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

Keith W. Muir, MD, FRCP

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. 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. 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. Similar relationships with cytokines, adhesion molecules, or serum amyloid A protein have been found. Ischemic stroke has been included as an end point in some of these case-control studies, 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.

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 (α1 acid glycoprotein), ceruloplasmin, α1 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. In keeping with several epidemiological studies, cholesterol elevation in isolation was not an independent

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, and a cross-sectional study in a similar population correlated CRP with BP. 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. 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, 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 con-
tventional 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 exclu-
sively as an indicator of inflammation. A relationship be-
tween vascular events and fibrinogen has long been recog-
nized, although it has primarily been investigated as an
indicator of thrombotic activity. There is fairly robust evi-
dence that some markers of coagulation system activation
(eg, D-dimers, plasminogen activator inhibitor-1) are inde-
pendent predictors of ischemic stroke and other atheroscle-
rotic 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 treat-
ment will require the development of risk tables for stroke
that incorporate existing risk factors along with novel mark-
ers 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 atherogenesis, for example, then a distinction be-
tween lacunar syndromes and carotid disease could be
anticipated.

Excepting atrial fibrillation, pharmacological primary pre-
vention 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
340:115–126.
2. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH.
Inflammation, aspirin, and the risk of cardiovascular disease in apparently
3. Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the
predictive value of total and HDL cholesterol in determining risk of first
4. Ridker PM, Hennekens CH, Buring JE, Rifai N, C-reactive protein and
other markers of inflammation in the prediction of cardiovascular disease
5. Ridker PM. High-sensitivity C-reactive protein: potential adjunct for
global risk assessment in the primary prevention of cardiovascular
6. Ridker PM, Buring JE, Shih J, Mattias M, Hennekens CH. Prospective
study of C-reactive protein and the risk of future cardiovascular events
7. Rost NS, Wolf PA, Kase CS, Kelly-Hayes M, Silbershatz H, Massaro JM,
D’Agostino RB, Franzblau C, Wilson PW. Plasma concentration of
C-reactive protein and risk of ischemic stroke and transient ischemic
Effects of cholesterol and inflammation-sensitive plasma proteins on
9. Chae CU, Lee RT, Rifai N, Ridker PM. Blood pressure and inflammation
10. Rohde LE, Hennekens CH, Ridker PM. Survey of C-reactive protein and
11. Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beever G, Faire U,
Fyhrquist F, Isbom H, Kristiansson K, Lederballe-Pedersen O, Lindholm
LH, Nieminen MS, Onvik P, Oparil S, Wedel H. Cardiovascular mor-
bidity and mortality in the Losartan Intervention For Endpoint reduction
in hypertension study (LIFE): a randomised trial against atenolol. Lancet.
12. Wilhelmsen L, Svardsudd K, Korsan-Bengtson K, Larsson B, Welin L,
Tibblin G. Fibrinogen as a risk factor for stroke and myocardial
static factors as predictors of ischemic heart disease and stroke in the
Edinburgh Artery Study. Arterioscler Thromb Vasc Biol. 1997;17:
3321–3325.
14. Woodward M, Lowe GD, Rumley A, Tunstall-Pedoe H. Fibrinogen as a
risk factor for coronary heart disease and mortality in middle-aged men
and women: the Scottish Heart Health Study. Eur Heart J. 1998;19:
55–62.

Key Words: blood pressure  inflammasome  prevention  stroke
Inflammation, Blood Pressure, and Stroke: An Opportunity to Target Primary Prevention?
Keith W. Muir

Stroke. 2002;33:2732-2733; originally published online October 31, 2002;
doi: 10.1161/01.STR.0000041034.33647.41
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/33/12/2732