Prevalence and associations of an abnormal ankle-brachial index in systemic lupus erythematosus: a pilot study

A Theodoridou, L Bento, D P D’Cruz, M A Khamashta, G R V Hughes

Background: Accelerated atheroma is a well recognised complication of systemic lupus erythematosus (SLE). Its aetiology is multifactorial and several methods may be used to detect early signs of atheroma. Methods: Patients aged ≤ 55 years were screened using the ankle-brachial index (ABI). Ninety one patients aged ≤ 55 years and fulfilling the revised American College of Rheumatology criteria for SLE were studied. The ABI was measured using a contour wrapped 12 cm cuff attached to a mercury sphygmomanometer and an 8 MHz Doppler probe in the arms and legs; a ratio of <1 was considered abnormal. Results: The mean (SD) age of the patients was 39.0 (9.2) years. Of the 91 patients studied, 34 (37%) had an abnormal ABI. Only one patient was mildly symptomatic. Abnormal ABI correlated with age but not with disease duration, cumulative steroid dosage, ECLAM score, or any other traditional risk factors for atherosclerosis. In comparison with population studies, the prevalence of an ABI<1 in the patients with SLE with a mean age of 39 years was similar to that in adults aged over 80. Conclusion: In this pilot study, patients with SLE with a mean age of 39 years had a high prevalence of an abnormal ABI. The ABI is a simple non-invasive tool for the early detection of accelerated atheroma in SLE.
Most patients with a low ABI are asymptomatic and a low ABI suggests that additional risk assessments should be considered. The ability of a low ABI to predict subsequent events may be greatly increased by combining it with other risk factors.

The conventional cut off point of a pathological ABI is usually 0.9 and is arbitrary because it was originally developed from studies of patients referred for lower limb angiography. A cut off point of ≤0.9 to 1.0 has conventionally been used for ABI in the past. The sensitivity and specificity of an ABI <1.0 for CHD is 41% and 73%, respectively, and of an ABI >0.8 17% and 94%, respectively. A study from Japan calculated the sensitivity and specificity of the various cut off levels of ABI for atherosclerosis, ST segment depression, and ischaemic heart disease and concluded that an ABI ≤1.0 gives the maximum sensitivity and specificity. A recent consensus statement recommends a standard methodology and considers an ABI value <1.00 abnormal.

### PATIENTS AND METHODS

#### Patients

Ninety one consecutive patients aged ≤55 years and fulfilling the revised American College of Rheumatology classification criteria for SLE were recruited from our SLE clinics. The Louise Coote Lupus Unit is a tertiary referral centre, and the patients there are representative of lupus patients from all over Great Britain and are in general towards the more severe end of the spectrum of SLE.

Approval for the study was obtained from the St Thomas' Hospital ethics committee on medical research.

#### Non-invasive vascular assessment

The ankle-brachial index determination was performed by a single observer (AT) on all subjects after a five minute rest in a supine position. The systolic pressure in the brachial, radial, posterior tibial, and dorsalis pedis arteries in all limbs was measured with a contour wrapped 12 cm cuff attached to a mercury sphygmomanometer and an 8 MHz Doppler probe (MD 2000). The cuff was inflated to 20 mm Hg above the audible systolic pressure in each artery. The recorded systolic pressure was the pressure at which the Doppler probe sounds were first audible as the cuff was slowly deflated. The order of measurement in each limb was the same for all participants. To calculate the ABI we used the highest brachial pressure between the two arms. Where the brachial pressure could not be measured, we used the radial pressure instead. To obtain an ankle pressure—for example, on the left, we selected the higher of the left posterior tibial and left dorsalis pedis values. We then divided the highest brachial pressure with the selected ankle pressure to obtain the ABI value for that side. We then used the lower ABI value of the left and right limbs. We excluded participants with an ABI ≥1.5 because previous studies suggest that this is a falsely high level caused by non-compressible calcified vessels in the legs. We considered an ABI of <1.00 as abnormal as recommended by the consensus statement.

