Arterial Stiffness in Chronic Inflammatory Diseases


Abstract—Chronic inflammatory diseases are associated with premature atherosclerosis; however, it is unknown whether arterial stiffness is increased in this setting, possibly as a manifestation of vascular disease preceding and/or independent of atherosclerosis. Carotid ultrasonography and radial applanation tonometry were performed in 101 patients with systemic lupus erythematosus, 80 patients with rheumatoid arthritis, and 105 healthy control subjects. The 3 groups were comparable in age, gender, and carotid artery absolute and relative wall thickness. Atherosclerotic plaque was more common in lupus (46%) and rheumatoid arthritis (38%) patients than in controls (23%) (P<0.003). Although control subjects had higher central and peripheral blood pressures, arterial stiffness was increased in patient groups compared with controls (lupus, rheumatoid arthritis, controls, respectively: β: 3.36 versus 3.22 versus 2.60, P<0.001; Young’s modulus: 441 versus 452 versus 366 mm Hg/cm, P=0.004; Peterson’s elastic modulus: 278 versus 273 versus 216 mm Hg, P<0.001) after adjustment for differences in mean brachial pressure. In multivariate analysis involving the entire population, arterial stiffness was independently related to age, serum glucose, and the presence of chronic inflammatory disease. In multivariate analysis restricted to the patients, arterial stiffness was independently related to age at diagnosis, disease duration, serum cholesterol, and C-reactive protein (and IL-6, when substituted for C-reactive protein). When analyses were repeated in the 186 study subjects without carotid plaque, arterial stiffness remained significantly elevated in patient groups after adjustment for differences in age and mean brachial pressure. In conclusion, arterial stiffness is increased in chronic inflammatory disorders independent of the presence of atherosclerosis and is related to disease duration, cholesterol, and the inflammatory mediator C-reactive protein and the cytokine that stimulates its production, IL-6. (Hypertension. 2005;46:194-199.)

Key Words: arterial pressure ■ atherosclerosis ■ carotid arteries ■ elasticity ■ vascular disease

Arterial stiffening is caused by structural changes within the walls of the major conduit arteries resulting in an increase in pulse wave velocity. Systolic and pulse pressures are increased because of an alteration in the timing of reflected waves. Arterial stiffening occurs as a consequence of aging1 and is increased in the setting of risk factors for atherosclerosis such as hypertension,2 diabetes,3 hypercholesterolemia,4,5 and smoking.6 Furthermore, arterial stiffening predicts cardiovascular events independent of traditional risk factor.7,8 Given the relation of inflammation to atherosclerosis, elevated levels of inflammatory mediators might be associated with arterial stiffening. C-reactive protein was recently reported to be independently related to higher pulse wave velocity9 and pulse pressure,10 a surrogate for arterial stiffening, in 2 healthy British and US populations, respectively, but not to pulse wave velocity in healthy Japanese men after traditional risk factors were taken into account.11 Flow-mediated dilation of the brachial artery, a measure of endothelial function that may be altered in the setting of atherosclerosis, was not related to C-reactive protein or other circulating mediators of inflammation independent of traditional cardiovascular disease risk factors in the Framingham Offspring Study.12

Chronic inflammatory diseases might be associated with arterial stiffness, possibly as a manifestation of premature atherosclerosis.13 In 2 recent studies in small numbers of patients with rheumatoid arthritis and control subjects, arterial stiffness was marginally increased in patients after adjustment for traditional risk factors in one study,14 and significantly increased in another study involving 14 young patients with no cardiovascular disease risk factors.15 Thus the present study was designed to determine whether arterial stiffness is increased in a large sample of patients with chronic inflammatory diseases in comparison to healthy control subjects and to determine whether arterial stiffness associated with inflammation is independent of both traditional cardiovascular disease risk factors and of the presence of atherosclerosis.
Methods

