

# Systemic sclerosis is not associated with clinical or ambulatory blood pressure

N.A. Zakopoulos, V.Th. Kotsis, E.J. Gialafos, C.M. Papamichael,  
V.Ch. Pitiriga, D.N. Mitsibounas, M.E. Mavrikakis

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*Department of Clinical Therapeutics, Alexandra Hospital, University of Athens,  
National and Kapodestrian University, Athens, Greece.*

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## Abstract

### Background

*Raynaud's phenomenon is often the first symptom and occurs eventually in more than 95% of patients with systemic sclerosis (SSc). Angiographic studies disclose narrowing and obstruction of the digital arteries, which on autopsy histologic study show prominent subintimal connective tissue proliferation without inflammation, as well as adventitial fibrosis. It is also known that primary cardiac problems include pericarditis, left ventricular or biventricular failure, serious supraventricular or ventricular arrhythmias emerge in patients with SSc. It is not known if these patients present hypertension or hypotension and which parameter of the ambulatory blood pressure may influence such a disease course.*

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### Methods

*A total of 85 subjects underwent clinical blood pressure (BP) readings, 24-hour ambulatory BP monitoring, left ventricular assessment by echocardiography and measurement of intima media thickness (IMT) of the right-left internal carotid arteries (RICA and LICA) and right-left common carotid arteries (RCCA and LCCA). The population consisted of 40 subjects with SSc according to the criteria of the American College of Rheumatology (SCL-group) who were not receiving any antihypertensive treatment and 45 healthy volunteers (control group). The two groups did not differ in age.*

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### Results

*Clinical systolic and diastolic blood pressure, clinical heart rate, mean 24h systolic blood pressure, SD systolic blood pressure, mean 24h diastolic blood pressure, SD 24h diastolic blood pressure, mean 24h heart rate, SD 24h heart rate, pulse pressure 24h, serum glucose, cholesterol, triglycerides, HDL, LDL, creatinine, urea, potassium and sodium did not statistically significant differ between the two groups. Furthermore, the left ventricular mass/BSA and IMT of both carotid arteries did not show a statistically significant difference between the groups.*

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### Conclusion

*Systemic sclerosis is not associated with clinical blood pressure or the parameter of 24h blood pressure monitoring.*

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### Key words

Scleroderma, ambulatory blood pressure monitoring.

Nikos A. Zakopoulos, Assoc. Professor, MD; Vasilios Th. Kotsis, MD; Elias J. Gialafos, MD; Christos M. Papamichael, MD; Vassiliki Ch. Pitiriga, MD; Myron E. Mavrikakis, Professor, MD.

Please address correspondence to: Vasilios Kotsis, MD, Department of Clinical Therapeutics, Alexandra Hospital, Vas. Sofias 80 and Lourou str., 11528, Athens, Greece. E-mail: kotsisva@hol.gr

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## Introduction

Raynaud's phenomenon is defined as episodic triphasic color changes (pallor, cyanosis, erythema) occurring in response to environmental cold and/or emotional stress. The prevalence of Raynaud's phenomenon in the general population is not precisely known but may be as high as 10-20%. Raynaud's phenomenon is often the first symptom and occurs eventually in more than 95% of patients with systemic sclerosis (SSc). Angiographic autopsy studies disclose narrowing and obstruction of the digital arteries, which on histologic study show prominent subintimal connective tissue proliferation without inflammation, as well as adventitial fibrosis. The fibrotic arteriosclerotic changes of the small artery and arteriole are omnipresent in the internal organs of patients with SSc. Myocardial involvement is present at autopsy in the majority of patients and is a principal determinant of survival in systemic sclerosis (1-6). Electrocardiographic abnormalities including atrial fibrillation and ventricular arrhythmias have been confirmed by ambulatory echocardiographic studies (7-14). Increased arterial stiffness has also been demonstrated in systemic sclerosis patients (15). Sudden onset of accelerated hypertension, rapidly progressive renal insufficiency, microangiopathic hemolysis, and thrombocytopenia in the setting of hyper-reninemia constitutes the syndrome of "scleroderma renal crisis" (16-18).

