



Short Communication

The digital thermal hyperemia pattern is associated with the onset of digital ulcerations in systemic sclerosis during 3 years of follow-up



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ABSTRACT

Objectives: One of the most important skin complications in systemic sclerosis (SSc) is digital ulceration. Local thermal hyperemia (LTH) in the skin is a biphasic response to local heating involving both neurovascular and endothelial responses. Since LTH is abnormal in SSc patients, we aimed at testing whether LTH could be a prognostic tool for the onset of digital ulcers.

Methods: We prospectively enrolled 51 patients with SSc. Nailfold capillaroscopy and LTH were recorded at baseline, and patients were followed for 3 years.

Results: No patient with a LTH peak/plateau ratio ≥ 1 ($n = 19$) developed digital ulcerations during the 3 year follow-up (100% negative predictive value), while 6 out of 32 patients with a LTH peak/plateau ratio < 1 at enrolment presented with finger pad ulcerations within 3 years ($p = 0.05$). In contrast, when lidocaine/prilocaine was applied to the finger pad, no relationship between thermal hyperemia and digital ulcerations was observed.

Conclusions: A LTH peak/plateau ratio on the finger pad greater than 1, which can easily be determined in routine clinical practice, could be used to reassure patients, whatever the subtype of SSc, about the low probability of future digital ulceration. However, the prognostic value of this parameter should be confirmed in a larger cohort.

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Introduction

One of the most disabling cutaneous complications of systemic sclerosis (SSc) is the appearance of digital ulcers. Surrogate markers for the onset of digital ulcers are needed, and current research includes biological markers, anatomical markers (capillaroscopy) and markers of microvascular function (Smith et al., 2012a; Van Bon et al., 2014). Skin local thermal hyperemia (LTH) in response to local heating has a biphasic response, the initial peak involving neurovascular response while the delayed plateau reflects endothelial function. Both phases are abnormal in the finger pads of SSc patients (Roustit et al., 2008). We investigated whether a recording of digital LTH by laser Doppler flowmetry (LDF) could provide a potential prognostic test for the appearance of digital ulcers by following a cohort of patients for 3 years.

Methods

Study population

Patients with SSc were recruited from the outpatient clinic of the Department of Vascular Medicine Department. SSc was classified as the limited form of SSc (lSSc), limited cutaneous (lcSSc) or diffuse cutaneous SSc (dcSSc) using the criteria of LeRoy and Medsger (2001). Although, the study started before the new criteria of the American College of Rheumatology/European league against rheumatism collaborative initiative appeared in 2013, all patients met the new criteria for systemic sclerosis. Exclusion criteria included patients less than 18 years, any allergy to local anesthetics, cigarette smoking, diabetes mellitus, hypercholesterolemia or any associated severe disease (cancer, cardiac or pulmonary failure, myocardial infarction, and angina pectoris) and active digital ulcer at recruitment. All vasodilator treatments were stopped one week before the inclusion of the patient and were reintroduced after the laser Doppler measurements. Grenoble Institutional Review Board (IRB n°6705) approval was obtained in February 2007 and each subject gave written informed consent before participation.

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Study design

This was a physiological study performed in a temperature-controlled room ($23\text{ }^{\circ}\text{C} \pm 1$). Upon arrival at the laboratory, the patient's medical history was noted. Two sites were chosen on the ventral side of the left upper forearm and two sites on finger pads (index and middle finger if possible). Fingers with pitted scarring were excluded. One hour before starting thermal hyperemia tests, 1 g of lidocaine/prilocaine cream (5 g tubes containing 125 mg lidocaine and 125 mg prilocaine) was placed on one skin site of the forearm and on one fingertip. The initial application of lidocaine/prilocaine cream covered 1 cm (Smith et al., 2012a) of skin surface. Then, an occlusive transparent dressing covering a larger skin area was placed over the cream to enhance cutaneous diffusion. The anesthetized area of skin was larger than the size of the local heating devices. No cream was placed on the control sites. In order to avoid interference, the sites on the forearm were at least 3 cm apart. One hour later, the lidocaine/prilocaine cream was removed with a cotton swab. The subject remained supine for the duration of the whole experiment and before recordings started the arm was immobilized with a vacuum cushion as previously described (Roustit et al., 2009), to decrease artifacts associated with movement. Blood pressure was taken manually.

Laser Doppler measurements: thermal hyperemia

All the skin sites were instrumented for the measurement of skin blood flow using laser Doppler flowmetry (PeriFlux System 5000, Perimed, Järfälla, Sweden) with integrated local heaters (Probe 457, Perimed, Järfälla, Sweden) as previously described (Roustit et al., 2008). The laser wavelength was 780 nm and the processing frequency bandwidth was 20 Hz to 15 kHz. The sampling frequency was 32 Hz.