Study Population
The patient population consisted of patients with systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) participating in a study to determine the prevalence and correlates of premature atherosclerosis in these conditions. Patients were sequentially recruited for the study at the time of regularly scheduled outpatient visits with their rheumatologist at the Hospital for Special Surgery. Patients fulfilled strict diagnostic criteria for the presence of SLE or RA. Control subjects of a comparable age and gender who had undergone a similar protocol to assess arterial structure and function were drawn from a longitudinal study of employed individuals. Patients were excluded based on use of antihypertensive medications at the time of study; none had renal failure. Hypertensive control subjects were studied after withdrawal of antihypertensive medications for at least 3 weeks, and, in many instances, several months. A total of 105 control subjects, 101 patients with SLE, and 80 patients with RA were eligible for inclusion in the present study. Study protocols were approved by our institutions' institutional review boards; all subjects gave signed informed consent to study participation.

All patients were interviewed and examined with the use of standardized data collection instruments. Disease activity and disease-related damage in SLE patients was assessed with use of the Systemic Lupus Erythematosus Disease Activity Index and the Systemic Lupus International Collaborating Clinics Damage Index, respectively, whereas disease-related damage among RA patients was assessed by an index of irreversible joint damage. Laboratory evaluation of patients included erythrocyte sedimentation rate, serum complement (C3 and C4), and high-sensitivity C-reactive protein. Serum IL-6 was measured with the use of a kit (Biosource International).

Carotid Ultrasonography
All study participants underwent carotid ultrasonography; all studies were performed by an experienced research sonographer using an identical protocol and interpreted by a single cardiologist. In brief, as previously described, both extracranial carotid arterial systems were extensively scanned in multiple planes to optimize identification of atherosclerosis defined as discrete plaque protruding into the lumen ≥50% beyond the thickness of the adjacent wall. Intimal-medial thickness (IMT) and lumen diameter were measured from end-diastolic (minimum dimension) M-mode images of the far wall of the distal common carotid artery. IMT was never measured in a location containing plaque (uncommon in the common carotid artery, which is characterized by laminar flow). Minimum and maximum arterial diameters were obtained by continuous tracing of the intima–lumen interfaces of the near and far walls. Arterial cross-sectional area was calculated as a more comprehensive estimate of vascular volume or mass. Relative wall thickness of the artery was calculated as (2 × IMT)/end-diastolic diameter. Vascular strain was calculated as [(maximum diameter − minimum diameter)/minimum diameter] × 100. Brachial blood pressures were obtained in triplicate and averaged at the end of the ultrasound studies, ie, after 45 to 60 minutes in the supine position in a quiet, darkened room.

Assessment of Arterial Stiffness
Arterial stiffness was estimated from pressure–diameter relations of the common carotid artery and pressure waveforms obtained by applanation tonometry of the radial artery with a high-fidelity transducer; central arterial waveforms and pressures were calculated by the use of the SphygmoCor device using a generalized transfer function (AtCor Medical, Sydney, Australia) and calibration using the brachial mean and diastolic pressures. Orientation and pressure applied to the transducer were adjusted to achieve optimal applanation of the artery between the transducer and the underlying tissue. Applanation tonometry has been validated to yield accurate estimates of intra-arterial pulse pressure by comparison with simultaneous invasive pressure recordings. Minimum (end-diastolic) and maximum (peak systolic) diameters were obtained from carotid ultrasonography performed immediately before applanation tonometry with the position of the subject and ambient environment unchanged. Three measures of arterial stiffness were evaluated: (1) arterial stiffness index (β);26,27 ln(Ps/Pd)/([Ds−Dd]/Dd), where Ps and Pd are aortic systolic and diastolic pressures, respectively, and Ds and Dd are carotid systolic and diastolic diameters, respectively; (2) Young’s modulus:28 ([Ps−Pd]/[Dd−Dd])×(Dd/IMT), where IMT is common carotid artery far wall thickness at end diastole; and (3) Peterson’s elastic modulus:29 Ep = ([Ps−Pd]/[Dd−Dd])×(Dd/IMT)×IMT.

