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Title:
Evaluation of vasomotor responsiveness in the hand skin using sinusoidal thermal load: a comparison of glabrous and nonglabrous sites

正弦波状温熱負荷を用いた手部皮膚血管反応の評価：無毛部と有毛部の比較

Author: YAMAZAKI Fumio
山崎文夫

Institution: Graduate School of Health and Welfare, Yamaguchi Prefectural University
山口県立大学大学院　健康福祉学研究科

For correspondence:
Fumio Yamazaki, Ph.D.
Graduate School of Health and Welfare, Yamaguchi Prefectural University
6-2-1 Sakurabatake, Yamaguchi 753-0021, Japan
TEL 083-933-1450
連絡先：
山崎文夫
山口県立大学大学院　健康福祉学研究科
山口県山口市桜畠6-2-1
（〒753-0021）TEL 083-933-1450

Abstract：

The purposes of this study were to assess 1) whether the sinusoidal thermal load test can evaluate dynamic responsiveness of skin vessels in the extremities of limbs, and 2) whether the vascular responses to sinusoidal thermal load differ in glabrous and nonglabrous human skin. Ten healthy subjects immersed their hand into a water bath at 34℃ for 10 min, and for the next 60 min or 80 min, the water temperature was sinusoidally changed at an ambient temperature of 26℃ and relative humidity of 60%. The variation of sinusoidal thermal load ranged from 31.5℃ to 36.5℃ over three 20-min periods or from 29℃ to 39℃ over two 40-min periods. The phase and amplitude responses of cutaneous vascular conductance (CVC) in the dorsal hand (i.e. nonglabrous site) and palm (i.e. glabrous site) to sinusoidal changes in water temperature were measured. Skin blood flow (SkBF) was monitored by laser-Doppler flowmetry. CVC was evaluated from the ratio of SkBF to mean arterial pressure. During baseline measurement at 34℃, the CVC in the dorsal hand was lower than that in the palm ($P<0.05$). During sinusoidal thermal load in the two periods, the CVC in the dorsal hand changed almost sinusoidally with the change in water temperature. The CVC in the palm exhibited no clear sinusoidal change for a large variability in the SkBF value; however, when raw data for CVC were superimposed at each cycle, the changes demonstrated almost sinusoidal patterns. The amplitudes and phase lags in CVC of the dorsal hand were smaller than those in the palm in the two periods ($P<0.05$). These results suggested that 1) the sinusoidal thermal load test can quantitatively evaluate vasomotor responsiveness in the skin of the extremities, and 2) nonglabrous skin vasomotion has a smaller and prompter response than glabrous skin vasomotion during dynamic changes of local thermal load.

Key words：skin blood flow, skin temperature, glabrous skin, local heating, dynamic response

和文抄録：

本研究の目的は、1）正弦波状温熱負荷により四肢末端部の皮膚血管運動の動的反応性が評価できるか否か、そして2）正弦波状温熱負荷に対する皮膚血管反応は無毛部と有毛部で異なるかどうかを検討することであった。環境温26℃、相対湿度60％の条件下で、10名の健康な被験者が34℃に設定した恒温水槽に手を10分間浸漬し、続いて水温を60分間あるいは80分間正弦波状に変化させた。正弦波状温熱負荷は、31.5℃と36.5℃の間で20分の周期で3回、あるいは29℃と39℃の間で40分の周期で2回変動させた。水温の正弦波状変化に対する手背部（すなわち有毛部）と手掌部（すなわち無毛部）の皮膚血管コンダクタンス（CVC）の位相と振幅の応答を測定した。皮膚血流量（SkBF）はレーザードップラー法によりモニターされ、CVCはSkBFと平均血圧の比率から評価された。34℃でのベースライン測定中、手背部CVCは手掌部CVCよりも低かった（$P<0.05$）。2つの周期での正弦波状温熱負荷中、手背部CVCは水温の変化に伴ってほぼ正弦波状に変化した。手掌部CVCはSkBF値の大きな変動によって明らかな正弦波状変化を示さなかったが、CVCの生データを周期毎に重ね合わせることにより正弦波状パターンで変化していることが示された。いずれの周期においても手背部CVCの振幅と位相遅れ時間は、手掌部CVCのそれらよりも小さかった（$P<0.05$）。これらの結果から、1）正弦波状温熱負荷テストにより四肢末端部の皮膚血管運動の反応性を定量的に評価できること、そして2）動的な局所温熱負荷中に有毛部皮膚血管運動は無毛部皮膚血管運動よりも小さく速やかな反応性を有していることが示唆された。

