

**Skin perfusion of hands is associated with parasympathetic activity in systemic sclerosis**

Sirs,  
Raynaud's phenomenon (RP) and microvascular damage are the features of systemic sclerosis (SSc). Changes in the activity or responsiveness of neuroendothelial mechanisms may trigger vascular injury with imbalance of angiogenesis (1). The skin perfusion of hands, evaluated with laser Doppler perfusion imaging (LDPI), is reduced in SSc patients (2) and it decreases with the severity of capillaroscopic damage. In a previous study abnormal skin perfusion showed a negative correlation with pulsatility and stiffness of digital arteries (3). In this pilot study we aimed to evaluate skin perfusion of the hands in SSc using LDPI and correlate it with autonomic activity. The protocol, according to Declaration of Helsinki, was approved by local Ethics Committee. Twenty-five SSc patients [20 female, median age 47 (40-51)] were enrolled. Fifteen patients had diffuse cutaneous systemic sclerosis (dcSSc) and sixteen had a history of digital ulcers, no patient had active digital ulcers. Median value of modified Rodnan skin score was 13 (11-18). The nailfold videocapillaroscopy showed an early capillaroscopic pattern in 8 (32%) patients, active in 8 (32%) patients and late in 9 (36%) patients. Exclusion criteria were active digital ulcers, peripheral arterial diseases, diabetes, thrombophilia, cigarette smoking, cardiac arrhythmias and conduction disorders. Five patients were treated with bosentan for digital ulcers prophylaxis, no patient was treated with phosphodiesterase type 5 (PDE5) inhibitor. Calcium channel blockers therapy, bosentan and iloprost infusion was discontinued 72 hours before the LDPI. Baseline images were taken of dorsum of both hands with Lisca Laser Doppler Perfusion Imager (Perimed AB, Stockholm, Sweden). The dorsum of the hand was divided into regions of interest (ROI) and ac-

ording to our previous study we analysed fingers from the second to the fourth (4, 5): ROI1 included three fingers of the hand from the second to the fourth distally to the proximal interphalangeal finger joint and ROI2 included the area between the PIP (proximal interphalangeal) and the MCP (metacarpophalangeal) joint (5). Perfusion has been expressed by arbitrary perfusion units (pU). All patients underwent to 24-h Holter monitoring and electrocardiography (ECG) to assess autonomic nervous system by heart rate variability (HRV) analysis. The time domain analysis was evaluated for the activity of the cardiac system. Parasympathetic system was represented by the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD) while global autonomic activity was represented by the standard deviation of normal-to-normal RR intervals (SDNN) (6). All the results were expressed as median and CI (confidence interval). Group comparisons were made by Kruskal-Wallis test. Spearman correlation coefficients (r) was used. *p*-values <0.05 were considered significant.  
The median value of perfusion of both hands was 61.3 (53.6–72.2) pU, the median value of ROI1 was 62.1 (54.5–70.2) pU, the median value of ROI2 was 93.7 (86.7–131.1) pU. The median value of SDNN was 122 (119-138) ms and the median value of RMSSD was 40 (37–53) ms.  
We have not observed correlation between SDNN and median value of perfusion of hands, ROI1 and ROI2. Conversely, we have observed a positive linear correlation between RMSSD and perfusion of hands ( $r=0.61, p<0.001$ ) and ROI1 ( $r=0.51, p<0.01$ ) (Fig. 1). There was no correlation between RMSSD and perfusion of ROI2. Impaired neuroendothelial mechanisms between vasoconstriction and vasodilatation are present in course of RP (7). HRV in SSc is reduced and plays a key role in determining and maintaining the mechanisms responsible for the vasodilation and vasoconstriction (8, 9). Recently we have demonstrated that parasympathetic activity is

associate with vascular endothelial growth factor expression (10). In the present study skin perfusion is favoured by vasodilation mediated to parasympathetic system. First line of treatment in course of SSc is represented by vasodilatory medications for RP and digital ulcers (11). We can suppose that the perfusion of the hands and especially of the distal phalanges is modulated by parasympathetic activity.

M.L. GASPERINI, MD  
A. GIGANTE, MD  
A. IACOLARE, MD  
C. PELLICANO, MD  
G. COLLALTI, MD  
E. ROSATO, MD, PhD

Department of Translational and Precision Medicine, Sapienza University of Rome, Italy.

Please address correspondence to:  
Dr Edoardo Rosato,  
Department of Translational and Precision Medicine, Sapienza University of Rome,  
Viale dell'Università 37,  
00185 Rome, Italy.

