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Thermography in systemic sclerosis patients and other rheumatic diseases: diagnosis, disease activity assessment, and therapeutic monitoring

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Dear Sir,

The recent advancement of knowledge and management strategies of patients with autoimmune conditions such as systemic sclerosis (SSc), inflammatory arthritis, and systemic lupus erythematosus (SLE) achieved during the last years lead to the clear-cut improvement of patients' quality of life and reduced long-term disability [1–5]. Nowadays, new imaging techniques in autoimmune-rheumatic diseases are expanding the possibilities to achieve an early diagnosis, an appropriate follow-up, evaluation of disease activity, monitoring and response to treatment in the affected patients. Among these techniques, infrared thermography represents a promising tool in order to assess vascular and joint involvement in autoimmune patients.

Since the initial enthusiasm in medical use of thermal photography over 2 decades ago, only few clinical practical applications were developed until past years, when the technical quality of available imaging systems advanced immensely. Improved data quality enhances the capability for detecting diagnostically relevant information in the thermal images and reduces human errors and variations in the image interpretation.

Modern thermal imaging systems are equipped to detect this radiation and can be used to form a dynamic map of temperature distribution at a surface. In brief, infrared camera generates images with thermal data in real time, and it is possible in a fraction of a second to image large areas of the human body, for example all the joints of both hands.

Thermal cameras images can be taken as a pseudo-measure of blood flow due to the convection of heat from the blood vessels in the skin and muscle in response to thermoregulation.

Moreover, as infrared thermography can give an indirect measure of blood flow and articular inflammation, it can be useful to assess peripheral vasculopathy and synovitis in active rheumatic arthritis, both at baseline and in response to treatment.

1. Arthritis

Synovitis represents the cardinal sign of arthritis, and therefore its assessment in patients with inflammatory arthritis is a major issue for proper treatment. The complementary methods of images have become increasingly relevant, being the magnetic resonance imaging (MRI) and ultrasound (US) widely used for this purpose. Nevertheless, both techniques have several limitations and the need for an ideal imaging method is still a matter of research.

In this context, thermography represents a promising imaging tool which has been not yet exhaustively explored.

Among others, Collins and Cosh and Ring and Collins [6,7] showed that the surface temperature of an arthritic joint was related to the temperature in intra-articular joint, and to other serological markers of inflammation. More recently, Brenner and colleagues demonstrated that changes observed in the thermal signature correlated with disease severity in rodent models of mono-arthritis and systemic autoimmune arthritis, suggesting that the novel thermal imaging techniques could provide useful and objective measurements of joint inflammation based on two cardinal inflammatory signs: joint swelling/edema (joint diameters) and warmth [8] (Figure 1a). New thermal imaging devices have shown to be effective at detecting changes in temperature in the context of inflammation and arthritis in *in vivo* models [9].

An early detection of articular inflammation, even before a definitive diagnosis is established, can be crucial, since starting an appropriate treatment at early stages of the pathological process seems to prevent disease persistence, joint destruction, and long-term disability [10].

Assessment of thermal imaging could be an easy to use and cost-effective technique in the general clinical practice especially when firstly assessing a new onset of arthalgia in patients suspected for rheumatic diseases. Critically, it might represent a tool to investigate the presence of active joint inflammation in the armamentarium of general practitioners when considering referring a patient for a rheumatologic evaluation and when high resolution ultrasound examination is not available or pending. Nevertheless, larger studies are still needed to confirm and validate the usefulness of

thermography in this setting as the previous studies centered mainly in exploring the thermographic differences between arthritic patients and healthy subjects.

2. Critical Digital Ischemia

Critical digital ischemia is a rare but serious complication of rheumatic diseases, mainly systemic sclerosis (SSc). It is characterized by the obstruction of the arterial flow, which causes severe pain at rest, compromising tissue viability, potentially leading to ulceration, gangrene, and ultimately amputation. In patients with SSc, this complication is the result of both progressive microangiopathy and digital artery vasculopathy [11], rather than to large vessel disorder which occurs in patients with atherosclerotic peripheral disease.

It is well recognized that microvascular changes can be easily demonstrated by nailfold capillaroscopy, which cannot provide yet functional measure of blood flow [12].

