Reduction of carotid baroreceptor sensitivity in systemic sclerosis

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Abstract

Objective

Systemic sclerosis (SSc) is an autoimmune disease characterised by diffuse vasculopathy and fibrosis of skin and visceral organs. Moreover, autonomic dysfunction is also suggested as an important step during the multifactorial SSc pathogenesis. Baroreceptors are responsible for maintaining blood pressure by means of autonomic system modulation. Considering that autonomic dysfunction and arteriosclerosis can both reduce baroreceptor sensitivity (BRS), in this cross-sectional study we investigated BRS in SSc patients.

Methods

Twenty-one SSc patients (mean age 55±10 years, 18 females) and 147 age/sex-matched healthy controls were recruited for the study. BRS (ms/mmHg) was measured by a Finapres® Midi device (Finapres Medical Systems, Amsterdam, The Netherlands). Other parameters were measured: blood pressure, heart rate, heart rate variability triangular index (HRVI), intima-media thickness (IMT), carotid distensibility and pulse wave velocity (PWV).

Results

BRS was significantly lower in SSc patients compared to controls (6.3±3.3 vs. 10.7±6.8 ms/mmHg; p=0.004). IMT was comparable between SSc and controls, whereas carotid distensibility was lower in SSc (20.1±7.6 vs. 26.6±13.3 KPa-1·10-3; p=0.02) and PWV higher in SSc (8.4±1.3 vs. 7.1±1.1 m/sec; p=0.01). Furthermore, HRVI was lower in SSc (4.5±2.1 vs. 7.5±2.8; p<0.001). BRS impairment was independent from age and carotid distensibility in SSc patients, suggesting that BRS dysfunction could be only partially a consequence of SSc vasculopathy.

Conclusion

BRS was reduced in SSc patients compared with healthy controls. This finding could represent a SSc-related alteration involving the autonomic system, besides being the mere consequence of sclerodermic vasculopathy.

Key words

scleroderma, systemic sclerosis, baroreceptors, baroreflex, dysautonomia, vasculopathy

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Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterised by fibrosis of skin and visceral organs and diffuse vasculopathy. The latter is determined by endothelial dysfunction with prominence of vasoconstriction and widespread microangiopathy. The final consequences are tissue ischaemia (1) and accelerated atherosclerosis involving also the large vessels (2).

Moreover, a pathogenetic role of the autonomic system dysregulation was also suggested, even though the mechanisms underlying dysautonomia were not yet clearly understood (3-5). In SSc, previous studies described an imbalance between sympathetic and parasympathetic tones, with overactivity of the former and dysfunction of the latter (6-10). Indeed, the clinical importance of dysautonomia may be shown by typical SSc features, such as gastrointestinal dysmotility and arrhythmias.

Both endothelial dysfunction and dysautonomia were already reported in the early phase of SSc, suggesting their roles in SSc pathogenesis. Raynaud's phenomenon, which generally characterises early SSc, may be the result of both imbalance between vasoconstrictor/vasodilator agents and sympathetic/parasympathetic modulation (3, 8).

Subclinical atherosclerosis may be easily assessed by measuring intima-media thickness (IMT) by means of echographic evaluation of the common carotid artery (1, 2). Moreover, the vascular stiffness may be studied by the measurement of the pulse wave velocity (PWV), that is the velocity of propagation of the pressure wave from the left ventricle to the peripheral vessels. In fact, the reduction of arterial compliance determines an increased speed at which the pressure wave moves (1, 2).

In literature, sclerodermic dysautonomia was studied through the analysis of heart rate variability (HRV), considering the relevant role of the autonomic system in the control of heart rate and the feasibility of its analysis (9-16). HRV and blood pressure modulation are controlled by the baroreceptor reflex.

