

Review

Selective Peripheral Heating Without Hand Enclosure for Raynaud's Phenomenon via Upregulation of Angiopoietin-1

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Abstract

Peripheral capillaries are damaged, and Raynaud's phenomenon occurs frequently in patients with systemic sclerosis (SSc). Treatment with vasodilators often results in adverse effects, such as headache and facial flushing, and does not lead to sufficient therapeutic effects. The transient receptor potential V4 (TRPV4) channel is a thermoreceptor that contributes to capillary dilation and growth. Recent studies have explored whether local thermal stimulation sufficient to activate TRPV4 can alleviate RP. This heating resulted in improvements in the severity, frequency, and duration of RP, and the area around the elbow was found to be an appropriate site for heating. During heating, an increase in the capillary-stabilizing factor angiopoietin-1 was observed in the fingertips, and improvements in capillary morphology were confirmed. Collectively, these findings suggest that controlled thermal stimulation around the elbow may represent a safe and practical adjunctive strategy for alleviating RP and improving peripheral microvascular function.

Keywords: Raynaud's phenomenon; systemic sclerosis; heat therapy; transient receptor potential; angiopoietin

1. Introduction

In patients with systemic sclerosis (SSc), Raynaud's phenomenon (RP), in which peripheral blood circulation suddenly worsens in response to cold stimuli or mental stress, occurs frequently. RP can manifest in various peripheral tissues throughout the body; however, it is particularly prevalent in the fingers [1]. The mechanisms underlying this phenomenon are not yet fully understood. Our previous survey of 300 SSc patients found that the most common answer to the question "What is your troublesome symptoms?" was "Raynaud's phenomenon." [2] RP sometimes progresses to fingertip ulcers and necrosis, necessitating the implementation of preventative measures. Treatment with vasodilators often results in adverse events (Table 1) [3–8], such as headaches, and frequently fails to achieve satisfactory therapeutic effects. Currently available drug-based treatments that suppress RP have limitations, and we are seeking practical solutions that are simple, inexpensive, and easy to implement. This section discusses the thermotherapy for RP, with a particular focus on the thermoreceptor, and introduces our current findings regarding the mitigating effects of thermal stimulation on RP and the mechanisms underlying these effects.



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2. Raynaud's Phenomenon and the Current Treatments

Maurice Raynaud (1834–1881) published a paper in 1862 regarding 25 patients with paroxysmal finger ischemia [9]. He reported that this ischemic phenomenon (a) was more common in women, (b) was triggered by cold stimuli or mental stress, (c) had a duration that varied from a few minutes to several hours, (d) was accompanied by numbness or pain, and e) had a color change that differed depending on the severity of the disease. He documented most of the characteristics of the phenomenon that we now recognize as RP. RP can occur in various diseases, including systemic lupus erythematosus and rheumatoid arthritis, but occurs more frequently in SSc [10].

This phenomenon is a symptom of ischemia; therefore, treatment involves the administration of vasodilators. The 2023 EULAR guideline for SSc advocates the use of dihydropyridine-type calcium antagonists, typically nifedipine, as the primary treatment option [11]. The use of phosphodiesterase type 5 (PDE5) inhibitors or iloprost is recommended as a second-line treatment option. Nifedipine is a drug that induces vasodilation by inhibiting the influx of calcium ions necessary for the contraction of vascular smooth muscle and is mainly used as an antihypertensive agent [12]. PDE5 inhibitors inhibit the enzyme phosphodiesterase 5, thereby increasing cyclic guanosine monophosphate (cGMP) levels and consequently relaxing vascular smooth muscle. They are primarily used to treat pulmonary hypertension [13]. Iloprost is a prostacyclin receptor agonist that relaxes the vascular smooth muscle and is primarily used to treat pulmonary hypertension [14]. These medications are recommended based on evidence from randomized controlled trials demonstrating their efficacy in treating RP. However, upon reviewing the original research, it becomes clear that adverse events frequently occur with all these drugs. In a trial of nifedipine, facial flushing occurred in 52% of participants, numbness in the hands and feet in 35%, and headache in 26% of participants [3] (Table 1). In a trial of the PDE5 inhibitor sildenafil, 20% of participants experienced headaches, and one participant withdrew because of severe headache. Headaches and facial flushing are thought to be caused by vasodilation in the head and face associated with systemic administration of vasodilators [7].

