Thermal Disparity between Fingers after Cold-water Immersion of Hands: A Useful Indicator of Disturbed Peripheral Circulation in Raynaud Phenomenon Patients

Masanobu Horikoshi, Shigeko Inokuma, Yasuo Kijima, Mika Kobuna, Yoko Miura, Rika Okada and Shoko Kobayashi

Abstract

Objective To devise an effective method to assess the peripheral circulation using an infrared thermographic analysis.

Methods Sequential measurements of the skin temperature before and after cold-water immersion of the hands were analyzed by a thermographic examination in healthy controls and patients diagnosed to have Raynaud phenomenon (RP). The skin temperatures of the dorsum of all fingernail folds and the metacarpophalangeal (MCP) joints were measured at baseline. Then the hands were immersed in 10°C water for 10 s, and the skin temperatures were measured at 0, 3, 5, 10, 15, 20 and 30 min after immersion. The mean temperature, recovery rate and disparity (coefficient of variation) of the nail fold temperatures were calculated. The distal-dorsal difference (DDD) was calculated by subtracting the mean MCP temperature from the mean nail fold temperature. Receiver operating characteristic (ROC) curves were generated to compare these parameters in terms of their capability to differentiate patients with RP.

Results Thirty-one RP patients and 25 controls were included in the study. The baseline nail fold temperature was significantly lower in RP patients than in the controls. The RP patients had a lower recovery rate, lower DDD and higher disparity than the controls. The disparity and DDD were negatively correlated ($r=-0.63$, $p<0.01$), whereas the recovery rate and DDD were positively correlated ($r=0.91$, $p<0.01$). The ROC curve analysis revealed that the disparity in nail fold temperature effectively differentiated RP patients from controls (area under the curve: recovery rate 0.72; disparity 0.88; DDD 0.79).

Conclusion The temperature disparity between fingers is a useful thermographic parameter for evaluating disturbed peripheral circulation in patients with Raynaud phenomenon.

Key words: Raynaud phenomenon, connective tissue diseases, thermography

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Introduction

The peripheral vasculature is one of the major organs involved in connective tissue diseases (CTDs). Among the peripheral circulation disturbances, the Raynaud phenomenon (RP) is prevalent in, and considerably characteristic of, CTDs. RP entails paroxysmal vasospasm in the digits in response to cold exposure or emotional stress, and is typified by triphasic color changes of the skin: white due to vasospasm, followed by blue due to cyanosis and finally a red flush due to reactive hyperperfusion (1-3). In addition, we have long noticed in our clinical practice that the color of each finger differs during an attack in patients with RP.

RP has generally been assessed mainly by evaluating the patient’s medical history, as no objective measure had been established (4). Infrared thermography has traditionally been used to assess the peripheral circulation (5-7), and some pa-
rameters and protocols, including cold challenge by immersing hands in cold water, have been proposed to differentiate patients with RP (8, 9). However, to the best of our knowledge, there have been no studies of the temperature disparity between fingers in RP. In the present study, we analyzed the changes in finger temperature parameters after hand immersion in cold water, with a focus on the temperature disparity between fingers.

**Materials and Methods**

**Patients and controls**

Patients who visited the Japanese Red Cross Medical Center in Tokyo from 2009 to 2013, who were diagnosed as having RP and who underwent thermography of their hands were enrolled in the study. RP was defined as an episodic paroxysmal finger color change to white, triggered by any stimulus (including cold), as diagnosed by the attending physician (3, 4). Thermography, a test approved by the National Health Insurance System of Japan, was performed as necessary by the attending physician. Healthy individuals without pre-existing CTD or the use of medication that could affect the peripheral perfusion were enrolled as controls. This study was approved by the ethics committee of the hospital (permit number: 540).

**Thermography**

Thermographic examinations were performed using a Thermo-Tracer 3107 ME (NEC, Tokyo, Japan). After acclimatization at 25°C for 15 min in a temperature-controlled room, baseline images of the dorsum of both hands were captured. The hands were then immersed in a cold water bath set at 10°C for 10 s, and thermographic images were captured at 0, 3, 5, 10, 15, 20 and 30 min after immersion. The target points for the temperature analysis were the nail fold and dorsum of the metacarpophalangeal joints (MCP) of all fingers.