Baroreceptors are stretch-sensitive mechanoreceptors placed in the carotid sinuses and aortic arch. The study of the sensitivity of carotid baroreceptors may be easily conducted and it has been proven to be useful in stratifying patients for cardiovascular risk (17, 18). In SSc, baroreflex sensitivity (BRS) could represent a useful target for the study of dysautonomia. Furthermore, it may be assumed that SSc-related vasculopathy can impair BRS as it happens in atherosclerotic patients. For these reasons, we aimed to evaluate BRS in SSc, in comparison with healthy controls, in order to characterise both autonomic dysfunction and large vessel vasculopathy.

Patients and methods

Patients

In this cross-sectional study, we included consecutive SSc patients classified according to the 2013 ACR/EULAR criteria (19) and referred to the Rheumatology Clinic of the Cannizzaro hospital or to the Rheumatology Unit of the ARNAS Garibaldi hospital, both in Catania, Italy.

The SSc group was paired with a control group of the same ethnicity matched for age and sex, recruited from a community database and with an available non-invasive BRS study.

The clinical records of SSc patients included demographic, clinical, laboratory and instrumental features. In particular, data on lung [spirometry, DLCO measurement, chest high-resolution computed tomography (HRCT)] and heart (ECG, echocardiography) involvements were previously collected. Moreover, complete blood counts, indices of liver and renal functions, autoantibody profiles and plasma NT-proBNP were available for all SSc patients.

Patients with SSc and controls affected by diseases associated with arterial stiffening [diabetes, chronic kidney disease, dyslipidaemia, stroke, ischaemic heart disease and current or former tabagism were excluded from this study. Furthermore, we excluded the subjects who took drugs that could potentially modify vascular function (*i.e.* antihypertensive drugs), with the exception of calcium channel blockers used for Raynaud's phenomenon in SSc. In the case of patients treated with

prostanoids, the study was performed at least 3 weeks after the infusion.

All patients gave their informed consent to the study, which was carried out in accordance with the ethical standards of 1964 Helsinki Declaration and its later amendments, and approved by the local Ethis Committee.

Methods

All participants were studied between 09:00 and 11:00 a.m. while fasting, in a centralised vascular laboratory by an expert operator (LZ) blinded to the patients clinical data and in a quiet room with a controlled temperature of 22±1°C. The patients refrained from caffeine, alcohol and exercise before the study from at least 12 hours. After 15 minutes of rest in a supine position, brachial blood pressure was measured three times, 2 minutes apart, using a validated oscillometric device (Spacelabs 90217 ambulatory blood pressure monitor; Issaquah, WA, USA) (20). The mean value of the last two measurements was used in this study. BRS was evaluated using a non-invasive method, by means of the Finometer® Midi device (Finapres Medical System, Amsterdam, The Netherlands). We recorded R-R intervals and beat-to-beat finger blood pressure for 5 min, during which patients were instructed to breathe spontaneously (range, 10-18 breaths/min) and to refrain from sleeping or speaking. Mean BRS was calculated by the device from 256 consecutive beats (21). As the primary endpoint of this study, we considered an outcome of interest the report of a significant reduction of BRS in SSc patients in comparison with healthy controls.

R-R intervals were also analysed by Kubios HRV v.2.2 software (Biosignal Analysis Medical Imaging Group, Kuopio, Finland) in the frequency domain through power spectral analysis for the assessment of the sympathetic/parasympathetic balance, calculated as the low frequency (0.04-0.15 Hz) to high frequency (0.15–0.40 Hz) power ratio (LF/HF ratio) (22), and in the time domain for the calculation of the heart rate variability triangular index (HRVI) (23).

