

Aortic pulse wave velocity measurement in systemic sclerosis patients

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SUMMARY

Background. Systemic sclerosis (SSc) is characterized by endothelial dysfunction and widespread microangiopathy. However, a macrovascular damage could be also associated. Aortic pulse wave velocity (aPWV) is known to be a reliable indicator of arterial stiffness and a useful prognostic predictor of cardiovascular events. Moreover, aPWV may be easily measured by non-invasive, user-friendly tool. Aim of our study was to evaluate aPWV alterations in a series of SSc patients.

Methods. The aPWV was evaluated in 35 consecutive female SSc patients and 26 sex- and age-matched healthy controls. aPWV alterations were correlated with cardiopulmonary involvement.

Results. A significant increase of aPWV was observed in SSc patients compared to controls (9.4 ± 3.2 m/s vs 7.3 ± 1 m/s; $P=0.002$). In particular, 14/35 (40%) SSc patients and only 1/26 (4%) controls ($P=0.0009$) showed increased aPWV (>9 m/s cut-off value). Moreover, echocardiography evaluation showed an increased prevalence of right atrial and ventricular dilatation (atrial volume: 23.6 ± 6.2 mL vs 20.3 ± 4.3 mL, $P=0.026$; ventricular diameter 19.5 ± 4.9 mm vs 15.9 ± 1.6 mm; $P=0.001$) associated to higher values of pulmonary arterial systolic pressure (PAPs) in SSc patients (31.5 ± 10.4 mmHg vs 21.6 ± 2.9 mmHg; $P<0.0001$; 40% of SSc patients showed an abnormal PAPs). Clinically, SSc patients presented a reduction of six-minute walking test (413 ± 96 m vs 491 ± 49 m; $P=0.001$), not correlated with pulmonary function tests. Increased aPWV values were evidenced only in SSc patients >50 years old. Furthermore, altered aPWV was more frequently associated with limited cutaneous pattern, longer disease duration (≥ 5 years), and/or presence of anticentromere antibody (ACA).

Conclusions. A significantly higher prevalence of abnormally increased aPWV was evidenced in SSc patients compared to healthy controls. The possibility of more pronounced and diffuse vascular damage in a particular SSc subset (ACA-positive subjects with limited cutaneous scleroderma and longer disease duration) might be raised.

Key words: Pulse wave velocity, scleroderma, systemic sclerosis, pulmonary arterial hypertension, arterial stiffness.

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INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disease characterized by abnormal production of fibrotic tissue in the skin and internal organs, and by endothelial dysfunction. The latter leads to a number of clinical manifestations, from Raynaud's phenomenon to pulmonary arterial hypertension. In this respect, an unbalance between vasodilator and vasoconstrictor agents secreted by endothelium can be

evidenced in scleroderma patients (1-3). Moreover, a stimulation of both the innate and adaptive immune responses coexists, resulting in B-cell and T-cell activation and, in many cases, autoantibody production (1). Inflammation leads to fibroblasts activation and to collagen deposition.

A diffuse vascular damage may be easily evidenced at capillary loops by means of nailfold capillaroscopy, as well as at large vessel wall where atherosclerotic changes may be shown, regardless the classical

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cardiovascular risk factors (4-6). Therefore, even though SSc was traditionally considered a disease involving the microvasculature, many studies have demonstrated an involvement of the whole vascular system (7-11).

In particular, an increased arterial wall stiffness and an impaired flow mediated dilatation have been shown at the carotid or brachial arteries (12, 13). Furthermore, more recent studies demonstrated a relevant prevalence of autopsy-proven macrovascular involvement in SSc patients, occurring in more than a decade earlier than the general population (4).

Currently, several non-invasive tools are available in clinical practice in order to study the vascular function, among them the pulse wave velocity measurement. This technique is based on a well-known physiologic principle: systolic contraction of the left ventricle causes pulse waves in the aorta wall, intensified by his elastic medial layer. The waves propagate to peripheral vessels through the main aortic branches, being reflected at the bifurcations. Therefore, a second reflected wave appears as a late systolic peak within the sphygmocardiogram waveform. The morphology of the sphygmocardiogram wave depends upon the stiffness of the artery walls (14, 15) since an increase in arterial stiffness is related to a proportional increase of the velocity of the wave propagation.

