Editorial

The Endothelium and Coagulopathy in Systemic Lupus Erythematosus: Hyperhomocysteinemia as a Developing Risk Factor

Endothelial function, primarily involving regulated mediator secretion and altered surface glycoprotein expression, is vital for normal homeostasis. This process is associated with the secretion of a large number of molecules, including the potent antplatelet agent prostacyclin and the major regulator of fibrinolysis, circulating tissue plasminogen activator (tPA), as well as the expression at the cell surface of molecules such as tissue factor (Table 1)\(^1\). The properties of healthy endothelium ensure that an antithrombotic and anticoagulant balance is maintained. Disturbances of normal endothelial function are implicated in the pathogenesis of vascular complications in many diseases, including atherosclerosis and the connective tissue diseases (CTD) such as rheumatoid arthritis (RA)\(^2-4\). Each of the risk factors for atherosclerosis, as well as the disease itself, is characterized by increased plasma levels of markers of endothelial function [such as von Willebrand factor (vWf)] that predict cardiovascular events. Raised vWf is also present in almost all CTD, and in some cases, as in atherosclerosis, also predicts adverse outcome\(^5,7\).

Thus it is clear that endothelial perturbation is not only apparent in atherosclerosis and CTD\(^7,8\), but may also contribute to a worsening outcome. Although it is relatively easy to envisage the mechanism whereby the “classical” risk factors for atherosclerosis contribute to vascular malfunction, no such simple or general paradigm exists for CTD (e.g., lack of excess hypercholesterolemia), although systemic lupus erythematosus (SLE) may be a special case\(^8\). Instead, chronically raised concentrations of cytokines may drive the inflammation that could, over years, cause vascular deterioration, as long-standing activation may lead to endothelial injury\(^10\). However, mechanisms other than inflammatory cytokines (such as autoantibodies) may, at least in part, be responsible for contributing to vascular disease in the CTD in general and in SLE in particular.

These alternative mechanisms include hyperhomocysteinemia, a developing risk factor for atherosclerosis. Although raised concentrations of homocysteine have been recognized in SLE\(^11,12\), in this issue of The Journal, Tam, et al\(^13\) provide additional evidence of a mechanism for relating this amino acid to pathophysiology. Compared with a placebo, an acute hyperhomocysteinemia induced by dietary methionine induced increased vWf and increased binding of fibrinogen by platelets, neither of which, according to current pathophysiological dogma, is desirable. The increase in vWf of perhaps 20% was more pronounced than the increase in control subjects of about 8%, implying that the endothelium in SLE is more fragile and more susceptible to what would otherwise be a relatively inoffensive stimulus. Notably, there was no such acute change in flow-mediated dilatation, an alternative estimate of endothelial function that is impaired in overtly inflammatory vasculitis\(^8\). Their study underlines the presence of latent endothelial and platelet activation in lupus and the role of external classical prothrombotic factors on the endothelium.

The role of homocysteine and other cardiovascular risk factors (hypertension, smoking, obesity) in lupus is clear and is a potential tool for prevention\(^9,11,12,14\). In particular, lupus patients with a history of arterial thrombosis have an elevated homocysteine concentration\(^14\). From non-SLE patients there is good evidence that hyperhomocysteinemia confers an increased risk of occlusive vascular disease, mainly of the carotid and coronary arteries. It has been estimated that lowering homocysteine concentrations by 3 \(\mu\)mol/l (which can be achieved by increasing folic acid intake) would reduce the risk of ischemic heart disease by 16% and stroke by 24%\(^15\). This has a practical value as, in non-lupus cardiovascular patients, treatment with folic acid, vitamin B12, and pyridoxine not only reduces homocysteine levels (as we would expect) but crucially decreases the rate.
Table 1. Endothelial factors important in thrombosis and hemostasis.

<table>
<thead>
<tr>
<th>Soluble Products</th>
<th>Anticoagulants/Antithrombotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procoagulants/Prothrombotics</td>
<td>Tissue plasminogen activator</td>
</tr>
<tr>
<td>von Willebrand factor</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>Thromboxanes</td>
<td>Prostacyclins</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor</td>
<td>Tissue plasminogen activator</td>
</tr>
<tr>
<td>Coagulation factor V</td>
<td>Heparin(s)</td>
</tr>
<tr>
<td>Platelet activating factor</td>
<td>Ectonucleotidases</td>
</tr>
</tbody>
</table>

Cell Surface Glycoproteins

| Tissue factor | Thrombomodulin |

status are all associated with an increased risk of thrombosis. Strategies focused on these risk factors may well lead to a decrease in cardiovascular disease in SLE. However, additional insights into lupus-mediated endothelial cell perturbation are needed to clarify the mechanisms of vessel wall damage that are independent of the classical risk factors. It is clear from the studies of Tam, et al and others that latent endothelial cell and platelet activation occurs in SLE and that homocysteine adversely affects the endothelial cells. Aggressive treatment of the traditional and newer risk factors for cardiovascular disease should result in a lower morbidity and mortality in patients with lupus.

ROB FIJNHEER, MD, PhD,
Department of Hematology,
University Medical Center,
Utrecht, The Netherlands;
ANDREW D. BLANN, PhD, MRCPath,
Department of Medicine,
City Hospital,
Birmingham B18 7QH, United Kingdom.

Address reprint requests to Dr. Blann, E-mail: a.blann@bham.ac.uk

REFERENCES