Pulmonary Arterial Hypertension in Systemic Sclerosis Is Associated with Profound Impairment of Microvascular Endothelium-dependent Vasodilatation

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ABSTRACT. ***Objective.*** Impaired microvascular function may contribute to organ complications in patients with systemic sclerosis (SSc). We investigated whether SSc patients with and without pulmonary arterial hypertension (PAH) show a graded impairment of microvascular function compared to healthy controls.
Methods. Twenty-two patients with SSc and 22 controls were studied. All patients underwent right heart catheterization; 6 had no PAH (SSc-nonPAH) and 16 had PAH (SSc-PAH). Acetylcholine (ACh)-mediated endothelium-dependent vasodilatation and sodium nitroprusside (SNP)-mediated endothelium-independent vasodilatation were assessed by iontophoresis combined with laser Doppler flowmetry.
Results. Compared to sex- and age-matched controls, ACh-mediated vasodilatation was reduced in SSc-PAH (340.4% vs 79.5%, respectively; $p < 0.01$), but not in SSc-nonPAH (340.4% vs 397.9%; $p = 0.90$). No significant differences were present between the groups in SNP-mediated vasodilatation.
Conclusion. Systemic microvascular endothelium-dependent vasodilatation is markedly reduced in SSc complicated by PAH. (J Rheumatol First Release Dec 15 2011; doi:10.3899/jrheum.110397)

Key Indexing Terms:
SYSTEMIC SCLERODERMA PULMONARY HYPERTENSION
MICROVESSELS ENDOTHELIUM VASODILATION

Systemic sclerosis (SSc) is characterized by microvascular abnormalities, some of which may be present years before a diagnosis of SSc is made[1,2]. These microvascular changes are thought to constitute an important mechanism underlying SSc-associated organ involvement, such as pulmonary arterial hypertension (PAH). PAH is a devastating complication of SSc, affecting an estimated 12% of patients with systemic sclerosis (SSc)[3].

We and others have shown that in the systemic circulation the extent of structural capillary rarefaction, i.e., a decrease in capillary density, is associated with the presence and severity of PAH in SSc[4,5]. However, it is unclear whether PAH in patients with SSc is also associated with systemic functional derangements, i.e., impairment of microvascular endothelium-dependent and/or -independent vasodilatation. More knowledge of the microvascular involvement may illuminate the complex pathophysiology of SSc-associated organ damage, including PAH. Thus, assessment of microvascular function may identify those patients with SSc at risk of progression to PAH.

In a group of patients with SSc who had not been exposed to PAH treatment, and in whom PAH was diagnosed or excluded by means of right heart catheterization (RHC), we assessed whether a graded impairment of endothelium-dependent and -independent vasodilatation was present in patients with and without PAH compared to healthy controls.

MATERIALS AND METHODS

Subjects. Consecutive patients with SSc admitted to the Pulmonology Department for evaluation of dyspnea and suspected PAH between June 2007 and February 2010 were recruited. Healthy controls were recruited through advertisements. All patients with SSc were evaluated by a rheumatologist and fulfilled the American College of Rheumatology criteria for SSc[6]. These patients were subsequently categorized into a limited (lcSSc) and a diffuse (dcSSc) cutaneous group, according to LeRoy, *et al*[7]. The modified Rodnan skin score was used to score the severity of skin involvement[8]. All patients with SSc underwent RHC if PAH could not be excluded during extensive investigations. PAH was diagnosed according to the clinical classification of Venice 2003[9], with PAH defined as a mean pulmonary artery pressure (PAP) > 25 mm Hg at rest or > 30 mm Hg during exercise and a pulmonary capillary wedge pressure < 15 mm Hg as determined by RHC. Only those with a

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normal PAP at rest and during exercise were considered SSc patients without PAH (SSc-nonPAH). To exclude significant pulmonary fibrosis, all patients with SSc had to have a total lung capacity > 70% of predicted and pO_2 > 60 mm Hg. Patients were excluded if they had prior or current (mono- or combination) therapy with prostaglandin/prostacyclin analogs, endothelin receptor antagonists, or phosphodiesterase-5 inhibitors for PAH. Antihypertensive medication was continued in the subjects with a history of hypertension. Control subjects without SSc were matched for age and sex with the SSc-nonPAH group. In order to match controls to patients with SSc as closely as possible, we also included control subjects with conditions such as hypertension and obesity known to be associated with impaired microvascular endothelium-dependent vasodilatation. All participants gave written informed consent according to the Declaration of Helsinki. The study protocols were approved by the local ethics committee of the VU University Medical Center.