キーワード：皮膚血流量、皮膚温、無毛皮膚、局所加温、動的反応

Introduction

Temperature environments where humans live usually fluctuate with changes in natural (e.g. seasonal and diurnal variations) and artificial (e.g. uses of heater or cooler) factors. Under a variety of temperature conditions, the human body needs to respond appropriately in order to maintain homeostasis of the core body temperature and the system controlling blood flow in the skin plays a role in this thermoregulation.

Skin blood flow (SkBF) in humans is controlled by both neurogenic reflexes and local factors (1, 2). In skin of nonglabrous (hairy) regions, such as the dorsal hand, forearm, or torso, reflex control of the skin vasculature is mediated by two sympathetic pathways: a noradrenergic vasoconstrictor system and an active vasodilator system, whereas in skin of glabrous (nonhairy) regions, such as the palm, sole, or lips, the reflex control is mediated by a noradrenergic vasoconstrictor system only (3). Studies of thermoregulatory reflexes in resting subjects revealed that during heat stress, there is an initial abolition of all vasoconstrictor tone. As the core body temperature increases further, the active vasodilator system is activated along with sweating in the nonglabrous skin. Under a cool environmental condition, the noradrenergic vasoconstrictor system plays a major role in inhibiting heat dissipation via vasoconstriction in both glabrous and nonglabrous skin of the extremities.

One local factor important for SkBF control is the temperature of the blood vessels and surrounding tissues themselves. The mechanisms for the vascular effects of local temperature include both adrenergic and non-adrenergic (e.g. nitric oxide) elements (4-6). The participation of these mechanisms differs in the initial phase and the latter phase of local thermal stress (5-7). However, the characteristics in SkBF responses to the dynamic changes in local temperature are unclear. They may be further clarified by comparing vasomotor responses between nonglabrous skin and glabrous skin during dynamic thermal load.

The sinusoidal load test presents some advantages in the evaluation of the dynamic characteristics of physiological responses to stress (e.g. exercise and environmental temperature) (8-11). For example, although the reproducibility of physiological responses to stress is not always high, the elimination of noise by superimposing response data at repeated sinusoidal loads may clarify the features of the response and increase the reliability of the obtained data. It is also possible to express the characteristics of the physiological response to stress as the phase lag and amplitude of response. Therefore, the characteristics of the skin vasomotor response to dynamic thermal load can be quantitatively determined using sinusoidal load.

In the present study, to further elucidate the characteristics in skin vasomotor responses to the changes in local temperature, we compared the responses of cutaneous vascular conductance (CVC) in the dorsal hand and palm to sinusoidal thermal load.

Methods

1. Subjects

Ten healthy subjects (9 males and 1 female) participated in this study. Their average age was 22 ± 2 (SD) yr, average weight was 63 ± 8 kg, and average height was 170 ± 7 cm. Each subject was given complete information regarding the procedures and informed consent was received. The experiments on the female subject were conducted in the follicular phase of the menstrual cycle.

2. Experimental conditions and procedures

Each subject underwent two sequential tests (i.e. sinusoidal thermal load test and local warming test). The experiments for the two periods (i.e. 20 min and 40 min) of sinusoidal thermal load were performed at two-week or longer intervals in random order. In each experiment, subjects rested for 50 min prior to the test under constant environmental conditions (ambient temperature; 26℃, relative humidity; 60%). During this period, electrodes and probes for measurements were applied, and the laser-Doppler flux data for the dorsal and palmar aspects of the right hand (9 cm^2 area) were acquired using a laser Doppler imager (Moor Instruments, Axminster, UK). The scan speed was 10 $ms \cdot pixel^{-1}$.

