Increased Arterial Stiffness as the Marker of Vascular Involvement in Systemic Sclerosis

ORSOLYA TIMÁR, PÁL SOLTÉSZ, SZILVIA SZAMOSI, HENRIETTA DÉR, SÁNDOR SZÁNTÓ, ZOLTÁN SZEKANECZ, and GABRIELLA SZÜCS

ABSTRACT. Objective. Endothelial dysfunction and vasculopathy of the small and large vessels are crucial pathogenic factors in systemic sclerosis (SSc). Accelerated atherosclerosis and impaired flow-mediated vasodilation have been described in SSc. We evaluated arterial stiffness in patients with SSc compared to healthy controls.

Methods. Augmentation index (AI) and pulse wave velocity (PWV) of the brachial artery were measured in 40 patients with SSc and 35 age and sex matched healthy controls using an arteriograph system.

Results. AI was significantly higher in SSc patients (9.02) compared to controls (–41.15) (p < 0.0001). PWV was similarly higher in patients with SSc (9.67 m/s) than in controls (8.00 m/s) (p = 0.0017). PWV was significantly higher in patients with localized SSc (10.04 ± 2.01 m/s) compared to those with diffuse SSc (8.39 ± 1.87 m/s) (p = 0.034). There was a significant, positive linear correlation between AI and PWV (r = 0.32, p = 0.045). We also observed significant correlations between AI and age (r = 0.31, p = 0.048), PWV and age (r = 0.36, p = 0.021), and PWV and disease duration (r = 0.40, p = 0.011) in SSc patients.

Conclusion. Increased AI and PWV of the aorta in comparison to age and sex matched healthy controls indicate increased large-vessel stiffness in patients with SSc. PWV and AI are reproducible indicators of the presence and degree of arterial stiffening. Because arterial stiffness may correlate with disease duration and age in patients with SSc, it may be a useful diagnostic test in the assessment of arterial function. Increased vascular stiffness may be therapeutically targeted by statins and other vasoprotective agents during the management of SSc. (First Release May 15 2008; J Rheumatol 2008;35:1329–33)

Key Indexing Terms: SYSTEMIC SCLEROSIS, ATHOSCLEROSIS, ARTERIAL STIFFNESS, PULSE WAVE VELOCITY

Systemic sclerosis (SSc) is a connective tissue disease characterized by extensive fibrosis in the skin and internal organs including the lungs, kidneys, myocardium, and gastrointestinal tract. Three major types of abnormalities have been described in the pathogenesis of the disease. First, there is an impairment of the immune system resulting in chronic inflammation, abnormal T cell activation, abundant production of proinflammatory cytokines such as interleukin 4, B cell dysfunction, and the production of characteristic autoantibodies including anticientromere antibodies in limited SSc (lSSc) and antitopoisomerase I and anti-RNA polymerase I/III antibodies in diffuse SSc (dSSc). Second, there is functional impairment of the microvasculature including the vascular endothelium, contributing to tissue hypoxia. Finally, there is a structural vasculopathy caused by extracellular matrix deposition into the vessel wall. At the cellular and molecular level, this phenomenon has been associated with disproportionate fibroblast activity, as well as increased serum levels of hyaluronan, matrix metalloproteinases (MMP), and tissue inhibitors of metalloproteinases (TIMP). Some features of the disease resemble the processes taking place in an atherosclerotic plaque.

Arterial stiffness is unambiguously a novel marker of vascular dysfunction, and it has recently been recognized as an independent risk factor of cardiovascular disease. Physiological elasticity of the vessel wall can be decreased by both vascular and extravascular factors. The key feature of the structural change in the vascular wall is the imbalance between collagen and elastin, resulting in overproduction of the former and relative lack of the latter. In addition, infiltration of the vessel wall by vascular smooth-muscle cells,
mononuclear leukocytes, and other inflammatory cells, as well as increased production of MMP, cytokines, cell adhesion molecules, and transforming growth factor-β (TGF-β) contribute to arterial wall stiffening. Extravascular factors of arterial stiffness include the angiotensin II-aldosterone system, chronic renal failure, hyperglycemia, dyslipidemia, and excessive dietary salt intake. Arterial stiffness is recommended by the European Network for Non-invasive Investigation of Large Arteries to be considered as a major indicator of organ damage in patients with hypertension.