According to the classical formula $\text{velocity} = \text{distance}/\text{time}$, aortic pulse wave velocity (aPWV) may be easily obtained measuring the time of progression of the sphygmocardiogram wave on the aortic path length. In clinical practice, the length between the carotid and the femoral pulse locations is used to calculate aPWV. Given its high predictive value, simplicity, and reproducibility, the measurement of aPWV can be considered the gold standard in the evaluation of vessel wall elasticity (14, 15).

Aim of the present study is to evaluate aPWV in a series of unselected SSc patients compared to healthy controls, in order to define the actual prevalence of aortic wall stiffness and its possible correlations with typical SSc features.

■ PATIENTS AND METHODS

Patients

Thirty-five unselected female patients followed at our Rheumatology Centre and affected by SSc (mean age 56.9 ± 12.6 SD; disease duration 9.6 ± 5.4 SD years) were consecutively enrolled in the study from January to April 2010. All recruited female patients (out of our entire series of 300 SSc) were programmed to re-evaluate their heart involvement in that time period. Males were excluded in order to eliminate gender as confounding factor. All patients met the 1980 American College of Rheumatology Classification criteria for scleroderma (16); their clinico-serological features are shown in Table I. A series of 26 sex- and age-matched healthy individuals, consecutively evaluated for primary prevention at the cardiology unit of our hospital in the same period, were used as control group (Tab. I). These subjects presented one or more cardiovascular risk factor (hypertension, diabetes, hypercholesterolemia, smoke, high body mass index, familiarity for cardiovascular diseases), but did not refer any cardiovascular events previously. The study was approved by the local ethical committee and all patients gave their consent to participate to the study.

Methods

The aPWV measurement was performed in all SSc patients and controls at the time of cardiological evaluation. All instrumental examinations were performed by the same trained cardiologist (C.F.). In SSc patients, cardiological evaluation was routinely performed every year, including physical examination, ECG, echocardiography with pulmonary arterial systolic pressure (PAPs) assessment, 6-minutes walking test, and pulmonary function tests, including the measurement of diffusing capacity for carbon monoxide (DLCO) test. Moreover, control subjects underwent a careful clinical evaluation at cardiological visit, followed by instrumental examinations.

At the time of the study, urinalysis and blood chemistry, including blood cell counts, total cholesterol, HDL, triglycer-

Table 1 - Clinico-serological features and therapies of systemic sclerosis patients and healthy controls.

	SSc patients	Healthy controls	P value
Age (yrs)	56.9±12.6	56.5±11.7	ns
Disease duration (yrs)	9.6±5.4		
BMI	22.3±3.6	25±2.7	0.006
Hypertension	13/35	15/26	ns
Diabetes	0/35	0/26	ns
Dyslipidemia	8/35	2/26	ns
CVD familiarity	2/35	7/26	0.02
Smoke history	2/35	4/26	ns
Skin subsets (L/D); (L/I/D)	28/7; 22/6/7		
Autoantibodies (Sci70/ACA/ANoA/ANA)	13/9/7/5		
Digital ulcers	20/35		
Ca-channel blockers	24/35	6/26	0.0004
ACE-inhibitors	3/35	7/26	0.056
Sartans	2/35	5/26	ns
Statins	5/35	4/26	ns
Diuretics	4/35	7/26	ns
Beta-antagonists	0/35	5/26	ns
Prednisone (≤5 mg/day)	12/35	0/26	0.0008

SSc, systemic sclerosis; BMI, body mass index; CVD, cardiovascular diseases; skin subsets: L = limited, I = intermediate, D = diffuse; ACA, anticentromere antibodies; ANoA, anti-nucleolar antibodies; ANA, antinuclear antibodies.

ides, fasting glucose at the morning, creatinine, transaminases, and thyroid stimulating hormone were performed in both SSc patients and controls. The 6-minutes walking test was performed in a comfortable temperature-controlled (22-24°C) indoor floor, measuring the distance covered within 6 minutes, and the oxygen blood saturation at baseline and at the end of the test by using a handheld pulse oximeter. All echocardiograms are performed at the echocardiography clinic of our cardiology unit, by using a General Electric machine (Vivid E). M-Mode, B-Mode, Doppler, and Doppler tissue imaging were performed according to the guidelines of the American Society of Echocardiography (17). The exams included the estimation of PAPs, which was based on the peak velocity of the tricuspid regurgitation jet, using the simplified Bernoulli equation (18). The measurement of aPWV was performed in the supine position in a quiet, temperature-controlled room (22-24°C) in the early morning hours. Age, body weight, stature, and systemic arterial blood pressure, by using a sphygmomanometer, were previously collected. The distance between the carotid pulse and the femoral pulse loci was mea-

