Fibrinogen, viscosity and ischaemic heart disease risk

See page 1814 for the article to which this Editorial refers

In their paper Sweetnam et al.[1] present data on the predictive value of fibrinogen and plasma viscosity for ischaemic heart disease during a 10-year follow-up period. In the Caerphilly and Speedwell studies, relative risks of more than 2 for men in the lowest compared to men in the highest quintiles were found. The association could not be attributed to age, smoking, cholesterol, blood pressure or body mass index. Interestingly, the cases which occurred during the second half of the follow-up period had lower baseline levels of fibrinogen and viscosity than the cases which occurred during the first part, but their levels were still significantly elevated relative to the non-cases. The association between fibrinogen and ischaemic heart disease risk was partly, but not completely, explained by plasma viscosity.

During the last decade, evidence has accumulated that fibrinogen level is predictive of major cardiovascular disease in the general population[2], and of recurrent events in coronary heart disease patients[3]. The association seems to be independent of other cardiovascular risk factors, notably smoking (which raises plasma fibrinogen) and cholesterol. This is again confirmed in the study by Sweetnam et al. Fibrinogen is now an established risk indicator for cardiovascular disease.

However, because fibrinogen is still a relatively 'new' risk factor, the mechanisms underlying the association are still unclear. It is known that inflammation elevates fibrinogen levels, and fibrinogen may be an indicator of (severity of) prevalent atherosclerosis rather than a true 'cause'. The follow-up duration from available prospective studies is still insufficient to preclude this possibility. The present study shows that the relationship persists after 6-7 years, but weakens over time. Almost 25% of the Speedwell and Caerphilly men had some evidence of prevalent disease at baseline. Because prevalent heart disease was associated with both higher risk of ischaemic events and higher levels of fibrinogen and viscosity, there may be some concern whether this explains the observed associations. When a strong relationship between fibrinogen and ischaemic heart disease incidence is present in subjects with prevalent disease, and no association in healthy men, the inclusion of prevalent disease in multivariate analyses would obscure this effect modification. However, Sweetnam et al. report that in the men without evidence of pre-existent disease, the associations were even slightly stronger (in the Method section). Further, in subjects without prevalent cardiovascular disease (defined by absence of a history of angina pectoris, claudication, myocardial infarction, stroke, coronary angioplasty, cardiovascular surgery or electrocardiographic signs of prior myocardial infarction) greater fibrinogen levels have also been associated with greater carotid wall thickness, an indicator of early atherosclerosis[5]. This suggests that fibrinogen is not only implicated in acute phase reactions, but possibly in the process of atherogenesis.

Meade has listed several mechanisms linking high fibrinogen to ischaemic heart disease[6]. One important pathway is its effect on plasma viscosity. The Caerphilly and Speedwell data confirm that this may be a major pathway. Other contributing mechanisms are the influence of fibrinogen on platelet aggregability, and the amount of fibrin produced during thrombosis.

The consistent association of fibrinogen with risk of ischaemic events observed in prospective studies, and the presence of plausible causal mechanisms, urge us to consider what can be done with this knowledge. In addition to cholesterol and blood pressure, should clinicians routinely determine fibrinogen levels? For this purpose, standardization of methods for fibrinogen measurement will be necessary. And if elevated fibrinogen is detected, what consequences does that have for treatment? Presently, we do not know whether lowering fibrinogen will be beneficial, but the results of intervention studies are under way. Most traditional treatments in patients with high cholesterol will also lower fibrinogen. Therefore, while we are trying to unravel the nature of the link between elevated fibrinogen and risk of ischaemic heart disease, we can safely advise the high risk population to follow a prudent diet, avoid smoking, and exercise regularly, and effectively treat hyperlipidaemia.

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References

Biochemical markers in acute myocardial infarction — the beginning of a new era?

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The use of biochemical markers in acute myocardial infarction has developed rapidly since the first description by La Due et al. of increases in serum glutamic oxaloacetate transaminase as a reflection of myocardial damage1. Several enzymes with different properties have since then been evaluated and more myocardial-specific enzymes such as creatine kinase MB and α-HBD are now used routinely in clinical practice. Lately troponin T and myoglobin have been evaluated and shown to further improve our diagnostic capability. Today biochemical markers are used not only for the diagnosis of acute myocardial infarction but also to assess the extent of myocardial damage, evaluation of reperfusion after thrombolysis and risk stratification in patients with acute coronary syndromes.

Clinicians have for decades known that following an acute myocardial infarction patients will develop fever, leucocytosis, and an increase in SR reaction. The mechanism behind the fever reaction and the rise of acute phase plasma proteins has received attention in recent years. A specific group of substances, the cytokines, have been shown to orchestrate a number of inflammatory and immunological events. Cytokines have pronounced effects both locally and systematically on the cardiovascular system including promotion of inflammation, intravascular coagulation and cell adhesion, free radical generation, endothelial injury and possibly progression of coronary atherosclerosis2,3. Following an acute myocardial infarction several of these cytokines are released, particularly the interleukins and tumour necrosis factor alpha2,4,5. Although cytokines are present in many different cells, it is suggested that their release following an ischaemic event is mainly caused by activation of monocytes6. In contrast to previously used biochemical markers, cytokines are secreted from activated immunocompetent cells and possess properties of their own which may be deleterious to the heart.

Tumour necrosis factor alpha is a cytokine which enhances procoagulant activity in endothelial cells, activates neutrophils, stimulates fibroblast growth and suppresses adipocyte lipoprotein lipase. Infusion of tumour necrosis factor alpha may induce a shock-like state with peripheral vasodilatation and pulmonary oedema. Repeated infusions of tumour necrosis factor alpha can lead to a permanent decrease in myocardial contractility and ultimately to dilated cardiomyopathy. Tumour necrosis factor alpha also promotes left ventricular remodelling experimentally and may play a role in chronic heart failure in humans. The negative inotropic effects of tumour necrosis factor alpha are suggested to result from alterations in intracellular calcium homeostasis8. It has also been postulated that the contractile dysfunction may result from enhanced activity of constitutive nitric oxide synthase in the myocardium, but current data are conflicting8,9.

Hirschl et al.10 measured tumour necrosis factor alpha in 50 patients following myocardial infarction. Increased tumour necrosis factor alpha values were found to be associated with signs of heart failure and the presence of rhythm disturbances. A relationship was also found between tumour necrosis factor alpha and the accumulative release of α-hydroxybutyrate-dehydrogenase as a measurement of infarct size. This relationship was further supported by a positive correlation to larger myocardial