Arterial stiffness is increased in systemic sclerosis: a cross-sectional comparison with matched controls

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ABSTRACT

Objective. *Increased arterial stiffness is a predictor of cardiovascular and all-cause mortality. Atherosclerosis may be increased in systemic sclerosis (SSc). Our aims were to determine if arterial stiffness is elevated and to evaluate correlates of arterial stiffness in SSc.*

Methods. *We carried out two studies: 1. a comparison of arterial stiffness in 40 SSc patients free from cardiovascular disease or significant vascular manifestations of SSc and 40 healthy controls (HC), and 2. an analysis of determinants of arterial stiffness in 80 SSc patients free from cardiovascular disease.*

Results. *In Study 1, the groups were well-matched for age (52.2 vs. 50.0 years, p=0.432) and sex (80% female in both). SSc patients had higher augmentation index (AIx) than HC (31.0% [IQR 25.7–38.7] vs. 23.8% [IQR 13.5–30.1], p<0.001). Pulse wave velocity (PWV) was also higher, however this did not reach statistical significance (6.9 m/s [IQR 6.0–8.3] vs. 6.5 m/s [IQR 6.1–7.4], p=0.275).*

In Study 2, age (p<0.001) and calcium channel blocker (CCB) therapy (p=0.016) were independently associated with higher AIx; and age (p<0.001), disease duration (p=0.042) and systolic blood pressure (p=0.001) with higher PWV.

Conclusion. *SSc patients had higher AIx than HC. The paradoxical association between CCB therapy and higher AIx could reflect generalised vasculopathy rather than atherosclerotic disease. Prospective studies in larger cohorts are warranted to clarify this point and elucidate other determinants of arterial stiffness in SSc.*

Introduction

Systemic sclerosis (SSc) is a multisystem connective tissue disorder characterised by vascular dysfunction, immune dysregulation and fibrosis. Microvascular damage occurs early in the onset of SSc and gives rise to clinical manifestations such as Raynaud's phenomenon, digital ulceration, pulmonary arterial hypertension (PAH) and scleroderma renal crisis (SRC). Although macrovascular disease was not originally considered a manifestation of SSc, an increased prevalence of peripheral vascular disease in the upper and lower limbs (1, 2) has been reported. In terms of coronary heart disease, there is conflicting data regarding its prevalence in SSc (3). We (4), and others (5), have reported an increased prevalence of coronary heart disease in SSc patients compared with the general population, however non-SSc-related cardiac disease was not a significant cause of mortality in a large, European, multicentre SSc cohort (6). Furthermore, angiographic studies have not demonstrated a difference in the prevalence of coronary artery lesions between SSc patients and controls (7). Whilst the extent of coronary heart disease in SSc remains unclear, potential contributing factors may include direct SSc-related macrovascular involvement, primary myocardial disease and atherosclerosis accelerated by the presence of systemic inflammation.

SSc is a rare condition and "hard" clinical outcomes such as myocardial infarction, although increased in prevalence (4), are still relatively infrequent events in SSc cohorts. Therefore, in an attempt to further understand the factors underlying the increase in coronary events in SSc, it is helpful to consider surrogate measures of vascular disease. Arterial stiffness, measured using the techniques of pulse wave analysis (PWA) and pulse wave velocity (PWV), is a dynamic property determined by arterial wall structure, endothelial and vascular smooth muscle function, and arterial pressure. It is an independent predictor of cardiovascular events and cardiovascular and all-cause mortality across a

range of patient populations (8, 9) and is a well-validated surrogate marker of subclinical atherosclerosis.

The aims of this study were to determine if arterial stiffness is elevated in SSc patients compared with healthy controls (HC) and to investigate the correlates of arterial stiffness in SSc patients.