In a recent review, Laurent, et al. discussed the methodological and clinical aspects of arterial stiffness. Among the various existing methods developed for determination of vascular stiffness, assessment of pulse wave velocity (PWV) is considered to be the simplest and least invasive and is thus the “gold standard” technique. In a study of about 100 healthy individuals, endothelial function was inversely correlated with aortic PWV and augmentation index (AI), indicating that endothelial dysfunction was associated with increased large-arterial stiffness. Similar observations were reported in patients with hypertension, hyperlipidemia, and type 2 diabetes. We recently investigated functional vasculopathy in SSc by assessing flow-mediated (FMD) and nitroglycerine-mediated dilatation (NMD) of the brachial artery in a cohort of 29 patients with SSc and compared their results to those of healthy controls. We observed a lower FMD, indicating impaired endothelium-dependent vasodilatation, yet preserved NMD in SSc patients compared to controls.

Our study examined the involvement of large vessels using an arteriograph system and by measuring 2 arterial stiffness indicators, PWV and AI, in patients with SSc in comparison to control subjects.

**MATERIALS AND METHODS**

*Patients.* Forty-six consecutive patients (40 women, 6 men) appearing for regular followup at our clinic were screened for the study. Exclusion criteria included known cardiovascular and cerebrovascular disease, diabetes mellitus, cigarette smoking, arthriymia, obesity (body mass index ≥ 30), vasculitis, infection, and renal failure (serum creatinine ≥ 117 mmol/l). Finally, 40 patients (36 women, 4 men) were eligible for this study. All patients fulfilled the American College of Rheumatology criteria for SSc.

The mean age of eligible patients was 58.0 ± 12.3 years (range 33–81 yrs). Altogether, 31 patients had ISSc and 9 dSSc. For comparison, we studied 35 age and sex matched healthy controls (32 women, 3 men; mean age 53.0 ± 10.5 yrs, range 30–77 yrs). Among SSc patients, the mean disease duration was 12.5 ± 6.7 years (range 1–27 yrs). Traditional Framingham risk factors for cardiovascular diseases, such as age, body mass index, plasma total cholesterol, LDL-C, HDL-C and triglyceride levels, and systolic and diastolic blood pressure were assessed at the time of the study. Differences in any of these measures between SSc patients and controls were non-significant (data not shown).

We obtained a signed consent form from each participating individual, as well as Institutional Review Board approval.

**Assessment of augmentation index.** The pressure waveform of the arteries originates from the superposition of the forward pressure wave caused by the contraction of the left ventricle and the waves reflected from the periphery, mostly from branchpoints, such as the aortic bifurcation and sites where a change in impedance occurs. The second, reflected wave depends on the stiffness of the large artery, the reflection time at 35 mm Hg suprasystolic pressure (RT S35), and the peripheral resistance-dependent amplitude. The first wave reflects on the aorta at the bifurcation, thus during systole the second wave is easily detectable and the late systolic peak appears. If an artery is elastic, PWV is low, and the reflected wave causes a diastolic peak on the aortic pressure wave. With decreased arterial elasticity, PWV rises and the reflected wave reaches the aortic root during late systole, augmenting the systolic pressure wave. The augmentation index quantifies the phenomenon, defined as follows: AI = (P2 – P1)/PP (%), where (P2 – P1) is the difference between the 2 systolic pressure peaks (P1 = early systolic peak on the pressure wave; P2 = late systolic peak) and PP represents pulse pressure. We assessed AI using a TensioClinic arteriograph (Tensiomed Ltd., Budapest, Hungary). The arteriograph has recently been validated by comparing it to 2 clinically validated, broadly accepted tonometric (SphygmoCor) and piezo-electronic systems (Complior). The arteriograph assesses this parameter from the oscillographic data obtained from the 35 mm Hg suprasystolic pressure of the brachial artery.

**Assessment of pulse wave velocity.** PWV was calculated automatically by the arteriograph system as the quotient of the distance between the jugular fossa and symphysis (RT S35, reflection time at 35 mm Hg suprasystolic pressure). A jugular fossa–symphysis distance measurement can be used as a substitute for the length of the descending aorta between the aortic trunk and the bifurcation. In order to produce reproducible results, the patient had to rest in a supine position at least 10 minutes before the assessment, in a quiet examination room, with no effects that could disturb the patient. Other recommendations regarding the study conditions included full abststence from alcohol and caffeine consumption before the examination.