Right heart catheterization. RHC was performed with continuous ECG monitoring, while patients were breathing room air. A balloon-tipped, flow-directed 7F Swan-Ganz catheter (131HF7; Baxter Healthcare, Irvine, CA, USA) was inserted in the right internal jugular vein. PAP were taken at the end of expiration. Hemodynamic measurements were obtained at baseline and, if baseline mean PAP was < 25 mm Hg, during exercise. The exercise protocol consisted of a 3-min period of cycling in supine position on a recumbent bicycle. Work rate was increased in the first minute to 40% of maximal workload as previously determined during maximal exercise testing.

Iontophoresis and laser Doppler flowmetry. After refraining from eating and beverages for at least 4 h and acclimatization for 20 min in a quiet, temperature-controlled room at 23°C, iontophoresis combined with laser Doppler flowmetry was performed as described[10], with the subjects in a sitting position and the investigated hand at heart level. In patients with SSc, iontophoresis was performed the day before RHC. The heater of the probe was set at 28°C. A protocol of multiple fixed doses (current intensity × delivery time) was employed, resulting in an incremental dose-response curve. Seven doses were delivered: 0.1 milliamps for 20 s of 1% acetylcholine (ACh; Miochol, Bournonville Pharma, Netherlands) with a 60-s interval between each dose using an anodal current and 9 doses (0.2 mA for 20 s) of 0.1% sodium nitroprusside (SNP; Nipride, Roche, Netherlands) with a 90-s interval between each dose using a cathodal current. Laser Doppler flux was measured on the middle phalanx of the left (ACh) and right (SNP) middle finger with the Periflux 4000 system (Perimed) and expressed as arbitrary perfusion units (PU). Baseline and peak plateau phase (final 2 iontophoresis deliveries) were measured and absolute and percentage increase were calculated.

Statistical analysis. Numerical data are presented as means and SD in case of normal distribution and otherwise as medians and ranges. Accordingly, means of 2 independent categories were analyzed using Student's t test and medians using the Mann-Whitney U test. To adjust for age, nonparametric variables were log-transformed and differences between groups were analyzed using general linear modeling. Categorical variables were analyzed using the chi-square or Fisher's exact test when appropriate. Statistical significance was set at $p < 0.05$. Results were calculated using SPSS (version 15.0 for Windows; SPSS, Chicago, IL, USA).

RESULTS

Subject characteristics. Twenty-two patients with SSc were included, of whom 6 had no PAH (SSc-nonPAH) and 16 had PAH (SSc-PAH). Of the 16 SSc-PAH patients, 7 had SSc-PAH during exercise and 9 had SSc-PAH at rest. The mean PAP in SSc-non PAH patients was 16 (± 3) mm Hg at rest and 26 (± 3) mm Hg during exercise; in SSc-PAH during exercise the mean PAP was 18 (± 2) at rest and 34 (± 3) mm Hg during exercise; in SSc-PAH at rest the mean PAP at rest was 39 (± 7) mm Hg. Subject characteristics are shown in Table 1. No significant differences in characteristics were present between controls and SSc-nonPAH, whereas age was significantly higher and diastolic blood pressure was significantly lower in SSc-PAH compared to controls. No participants were smokers and none had diabetes mellitus. Clinical characteristics of the patients with SSc are shown in Table 2. All patients with SSc had Raynaud's phenomenon and sclerodactyly. Only 1 patient with SScPAH had dcSSc. All others had the limited cutaneous variant. Compared to SSc-nonPAH, SSc-PAH patients had a longer duration of Raynaud's phenomenon and a shorter time since diagnosis of SSc, although these differences were not significant. In comparison with SSc-nonPAH, SSc-PAH patients had significantly less severe skin involvement as judged by a lower modified Rodnan skin score (10 vs 17; $p < 0.05$). Three patients with SSc-PAH had a history of digital ulcers. Only 1 patient (a patient with SSc-PAH) received a course of iloprost therapy because of digital ulcers, 3 years before the study. No differences in autoantibody status between the groups were present. Although pulmonary function tests in patients with SSc-PAH showed a lower DLCO/VA and a higher prevalence of forced vital capacity/DLCO ratio > 1.4 compared to SSc-nonPAH patients, the differences did not reach statistical significance.