### Demographic and other data

All patients were screened clinically for conventional atherosclerotic risk factors (weight, height, smoking status, family history of cardiovascular disease) and by notes review (diabetes, nephrotic syndrome, history of thrombosis, presence of Raynaud's phenomenon, current or past steroid treatment). We calculated the European Consensus Lupus Activity Measurement (ECLAM) score and took blood to determine random blood cholesterol, triglyceride and glucose concentrations, thyroid function test status, and lupus serology (anti-DNA, complement, antiphospholipid antibodies (aPL), including anticardiolipin antibodies (aCL) and the lupus anticoagulant (LA)), on the day of the ABI measurement. We also reviewed the files for the presence of at least one previous positive testing of aPL (aCL and LA) and for the presence of antiphospholipid syndrome according to the Sapporo classification criteria.

### Statistical analysis

Univariate associations between demographic, atherosclerotic risk factors, and abnormal ABI ratios were analysed using $\chi^2$ test and Student’s $t$ test when appropriate. Multivariate analysis was performed with logistic regression for the presence of pathological ABI. All analyses were performed using the NCSS statistical software. A $p$ value <0.05 (two tailed) was considered significant.

### RESULTS

Thirty four of the 91 patients studied (37%) had an abnormal ABI (ABI<1.0) and the other 57 (63 %) had normal ABI values. Only one patient aged 26 had mild calf pain on walking 500 m and none of the others had symptoms or signs of peripheral vascular disease. The ABI values (mean value and standard deviation) were 1.015 (0.126), 1.097 (0.082), and

### Table 1: Summary of techniques for the detection of subclinical atherosclerosis

<table>
<thead>
<tr>
<th>Technique</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary angiography</td>
<td>Invasive and relatively insensitive (does not detect minor stenosis due to unstable plaque)</td>
</tr>
<tr>
<td>Intracoronary ultrasonography</td>
<td>Sensitive and detects plaque. Invasive and not practical for screening</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Non-invasive but not sensitive. Detects left ventricular hypertrophy, a strong risk factor for adverse outcome</td>
</tr>
<tr>
<td>Coronary perfusion</td>
<td>Thallium perfusion studies and dual isotope myocardial perfusion imaging (DIMP), relatively insensitive and may underestimate the prevalence of atherosclerosis</td>
</tr>
<tr>
<td>Electron beam computed tomography (EBCT)</td>
<td>Non-invasive and accurate; detects calcified plaque, a marker of future cardiac events. Useful only in clinical trials; involves radiation</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>Limited resolution owing to cardiac motion</td>
</tr>
<tr>
<td>B mode ultrasound</td>
<td>Non-invasive, detects subclinical carotid plaque and intima-media wall thickness. Accurate and reliable but is operator dependent</td>
</tr>
<tr>
<td>Myocardial SPECT scan</td>
<td>Performed after treadmill exercise or dipyridamole stress. Not always concordant with carotid duplex-ascertained plaque</td>
</tr>
<tr>
<td>Transcranial Doppler</td>
<td>Microembolic signals on transcranial Doppler ultrasonography are correlated with atherosclerotic disease</td>
</tr>
<tr>
<td>Vascular stiffness</td>
<td>Aortic pulse wave velocity (PWV) is an early marker of atherosclerotic risk. Has been used in SLE</td>
</tr>
<tr>
<td>Endothelial function</td>
<td>Flow mediated dilatation measures the brachial artery in response to reactive hyperaemia. Not yet widely used in routine clinical practice</td>
</tr>
</tbody>
</table>
### Table 2: Comparison between the normal ABI group (ABI > 1.00) and the low ABI group (ABI < 1.00)

