

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 antiplatelet 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 outcome⁵⁻⁷.

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 case⁹. 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 injury¹⁰. 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 vasculitis⁸. 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 concentration¹⁴. 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 $\mu\text{mol/l}$ (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

See Patients with SLE show increased platelet activation and endothelial dysfunction induced by acute hyperhomocysteinemia, page 1479

Table 1. Endothelial factors important in thrombosis and hemostasis.

Soluble Products	
Procoagulants/Prothrombotics	Anticoagulants/Antithrombotics
von Willebrand factor	Nitric oxide
Thromboxanes	Prostacyclins
Plasminogen activator inhibitor	Tissue plasminogen activator
Coagulation factor V	Heparin(s)
Platelet activating factor	Ectonucleotidases
Cell Surface Glycoproteins	
Tissue factor	Thrombomodulin

of re-stenosis and the need for revascularization after coronary angioplasty¹⁶.

Cardiovascular disease accounts for up to 30% of all deaths in patients with SLE, and age-specific incidence rates of the manifestations of coronary artery disease are increased up to 50 times for young female lupus patients compared to controls^{9,17}. Indeed, it has recently been established that, compared to osteoarthritis, patients with RA are at an increased risk of myocardial infarction, stroke, and congestive heart failure¹⁸. This may be pathophysiologically related to the high levels of markers of thrombosis (fibrinogen, D-dimer) and vascular damage (vWf, tPA) in RA patients^{5,19}. Reducing cardiovascular disease in patients with CTD by modifying potential risk factors (such as persistent inflammation and hyperhomocysteinemia) is therefore a major challenge. Antiphospholipid antibodies also play an important role in the pathogenesis. Nevertheless, not all patients with the lupus anticoagulant develop thrombosis (40% do not have thrombosis), and not all patients with SLE with thrombosis have these antibodies (40% do not have a lupus anticoagulant)²⁰. So, besides the antiphospholipid antibodies there are more factors involved in the tendency for thrombosis. Perhaps endothelial cell-directed antibodies can give more insight into the inflammatory role of the immune system in premature atherosclerosis. Up to now these antibodies are not clearly correlated with cardiovascular disease, but their detection is technically difficult^{21,22}. The precise mechanism(s) of endothelial cell damage and platelet activation in patients with SLE is unclear but is likely to be multifactorial. Nevertheless, the traditional risk factors cannot by themselves explain the increased and accelerated atherosclerosis, and SLE itself may well be a risk factor for cardiovascular disease similar to diabetes.

Increased plasma homocysteine is a risk factor for atherosclerotic — not venous — thrombosis in SLE¹⁴, and abnormalities associated with a procoagulant state may play a role in cardiovascular disease in lupus. For example, fibrinogen, plasminogen activator inhibitor-1, and the factor V Leiden

status are all associated with an increased risk of thrombosis^{18,20}. 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.

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