Measurement of cold challenge responses in primary
Raynaud’s phenomenon and Raynaud’s phenomenon
associated with systemic sclerosis

D O’Reilly, L Taylor, K El-Hadidy, M I V Jayson

Abstract
Using computed thermography continuous
temperature recordings were made before and
after cold challenge of the fingers of control
subjects and patients with primary Raynaud’s
phenomenon and Raynaud’s phenomenon
associated with systemic sclerosis. Basal
skin temperature measurements (T_pre) were
significantly lower in patients with primary
Raynaud’s phenomenon and Raynaud’s pheno-
menon associated with systemic sclerosis
than in the controls. Temperatures immedi-
a
cately after cold challenge (T_a) were significantly
lower in patients with primary Raynaud’s
phenomenon and Raynaud’s phenomenon
associated with systemic sclerosis than in
controls. The lag phase before the start
of temperature recovery (Tlag) was signifi-
cantly greater in patients with primary
Raynaud’s phenomenon and Raynaud’s
phenomenon associated with systemic
sclerosis than in control subjects. The
maximum recovery index (Rmax) was signifi-
cantly less in patients with primary Raynaud’s
phenomenon and Raynaud’s phenomenon
associated with systemic sclerosis than in
controls. The maximum rate of change of
temperature during the rapid phase of
rewarming (Gmax) was significantly greater in
controls than in patients with primary
Raynaud’s phenomenon and Raynaud’s
phenomenon associated with systemic
sclerosis. Discriminant analysis showed that
the dynamic parameters of rewarming (Tlag,
Gmax, and Rmax) showed greater variation
between the patients with primary Raynaud’s
phenomenon and those with Raynaud’s
phenomenon associated with systemic
sclerosis than did T_pre or T_a. This method
of analysis of cold challenge will be used in
studies of the effects of treatment of Raynaud’s
phenomenon.


In Raynaud’s phenomenon there is episodic
digital ischaemia with phasic colour changes on
exposure to cold or emotional stress. Although
the clinical appearances are well recognised it
has proved difficult to quantify the changes in
the microcirculation. Using modern techniques
of thermography and computed image analysis
it is possible to make continuous real time
recordings of the rewarming curves of subjects
after a cold challenge. We have used these
techniques to measure the differing micro-
circulatory response to cold challenge in control
subjects and patients with primary Raynaud’s
phenomenon and Raynaud’s phenomenon
associated with systemic sclerosis.

Subjects and methods
Raynaud’s phenomenon is defined as at least
two years of abnormal responses to exposure to
cold with skin colour changes of pallor followed
by cyanosis or erythrocyanosis, or both. The
patients with primary Raynaud’s phenomenon
had no history, physical signs, nor serological
features suggestive of connective tissue disease.
The patients with Raynaud’s phenomenon asso-
ciated with systemic sclerosis fulfilled the
diagnostic criteria of the American Rheumatism
Association for systemic sclerosis.

There were 21 control subjects (14 women,
seven men; mean age 39-2 years, range 29-71),
16 patients with primary Raynaud’s pheno-
menon (12 women, four men; mean age 44-18
years, range 24-72) and 20 patients with
Raynaud’s phenomenon associated with systemic
sclerosis (19 women, one man; mean age
49-63 years, range 24-67) (table 1).

The subjects were asked not to smoke or to
take any drugs from midnight before the study.
They were rested for 20 minutes in a controlled
environment at a temperature of 23±0-5°C and
humidity 45±5%. The right hand was then
placed in a frame such that the position of the
fingers was fixed and using an Inframetrics
600m thermography camera a baseline image of
the dorsal surface was recorded onto a video
tape. A disposable latex glove was then put on
and the hand immersed in water at 15°C for one
minute. After removal of the glove the hand was
returned to the same position. Continuous
thermographic video tape recordings were made
for 15 minutes.

Using the commercially available Thermotech-
ics TTX2 thermography program on a
standard IBM microcomputer three points were
selected over the distal interphalangeal joints of
the index, middle, and ring fingers during
replay of the video taped recording. The
temperature at each point was plotted at 15
second intervals as rewarming curves.