The aim of the present study was to estimate the presence of hypertension (possible dysregulation of vessel tone or distal vasoconstriction) or hypotension (possible dysregulation of the autonomic nervous system) in patients with systemic sclerosis. We also sought to determine which parameter of ambulatory blood pressure monitoring may be influenced in such patients with arteriosclerotic changes of the small artery and arteriole. We investigated the left ventricular structure and the intima media thickness of both carotid arteries of these patients.

## Subjects and methods

### Subjects

The study population consisted of 40

subjects with systemic sclerosis according to the criteria of the American College of Rheumatology. Patients did not receive any anti-hypertensive treatment or treatment withdrawals at least two week before ambulatory blood pressure monitoring. The control group consisted of 45 healthy volunteers. The two groups did not differ in age. All patients had granted their informed consent to participate in the study. All subjects underwent 24-hour ambulatory BP monitoring, left ventricular assessment by echocardiography and measurement of intima media thickness (IMT) of the carotid arteries. The two groups did not differ in age, sex, and serum glucose or cholesterol levels.

### Clinical blood pressure measurements

Blood pressure was measured 3 times using a mercury sphygmomanometer (standard cuff applied around the non-dominant arm and systolic and diastolic values identified from the first and fifth phase of Korotkoff sounds). During the measurements the participant remained seated with the arm comfortably placed at the heart level. The same doctor obtained all the sphygmomanometric measurements.

### Ambulatory BP monitoring

All subjects underwent 24h ABPM on a usual working day (19:00 – 20:00). They were instructed to act and work as normal. The Spacelabs 90217 ambulatory BP monitor (Spacelabs Inc., Redmond, Wash.) was used. The cuff was placed around the non-dominant arm and 3 BP determinations were made, along with sphygmomanometric measurements to verify that the average of the two sets of values did not differ by more than 5 mmHg. Readings were obtained automatically at 15-minute intervals throughout the 24h study period. All subjects included in the study had at least 3 valid readings per hour. The resulting 80 to 96 pairs of systolic and diastolic BP readings per recording, together with the corresponding time of measurement, were used to calculate the BP derivatives. All subjects were instructed to rest or sleep between 22:00 and 06:00 and to maintain their

usual activities between 06:00 and 22:00.

#### Ultrasound measurements

All participants were examined in the supine position with the head slightly elevated. The scans were performed with a high resolution Ultrasound-Doppler system (Acuson 128 XP, Mountain View, Calif.) using a 7 MHz linear transducer. Both carotid arteries were scanned longitudinally to visualize the intima-medial complex in the far wall of the artery. The best images of the far wall that could be obtained were used to determine the common and internal artery IMTs. The reading and analysis of the data were carried out as previously described (21).

Measurements were made on frozen images, magnified to standard size, on-line. The IMT value was defined as the mean of the right and left IMT-CCA or IMT-ICA, calculated from 10 measurements on each side, taken within 10 mm proximal to the carotid bifurcation. The lumen/intima leading edge (I line) to media/adventitia leading edge (M line) method was used. MICA was calculated as (RICA+LICA)/2 and MCCA was calculated as (RCCA+LCCA)/2 (21).

#### Echocardiography

All subjects underwent standard two-dimensional M-mode echocardiograms using a 3.5-MHz imaging transducer. Left ventricle dimensions were measured using the guidelines of the American Society of Echocardiography (22). The left ventricular mass was calculated according to an anatomically validated formula (23).

#### Statistical analysis

The SPSS (SPSS Inc., Chicago, IL.) statistical package was used to analyze the data. Standard descriptive statistics and the two-tailed Student's t-test were used.  $P < 0.05$  was considered statistically significant.