Materials and methods

We carried out two studies: *1*. a comparison of arterial stiffness in 40 SSc patients free from cardiovascular disease or significant vascular manifestations of SSc (*i.e*. PAH or SRC) and 40 age- and sex-matched HC (who were also free from cardiovascular disease), and *2*. an analysis of determinants of arterial stiffness in a larger, unselected cohort of 80 SSc patients free from cardiovascular disease (which included the 40 patients from Study 1). Consecutive SSc patients attending the outpatient rheumatology clinics of two tertiary hospitals, The Royal Melbourne Hospital and Monash Medical Centre, were screened for the study. All patients satisfied the American College of Rheumatology (10) or the LeRoy and Medsger criteria (11) for SSc. Exclusion criteria included past diagnosis of cardiovascular disease (coronary heart disease, stroke or peripheral vascular disease). Patients with PAH diagnosed on right heart catheter (12) or SRC (defined as the presence of at least two of new-onset hypertension, microangiopathic anaemia or rising creatinine) were excluded from Study 1 but were included in Study 2. HC were recruited from outpatient rheumatology clinics and the friends and family of SSc patients. All HC were free from coronary heart disease, stroke, peripheral vascular disease or inflammatory rheumatological disease.

All arterial stiffness studies were performed by a single investigator (GSN) under standardised conditions (13). Measurements were performed in the morning after an overnight fast and abstinence from smoking, alcohol and caffeine for 12 hours. Subjects were placed supine and, after resting for several minutes in a quiet environment, blood pressure (BP) was measured at the right brachial artery. Applanation tonometry was performed using the Sphygmocor device (Sphygmocor (v7.01) AtCor Medical Pty Ltd 1999–2002, Sydney, Australia), consisting of a hand-held pressure sensor (Millar tonometer, Houston, TX, USA) connected to a computer. For PWA, the tonometer was used to produce a high-fidelity waveform at the right radial artery, with a general transfer factor applied to obtain the aortic pulse contour. The augmentation index (AIx) was calculated as the difference between the second and first systolic peaks of the wave (the augmented pressure), expressed as a percentage of the pulse pressure and standardised to 75 beats/min. Three consecutive measurements were obtained and the mean used for analysis.

Carotid-femoral PWV was calculated using the foot-to-foot method and the formula:

PWV = distance(m)/time(s).

Sequential tonometry was performed at the right carotid and right femoral arteries with electrocardiogram gating. The time delay between the R-wave of the electrocardiogram and the arrival of the foot of the pressure wave was measured at each site and the difference in time between the two sites calculated. The distance between the sites was measured across the surface of the body as the distance between the carotid location and the sternal notch, subtracted from the distance between the sternal notch and the femoral location (to account for opposite directions of pulse wave propagation). Finally, velocity was calculated using the above formula. Three consecutive measurements were obtained and the mean used for analysis.

Disease manifestations, anti-centromere or anti-Scl-70 antibody status and drug therapy were recorded in all SSc patients. A modified Rodnan skin score was also performed. Traditional Framingham cardiovascular risk factors were assessed in all participants. Erythrocyte sedimentation rate and C-reactive protein were measured in all SSc patients. The study had ethics approval according to the Helsinki Declaration of 1975 as revised in 1983 from the Melbourne Health and Southern Health Human Research Ethics Committees and written informed consent was obtained from all participants.

Data are expressed as mean ± standard deviation (SD), median (interquartile range [IQR]), or percentage, as appropriate. SSc and HC groups were compared using the independent *t* test for normally distributed continuous data and the Wilcoxon-Mann-Whitney test for non-normally distributed continuous data. Categorical data were compared using the chi square test. Correlation between PWV and AIx measurements was determined using Pearson's correlation coefficient. To satisfy conditions of normality, AIx was transformed to the square and PWV to the inverse square root. To determine associations between arterial stiffness and variables relating to patient characteristics, simple linear regression was used for continuous variables and the independent *t*-test for categorical variables. Backward stepwise multiple linear regression was performed to determine independent predictors of arterial stiffness commencing with all variables that were significant on simple linear regression. Individual variables were eliminated in a stepwise fashion until the best model was obtained. p values <0.05 were considered statistically significant. All analyses were performed using the statistical software Stata/IC, version 12.1 (StataCorp, College Station, TX).

Results

Study 1

The SSc and control groups were well matched with a mean ± SD age of 52.2±12.0 years in SSc patients and 50.0±12.8 years in HC (p=0.432). Thirty-two patients (80%) in each group were female (p=1.000). There were no significant differences in the prevalence of hypertension, hypercholesterolaemia, diabetes mellitus and smoking between the two groups (Table I). Body mass index (BMI) was significantly lower in SSc than HC, with a mean ± SD BMI of 24.7±4.3 kg/m^2 and 28.0±5.6 kg/m^2 respectively (p=0.004). Systolic and diastolic BP were similar in the two groups, but heart rate was significantly higher in SSc patients (68±10 beats/

Table I. Demographic details and arterial stiffness in SSc patients and HC (Study 1).