Microvascular function. The results of laser Doppler flux responses to ACh and SNP iontophoresis in controls, SSc-nonPAH, and SSc-PAH patients are shown in Table 3. Comparisons between the groups were adjusted for age. No significant differences in baseline flux at the start of ACh iontophoresis were present among the groups. Compared to controls, SSc-nonPAH patients showed no significant differences in absolute and relative increases of ACh-mediated vasodilatation [74.5 vs 94.1 PU ($p = 0.54$); 392.3% vs 340.4% ($p = 0.90$), respectively]. But patients with SSc-PAH showed marked reductions compared to controls [15.2 vs 74.5 PU ($p < 0.01$); 79.5% vs 392.3% ($p < 0.01$), respectively] and SSc-nonPAH patients [15.2 vs 94.1 PU ($p < 0.01$); 79.5% vs 340.4% ($p < 0.01$), respectively; Figure 1]. No significant differences in baseline flux and after SNP-mediated endothelium-independent vasodilatation were present among the groups (Figure 1). No significant differences in endothelium-dependent and -independent vasodilatation between SSc-PAH at rest and SSc-PAH during exercise were found. Further, when the SSc-PAH during exercise group was left out of the analysis, there was no influence on the results, as shown in Table 4.

DISCUSSION

The key and novel finding of our study was that microvascular endothelium-dependent vasodilatation was severely impaired in SSc patients with PAH, but not in SSc patients without this complication. The strength of our study was the strict selection of SSc patients with and without PAH, who had not been exposed to PAH treatment, and in whom PAH was diagnosed or excluded by means of right heart catheterization.

Table 1. Subject characteristics.

Characteristic	Controls, n = 22	SSc-nonPAH, n = 6	SSc-PAH, n = 16
Age, mean yrs (SD)*	57 (8.1)	57 (16.2)	68 (12.9)
Female (%)	22 (100)	6 (100)	16 (100)
Systolic BP, mean mm Hg (SD)	132 (18.9)	132 (18.9)	133 (19.9)
Diastolic BP, mean mm Hg (SD)*	81 (8.3)	76 (11.5)	70 (9.0)
Body mass index, median (range)	25 (19–38)	2 (18–39)	23 (19–32)
History of hypertension (%)	7 (31.8)	3 (50.0)	4 (25.0)
Smoking in last 5 yrs (%)	0 (0)	0 (0)	0 (0)
History of diabetes mellitus (%)	0 (0)	0 (0)	0 (0)

* Controls vs SSc-PAH $p < 0.05$. SSc: systemic sclerosis; PAH: pulmonary arterial hypertension; BP: blood pressure.

Table 2. Clinical characteristics of the patients with SSc.