Table 1 Characteristics of subjects studied

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Male/female</th>
<th>Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n=21)</td>
<td>7/14</td>
<td>39-2 (24-71)</td>
</tr>
<tr>
<td>PRP (n=16)</td>
<td>4/12</td>
<td>44-2 (24-72)</td>
</tr>
<tr>
<td>SSRP (n=20)</td>
<td>1/19</td>
<td>49-6 (24-67)</td>
</tr>
</tbody>
</table>

PRP=primary Raynaud’s phenomenon; SSRP=Raynaud’s phenomenon associated with systemic sclerosis.
this recovery index (T<sub>lag</sub>) was recorded in each subject (figure). Using a locally written program the first differential of the temperature-time curve was plotted. This allowed measurement of the change in temperature with time (°C/minute) and from this the maximum temperature recovery rate (G<sub>max</sub>) could be measured. This curve was redifferentiated to give the rate of change of temperature gradient with time. The peak of this second differentiation curve indicated the point at which there was the maximum increase in the rate of change of temperature (°C/minute/minute) and the time at which this occurred (T<sub>lag</sub>) represented the lag phase from cold challenge until rewarming began.

Using the SPSS statistical program the temperature measurements and R<sub>rec</sub> were analysed using Student’s t test; the G<sub>max</sub> and T<sub>lag</sub> measurements were not normally distributed and so were transformed to log<sub>10</sub> values before t test analysis. Discriminant analysis (Wilks’ method minimising lambda) was performed on all these variables to estimate which parameters best discriminated between the subject groups.

**Results**

The mean basal temperature (T<sub>bas</sub>) was lower in patients with primary Raynaud’s phenomenon and Raynaud’s phenomenon associated with systemic sclerosis than in controls (table 2). These differences were statistically significant. The mean basal temperature in patients with Raynaud’s phenomenon associated with systemic sclerosis was not lower than that in patients with primary Raynaud’s phenomenon. The absolute temperature immediately after cold challenge (T<sub>0</sub>) was significantly higher in controls than in patients with primary Raynaud’s phenomenon and Raynaud’s phenomenon associated with systemic sclerosis; however, there was no difference in T<sub>0</sub> between the patients with primary Raynaud’s phenomenon and Raynaud’s phenomenon associated with systemic sclerosis.

In controls there was a short lag phase and then a rapid recovery to above basal levels, reflected by the significant differences in G<sub>max</sub>, T<sub>lag</sub>, and R<sub>rec</sub> compared with the other groups. In patients with primary Raynaud’s phenomenon there was a longer lag phase with slower and incomplete temperature recovery. In patients with Raynaud’s phenomenon associated with systemic sclerosis there was a prolonged period without rewarming with no definite phase of rewarming, and often no significant recovery by 15 minutes. In these subjects the lag time was

![Graph](image)

(A) Typical rewarming curve of a control subject; arrows indicate recovery index at 1, 5, 10, and 15 minutes. (B) First differentiation of rewarming curve to estimate G<sub>max</sub>, the maximum temperature gradient. (C) Second differentiation of rewarming curve to estimate T<sub>lag</sub>, the lag phase before the rapid phase of rewarming. R<sup>%</sup>= recovery index.

The temperature recovery curves (figure) following a cold challenge typically showed a lag phase when there was little alteration in temperature followed by a phase of rapid increase in temperature. In normal subjects the temperature usually exceeded the baseline temperature after the rapid rewarming phase but in patients with primary Raynaud’s phenomenon and Raynaud’s phenomenon associated with systemic sclerosis temperatures usually did not reach baseline values by 15 minutes after cold challenge.

For each subject the mean temperature decrease on cooling was measured. At 1, 5, 10, and 15 minutes after cold challenge an index of percentage recovery was calculated (index=temperature increase/initial temperature decrease)×100%. The maximum value of

**Table 2 Results of cold challenge in subjects studied**

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=21)</th>
<th>Patients with PRP* (n=16)</th>
<th>Patients with SSRP* (n=20)</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39-2</td>
<td>44-2</td>
<td>49-6</td>
<td></td>
</tr>
<tr>
<td>T&lt;sub&gt;rec&lt;/sub&gt; (°C)</td>
<td>30-04</td>
<td>25-9</td>
<td>25-49</td>
<td>0.006</td>
</tr>
<tr>
<td>T&lt;sub&gt;0&lt;/sub&gt; (°C)</td>
<td>22-6</td>
<td>20-02</td>
<td>20-16</td>
<td>0.004</td>
</tr>
<tr>
<td>Log&lt;sub&gt;10&lt;/sub&gt;G&lt;sub&gt;max&lt;/sub&gt;</td>
<td>0-2351</td>
<td>-9-16</td>
<td>-9-353</td>
<td>0.006</td>
</tr>
<tr>
<td>Log&lt;sub&gt;10&lt;/sub&gt;T&lt;sub&gt;lag&lt;/sub&gt;</td>
<td>0-1934</td>
<td>0-654</td>
<td>0-982</td>
<td>0.005</td>
</tr>
<tr>
<td>Maximum observed recovery index (%)</td>
<td>131-2</td>
<td>66-6</td>
<td>40-35</td>
<td></td>
</tr>
</tbody>
</table>

*PRP=primary Raynaud’s phenomenon; SSRP=Raynaud’s phenomenon associated with systemic sclerosis.