One hour after local anesthesia, LTH assessment using LDF was started by local heating at $42\text{ }^{\circ}\text{C}$ and maintained at this temperature for 30 min. Then, the skin sites were heated to $44\text{ }^{\circ}\text{C}$ for 5 min to obtain maximal skin blood flow (Roustit et al., 2010).

Capillaroscopy

At inclusion the nailfolds of the second, third, fourth and fifth fingers in each patient were examined bilaterally by videocapillaroscopy with a Micro-scopeman®, MS-500C (Moritex, United Kingdom) at $\times 100$ magnification. The practitioner used a qualitative assessment to grade the

nailfold videocapillaroscopy patterns as “early”, “active” or “late”, as already described by Cutolo (Smith et al., 2012b).

Follow-up

All patients were followed at least annually at the scleroderma clinic. Clinical data concerning the occurrence of digital ulcerations and their potential pathogenesis (ischemic, fibrosis or calcinosis) were prospectively recorded up to 3 years. New finger ulceration was counted as a new event when the ulceration was considered as ischemic, with the exclusion of ulcers located on an extensor surface or on metacarpophalangeal joints (Herrick et al., 2009).

Data analysis

Data were digitized and analyzed off-line with signal processing software (PeriSoft 2.5.5, Perimed, Järfälla, Sweden). We analyzed baseline flux as well as the amplitude of LTH expressed as the initial peak and the 10–30 min $42\text{ }^{\circ}\text{C}$ thermal plateau. Data were subsequently expressed as cutaneous vascular conductance (flux in mV divided by mean arterial pressure). Conductance values for the initial peak were averaged over 1 min between the 150th and 210th seconds, as 3 min is the consistent mean time to peak (Salvat-Melis et al., 2006). Conductance values for the $42\text{ }^{\circ}\text{C}$ thermal plateau phase, and the $44\text{ }^{\circ}\text{C}$ plateau phase, were each averaged over a 3 min period. We also expressed thermal hyperemia using peak/plateau ratio, a normal ratio being >1 on the finger pad and <1 on the forearm (Fig. 1). The day-to-day reproducibility of the thermal hyperemia has been demonstrated previously, the individual coefficients of variation were 17% for the peak and 25% for the plateau (Boignard et al., 2005; Roustit et al., 2010).

Statistical analysis

Quantitative data are expressed as the median and interquartile. Qualitative data are expressed as numerical values and percentage and were analyzed with the Chi2 test or Fisher's exact test as appropriate. We plotted survival curves using the Kaplan–Meier estimates. Patient data was censored at 3 years or at time of ulcer occurrence. P-values less than 0.05 were considered statistically significant. Statistical analysis was performed with SPSS 13.0 for Windows (SPSS Inc., Chicago IL, USA).

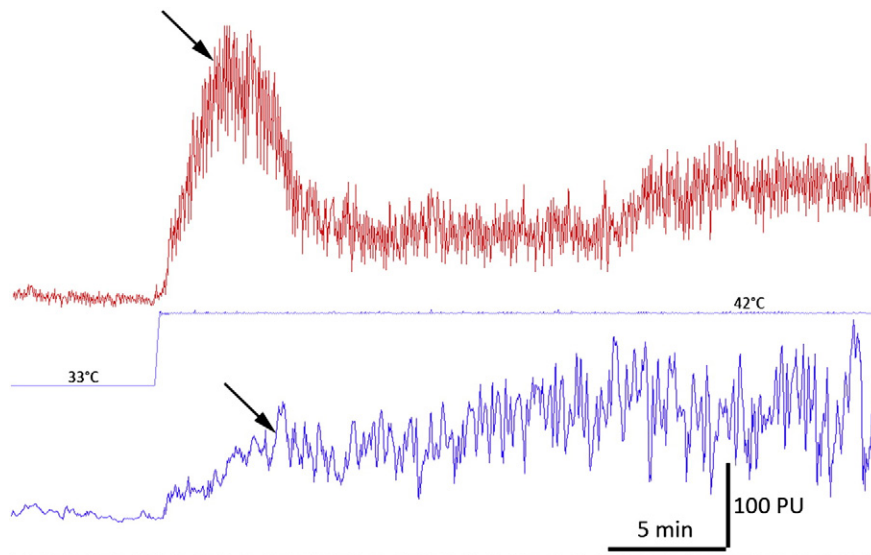


Fig. 1. Tracings of the local thermal hyperemia recorded on the finger pad of SSc patients. The tracing at the top shows normal, clear cut initial axon reflex vasodilation (arrow) with a peak/plateau ratio ≥ 1 . The tracing at the bottom shows delayed and blunted axon reflex vasodilation (arrow) with a LTH peak/plateau ratio < 1 .

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