Microvascular Research 110 (2017) 1–4

Contents lists available at ScienceDirect

Microvascular Research

journal homepage: www.elsevier.com/locate/ymvre

# In systemic sclerosis skin perfusion of hands is reduced and may predict the occurrence of new digital ulcers

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ARTICLE INFO

*Article history:*
Received 15 June 2016
Revised 26 October 2016
Accepted 4 November 2016
Available online 09 November 2016

*Keywords:*
Systemic sclerosis
Digital ulcers
Laser Doppler Perfusion Imager
Nailfold videocapillaroscopy

ABSTRACT

Systemic sclerosis (SSc) patients are at high risk for the development of ischemic digital ulcers (DUs). The aim of this study was to assess in SSc patients a correlation between skin perfusion evaluated by LDPI and DUs and to evaluate the prognostic value of skin perfusion to predict the new DUs occurrence.
Fifty eight (47 female, 11 male) SSc patients were enrolled. Skin perfusion of hands and region of interest (ROIs) was measured by Laser Doppler perfusion Imager (LDPI). The proximal-distal gradient (PDG) was present when the perfusion mean difference between ROI1 and ROI2 was >30 pU.
The skin perfusion of hands is lower in SSc patients than in healthy controls. The skin perfusion decreased with severity of capillaroscopic damage. Both mean perfusion of hand and PDG are significantly ($p < 0.01$ and $p < 0.0001$, respectively) lower in SSc patients with new DUs than in SSc patients without DUs. Only 2 of 11 SSc patients (18.2%) with PDG developed new digital ulcers, conversely 36 of 47 (76.6%) SSc patients without PDG developed new digital ulcers ($p < 0.001$). The ROC curves demonstrated a good accuracy of new DUs prediction for PDG (0.78, $p < 0.0001$). Using this cut-off value of 30 pU, RR for new DUs development in SSc patients without PDG is 4,2 ($p < 0.001$).
LDPI indices could be used in association to the capillaroscopic and clinical findings or serological tests in the identification of patients at high risk of developing DUs.



## 1. Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterized by endothelial dysfunction and fibrosis of the skin and internal organs. Endothelial dysfunction, microvascular and macrovascular damage are the hallmarks of SSc (Campbell and LeRoy, 1975; Rosato et al., 2011a).

Patients with SSc are at high risk for the development of ischaemic digital ulcers (DUs), which occur in 35% to 60% of SSc patients (Matucci-Cerinic et al., 2011). The early detection of patients with a high risk of developing DUs could allow a preventive treatment of these complications, with a reduction of morbidity and social costs. Nailfold videocapillaroscopy (NVC) represents the best method to evaluate digital capillaroscopic damage. Capillaroscopic skin ulcer risk index (CSURI) may represent a novel tool with the ability to predict the development of DUs in SSc patients (Sebastiani et al., 2009).

Laser Doppler Perfusion Imager (LDPI) is a method used to evaluate hand skin perfusion in patients with primary and secondary Raynaud's phenomenon (Rosato et al., 2009; Cracowski and Roustit, 2016).

A negative correlation exists between nailfold microvascular damage severity and fingertip blood perfusion (Sulli et al., 2014). A negative correlation between skin perfusion and digital artery pulsatility was observed (Rosato et al., 2011b). With the progression of capillaroscopic damage the abnormal microvascular response to cold stimulation, evaluated by LDPI, appears in the hand dorsum skin (Rosato et al., 2011c).

The aim of this study was to asses in SSc patients a correlation between skin perfusion evaluated by LDPI and DUs and to evaluate the prognostic value of skin perfusion to predict the new DUs occurrence.

## 2. Materials and methods

### 2.1. Patients

Fifty eight (47 female and 11 male; mean age 48.8 ± 15.3 years) consecutive patients with SSc were enrolled in this study. All patients met the American College of Rheumatology/European League criteria for classification and diagnosis of SSc (van den Hoogen et al., 2013). Mean duration of Raynaud's phenomenon (RP) and mean duration of disease were 10.8 ± 5.5 years and 8.4 ± 5.4 years, respectively. Thirty-four patients had limited cutaneous SSc (lcSSc) and 24 had diffuse cutaneous SSc (dcSSc) as defined by Le Roy et al. (LeRoy et al., 1998). Table 1 showed the SSc patients' epidemiological and clinical features.