	SSc patients (n=40)	HC (n=40)	*p*-value
Age, years	52.2 ± 12.0	50.0 ± 12.8	0.432
Female	32 (80%)	32 (80%)	1.000
Hypertension	8 (20%)	5 (13%)	0.363
Hypercholesterolaemia	12 (30%)	8 (20%)	0.302
Diabetes mellitus	0	1 (3%)	0.314
Current smoker	5 (13%)	5 (13%)	1.000
Family history CHD	12 (31%)	12 (31%)	1.000
Systolic BP, mmHg	124 ± 20	120 ± 15	0.270
Diastolic BP, mmHg	75 ± 9	75 ± 12	0.732
Heart rate, beats/min	68 ± 10	63 ± 11	0.040
BMI, kg/m^2	24.7 ± 4.3	28.0 ± 5.6	0.004
AIx, %	31.0 (25.7 – 38.7)	23.8 (13.5–30.1)	<0.001
PWV, m/s	6.9 (6.0 – 8.3)	6.5 (6.1–7.4)	0.275

Data are mean ± SD, median (IQR) or N(%). SSc: systemic sclerosis; HC: healthy controls; CHD: coronary heart disease; BP: blood pressure; BMI: body mass index; AIx: augmentation index; PWV: pulse wave velocity.

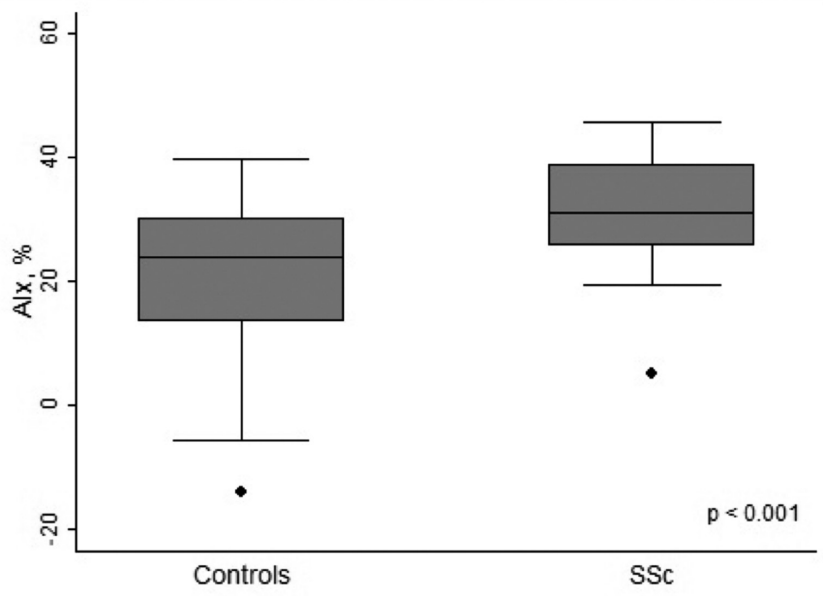

Fig. 1. AIx in SSc patients and HC (Study 1).
AIx: augmentation index; SSc: systemic sclerosis; HC: healthy controls. Boxplot with whiskers extending to 1.5 IQR below the lower quartile and 1.5 IQR above the upper quartile. Outliers represented by circles.

min *vs*. 63±11 beats/min [*p*=0.040]). In the SSc group, 24 patients (60%) had limited and 16 patients (40%) had diffuse disease. Fifteen patients (38%) were anti-centromere antibody positive and 11 patients (28%) were anti-Scl-70 antibody positive. SSc patients had a mean ± SD disease duration of 11.0±8.9 years.

Median arterial stiffness as measured by AIx was significantly higher in the SSc group than the HC (31.0% [IQR 25.7–38.7] *vs*. 23.8% [IQR 13.5–30.1] respectively, *p*<0.001) (Fig. 1). Arterial stiffness as measured by PWV was also increased in the SSc group (6.9 m/s [IQR 6.0–8.3] *vs*. 6.5 m/s [IQR 6.1–7.4], respectively, *p*=0.275), however this did not reach statistical significance.