<table>
<thead>
<tr>
<th>Group study</th>
<th>SLE</th>
<th>SLE + aCL/LA</th>
<th>SLE + APS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>39.0 (9.2)</td>
<td>37.5 (8.78)</td>
<td>37.5 (8.24)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>25.06 (5.46)</td>
<td>25.22 (5.32)</td>
<td>24.79 (5.74)</td>
</tr>
<tr>
<td>ECLAM score, mean (SD)</td>
<td>2.36 (1.52)</td>
<td>2.57 (1.54)</td>
<td>2.0 (1.43)</td>
</tr>
<tr>
<td>Duration of disease (years), mean (SD)</td>
<td>9.0 (7.5)</td>
<td>7.97 (6.36)</td>
<td>10.9 (8.74)</td>
</tr>
<tr>
<td>Sex (female, male)</td>
<td>86, 5</td>
<td>53, 4</td>
<td>33, 1</td>
</tr>
<tr>
<td>Race (white, black, oriental-Asian, Indian-Asian)</td>
<td>59, 22, 7, 3</td>
<td>37, 12, 7, 1</td>
<td>22, 10, 0, 2</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>38.5</td>
<td>40.4</td>
<td>35.3</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>23.1</td>
<td>28.1</td>
<td>14.7</td>
</tr>
<tr>
<td>Arterial hypertension (%)</td>
<td>24.2</td>
<td>29.8</td>
<td>14.7</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>5.5</td>
<td>5.3</td>
<td>5.9</td>
</tr>
<tr>
<td>Hypothyroidism (%)</td>
<td>9.9</td>
<td>8.8</td>
<td>11.8</td>
</tr>
<tr>
<td>Hypertrophic (%)</td>
<td>24.2</td>
<td>19.3</td>
<td>33.3</td>
</tr>
<tr>
<td>Nephrotic syndrome (%)</td>
<td>19.8</td>
<td>26.3</td>
<td>8.8</td>
</tr>
<tr>
<td>Family history positive (%)</td>
<td>35.2</td>
<td>29.8</td>
<td>44.1</td>
</tr>
<tr>
<td>Raynaud's phenomenon (%)</td>
<td>50.5</td>
<td>50.9</td>
<td>50.0</td>
</tr>
<tr>
<td>Arterial thrombosis (%)</td>
<td>5.5</td>
<td>7.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Venous thrombosis (%)</td>
<td>16.5</td>
<td>15.8</td>
<td>17.6</td>
</tr>
<tr>
<td>AN (%)</td>
<td>1.1</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>4.4</td>
<td>5.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Thrombosis (%)</td>
<td>18.7</td>
<td>19.3</td>
<td>17.6</td>
</tr>
<tr>
<td>Steroid treatment (years), mean (SD)</td>
<td>3.73 (4.49)</td>
<td>3.96 (4.62)</td>
<td>3.34 (4.31)</td>
</tr>
<tr>
<td>Multivariate analysis</td>
<td>Age</td>
<td>0.03</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

**Note:** NS indicates not significant.
0.89 (0.08) for the whole group (n = 91), the group with normal ABI (n = 57), and the group with low ABI (n = 34), respectively. Fifty nine patients (65%) were white, 22 (24%) were black, 7 (8%) were oriental-Asian, and 3 (3%) were Indian-Asian. In the normal ABI group the distribution was: 37 (65%), 12 (21%), 7 (12%), and 1 (2%), respectively, and in the abnormal ABI group the distribution was: 22 (65%), 10 (29%), 0, and 2 (6%), respectively. No statistical differences were found between the 86 female patients and the five men. Five patients had antiphospholipid syndrome, of whom two had an abnormal ABI. No significant differences were found between the normal and the abnormal ABI groups for the various risk factors and other variables, except in the age of the patients.

We divided the patients with SLE into two groups according to the presence or absence of aCL/LA or the presence of the antiphospholipid syndrome. We found no difference between the normal/abnormal groups except in the age of the patients. Table 2 shows these results.

### DISCUSSION

It is estimated that mortality due to coronary artery disease accounts for up to 30% of all deaths in patients with SLE.1–7 The prevalence of coronary artery disease is estimated to be 8.3–15%, with a mean age of onset of coronary artery disease of 47.5 years.2,8 The female lupus patients from the Pittsburgh SLE cohort in the 35–44 age group were over 50 times more likely to have an MI than controls.9 According to Ward’s study, the risk of admission to hospital owing to a cerebrovascular accident was 2.03 times greater for lupus patients aged 18–44 years,10 and according to a Canadian study, the overall risk for MI conferred by SLE after controlling for the Framingham risk factors was increased by an estimated 8.3-fold.11 The true prevalence of subclinical disease is not yet certain but there is evidence that markers of subclinical disease may be able to identify subjects at high risk of clinical CHD and those most likely to benefit from aggressive treatment.12–14

There has been a dramatic change in the approach to studying cardiovascular disease. Table 1 summarises the techniques used for the detection of subclinical atherosclerosis. The current “gold standard” non-invasive method for detecting subclinical atherosclerosis is B mode carotid ultrasound to assess plaque and intima-media thickness. The ABI measurement can be conducted at low cost, using simple techniques and is non-invasive and not as operator-dependent as carotid ultrasound. It is an easy, accurate, and reproducible measurement using a portable probe and sphygmomanometer that is relatively inexpensive. Furthermore, only minimal training is required to use the technique. It can be used as a primary prevention tool in routine screening of cardiovascular status in the community.15–17 There is high patient acceptability. Even though the ability of ABI to predict subsequent events is increased by combining a low ABI (<1.00) with other risk factors,18 its association with cardiovascular events is strongly independent of these other risk factors.19–21 The ability of ABI to predict cardiovascular events is increased in those subjects with no clinical cardiovascular disease.21