After the measurement of laser-Doppler flux, the left hand of the subject, to which skin thermocouples and laser-Doppler flow probes were attached, was immersed in a water bath (EL-15F, TAITEC, Koshigaya, Japan). The temperature of the water bath was controlled via a digital-to-analog conversion board (DA12-4C (98), CONTEC, Osaka, Japan) by a personal computer (PC9801BX, NEC, Tokyo, Japan). An example of changes in the water temperature during the sinusoidal thermal load test is shown in the top panel in Fig. 1. After 10 min of constant temperature at 34℃ the water temperature was varied in a sinusoidal pattern over a period of 20 min or 40 min, and the sinusoidal load continued for an additional 60 min or 80 min, comprising three 20-min cycles or two 40-min cycles, respectively. The sinusoidal load variation ranged from 31.5℃ to 36.5℃ over 20-min or from 29℃ to 39℃ over 40-min period. The periods and amplitudes of water temperature were selected to minimize changes in core body temperature and whole-body skin temperature (Tsk), and to avoid abrupt increases in SkBF via axon reflexes.

The local warming test was successively performed after the sinusoidal thermal load test (Fig. 1). In the local warming test, the water temperature in the bath was increased from 34℃ to 43℃ to maintain the Tsk of the hand at 41-42℃ for 30-35 min for inducing robust vasodilation (12).

3. Measurements

As an index of core body temperature, esophageal temperature (Tes) was measured using a polyethylene-sealed thermocouple swallowed to the level of the heart. Tsk was measured by copper-constantan thermocouples attached to the chest, upper arm, thigh, lower leg, right forearm, dorsal aspect of the left hand, and left palm, and the mean Tsk was calculated using the weighting factors of Ramanathan (13). The heart rate (HR) was determined by electrocardiography (CM_5 lead). The mean arterial pressure (MAP) was measured continuously by arterial tonometry (JENTOW-7700, Colin, Komaki, Japan) using the right radial artery. SkBF was monitored continuously with laser-Doppler flow meters (ALF21, Advance, Tokyo, Japan), and glass-fiber sensor probes were placed at the dorsal and palmar aspects of the left hand and flexor aspect of the left forearm. The SkBF probes were always positioned at 15 cm below the heart by controlling the location of the water bath. CVC was calculated from the ratio of SkBF to MAP. The measured variables were recorded by a data logger (7V07 San-Ei Sokki, Tokyo, Japan) every 10 s.

4. Analysis

To determine the responses of each variable to sinusoidal thermal load, the amplitude of fluctuation and the phase lag of the response were calculated (Fig. 2). The law data were superimposed every