Study 2

Study 2 comprised 80 SSc patients with a mean ± SD age of 56.7±14.2 years and a mean ± SD disease duration of 12.1±9.2 years. Sixty-six patients (83%) were female. Twenty-three patients (29%) had diffuse disease and 57 patients (71%) had limited disease, whilst 33 patients (41%) were anti-centromere antibody positive and 15 patients (19%) were anti-Scl-70 antibody positive. Other patient characteristics are shown in Table II.

Arterial stiffness measurements in Study 2 did not differ significantly from those of the SSc patients in Study 1, with a median AIx of 30.2 % (IQR 26.0–37.0) and a median PWV of 7.2 m/s (IQR 6.1–8.5). There was a significant positive correlation between AIx and PWV, with r=0.499 (*p*<0.001) when all patients from both studies (80 SSc patients and 40 HC) were included (Fig. 2).

Simple linear regression analysis of the entire SSc cohort revealed that higher AIx was significantly associated with age (*p*<0.001), disease duration (*p*=0.002), anti-centromere antibody (*p*=0.004), calcium channel blocker (CCB) therapy (*p*=0.004), systolic BP (*p*<0.001) and diastolic BP (*p*=0.021). Higher PWV was significantly associated with age (*p*<0.001), disease

Table II. SSc patient characteristics (Study 2).

	SSc patients (n = 80)
Age, years	56.7 ± 14.2
Female	66 (83%)
Hypertension	20 (25%)
Hypercholesterolaemia	25 (31%)
Diabetes mellitus	2 (3%)
Current smoker	12 (15%)
Systolic BP, mmHg	126 ± 22
Diastolic BP, mmHg	75 ± 10
Heart rate, beats/min	68 ± 11
BMI, kg/m^2	25.5 ± 4.6
Modified Rodnan skin score	9 ± 7
Diffuse SSc	23 (29%)
Anti-centromere Ab	33 (41%)
Anti-Scl-70 Ab	15 (19%)
GORD	71 (89%)
Bowel dysmotility	30 (38%)
ILD	31 (39%)
Digital ulcers	33 (41%)
PAH	5 (6%)
SRC	3 (4%)
CCB therapy	36 (45%)
ACE inhibitor therapy	13 (16%)

Data are mean ± SD or N(%). SSc: systemic sclerosis; BP: blood pressure; BMI: body mass index; Ab: antibody; GORD: gastro-oesophageal reflux disease; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; SRC: scleroderma renal crisis; CCB: calcium channel blocker; ACE: angiotensin converting enzyme.

duration (p=0.001), anti-centromere antibody (p=0.020), absence of anti-Scl-70 antibody (p=0.001), absence of past or current digital ulcers (p=0.022), non-smoking status (p=0.038), lower modified Rodnan skin score (p=0.014), angiotensin converting enzyme inhibitor therapy (p=0.034), systolic BP (p<0.001) and diastolic BP (p<0.001). Neither AIx nor PWV were associated with SSc disease subtype, inflammatory markers or significant vascular manifestations of SSc (PAH or SRC), although the number of patients with PAH or SRC was small.

Using backward stepwise multiple linear regression, age and CCB therapy were independently associated with higher AIx; and age, disease duration and systolic BP were independently associated with higher PWV (Table III).