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http://dx.doi.org/10.1016/j.mvr.2016.11.003
0026-2862/

Patients with a history of uncontrolled systemic hypertension, hyperlipidaemia, cardiac failure, cardiac valve diseases (insufficiency or stenosis of aortic and mitralic valve), hepatic failure, diabetes, cerebrovascular diseases, peripheral vascular diseases, coagulopathy, smokers, pregnant or breastfeeding women were excluded. SSc patients with active digital ulcers at baseline were excluded from this study. We did not consider as eligible for the work patients with ulcers on the extension faces and related to calcinosis. All patients were taking nifedipine at a stable dose (30 mg/day) for at least three months. Only patients who receive a stable therapy with Bosentan (250 mg/day) for 6 months were enrolled in the present study. Patients in current therapy with phosphodiesterase-5 inhibitors and endothelin receptor antagonists for pulmonary arterial hypertension, prior sympathectomy of the upper limb were excluded. None of patients were treated with immunosuppressive agents (e.g., cyclophosphamide or mycophenolate mofetil). After LDPI examination, the patients were examined for the appearance of new DUs after 3, 6, 9 and 12 months of follow-up without any changes in previous treatments.

Thirty (26 female and 4 male, mean age 46 ± 11.5 years) healthy controls (HC) were also recruited. The subjects' written consent was obtained according to the Declaration of Helsinki and the study was approved by ethics committee of Sapienza University.

### 2.2. Laser Doppler Perfusion Imager (LDPI) and nailfold videocapillaroscopy (NVC)

LDPI and NVC were performed after resting the subject in a temperature controlled room at 24 ± 0.4 °C for 20 min. Patients and healthy controls did not drink alcoholic beverages and coffee for two days before the examination. The investigator who analyzed the LDPI was blinded for NVC findings.

### 2.3. LDPI assessment

Calcium channel blockers therapy was discontinued 72 h before the LDPI. Patients in therapy with iloprost underwent to LDPI examination the day before the next infusion. Baseline perfusion of hands dorsal region was registered by laser speckle contrast analysis device (PeriCam PSI, Perimed, Sweden). The mean perfusion has been expressed by arbitrary perfusion units (pU), which are directly proportional to the product of the mean speed and the concentration of red blood cells. According to our previous studies, the dorsum of hand was divided in three regions of interest (ROI). ROI 1 included three fingers of the hand from the second to the four distally to proximal interphalangeal finger joint. ROI 2 included the area between the proximal interphalangeal and the metacarpophalangeal joint. ROI 3 included only the dorsal surface of the hand without the fingers. The proximal-distal gradient was present when the perfusion mean difference between ROI 1 and ROI 2 was >30 pU (Rosato et al., 2009; Rosato et al., 2011c).

**Table 1**
SSc patients' epidemiological and clinical features.

| | |
|---|---|
| Sex (female/male) | 47/11 |
| Age, years | 48.8 ± 15.3 |
| Disease duration, years | 8.4 ± 5.4 |
| mRSS | 11 ± 5.7 |
| dcSSc/lcSSc | 34//24 |
| SSc-specific autoantibodies, n (%) | |
| Anti-topoisomerase I | 35 (60.4) |
| Anticentromere | 16 (27.6%) |
| None | 7 (12%) |
| Patients with digital ulcers history, n (%) | 40 (70%) |
| Patients with new digital skin ulcers, n (%) | 38 (65.5%) |
| Number of digital ulcers/patients | 1.9 ± 2.5 |
| Capillaroscopic pattern, n (%) | |
| Early | 15 (25.9) |
| Active | 21 (36.2) |
| Late | 22 (37.9) |

### 2.4. NVC

NVC was performed with a videocapillaroscope (Pinnacle Studio version 8) equipped with a 500 × optical probe. The nailfold of the second, third, fourth and fifth finger was examined in each patient. According to Cutolo et al. the patterns identified within the "SSc pattern" include: early, active and late (Cutolo et al., 2006).