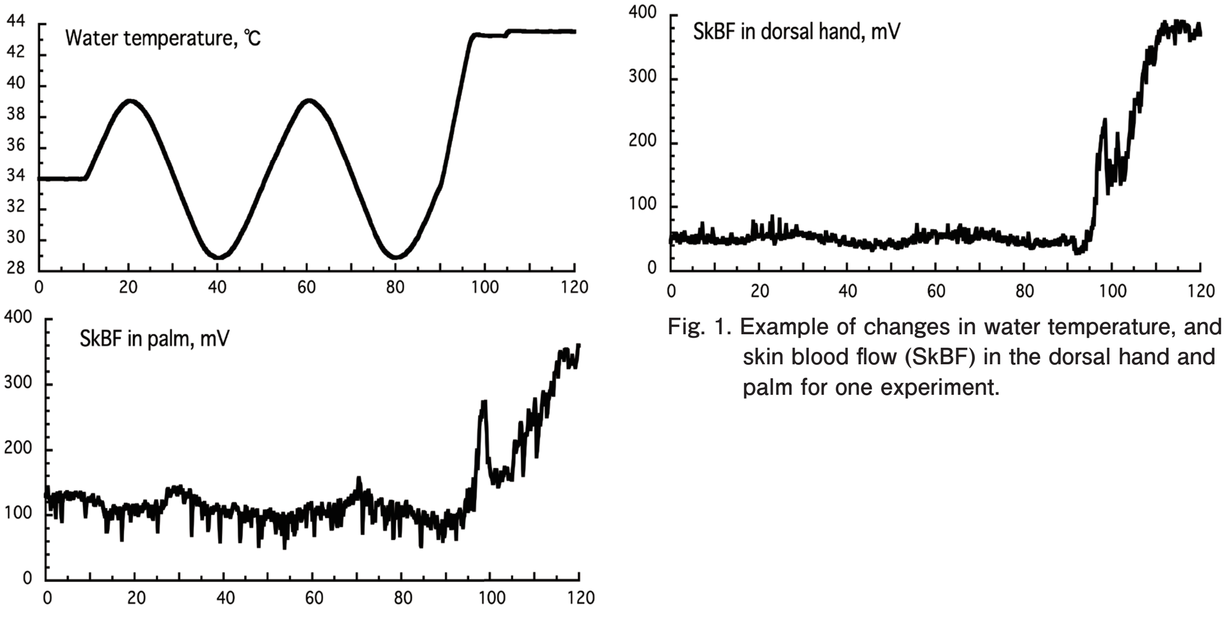

Fig. 1. Example of changes in water temperature, and skin blood flow (SkBF) in the dorsal hand and palm for one experiment.

cycle and fitted to a sine model as follows using the least-squares error approach.

$$Y = A \cdot \sin 2\pi \cdot T^{-1} \cdot (t - ø) + B$$

where Y is each value in the sine model; A is amplitude of response; T is period of sinusoidal thermal load (1200 or 2400 s); t is time in s; ø is phase lag of response in s; and B is baseline value.

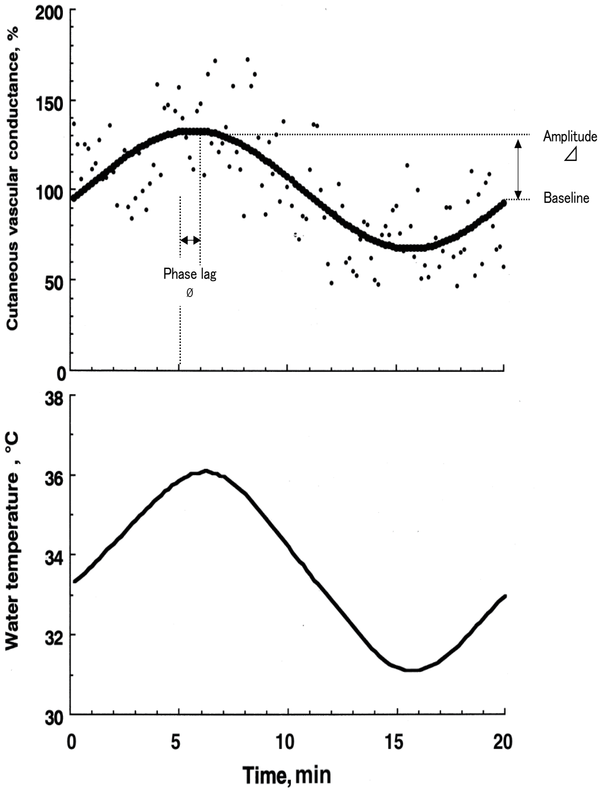

Fig. 2. Responses of cutaneous vascular conductance in the dorsal hand (upper panel) to a sinusoidally varying water temperature (lower panel) over a period of 20 min in one subject. The thick line in the upper panel shows the data fitted by the sine model.

5. Statistical analysis

Data are presented as the mean ± SD. Statistical analysis was performed using analysis of variance followed by Fisher's protected least significant difference test. The significance level used was $P<0.05$.

Results

During sitting rest under normal temperature condition, laser-Doppler flux (49.7 ± 3.7 units) in the dorsal hand was smaller than that (145.3 ± 16.2 units) in the palm (Fig. 3, $P<0.001$). Similar to the flux data, the absolute values of CVC in the dorsal hand (0.61 ± 0.15 mV·mmHg^{-1}) were smaller than those in the palm (1.47 ± 0.75 mV·mmHg^{-1}) ($P<0.01$). The CVC in forearm (0.36 ± 0.18 mV·mmHg^{-1}) was the smallest of the three ($P<0.01$). Tes (36.8 ± 0.3℃), mean Tsk (33.2 ± 0.6℃), forearm Tsk (32.6 ± 0.7℃), MAP (86.6 ± 9.0 mmHg), and HR (61.6 ± 8.5 beats/min) were within normal ranges, and these variables remained unchanged during the following sinusoidal thermal load test.