Characteristic	SSc-nonPAH, n = 6	SSc-PAH, n = 16
lcSSc/dcSSc	6/0	15/1
Raynaud (%)	6 (100)	16 (100)
Duration of Raynaud, median yrs (range)	5.5 (0.5 to 20.6)	11.5 (0.9 to 68.2)
Duration of SSc, median yrs (range)	4.2 (0.5 to 16.1)	1.8 (–0.8 to 23.4)
Sclerodactyly (%)	6 (100)	16 (100)
Rodnan skin score, median (range)*	17 (8 to 22)	10 (4 to 24)
Telangiectasia (%)	3 (50)	10 (63)
History of digital ulcers (%)	0 (0)	3 (19)
Anticentromere antibodies (%)	3 (50)	9 (56)
Antitopoisomerase I antibodies (%)	1 (17)	3 (18)
6 MWD, mean % predicted (SD)	79 (20)	82 (19)
FVC, mean % predicted (SD)	95.2 (19.7)	101.5 (24.2)
DLCO/VA, mean % predicted (SD)	77.6 (19.5)	61.8 (15.2)
FVC/DLCO ratio > 1.4 (%)	3 (50.0)	14 (87.5)

* SSc-nonPAH vs SSc-PAH $p < 0.05$. SSc: systemic sclerosis (lc: limited cutaneous, dc: diffuse cutaneous); PAH: pulmonary arterial hypertension; 6MWD: 6-minute walk distance; FVC: forced vital capacity; DLCO: diffusing capacity of the lungs for carbon monoxide; DLCO/VA: transfer factor for carbon monoxide.

Table 3. Acetylcholine (ACh) endothelial-dependent and sodium nitroprusside (SNP)-independent vasodilatation in controls, patients with SSc-nonPAH, and patients with SSc-PAH. Comparisons between groups corrected for age. Data are median perfusion units.

Group	Controls, n = 22	SSc-nonPAH, n = 6	SSc-PAH, n = 16	Controls vs SSc-nonPAH, p	Controls vs SSc-PAH, p	SSc-nonPAH vs SSc-PAH, p
ACh baseline (range)	18.7 (8.4 to 38.5)	23.4 (17.2 to 55.6)	24.7 (7.6 to 44.0)	0.11	0.12	0.72
ACh peak (range)	95.3 (10.8 to 225.3)	117.8 (41.8 to 196.0)	37.4 (8.2 to 97.4)	0.52	< 0.01	< 0.01
ACh increase (range)	75.8 (19.7 to 209.1)	94.1 (24.7 to 140.4)	15.2 (0.6 to 70.0)	0.74	< 0.01	< 0.01
ACh % increase (range)	397.9 (63.7 to 1293.4)	340.4 (143.8 to 559.3)	79.5 (5.5 to 256.0)	0.70	< 0.01	< 0.01
SNP baseline (range)	18.6 (5.3 to 27.7)	27.7 (11.9 to 52.3)	21.9 (3.6 to 55.2)	0.12	0.19	0.63
SNP peak (range)	108.2 (31.5 to 202.1)	108.3 (64.7 to 200.3)	90.0 (23.6 to 208.9)	0.58	0.71	0.44
SNP increase (range)	98.7 (13.1 to 769.0)	88.4 (34.0 to 152.5)	57.9 (20.0 to 195.8)	0.86	0.35	0.61
SNP % increase (range)	469.3 (40.9 to 2371.9)	431.4 (110.1 to 490.6)	333.6 (80.3 to 1491.5)	0.66	0.37	0.80

SSc: systemic sclerosis; PAH: pulmonary arterial hypertension.

Previous studies demonstrated an impaired microvascular endothelium-dependent vasodilatation in groups of unselected patients with SSc[11,12,13,14,15,16], whereas endothelium-independent vasodilatation was found preserved in some[11,14,16] but not all studies[12,15]. The potential disadvantage of previous laser Doppler studies is that most did not assess the presence of PAH. Only 1 age-adjusted study described a patient with SSc with PAH based on RHC, and this patient had the lowest endothelial response[16]. In order to match controls to the patients with SSc as closely as possible, we included control