These measures provide indices of regional arterial stiffness under the vessel’s usual loading conditions (Peterson’s elastic modulus) or adjusted for the effects of arterial wall thickening (Young’s modulus) and distending pressure (stiffness index). The arterial stiffness index is considerably less pressure-dependent than is Peterson’s elastic modulus.

Statistical Analyses
Comparisons were made between the three groups using χ² statistic for categorical variables and 1-way analysis of variance for continuous variables with post hoc testing for multiple comparisons (Scheffé). Continuous variables are expressed with the standard deviation as the index of dispersion and the standard error for adjusted means. Independence of association with arterial stiffness was performed by stepwise linear regression analysis using those variables found to have a bivariate relation (P<0.1) to arterial stiffness as potential predictors.

Results
Comparison of Demographics Characteristics and Arterial Structure
By design, patients and control subjects were comparable in age and gender (Table 1). Weight and height were similar in the 3 groups. Although the rates of diagnosed hypertension did not differ among the 3 groups, both brachial and central
TABLE 2. Common Carotid Artery Structure in Patient and Control Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>SLE</th>
<th>RA</th>
<th>ANOVA or χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>105</td>
<td>101</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Diastolic diameter, mm</td>
<td>5.24±0.5</td>
<td>5.45±0.47*</td>
<td>5.28±0.47</td>
<td>0.01</td>
</tr>
<tr>
<td>Systolic diameter, mm</td>
<td>5.85±0.60</td>
<td>6.06±0.56*</td>
<td>5.89±0.52</td>
<td>0.014</td>
</tr>
<tr>
<td>IMT, mm</td>
<td>0.63±0.13</td>
<td>0.63±0.16</td>
<td>0.61±0.16</td>
<td>0.67</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.24±0.05</td>
<td>0.23±0.06</td>
<td>0.23±0.06</td>
<td>0.67</td>
</tr>
<tr>
<td>CSA, mm²/m²</td>
<td>6.76±1.92</td>
<td>7.02±2.24</td>
<td>6.78±2.07</td>
<td>0.62</td>
</tr>
<tr>
<td>Plaque, %</td>
<td>23</td>
<td>46</td>
<td>38</td>
<td>0.003</td>
</tr>
<tr>
<td>Strain, %</td>
<td>11±3</td>
<td>11±4</td>
<td>11±3</td>
<td>0.90</td>
</tr>
</tbody>
</table>

CSA indicates cross-sectional area; IMT, intimal-medial thickness. *P<0.05 vs control.

Comparison of Arterial Stiffness

In view of differences in blood pressures between patients and control subjects, and to avoid autocorrelation, estimates of arterial stiffness were adjusted for differences in mean brachial blood pressure. All 3 estimates of arterial stiffness were significantly greater in the 2 patient populations than in control subjects (Figure, Table 3). Heart rate did not relate to the 3 estimates of arterial stiffness; therefore, further adjustment for heart rate did not alter the findings.

Because atherosclerosis promotes arterial stiffening, analyses were repeated in the control subjects and SLE and RA patients without atherosclerotic plaque. Control subjects were older (46±9 years) than the SLE and RA patients (39±4 and 40±11, respectively; P<0.001), with higher mean brachial blood pressures (85±10 versus 78±11 and 78±7 mm Hg, respectively; P<0.001). After adjustment for differences in age and mean brachial blood pressure, all 3 measures of arterial stiffness remained elevated in patients without plaque compared with control subjects without plaque (Table 3). Further adjustment of the arterial stiffness index and Peterson’s elastic modulus for carotid wall thickness or cross-sectional area had no effect on results.