A carotid study was performed, as previously reported (24). Longitudinal B-mode (60 Hz, 128 radiofrequency lines) and fast B-mode (600 Hz, 14 radiofrequency lines) images of the right common carotid artery 2 cm below the carotid bulb were obtained using a high-precision echo tracking device (MyLab One; Esaote, Maastricht, The Netherlands) equipped with a high-resolution (13 MHz) linear-array transducer. The diastolic internal diameter (Dd) and IMT (B-mode), as well as the stroke change in diameter (fast B-mode) were measured online in the right common carotid artery. The right arm radial pulse wave profile was recorded by applanation tonometry (SphygmoCor system®, AtCor Medical, Sydney, Australia) after recalibration with brachial mean blood pressure (MBP) and diastolic blood pressure (DBP) in the contralateral arm and was used to calculate carotid pulse pressure (PP). Brachial MBP was calculated as brachial DBP + 1/3 × brachial PP. The carotid PP was used for the calculation of carotid stiffness indexes (25). The carotid distensibility, defined as the relative change in luminal area (ΔA) during systole for a given pressure change was calculated as previously described, assuming the lumen to be circular (24), using the following equation: carotid distensibility = ΔA/A x carotid PP.

Finally, the carotid-femoral PWV was measured with a SphygmoCor device (SphygmoCor system®, AtCorMedical, Sydney, Australia) as previously reported (25), using the foot-to-foot velocity method, the intersecting tangent algorithm and the direct distance between the measurement sites (26): aPWV (m/s) = 0.8 × [carotid-femoral direct distance (m)/Δt]; bPWV (m/s) = 0.8 × [carotid-radial direct distance (m)/Δt]. The mean value of two consecutive recordings was used for this analysis. When the difference between the two measurements was ≥0.5 m/s, a third recording was performed, and the median value was used.

Table I. The findings in the SSc group and healthy controls.

Parameters	Healthy controls (n=147)	Systemic sclerosis (n=21)	*p*-values
Mean age (SD), years	53 (12)	55 (10)	0.42
Females, %	95	95	1.00
Body mass index, kg/m2	25 (4.3)	23.6 (3.5)	0.15
Mean systolic BP (SD), mmHg	123 (18)	120 (19)	0.45
Mean diastolic BP (SD), mmHg	74 (9)	68 (9)	0.003
Mean heart rate (SD), b/m	66 (10)	66 (9)	0.87
Mean PWV (SD), m/s	7.7 (1.1)	8.4 (1.3)	0.01
Mean AI% (SD), %	28 (13)	38 (7)	0.002
Mean IMT (SD), μm	652 (133)	693 (131)	0.18
Mean distensibility (SD), $KPa^{-1} \cdot 10^{-3}$	26.6 (13.3)	20.1 (7.6)	0.02
Mean BRS (SD), ms/mmHg	10.7 (6.8)	6.3 (3.3)	0.004
Mean HRVI (SD)	7.5 (2.8)	4.5 2.1)	<0.001

SD: standard deviation; BP: blood pressure; PWV: pulse wave velocity; AI: augmentation index; IMT: intima-media thickness; BRS: baroreceptor sensibility; HRVI: heart rate variability triangular index.

Statistical analysis

Statistical analysis was performed using NCSS 2007 and PASS 11 software (Gerry Hintze, Kaysville, Utah, USA).

All continuous variables are presented as mean± standard deviation (SD), after confirming their normal distribution by means of the Kolmogorov-Smirnov test; categorical variables are presented as a percentage value.

Clinical and haemodynamic variables were compared using analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables. A Spearman linear regression analysis was also performed to verify the existence of any significant correlation between two quantitative variables. *p*-values <0.05 were considered statistically significant.

Results

In this cross-sectional study, we enrolled 21 consecutive SSc patients (M/F 1/20; mean age 55±10 years; mean disease duration from the first non-Raynaud SSc feature 9±5 years). Two SSc patients presented a diffuse

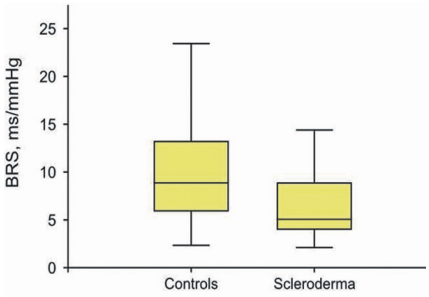

Fig. 1. Baroreceptor sensibility (BRS) in SSc patients and healthy controls. The values were significantly lower in SSc patients than in controls (p=0.004).