Clinical assessment and investigation need to center on establishing the underlying cause, in order to optimize treatment strategies. However, to date, the overall management of patients affected by critical digital ischemia is difficult for the treating clinician and new tools both for diagnosis and monitoring ongoing treatment are highly needed. Infrared thermal system has been previously applied as non-invasive monitoring tool that provides real-time screening information of tissue perfusion based on infrared thermal signals. Therefore, the use of thermal imaging might be an additional tool to assess critical digital ischemia and to monitor it during therapy (Figure 1b). Therefore, this approach might potentially provide helpful supplementary information about tissue perfusion in patients suffering from SSc and in those patients who experience this severe complication. Further studies are warranted to validate the diagnostic and the reproducibility of the approach.

3. Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is characterized by a broad spectrum of clinical manifestations enfolding different tissues and organs at the onset and during the course of the disease. Among

these, the presence of synovitis, meaning "non-erosive arthritis" involving ≥2 peripheral joints, characterized by tenderness, swelling or effusion or "inflammatory synovitis" in ≥ 2 joints characterized by: a) swelling or effusion, or b) tenderness and 30 minutes of morning stiffness [13] are included in the classification criteria. The joint involvement in SLE is non-erosive, non-deforming arthralgias/arthritis primarily affecting small joints of both hands, wrists and knees, and few patients show a major synovitis indistinguishable from rheumatoid arthritis (RA), the *so-called* "rhupus".

A number of techniques are available in order to objectify inflammation and joint swelling, such as MRI, which however is expensive and not practical for repetitive use. The use of high-resolution US examination represents a reliable technique when performed by expert and trained operators. However, it is not always available outside rheumatologic practise or might request a further referral. Assessment of thermal imaging could be a useful, easy to perform and cost-effective tool to be applied in both general and rheumatic settings in order to improve the management of patients with SLE complaining for arthalgia, providing a fast and reproducible methods with the potential to guide therapeutic choices (Figure 1c).

4. Systemic Sclerosis

SSc is a chronic autoimmune disorder with high morbidity and mortality. The pathogenesis of the disease is characterized by the presence of both micro- and macro-vascular damage and fibrosis. Skin lesions represent the leading feature of the disease and Raynaud's phenomenon (RP) is the most frequent and early clinical manifestation. Digital vasculopathy severely affects SSc patients, negatively impacting on their daily functions. In addition, recent evidences have shown that the presence of digital ulcers at the beginning of the disease is associated with poor cardiovascular prognosis and decreased survival rate [14]. Nevertheless, adequate treatment strategies for the management of RP and skin manifestations are lacking, mainly due to the absence of reliable outcome measures in clinical trials [15]. Therefore, identifying new tools for an early diagnosis and

monitoring of vasculopathy in SSc patients represents an urgent clinical need. Moreover, the recent development of new therapeutic agents makes this need even more important in order to assess their efficacy in preventing and treating skin and vascular involvement in this setting. In fact, as stated before, even if nailfold capillaroscopy has been already validated as an accountable tool for the analysis of those structural changes that can differentiate between primary and secondary RP, it cannot provide functional analysis of blood flow.

Previous studies have evaluated the possible role of infrared thermography imaging for the assessment of vascular damage and RP in affected patients [16–19], but its role needs further validation in SSc setting and its use in monitoring the clinical evolution and/or response to therapy has been only anecdotally explored.

Therefore, in order to evaluate the efficacy of infrared thermography in the assessment of peripheral vasculopathy in a cohort of SSc patients treated with cyclic intravenous infusions with synthetic analogue of prostacyclin (Iloprost), we designed this pilot prospective study. Critically, taking into account the lack of standard protocol timing the use of synthetic prostanoids for SSc patients, we also aimed to identify those patients who might benefit from an intensified infusional treatment protocol with prostanoids. For the sake of this study, we enrolled patients diagnosed with SSc [20], attending the San Giovanni Bosco Hospital of Turin (Italy) for their routinely 28-days apart intravenous therapy with Iloprost based on the presence of severe secondary RP and/or digital ulcers. Thermographic evaluation of both hands was performed at baseline (T0) before prostanoid infusion, and at days 14 and 28 after the first prostanoid infusion (named T1 and T2, respectively). For the thermographic recordings, a digital infrared camera FLIR ONE (FLIR Systems Inc., USA) was used. The acquired thermal images were analyzed with software dedicated to thermographic analysis FLIR Tools (FLIR Systems Inc., USA). Camera was placed on horizontal surface at 1 m distance (field of view 25° × 19°) perpendicular to skin surface. The significance of baseline differences was determined by the chi-squared test, Fisher's exact test or the unpaired t-test, as