### 2.5. Statistical analysis

All the results were expressed as mean and standard deviation. Commercially software (SPSS version 21.0) was used for statistical analysis. The coefficient of skewness and coefficient of kurtosis were used to evaluate normal distribution of data. Multivariate analysis was applied for the estimation of relationship of Doppler indices with clinical features (e.g. age, duration of disease). A receiver operating characteristic (ROC) curve analysis was performed to analyze the prognostic accuracy of each Doppler indices in regard to ulcer development. Group comparisons were made by Student's unpaired 2-tailed *t*-test. Pearson product-moment correlation coefficient (r) was used to test for an association between numerical variables. The chi-square test or Fisher's exact test, as appropriate, were used to compare categorical variables. Relative risk (RR) and 95% confidence intervals (95% CI) are reported. Comparisons between the three NVC patterns were by non parametric Kruskal-Wallis test and the data were expressed as median and range. P-values < 0.05 were considered significant.

## 3. Results

In SSc patients the mean perfusion is significantly ($p < 0.01$) lower than in HC (39 ± 2.1 pU vs 49.9 ± 13.9 pU). The mean perfusion of ROI 1 and ROI 2 is significantly lower in SSc patients than HC. A significant difference of mean perfusion was observed in ROI 3 (Table 2). The PDG is significantly higher ($p < 0.0001$) in HC than in SSc patients (50.3 ± 11.9 vs −0.19 ± 41.1) (Table 2). The PDG is present in 100% of HC and in 18.9% of SSc patients ($p < 0.0001$).

In three capillaroscopic groups (early, active and late) the mean values of perfusion were different. In early and active capillaroscopic groups the mean perfusion of hand is significantly ($p < 0.0001$) higher than in late capillaroscopic group (Table 3). The mean values of perfusion of ROI 1 and ROI 2 significantly decreased with severity of capillaroscopic damage. The mean values of perfusion of ROI 3 did not show any significant differences between early and active capillaroscopic groups. Therefore the mean value of ROI 3 perfusion is significantly lower ($p < 0.0001$) in late capillaroscopic group than in early and active capillaroscopic groups. The PDG significantly ($p < 0.01$) decreased with capillaroscopic severity damage (Table 3). The PDG is present in 10 of 15 (66.7%) early SSc patients, in 1 of 21 (4.8%) active SSc patients and in none of 22 late SSc patients.

The principal features of SSc patients with or without new DU were showed in Table 4. Within 12 months since basal LDPI assessment 38 of 58 patients (44.8%) experienced new DUs. The new DU are more

**Table 2**
Mean perfusion, expressed as perfusion unit (pU), of hand and region of interest (ROIs) in SSc patient and healthy controls. The proximal-distal gradient (PDG) was expressed by perfusion mean difference between ROI1 and ROI2.

| | SSc patients | Healthy controls | p |
|---|---|---|---|
| Hand (pU) | 39 ± 2.1 | 49.9 ± 13.9 | $p < 0.01$ |
| ROI 1 (pU) | 71.7 ± 41.5 | 128.9 ± 26.2 | $p < 0.0001$ |
| ROI 2 (pU) | 66.6 ± 37.7 | 97.5 ± 38.8 | $p < 0.0001$ |
| ROI 3 (pU) | 72.9 ± 41.9 | 78.7 ± 26 | $p > 0.05$ |
| PDG | −0.19 ± 41.1 | 50.3 ± 11.9 | $p < 0.0001$ |

**Table 3**
Mean perfusion, expressed as perfusion unit (pU), of hand and region of interest (ROIs) in three capillaroscopic groups. The proximal-distal gradient (PDG) was expressed by perfusion mean difference between ROI1 and ROI2.