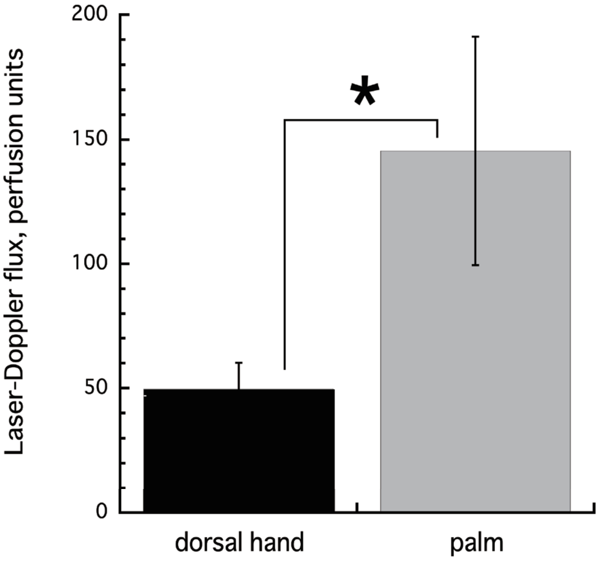

Fig. 3. Skin laser-Doppler flux in the dorsal hand and palm at sitting rest at 26℃ and 60% relative humidity.
* $P<0.05$ dorsal hand vs. palm.

1. Sinusoidal thermal load test

The CVC in the dorsal hand changed almost sinusoidally with the change in water temperature, whereas that in palm exhibited no clear sinusoidal change for a large variability in the SkBF value (Fig. 1). However, when raw data for CVC were superimposed at every cycle, the changes demonstrated almost sinusoidal patterns. The CVC in the forearm remained unchanged during the sinusoidal thermal load test. The amplitude and the phase lag responses for each variable fitted by the sine model are

Table 1. Amplitude and phase lag of responses to sinusoidal thermal load.

	20-min period			40-min period		
	baseline	amplitude	phase lag	baseline	amplitude	phase lag
Water temperature, ℃	33.9±0.1	2.4±0.1	53±11	33.9±0.1	5.0±0.1	46±8
Tsk in dorsal hand , ℃	34.0±0.1*	1.9±0.2*	87±15	34.1±0.2 *	4.2±0.2 *	91±26 *
Tsk in palm, ℃	34.7±0.3	1.4±0.2	58±14	34.6±0.2	3.2±0.5	124±61
CVC in dorsal hand, %	100±0	10.3±4.1	89±29*	100±0	24±12	372±138 *
CVC in palm, %	100±0	15.0±12.2	508±467	100±0	24±9	602±347

The phase lag is shown in sec. Tsk: skin temperature, CVC: cutaneous vascular conductance. * $P<0.05$ vs palm.

shown in Table 1. The absolute values for amplitude of CVC in the dorsal hand (0.06±0.01 mV·mmHg^{-1} in 20-min period, 0.15±0.07 mV·mmHg^{-1} in 40-min period) were smaller than those in the palm (0.22±0.18 mV·mmHg^{-1}, 0.35±0.13 mV·mmHg^{-1}, respectively) ($P<0.01$ in both periods). As shown in Table 1, however, when the amplitude of CVC was presented as a percent change from the baseline value, the values for the amplitude of CVC in the dorsal hand did not differ from those in the palm. The phase lags were smaller in the CVC in the dorsal hand than in those in the palm ($P<0.05$). The differences in phase lags between water temperature and CVC, i.e., the net phase lags of CVC responses to changes in water temperature, were also smaller in the dorsal hand (36±28 sec in 20-min period, 326±133 sec in 40-min period) than in the palm (455±146 sec, 556±333 sec, respectively) ($P<0.05$ in both periods).

The baseline Tsk values were lower in the dorsal hand than in the palm ($P<0.001$). During sinusoidal thermal load, the amplitude values of Tsk in the dorsal hand were significantly smaller than those in the palm (Table 1). In the 40-min period, the phase lags in Tsk were smaller in the dorsal hand than in the palm ($P<0.05$), whereas in the 20-min period, their phase responses did not differ between the two regions.

