Control of Circadian Variation in Skin Blood Flow Response to Heat Stress

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Summary: Six male subjects had their lower legs immersed in water at 42°C for 60 min at 4 different times of the day to study whether the skin blood flow response to passive heat stress shows circadian variation in the relationship between skin blood flow and local sweating rate. When skin blood flow was plotted against local sweating rate, three distinct phases were observed. Phase A, an increase in skin blood flow

without sweating was maximal at night. But the slope of the regression line did not change over the day in Phase C. These findings suggest that there is circadian variation in the skin blood flow response before onset of sweating during passive heat stress. This variation might be related, in part, to the circadian rhythm in vasoconstrictor activity. [Japanese Journal of Physiology, 48, 95–98, 1998]

Key words: vasoconstrictor activity, vasodilator activity, sweating rate.

In humans, there is a circadian change in internal body temperature, which is the consequence of an endogenous rhythm in heat production and heat loss while at rest [1]. The peak of skin blood flow (SkBF) rhythm in the extremity of the body precedes the nadir of internal temperature rhythm by an average of 4 h [2]. It has been reported that there is circadian variation in the relationships between internal temperature and SkBF or local sweating rate ($\dot{m}_{sw}$) during exercise [3, 4] and during passive heat stress [5, 6]. Furthermore, SkBF is under dual sympathetic nervous control by the noradrenergic vasoconstrictor system and by the sympathetic active vasodilator system [7]. However, it is not clear whether the vasoconstrictor or vasodilator system determines the circadian variation in the SkBF response to heat stress.

Active vasodilation may be linked to the sudomotor system [7]. Hirata *et al.* [8] described a simple method to investigate the vasomotor activity from the view-

point of the two systems by using the relationship between SkBF, measured by the laser-Doppler flowmetry, and $\dot{m}_{sw}$ while immersing the lower legs in hot water. When SkBF was plotted as a function of $\dot{m}_{sw}$, there were three distinct phases. Phase A is an initial increase in SkBF without sweating, Phase B a subsequent increase in $\dot{m}_{sw}$ without any change in SkBF, and Phase C a proportional increase in SkBF and $\dot{m}_{sw}$ [8]. They suggested that Phase A may be the result of reduced vasomotor tone (the release of sympathetic vasoconstrictor activity). The end of Phase B may be the $\dot{m}_{sw}$ threshold for active vasodilation, and Phase C may be caused by a response of the active vasodilator system that accompanies sweating activity.

There are regional differences in skin blood flow [9] and sweating responses [4, 10] during heat stress. It is natural to ask whether the relationship between SkBF and $\dot{m}_{sw}$ differs in different parts of the body at different times of the day. The purpose of this study was to

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investigate whether the skin blood flow response to passive heat stress shows a circadian variation in the relationship between SkBF and $\dot{m}_{sw}$, and whether there are regional differences in the body.

Six healthy male subjects (height 172.1 ± 1.7 cm, body mass 67.3 ± 4.4 kg, body surface area 1.79 ± 0.06 m², and age 22.7 ± 0.5 years, mean $\pm$ SE) participated in this study. The subjects' consents were obtained after they had been given information about the purpose of the study and after procedures had been described. Each subject was tested at 4 different times in a random order: 0400–0700 (morning), 1000–1300 (daytime), 1600–1900 (evening), and 2200–0100 (night) hours. Each test was conducted on a different day. The tests were performed at an ambient temperature of $28.8 \pm 0.8^\circ\text{C}$ and an average relative humidity of 36.1 ± 8.4 %.

The probes of the laser-Doppler flowmeter (LDF, type ALF-21, Advance, Japan) were attached to the back and forearm of each subject. A coiled tube was placed around each probe, and the flow of water through this tube could be controlled to regulate temperature. It has been reported that the local elevation of skin temperature to 42°C for 30–40 min elicits maximal vasodilation [11]. After an initial control period, the water temperature was raised to produce a skin temperature of 42°C for 45 min in order to measure maximal skin blood flow (SkBF_{max}). Afterward, SkBF and local skin temperature (T_{sl}) in the regions of the back and forearm tested were allowed to return to preheated levels. This took 50–60 min. Then both lower legs were immersed in 42°C water for 60 min.