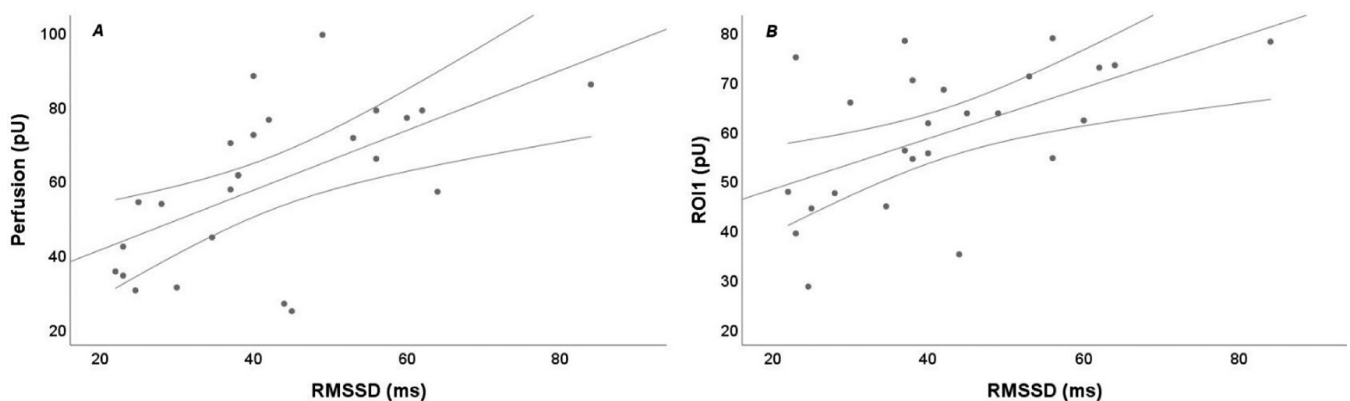
E-mail: edoardo.rosato@uniroma1.it

Competing interests: none declared.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2019.

**References**

1. ROMANO E, ROSA I, FIORETTO BS, GUIDUCCI S, MANETTI M, MATUCCI-CERINIC M: A new avenue in the pathogenesis of systemic sclerosis: the molecular interface between the endothelial and the nervous systems. *Clin Exp Rheumatol* 2019; 37 (Suppl. 119): S134-41.
2. BARBANO B, MARRA AM, QUARTA S *et al.*: In systemic sclerosis skin perfusion of hands is reduced and may predict the occurrence of new digital ulcers. *Microvasc Res* 2017; 110: 1-4.
3. ROSATO E, GIGANTE A, BARBANO B *et al.*: In systemic sclerosis macrovascular damage of hands digital arteries correlates with microvascular damage. *Microvasc Res* 2011; 82: 410-5.
4. ROSATO E, BORGHESE F, PISARRI S, SALSANO F: Laser Doppler perfusion imaging is useful in the study of Raynaud's phenomenon and improves the capillaroscopic diagnosis. *J Rheumatol* 2009; 36: 2257-63.
5. ROSATO E, ROSSI C, MOLINARO I, GIOVANNETTI A, PISARRI S, SALSANO F: Laser Doppler perfusion imaging in systemic sclerosis impaired response to cold stimulation involves digits and hand dorsum. *Rheumatology* 2011; 50: 1654-8.



**Fig. 1.** Linear positive correlation between RMSSD and median perfusion of both hands (A) and ROI1 (B).

## Letters to the Editors

---

6. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology: heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 1996; 93: 1043-65.
7. HERRICK AL: Pathogenesis of Raynaud's phenomenon. *Rheumatology* 2005; 44: 587-96.
8. GIGANTE A, ROSATO E, LIBERATORI M *et al.*: Autonomic dysfunction in patients with systemic sclerosis: correlation with intrarenal arterial stiffness. *Int J Cardiol* 2014; 177: 578-80.
9. DI FRANCO M, PARADISO M, RICCIERI V *et al.*: Autonomic dysfunction and microvascular damage in systemic sclerosis. *Clin Rheumatol* 2007; 26: 1278-83.
10. GIGANTE A, MARGIOTTA D, NAVARINI L *et al.*: Parasympathetic activity increases with digital microvascular damage and vascular endothelial growth factor in systemic sclerosis. *Clin Exp Rheumatol* 2018; 36 (Suppl. 113): S24-27.
11. KOWAL-BIELECKA O, FRANSEN J, AVOUAC J *et al.*: Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis* 2017; 76: 1327-39.