2. Local warming test

Changes in SkBF in the dorsal hand and palm during local skin warming are shown in Fig. 4. When the Tsk in the hand was at ~34℃ (0-3 min in the figure), SkBF was smaller in the dorsal hand than in the palm ($P<0.01$). The local warming for 30-35 min increased blood flow in biphasic patterns, the SkBF in the dorsal hand and palm increased to 9.8±0.7- and 4.1±0.7-times the pre-warming levels, respectively. Local warming did not change MAP, thus there was no difference in CVC between the dorsal hand (5.84±1.64 mV·mmHg^{-1}) and palm (5.12±1.67 mV·mmHg^{-1}) at the end of local warming.

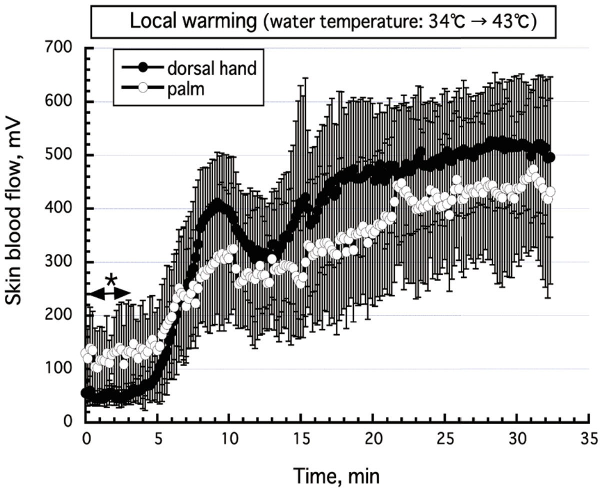

Fig. 4. Changes in skin blood flow in the dorsal and and palm during local skin warming. The skin temperature of the hand was sinusoidally changed for 60-80 min and then increased to 41-42℃ by immersing it in a hot water bath (43℃). * $P<0.05$ dorsal hand vs. palm.

Discussion

This study provided four major findings: 1) the sinusoidal thermal load test can be used for evaluating dynamic vasomotor responses in the skin; 2) the baseline and amplitude values in CVC were smaller in the dorsal hand than in the palm during sinusoidal load; 3) the phase lags of CVC to sinusoidal thermal load were smaller in the dorsal hand than in the palm; and 4) peak values in CVC did not differ between the dorsal hand and palm during local warming. This suggests different vasomotor control in glabrous and nonglabrous skin during consecutive change in the local temperature.

The Tes, mean Tsk, and MAP remained unchanged during the sinusoidal thermal load test, suggesting that the responses of CVC in the hand was mainly influenced by local temperature. Thus, the sinusoidal thermal load using immersion of the hand in water can be used as a novel stress test for evaluating dynamic characteristics of skin vasomotion in limbs.

During sitting rest, even when local Tsk was maintained at approximately 34℃, the CVC in the palm was approximately 2.4-times greater than that in the dorsal hand. The laser-Doppler flow meter that was used in this study measures blood flow within a small volume of cutaneous tissue (2 mm^3). The cutaneous tissue included in the SkBF measurement was insufficient to have uniform responses of perfused microvessels from site-to-site (14,15). However, the average laser-Doppler flux within a 9-cm^2 area in the palm was 2.4-times greater than that in the dorsal hand, suggesting that the regional difference in CVC was not invalid. Glabrous skin is heavily endowed with arteriovenous anastomoses under the control of adrenergic vasoconstrictor nerves (16,17). Arteriovenous anastomoses may lead to much higher blood flow to glabrous skin than to nonglabrous skin.

The difference in the baseline values in CVC between the dorsal hand and palm was considered to be responsible for the different amplitude responses in the two sites. When the amplitude of CVC was presented as a percent change from the baseline value, the difference in the amplitude responses in the dorsal hand and palm disappeared. Thus, the higher CVC in palm may help to increase the decreasing levels of blood flow within the submaximal range.

The reasons why phase lags differed between the dorsal hand and palm are unclear, but the thicker epidermis (especially stratum corneum) in glabrous skin than in nonglabrous skin may have caused a slower response because palmer skin is 6-times thicker than nonglabrous skin (18). The structural differences in the skin may influence the smaller amplitude responses in the Tsk in the palm. In addition, the higher SkBF in the palm may induce the slower phase response because of greater inertia of blood stream.

