The Edinburgh Artery Study: is lytic activity bad for the heart?

See page 1607 for the article to which this Editorial refers

In this issue Smith et al. report the results of a study of a variety of haemostatic and rheological factors in relation to vascular outcome in subjects with established coronary artery disease. Of 207 subjects with angina pectoris at entry, 67 developed a fatal or non-fatal vascular event during the 5 years of follow-up. Entry levels of tissue plasminogen activator antigen (tPA) and leukocyte elastase were related to subsequent vascular outcome, whilst other measures, most notably fibrinogen, von Willebrand factor, D-dimer and Factor VII were no different in the two groups.

These findings contribute to our understanding of possible mechanisms in vascular disease, and question the role of the fibrinolytic system in the pathogenesis of myocardial infarction. There have been a large number of prospective and case control studies of vascular risk involving various recruitment criteria and clinical end-points over the last 30 years. These have led to an increased awareness of risk factor involvement, but the differences in design have led to difficulties in consistent interpretation. Perhaps one of the closest in design is the European Concerted Action on Thrombosis (ECAT) study which followed 3043 patients for 2 years and had 106 definite coronary events. They reported elevated levels of fibrinogen, von Willebrand factor and tPA in those who developed coronary events. Although the authors of the Edinburgh study imply that a different recruitment strategy explains the discrepancies between the two studies, it is equally possible that the Edinburgh study is under-powered to pick up differences in the other factors.

In the literature there is a large body of work implicating variation in the coagulation and fibrinolytic systems in relation to the development of myocardial infarction. The prejudice of most investigators would have been that a thrombotic disorder had enhanced risk in the presence of increased thrombotic risk and this view has been borne out by various studies indicating that fibrinogen, plasminogen activator inhibitor-1, Factor VII and von Willebrand factor relate to vascular disease. These findings helped to develop a simple but entirely logical view that procoagulant or anti-fibrinolytic changes in the blood were most likely to increase risk of myocardial infarction. The reports from several studies that both tPA and D-dimer relate to vascular risk seemed counter-intuitive as they are considered indicators of either enhanced fibrinolytic potential or enhanced fibrinolysis (D-dimer). There are a number of ways of interpreting the data to explain this relationship. First is the view that enhanced fibrinolysis actually represents a protective response to an increasingly procoagulant milieu as risk factor clustering progresses. Second, as fibrin is an important component of atheroma, enhanced fibrinolysis may lead to plaque instability and increased risk of myocardial infarction. Finally, as tPA clusters with features of insulin resistance, it may be either having a clinical effect because of this association or acting as a risk marker without involvement in disease processes. It is currently not possible to state which of these positions is tenable, although a possible explanation is that tPA is elevated early in response to insulin resistance and later becomes involved in the processes of plaque rupture.

Whilst coagulation processes have a fairly long history of involvement in vascular disease, it is only relatively recently with the advent of innovative cell biology techniques that the role of cellular components of the blood has become clearer. It is established that the macrophage has a role in atheroma formation, but the role of neutrophils has been less clear. Neutrophil elastase is an enzyme released by activated neutrophils that is involved in the solubilization of elastin, an important component of the extracellular matrix. There is abundant evidence that activation of this system occurs in chronic pulmonary disease in which inflammation plays a role. More recently evidence has emerged that indicates that elastase activity may be related to endothelial cell damage. This opens the door for an involvement in vascular disease and to support this, in a rat heart model, inhibition of neutrophil elastase was associated with cardioprotection from repetitive ischaemia and myocardial infarction. In the current study elevated elastase activity was associated with progression to myocardial infarction which provides support to the view that leukocytes and neutrophil elastase are important in vascular disorders.

Taken overall, the current findings of the Edinburgh Artery Study provide further information on risk factor involvement in the progression to myocardial infarction in subjects with pre-existing coronary artery disease. The Edinburgh Artery Study is interesting because it is studying the propensity of...
individuals with established ischaemic heart disease to progress to myocardial infarction. This, in theory at least, should give some insight on factors involved in plaque instability and rupture if the groups were adequately matched for atheroma burden and other features of ischaemic heart disease. The drawback in extrapolating these findings to the very important issues of plaque instability and rupture is related to the difficult problem of identifying this phenotype in population studies.

However, both tPA and elastase are enzymes that are indirectly or directly involved in the degradation of components of the extracellular matrix and it is an attractive hypothesis that the elevations in levels reported in this study may be related to increased plaque instability. This remains speculation at present but further information on these issues will be valuable in both our understanding of disease mechanisms and in the development of novel approaches towards therapeutic intervention.

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References

Erythrocyte sedimentation rate: is it a useful risk marker for coronary heart disease?

See page 1614 for the article to which this Editorial refers

Intense interest has been generated in recent years on the role of inflammation in the pathogenesis of atherosclerosis. Coronary atheroma vulnerable to plaque erosion or fissuring are characterized microscopically by abundant macrophages and T-cell lymphocytes which lead to the over-expression of adhesion molecules, growth factors, metalloproteases and cytokines. It has been noted that the inflammatory reaction within atherosclerotic plaques is of equal intensity to that found within the synovia of patients with acute rheumatoid arthritis[1]. This evidence of inflammation has led to close scrutiny of various serum markers which might reflect evidence of underlying low-grade inflammation and prove helpful in predicting the likelihood of future acute coronary events. One would hardly expect that a single vulnerable atherosclerotic plaque would be of sufficient volume to produce an inflammatory response capable of inducing detectable rises in serum

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