During the experiments several variables were measured. These included esophageal temperature (T_{es}); T_{sl} at 7 sites (for the calculation of mean skin temperature [12], $\bar{T}_{sk}$); $\dot{m}_{sw}$ on the back and forearm by using a ventilated capsule method with a hygrometer (HMP133Y, Takara Vaisara, Japan); and SkBF on the back and forearm. All the SkBF values were converted to percentages of maximal skin blood flow (%SkBF; $\text{SkBF}/\text{SkBF}_{\text{max}} \times 100$). A personal computer (PC9801T, NEC Co. Ltd., Japan) and a data logger (HR2300, Yokogawa Co. Ltd., Japan) were used to record temperature parameters, $\dot{m}_{sw}$, SkBF_{max}, and SkBF, every second. These values were used to calculate the average for each minute.

The data were subjected to an analysis of variance (ANOVA) with repeated measures. Furthermore, the Student-Newman-Keuls multiple-comparison test was used to test treatment mean values against times of day when there were significant differences because of the time. The Student's *t*-test was used to assess regional differences for each time of day, and any *p*

Fig. 1. Time course of local sweating rate ($\dot{m}_{sw}$) and skin blood flow (SkBF) on the back in the first 30 min following immersion of the lower legs in hot water at 4 different times of the day. The mean and SE are indicated for each plot. $N=6$ male subjects.

value of less than 0.05 was considered significant. All temperatures are given as mean $\pm$ SE.

The resting T_{es} was 36.55 ± 0.10 in the morning, 36.84 ± 0.09 in the daytime, 37.19 ± 0.07 in the evening, and $36.99 \pm 0.08^\circ\text{C}$ at night. The resting T_{es} was significantly higher in the evening and at night than in the morning. On the other hand, the resting $\bar{T}_{sk}$ did not vary over the day. It was 33.50 ± 0.26 in the morning, 33.95 ± 0.25 in the daytime, 33.95 ± 0.20 in the evening, and $34.40 \pm 0.20^\circ\text{C}$ at night.

The respective values of resting T_{sl} on the back and forearm was 33.68 ± 0.18 and 33.76 ± 0.16 in the morning, 34.29 ± 0.27 and 34.16 ± 0.28 in the daytime, 34.26 ± 0.14 and 33.98 ± 0.17 in the evening, and 34.54 ± 0.20 and $34.66 \pm 0.17^\circ\text{C}$ at night. The resting T_{sl} on the back and on the forearm was significantly higher at night than in the morning.

The time courses of $\dot{m}_{sw}$ and SkBF in the first 30 min after the lower legs were immersed in hot water did not differ over the day (Fig. 1).

There were three distinct phases (A, B, and C) in the relationship between SkBF, %SkBF, and $\dot{m}_{sw}$ on the back and forearm, from when the lower legs were first immersed until T_{es} reached a steady state (Fig. 2 and Table 1). Phase A was the period before the onset of sweating. Phase B started with the onset of sweating and ended when the SkBF suddenly increased above its baseline value at the onset of sweating.

Phase C followed the sudden increase in SkBF, and a regression between SkBF and $\dot{m}_{sw}$ was calculated for this phase. In Phase A, the increase in SkBF without sweating was significantly higher at night than in the daytime and evening for both body sites. However, the SkBF threshold at the onset of sweating in Phase B ($Th_{(\dot{m}_{sw})}$) and the $\dot{m}_{sw}$ threshold at the secondary increase in SkBF at the end of Phase B ($Th_{(SkBF)}$) did not differ significantly over the day. The slope of regression line in the relationship between SkBF and $\dot{m}_{sw}$ in Phase C varied greatly between subjects, but for each

Fig. 2. The relationship between skin blood flow (SkBF) and local sweating rate ($\dot{m}_{sw}$) on the back during immersion of the lower legs in hot water until the esophageal temperature (T_{es}) reaches a steady state at 4 different times of the day in one subject. ○, morning; ●, daytime; □, evening; ■, night.

subject the slope did not differ significantly over the day (Fig. 2). Moreover, in all phases there were no regional differences between back and forearm.

Although the increase in %SkBF without sweating, as determined from the relationship between %SkBF and $\dot{m}_{sw}$, was maximal during the night at both sites in Phase A, no significant differences were observed in Phases B and C.