skin subset, 10/21 digital ulcers in their clinical histories, none pulmonary arterial hypertension according to the DETECT algorithm (27). One patient developed a renal crisis after the study, and 10 showed interstitial lung disease at the chest HRCT. At echocardiography. none of the SSc patients showed signs of systolic right (*i.e.* tricuspid annular plane excursion >20 mm) or left (*i.e.* ejection fraction >50%) ventricular dysfunction, nor moderate-severe diastolic dysfunction (*i.e.* E/A ratio <0.8). Three SSc patients were treated with mofetil mycophenolate, while none with medium-high dosage of steroids (>7 mg/day of prednisone).

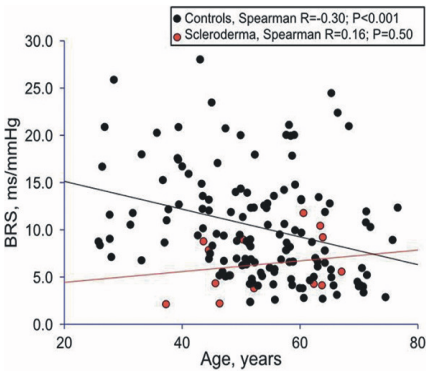

Fig. 2. Relationship between age and BRS in SSc patients and healthy controls.

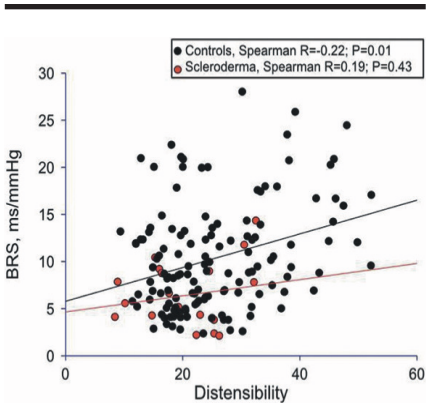

Fig. 3. Relationship between carotid distensibility and BRS in SSc patients and healthy controls.

The SSc series was paired with a control group of 147 subjects (7 controls/1 patient) of the same ethnicity, matched for age and sex. No significant differences about body mass index between SSc patients and controls were noted.

The present study showed several differences between SSc patients and controls (Table I). BRS was significantly lower in SSc than controls (6.3±3.3 *vs.* 10.7±6.8 ms/mmHg; p=0.004; Fig. 1). SSc patients presented more pronounced vascular alterations than controls. PWV and augmentation index were significantly higher, and IMT tended to be thicker in sclerodermic patients. Moreover, carotid distensibility was significantly lower in SSc than controls (Table I).

Even dysautonomia was more evident in SSc, in fact HRVI was significantly lower in SSc patients than in controls. Instead, the mean heart rate at rest was the same between the two groups.

Of note, diastolic blood pressure was lower in SSc, likely as a consequence of the use of vasodilators (*i.e.* calcium channel blockers prescribed for Raynaud's phenomenon).

Interestingly, a linear regression plot between BRS and age showed a strong inverse correlation only in controls, whereas the relationship was absent in SSc (Fig. 2). As expected, ageing vasculopathy is able to reduce the function of carotid baroreceptors, with consequent reduction of BRS in the elderly. On the contrary, SSc patients showed impaired BRS at any age, suggesting a role of SSc in the impairment of BRS.

Consistently, the significant relationship between carotid distensibility and BRS observed in controls was not confirmed in SSc (Fig. 3). Indeed, BRS reduction is directly correlated with the impairment of carotid distensibility, a sign of structural vasculopathy. Instead, in SSc, low BRS values seemed to be determined by factors other than vascular deterioration in SSc. On the other hand, it cannot be excluded that the small sample size of SSc patients might have affected the findings.