Table 1. Recommended medications for treating Raynaud's phenomenon and their associated adverse events.

Drug Category	Recommended Medicine	Subject	Main Adverse Event	Source
Ca channel antagonist	Nifedipine	Primary RP	Flushing (52%) Acroparesthesia (35%) Headache (26%) Ankle swelling (22%)	[3]
	Nifedipine	RS	Headache (26%) Ankle oedema (26%) Facial flushing (20%)	[4]
Prostanoids	Intravenous Iloprost	SSc	Flushing (48%, 40%) * Headache (24%, 12%) *	[5]
PDE III inhibitor	Cilostazol	RS	Headache (35%)	[6]
PDE V inhibitor	Sildenafil	RS	Headache (20%)	[7]
	Tadalafil	SSc	Headache (15%) Back pain (18%)	[8]

* The left values indicate the data of the high dose, and the right indicates the lower dose test. Ca: calcium; RP: primary Raynaud's phenomenon; RS: Raynaud's syndrome including patients with SSc; SSc: systemic sclerosis; PDE: phosphodiesterase.

Capillaries in the nail fold of patients with SSc appear tortuous when observed using capillaroscopy, and many studies have reported that capillary tortuosity exacerbates as the disease progresses. Arterial blood flows forward due to cardiac output pressure. When vascular tortuosity becomes severe, the forward progression of blood is hindered by this curvature. Thus, even with the administration of a drug with strong vasodilatory effects, there are persistent concerns regarding its effectiveness in delivering medication to peripheral regions characterized by high tortuosity. If drugs administered orally or by injection are not delivered to the local area, it is necessary to induce local vasodilation through external stimulation. Non-pharmacological treatments for Raynaud's phenomenon include immersing the hands in hot water or a high-concentration CO₂ solution, paraffin baths, and infrared irradiation [15,16]. Various approaches have been suggested that involve the use of gloves equipped with integrated heat sources [17,18]. The patient information sheet by the American College of Rheumatology (ACR) instructs patients to wear thick gloves to keep their hands warm when experiencing RP [19]. However, covering the hands with thick gloves or soaking them in hot water can interfere with daily tasks. We are exploring methods to dilate local capillaries and improve their morphology by externally stimulating the thermoreceptor transient receptor potential (TRP) V4 channel.

3. TRP Channels

TRP channels are thermosensitive receptors. The *Trp* gene was discovered by Cosens and was originally reported as a gene related to light sensitivity [20]. Patapoutian [21] and Julius [22] found that this homologue functioned as a thermosensor, and they were awarded the 2021 Nobel Prize in Physiology or Medicine, respectively, for this discovery. If this potential is transmitted to the central nervous system, it becomes possible to recognize cold and thermal stimuli. These thermoreceptors are known as TRP channels. To date, several types of TRP channels have been identified as thermosensitive TRPs (thermo-TRPs) in humans [23] (Figure 1). Each TRP channel has a specific temperature range; for example, the TRPA1 channel responds to a cold stimulus at approximately 10 °C, whereas the TRPV1 channel responds to a hot stimulus at approximately 50 °C [24]. In addition to thermal stimuli, these receptors respond to chemicals. TRPM8 channel reacts to menthol [25], and the application of menthol to skin induces a cooling sensation due to its interaction with the M8 channels. This interaction prompts the central nervous system to interpret a cold stimulus of 10–20 °C as being applied to the region of the M8 channel activation. Similarly, the TRPV1 channel can be stimulated by capsaicin [26], and when capsaicin is applied to the skin, a sensation of heat is perceived because the TRPV1 channel responds to a temperature range of approximately 50 °C.