sured. To determine aPWV, two readings at the carotid artery and the femoral artery were sequentially obtained by using a tonometer (SphygmoCor® VX, AtCor Medical Pty Ltd., West Ryde, Australia). The registered waves were analyzed by an integrated software, and outputted on a laptop screen as the corresponding waveforms. A rapid sampling of the wave registered was automatically done to calculate a quality index (%) and to guarantee the intra-/inter-operator reproducibility. aPWV is obtained from the formula $velocity = distance/time$: the *distance* is the length between the carotid and the femoral pulse locations, while the *time* is measured by the tonometer.

Besides aPWV measurement, the following parameters were obtained: heart rate, main diastolic and systolic blood pressure, ejection length of left ventricle, width (mmHg) of incident wave, sub-endocardial viability ratio, aortic augmentation, and augmentation index (adjusted for heart rate 75 bpm). Among them, the latter is the pivotal parameter expressing the stiffness of the arterial walls (14). The systolic part of the central arterial wave is characterized by two pressure peaks, the first one caused by left ventricular ejection, while the second is the result of the pulse wave reflection. The sub-endocardial viability ratio indicates the ratio between availability and request of energy for the heart to pump.

Statistical analysis

Values are given as mean±SD for normally distributed variables, or as median (range) for not-normally distributed variables. To compare parameters from SSc patients and controls, Student's t test for normally distributed and Mann-Whitney u test for not normally distributed parameters were used. Chi-square with Pearson's correction was used for binomial variables, while the linear regression was used for continuous variables. Fisher's exact test was performed for the statistical analysis among the SSc patients, and the multivariate logistic regression analysis was used to consider the eventual weight of the single scleroderma parameters. A P value ≤0.05 was considered statistically significant.

IBM SPSS® (IBM, Armonk, New York, USA) software version 17.0 was used for statistical analysis.

■ RESULTS

The aPWV measurements along with cardiovascular risk factors and echocardiography findings in SSc patients are shown in Table II. Compared to controls, no differences about the prevalence of arterial hypertension, diabetes, dyslipidemia, smoking habit, and cardiovascular diseases history were recorded. On the contrary, a significantly higher body mass index (BMI) (25 ± 2.7 vs 22.3 ± 3.6 ; $P=0.006$), as well as a cardiovascular disease familiarity ($7/26$ vs $2/35$; $P=0.02$) were observed in controls compared to SSc patients. As regards the ongoing treatments, only SSc patients were taking calcium-channel blockers ($24/35$) and steroids ($12/35$; average dosage 5 mg/day of prednisone (for few weeks only), while the use of angiotensin converting enzyme (ACE) inhibitors, sartans, statins, diuretics, and beta-antagonists was comparable in the two groups. None of scleroderma patients was receiving immunosuppressors, endothelin receptor antagonists, or phosphodiesterase inhibitors. The values of aPWV were statistically higher in SSc patients compared to controls (9.4 ± 3.2 SD vs 7.3 ± 1 SD m/s; $P=0.002$). Considering as cut-off 9 m/s (the median value of aPWV in scleroderma patients is 8.7 m/s), an abnormally high aPWV was detected in $14/35$ (40%) SSc patients and in only $1/26$ (4%) controls (Fisher's $P=0.0009$). The subject in the control group with altered PWV (9.1 m/s) is a 77 year-old female, with hypertension and hypercholesterolemia, and BMI 27.6.

The exclusion of SSc patients treated with steroids (12 patients) did not change the statistical difference between the two groups (aPWV 9.1 ± 2.7 for SSc vs 7.3 ± 1 for controls; $P=0.003$; aPWV > cut-off 9 m/s: $10/23$ SSc vs $1/26$ controls, $P=0.001$). The echocardiography evidenced several differences between SSc patients and controls; namely, an increased volume of the right atrium

(23.6 ± 6.2 mL vs 20.3 ± 4.3 mL; $P=0.026$) and the diameter of the right ventricle (19.5 ± 4.9 mm vs 15.9 ± 1.6 mm; $P=0.001$), an augmented prevalence of left ventricle hypertrophy ($20/35$ vs $3/26$; $P=0.0001$), and higher values of PAPs (31.5 ± 10.4 mmHg vs 21.6 ± 2.9 mmHg; $P<0.0001$). Fourteen SSc patients (40%) presented a PAPs > 35 mmHg. Moreover, evaluating the 6-minutes walking test, scleroderma patients showed a lower performance compared to controls (413 ± 96 SD vs 491 ± 49 SD m; $P=0.001$).

