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Bosentan for digital ulcers prevention does not worsen cardiopulmonary exercise test parameters in SSc patients with interstitial lung disease



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Pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD) are serious pulmonary complications in patients with Systemic sclerosis (SSc) [1] and despite recent advances in the treatment, remain the major causes of death. Bosentan, a dual endothelin-1 receptor antagonist is an effective approach to therapy for PAH, improving pulmonary hemodynamics and functional capacity, and it is also able to reduce the number of new digital ulcers in patients with SSc [2].

By contrast, Endothelin-1 receptor antagonist administered in idiopathic pulmonary fibrosis was not associated with clear benefits increasing risk for disease progression and respiratory hospitalizations [3].

The aim of this study is to evaluate the effects of bosentan administered as prevention for digital ulcers (DUs), in SSc patients affected by ILD, at baseline and post therapy with cardiopulmonary exercise test (CPET) and pulmonary function tests (PFT).

Twelve consecutive SSc patients [8 females and 4 males; median age 45 years (35–60)] in bosentan therapy for DUs prevention were enrolled in this study. Median duration of disease was 4.5 (1–15) years. Four patients had limited cutaneous SSc and eight had diffuse cutaneous SSc.

Twelve consecutive SSc patients [9 females and 3 males; median age 46 years (37–58)] were enrolled in this study as control group. Median duration of disease was 4.3 (1–14) years. Four patients had limited cutaneous SSc and eight had diffuse cutaneous SSc.

All SSc patients underwent treatment with calcium channel blockers (Nifedipine 30 mg/day). None of the patients were treated with immunosuppressive agents. Scleroderma patients with coronary artery disease, congestive heart failure, left ventricular dysfunction, pulmonary hypertension, valvular abnormalities and arrhythmias were not included in the study. Patients with diabetes mellitus, renal failure, hepatic or thyroid dysfunction and anemia were excluded. Patients were not taking β -blockers, antiarrhythmic drugs, ACE inhibitors or angiotensin receptor antagonists.

The subjects' written consent was obtained according to the Declaration of Helsinki and the study was approved by the Ethics Committee of the Sapienza University. All examined patients underwent clinical evaluation, electrocardiography, transthoracic echocardiogram, baseline PFT and high resolution computed tomography (HRCT) of the chest. A maximal symptom-limited CPET was performed on an electronically braked cycle ergometer (Ergoline-800, Mortara, Bologna, Italy) according to the recommendations on the use of exercise testing in clinical practice [4]. The SSc patients with DUs underwent to CPET before bosentan therapy (T0) and 24 months after bosentan therapy (T1). A SSc group matched for sex and age was enrolled as control group and underwent to CPET at enrollment (T0) and after 24 months (T1).

All data were expressed as median and range. The Mann-Whitney *U* test or the Kruskal-Wallis was used to test differences between two individual study groups. *P*-values <0.05 were considered significant.

In the SSc patients group treated with bosentan we did not observed any significant ($p > 0,05$) modification of PFTs and CPET parameters after 24 months of bosentan therapy (Table 1). The median value of single-breath carbon monoxide (CO) diffusing capacity (DLCO) was 80,6% (66,6–101,4%) at baseline and 72,5% (63,1–90,2%) post bosentan therapy. Also the relation between minute ventilation (VE) and carbon dioxide output (VCO₂) (VE/VCO₂ slope) did not showed any significant modification ($p > 0,05$) post bosentan therapy: 26,4 (18,2–51,2) vs 26,7 (21,4–44,4).

Also in SSc control group we did not observed any significant modification of PFTs and CPET parameters at T1 (Table 1). The median value

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Table 1
Pulmonary function tests (PFT) and cardiopulmonary exercise test parameters in SSc patients in bosentan therapy and in SSc control group. All PFTs parameters are expressed as percentage of predicted.

	SSc patients in bosentan therapy		SSc control group		
	Pre	Post	Pre	Post	Post
FVC (%)	87,3 (62,6–108,8)	79,8 (56,8–102,9)	112,3 (61,5–120)		113,3 (71,9–121,5)
FEV1 (%)	87,3 (65,2–104,8)	85,8 (59–106,2)	108,9 (50,8–134)		107,5 (68,3–131,8)
DLCO (%)	80,6 (66,6–101,4)	72,5 (63,1–90,2)	78,9 (64,5–110)		78,8 (56–102,5)
VO ₂ max (L/min)	1335 (938–2048)	1293 (902–1867)	1328 (883–2521)		1259 (842–2095)
VE/VCO ₂ slope	26,4 (18,2–51,2)	26,7 (21,4–44,4)	29,5 (21,2–38,4)		25,8 (20,3–32,9)
PAPs (mm Hg)	26,5 (18–36)	27 (23–33)	30 (25–37)		29 (25–35)

FVC: Forced vital capacity, FEV1: forced expiratory volume in the 1st second, DLCO: single-breath carbon monoxide (CO) diffusing capacity, VO₂ max: maximal oxygen consumption, PAPs: pulmonary artery systolic pressure, VE/VCO₂ slope: relation between minute ventilation (VE) and carbon dioxide output (VCO₂).

of DLCO was 78,9% (64,5–110,4%) at baseline and 78,8% (56–102,5%) at T1. Also The VE/VCO₂ slope did not show any significant modification a T1: 29,5 (21,2–38,4) vs 25,8 (20,3–32,9) (Fig. 1).

