Concise report

A longitudinal study of ankle brachial pressure indices in a cohort of patients with systemic sclerosis

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Abstract

Objectives. Digital ischaemia, often progressing beyond RP to digital ulceration and sometimes even gangrene, is the most common vascular manifestation of SSc. Both microvascular and macrovascular disease can contribute and coexistence of microvascular and macrovascular (proximal vessel) disease in patients with SSc is potentially limb threatening. The aims of this study were to examine the change over time in the ankle brachial pressure index (ABPI) in a cohort of patients with SSc and to examine whether age, gender, smoking status, disease duration, disease subtype and ACA are associated with ABPI.

Methods. The clinical and laboratory data of 217 patients attending the SSc clinic at a tertiary referral centre and who had their ABPIs checked between 1996 and 2011 were reviewed retrospectively. Data were analysed to see how the ABPI changed with time and linear mixed effects modelling was used to determine which factors were associated with ABPI.

Results. In most patients with SSc, the ABPI remained constant over time [median rate of change 0 units/year, interquartile range (IQR) –0.01–0.01]. There was a significant association between lower ABPI and increasing age (P = 0.04), the limited cutaneous subtype of SSc (P = 0.01) and ACA positivity (P = 0.03). Additionally there was an association between ABPI and smoking status of borderline statistical significance (P = 0.08).

Conclusion. This study provides further evidence for associations between the severity of vascular disease in patients with SSc and increasing age, smoking, limited cutaneous disease and positive ACA. Reassuringly, in most patients ABPI remains stable over time.

Key words: systemic sclerosis, ankle brachial pressure index, peripheral vascular disease, arterial Doppler.

Introduction

SSc is a multisystem CTD characterized by vascular abnormalities, fibrosis and activation of the immune system. Vascular abnormalities have long been recognized as being central to its pathogenesis, and digital ischaemia is the most characteristic clinical manifestation of this vasculopathy. Almost all patients with SSc have RP, and many go on to develop digital ulcers and sometimes even gangrene necessitating amputation [1].

SSc-related vasculopathy is primarily due to problems with the microvasculature. However, some studies have revealed an increased prevalence of proximal limb large vessel disease in patients with SSc [2, 3]. Techniques used to diagnose peripheral vascular disease have included lower limb Doppler US [measuring the ankle brachial pressure index (ABPI)] and angiography [4–6]. Ho et al. [3] performed a case–control study of 54 patients with SSc and 43 controls of similar age and gender. Peripheral vascular disease, as diagnosed by the ABPI, was present in 17% of patients with SSc and in none of the controls (P = 0.003).

Early diagnosis of proximal vessel disease is clinically relevant because large vessel peripheral vessel disease is
strongly predictive of all-cause mortality, with the excess risk of deaths mainly due to coronary artery disease [7]. Also, in patients with SSC, the presence of proximal vessel disease could have an additive effect with the already present microvascular disease and worsen digital ischaemia, leading to upper and lower limb digital ulcers and to critical limb ischaemia. There is anecdotal evidence to support this: descriptive studies have reported large vessel disease leading to lower limb amputation in patients with SSC [8, 9]. Thus it is important to identify early the presence of coexistent macrovascular disease in patients presenting with digital ulcers to allow early treatment that could be limb saving.

Measurement of the ABPI is a simple, non-invasive and reproducible test to detect peripheral vascular disease and subclinical atherosclerosis. It is calculated by dividing the systolic blood pressure measured in the dorsalis pedis and posterior tibial arteries at the level of the ankle by the systolic blood pressure measured in the brachial artery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines states that the normal range of ABPI is 1.00–1.40 [10]. Values of < 0.90 are abnormal [10]. Having a low ABPI ratio is an independent risk factor for cardiovascular disease, including fatal and non-fatal complications [11].

Because of the increased interest in the suggestion of an increased prevalence of proximal vessel disease in patients with SSC [2, 3], ABPIs were included in the assessment of patients with SSC attending Salford Royal NHS Foundation Trust.

The primary aim of this retrospective study was to examine the change over time in ABPI in a cohort of patients with SSC. In addition, we also examined whether age, gender, smoking status, disease duration, disease subtype and ACA are associated with ABPI.

Materials and methods

The clinical and laboratory data of patients attending the SSC clinic at Salford Royal NHS Foundation Trust and who had their ABPI checked between 1996 and 2011 were reviewed retrospectively. The ABPI data are composed of serial measurements. The ABPIs were measured at the time of each patient’s annual review clinic visit.