**Statistical analysis.** Descriptive data of normally distributed variables are expressed as mean ± standard deviation (SD). Statistical analysis was carried out by a paired, 2-tailed Student t-test. Correlations between variables were determined using the Pearson correlation coefficient. P values < 0.05 were considered significant.

**RESULTS**

The mean AI of SSc patients was significantly higher (9.02 ± 30.32) compared to controls (–41.15 ± 22.47) (p < 0.0001). Similarly, PWV was significantly higher in SSc patients (9.67 ± 2.08 m/s) compared to controls (8.00 ± 1.46 m/s) (p = 0.00017). Results are shown in Table 1. Comparing results in patients with ISSc versus dSSc, we observed a significant difference in PWV (10.04 ± 2.01 m/s vs 8.39 ± 1.87 m/s, respectively; p = 0.034). In contrast, AI results did not differ significantly in the 2 groups (Table 2). Comparing ISSc and dSSc patients, serum total cholesterol, triglyceride levels, and disease durations showed only minor, nonsignificant differences; however, patients with ISSc were significantly older than those with dSSc (61.7 vs 45.0 yrs, respectively; data not shown).

We observed a significant positive correlation between

**Table 1.** Augmentation index (AI) and pulse wave velocity (PWV) in patients with SSc compared to controls. Values are mean ± SD.

<table>
<thead>
<tr>
<th>Measure</th>
<th>SSc n = 40</th>
<th>Controls, n = 25</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI, %</td>
<td>9.02 ± 30.32</td>
<td>–41.15 ± 22.47</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>9.67 ± 2.1</td>
<td>8 ± 1.46</td>
<td>0.0017</td>
</tr>
</tbody>
</table>
AI and PWV in patients with SSc (r = 0.32, p = 0.045). Further, both AI and PWV showed significant correlations with age in patients with SSc (r = 0.31, p = 0.048 and r = 0.36, p = 0.021, respectively; Table 3). Serum total cholesterol and triglyceride levels did not correlate with AI or PWV (Table 3).

PWV also showed a significant positive correlation with disease duration (r = 0.40, p = 0.011; Figure 1). In contrast, AI showed no correlation with disease duration (data not shown).

**DISCUSSION**

Acceleration of the atherosclerotic process, as concluded by an excellent overview of the current literature, is a hallmark of several autoimmune rheumatic diseases. Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and antiphospholipid syndrome are already considered risk factors for cardiovascular disease; whereas in SSc and primary systemic vasculitis, involvement of the large vessels is undeniable, but more data are needed to support accelerated atherosclerosis. Increased arterial stiffness, assessed by carotid ultrasonography or radial applanation tonometry, has been described in patients with various chronic inflammatory conditions such as SLE and RA. Roman, et al described an independent correlation between arterial stiffness and disease duration and serum cholesterol and C-reactive protein levels in these disorders. In our study, we assessed and quantified the stiffness of large arteries, the correlation between arterial stiffness and disease duration, and plasma lipid levels in patients with SSc. We also compared these results in iSSc and dSSc.

SSc patients had significantly higher arterial stiffness measures (AI and PWV) compared to healthy controls, showing large-vessel involvement in SSc, in addition to the well known microvascular abnormalities. Among the arterial stiffness measures, only PWV showed significant correlations with disease duration; thus PWV could be a useful marker of macrovascular disease during followup of patients.

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**Table 2.** Comparison of results of patients with limited and diffuse form of SSc. Values are mean ± SD.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Diffuse SSc, n = 31</th>
<th>Limited SSc, n = 9</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI, %</td>
<td>–4.04 ± 36.2</td>
<td>11.75 ± 24.49</td>
<td>NS (p = 0.296)</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>8.4 ± 1.87</td>
<td>10.04 ± 2.07</td>
<td>0.034</td>
</tr>
<tr>
<td>Cholesterol, mmol/l</td>
<td>4.61 ± 1.34</td>
<td>5.24 ± 1.00</td>
<td>NS (p = 0.136)</td>
</tr>
<tr>
<td>Triglyceride, mmol/l</td>
<td>1.53 ± 0.61</td>
<td>1.4 ± 0.61</td>
<td>NS (p = 0.558)</td>
</tr>
<tr>
<td>Disease duration, yrs</td>
<td>11.67 ± 7.21</td>
<td>12.74 ± 6.67</td>
<td>NS (p = 0.678)</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>45.2 ± 8.73</td>
<td>61.74 ± 10.57</td>
<td>0.000125</td>
</tr>
</tbody>
</table>

AI: augmentation index; PWV: pulse wave velocity; NS: nonsignificant.

