

# Effects of muscle metaboreceptor stimulation on cutaneous blood flow from glabrous and nonglabrous skin in mildly heated humans

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**Kondo, Narihiko, Shuji Yanagimoto, Takeshi Nishiyasu, and Craig G. Crandall.** Effects of muscle metaboreceptor stimulation on cutaneous blood flow from glabrous and nonglabrous skin in mildly heated humans. *J Appl Physiol* 94: 1829–1835, 2003. First published January 17, 2003; 10.1152/jappphysiol.00810.2002.—Given differences in sympathetic innervation to glabrous and nonglabrous skin, we tested the hypothesis that muscle metaboreceptor regulation of cutaneous vascular conductance (CVC) differs between these skin regions. Subjects ( $n = 21$ ) performed isometric handgrip exercise (IHG; 50% maximal voluntary contraction for 60 s), followed by 2 min of postexercise ischemia. Throughout IHG and postexercise ischemia, CVC was measured from glabrous (palm) and nonglabrous (forearm and chest) regions contralateral to the exercising arm. These procedures were conducted after the subjects had been exposed to an ambient temperature of 35°C and a relative humidity of 50% for 60 min. These thermal conditions were intended to cause slight increases in cutaneous blood flow via sympathetic withdrawal. Esophageal, sublingual, and mean skin temperatures did not change markedly during IHG or postexercise ischemia. During IHG, forearm CVC did not change, chest CVC increased slightly, and palm CVC decreased substantially (from 100 to  $34.8 \pm 3.5\%$ ;  $P = 0.001$ ). During muscle metaboreceptor stimulation due to postexercise ischemia, CVC from nonglabrous regions returned to preexercise baselines, whereas CVC at the palm remained below preexercise baseline ( $68.2 \pm 4.2\%$ ;  $P = 0.001$  relative to preexercise baseline). These results indicate that in mildly heated humans muscle metaboreflex stimulation is capable of modulating CVC in glabrous, but not in nonglabrous, skin.

skin blood flow; cutaneous vasoconstriction; active vasodilation; sudomotor activity

SKIN BLOOD FLOW (SkBF) is important for controlling internal temperature in passively heated humans as well as during exercise. In nonglabrous skin (i.e., hairy skin), during a heat stress the initial increase in SkBF occurs via withdrawal of cutaneous vasoconstrictor activity. As the heat load increases, a separate active vasodilator system is engaged that is responsible for 85–95% of the elevation in SkBF (9, 12). This is in

contrast to glabrous skin (i.e., nonhairy skin such as soles of feet and palms of hands) in which changes in SkBF occur only through modulation of tonic vasoconstrictor tone, because these regions of skin do not have an active vasodilator system (8).

Isometric handgrip (IHG) exercise increases heart rate (HR), mean arterial blood pressure (MAP), sweat rate (SR) (under moderately warm conditions), and sympathetic nerve activity to skin and muscle (16–17, 20–24). During IHG under normothermic (19) and mildly hyperthermic (25) conditions, cutaneous vascular conductance (CVC) of glabrous skin decreases, whereas CVC of nonglabrous regions does not change markedly. These physiological responses associated with isometric exercise are related to mechanisms involving central command (stimulation originating from the parallel activation of motor and autonomic pathways) and the activation of mechanosensitive or metabosensitive receptors in exercising muscle (2–3, 13, 17, 20–24). However, it remains unknown which of these mechanisms are responsible for the reduction in CVC observed in glabrous skin during IHG (19, 25).

The observation that arterial blood pressure and muscle sympathetic nerve activity remains elevated during postexercise ischemia suggests that these responses are due to chemosensitive afferents within the muscle (16–17, 20). It is clear from prior studies that muscle metaboreceptor stimulation associated with isometric exercise is capable of modulating CVC in nonglabrous skin during moderate and more pronounced heat stress (2, 3). However, given differences in innervation of glabrous and nonglabrous skin (8), observed CVC responses during muscle metaboreceptor stimulation in nonglabrous skin (2, 3) may not mirror responses in glabrous skin.

Therefore, the purpose of this study was to investigate the hypotheses that metaboreceptor regulation of CVC differs between glabrous and nonglabrous skin and that muscle metaboreceptor stimulation is one of the mechanisms leading to reductions in CVC of glabrous skin during IHG. To test these hypotheses, in

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mildly heated humans we measured cutaneous blood flow from glabrous and nonglabrous skin during IHG followed by postexercise ischemia; the latter of which selectively stimulates muscle metaboreceptors.

## METHODS

**Subjects.** We studied 21 healthy male subjects with the following characteristics: age  $20.6 \pm 1.1$  (SD) yr, height  $1.69 \pm 0.01$  m, and mass  $56.7 \pm 1.1$  kg. Each subject was informed in advance of the purpose of the study and of the procedures involved, and his consent was obtained. This study was approved by the human subjects committee at our department in Kobe University.