Epidemiological studies show that subjects with clinical cardiovascular disease related to one specific vascular bed (for example, intermittent claudication), are at higher risk of clinical disease caused by atherosclerosis (which is a diffuse disease) in other vascular beds. Most subjects with decreased ABI are asymptomatic and a high percentage of these subjects have other aspects of subclinical or clinical cardiovascular disease.22–24 Thus a decreased ABI is predictive in an individual patient of a high risk of future cardiovascular events. Such asymptomatic patients are amenable to further investigations and interventional treatments. In asymptomatic disease, aspirin may be as effective as in symptomatic disease, because the cardiovascular disease rate in asymptomatic subjects with a low ABI, is similar to those with clinical disease.21–23

In attempting to prevent initial cardiovascular events for patients with SLE, a reasonable strategy would be to target and treat patients with asymptomatic subclinical atherosclerosis. It might then be possible to reduce their risk with additional monitoring and careful control of risk factors, such as hyperlipidaemia, considering antithrombotic drugs, and encouraging lifestyle changes such as stopping smoking, diet, and exercise. Several studies suggest that SLE itself is a risk factor for atheroma and may result from vascular inflammation mediated by immune complexes. Thus control of disease activity may also help to reduce the burden of atherosclerotic disease.

Measurement of the ABI can identify subjects at high risk, but in general cannot be used to exclude subjects believed not to be at risk of cardiovascular disease.24 In other words, a normal ABI does not rule out the presence of atherosclerosis. Although sensitivity is low, it does not differ appreciably from the sensitivity of more common risk factors for cardiovascular disease mortality. In addition, the magnitude of risk for cardiovascular disease that is associated with a low ABI is similar to findings from more extensive testing, including echocardiography and carotid ultrasound.25–28

We studied 91 patients with SLE for traditional risk factors for atherosclerosis and we screened them with an ABI for possible subclinical atherosclerosis. Using a cut off point of <1.00 for ABI, we found that 37% of our patients had an abnormal ABI. In population studies of adults aged under 55 the prevalence of an ABI ≤0.9 is below 4%,29–32 and this percentage increases rapidly with age. In a prospective population study of healthy adults33 the highest prevalence of an abnormal ABI (35%) was in the 80–84 year old age group. Thus our young patients with SLE had a prevalence of abnormal ABI values comparable with that of a much older age group. Interestingly, no correlation was found between a low ABI and the prevalence of aPL, which are a strong predictor of arterial and venous cardiovascular events. Again, this may be a function of the small study numbers but may also be because aPL and the ABI are markers for different vascular processes.

In contrast with other studies,19–21,24–26,30–32,36–37 our study failed to show a statistically significant correlation between low ABI and common risk factors. This may be due to (a) the small number of subjects in this pilot study; (b) the fact that the ABI is an independent predictor of mortality, as shown by previous studies,19,20,36–37 There is also a paradox in our results relating to steroid treatment: this is of slightly shorter duration in the group with a low ABI which has longer disease duration than in the group with normal ABI. This is not of statistical significance and may reflect the small number of subjects, or the possibility that the immune-inflammatory nature of the disease influences this phenomenon of early atherosclerosis independently of the traditional risk factors.1,15,27,32 and, according to Manzi et al.,7 may be stronger than traditional factors.

In conclusion, the ABI is a simple, non-invasive technique for the detection of accelerated atheroma in young patients with SLE. Our pilot study demonstrates that young patients with SLE have a high prevalence of an abnormal ABI suggesting widespread asymptomatic vascular dysfunction. Clearly, further studies with a control group will help to define the clinical use of this test and how individual patients should be investigated.
ACKNOWLEDGEMENTS

We are grateful to the St Thomas’ Lupus Trust for the purchase of the Doppler probe.

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*Ann Rheum Dis* 2003 62: 1199-1203
doi: 10.1136/ard.2002.001164

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