Inflammation, Cell Adhesion Molecules, and Stroke: Tools in Pathophysiology and Epidemiology?

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Since their development approximately a decade ago, cell adhesion molecules have been attracting interest for a number of reasons. For example, the blockade of the interaction between leukocytes and the endothelium by agents that mimic or inhibit these adhesion molecules may provide the basis for a new class of therapeutic agents, although promising studies in animals have yet to be translated into products proven to be effective in humans. Study of the expression of the molecules on the surface of various cells or of the soluble form in the plasma may provide insights into their role(s) in pathophysiology in cardiovascular, connective tissue and neoplastic diseases, and differences in levels of soluble cell adhesion molecules in the plasma may be useful tools in stratifying disease severity or prognosis. However, these aspects may be related, as soluble forms themselves may interfere with leukocyte/endothelial cell interactions, at least in vitro. Despite this, soluble adhesion molecules may be useful in dissecting the pathophysiological events in cardiovascular disease, as it may be presumed that changes in levels may relate to activation or damage to various cells such as the platelet and endothelium.

The selectin family of adhesion molecules has two principal members. Soluble P-selectin is believed to be the product of activated platelets, although the endothelium displays a membrane-bound form. Increased levels are found in a number of conditions, including thrombotic disorders, diabetes, and ischemic heart disease, and raised levels predict adverse events, even in apparently healthy individuals. Although increased levels of soluble E-selectin are the result of cytokine activation of endothelial cells in vitro, and raised levels in the plasma have been reported in variant (but not stable) angina and in ischemic heart disease, such raised levels seem unable to predict adverse cardiovascular events but do predict restenosis following percutaneous angioplasty in the peripheral arteries.

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The second major group of adhesion molecules belong to the immunoglobulin supergene family, and 2 members warrant attention. Soluble intercellular adhesion molecule-1 (sICAM-1) is a likely product of many cells, including the endothelium and leukocytes. Also influenced by inflammatory cytokines in vitro, raised levels are found in many conditions, including angina and both coronary and peripheral artery disease. However, although raised levels of sICAM-1 in healthy men and women predict adverse events, the association is weaker when there is a background of existing atherosclerosis. Conversely, despite reports of raised vascular cell adhesion molecule-1 (sVCAM-1) in various cardiovascular conditions, such levels seem unable to predict adverse outcome.

Increased levels of sICAM-1 and sVCAM-1 are often taken to imply damage and/or stimulation of the endothelium, but the expression of these molecules on smooth muscle cells, leukocytes, and tumor cells suggests some caution may be necessary. However, despite these caveats, increased levels of these molecules in a variety of cardiovascular, inflammatory, and neoplastic disease are widely reported, and in many individual reports they seem useful in predicting clinical outcome, but the precise mechanisms and consequences of increased levels are often unclear. However, there is also possible conflict: Blankenberg et al reported that baseline sVCAM-1, sICAM-1, and sE-selectin were all significantly related to future death from cardiovascular causes among 1246 patients with documented coronary artery disease. Conversely, Malik et al following up 643 men with coronary artery disease and 1278 controls, found that measurement of cell adhesion molecules, while having univariate predictive value, had limited clinical utility in multivariate models, which accounted for established risk factors.

Stroke is also a case in point. Not surprisingly, numerous groups have reported raised levels of various markers in the short period following stroke, some proposing that changes may be related to the profound alterations in the metabolic homeostasis in the patients. Therefore, the pursuit of the mechanisms leading to the changes in these markers may provide additional clues to the pathophysiology of this disease. In this respect, Rohde et al reported a strong correlation between carotid artery intima-media thickness and plasma sICAM-1. However, despite these interesting short-term and cross-sectional reports, what would be most valuable to the clinician would be to know whether these raised levels predict adverse outcome in a long-term study. To date, few prospective data have been available for cerebrovascular disease, although in the Women’s Health Study, sICAM-1
levels were predictive of future thromboembolic stroke events.22

The article by Tanne et al36 in this current issue of Stroke goes some way to answer this question. Their nested case-control study of subjects with existing coronary artery disease found raised diabetes, smoking, plasma fibrinogen, and serum sICAM-1 (see Table 1 in the article) in the 134 cases who, after 8.2 years, suffered a stroke, compared with 134 controls who did not have an end point. It has long been established that fibrinogen is a risk factor for cardiovascular disease,37 and those patients whose fibrinogen and sICAM-1 were both in the highest tertile were at the highest risk of stroke, suggesting an additive effect (see Figure 2). However, smoking and diabetes can influence sICAM-1,38,39 and smoking can increase fibrinogen.40 After multivariable adjustment for either smoking or lipids, the relative risk of stroke became more significant. However, after adjustment for the combination of diabetes, smoking, hypertension, and previous myocardial infarction, with or without fibrinogen or white blood cell count, these previously significant trends became not significant (see Table 2).

A further mechanism to linking sICAM-1, thrombosis, and fibrinogen (and, indeed, many other possible plasma molecules and markers) is inflammation, possibly related to smoking.16,41,42 Like fibrinogen and smoking, the most widely accepted marker of inflammation (C-reactive protein [CRP]) is also associated with an increased risk of the development of cardiovascular disease,43 including stroke.22,44,45 Two questions, one pathophysiological and one clinical, are therefore immediately relevant. First, what are the interrelationships between different plasma markers of inflammation and what do these tell us about the pathophysiology of cardiovascular and cerebrovascular disease? Second, which of the inflammatory markers has the most to offer clinically in terms of predicting which apparently healthy patients are at highest risk of suffering a future vascular event? The answer to the former will be of interest to those seeking to understand the mechanisms leading to thrombosis, and thus how to minimize the risk of its occurrence. The answer to the latter will be eagerly awaited by epidemiologists and clinicians. To date, few studies have directly compared fibrinogen, IL-6, ICAM, VCAM, P-selectin, and CRP, but those that have consistently found CRP to have the greatest prognostic utility.22,46 It is important to recognize, however, that the apparent superior clinical performance of CRP is due largely to the fact that this biomarker has a long half-life, is stable from a clinical chemistry perspective, has no circadian variation, and can be measured with a simple reproducible bioassay in a wide variety of clinical outpatient settings.47 Thus, while CRP is likely to be the inflammatory biomarker of choice for clinical purposes, these data do not imply that CRP is necessarily more important from a biologic perspective when compared with upstream cytokines, fibrinogen, or soluble cell adhesion molecules. We must therefore keep an open mind as to what the appropriate pharmacologic targets for vascular inflammation might be in the future.

References


Key Words: cell adhesion molecules • inflammation • risk factors • stroke, ischemic