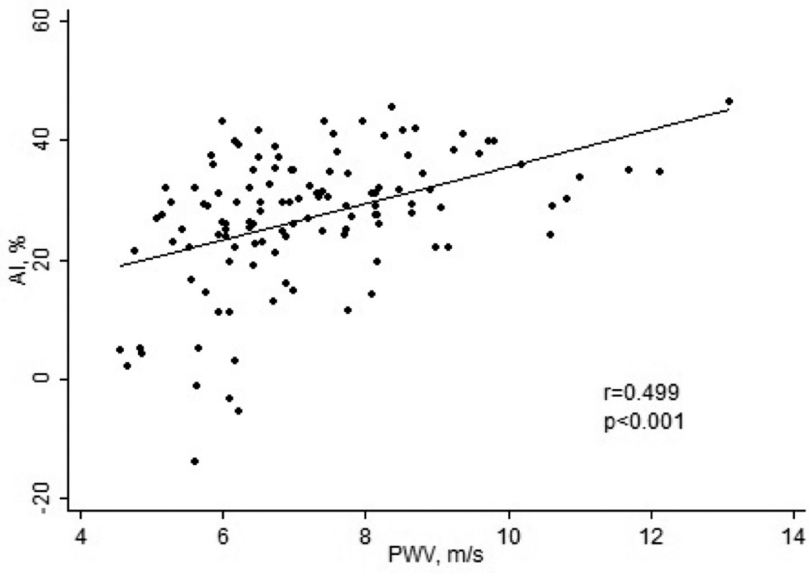

Fig. 2. Correlation between PWV and AIx (Study 1 and Study 2).
PWV: pulse wave velocity; AIx: augmentation index.

Table III. Associations of arterial stiffness in the total SSc cohort (Study 2).

	Independent variable	p-value
AIx	Age	<0.001
	CCB therapy	0.016
PWV	Age	<0.001
	Disease duration	0.042
	Systolic BP	0.001

AIx: augmentation index; CCB: calcium channel blocker; PWV: pulse wave velocity; BP: blood pressure.

Discussion

In these two overlapping studies we compared arterial stiffness in 40 SSc patients and 40 matched controls (all of whom were free from clinical cardiovascular disease) and examined correlates of arterial stiffness in a larger, unselected cohort of 80 SSc patients. To our knowledge, this is the largest study to date to examine correlates of arterial stiffness in SSc patients. We collected comprehensive data from a cohort of patients with a wide range of SSc manifestions and were therefore able to interrogate a large number of parameters for association with arterial stiffness. In Study 1, we demonstrated that AIx, but not PWV, was increased in SSc patients compared with controls. In Study 2, we found that age and CCB therapy were independently associated with higher AIx; whilst age, disease duration and systolic BP were independently associated with higher PWV.

Arterial stiffening occurs as a result of vascular fibrosis, elastin fibre degradation and calcification of the vessel wall. It is influenced by factors such as age, hypertension, diabetes, hyperlipidaemia, smoking, obesity, high sodium intake and the neuroendocrine milieu. There is also evidence that an inflammatory state increases arterial stiffness, with increased levels of C-reactive protein, interleukin-6 and tumour necrosis factor-α reported to correlate with PWV in several studies (14). Activated inflammatory cells such as polymorphonuclear cells and macrophages produce elastases and matrix metalloproteinases (15), which leads to abnormal collagen production and a reduction in normal elastin synthesis. Inflammatory processes may therefore contribute to arterial stiffness in SSc, as has been suggested to occur in both rheumatoid arthritis and systemic lupus erythematosus (16). It is also possible that microvascular disease contributes, either directly or indirectly, to increased arterial stiffness in SSc. The microvasculature is the site of most resistance within the vascular system and the point of origin of wave reflections in the periphery (17). SSc-related changes in the microvasculature may therefore have an "upstream" effect on arterial stiffness in the central elastic arteries, as has been suggested to occur in hypertension (18) and diabetes mellitus (19). Whilst PWV is considered the current "gold-standard" technique in measurement of arterial stiffness (20), AIx is a composite measure determined by PWV, reflectance point in the periphery and left ventricular ejection characteristics. Given that it encompasses the effect of wave reflection, AIx is considered by some researchers to be superior to PWV as a measure of the effects of different disease states on arterial stiffness (21). This may explain why we were able to demonstrate a statistically significant difference in AIx, but not PWV, between SSc patients and HC. AIx and PWV were, however, positively correlated with each other.

Other studies on arterial stiffness in SSc have revealed disparate results. Timar *et al*. (22) found both AIx and PWV to be elevated in 40 SSc patients compared with 34 HC. Cypiene *et al*. (23) also found both AIx and PWV to be higher in 17 patients with diffuse SSc than in17 HC. Using ultrasono-