Among the TRP channels discovered in humans, we are focusing on the TRPV4 channel. The TRPV4 channel is a thermoreceptor that operates in the temperature range of approximately 40 °C [27]. In addition to recognizing heat at 40 °C, this receptor senses mechanical pressure and plays an essential role in angiogenesis and in maintaining the function of bones, joints, and cartilage. Using a patch-clamp technique, Köhler et al. reported that TRPV4 channel stimulation induces vasodilation [28]. They demonstrated that vasodilation occurred in the common carotid and gracilis arteries of rats upon stimulation with the TRP V4 channel agonist 4-phorbol-12,13-didecanoate (4αPDD), and that this dilating effect was abolished by the V4 channel blocker ruthenium red (RuR). Chen et al. created an artificial cerebral infarction model in animals and observed that administering 4αPDD, a TRPV4 agonist, resulted in vigorous capillary growth around the infarction area [29].

In animals, after 4αPDD was administered, a significant number of CD31-positive cells, indicative of capillary endothelial cells, were observed surrounding the infarction area,

accompanied by a reduction in infarction size. TRPV4 is also involved in bone growth and cartilage maintenance and is therefore considered a therapeutic target for pharmaceutical companies [30] (Figure 2). A well-known test drug is GSK101 (GSK1016790A) [31]. GSK101 acts as an agonist of TRPV4; nevertheless, an animal study showed some issues [32]. As a result, this receptor agonist has not been used for human applications.

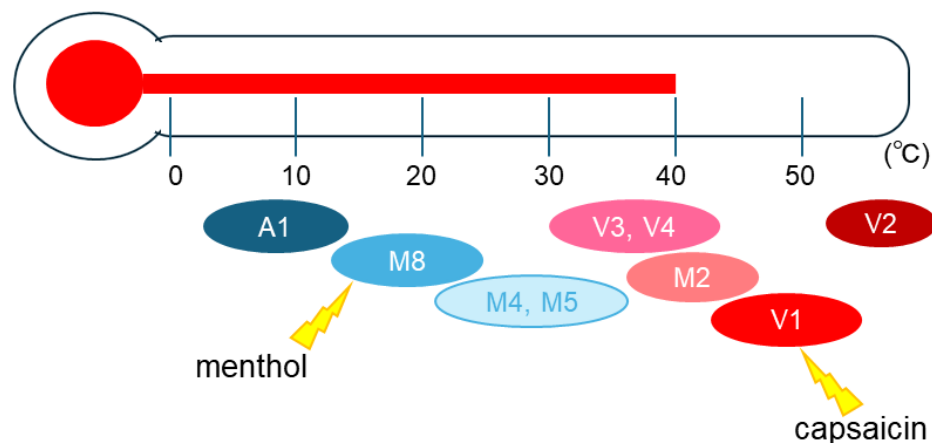


Figure 1. Thermoreceptors of humans. TRP channels work as a thermo-sensor on mammals. When a channel receives a thermal (or cold) stimulus, cation influx occurs, generating an electrical potential. When this electrical stimulus is transmitted to the central nervous system, we can perceive a sensation of heat (or cold). Menthol can bind to the TRPM8 channel, resulting in a cold sensation. Capsaicin can bind to the TRPA1 channel, causing a heat sensation in the skin.