**Data analysis**

The recovery rate of the nail fold temperature of each finger (Fig. 1) was calculated as the temperature recovery from just after immersion divided by the temperature decrease from baseline to just after immersion. The disparity of the nail fold temperature of the five fingers was calculated as the standard deviation in temperature divided by the mean temperature. The distal-dorsal difference (DDD) was calculated as the mean nail fold temperature minus the mean MCP temperature. Both hands were assessed for each subject.

**Statistical analysis**

The significance of the differences between groups was assessed using the Mann-Whitney U-test. The significance of the correlations between parameters was assessed using Spearman’s rank correlation coefficient. A value of p<0.05 was considered to be significant.

**Results**

Thirty-one patients and 25 controls were enrolled in the study. The characteristics of the subjects are shown in Table. The age differed significantly between the patients and controls (p<0.01). RP was not induced by the brief cold-water immersion of the hands in any patient or control.

**Nail fold temperature before and after cold-water immersion**

The changes in nail fold temperature from baseline after cold-water immersion in controls and patients with RP are shown in Fig. 2A and B, respectively. The mean nail fold temperature of each patient and control are shown in Fig. 2C and D, respectively. The comparison of the nail fold temperature at baseline and after immersion between controls and patients with RP is shown in Fig. 3A. The baseline nail fold temperature was significantly lower in patients with RP than in controls (30.8±3.1°C vs. 33.2±1.8°C, p<0.01). Except for the time point just after immersion, the nail fold temperature was significantly lower in patients with RP at

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**Table.** **Subject Characteristics.**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Raynaud phenomenon patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, range)</td>
<td>40 (20-67)</td>
<td>60* (21-83)</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Systemic sclerosis 11</td>
<td>Primary Raynaud 10</td>
</tr>
<tr>
<td></td>
<td>SLE 4</td>
<td>MCTD 3</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis 2</td>
<td>Sjögren syndrome 1</td>
</tr>
<tr>
<td>Anti-nuclear antibody</td>
<td>28/30 (93.3%)</td>
<td></td>
</tr>
<tr>
<td>Anti-centromere antibody</td>
<td>10/30 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>Anti-RNP antibody</td>
<td>8/26 (30.8%)</td>
<td></td>
</tr>
<tr>
<td>Anti-Scl-70 antibody</td>
<td>3/26 (11.5%)</td>
<td></td>
</tr>
<tr>
<td>Use of vasodilators</td>
<td>Beraprost sodium 7</td>
<td>Bosentan 1</td>
</tr>
<tr>
<td></td>
<td>Sildenafil</td>
<td>Sildenafil 1</td>
</tr>
</tbody>
</table>

*p=0.001 vs controls

Abbreviations: SLE: systemic lupus erythematosus, MCTD: mixed connective tissue disease
all time points.

**Temperature recovery after cold-water immersion**

The recovery rates after cold-water immersion are shown in Fig. 3B. At 3 and 5 min after immersion, the recovery rate was significantly lower in patients with RP than in controls, and the difference was highest at 5 min (patients with RP: 49.6±27.7; controls: 71.5±26.8; p<0.01).

**Disparity of nail fold temperature**

The temperature disparity was significantly higher in patients with RP than in the controls both at baseline and at all time points after immersion (Fig. 3C). The difference between the groups was highest at 5 min (patients with RP: 0.053±0.024; controls: 0.021±0.015; p<0.01).

**The nail fold temperature was inversely proportional to the MCP temperature in patients with RP**

The DDD values at baseline and after cold-water immersion are shown in Fig. 3D. In the controls, the mean DDD was positive (the nail fold was warmer than the MCP) at all time points except for 0 and 3 min after immersion. On the contrary, the mean DDD was constantly negative (the nail fold was cooler) in patients with RP at all time points. The DDD differed significantly between the groups at all time points except for that just after immersion. The difference was highest at 5 min after immersion (patients with RP: -1.4±2.8; controls: 0.85±2.7; p<0.01).

**Correlations between thermographic parameters**

The recovery rate showed a significant negative correlation with the coefficient of variation in all controls, but no correlations were observed in the RP patients (Fig. 4A). The recovery rate had a significant positive correlation with the DDD in all controls and patients with RP (Fig. 4B).