ABPI of both right and left lower limb was measured (using Doppler) and each value of ABPI was considered separately for each patient. The ABPI was measured by senior vascular technicians (T.M., J.M.). The brachial artery pressure was measured twice. The pressure in the dorsalis pedis and posterior tibial arteries was measured twice for each artery and the ABPI was calculated by dividing the highest ankle systolic pressure by the highest brachial artery systolic pressure to two decimal places. The study was approved by the Salford and Trafford Local Research Ethics Committee and all patients gave written informed consent. A basic continuous wave Doppler machine (Atys Medical, Soucieu-en-Jarrest, France) was used to record the ABPI using an 8 MHz probe. The lower of the two ABPI values for each patient (right or left) on a given date was used for the analysis.

Statistical analysis

Statistical analysis was conducted using the statistical software R (R Project for Statistical Computing). Simple linear regression of ABPI on age was performed for each patient. The gradient of each regression line was used as a summary of the patient’s rate of change in ABPI (units/year).

Associations between patient characteristics and the absolute ABPI measurements were investigated. We used all available longitudinal data on ABPI and relevant covariates to investigate factors that may explain differences in ABPI levels. We allowed covariates to change over time as appropriate. A process of model selection was conducted in order to identify a parsimonious representation of the data. The initial linear regression model contained ABPI as the dependent variable, with age, gender, smoking status, disease duration (from date of onset of first non-RP clinical feature), disease subtype (limited cutaneous or diffuse cutaneous [12]), ACA status and a constant intercept term as fixed effects. Covariates were set to their values at the time of the corresponding ABPI measurement for that patient (so that, e.g., age was set to the patient’s age at the time of the observation and was allowed to increase over the duration of the study period). In order to account for the longitudinal nature of the data, random intercept and age terms were included. Model selection was then conducted as an eliminative process; each of the fixed and random terms were removed from the model, with a comparison being made between models with and without each term included. Models with lower values of the Akaike information criterion (AIC) were favoured on the grounds of parsimony. AIC is a measure of goodness of fit that penalizes unnecessary complexity.

Parameter estimates and 95% CIs were obtained from the preferred model in order to assess the association of each covariate with ABPI. Diagnostic plots of residuals were used to verify the assumption of normality underlying the analysis.

Results

Between 1997 and 2011, 217 patients who had consented to being studied were reviewed in the SSC clinic at Salford Royal NHS Foundation Trust. The patients were followed up for a median of 8 years. Fifteen patients were excluded from the analysis, as they had fewer than three ABPI measurements, which was deemed too few to give a reasonable representation of a patient’s change over time. One patient with unknown disease duration was excluded and another patient was excluded because the ABPI displayed a dramatic increase following surgical intervention. Following these exclusions, data were available on 200 patients.
The gradients represent the rate of change in ankle brachial pressure index (ABPI) (units/year). It is apparent that most patients displayed very little change in ABPI across the study period.

Demographic data
The median age of patients at first visit within the time frame of the study was 52 years (range 17–79). The majority of the patients were female (83%) and 89% were non-smokers. Median disease duration was 5 years (range 1–50). Most patients (76%) had lcSSc and 24% had dcSSc. Thirty-five per cent were ACA positive.

Gradients of linear regression to observe change in ABPI with time
A histogram of gradients from the exploratory simple linear regression models for each patient is displayed in Fig. 1. Each gradient can be interpreted as the change in ABPI per year for each patient, so that negative values mean that ABPI decreased over time and positive values mean that ABPI increased over time. The median gradient was 0.00 units/year [interquartile range (IQR) –0.01–0.01], indicating little to no change in ABPI over time.

Factors influencing ABPI
The median ABPI was 1.08 (IQR 1.03–1.15, range 0.48–1.52). The regression model selected for analysis was the linear mixed model with ABPI as the dependent variable with age, smoking status, disease subtype, antibody status and a constant intercept term as fixed effects, with random intercept and age terms. Disease duration and gender were found to lack explanatory value once the other predictors had been accounted for. Results from this analysis are presented in Table 1. There were small but statistically significant associations between ABPI and each of the factors age, disease subtype and ACA status. Furthermore, the results suggested a small effect of smoking status of borderline statistical significance.

Discussion
In most patients with SSc in our study, the ABPI remained consistent over a median of 8 years. The factors that were significantly associated with lower ABPI were an increase in age, lcSSc and a positive ACA status. Disease duration and gender did not have a significant influence on ABPI.