appropriate. A two-sided P-value <0.05 was statistically significant. All statistical analyses were performed using SPSS version 19.0 (IBM, Armonk, NY, USA). As result, among the 26 enrolled patients, 24 (92.3%) were female, mean age was 65.3 ±12.6 years, and mean disease duration at time of data collection was 12.4 ±6.6 years. Fifteen patients (57.7%) presented with a limited cutaneous form of SSc, while 11 patients (42.3%) showed a diffuse cutaneous form of SSc with a high rate of interstitial lung disease as high as 63.6%. The thermographic assessment showed a substantial stability of the temperature values when comparing T0 and T1 (mean differences of the right hands 0.4 ±5.6; mean differences of the left hands 1.2 ±4.5), while they are significantly reduced when comparing T1 and T2 (mean differences of the right hands -3.1 ± 9.3, p=0.049; mean differences of the left hands -3.4 ±8.5, p=0.012) (Figure 2a). When stratifying according to clinical manifestation, a higher difference in temperature variations were observed between T1 and T2 in patients with diffuse cutaneous SSc, when compared to those with limited cutaneous SSc (mean of the differences of the right hands -5.0 ±11; mean of left-hands differences -4.9 ±11.5 Vs. mean right-hands differences -2.5 ±11; mean left-hands differences -3 ±8.6; p=0.035 respectively) (Figure 2b).

5. Conclusion and future prospective

Autoimmune rheumatic diseases are a heterogeneous group of chronic pathologic conditions affecting joints and connective tissue, often leading to permanent damage and disability, lowering the quality of life of the affected patients. An early diagnosis, an appropriate therapeutic strategy and monitoring are therefore mandatory and highly needed. In this setting, infrared thermography might represent a reliable, non-invasive, portable, and cost-effective diagnostic tool both in expert centers and in general practice. Moreover, although limited, the results of this prospective pilot study seem very promising to reinforce the role of thermography as suitable outcome measure of novel treatments for SSc-related RP and vasculopahy in clinical trials. Moreover, these data show that patients with diffuse cutaneous form of SSc could benefit more from an intensified infusion

protocol with prostanoids compared to those SSc patients with a limited cutaneous form of the disease. Indeed, further longitudinal studies are needed in order to assess the validity and the reproducibility of this technique.