#### Results

The relevant data is listed in Tables I and II. The mean clinical systolic blood pressure, mean clinical diastolic blood pressure, and mean clinical heart rate

did not differ between the two groups. Furthermore, parameters of ambulatory blood pressure monitoring (mean 24h systolic blood pressure, SD of 24h systolic blood pressure, mean 24h diastolic blood pressure, SD of 24h diastolic blood pressure, mean 24h heart rate, SD of 24h heart rate, 24h pulse pressure) did not statistically differ. The haematocrit was significantly lower in patients with scleroderma but the white blood cell and platelet counts did not differ from the controls. Also the serum cholesterol level, or HDL, LDL and triglyceride levels did not differ, nor did the creatinine, urea, potassium and

sodium levels. The left ventricular mass normalized for body surface area and mean IMT of the common and internal carotid arteries did not differ between groups.

In order to obtain the nocturnal fall in systolic BP as a continue parameter we calculated the difference between the mean daytime minus night-time systolic blood pressure. The mean fall in nocturnal systolic BP for the control group was  $11.03 \pm 6.41$  and for SSc patients it was  $10.18 \pm 6.86$ . The difference in nocturnal systolic BP fall between the two groups was not statistically significant (24).

**Table I.** Parameters of ambulatory blood pressure monitoring.

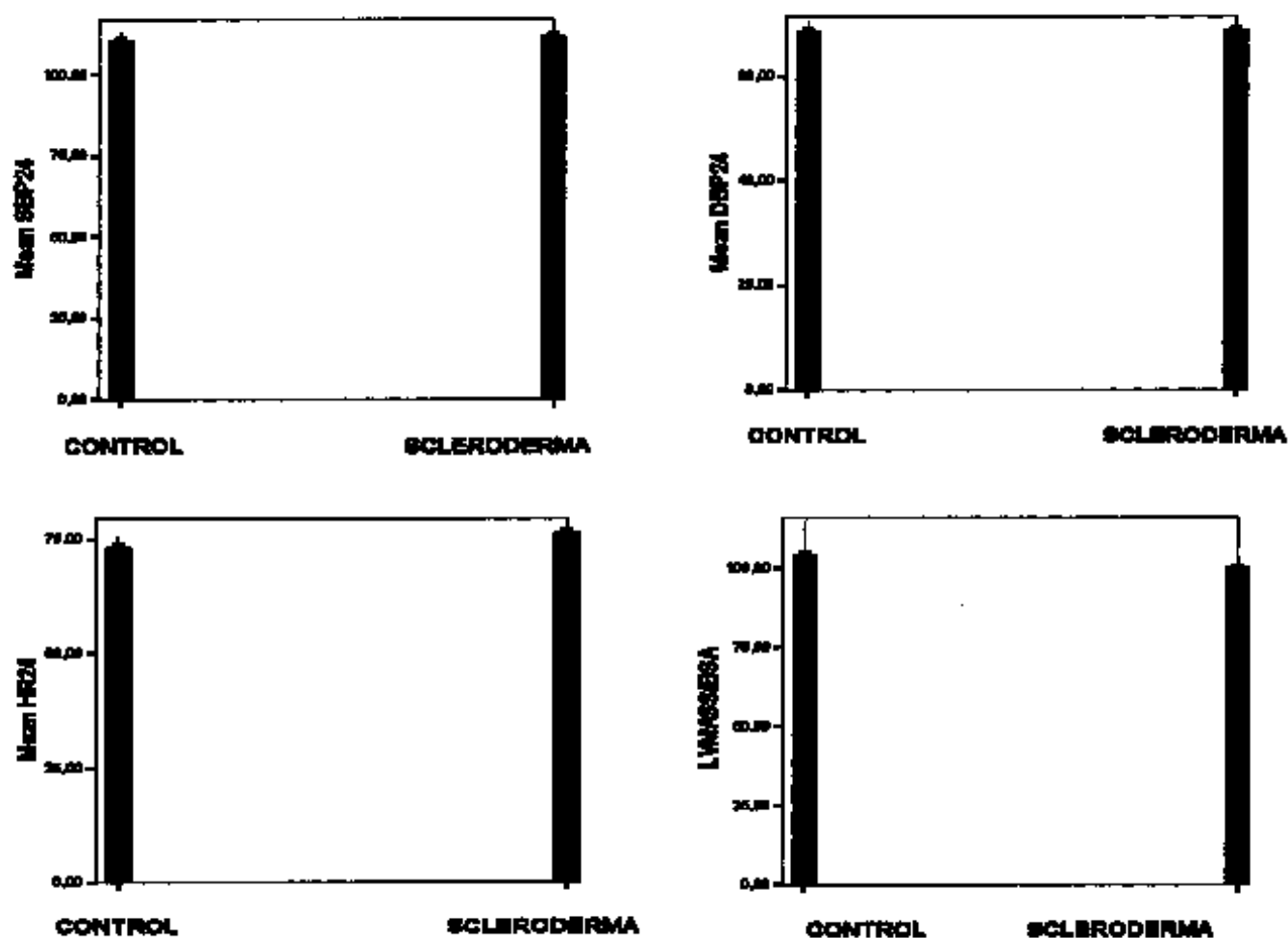
	Control		Scleroderma		P
	Mean	SD	Mean	SD	
CSBP (mmHg)	119.22	10.71	122.75	23.20	N.S.
CDBP (mmHg)	78.88	8.11	79.12	12.50	N.S.
Clinical heart rate (beats/min)	74.66	8.90	78.56	9.97	N.S.
SBP24 (mmHg)	110.35	8.66	111.89	14.27	N.S.
SD SBP24(mmHg)	12.48	2.67	12.84	3.69	N.S.
DBP24 (mmHg)	68.46	6.61	68.82	7.61	N.S.
SD DBP24(mmHg)	11.15	2.29	10.36	2.59	N.S.
HR24 (beats/min)	72.98	7.97	76.28	8.05	N.S.
SD HR24	12.46	3.75	12.37	2.55	N.S.
PP24 (mmHg)	40.93	9.16	41.99	12.49	N.S.