**Table 3.** Correlation of augmentation index (AI) and pulse wave velocity (PWV) with measures in patients with SSc.

<table>
<thead>
<tr>
<th>Measure 1</th>
<th>Measure 2</th>
<th>R</th>
<th>p</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI</td>
<td>Age</td>
<td>0.31</td>
<td>0.048</td>
<td>+</td>
</tr>
<tr>
<td>PWV</td>
<td>Age</td>
<td>0.36</td>
<td>0.021</td>
<td>+</td>
</tr>
<tr>
<td>AI</td>
<td>PWV</td>
<td>0.32</td>
<td>0.045</td>
<td>+</td>
</tr>
<tr>
<td>PWV</td>
<td>TG</td>
<td>–0.995</td>
<td>0.541</td>
<td>NS</td>
</tr>
<tr>
<td>PWV</td>
<td>Chol</td>
<td>0.0783</td>
<td>0.631</td>
<td>NS</td>
</tr>
<tr>
<td>AI</td>
<td>TG</td>
<td>0.0136</td>
<td>0.934</td>
<td>NS</td>
</tr>
<tr>
<td>AI</td>
<td>Chol</td>
<td>0.1216</td>
<td>0.455</td>
<td>NS</td>
</tr>
</tbody>
</table>


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**Figure 1.** Correlation between PWV and disease duration in patients with SSc.
with SSc. Higher PWV in patients with the limited form of SSc compared to the diffuse form could indicate more severe macrovascular involvement in this subgroup, providing an opportunity for early diagnosis and treatment. (We must point out that pulmonary hypertension is also more common in ISSc than in dSSc.)

Our results are in concordance with earlier observations in patients with SSc. In 1996, a 3-year multicenter followup study of SSc patients showed that increased arterial stiffness, measured by QKd 100-60, was associated with severe progression of SSc. QKd 100-60 interval is the time between the onset of the depolarization (QRS) on the electrocardiogram (Q) and detection of the last Korotkoff (K) sound at the level of brachial artery, representing diastolic blood pressure. The value is normalized by correction to a systolic blood pressure of 100 mm Hg and a heart rate of 60/min. QKd is the sum of the pre-ejection period and the pulse transmission time from the aortic valves and the detector

Hypertension, as well as aging or arterial stiffening, was associated with lower QKd 100-60 values (<200 ms). Using the Complior device, Yildiz, et al also found an increased carotid-femoral PWV in a small group of patients with RA, and suggested this method for identifying patients at high risk for vascular disease. Recently, a study involving 44 patients with SSc found an increased carotid artery intima-media thickness (cIMT), a sign of early atherosclerosis, in patients compared to controls, independent of disease duration, SSc subtype, lung function test results, and traditional risk factors. Increased cIMT showed no correlation with the autoantibodies assessed, oxLDL, HSP-60, and HSP-65.

The precise pathogenetic background underlying the microvascular and macrovascular changes observed in SSc by our group and others remains unknown. However, several factors, such as antiendothelial cell antibodies (AECAs), disorders of the fibrinolytic system, and elevated levels of CRP, intercellular adhesion molecule-1 and homocysteine might contribute to increased endothelial shear stress and early atherosclerosis in SSc. AECAs have been reported to correlate with vascular abnormalities and alveolo-capillary dysfunction. AECA-positive SSc cases have reached the ratio of 49.5%. Administration of intravenous immunoglobulins (IVIG) successfully decreased cutaneous involvement and skin fibrosis in SSc by lowering levels of transforming growth factor-β and interleukin 4. It can be assumed that the beneficial effect of therapy with statins reaches beyond their lipid-lowering ability. The beneficial effects of statins on arterial stiffness have also been evaluated in patients who had systolic hypertension but normal serum cholesterol levels, and in hemodialysis patients with type 2 diabetes.

In summary, SSc may be associated with higher aortic PWV, a hallmark of increased arterial stiffness and a marker of vascular dysfunction. Assessment of AI and PWV may be a useful, reproducible method for characterizing arterial stiffness. We found that increased PWV correlated with age, disease duration, and AI in patients with SSc. Based on previous therapeutic studies, statins and perhaps other vasoprotective agents, such as antioxidants, may exert beneficial effects on patients with autoimmune diseases similar to the effects on hypertension and diabetes. It is likely that such agents may also be used to normalize the increased arterial stiffness associated with SSc.

REFERENCES