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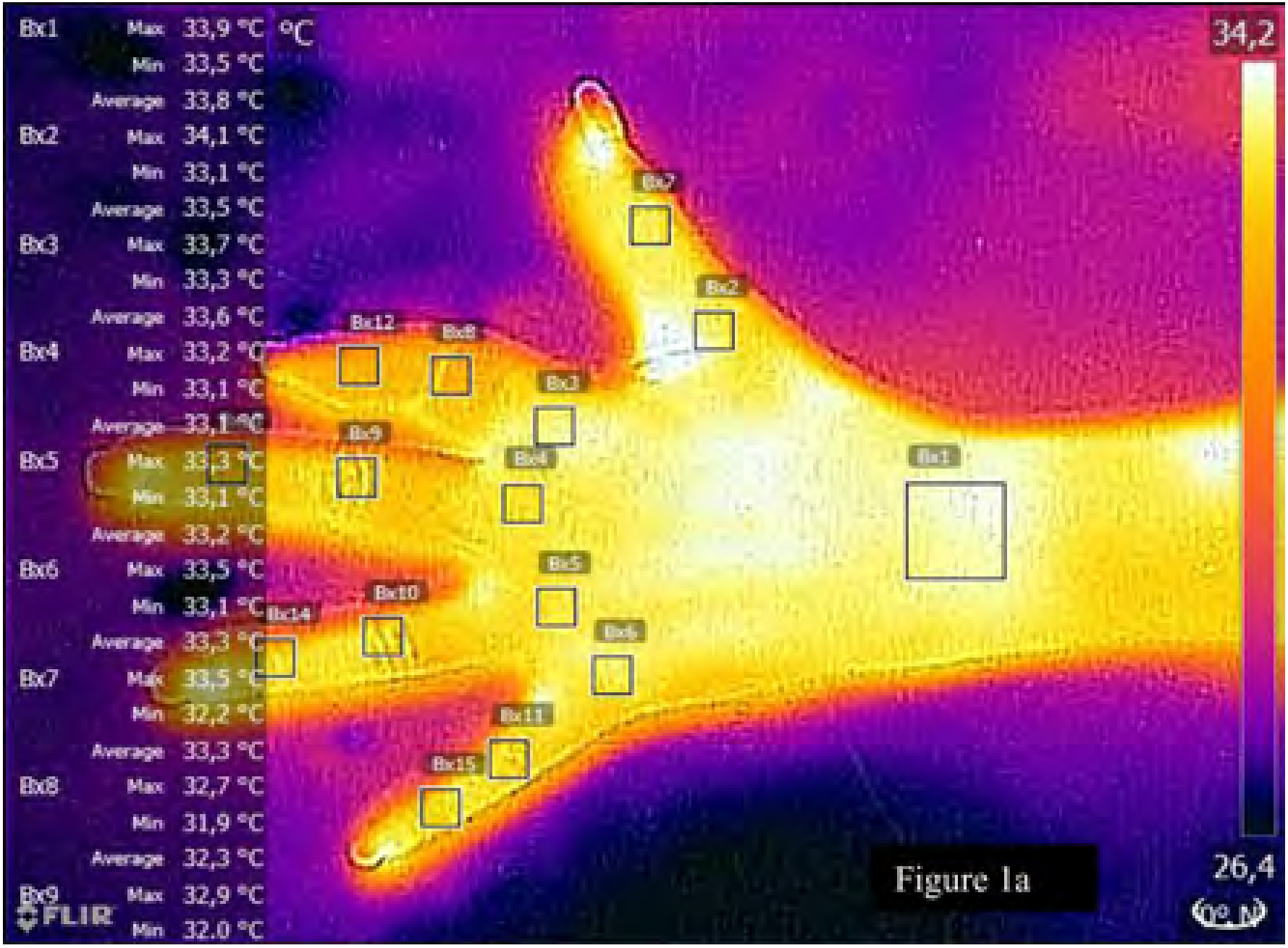
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Min 33,5 °C
Average 33,8 °C
Bx2 Max 34,1 °C
Min 33,1 °C
Average 33,5 °C
Bx3 Max 33,7 °C
Min 33,3 °C
Average 33,6 °C
Bx4 Max 33,2 °C
Min 33,1 °C
Average 33,1 °C
Bx5 Max 33,3 °C
Min 33,1 °C
Average 33,2 °C
Bx6 Max 33,5 °C
Min 33,1 °C
Average 33,3 °C
Bx7 Max 33,5 °C
Min 32,2 °C
Average 33,3 °C
Bx8 Max 32,7 °C
Min 31,9 °C
Average 32,3 °C
Bx9 Max 32,9 °C
Min 32,0 °C
°C
34,2
26,4
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Bx2
Bx12
Bx8
Bx3
Bx9
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Bx1
Bx5
Bx10
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Bx15
Figure 1a