Among SSc patients, few clinico-serological features correlated with increased aPWV (Figs. 1 and 2). Firstly, aPWV strictly correlated with the patients' age, as expected ($R=0.669$; $P<0.0001$); indeed, all patients with abnormally increased aPWV were ≥ 50 years-old. In addition, even though a statistical significance was not found, SSc patients with longer disease duration tended to present aPWV alterations. In particular, abnormal aPWV was almost constantly observed in subjects with disease duration ≥ 5 years, except for one patient with recent SSc onset but concomitant hypertension and hypercholesterolemia.

As regards SSc cutaneous subsets, a trend ($P=ns$) to higher percentage of abnormal aPWV in limited SSc patients was recorded (Fig. 1); namely, considering the LeRoy division in two patterns (19), the 42% of limited SSc and the 9% of diffuse SSc patients presented abnormally high aPWV values. Instead, according to the three-pattern subsetting, 50% of limited, 33% of interme-

Table II - Instrumental findings in systemic sclerosis patients and healthy controls.

	SSc patients	Healthy controls	P value
aPWV (m/s)	9.4 ± 3.2	7.3 ± 1	0.002
Increased aPWV (>9 m/s)	$14/35$	$1/26$	0.0009
RV diameter (mm)	19.4 ± 4.9	15.9 ± 1.6	0.001
PAPs (mmHg)	31.5 ± 10.4	21.6 ± 2.9	<0.0001
PAPs ≥ 35 mmHg	$14/35$	$0/26$	0.0001
FVC%	87.3 ± 20.3		
DLCO%	47.2 ± 12.2		
6-minutes walking test (m)	413 ± 96	491 ± 49	0.0004

SSc, systemic sclerosis; aPWV, aortic pulse wave velocity; RV, right ventricle; PAPs, pulmonary arterial systolic pressure; FVC, forced vital capacity; DLCO, diffusing capacity for carbon monoxide.

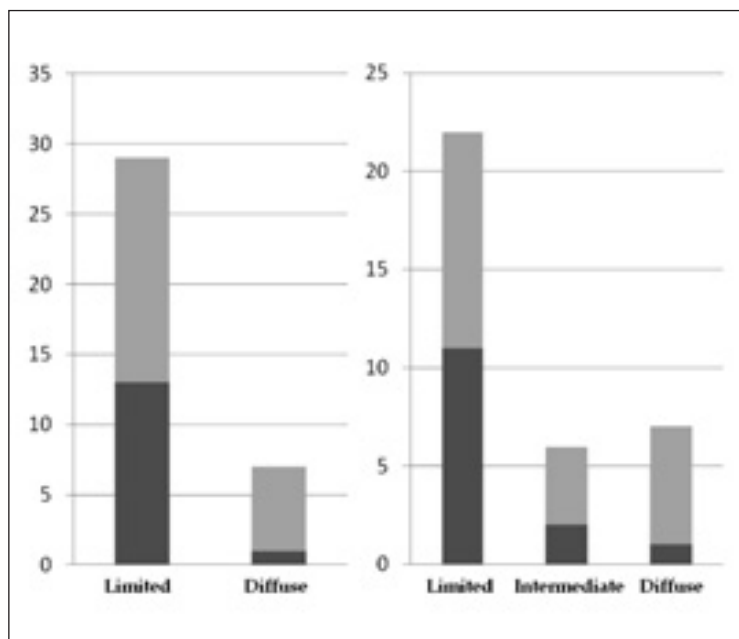


Figure 1 - Representation of systemic sclerosis patients divided for the cutaneous subsets, namely limited and diffuse (on the left) or limited, intermediate and diffuse (on the right). Systemic sclerosis patients with increased aortic pulse wave velocity are in black.