Discussion

In the present study, we evaluated BRS and several regions of the arterial bed in SSc patients versus healthy controls. Our findings showed significant alterations in SSc patients, namely elastic arteries of sclerodermic cases were more rigid than controls, as shown by significantly higher aortic PWV and AI, and lower distensibility in the former group. Furthermore, lower HRVI suggested dysautonomia in SSc. Finally, BRS was significantly lower in patients with SSc, independently from age, suggesting a direct pathogenetic role of SSc, besides the physiological vascular ageing evidenced in healthy controls.

BRS may be considered the crossroad of vascular and autonomic alterations, because both vasculopathy and dysautonomia can impair the baroreflex function (28-30). Interestingly, in our SSc series, BRS values did not correlate with vascular parameters, differently from controls, suggesting that SSc could directly lead to baroreflex dysfunction. In this regard, carotid baroreceptors modulate blood pressure by controlling the heart rate through the autonomic system. Therefore, SSc dysautonomia may be pathogenetically involved in BRS alterations.

Our findings are consistent with literature as regards SSc vasculopathy of large arteries. Several studies demonstrated increased aortic stiffness in SSc, by means of aortic PWV study, carotid IMT measurement or flow-mediated dilation (FMD) investigation (2, 31, 32). However, the pathogenesis of SSc macrovascular alterations is not clearly understood, even though a role of endothelial dysfunction (and, consequently, functional arterial stiffening) was postulated.

Previous studies evidenced dysautonomia in SSc, especially impaired parasympathetic activity, even though the methods used were heterogeneous and lacking standardisation (3-16). Moreover, the wide variability of SSc patient characteristics could explain the large differences in the incidence reporting of SSc autonomic dysfunction. Autonomic dysfunction is supposed to start earlier in SSc, as evidenced by the presence of Raynaud's phenomenon

even before the disease onset. Consistently, the study by Masini *et al*. (33) did not find correlation between SSc dysautonomia and disease duration, as well as in the present study.

The study of SSc dysautonomia should be considered important, since cardiac autonomic dysfunction correlates with the appearance of potentially malignant ventricular arrhythmias (9, 16, 34), thus predicting mortality of SSc patients. Furthermore, an early diagnosis of dysautonomia could be crucial for guiding disease management.

To the best of our knowledge, this is the first study evaluating BRS through the Finometer® Midi device in SSc patients. Moreover, in literature, only Bajocchi *et al*. (35) evaluated the baroreceptor sensitivity in a series of 12 SSc patients in 2009, without finding any abnormalities, probably because of the low number of cases and/or differences in SSc subsets. On the other hand, HRVI or PWV were investigated in previous studies (9-16,31). Both the 2 techniques showed alterations in SSc, namely lower HRVI and higher PWV in sclerodermic patients than controls, demonstrating the coexistence of large vessel vasculopathy and dysautonomia. To this purpose, BRS evaluation could be considered a rapid, synoptic view of SSc vascular and autonomic alterations. Subsequently, other instrumental evaluations, such as PWV and HRVI measurements, may better define the abnormalities found. Ultimately, selected parameters of endothelial dysfunction may contribute to better characterise SSc patients' vasculopathy, in order to permit a more tailored therapeutic regimen (36, 37).

Our study has a limitation: it is a pilot study including a small number of SSc patients. Therefore, these preliminary findings should be confirmed in larger studies. Nonetheless, our case-control study design allowed us to obtain statistically significant results.

In conclusion, we studied vascular and autonomic function in a series of SSc patients in comparison with healthy controls. Several parameters, including BRS evaluation with an innovative tool, showed both large vessel vasculopathy and dysautonomia in SSc. Therefore, we suggest including a complete work-up of vascular and autonomic functions in SSc, in order to obtain an adequate stratification of their cardiovascular risk.

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