Endothelial cell damage and the development or progression of atherosclerosis

Atherosclerosis is a process from which there is little escape; it is likely that the clinical consequences of this disease (myocardial infarction, stroke, intermittent claudication) will strike most of us. The question is, therefore, how do we go about delaying its appearance? The huge epidemiological studies initiated in the 1960s to 1980s defined and then demonstrated the importance of risk factors such as hypercholesterolaemia, diabetes, smoking and hypertension. Subsequent studies showed that the reversal or control of these risk factors was beneficial, and that they probably exerted their atherogenic effect via one or more physiological systems that included the platelet and soluble coagulation factors such as fibrinogen. More recently, the endothelium has been identified as a target for the disease process [1].

A corollary of the view that correct endothelial cell function is essential for the adequate regulation of blood pressure tone and haemostasis is that hypertension, thrombosis and coagulopathy are the consequences of the loss of endothelial cell integrity. Therefore a good technique for assessing endothelial cell function may be useful in defining those at risk of developing disease [2]. One such technique measures the ability of the endothelium to influence blood flow via its effect on the smooth muscle cells of the arterial media. This demands a sensitive measure of the change in blood flow following pharmacological (e.g. infused acetylcholine) or physiological (e.g. temporary vasoconstriction) stimulus. Although these techniques have provided useful data on mechanisms and markers such as nitric oxide, the demands of this method mean that large numbers of subjects cannot be studied in a short period of time.

An alternative method of assessing endothelial damage is to look for changes in the levels of various secreted products such as von Willebrand factor, soluble thrombomodulin, soluble E-selectin and tissue plasminogen activator in the plasma. The advantages of this 'serological' approach is that large numbers can be processed (by ELISA) in a small period of time, and that plasma can be safely stored frozen for batch analysis. However, one concern with the use of these markers is that plasma levels may also arise from non-endothelial sources, such as platelets, giving rise to problems of specificity [3,4]. Despite this caveat, increased levels of these plasma markers are generally found in the risk factors for atherosclerosis and in frank disease. Furthermore, increased levels fall as the risk factors are themselves treated, strengthening the hypothesis that damage to the endothelium by the risk factors leads to higher levels of the plasma markers, and that this damage is reversible [2,5]. So not only are high levels of plasma markers present in risk factors and disease, and are amenable to treatment, but high levels are also harbingers of adverse events to come. Of the plasma markers, von Willebrand factor and tissue plasminogen activator have been amongst those most intensively studied.

Boneu et al. [6] were the first to describe and suggest that raised levels of von Willebrand factor indicate damage to the endothelium in diabetes, sepsis and atherosclerosis. Reports of raised levels in smoking, essential hypertension, hyperhomocysteinaemia and hypercholesterolaemia followed (see references in [2]), but in 1991 Jansson et al. [7] were the first to note that raised levels in survivors of a myocardial infarction predicted re-infarction or death. This finding has since been reported in those with peripheral atherosclerosis [8], angina [9], and, more crucially, in apparently healthy members of the community [10,11]. Similarly, increased levels of tissue plasminogen activator also predict those at risk of disease progression, whether against a background of apparent health [12–14] or angina [9,15]. Of further interest are reports that raised levels of von Willebrand factor and tissue plasminogen activator predict adverse events in patients with rheumatoid arthritis and systemic sclerosis [16–18].

Another laboratory index of note is the rate of excretion of albumin, measured in the urine (UAER). As a healthy glomerulus will retain albumin, it follows that a raised UAER implies damage to the endothelium of the kidney. A further corollary may be that those factors damaging the glomerular endothelium also damage endothelial beds elsewhere, and hence, possibly systemically. Therefore as a raised UAER also predicts the development of vascular disease and mortality [19,20], it would seem that this also could be a useful surrogate marker for those at risk of disease progression.

In diabetes, several groups have measured von Willebrand factor, tissue plasminogen activator and UAER concurrently. Collier et al. [21] in non-insulin-dependent diabetes mellitus (NIDDM), found that both plasma markers were highest in patients with microalbuminuria. The longitudinal studies of Stehouwer et al. [22,23] show not only that von Willebrand factor and UAER in NIDDM are linked, but that raised von Willebrand factor precedes the development of microalbuminuria in insulin-dependent diabetes mellitus. The contribution of Clausen et al. [24] in the current issue of Clinical Science provides much the same data, but crucially in apparently healthy subjects. After a mean of 4.1 years, those subjects who had levels of von Willebrand factor or tissue
plasminogen activator above the median at outset experienced a rise in UAER, whereas UAER did not change in those whose plasma markers were less than the median. Notably, this increase in UAER could not be predicted by levels of classical risk factors (blood pressure, body mass index or serum lipoproteins).

It now seems clear that endothelial cell damage/dysfunction leads to the progression of UAER in diabetes [23] and in health [24]. Since increased UAER [19,20,25], von Willebrand factor [7–11] and tissue plasminogen activator [9,12–15] are all harbingers of adverse events and mortality, how can we best make use of this information? The protection of the endothelium from damage seems to be a good strategy, and the avoidance/control of risk factors is one mechanism to achieve this. Another is the use of appropriate pharmaceutical agents, and the beneficial activity of certain angiotensin-converting-enzyme inhibitors may point the way [26,27]. A second question is, which is the best and most convenient marker? The answer to this question is less clear as there have been few large-scale side-by-side comparisons, one of these being conducted in subjects with angina pectoris on outset [28,29]. A final point is are we focussing too sharply on the endothelium? If we wish to identify those at greatest risk of disease, then the recent interest in von Willebrand factor [7–11] and tissue plasminogen activator [9,12–15] are all harbingers of adverse events predicted by levels of classical risk factors (blood pressure, blood group and the incidence of coronary heart disease. Circulation 96, 1102–1108


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REFERENCES