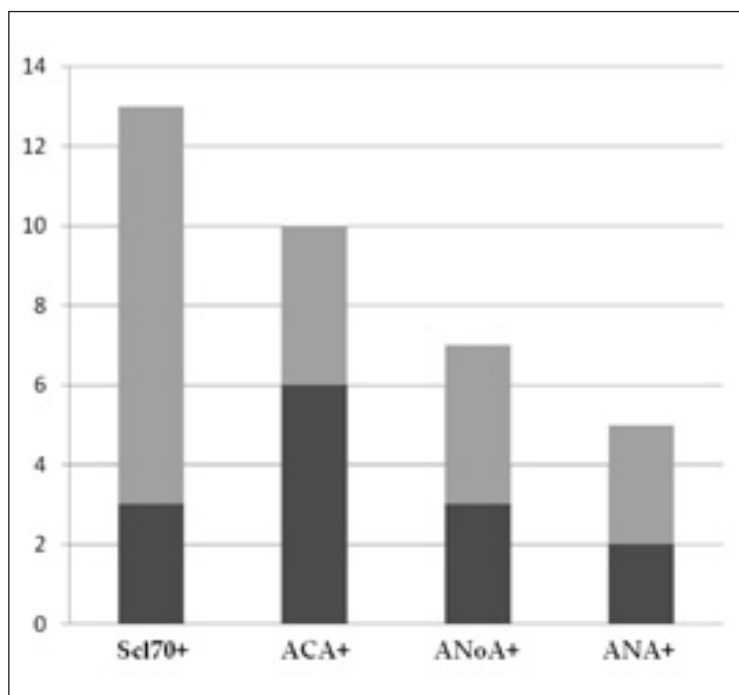


Figure 2 - Representation of systemic sclerosis patients divided for the presence of anti-Scl70, anti-centromere (ACA), anti-nucleolar (ANoA), and anti-nuclear (ANA) antibodies. Systemic sclerosis patients with increased aortic pulse wave velocity are in black.

diate, and 14% of diffuse SSc presented increased aPWV. An association between aPWV and specific SSc auto-antibodies was also found (Fig. 2); namely abnormally high values of aPWV were detected in 60% of patients with serum anticentromere antibody (ACA), compared to 23% of anti-Scl70-positive and 43% of antinucleolar-positive SSc patients ($P=ns$).

Finally, in SSc patients no correlations were found between aPWV alterations and presence/absence of digital ulcers, abnormal pulmonary function tests (forced vital capacity (FVC) <75% or DLCO<50%), abnormal PAPs, presence of cardiovascular risk factors (smoking habit, hypertension, diabetes, hypercholesterolemia, increased BMI), and treatments (ACE inhibitors, calcium-channel blockers, statins, steroids, and L-thyroxin).

■ DISCUSSION

The present study demonstrated an abnormally increased aPWV in SSc patients compared to controls. Besides the expected correlation between aPWV increase and the patients' age, a tendency to an association between aPWV alteration and limited cutaneous pattern of SSc and/or presence of circulating ACA was evidenced. The absence of statistical significance is possibly due to the low number of patients in different clinico-serological SSc subgroups. In this respect, it is well known that SSc patients with serum ACA and/or limited cutaneous involvement show an increased risk to develop peripheral vasculopathy, often complicated by severe digital ulcers (20-22). Our findings are consistent with those published by Timär et al. (10). In fact, the aPWV measurement in 50 SSc patients showed higher values in limited compared to diffuse cutaneous SSc subset, in addition to a direct correlation with age and disease duration. By contrast, the study by Cheng et al. (13) on 52 SSc patients revealed a lower arterial compliance and a higher stiffness in diffuse SSc. However, the evaluation was performed using real-time B-mode and M-mode images of

the motion of the arterial wall and intima-media thickness evidenced by echography. Again, a study by Wan et al., using the ankle brachial pressure index in SSc patients, suggested a lower median value of the index in ACA-positive patients, with increased prevalence of these subjects in the symptomatic group presenting intermittent claudication or distal amputations (23). The increase of aPWV in scleroderma was described by Cypiene et al. (8) studying a small series of 17 SSc patients compared to 34 healthy controls. The authors excluded individuals presenting diabetes, hypercholesterolemia, hypertension, renal disease, and current smoking history; only triglyceride concentration was significantly higher in SSc patients than in controls. Overall, our findings are consistent with this previous work. We did not exclude subjects presenting some known cardiovascular risk factors, but the larger number of patients enrolled in our study permitted to evaluate also the impact of these factors, as well as the difference between patient subgroups with/without increased aPWV and the possible relevance of ongoing therapies.

The lack of possible correlation between aPWV and complicating digital ulcers is worthy of attention. One reasonable explanation is that ischemic digital lesions may be considered a typical consequence of scleroderma microangiopathy, whereas increased aPWV is a direct expression of large artery involvement, mainly the aorta and its branches. Therefore, we can presume that digital ulcers and arterial stiffness are not clinically correlated, even though they may be the consequence of the same SSc pathogenetic process.