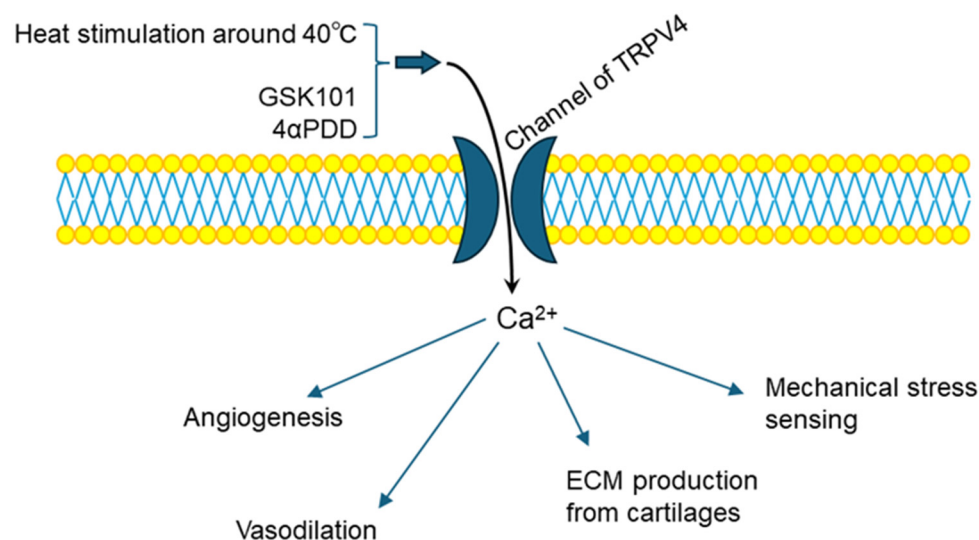


Figure 2. Thermoreceptors of humans. The TRPV4 channel is a thermoreceptor with various functions other than heat sensing. 4αPDD: 4-phorbol-12,13-didecanoate; ECM: extracellular matrix.

4. Heating Therapy for RP

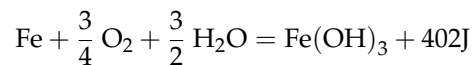
4.1. Thermal Stimulation via TRPV4

It is known that warming the body improves blood circulation. Thermal stimulation relaxes vascular smooth muscles via the autonomic nervous system [33], and this is widely accepted to lead to vasodilation and increased blood flow. However, because thermal stimulation is transmitted via thermoreceptors, the local response at the heat exposure point is critical. The enhancement in blood circulation attributable to heat exposure can be attributed to vasodilation, which is likely induced by the activation of TRPV4, as previously described. Furthermore, if TRPV4 stimulation promotes capillary growth, it is expected that vasodilation, as well as tissue blood flow, will improve through the growth

of new capillaries. Nonetheless, there is currently a paucity of data regarding the impact of temperature application on TRPV4 channels in relation to circulatory disorders and capillary function in diseases such as SSc. We developed a heating pad that maintained a temperature sufficient to activate TRPV4 and examined its effects on RP.

4.2. Development of the Heating Pad

Heat is generated when iron powder oxidizes to form ferric hydroxide. The chemical formula for the oxidation of iron powder is as follows:



The thermal output can be regulated by modulating the iron and oxygen supply. Kobayashi Pharmaceutical Co., Ltd. (Osaka, Japan), a manufacturer of disposable hand warmers, created a disposable heating pad that could continuously stimulate TRPV4. This heating pad is designed to raise the temperature of the skin surface to approximately 40 °C when inserted into its dedicated holder and applied to the skin. On the basis of experimental data from Moritz et al. [34], we hypothesized that burns would not occur if the duration of heat exposure remained within a 6-h period. Following the development of the heating pad, the subsequent challenge involved identifying specific areas to target for heating to alleviate the symptoms of RP in the hands. While covering and heating the fingers is expected to be effective at treating RP, it interferes with the performance of daily activities. Covering the hands prevents patients from using smartphones or washing their hands. It is difficult to predict the onset of RP. Assuming that a heating device is worn preventively during the day, it might be necessary to heat other parts of the body without covering the hands. Candidate sites for heating were selected based on the following criteria: the absence of large muscles immediately beneath the skin surface and close proximity to relatively large blood vessels or nerves. Large muscles were avoided to prevent the holder containing the heating pad from shifting as a result of muscle contraction. Based on these criteria, the following regions were selected as candidate sites: the posterior neck (where despite the presence of several striated muscles, including the trapezius, the superficial layer is covered by the nuchal ligament); the proximal lateral aspect of the elbow (where the subcutaneous tissue consists primarily of the triceps brachii tendon rather than striated muscle); and the dorsal aspect of the wrist (where the subcutaneous tissue contains the common extensor tendon rather than muscle). We created mounting holders for the neck, elbow, and wrist to compare site-specific effects by inserting heating pads with the same heating performance. We recruited 30 healthy volunteers who experienced cold hands in the winter. Twelve participants wore only the holders in a random order, whereas the other 17 wore the holders with heating pads daily in a random order. Each participant documented their daily experiences of feeling cold in a diary using a self-assessment format. Consequently, the group that did not utilize the heating pad exhibited no alteration in their perception of coldness compared with the period when the holder was not used. Conversely, within the cohort utilizing holders with heating pads, the sensation of coldness was alleviated when the pads were positioned on the posterior neck or the elbows. In contrast, no such improvement was observed when the pads were applied to the wrists [35]. Next, a similar trial was conducted with 14 patients with SSc, using the Raynaud Condition Score (RCS), used to determine the severity of RP, as the primary endpoint. Consistent with the previous results in healthy volunteers, a reduction in the RCS was observed when heat was applied to the neck and elbows. In contrast, no reduction in the RCS was observed when the wrists were heated [36] (Figure 3).

