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

C hronic inflammatory rheumatic disorders such as rheumatoid arthritis and systemic lupus erythematosus are associated with high cardiovascular mortality. Compared with age-matched populations, women with systemic lupus erythematosus have a 50-fold higher rate of myocardial infarction and, in patients with rheumatoid arthritis, the risk of death from cardiovascular disease is doubled. We proposed that this increased risk is a consequence of arteriosclerosis resulting from inflammatory vessel wall damage by vasculitis, a contention supported by a murine model in which vasculitis and a high cholesterol diet interacted to precipitate atherosclerosis.

Vascular endothelial injury is the primary event in atherosclerosis, and many conventional risk factors for atherosclerosis are associated with endothelial dysfunction. We hypothesized that vasculitis results in arteriosclerosis by causing endothelial dysfunction, and we studied patients with primary SNV as a model for this. Endothelial function was assessed by measuring brachial artery flow-mediated, endothelium-dependent vasodilatation (EDV). In a cross-sectional study, we tested the hypothesis that endothelial function is impaired in primary SNV. The effect on endothelial function of reducing vasculitis disease activity using immunosuppression was then examined in a longitudinal study.

Methods

Patients

Ethical approval was given and informed consent obtained from all patients. We studied 24 patients with primary SNV (14 with Wegener’s granulomatosis, 7 with polyarteritis nodosa, and 3 with Churg-Strauss syndrome, according to the criteria of the American College of Rheumatology) who had a median age of 54.5 years (interquartile range [IQR], 48.5 to 63.5 years); 17 were men. The median interval from disease onset was 13 months (IQR, 4 to 86.5 months). Eight patients had a history of hypertension (systolic blood pressure >160 mm Hg and/or diastolic blood pressure >90 mm Hg), and 7 were current or ex-smokers (stopped smoking within the last year).

Vasculitis disease activity was measured using the Birmingham Vasculitis Activity Score (BVAS). Clinical remission was defined as the absence of significant disease activity for ≥1 month (BVAS, 0 to 1) and partial remission as a >50% reduction in BVAS. Thirteen patients had active vasculitis (7 at disease presentation and 6 at relapse), and 11 had vasculitis in remission. The median time since last disease flare for those in remission was 19.5 months (IQR, 9 to 64.5 months).
Twenty-four age- and sex-matched controls were also studied; their median age was 56.5 years (IQR, 44.5 to 65.5 years). Two had a history of hypertension, and 10 were current or ex-smokers (stopped smoking within the last year).

The longitudinal study reassessed endothelial function in 12 patients after a median interval of 26.5 weeks (IQR, 15 to 39.5 weeks). Group 1 was composed of 7 patients (2 with Wegener’s granulomatosis and 5 with polyarteritis nodosa; all were men) with active vasculitis whose second brachial scan followed 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.

Brachial Artery Ultrasonography
Brachial artery ultrasonography was performed using standard techniques. In healthy arteries, reactive hyperemia increases shear stress, which results in vasodilatation mediated by endothelial-derived nitric oxide. Endothelium-independent vasodilatation (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 (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 subjects’ clinical details. Intraobserver variability, based on 6 and 17 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 subjects’ clinical details. Intraobserver variability, based on 6 and 17

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 presented as 2-tailed values, and significance was inferred at P<0.05. The Spearman rank test was used to analyze correlation.

Longitudinal Study of EDV and EIV

<table>
<thead>
<tr>
<th>Group 1 (n=7)</th>
<th>Group 2 (n=5)</th>
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<tbody>
<tr>
<td><strong>Scan 1</strong> (Active)</td>
<td><strong>Scan 2</strong> (Remission)</td>
</tr>
<tr>
<td><strong>EDV, % change</strong></td>
<td>1.6 (−12.9–4.3)</td>
</tr>
<tr>
<td><strong>EIV, % change</strong></td>
<td>9.5 (6.4–21.3)</td>
</tr>
<tr>
<td><strong>Baseline diameter, cm</strong></td>
<td>0.41 (0.31–0.57)</td>
</tr>
</tbody>
</table>

*Group 1, patients with active vasculitis before and after suppression of inflammation. Group 2, patients with disease in remission on 2 occasions.

Values are median (range). *P=0.016; other comparisons not significant.

Results
Cross-Sectional Study
EDV was significantly impaired in patients with primary SNV compared with controls (median [IQR], 1.7% [0% to 3.4%] versus 6.4% [4.7% to 9.5%]; P<0.0001; Figure 1). Peak systolic velocity was measured in 12 patients and 12 controls between whom no significant difference existed (patients, 173% [160% to 225%]; controls, 213% [181% to 262%]). No significant difference existed between patients and controls in EIV (patients, 11.7% [9.2% to 17.0%]; controls, 16.6% [10.8% to 19.1%]) or baseline diameter (patients, 0.42 cm [0.34 to 0.45 cm]; controls, 0.46 cm [0.39 to 0.51 cm]). In this cross-sectional study, no significant difference in EDV was detected between the 13 patients with active primary SNV (1.6% [0% to 2%]) and the 11 in remission (1.8% [−0.4% to 3.8%]). No correlation existed between EDV and disease duration or, for those in remission, between EDV and the time since last flare.

Longitudinal Study
EDV improved significantly after the suppression of inflammation (group 1), with all patients showing enhanced responses (Table and Figure 2); no significant change occurred in EIV (Table). One patient with active vasculitis showed pronounced vasoconstriction (EDV, −12.9%) on cuff release. This repeatable result is an unusual response; however, if this patient is excluded from analysis, the improvement in EDV in the remaining 6 patients is still significant (P=0.031). After remission induction, EDV in patients with primary SNV (group 1) did not differ significantly from that of healthy controls. In group 2 (patients with stable disease), no significant change occurred in either EDV or EIV between scans (Table).

Figure 1. Cross-sectional study of endothelium-dependent vasodilatation. Individual values and medians (horizontal bars) are shown. 1*SNV indicates primary SNV.
 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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References

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