CSBP: clinical systolic blood pressure; CDBP: clinical diastolic blood pressure; SBP24: mean 24-hour systolic blood pressure; DBP24: mean 24-hour diastolic blood pressure; HR24: mean 24-hour heart rate; PP24: 24-hour pulse pressure.

**Table II.** Biochemical and ultrasonography profile of the systemic sclerosis patients and normal controls.

	Control		Scleroderma		P
	Mean	SD	Mean	SD	
Haematocrit (%)	41.18	4.82	36	3.78	0.001
White haemocyte ( $\text{mm}^{-3}$ )	7059	1382	7041	2343	N.S.
Platelets ( $\text{mm}^{-3}$ )	240555	47987	240214	90757	N.S.
Glucose (mg/dL)	97.77	17.29	116	62.98	N.S.
Cholesterol (mg/dL)	211.10	26.76	214.53	41.82	N.S.
Triglycerides (mg/dL)	94.55	39.22	111.13	53.94	N.S.
HDL (mg/dL)	55.96	12.35	51.23	14.21	N.S.
LDL (mg/dL)	132.34	28.87	143.07	37.13	N.S.
Creatinine (mg/dL)	0.87	0.10	0.79	0.12	N.S.
Urea (mg/dL)	35.91	7.79	30.16	9.59	N.S.
Potassium (mEq/L)	4.39	0.43	4.41	0.36	N.S.
Sodium (mEq/L)	140.85	2.23	141.76	2.94	N.S.
LVMA/BSA ( $\text{g}/\text{m}^2$ )	104.10	23.23	99.67	18.57	N.S.
MCCA	0.59	0.10	0.69	0.25	N.S.
MICA	0.59	0.12	0.59	0.15	N.S.