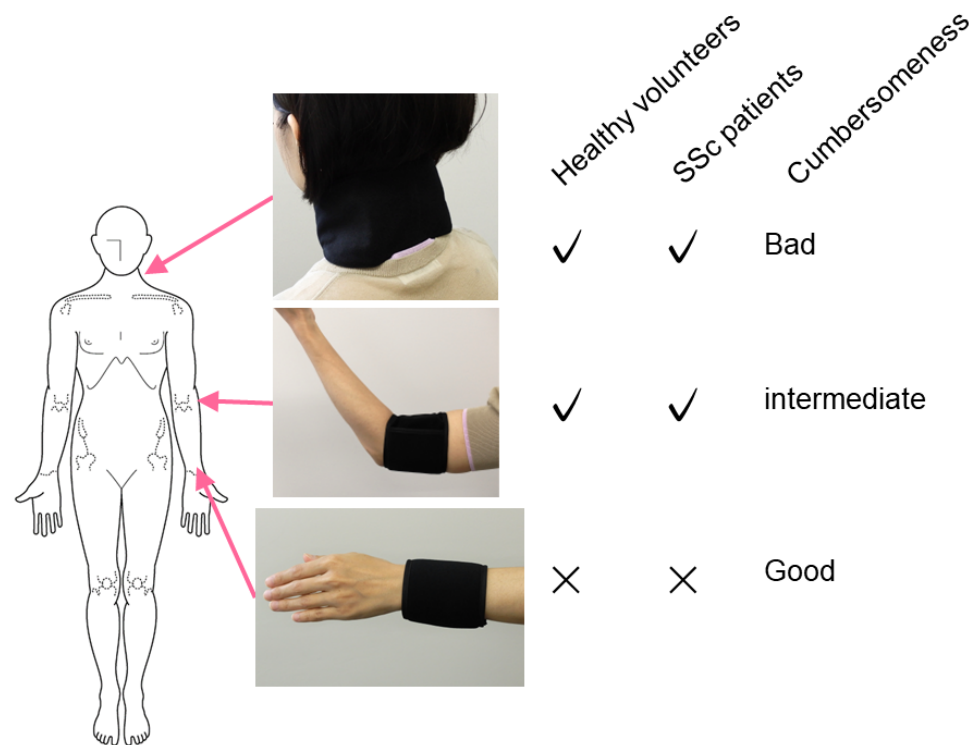


Figure 3. Site-specific effect of heating on Raynaud's phenomenon in the fingers. Evaluation of the improvement of hand coldness by healthy volunteers shows the effect of neck and elbow heating, but not wrist heating. Evaluation of the improvement of Raynaud's phenomenon in the hands of patients with systemic sclerosis shows similar results. ✓: improve the data statistically, ×: no improvement.

Furthermore, not only did the severity of RP decrease during the heating period, but the severity also gradually decreased with repeated heating periods. In this test, the “cumbersomeness” level assessment indicated that heating the back of the neck resulted in high discomfort. Based on these results, we determined that the area near the elbow was a suitable heating site for alleviating RP in the fingers. To confirm the effectiveness of this elbow heating device, a multicenter trial was conducted at eight medical institutions in Japan targeting patients with SSc, with RCS as the primary endpoint. This study involving 32 participants confirmed that heating the area around the elbow reduced RCS and decreased the frequency and duration of RP [37]. The mechanism by which heating the neck and elbows induces an RP-inhibiting effect, whereas heating the wrists does not, remains unclear. These differences might depend on the diameter of the blood vessels receiving thermal stimulation.