**Receiver operating characteristics analysis**

In the receiver operating characteristic (ROC) analysis, the areas under the curve (AUC) for the baseline nail fold temperature, recovery rate, disparity and DDD were 0.80, 0.72, 0.88 and 0.74, respectively (Fig. 5).

**Comparison of the thermographic parameters between RP patients with systemic sclerosis and other RP patients**

The recovery rate, temperature disparity and DDD at 5 min after immersion in 10 RP patients with systemic sclerosis were compared with the values for the other 21 patients with RP. The systemic sclerosis patients had a significantly lower recovery rate (35.5±24.8 vs. 57.3±26.7%, p<0.05) and DDD (-2.94±2.2 vs. -0.88±2.77, p<0.05), and a significantly higher temperature disparity (0.066±0.027 vs. 0.046±0.02, p <0.05) than the other patients with RP.
Discussion

In agreement with past studies (8, 10, 11), the present patients with RP had a significantly lower baseline temperature than the controls. Monitoring the temperatures after cold-water immersion revealed that there were differences in the response between the patients with RP and the controls. In most of the controls, the nail fold temperature recovered to the baseline level within 10 min, and the temperatures between fingers did not vary. In addition, the nail fold temperature was principally higher than the MCP temperature, which became inversely proportional only after immersion, and was almost the same at 3 min. On the other hand, in patients with RP, the mean nail fold temperature was consistently lower than the MCP temperature, and the recovery to baseline levels was delayed and sometimes did not recover at all during the monitoring period. In the healthy subjects, the response to the cold stimuli can be explained by the fact that peripheral vessels constrict to maintain the body core temperature. In contrast, this mechanism is altered in patients with RP (12). Furthermore, the nail fold temperature disparity between the fingers, as indicated by the mean coefficient of variation, was consistently higher in patients with RP. These results suggest that the peripheral circulation in patients with RP is altered not only in each finger, but also relatively evenly between the fingers.

Our results also showed a significant negative correlation between the temperature disparity and recovery rate, and a strong positive correlation between the recovery rate and the DDD.
Figure 5. The results of a receiver operating characteristic (ROC) curve analysis of the thermographic parameters. The ROC curve analysis and the area under the curve (AUC) of the baseline temperature (A), recovery rate (B), disparity of the nail fold temperature (C) and DDD (D) 5 min after cold-water immersion.

DDD. These findings suggest that the disparities in the nail fold temperature, recovery after immersion and the inversion of the nail fold and MCP temperature increases were in line with a peripheral perfusion disturbance. However, some patients showed a low temperature disparity, despite exhibiting extremely delayed recovery after immersion. Although we suspect that these subjects might have had the most impaired circulation as a result of probable remodeling of the small vasculature, their characteristics remain to be clarified.

An ROC curve analysis was performed to compare the diagnostic value of the tested parameters. The coefficient of variation had the highest AUC and the best discriminatory power to differentiate patients with RP from controls, and had values higher than those of the recovery rate (AUC, 0.72; coefficient of variation: 0.88) and DDD (AUC, 0.79). Because the AUC of these parameters was increased following cold-water immersion, we concluded that the immersion was useful to identify peripheral circulatory abnormalities, although there have been discordant reports about its usefulness in thermographic examinations (9, 13).

Several studies have reported that thermographic examinations are useful for differentiating secondary RP, such as systemic sclerosis, from primary RP (9, 13-17). In our study, the RP patients with systemic sclerosis had a significantly lower recovery rate and DDD and a significantly higher temperature disparity than the other patients with RP. Further investigation is needed to validate the use of these thermographic parameters for differentiating systemic sclerosis patients from other RP patients.

A limitation of this study is the significant difference in age between the patients with RP and the controls. However, we did not consider age to be an important factor, because it did not correlate with any of the thermographic parameters (data not shown). Another limitation was that the smoking status was not taken into account.

In conclusion, the present findings revealed a lower nail fold temperature, lower recovery rate and lower DDD in RP patients compared to controls. The most novel finding was the disparity in the nail fold temperature between the fingers in the RP patients. These findings suggest that the remodeling in RP patients may be due to the underlying abnormal vasculature, and may result in an uneven response to thermal stimuli.

The authors state that they have no Conflict of Interest (COI).
References


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