T_{es} at ($Th_{(\dot{m}_{sw})}$) and ($Th_{(SkBF)}$) on the back in Phase B were 36.77 ± 0.11 and 36.81 ± 0.12 in the morning, 37.06 ± 0.08 and 37.10 ± 0.08 in the daytime, 37.30 ± 0.09 and 37.47 ± 0.14 in the evening, and 37.21 ± 0.08 and $37.23 \pm 0.12^\circ\text{C}$ at night. The T_{es} at ($Th_{(\dot{m}_{sw})}$) was significantly lower in the morning than at other times, and T_{es} at ($Th_{(SkBF)}$) was significantly lower in the morning than in the evening. These parameters on the forearm showed a change similar to changes on the back over the day. However, there was no significant difference in T_{es} at ($Th_{(\dot{m}_{sw})}$) and ($Th_{(SkBF)}$) at both sites. $\bar{T}_{sk}$ at both thresholds in Phase B did not change over the day, and there was no significant difference between both thresholds.

The T_{es} thresholds for the onset of sweating and cutaneous vasodilation during exercise change with circadian rhythm in the resting T_{es} [3, 4]. This suggests that the rhythms in sweating and skin blood flow responses are mainly the result of activity in a thermoregulatory center [3]. This agrees with our results; however, there was no significant difference in T_{es} at ($Th_{(\dot{m}_{sw})}$) and ($Th_{(SkBF)}$). It has been reported that T_{es} threshold for the onset of sweating is significantly lower than it is for cutaneous vasodilation [3, 4]. We

Table 1. The relationship between skin blood flow (SkBF) and local sweating rate ($\dot{m}_{sw}$) during passive heat stress.

	Morning	Daytime	Evening	Night
Phase A (mV)				
Back	18.00 ± 4.04	9.55 ± 1.24	9.09 ± 1.21	$25.14 \pm 4.42^{\S,*}$
Forearm	24.84 ± 4.22	14.58 ± 2.97	15.26 ± 2.44	$31.37 \pm 6.33^{\S,*}$
Phase B				
($Th_{(\dot{m}_{sw})}$) (mV)				
Back	50.54 ± 9.75	48.31 ± 6.35	44.46 ± 6.36	76.48 ± 10.16
Forearm	61.93 ± 9.16	47.05 ± 7.68	64.21 ± 9.65	69.00 ± 8.88
($Th_{(SkBF)}$) ($\text{mg} \cdot \text{cm}^{-2} \cdot \text{min}^{-1}$)				
Back	0.25 ± 0.03	0.25 ± 0.04	0.24 ± 0.04	0.20 ± 0.03
Forearm	0.17 ± 0.04	0.22 ± 0.03	0.17 ± 0.02	0.17 ± 0.01
Phase C ($\text{mV} \cdot (\text{mg} \cdot \text{cm}^{-2} \cdot \text{min}^{-1})^{-1}$)				
Back	233.58 ± 56.53	291.29 ± 98.82	232.05 ± 61.39	361.70 ± 117.88
Forearm	513.96 ± 130.91	365.29 ± 90.91	627.71 ± 231.57	324.48 ± 58.28

Phase A: the increase in SkBF without sweating; ($Th_{(\dot{m}_{sw})}$): the values of SkBF threshold at the onset of $\dot{m}_{sw}$ in Phase B; ($Th_{(SkBF)}$): the values of $\dot{m}_{sw}$ threshold at secondary point of increase in SkBF at the end of Phase B; Phase C: the slope of regression line in the relationship between SkBF and $\dot{m}_{sw}$. * Significant difference from daytime ($p < 0.05$). $\S$ Significant difference from evening ($p < 0.05$). Values are means $\pm$ SE. $N=6$ male subjects.

used passive heat stress rather than dynamic exercise used in earlier studies [3, 4]. Since T_{es} threshold for cutaneous vasodilation during exercise is higher than during passive heat stress [13], the difference between these studies is strictly because of different types of heat stress.

In this study, Phase A of the relationship between SkBF or %SkBF and $\dot{m}_{sw}$ was higher at night than in the daytime and evening at each site. This may be the product of a reduction in vasomotor tone [8]. However, the resting T_{sk} at night on the back and forearm was only significantly higher than the resting T_{sk} in the morning. Thus circadian variation in Phase A may not be greatly influenced by T_{sk} at each site. Smolander *et al.* [2] have indicated that at rest, skin blood flow in the extremity of the body has a circadian rhythm and peaks after midnight. It has been reported that at rest, the maximal forearm blood flow and minimal vascular resistance occur early in the night. In this report, the experiments were performed in the morning, daytime, and early at night [14]. Furthermore, Panza *et al.* [14] have suggested that the circadian rhythm in vascular tone at rest is associated with α -sympathetic vasoconstrictor activity. This implies that the higher values in Phase A at night in this study are due to lower sympathetic vasoconstrictor activity.