5. Angiopoietins

As mentioned above, TRPV4 stimulation contributes to vasodilation and capillary growth. We hypothesized that the stimulation of TRPV4 by wrist heating induces capillary expansion and proliferation in the hand. However, the aforementioned test results show a spatial mismatch between the heated area (elbow) and the site of improvement (fingers), indicating that TRPV4-mediated vasodilation alone cannot explain the relief of RP in the fingers. Thus, it is necessary to verify the internal modifications in the fingers where the RP was mitigated. In general, capillaroscopy in patients with SSc has revealed that capillaries in the nail fold become more tortuous as the condition worsens [38]. Blood has difficulty passing through severely tortuous capillaries, and the blood flow in the tissues is gradually lost as a result. One of the mechanisms underlying RP is a decrease in the tissue blood flow related to changes in capillary morphology. Although RP was alleviated

by heating around the elbow, it was necessary to confirm whether the morphology of the capillaries in the fingers improved. To investigate changes in the fingertips induced by the application of heat to the elbow, we performed fingertip blood sampling using a blood glucose lancet. Blood samples were obtained from the antecubital vein and fingertip before and after a 7-day period of exposure to a heating pad. These samples were used to measure angiopoietin-1, angiopoietin-2, vascular endothelial growth factor (VEGF), and other substances involved in capillary metabolism by ELISA [36]. These factors did not change in blood samples taken from the antecubital vein, regardless of whether the participants received heating treatment. However, an increase in angiopoietin-1 blood levels taken from the fingertips was observed after the heating period. Angiopoietin-1 binds to Tie2 receptors on capillary endothelial cells and, in conjunction with VEGF, plays a crucial role in capillary development and stabilization [39,40] (Figure 4). Angiopoietin-1 is also known to have an antagonist, Angiopoietin-2, and when Angiopoietin-2 binds to the Tie2 receptor, it causes capillaries to bend [41]. It has been reported that angiopoietin-1 concentrations in SSc were lower in patients with more severe capillary curvature and deformation when observed by capillaroscopy [42].

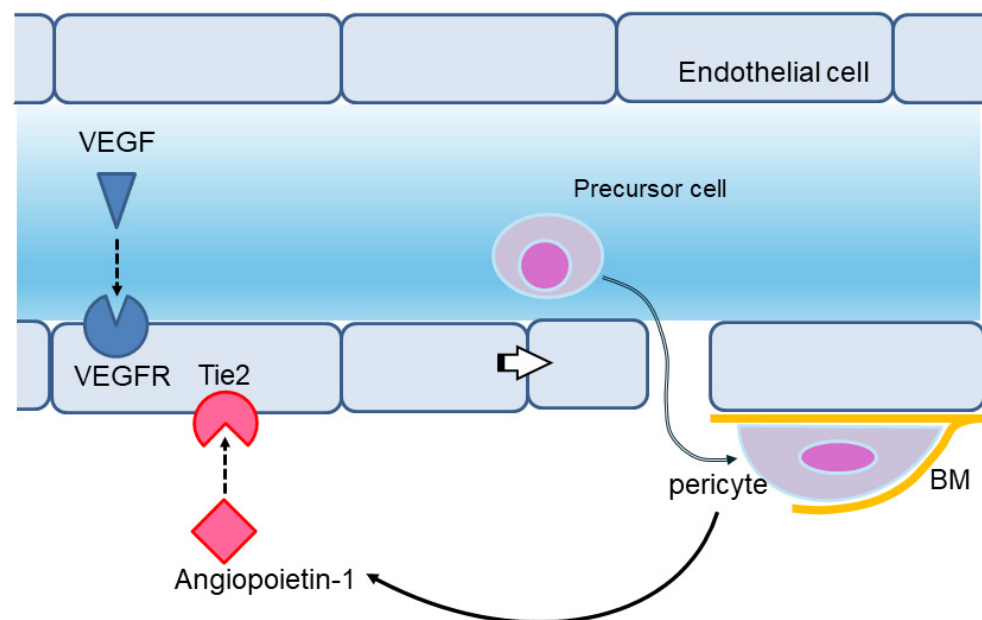


Figure 4. Angiopoietins and endothelial cell growth. The precursor cells mature into pericytes. Matured pericytes secrete angiopoietin-1, and angiopoietin-1 binds to the Tie2 receptor expressed on endothelial cells. VEGF stimulation and Tie2 signaling promote endothelial cell proliferation. Pericytes support the capillary walls from the outside, thus stabilizing the capillary structure.