In our study bosentan was safe in SSc patients with ILD not causing imbalance ventilation perfusion as shown by parameters VE/VECO₂ slope.

It is well known that in SSc patients endothelin 1 (ET-1) is able to induce fibroblast chemotaxis and proliferation [5]. Although bosentan has not shown antifibrotic effects, it is safe in the treatment of vascular complications of SSc patients with ILD [6].

However, these vasodilators can worsen pulmonary hemodynamic, producing an imbalance ventilation/perfusion due to inhibition of hypoxic pulmonary vasoconstriction [7].

Rosato et al. have demonstrated that VE/VCO₂ slope correlates with disease severity and activity, thus suggesting a relationship between

this marker of ventilation-perfusion mismatch and SSc severity [8]. Moreover CPET was able to detect the early renal and cardiopulmonary damage in asymptomatic SSc patients [9].

Thus, CPET is useful to assess ventilation/perfusion in ILD SSc patients to evaluate any vasodilators side effects.

In conclusion we can assume that bosentan, administered to prevention digital ulcers in SSc patients affected by ILD without PAH, do not cause a worsening CPET parameters and gas exchange.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

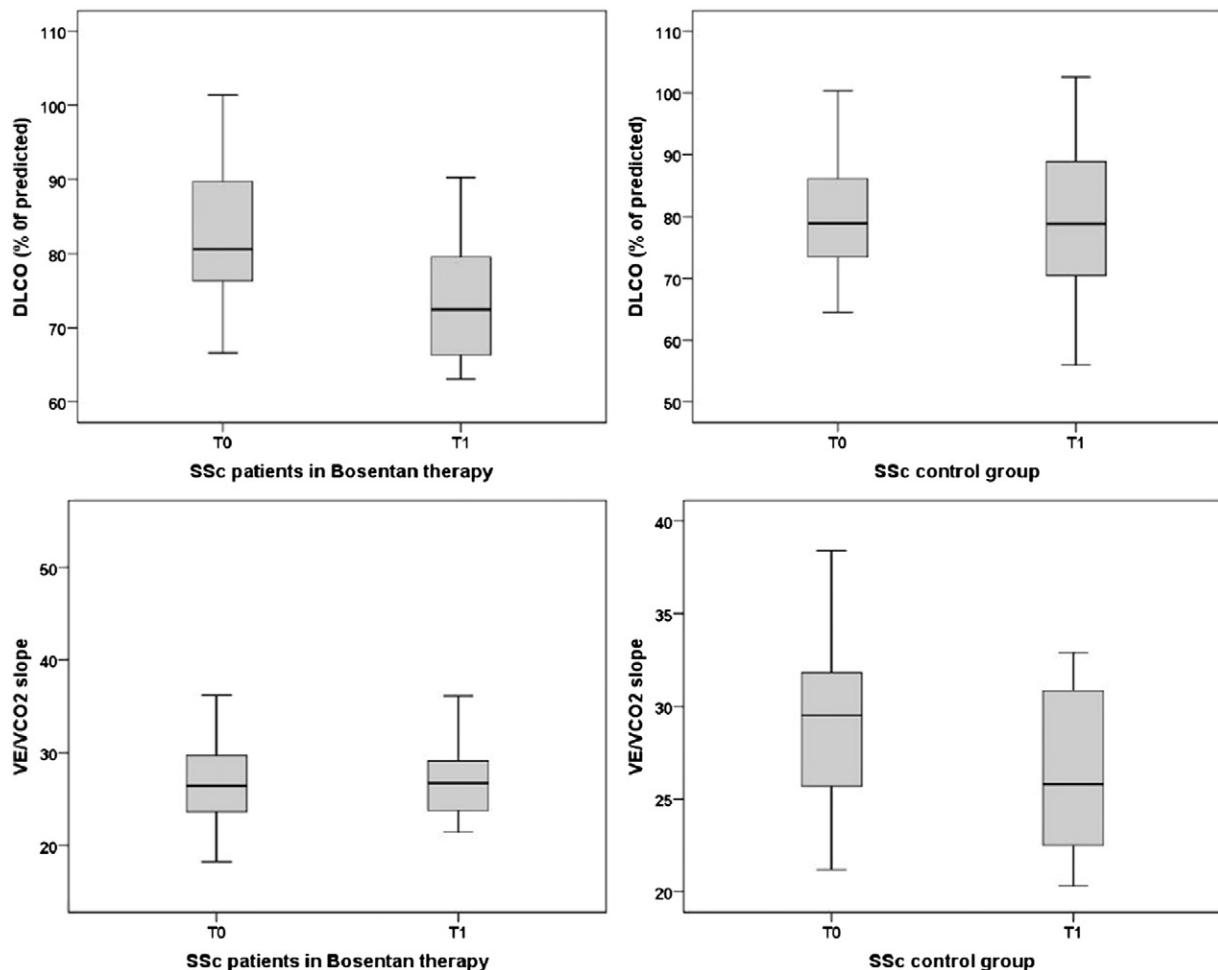


Fig. 1. DLCO and VE/VCO₂ slope in SSc patients in bosentan therapy (T0–T1) and control group (T0–T1).

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