In contrast, $(Th_{(\dot{m}_{sw})})$ and $(Th_{(SkBF)})$ in Phase B and the slope of regression line in Phase C did not differ significantly over the day. It has been reported that the active vasodilation that accompanies sweating is influenced by vasoactive intestinal polypeptide (VIP) in the cholinergic neuron innervating eccrine sweat glands [15], calcitonin gene-related peptide (CGRP), and substance P [16]. In this study, however, the slope of regression line in Phase C did not differ significantly over the day because of the greater variation seen between subjects in this phase. Thus the circadian rhythm in skin blood flow response to passive heat stress may not be influenced entirely by the vasodilative activity.

In summary, we found that Phase A on the back and forearm was higher at night, although the $(Th_{(\dot{m}_{sw})})$ and $(Th_{(SkBF)})$ in Phase B and the slope of regression line in Phase C did not differ significantly over the day. Moreover, in all phases there were no regional differences between back and forearm. Therefore we suggest that skin blood flow response before the onset of sweating, in response to passive heat stress, shows a circadian variation, and that this variation might be related in part to the rhythm in vasoconstrictor activity.

REFERENCES

1. Kräuchi K and Wirz-Justice A: Circadian rhythm of heat production, heart rate, and skin and core temperature under masking conditions in men. *Am J Physiol* 267: R819–R829, 1994
2. Smolander J, Härmä M, Lindqvist A, Kolari P, and Laitinen LA: Circadian variation in peripheral blood flow in relation to core temperature at rest. *Eur J Appl Physiol* 67: 192–196, 1993
3. Stephenson LA, Wenger CB, O'Donovan BH, and Nadel ER: Circadian rhythm in sweating and cutaneous blood flow. *Am J Physiol* 246: R321–R324, 1984
4. Aoki K, Shiojiri T, Shibasaki M, Takano S, Kondo N, and Iwata A: The effect of diurnal variation on the regional differences in sweating and skin blood flow during exercise. *Eur J Appl Physiol* 71: 276–280, 1995
5. Aoki K, Kondo N, Shibasaki M, Takano S, and Katsuura T: Circadian variation in skin blood flow responses to passive heat stress. *Physiol Behav* 63: 1–5, 1998
6. Aoki K, Kondo N, Shibasaki M, Takano S, Tominaga H, and Katsuura T: Circadian variation of sweating responses to passive heat stress. *Acta Physiol Scand* 161: 397–402, 1997
7. Fox RH and Edholm OG: Nervous control of the cutaneous circulation. *Br Med Bull* 19: 110–114, 1963
8. Hirata K and Kondo N: Skin blood flow and local sweat rate during heat loads by leg water immersion and heat exposure. *Jpn J Physiol* 44: S 248, 1994
9. Shibasaki M, Inoue Y, Kondo N, and Iwata A: Thermoregulatory responses of prepubertal boys and young men during moderate exercise. *Eur J Appl Physiol* 75: 212–218, 1997
10. Takano S, Kondo N, Shibasaki M, Aoki K, Inoue Y, and Iwata A: The influence of work loads on regional differences in sweating rates. *Jpn J Physiol* 46: 183–186, 1996
11. Taylor WF, Johnson JM, O'Leary D, and Park MK: Effect of high local temperature on reflex cutaneous vasodilation. *J Appl Physiol* 57: 191–196, 1984
12. Inoue Y and Shibasaki M: Regional differences in age-related decrements of the cutaneous vascular and sweating responses to passive heating. *Eur J Appl Physiol* 74: 78–84, 1996
13. Kellogg DL Jr, Johnson JM, and Kosiba WA: Control of internal temperature threshold for active cutaneous vasodilation by dynamic exercise. *J Appl Physiol* 71: 2476–2482, 1991
14. Panza JA, Epstein SE, and Quyyumi AA: Circadian variation in vascular tone and its relation to α -sympathetic vasoconstrictor activity. *N Engl J Med* 325: 986–990, 1991
15. Yamashita Y, Ogawa T, Ohnishi N, Imamura R, and Sugeno Y: Local effect of vasoactive intestinal polypeptide on human sweat-gland function. *Jpn J Physiol* 37: 929–936, 1987
16. Savage MV, Brengelmann GL, Buchan AMJ, and Freund PR: Cystic fibrosis, vasoactive intestinal polypeptide, and active cutaneous vasodilation. *J Appl Physiol* 69: 2149–2154, 1990