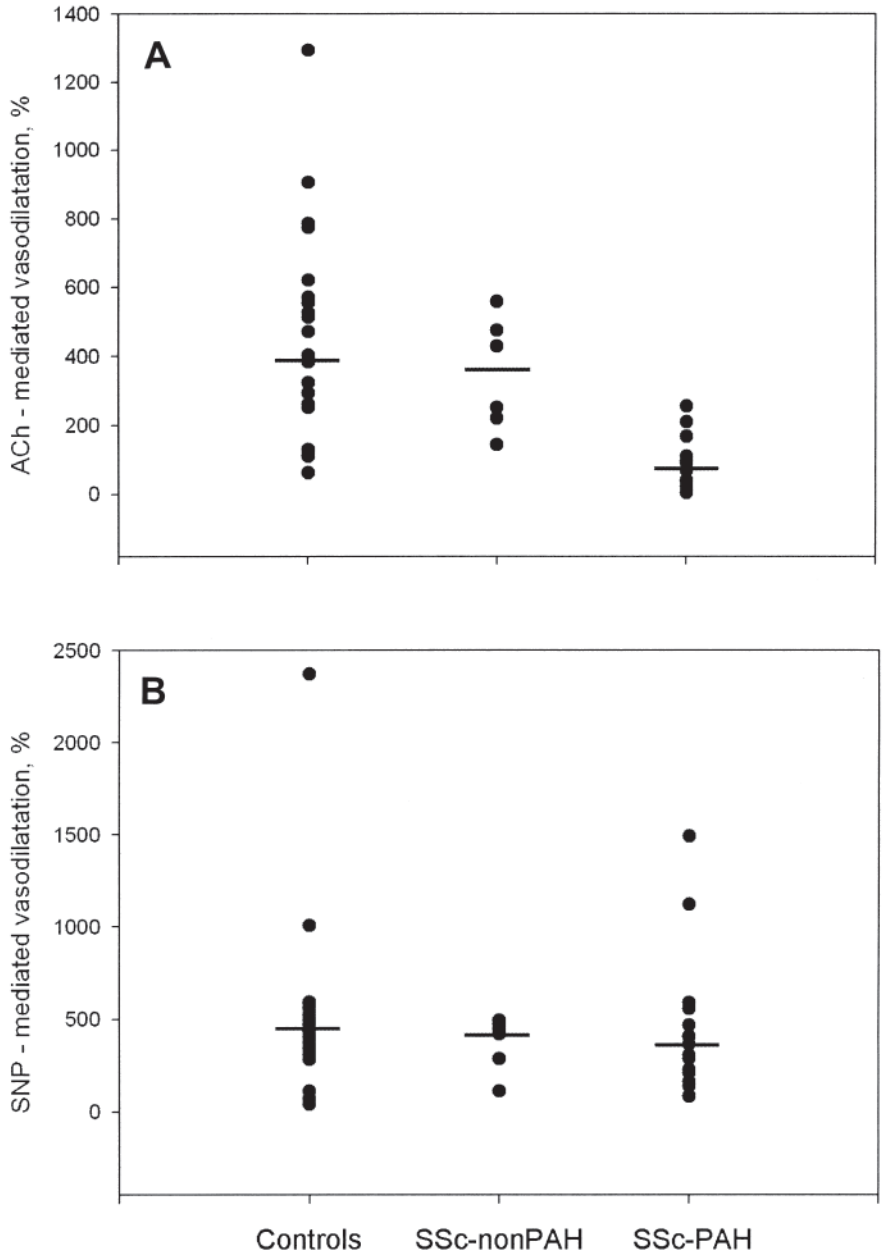

Figure 1. Compared to controls, SSc-nonPAH showed no significant differences in absolute and relative increases of ACh-mediated vasodilatation, whereas SSc-PAH patients showed marked reductions compared to controls and SSc-nonPAH patients. No significant differences in baseline flux and after SNP-mediated endothelium-independent vasodilatation were present among the groups. SSc: systemic sclerosis; PAH: pulmonary arterial hypertension; ACh: acetylcholine; SNP: sodium nitroprusside.

subjects with conditions such as hypertension and obesity known to be associated with impaired microvascular endothelium-dependent vasodilatation[17,18]. This may explain why we did not find a difference in microvascular function between controls and SSc patients without PAH. Another explanation could be that SSc patients with preserved microvascular function are protected from organ complications, and that the presence of impaired microvascular endothelium-dependent vasodilatation in SSc patients is indicative of organ involvement. In support of this, we and others have shown that the extent of structural capillary rarefaction in skin, i.e., a decrease in capillary density, is associated with the presence and severity of PAH in SSc[4,5]. Further research is needed to assess whether these noninvasive assessments of skin microvascular function could be used to examine disease progression over time and responsiveness to vasoactive treatment[19].