Figure 1A

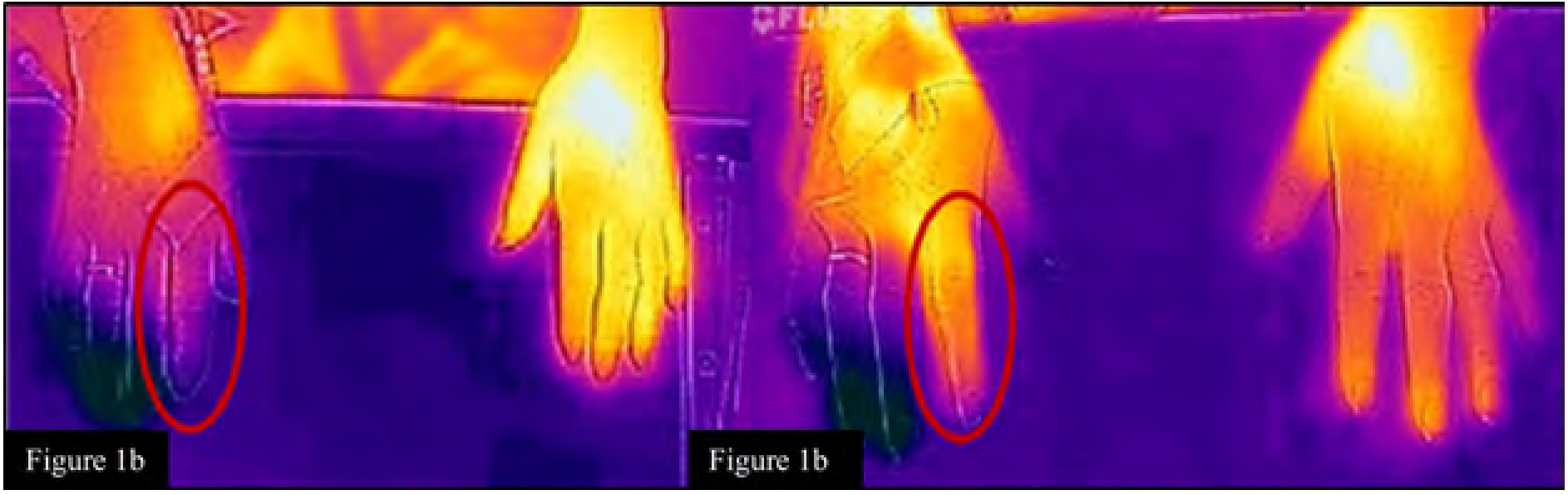


Figure 1B

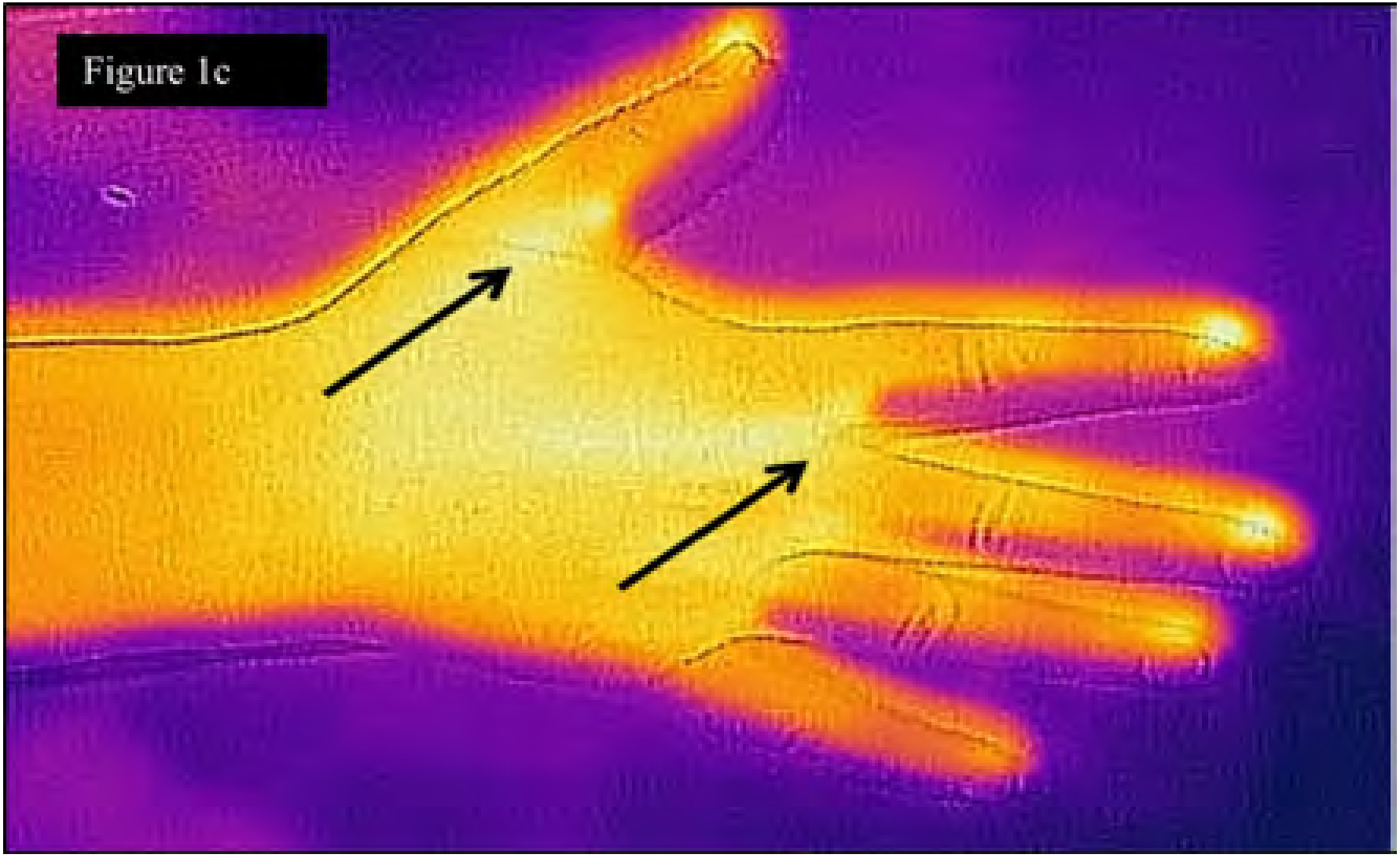
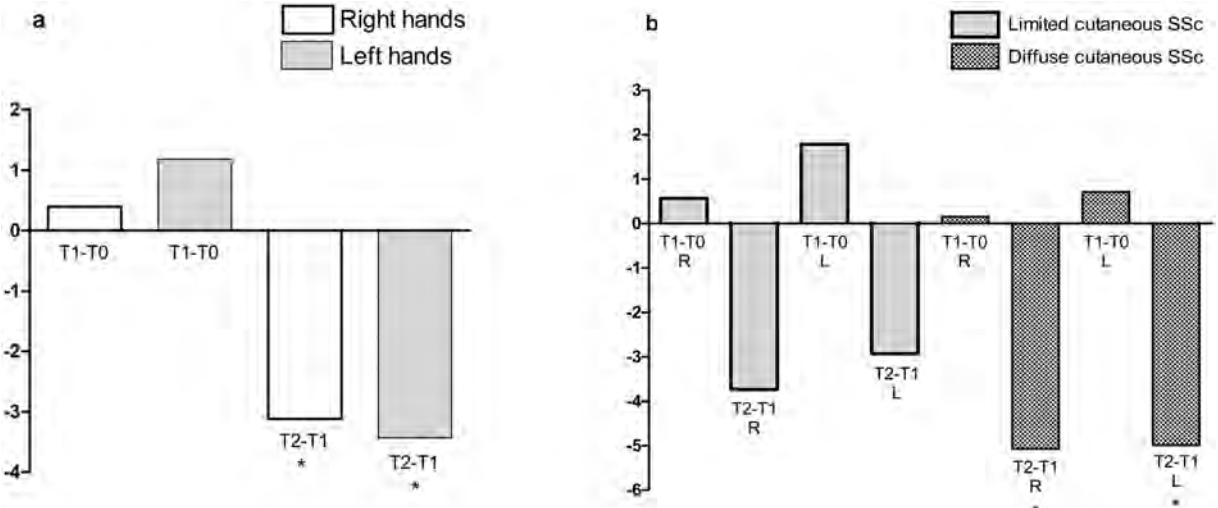


Figure 1C


a
Right hands
Left hands
2
1
0
-1
-2
-3
-4
T1-T0
T1-T0
T2-T1
*
T2-T1
*
b
Limited cutaneous SSc
Diffuse cutaneous SSc
3
2
1
0
-1
-2
-3
-4
-5
-6
T1-T0
R
T2-T1
R
T1-T0
L
T2-T1
L
T1-T0
R
T2-T1
R
*
T1-T0
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T2-T1
L
*

Figure 2