Determinants of Arterial Stiffness

Independent correlates of the arterial stiffness index (β) in the entire population were age, fasting glucose level, and the presence of either systemic lupus erythematosus or rheumatoid arthritis (Table 4). When analyses were restricted to the patients, age at diagnosis, duration of disease, level of C-reactive protein, and fasting, serum cholesterol entered the model (Table 5). In models predicting either Peterson’s elastic modulus or Young’s modulus, mean arterial pressure also entered the equation, supporting the lesser pressure dependence of the arterial stiffness index relative to the other estimates of arterial stiffness; the association between inflammatory disease and increased arterial stiffness was significant in all analyses. Substitution of erythrocyte sedimentation rate, C3 or C4 for C-reactive protein weakened the model. In contrast, IL-6, which stimulates the production of acute phase reactants including C-reactive protein, entered the model when substituted for C-reactive protein. Among patients with SLE, arterial stiffness was not related to either disease activity or disease-related damage, as assessed by the SLE Disease Activity Index and Systemic Lupus International Collaborating Clinics Damage Index, respectively. Among patients with RA, arterial stiffness was not related to irreversible joint damage.

Discussion

The present study is the first to demonstrate that arterial stiffness is increased in the chronic inflammatory diseases SLE and RA relative to a control population independent of traditional risk factors for atherosclerosis. Furthermore, arterial stiffening is not attributable to the premature atherosclerosis detected in these diseases. Rather, the similarity in vascular structure in the 3 groups and the confirmation of findings when distending pressure is taken into account by use of the arterial stiffness index suggest an alteration in underlying physical properties of the vessel wall and/or vascular tone in the setting of chronic inflammation even in the absence of atherosclerosis. The independent association of fasting glucose with arterial stiffness noted in the present study is in keeping with earlier observations in diabetic patients and in the general population, possibly as a consequence of accumulation of advanced glycation end-products. The associations of disease duration and level of C-reactive protein with arterial stiffening in patients with SLE and RA suggest that the cumulative burden of inflam-
mation is of primary importance in this abnormality. The independent relation of cholesterol to arterial stiffness in our patients with chronic inflammatory diseases is of interest given the recent observation that low-grade systemic inflammation may be a primary mediator of increased arterial stiffness in individuals with hypercholesterolemia.5

To date, few studies have evaluated arterial function in chronic inflammatory diseases. Carotid femoral pulse wave velocity was determined in 220 women with SLE participating in the Pittsburgh SLE Registry and was significantly related to mean arterial pressure, age, impaired fasting glucose, low white blood cell count, and serum creatinine in postmenopausal women, and to carotid atherosclerosis, C3 level, and lack of use of hydroxychloroquine in premenopausal women.33 The study lacked a control population to determine whether arterial stiffness was actually increased in comparison to a control population, but only among those patients with active disease.36 Again, the relation of these findings to premature atherosclerosis was not investigated.

Although premature atherosclerosis might be expected to promote arterial stiffening in chronic inflammatory diseases, our study indicates that factors other than arterial wall thickness, as a possible measure of early or diffuse atherosclerosis, or discrete atherosclerotic plaque detectable by noninvasive ultrasonography, are responsible and are consistent with the hypothesis that C-reactive protein or IL-6, the cytokine that stimulates its synthesis, has a direct role. C-reactive protein is deposited in the arterial intima in early atherosclerotic lesions,37 induces an inflammatory and atherogenic phenotype in endothelial cells,38,39 interferes with endothelial function, was reduced in 62 patients with SLE in comparison to 38 control subjects in a recent study from the United Kingdom and was not related to specific disease attributes, although C-reactive protein was not evaluated.34 In contrast, a small study of 25 patients with RA and 25 control subjects did not detect differences between the 2 groups in flow-mediated dilatation,35 whereas arterial compliance was reduced in a subset of patients, although results were not adjusted for higher blood pressure in the patients. In a small study of another chronic inflammatory disease, systemic vasculitis, pulse wave velocity, and augmentation index, an indirect measure of arterial stiffness, were increased in comparison to a control population, but only among those patients with active disease.36 Again, the relation of these findings to premature atherosclerosis was not investigated.