graphic methods to measure arterial stiffness, Turiel *et al*. (24) and Piccione *et al*. (25) found PWV to be higher in patients with SSc than HC, whilst Liu *et al*. (26) found regional differences in PWV, with elevation at the forearm and arm, but no difference at the upper arm, aorta or leg. Several other studies have found no elevation of arterial stiffness in SSc patients (27-30). These studies have all been limited by small sample size. Our study with matched controls was roughly equivalent in size to the largest studies performed to date (22, 28, 30). Furthermore, our groups were well-matched, with no significant differences in age, sex, hypertension, hypercholesterolaemia, diabetes mellitus, smoking or family history of coronary heart disease. There was, however, a significant difference in BMI between our two groups, with a lower BMI in SSc patients (24.7 *vs*. 28.0 kg/m^2 respectively, p=0.004). This is in keeping with our previous finding of significantly lower adjusted mean BMI in SSc patients from a large, nationwide study that compared SSc patients with HC drawn from a contemporaneous population-based study (4). As obesity is associated with increased arterial stiffness, lower BMI in SSc patients would be expected to decrease arterial stiffness in this group, or result in a smaller difference between patients and HC. In the current study, SSc patients also had a significantly higher mean heart rate than HC, however AIx measurements were standardised to 75 beats/min.

In Study 2, the association of age and BP with increased arterial stiffness was not surprising, given that these variables are known determinants of arterial stiffness. Likewise, the association of disease duration with PWV was not unexpected as we were hypothesising an association between SSc and arterial stiffness. The association between AIx and CCB therapy, however, was unanticipated, as CCBs act by decreasing peripheral arteriolar resistance. For example, both nifedipine and amlodipine have been shown to reduce central aortic pressures in subjects with hypertension (31, 32). We did not, however, have access to the indication for CCB therapy in our study, and as CCBs are first-line therapy for Raynaud's phenomenon, this may have been the primary indication in some patients. In support of this possibility, of the 36 SSc patients on CCB therapy, only 12 (33%) had a diagnosis of hypertension. The higher AIx observed in patients on CCB therapy, which was independent of measured blood pressure, could reflect the presence or severity of Raynaud's phenomenon in these patients, and potentially the indirect "upstream" effect of microvascular involvement on arterial stiffness. Unlike Timar *et al*. (22) who found an association between limited SSc and higher PWV, we did not find disease subtype to be associated with either parameter of arterial stiffness. Furthermore, we found no association between arterial stiffness and vascular manifestations of SSc, such as PAH or SRC. As there were only three patients with SRC, however, sample size may have limited our ability to demonstrate a statistically significant relationship. In addition, all patients with PAH were on pulmonary vasodilator therapy and this may have had an effect on their arterial stiffness. We did not find any association between inflammatory markers and arterial stiffness in our study. However, as SSc is a progressive condition in which skin manifestations can subside in later stages, inflammatory markers performed at a single point in time may not accurately represent the cumulative inflammatory burden to which an individual has been exposed.

Our study has a number of limitations. Although we were able to demonstrate a significant difference in AIx between patients and controls, it may be that sample size was insufficient to detect a difference in PWV. Furthermore, a larger sample size would have conferred greater power to detect additional associations between arterial stiffness and patient variables. Arterial stiffness is a surrogate marker of cardiovascular disease and as yet, no studies have examined whether arterial stiffness is predictive of cardiovascular events or mortality in patients with SSc. Similarly, no studies have examined the relationship of microvascular disease with macrovascular disease or arterial stiffness in SSc, as has been done in hypertension (18). Lastly, due to the cross-sectional nature of our study we were able to demonstrate association but not causality.

We found AIx to be elevated in SSc patients compared with HC. This suggests that patients with SSc may have an increased prevalence of subclinical atherosclerosis, however microvascular disease or myocardial dysfunction could also contribute to the observed abnormality. As AIx is a measure of arterial stiffness that encompasses factors such as reflectance point and left ventricular ejection, it may provide additional information regarding vascular dysfunction in SSc to PWV alone. We also found that age and systolic BP were independently associated with higher PWV; whilst age, disease duration and CCB therapy were independently associated with higher AIx. The latter relationship was unexpected, as CCB therapy decreases arterial stiffness in hypertensive individuals. Given that the most common indication for CCB therapy in SSc is Raynaud's phenomenon, the observed association with higher AIx could reflect a greater burden of microvascular disease, rather than atherosclerotic disease. Prospective studies in larger cohorts of patients are warranted to clarify this important point and also to determine the relationship of arterial stiffness with "hard" clinical endpoints such as cardiovascular events or mortality.

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