Table 4. Acetylcholine (ACh) endothelial-dependent and sodium nitroprusside (SNP)-independent vasodilatation in controls, patients with SSc-nonPAH, and patients with SSc-PAH at rest only. Comparisons between groups corrected for age. Data are median perfusion units.

Group	Controls, n = 22	SSc-nonPAH, n = 6	SSc-PAH rest, n = 9	Controls vs SSc-PAH rest, p	SSc-nonPAH vs SSc-PAH rest, p
ACh baseline (range)	18.7 (8.4 to 38.5)	23.4 (17.2 to 55.6)	15.4 (8.1 to 43.5)	0.25	0.82
ACh peak (range)	95.3 (10.8 to 225.3)	117.8 (41.8 to 196.0)	27.2 (15.7 to 73.0)	< 0.01	< 0.01
ACh increase (range)	75.8 (19.7 to 209.1)	94.1 (24.7 to 140.4)	14.1 (1.9 to 29.6)	< 0.01	< 0.01
ACh % increase (range)	397.9 (63.7 to 1293.4)	340.4 (143.8 to 559.3)	90.5 (5.51 to 209.8)	0.02	< 0.01
SNP baseline (range)	18.6 (5.3 to 27.7)	27.7 (11.9 to 52.3)	18.1 (3.6 to 34.2)	0.40	0.61
SNP peak (range)	108.2 (31.5 to 202.1)	108.3 (64.7 to 200.3)	97.6 (23.6 to 208.9)	0.93	0.66
SNP increase (range)	98.7 (13.1 to 769.0)	88.4 (34.0 to 152.5)	77.2 (20.0 to 195.8)	0.77	0.84
SNP % increase (range)	469.3 (40.9 to 2371.9)	431.4 (110.1 to 490.6)	466.6 (86.2 to 1491.5)	0.65	0.90

SSc: systemic sclerosis; PAH: pulmonary arterial hypertension.

Whereas our study groups were well characterized and established tools were used to investigate the microcirculation, several limitations of the study have to be addressed. First, due to the strict selection criteria based on right heart catheterization, the groups were quite small, so the study may be underpowered to detect differences between controls and SSc-nonPAH. Second, although iontophoresis is widely used to investigate microvascular function in SSc, the use of techniques that involve the skin in a disease characterized by skin changes may raise questions. Several groups have addressed this issue[12,15,20]. However, in our study, patients with PAH had less skin involvement than SSc patients without PAH, and the findings on SNP iontophoresis did not differ significantly among patients with SSc and healthy controls, making it less likely that skin involvement would explain our results. Third, patients were included if they had PAH during exercise. In 2008, an expert consensus conference decided to withdraw exercise criteria from the definition of pulmonary hypertension because of insufficient certainty about the limits of normal[21]. Our study started in 2007 and the previously approved study protocol could solely adapt the 2003 Venice criteria that included PAH if mean PAP was > 30 mm Hg during exercise[9]. Recent studies have challenged the 2008 criteria, showing that exercise-induced PAH may indicate clinically relevant early pulmonary vasculopathy in patients with SSc[22,23]. Further, leaving the PAH during exercise group out of the analysis had no effect on the results.

Our findings demonstrate that systemic microvascular endothelium-dependent vasodilatation is profoundly disturbed in patients with SSc complicated by PAH, but not in patients without this complication. These data are compatible with the idea that the presence of impaired microvascular endothelium-dependent vasodilatation is indicative of organ complications in SSc, and in addition may play a pathophysiological role in its development.

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