| | Early | Active | Late | p |
|---|---|---|---|---|
| Hand (pU) | 45.2 (24.5–64.7) | 46.8 (22.3–114) | 17.6 (8.1–60.3) | $p < 0.0001$ |
| ROI 1 (pU) | 108.7 (60.0.8–158.6) | 78.2 (36.4–167.7) | 29.3 (11–125.8) | $p < 0.0001$ |
| ROI 2 (pU) | 87.3 (42.5–124.1) | 66.7 (29.7–175) | 28.4 (11.9–96.2) | $p < 0.0001$ |
| ROI 3 (pU) | 68.8 (39–121.6) | 74.4 (32.1–204) | 43.7 (15.1–136.1) | $p > 0.05$ |
| PDG | 34.9 (−61.2–57.5) | −8.3 (−134.4–92.2) | −3.5 (−38.4–99.5) | $p < 0.01$ |

frequent ($p < 0.05$) in patients with dcSSC (44.8%) than in patients with lcSSc (20.7%). The occurrence of new DUs is higher ($p > 0.05$) in patients with anti-topoisomerase I antibodies (40.3%) than in patients with others autoantibodies (22.4%). The new DUs occurrence is higher ($p < 0.0001$) in SSc patients with DUs history (62.1%) than in SSc patients without DUs history (3.4%). The new DU are more frequent ($p < 0.0001$) in patients with active and late capillaroscopic pattern than in patients with early capillaroscopic pattern (Table 4). Sixteen of 19 patients (27.6%) treated with Bosentan developed new DUs, 30 of 43 (69.8%) patients treated with intravenous Ioprost developed new DUs and 12 of 14 (20.7%) patients treated with Bosentan and intravenous Iloprost developed new DUs.

The values of perfusion in SSc patients with new digital ulcers and in SSc patients without new digital ulcers are reported in Table 4. The mean perfusion of hand is significantly ($p < 0.01$) lower in SSc patients with new DUs than in SSc patients without DUs [38 (8.15–114) vs 41.2 (14.9–74.8)]. Any significant difference of mean perfusion of ROIs was observed between SSc patients with new DUs and SSc patients without DUs. The PDG is significantly lower ($p < 0.0001$) in SSc patients with new DUs than in SSc patients without new DUs [−13.7(−134.4–57.5) vs 25.5 (−32.3–99.5)]. Only 2 of 11 SSc patients (18.2%) with PDG developed new digital ulcers, conversely 36 of 47 (76.6%) SSc patients without PDG developed new digital ulcers ($p < 0.001$).

The ROC curves demonstrated a good accuracy of new DUs prediction for PDG (0.78, $p < 0.0001$ 95% CI 0.66–0.91). Using this cut-off value of 30 pU, RR for new DUs development in SSc patients without PDG is 4.2 (95% CI 1.2–14.9 $p < 0.001$).

## 4. Discussion

In this study we demonstrated that skin perfusion of dorsal region of hands is lower in SSc patients than healthy controls. In SSc patients the skin perfusion decreases progressively with the severity of capillaroscopic damage. The SSc patients with absence of PDG showed an increased risk of DUs occurrence.

In SSc patients various author reported that the skin perfusion, evacuate by LDPI, is reduced in SSc patients and it correlated with progression of NVC patterns of microangiopathy (Rosato et al., 2009; Sulli et al., 2014; Rosato et al., 2011c; Ruaro et al., 2014a). With the capillaroscopic damage severity the skin perfusion worsens also in hand dorsum of hands (Rosato et al., 2011c). The skin perfusion showed a negative correlation with digital arteries pulsatility, evaluated by photopletismography, and with ecocolorDoppler indices of digital arterial stiffness (Rosato et al., 2011a).

Patients with SSc are at high risk for the development of ischaemic DUs, which occur in 35% to 60% of patients with SSc. However no serological or clinical markers have been proven safe in predicting the new DUs occurrence. Many authors have tried to identify markers that may be predictive for the development of new DUs.

The early occurrence and the high frequency of DUs complications are especially seen in patients with dcSSc and/or anti-topoisomerase antibodies. Male patients with early onset SSc, more severe skin fibrosis, impaired DLCO, and anti-topoisomerase I were most likely to exhibit prior or current DUs (Denton et al., 2012; Tiev et al., 2009). An observational cohort study of patients with pulmonary arterial hypertension (PAH) and multiple DUs at diagnosis were associated with future occurrence of DUs (Brand et al., 2015).