†Not significant.
Cold challenge responses in Raynaud's phenomenon

recorded as greater than 15 minutes and calculated as 15 minutes in the statistical tests. The lag times were longer in patients with Raynaud's phenomenon associated with systemic sclerosis than in those with primary Raynaud's phenomenon, though this did not achieve statistical significance (p=0.02). The maximum observed temperature recovery rate Rₚₙ was significantly lower in patients with primary Raynaud's phenomenon than in controls. Rₚₙ was lower in patients with Raynaud's phenomenon associated with systemic sclerosis than in those with primary Raynaud's phenomenon but again this did not achieve statistical significance (p=0.049). Gₘₐₓ did not significantly differ between patients with primary Raynaud's phenomenon and Raynaud's phenomenon associated with systemic sclerosis (p=0.841). Discriminant analysis of these five measurements in the primary Raynaud's phenomenon and Raynaud's phenomenon associated with systemic sclerosis groups showed that the dynamic parameters Tₚₑₑ, Gₘₐₓ, and Rₚₙ were more effective discriminants between patients with primary Raynaud's phenomenon and Raynaud's phenomenon associated with systemic sclerosis than the temperature measurements Tₚₑ and T₀. Using the discriminant analysis statistical model to predict actual group membership from the original data recorded from the patients with primary Raynaud's phenomenon and Raynaud's phenomenon associated with systemic sclerosis gave correct classification in 75% of cases with a sensitivity of 80% and a specificity of 68%.

Discussion

Continuous recording of the temperature changes in the skin using modern thermographic techniques with computed analysis provides a rapid and relatively simple method of quantifying Raynaud's phenomenon. Earlier techniques include plethysmography and the application of thermistors. These methods will produce local disturbance of the circulation and influence results. Point measurements can be made using a bolometer but this must be applied separately to each site, again disturbing the local microcirculation and introducing artifacts. The thermographic pictures are taken from a distance and provide high resolution with accurate recording of surface temperature. There is no local interference with the microcirculation and so the method is ideal for studying the temperature changes after cold challenge. The thermographic images are recorded onto video tape for later analysis. Sophisticated computer analysis of the images allows the continuous recording of surface temperature at selected points rather than calculation of the mean temperature of the whole image. The new methods of image analysis allow rapid measurement of these changes in a way suitable for clinical study.

Cold challenge has been reviewed elsewhere. There is no agreed protocol for cold challenge; however, the experimental conditions used in our study are similar to those widely used elsewhere. The environmental conditions for this study were chosen to be neither vaso-constrictive nor vasodilatory. The cold challenge (water bath at 15°C for one minute) used in this study was relatively mild but seems adequate for quantitative measurements of temperature recovery patterns. The severity of cold challenge in other studies varies from immersion in 'ice water', to challenge at 20°C. The more severe challenges are unpleasant for patients and potentially dangerous for those with severe Raynaud's phenomenon.