LVMA/BSA: left ventricular mass/body surface area; MCCA: mean IMT of common carotid arteries; MICA: mean IMT of internal carotid arteries.



**Fig 1.** Mean 24-hour systolic and diastolic blood pressure; mean 24-hour heart rate and left ventricular mass normalized for body surface area between control subjects and patients with scleroderma.

All subjects were classified into groups by their nocturnal systolic blood pressure fall (extreme-dippers had a  $\geq 20\%$  nocturnal systolic BP fall; dippers had a  $10\%$  but  $< 20\%$  fall; non-dippers a  $0\%$  but  $< 10\%$  fall; and reverse-dippers a  $< 0\%$  fall) (24). No difference in the dipping status was found between controls and SSc patients.

We also examined any possible correlation between the duration of the SSc and blood pressure and cardiovascular parameters. No correlation was found between the disease duration and clinical BP measurements, ambulatory BP measurements, left ventricular mass/BSA or IMT of the carotid arteries.

Systemic sclerosis patients were also divided into two subgroups, those with CREST syndrome ( $n = 15$ ) and those with diffuse systemic sclerosis ( $n = 30$ ). No difference was found between clinical

BP measurements, ambulatory BP measurements, left ventricular mass/BSA and IMT of the carotid arteries between CREST syndrome patients and those with diffuse systemic sclerosis.

### Discussion

We investigated the possible differences of clinical blood pressure, ambulatory blood pressure, ambulatory heart rate, left ventricular mass index and IMT of the carotid arteries between patients with scleroderma and healthy volunteers. We found that SSc patients did not show a statistically significant difference in clinical blood pressure or ambulatory blood pressure from controls. This finding is useful because these patients need to take drugs with peripheral vasodilatation that also have an antihypertensive effect. The use of those drugs may cause hypotension. The

drug should be chosen with care with regard to the duration and the strength of its action. The onset of hypertension in SSc patients who did not present with hypertension before should lead the clinician to investigate for a possible scleroderma renal crisis.

In most people, blood pressure displays a characteristic diurnal pattern, with a decline during sleep and a sharp increase around the time of awakening. The diurnal 24-hour circadian rhythm includes an early morning surge of blood pressure (morning peak), a smaller increase in blood pressure in the afternoon (evening peak), and a nocturnal blood pressure fall (25,26). Our two groups, the controls and the SSc patients, both showed a normal 24-hour circadian blood pressure rhythm (Fig. 2).

