholesterol and homocysteine.

Case-control studies conducted within several large clinical trials indicate that elevated CRP concentration increases the risk of coronary, and vascular, events, with a relative risk of 1.7 to 4.4, independent of conventional risk factors.\(^2\) \(^3\) \(^4\)

Inflammation interacts with cholesterol concentrations in prediction of coronary events, and adding CRP to conventional lipid measurement may transform the unfavorable economics of primary prevention with statins, with an order of magnitude difference in numbers needed to treat.\(^5\)

Similar relationships with cytokines, adhesion molecules, or serum amyloid A protein have been found.\(^6\)

Ischemic stroke has been included as an end point in some of these case-control studies,\(^7\) and an independent predictive value of CRP has been confirmed recently in a prospective cohort study of elderly subjects from the Framingham population, with follow-up averaging 13 years.\(^7\)

In this issue of Stroke, Engström and colleagues report further results from a prospective cohort of 6071 healthy middle-aged men in Malmö, Sweden, followed up for nearly 20 years, in whom baseline assessment included a panel of 5 “inflammation sensitive proteins” (ISPs): fibrinogen, orosomucoid (\(\alpha_1\) acid glycoprotein), ceruloplasmin, \(\alpha_1\) antitrypsin, and haptoglobin. The present article explores the relationship of blood pressure (BP), inflammation, and stroke and supplements recently published data from the same study confirming a relationship among inflammation, cholesterol, and stroke risk.\(^8\)

In keeping with several epidemiological studies, cholesterol elevation in isolation was not an independent risk factor, such as statins might be informative in this respect also. If stroke in the Malmö cohort, but it became so in subjects with raised ISPs.

A relationship between blood pressure and inflammation has been hinted at in previous studies. A case-control study in generally healthy men aged 59 years on average (a subset of participants in the Physicians’ Health Study) found BP to be correlated with 2 inflammation-related molecules, interleukin-6 and soluble intercellular adhesion molecule-1,\(^9\) and a cross-sectional study in a similar population correlated CRP with BP.\(^10\)

The present Swedish cohort is the largest to report on stroke incidence rather than coronary disease or composite vascular end points and is notable also for the duration of follow-up. Blood pressure correlated positively with inflammatory indices, with progressive rise in BP with numbers of ISPs in the top quartile. The difference across groups, although statistically significant, is clinically not terribly impressive (3/2 mm Hg difference between subjects with no ISPs and those with all 5 ISPs in the top quartile). However, it is important to bear in mind that both BP and protein assays were conducted at baseline, and that no data are presented on the evolution of either parameter over the subsequent 20 years. The extraordinarily long shadow cast by a solitary measure of inflammation (or for that matter, blood pressure) is striking: most strokes (189/238, 79%) occurred more than 10 years after the baseline data were collected. Indeed, the predictive value of a single BP and blood sample is all the more impressive because the strength of the relationship should be underestimated given the expected fluctuation of inflammatory responses and BP with time.

These data raise questions about the relationship between hypertension and inflammation. Inflammatory response activation may plausibly represent a consequence of hypertension: there are animal data that link angiotensin II, for example, with pro-inflammatory as well as vasoconstrictive actions.\(^1\) As with statins, it may be that drugs blocking angiotensin II action (converting enzyme inhibitors or angiotensin II receptor antagonists) act via anti-inflammatory mechanisms not originally suspected to reduce cardiovascular risk: the recently reported LIFE trial results suggest a protective effect of losartan over and above its antihypertensive effect,\(^11\) and it is tempting to speculate about the possible anti-inflammatory action as one potential action not shared by all classes of antihypertensive drugs.

Could inflammation trigger BP elevation? Longitudinal data have yet to be published, but the authors of the present study allude to just such an observation from this cohort.

Analysis of intervention trials using anti-inflammatory agents such as statins might be informative in this respect also. If
worsening BP elevation over a period of years could be prevented or attenuated by anti-inflammatory treatments, a new window on primary prevention could be opened. It may be that adding evaluation of inflammatory markers to conventional risk factors not only will allow intervention to be targeted to more appropriate patients but also will define which specific drugs an individual should receive.

How best to measure inflammation? The specific proteins measured in this study reflect assays available 20 years ago, and, with the exception of fibrinogen, the others are unlikely to be part of a routine laboratory panel. How specific they are as indicators of an inflammatory response is also open to question, given that, unlike CRP and many of the other molecules studied more recently, there is no defined role for the proteins used by Engström and colleagues in the initiation or maintenance of the inflammatory response; indeed, the physiological role for several of them remains to be fully determined. Fibrinogen certainly cannot be regarded exclusively as an indicator of inflammation. A relationship between vascular events and fibrinogen has long been recognized, although it has primarily been investigated as an indicator of thrombotic activity. There is fairly robust evidence that some markers of coagulation system activation (eg, D-dimers, plasminogen activator inhibitor-1) are independent predictors of ischemic stroke and other atherosclerotic vascular disease, so fibrinogen cannot be regarded as simply an acute phase reactant. Do the multiple assays strengthen the predictive value of inflammation, as suggested by the authors? The study’s results suggest that 2 abnormal assays yield greater relative risk than 1, but adding more did not contribute further. The existing literature on inflammation and vascular risk has established that a solitary, but specific, measure such as CRP confers a relative risk very similar to that observed for the panel of proteins in this study. It is unfortunate that stored samples do not seem to have been available from the Malmö cohort to permit comparison of the merits of multiple non-specific ISP testing and a specific marker.

Having established the credentials of a putative risk factor, clinical application necessitates an appraisal of absolute rather than relative risks. Doubling the risk of stroke means very different things depending on what that risk is to start with. The overall absolute ischemic stroke risk in the cohort reported by Engström et al was only 3.3%, reflecting the age and health of the participants. Only in those with elevated systolic BP (≥140 mm Hg) was the difference in absolute risk between those with and those without elevated ISPs significant (7.4% versus 4.0% for ischemic stroke, and 8.9% versus 4.9% for any stroke). Is an additional 1 in 25 to 30 chance of a stroke over a 20-year period justification for intensive drug treatment in a healthy middle-aged man? Realistic individual and collective decisions about drug treatment will require the development of risk tables for stroke that incorporate existing risk factors along with novel markers such as inflammation. The data to begin to explore this exist within studies such as the present one.

Despite the view of atherosclerosis as a single disease—currently much favored by the pharmaceutical industry—the risk factor profile of stroke and myocardial infarction clearly differ in important respects. Given that stroke is not a pathologically uniform condition, some mechanistic insights about the role of inflammation may well come from going beyond the crude separation into hemorrhage and ischemia and looking at stroke subtypes. If inflammation activation signifies athrogenesis, for example, then a distinction between lacunar syndromes and carotid disease could be anticipated.

Excepting atrial fibrillation, pharmacological primary prevention of stroke has relied on the blunt instrument of blood pressure treatment for some time. The Malmö data help to suggest that inflammation may become a valuable additional tool in targeting such treatment more effectively.

References


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