We conducted fixed-point observations of capillaries in patients with SSc over 6 months, repeatedly collecting blood samples from their fingertips. For 8 weeks during the study period, the participants were instructed to repeatedly apply heat to the area around their elbows daily. As a result, it was confirmed that angiopoietin-1 levels increased in the fingertips after the heating period. Capillaroscopy observations revealed that 20.2% of capillaries in the front row of the nail fold had a normal hairpin shape immediately before heating began. This value increased to 26.6% during heating around the elbow and was 25.7% 1 month after the end of heating. Furthermore, a correlation was observed between the degree of increase in angiopoietin-1 and the rate of increase in hairpin-shaped capillaries [43]. RP was alleviated by heating the elbow, which might be related to an increase in the angiopoietin-1 concentration and improvement in capillary morphology caused by heating. Chakroborty et al. reported that pericytes adjacent to capillaries pro-

duced angiopoietin-1 and that its production increased with dopamine stimulation [44]. Li et al. reported that elevating the culture temperature in a co-culture of endothelial cells and osteoblasts enhanced angiopoietin-1 production [45]. Moreover, Kuhlenhoelter et al. documented that external heating led to an increase in the concentration of angiopoietin-1 in human muscle tissue [46]. Based on these results, the following pathways are possible.

(1) Applying heat that stimulates TRPV4 channels near the elbow increases angiopoietin-1 in the fingertips.

(2) Increased angiopoietin-1 levels improve capillary morphology.

(3) The suppression of RP is facilitated not only by TRPV4-mediated vasodilation but also by the enhancement of capillary morphology.

6. Current Issues and Future Perspectives

In the assessment of RP, the participants recorded their RCS, the number of occurrences, and the duration of RP daily in a diary format. None of these recordings were made in real time regarding the occurrence or severity of RP. Therefore, methods for real-time RP monitoring should be explored.

There may be more effective approaches regarding the optimal warming sites and methods. In the present study, we applied heat to the neck or to both upper limbs because RP is generally recognized as a bilateral condition [47]. Although unilateral heating may be advantageous in terms of accommodating differences in the functional use of the left and right upper limbs, such as writing or carrying bags, its effectiveness remains to be investigated.

The optimal duration of thermotherapy remains unknown. Because RP is triggered by cold exposure, its frequency is likely to vary seasonally. Therefore, in regions with seasonal changes in ambient temperature, a practical strategy would be to administer thermotherapy during the winter months and discontinue it when temperatures rise. However, the potential for skin changes or damage associated with long-term use has not yet been clarified.

The therapeutic efficacy of thermotherapy for established digital ulcers also remains unclear. Although the thermotherapy described in this section has been shown to alleviate RP, its effectiveness in promoting the healing of existing digital ulcers has not yet been established. Because thermal stimulation cannot be blinded, accumulating further clinical evidence in patients with digital ulcers will be essential to determine its therapeutic value.

Although the heating pad is designed for the temperature of TRPV4, we have not yet verified whether TRPV4 is stimulated in patients who have used this device. Because TRPV3 is also stimulated at a similar temperature range [23], the possibility of another pathway being involved in the heating effects cannot be ruled out.

Although it has been documented that dopamine stimulation increased angiopoietin-1 production from pericytes in contact with capillaries, the relationship between TRPV4 stimulation and peripheral dopamine stimulation remains unclear.

The mechanisms by which thermal stimulation around the elbow influences distal microcirculation remain incompletely understood. The contribution of psychological relaxation cannot be excluded. Further investigation is needed to understand the changes in molecules, including angiopoietin-1, during thermal stimulation. Regardless of the underlying mechanism, maintaining elbow heating appears to be a safe, simple, and cost-effective approach for alleviating RP.

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Abbreviations

The following abbreviations are used in this manuscript:

SSc	systemic sclerosis
TRP	transient receptor potential
RP	Raynaud's phenomenon
PDE	phosphodiesterase
cGMP	cyclic guanosine monophosphate
ACR	The American College of Rheumatology
4αPDD	4-phorbol-12,13-didecanoate
RuR	ruthenium red
RCS	Raynaud Condition Score
VEGF	vascular endothelial growth factor

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