Previous studies that have examined ABPIs in SSc patients have been cross-sectional [3, 13–15]. Four previous studies evaluated the ABPI in patients with SSc compared with healthy controls [3, 13–15]. In three of these studies, the results suggested that there were no significant differences in the ABPI between patients with SSc and healthy controls [13–15]. However, one of the four studies showed a significantly higher prevalence of abnormal ABPI among the patients with SSc compared with healthy controls (17% vs 0%) [3]. The novelty of our study was to look for change in the ABPI over time and to make use of longitudinal data on both ABPI and potential correlates of ABPI to investigate factors associated with absolute ABPI levels: it was not our purpose to make comparisons with a control population.

Our study also looked for associations with ABPI in patients with SSc, expanding on our previous study of 119 patients [6], which reported that ABPI was weakly associated with ACA but not with age, smoking or disease subtype. The patients reported by Wan et al. [6] included a subgroup of those recruited into the current study: this previous study was cross-sectional and did not incorporate longitudinal measurements. Our findings suggest that an increase in age is significantly associated with lower ABPI. It is well described that the prevalence of peripheral vascular disease increases with age [16].

Patients with long-standing lcSSc are often considered to have more prominent vascular manifestations than patients with dcSSc, and this was confirmed in our study. Although Nihtyanova et al. [17] noted that in their cohort of 1168 patients with SSc, severe digital vasculopathy occurred in 27.5% of the patients with dcSSc vs 13% of

**Table 1** Results from a linear mixed effects model of longitudinal ABPI measurements

<table>
<thead>
<tr>
<th>Factor</th>
<th>Estimate</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>–0.001</td>
<td>(–0.002, 0.000)</td>
<td>0.04</td>
</tr>
<tr>
<td>Smoking status (positive)</td>
<td>–0.028</td>
<td>(–0.059, 0.000)</td>
<td>0.08</td>
</tr>
<tr>
<td>Disease subtype (limited)</td>
<td>–0.032</td>
<td>(–0.057, –0.008)</td>
<td>0.01</td>
</tr>
<tr>
<td>ACA positive</td>
<td>–0.024</td>
<td>(–0.047, –0.002)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

For age, estimates (95% CI) show the expected change in ankle brachial pressure index (ABPI) for a patient ageing 1 year, after adjusting for the other factors in the table. For the other factors, the estimates (95% CI) show the expected difference in ABPI for a patient displaying the characteristic shown compared with one who does not, after adjusting for the other factors in the table.
the patients with lcSSc (P < 0.0001), proximal vascular disease was not specifically looked for.

Our study suggests that in patients with SSC, smoking is associated with lower ABPI. Previously Wigley et al. [18] concluded that smoking was not a risk factor for digital ischaemic loss in 98 patients in their SSC cohort at a tertiary care centre. However, a previous analysis in patients with SSC attending Salford Royal NHS Foundation Trust [19] found that in a cohort of 101 SSC patients, current smokers were three to four times more likely than never smokers to incur digital vascular complications. After adjusting for age, gender and disease duration, current smokers were significantly more likely than never smokers to have required debridement [odds ratio (OR) 4.5, 95% CI 1.1, 18.3] or admission for i.v. vasodilators (OR 3.8, 95% CI 1.1, 12.9) [19]. Ideally we would have liked to examine associations of ABPI with other traditional cardiovascular risk factors (hypertension, diabetes), but this was not possible in the context of a retrospective study.

The results of our study confirm the previously reported association between severity of peripheral ischaemia and ACA in patients with SSC [6, 18, 20]. Our previous cross-sectional study [6] of 119 patients with SSC showed that the median ABPI in patients who were ACA positive was lower [1.07 (IQR 0.36–1.38)] than in those who were ACA negative [1.11 (IQR 0.66–1.36)]. The reason for the association between ACA and severity of peripheral ischaemia is unknown.

In conclusion, most patients with SSC in our study had an ABPI that remained constant over time. Patients who were older, who smoked, who had limited cutaneous disease and who were ACA positive had lower ABPI on average. We believe, therefore, that the routine checking of ABPI in patients with SSC without claudication or other lower limb ischaemic problems is unlikely to be cost or time effective. However, measuring ABPI is a very useful, easy and non-invasive method of detecting peripheral vascular disease or subclinical atherosclerosis in patients with SSC presenting with digital ulcers or worsening of digital ischaemia. A low value of ABPI should prompt further investigation to look for proximal vessel disease that may be amenable to treatment. Future studies should examine the relationship (in patients with SSC) of ABPI and the development of lower limb ulcers (especially of the toes) and/or of critical ischaemia.

References


Rheumatology key messages

- Ankle brachial pressure index remains stable over time in most patients with SSC.
- Older age, smoking, limited cutaneous disease and positive ACA are associated with lower ankle brachial pressure index in SSC.

Disclosure statement: The authors have declared no conflicts of interest.