**TABLE 3. Estimates of Arterial Stiffness in Patient and Control Groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>SLE</th>
<th>RA</th>
<th>ANCOVA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>105</td>
<td>101</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Stiffness index (β)</td>
<td>2.60±0.13</td>
<td>3.36±0.13</td>
<td>3.22±0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Young’s modulus, mm Hg/cm</td>
<td>365±19</td>
<td>441±19</td>
<td>452±21</td>
<td>0.004</td>
</tr>
<tr>
<td>Elastic modulus, mm Hg</td>
<td>216±11</td>
<td>278±11</td>
<td>273±12</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Control Subjects and Patients Free of Atherosclerotic Plaque**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>SLE</th>
<th>RA</th>
<th>ANCOVA†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>81</td>
<td>55</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Stiffness index (β)</td>
<td>2.39±0.11</td>
<td>3.08±0.13</td>
<td>2.99±0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Young’s modulus, mm Hg/cm</td>
<td>347±20</td>
<td>430±24</td>
<td>442±24</td>
<td>0.006</td>
</tr>
<tr>
<td>Elastic modulus, mm Hg</td>
<td>196±9</td>
<td>252±11</td>
<td>248±11</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for differences in mean brachial artery pressure; data are presented as adjusted means±SE.
†Adjusted for differences in age and mean brachial artery pressure; data are presented as adjusted means±SE.

**TABLE 4. Multivariate Correlates of Arterial Stiffness (β) in the Entire Population**

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>P</th>
<th>R² Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 y)</td>
<td>0.485</td>
<td>&lt;0.001</td>
<td>0.256</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>0.247</td>
<td>&lt;0.001</td>
<td>0.088</td>
</tr>
<tr>
<td>Disease status*</td>
<td>0.145</td>
<td>0.006</td>
<td>0.018</td>
</tr>
</tbody>
</table>

*Disease status: 0 indicates control subject; 1, presence of systemic lupus erythematosus or rheumatoid arthritis.
Not in model: mean arterial pressure, serum cholesterol, smoking status, intimal-medial thickness, and plaque.

**TABLE 5. Multivariate Correlates of Arterial Stiffness (β) in Patients with Systemic Lupus Erythematosus or Rheumatoid Arthritis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>P</th>
<th>R² Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (per 10 y)</td>
<td>0.453</td>
<td>&lt;0.001</td>
<td>0.185</td>
</tr>
<tr>
<td>Duration of disease (per y)</td>
<td>0.205</td>
<td>0.004</td>
<td>0.041</td>
</tr>
<tr>
<td>C-reactive protein*</td>
<td>0.176</td>
<td>0.032</td>
<td>0.011</td>
</tr>
<tr>
<td>Serum cholesterol, mg/dL</td>
<td>0.152</td>
<td>0.030</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Model: R²=0.527; R² Change = 0.278.
Not in model: mean arterial pressure, serum glucose, smoking status, intimal-medial thickness, and plaque.
*IL-6 entered the model when substituted for C-reactive protein.
between our patient and control groups does not preclude the occurrence of microscopic structural changes within the extracellular matrix of the vessel walls, which might alter endothelial cell function and physical properties of the vessel wall. Furthermore, current ultrasound techniques do not allow separate measurement of intimal and medial layers, which may be differentially affected by inflammation. Independent of the cause of alterations in arterial function in chronic inflammatory disease, 2 recent studies showed an improvement in endothelial function associated with infliximab therapy and a reduction in the augmentation index associated with atorvastatin therapy in small numbers of RA patients.

**Perspectives**

Our study documents substantial increases in arterial stiffness in patients with systemic lupus erythematosus and rheumatoid arthritis independent of the presence of atherosclerotic plaque and traditional risk factors. The association of arterial stiffening with disease duration and circulating levels of C-reactive protein and IL-6 implicates chronic inflammation as important mediators of this process. The cross-sectional nature of our study limits our ability to determine whether arterial stiffening precedes the development of atherosclerosis. However, the independent prognostic usefulness of arterial stiffness documented in other populations suggests that noninvasive measurement of arterial stiffness might be used as a biomarker for increased vascular risk in chronic inflammatory diseases and as a target of treatment efficacy.

**Acknowledgments**

Supported by National Institutes of Health grant AR 45591.

**References**