Non-nociceptive local warming increases blood flow in nonglabrous skin in a biphasic response: an initial rapid increase to a peak, followed by a prolonged plateau phase. The initial phase is mediated by antidromic neurotransmitter release from sensory afferents via temperature-sensitive vanilloid type 1 receptors (17,19). Sympathetic active vasodilator nerves are not involved in these responses (2). The plateau phase that is observed with prolonged local warming of the skin is mediated by the generation of nitric oxide (4). In the present study, the SkBF in the dorsal hand and palm demonstrated biphasic responses during local warming, suggesting that the vessels in glabrous skin also possess similar mechanisms of SkBF control. Moreover, there was no difference in the peak CVC between the dorsal hand and palm during local warming, suggesting that the maximal capacity for an increase in skin blood perfusion was not different between the dorsal hand and palm.

Perspectives. As the burden on the body is not high in the sinusoidal thermal load test during normothermia, it can be used to evaluate skin vasomotor control in the elderly, patients with peripheral circulatory failure, and individuals with a cold constitution (so-called ‘hi-e-sho’ in Japanese). During hyperthermia, the active vasodilator system is employed; however, the dynamic characteristics in vasomotor control may differ from those in normothermia. Further studies are required to

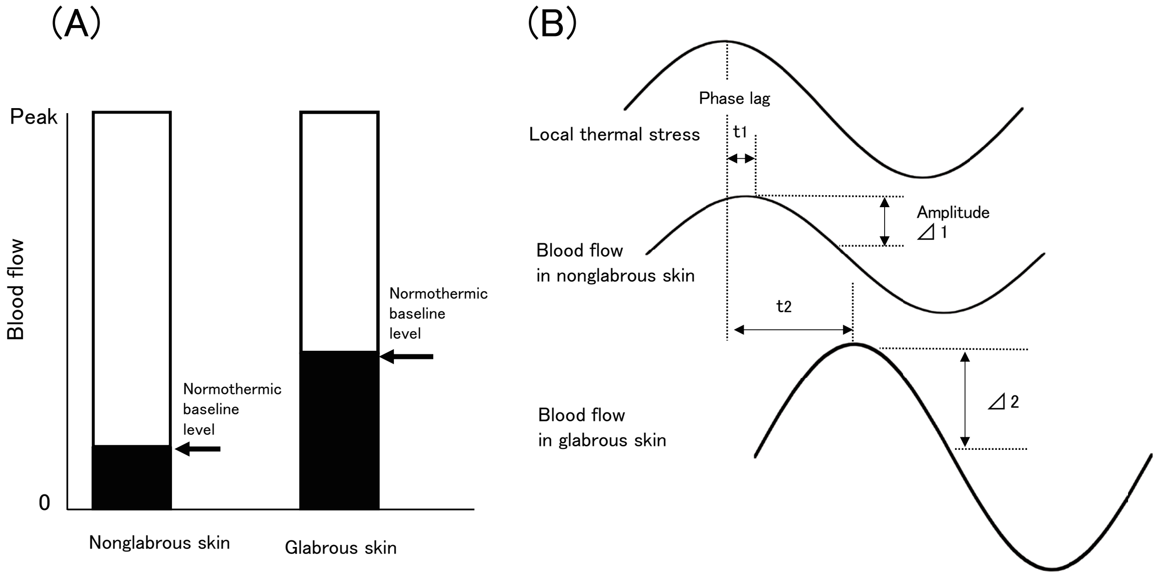

Fig. 5. Characteristics of the control of blood flow in glabrous and nonglabrous skin. A: Under normal temperature conditions, the resting baseline level of blood flow is lower in nonglabrous skin, demonstrating that the reserved capacity for vasodilator response to heat stress is larger in the area, whereas the reserved capacity for vasoconstrictor response to cold stress is larger in glabrous skin. B: During sinusoidal changes of local thermal stress, blood flow in nonglabrous skin exhibits a prompter phase response (t1 < t2) and a smaller amplitude response (⊿1 < ⊿2) than that in glabrous skin, revealing different roles in thermoregulatory control of blood flow in the two skin areas.

answer this question.

The major findings in the present study are summarized in Fig. 5. Under normal temperature conditions, the CVC in the dorsal hand exhibits a smaller amplitude response and prompter phase response than that in the palm during sinusoidal thermal load. The higher baseline values in palmar CVC enable a larger controlling capacity for heat dissipation via a large variation in blood flow.

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