Avouac et al. identified high placental growth factor serum levels and low circulating endothelial progenitor cells counts as predictors of new DUs in SSc. It highlights the critical role of angiogenesis in this vascular outcome. These markers may improve DUs risk stratification and therefore allow earlier therapeutic intervention (Avouac et al., 2012).

DUs occurrence was associated to capillaroscopic damage. Cutolo et al. demonstrated that skin DUs seem to be associated with the “late” NVC pattern, characterized by avascular areas (severe capillary loss) (Cutolo et al., 2010). Sebastiani et al. demonstrated that the proposed CSURI may represent a novel tool with the ability to predict the development of DUs in SSc patients. The development and validation of new outcome measures may facilitate the recognition of patients at high risk to develop DUs and may improve the monitoring of vascular complications and treatments (Sebastiani et al., 2009).

Rosato et al. demonstrated that intrarenal arterial stiffness, evaluated by renal ecocolorDoppler, represents are reliable markers of new DUs occurrence. Doppler indices could be used in association with the

**Table 4**
Clinical features of SSc patients with or without new digital ulcers (DU) and mean perfusion of hand and region of interest (ROIs) in SSc patient with or without new digital ulcers (DUs).

| | | Patient with new DU n (%) | Patients without new DU n (%) | |
|---|---|---|---|---|
| DU history | Yes | 36 (62.1) | 4 (6.9) | |
| | No | 2 (3.4) | 16 (27.6) | |
| Subset | dcSSc | 26 (44.8) | 8 (13.8) | |
| | lcSSc | 12 (20.7) | 12 (20.7) | |
| Autoantibodies | Anti-topoisomerase I | 25 (40.3) | 10 (17.2) | |
| | Others | 13 (22.4) | 10 (17.2) | |
| Capillaroscopy | Early | 5 (8.6) | 10 (17.2) | |
| | Active | 12 (20.7) | 9 (15.5) | |
| | Late | 21 (36.2) | 1 (1.7) | |
| Mean perfusion | Hand (pU) | 38 (8.15–114) | 41.2 (14.9–74.8) | $p < 0.01$ |
| | ROI 1 (pU) | 61.1 (11–167.7) | 91.8 (29.2–158.6) | $p > 0.05$ |
| | ROI 2 (pU) | 65.2 (11.9–175) | 69.1 (22.5–124.1) | $p > 0.05$ |
| | ROI 3 (pU) | 76 (15.1–204) | 67.2 (42.5–104.9) | $p > 0.05$ |
| | PDG | −13.7 (−134.4–57.5) | 25.5 (−32.3–99.5) | $p < 0.0001$ |

lcSSc: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis. pU: perfusion unit.
PDG: proximal-distal gradient, expressed by perfusion mean difference between ROI 1 and ROI 2.

capillaroscopic and clinical findings or serologic tests for the identification of patients at high risk of developing DUs (Rosato et al., 2014).

In the assessment of skin perfusion and for the monitoring of digital ulcers, LSCI is a useful tool, even if not superior to LDPI at the moment (Ruaro et al., 2014b; Gaillard-Bigot et al., 2014; Ruaro et al., 2015). Even the distal dorsal difference, a parameter derived from thermography, has been used to differentiate primary RP from SSC (Anderson et al., 2007).

For the first time we demonstrated that the PDG represents a reliable marker to predict new DUs in SSc patients. In our study group skin perfusion is reduced in SSc patients with new DUs compared to patients without new DUs. PDG showed a good accuracy of new DUs predictions.

Since LDPI indices are an easy tool, we could assume that the LDPI indices could be used in association to the capillaroscopic and clinical findings or serological tests in the identification of patients at high risk of developing DUs. We can conclude that LDPI indices of skin perfusion are reliable markers of new DU occurrence. Therefore, larges studies are needed to confirm our preliminary data.

## 5. Conclusions

In SSc patients the skin perfusion decrease with severity of capillaroscopic damage.

Both mean perfusion of hand and PDG are significantly ($p < 0.01$ and $p < 0.0001$, respectively) lower in SSc patients with new DUs than in SSc patients without DUs.

LDPI indices could be used in association to the capillaroscopic and clinical findings or serological tests in the identification of SSc patients at high risk of developing DUs.

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