Suppression of Inflammation in Primary Systemic Vasculitis Restores Vascular Endothelial Function: Lessons for Atherosclerotic Disease?

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Background—Chronic inflammatory rheumatic disorders are associated with excess cardiovascular mortality. This may result from arteriosclerosis following inflammatory damage to the vessel wall by vasculitis. Our hypothesis that vasculitis results in arteriosclerosis by causing vascular endothelial dysfunction was tested in patients with primary systemic necrotizing vasculitis (SNV).

Methods and Results—Endothelial function was assessed in cross-sectional and longitudinal studies of patients with primary SNV by measuring flow-mediated, endothelium-dependent brachial artery vasodilatation. These patients exhibited marked endothelial dysfunction compared with controls. Remission induction in patients with active primary SNV restored endothelial function.

Conclusions—Endothelial function is significantly impaired in adults with primary SNV, supporting the hypothesis that premature arteriosclerosis in chronic inflammatory rheumatic disorders results from endothelial dysfunction secondary to vasculitis. Normalization of endothelial function after the treatment of primary SNV suggests that early suppression of disease activity in chronic inflammatory rheumatic disorders may reduce long-term vascular damage. The role of inflammation in atheroma formation is increasingly appreciated; this work raises questions regarding the potential for anti-inflammatory therapy in atherosclerosis itself. (Circulation. 2000;102:1470-1472.)

Key Words: inflammation • endothelium • atherosclerosis
Brachial Artery Ultrasonography
Brachial artery ultrasonography was performed using standard techniques. In healthy arteries, reactive hyperemia increases shear stress, which results in vaso dilatation mediated by endothelial-derived nitric oxide. Endothelium-independent vaso dilatation (EIV), reflecting vascular smooth muscle function, can be assessed by the response to glyceryl trinitrate. A B-mode scan of the right brachial artery in a longitudinal section 2 to 12 cm proximal to the antecubital fossa was obtained in supine subjects using a 7.5 MHz phased-array transducer on a Sigma 44 HVD system. The anterior and posterior media-intima interfaces were used to demarcate artery diameter, which was calculated as the average of measurements during 4 cardiac cycles at end-diastole.

Each study was composed of the following artery diameter measurements: baseline (after a 10-minute rest period), EDV (60 to 90 seconds after the sudden release of a pneumatic cuff that had been inflated to suprasystolic pressure for 5 minutes on the ipsilateral forearm), second baseline (after another 10-minute rest period), and EIV (4 minutes after sublingual glyceryl trinitrate administration). The average baseline diameter was calculated from the 2 baseline recordings. EDV and EIV were expressed as the percentage change in artery diameter from baseline. The peak systolic velocity after reactive hyperemia was recorded as the maximum velocity in a single cardiac cycle within 15 seconds of cuff deflation and was expressed as a percentage of the average baseline velocity. Sonography was performed by 1 of 2 investigators who was blinded to the induction of complete (5 patients) or partial (2 patients) remission with immunosuppression (pulse cyclophosphamide and methylprednisolone in 6 patients and continuous oral steroids in 1). Group 2 consisted of 5 Wegener’s granulomatosis patients (4 men) who were in clinical remission between scans and on stable treatment.

Statistical Analysis
Results are presented as the median and either IQR or range as shown. Control and patient groups were compared with the Mann-Whitney test. Paired serial results in individual patients were compared using the Wilcoxon matched-pairs test. All results are shown. Control and patient groups were compared with the Mann-Whitney test. Paired serial results in individual patients were compared using the Wilcoxon matched-pairs test. All results are presented as 2-tailed values, and significance was inferred at P<0.05. The Spearman rank test was used to analyze correlation.
Discussion

Primary SNV provides a model to investigate the hypothesis that premature arteriosclerosis in chronic inflammatory rheumatic disorders results from vascular endothelial dysfunction secondary to vasculitis. This study demonstrates, for the first time, that endothelial function is significantly impaired in adults with primary SNV in both the active and chronic phases. Our results are consistent with a study of EDV in childhood vasculitis, which demonstrated impairment in 20 patients after acute Kawasaki disease. They are, however, at variance with those of a small study in which venous occlusion plethysmography, used to assess forearm blood flow change in response to acetylcholine, suggested enhanced endothelial function in systemic vasculitis. The difference between our results may reflect methodological differences. Venous occlusion plethysmography cannot distinguish between effects on different vascular beds; the contribution of cutaneous vasodilatation, for example, cannot be quantified. In addition, acetylcholine-mediated vasodilatation involves nitric oxide, prostanoids, and endothelium-derived hyperpolarizing factor, whereas brachial artery flow-mediated vasodilatation results from shear-stress-induced nitric oxide production alone.

The cross-sectional study was not designed to investigate the cause of endothelial dysfunction in primary SNV, and the lack of difference between EDV in the subgroups with active and inactive disease is not surprising in this relatively small and heterogenous cohort of patients. To control for patient heterogeneity, we conducted a longitudinal study to investigate the effects of disease activity on endothelial function. Here, we showed that suppression of acute inflammation in flares of primary SNV can normalize endothelial function.

A number of mechanisms may cause the endothelial dysfunction in primary SNV; these include pro-inflammatory cytokines depressing endothelial function, antineutrophil cytoplasmic antibody/neutrophil interaction close to the vessel wall triggering endothelial damage, and LDL oxidation, promoted by the inflammatory microenvironment, leading to direct endothelial cell toxicity. Treatment with corticosteroid and cyclophosphamide could affect all of these.

Our findings may be of clinical importance. Early treatment in primary SNV to suppress disease activity may reduce the risk of long-term vascular damage. In addition, the endothelial dysfunction seen in primary SNV may be the mechanism underlying the development of arteriosclerosis in vasculitis secondary to chronic inflammatory disorders such as rheumatoid arthritis and systemic lupus erythematosus. The potential for normalization of endothelial function, if present in these conditions too, has important therapeutic implications. Finally, these observations may have wider relevance to the study of atherosclerosis itself. Many similarities exist between the inflammatory response in atherosclerosis and that in diseases such as rheumatoid arthritis. A recent study found that CD4+/CD28+ T-cells were increased in patients with unstable, but not stable, angina, and, interestingly, higher levels of these cells are also present in those patients with rheumatoid arthritis who have extra-articular disease and vasculitis. The role of inflammation in atheroma formation is increasingly appreciated, and this work raises interesting questions regarding the potential for anti-inflammatory therapy in atherosclerosis itself.

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