In our study, we observed the lack of correlation between aPWV increase and pulmonary hypertension, restrictive respiratory syndrome as expressed by FVC reduction, as well as DLCO-decrease. The lack of correlation of aPWV with pulmonary hypertension can be explained following the above considerations for peripheral vascular manifestations; namely, by taking into account the vascular districts involved characterized by different structural and physiological features.

As regards the lung function tests, particularly the DLCO, which is an indirect functional index of the alveolar oxygen exchange, the influence of several factors, mainly lung fibrosis and pulmonary hypertension, have to be considered; consequently, the correlation with aPWV increase seems to be quite improbable.

The aPWV is generally accepted as the gold standard measurement of arterial stiffness because it is a simple, noninvasive, and very reproducible method (14, 15); indeed, several studies support the usefulness of this tool as a good predictor of cardiovascular events (24, 25). A recent meta-analysis of 17 longitudinal studies evaluating 15,877 individuals with aPWV for a mean of 7.7 years found that the risk of cardiovascular events raises proportionally in a linear-like fashion of more than 40% for 1 standard deviation of increased aPWV (24).

Waveforms are obtained transcutaneously with a tonometer over the common carotid artery and the femoral artery; aPWV is calculated as the distance (metres) between the two recording sites out of the time delay (seconds) measured between the feet of the two waveforms. The pressure wave features are related to the left ventricular contraction strength, to the properties of the blood (*i.e.* viscosity), and to the characteristics of the arterial tree (14, 15). When the wave reaches branch points, which are areas of turbulence, it is reflected back to the heart. So, the final pressure wave is the sum of the forward and reflected waves. The aPWV measurement focuses on the aorta and its first branches, whose walls contains elastic fibres in the tunica media; these fibres are responsible for the peripheral propagation of the pulse that follows left ventricular contraction during systole. In the case of individuals with stiffness, arteries are less compliant, because elastin/collagen ratio is reduced. Therefore, the reflected wave returns to left ventricle sooner increasing cardiac workload and decreasing the pressure support for coronary perfusion (14). For this reason, arterial stiffness is considered a risk factor for cardiovascular events and aPWV measure-

ment affords useful information in patients considered with a high cardiovascular risk. Indeed, arterial stiffness is a pivotal feature of the artery involvement in course of diseases such as hypertension, diabetes, as well as for smoking habit (25). Also age has a clear effect on aPWV, since years of pulsatile stress lead to fragmentation of vascular elastin elements, accumulation of load-bearing collagen, and consequently vascular calcifications (15). In our study, older subjects consistently presented an augmented aPWV. However, in SSc patients aPWV was even higher compared to the age-matched controls, suggesting that SSc itself may be considered, as well as diabetes or hypertension, a cause of arterial stiffness.

Interestingly, the classical cardiovascular risk factors considered, SSc and control groups were not homogeneous: control subjects showed significantly higher BMI and familiarity for cardiovascular events. These differences further stress our findings since they should increase the percentage of elevated aPWV in controls. Obesity, in the absence of the traditional cardiovascular risk factors, is associated with increased aPWV, while a significant weight loss results in its improvement (26). On the other hand, SSc patients were treated with low-dosage of prednisone, so a negative metabolic effect of chronic steroid treatment could be presumable. However, in the present SSc series no patients showed clear steroid-related side-effects, possibly due to the short-term and low-dosage of steroid treatment. Conversely, the long-lasting treatment with steroids should be considered as a possible worsening co-factor for the arterial damage caused by the disease; anyway, the exclusion of SSc patients treated with steroids did not alter the statistical difference reported between patients and controls. The majority of our patients were treated with calcium-channel blockers, able to reduce arterial stiffness and to prevent its progression (27). Therefore, the prevalence of aPWV alterations might be somewhat underestimated in the present SSc series due to chronic usage of these drugs.

On the whole, our study demonstrated a clear-cut prevalence of abnormally increased aPWV in SSc patients compared to healthy controls, possibly related to large artery alteration due to scleroderma pathogenetic process. A more pronounced vascular damage is detectable in SSc patients with limited scleroderma, serum ACA, and/or longer disease duration. One possible limitation of the present study is the size of SSc series, which might reduce the statistical significance of aPWV alterations among clinico-serological disease subsets. The study of larger patients' series is required to confirm our preliminary findings.

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