It is well known that subjects with Raynaud's phenomenon have abnormal cold challenge recovery curves, with lower basal temperatures and slower recovery. Until now, however, no attempt has been made to use cold challenge to discriminate between patients with primary Raynaud's phenomenon and those with Raynaud's phenomenon associated with systemic sclerosis. As Raynaud's phenomenon is often the first presenting symptom of systemic sclerosis the ability to discriminate between patients with primary Raynaud's phenomenon and Raynaud's phenomenon associated with systemic sclerosis would be a significant clinical advantage. The aim of this study was to take the data from standard cold challenge and to identify objective and quantifiable parameters of the response curves which relate in some way to the pathophysiological processes and can be used to discriminate patients with primary Raynaud's phenomenon from those with Raynaud's phenomenon associated with systemic sclerosis. In normal subjects rewarming begins in the finger pulps with the opening of arteriovenous shunts; the rewarming effect spreads proximally to the palm. In subjects with Raynaud's phenomenon, however, rewarming often starts at the base of the fingers and spreads up to the tips of the fingers; hyperaemia of the finger tips often does not occur. In following the cold challenge response curves a typical pattern is seen (figure). After cold challenge there is often a lag period when the skin surface warms slowly, if at all. There is then a phase of more rapid temperature change before the final phase when skin rewarming has stopped. Most of the controls are hyperaemic in this final phase with a recovery index greater than 100%. In the Raynaud's phenomenon associated with systemic sclerosis group most subjects had relatively flat curves; however, some did show temperature recovery. We used a simple microcomputer program to quantify objectively those characteristics of the recovery curves. The interval before rewarming begins, Tₚₑₑ, was significantly longer in patients with primary Raynaud's phenomenon than in controls. In many subjects with Raynaud's phenomenon associated with systemic sclerosis the rewarming was so slow that the lag time exceeded the length of the 15 minute study period. The rapid rewarming phase seen in most of the controls was also present in most, but not all of the group with primary Raynaud's phenomenon. This phase must correspond to a period of increased blood flow through the finger or a change in the distribution of that flow, either through the cutaneous microcirculation or through the deeper vessels with rewarming of the skin by conduction. Gₘₐₓ was derived as a means of quantifying this.
aspect of the rewarming curve and so must relate indirectly to the rate and distribution of blood flow through the finger. \( G_{\text{max}} \) was significantly greater in controls than in patients with primary Raynaud's phenomenon. \( G_{\text{max}} \) was greater in patients with primary Raynaud's phenomenon than in those with Raynaud's phenomenon associated with systemic sclerosis, but this did not achieve significance. The temperatures immediately before \( T_{\text{pre}} \) and after \( T_{\text{pre}} \) cold challenge were similar in patients with Raynaud's phenomenon associated with systemic sclerosis and primary Raynaud's phenomenon. Discriminant analysis of all the variables in the patients with primary Raynaud's phenomenon and those with Raynaud's phenomenon associated with systemic sclerosis showed that the dynamic parameters were more powerful discriminants than \( T_{\text{pre}} \) or \( T_{\text{pre}} \). The recovery index \( R_{\text{w}} \) was significantly greater in controls than in patients with primary Raynaud's phenomenon but did not differ in primary Raynaud's phenomenon and Raynaud's phenomenon associated with systemic sclerosis. This measurement is less useful in those subjects with Raynaud's phenomenon associated with systemic sclerosis where \( T_{\text{pre}} \) is only 1 or 2°C above the cold challenge water temperature. Rewarming of the skin surface by convection alone could then produce an \( R_{\text{w}} \) value close to 100%.

Rather than compare serial measurements of absolute temperature changes in subjects at sequential time points we have compared individual maximum dynamic responses. The statistical problems of analysing serial measurements are avoided and it is also possible to compare subjects with responses over different temperature ranges.

We found significant reductions in basal skin temperature compared with controls not only in patients with Raynaud's phenomenon associated with systemic sclerosis but also in those with primary Raynaud's phenomenon. Simple measurements of basal temperatures, however, are the same in patients with primary Raynaud's phenomenon and those with Raynaud's phenomenon associated with systemic sclerosis. We have also shown a significant reduction in the rate of increase in skin temperature in the rapid rewarming phase after cold challenge. This may reflect some permanent vascular compromise in primary Raynaud's phenomenon and thus implies that Raynaud's phenomenon is not completely reversible. Alternatively, this could be due to a greater degree of vasoconstriction in the primary Raynaud's phenomenon group at 23°C which persists during recovery from cold challenge.

A number of mechanisms have been suggested for the development of Raynaud's phenomenon. These include prolonged vasoconstriction, permanent narrowing of the digital arteries, and hyperviscosity of the blood. The lower basal temperatures in patients with primary Raynaud's phenomenon are compatible with the hypothesis that there is a permanent impairment of the microcirculation and that Raynaud's phenomenon is not entirely due to reversible vasoconstriction. The prolonged lag phase in patients with primary Raynaud's phenomenon and particularly in those with Raynaud's phenomenon associated with systemic sclerosis may be associated with arterial narrowing or with a disproportionate increase in blood viscosity on cooling. It is known that there is hyperviscosity of the blood in Raynaud's phenomenon associated with systemic sclerosis and primary Raynaud's phenomenon and this increases on cooling.

The technique of quantitative thermography and analysis of rewarming curves appears promising for measurement of the disturbance of the microcirculation in Raynaud's phenomenon and in differentiating between Raynaud's phenomenon associated with systemic sclerosis and primary Raynaud's phenomenon. The methods and all measurements and analyses take less than an hour. The technique of computed thermography measures the patient's actual observation that after cold exposure their fingers warm up slowly after a long delay.

The dynamic parameters reflect the characteristics of the individual rewarming curves and will be investigated as indicators of severity of disease and efficacy of treatment in future studies. The relation between \( G_{\text{max}} \) and red cell flux through the microcirculation will be investigated by simultaneous thermography and laser Doppler studies.

We acknowledge the help and advice of Dr D Taylor who wrote the program for differentiation of the rewarming curves and Ms S Hollis for her statistical advice. We are grateful to the Raynaud's and Scleroderma Association for financial support to purchase the computed image analysis system.


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