It is interesting to note that our study

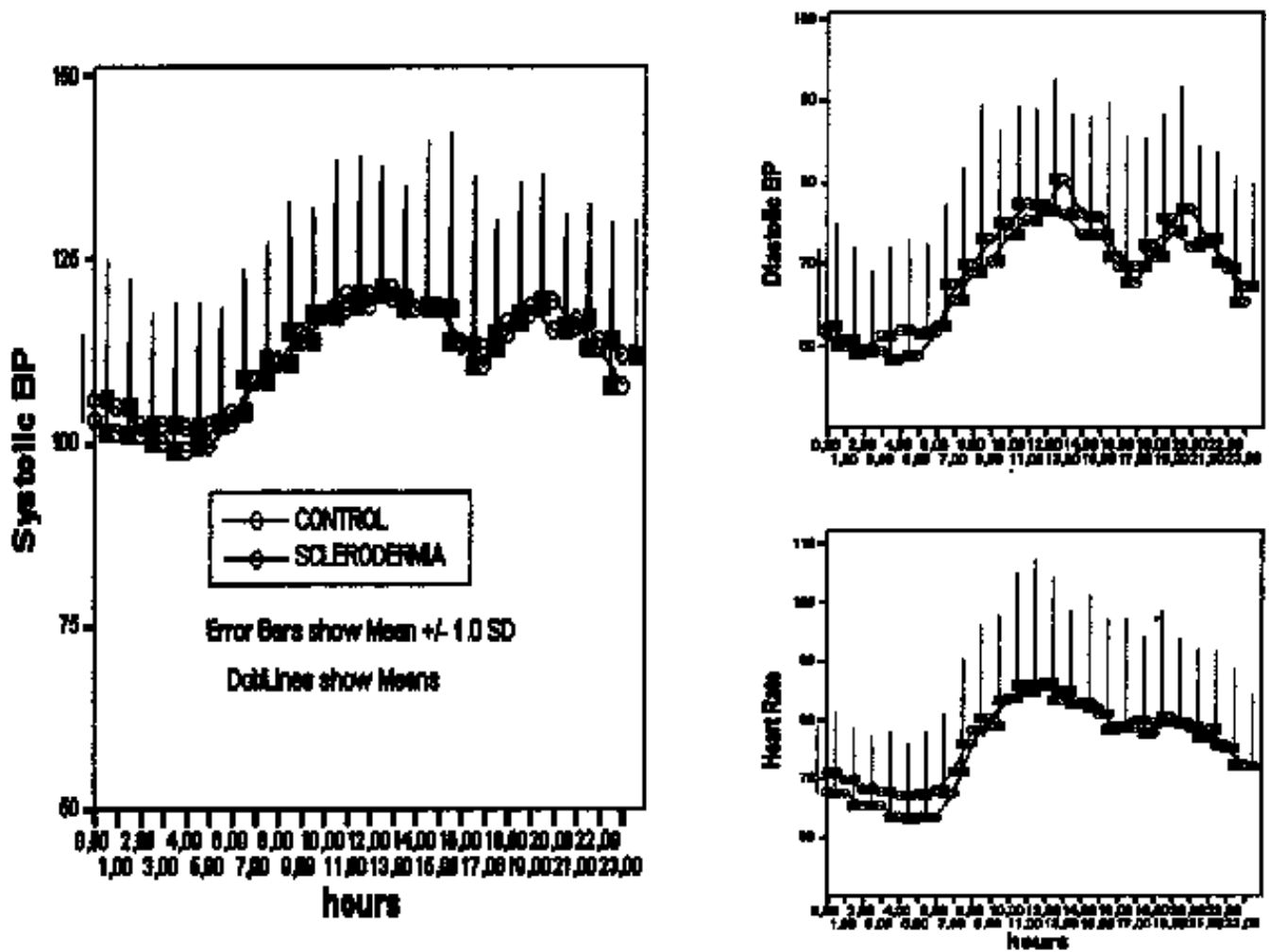


Fig 2. Circadian 24-hour profiles of the systolic and diastolic blood pressures and heart rate between control subjects and patients with scleroderma.

found no differences in the left ventricular mass index between the two groups. Left ventricular mass is an index of total cardiovascular morbidity and mortality. One could hypothesize that in patients with a high incidence of atrial fibrillation and other arrhythmias, the left ventricle could be influenced. It seems that the damage may not involve the myocardial tissue but the stimulus system of their heart. Fibrosis of the heart conduction system or dysfunction of the autonomic nervous system may possibly be involved (27).

We also found that the IMT of the carotid arteries did not differ between the two groups. Carotid IMT is a marker of vessel endothelium atherosclerosis. It is influenced by factors that act in the vessel wall such as cholesterol and blood pressure. It seems that narrowing

and obstruction of the arteries, which on autopsy histologic study show prominent subintimal connective tissue proliferation without inflammation, as well as adventitial fibrosis did not involve the carotid arteries of these patients. It is possible that the medial and large size arteries are not influenced.

In this study we investigated the 24h ambulatory blood pressure, monitoring the circadian and mean blood pressure of untreated patients with systemic sclerosis. We found no differences in blood pressure between control patients and patients with scleroderma. More studies must be carried out in SSc patients being treated with peripheral vasodilatation drugs, including studies of the circadian blood pressure rhythm over the course of the year in those patients.

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