**Procedures.** All procedures were conducted in an environmental chamber (SR-3000, Nagano Science, Osaka, Japan) maintained at an ambient temperature of  $35^{\circ}\text{C}$  and a relative humidity of 50%, with minimal air movement. These environmental conditions were selected to cause slight increases in cutaneous blood flow primarily via withdrawal of sympathetic vasoconstrictor activity, as well as slight increases in sudomotor activity. After entering the chamber, each subject rested in the semisupine position for  $\sim 60$  min until cutaneous blood flow and SR were slightly elevated and had reached a steady state. During this time, monitoring instruments were attached. While in the chamber, each subject performed two brief maximal voluntary contractions (MVCs) with his right and left hands using a handgrip dynamometer; the higher value was used to quantify the relative workload (50% MVC) for each hand. Baseline data were then recorded for 5 min at rest. The subject then performed 60 s of IHG at 50% MVC. A visual feedback system was used so that the subject could maintain the force throughout the exercise period. Five seconds before the end of the exercise bout, a cuff around the upper arm that was performing the contraction was inflated to supersystolic pressures ( $>240$  mmHg) for 120 s. After this period, the cuff was deflated and recovery data were obtained for another 120 s. This protocol permits the investigation of the effect of the muscle metaboreflex on cutaneous blood flow, because muscle metaboreceptor afferents are activated during posthandgrip forearm occlusion, whereas muscle relaxation eliminates both central command and the stimulation of muscle mechanoreceptor afferents (16–17, 20–24). Because skin sympathetic nerve activity is influenced by respiration (4), the subject's respiratory frequency was maintained at 15 breaths/min throughout the rest period, IHG, postexercise muscle ischemia, and the recovery with the aid of auditory signals. The same protocol was performed for both the right and left hands, and responses for both hands at each stage were averaged. Performing IHG from both hands required the removal of the sweat capsule and laser-Doppler probe on one palm and placing it on the other palm between two exercise bouts. Fifteen minutes elapsed between trials for each hand.

**Measurements.** Measurements included esophageal temperature ( $T_{\text{es}}$ ), sublingual temperature [oral temperature ( $T_{\text{or}}$ )], and local skin temperature ( $T_{\text{sl}}$ ) at eight sites on the body (chest, forearm, palm, forehead, abdomen, thigh, lower leg, and foot); SR and SkBF from the chest (nonglabrous skin), forearm (nonglabrous skin), and palm (glabrous skin); HR; and arterial blood pressure.  $T_{\text{es}}$  was measured from a thermocouple, with a silicon lubricant on the tip, inserted through the nose into the esophagus to a distance equal to one-quarter of the subject's height. Mean skin temperature ( $\bar{T}_{\text{sk}}$ ) was calculated according to the method of Hardy and

Dubois (6). HR was measured continuously from an electrocardiogram. Arterial blood pressure was measured by arterial tonometry over the radial artery from the nonexercising hand (Jentow-7700, Colin, Tokyo, Japan). MAP was calculated as diastolic blood pressure plus one-third of the pulse pressure. Temperature variables were measured by using copper-constantan thermocouples.

SR was measured continuously by the ventilated-capsule method with the capsule being attached to the skin by using collodion. Dry nitrogen gas was supplied to the capsules ( $1.54 \text{ cm}^2$ ) at a rate of 600 ml/min, and the humidity and temperature of the nitrogen gas flowing out of the capsules were measured by using a capacitance hygrometer (HMP 133Y, Vaisala, Helsinki, Finland) and recorded to calculate SR. The time delay for this system is 1 s and was accounted for in the SR calculation. SkBF was measured by laser-Doppler velocimetry (ALF21, Advance, Tokyo, Japan) with the probes located within 1 cm of the capsules used to assess SR. CVC was calculated from the ratio of SkBF to MAP. CVC responses were normalized relative to resting levels immediately before exercise, with the resting levels expressed as 100%. Body temperatures, SR, and SkBF were recorded every second and stored in a personal computer (PC9801RA, NEC, Tokyo, Japan) using a data logger (HR2300, Yokogawa, Tokyo, Japan).

**Statistics.** Values were calculated for the following periods: a 30-s preexercise period (rest), the final 30 s of the handgrip exercise (handgrip), the final 30 s of the postexercise ischemia (occlusion), and the final 30 s of recovery (recovery). One-way analysis of variance with repeated measures was performed (using a Dunnett's multiple-comparison test when  $F$  values were significant) to compare the responses between the aforementioned periods. Results are presented as means  $\pm$  SE. The  $P$  value for significance was set at 0.05.

## RESULTS

Sixty minutes of sitting quietly in the environmental chamber slightly increased SkBF (chest:  $33.29 \pm 3.30$  to  $52.14 \pm 3.46$  V; forearm:  $33.57 \pm 4.11$  to  $83.52 \pm 3.36$  V; palm:  $238.23 \pm 37.15$  to  $448.17 \pm 30.13$  V) and SR (chest:  $0.23 \pm 0.04 \text{ mg}\cdot\text{cm}^{-2}\cdot\text{min}^{-1}$ ; forearm:  $0.10 \pm 0.01 \text{ mg}\cdot\text{cm}^{-2}\cdot\text{min}^{-1}$ ; palm:  $0.25 \pm 0.08 \text{ mg}\cdot\text{cm}^{-2}\cdot\text{min}^{-1}$ ).

Figure 1 shows  $T_{\text{es}}$ ,  $T_{\text{or}}$ ,  $\bar{T}_{\text{sk}}$ , HR, and MAP as well as CVC and SR from glabrous and nonglabrous skin. HR increased during IHG and returned to baseline (preexercise levels) during occlusion, whereas MAP increased during IHG and remained above preexercise levels during occlusion (Fig. 2). Temperature values did not change substantially throughout the periods of IHG, postexercise ischemia, or recovery, although there were slight decrease in  $T_{\text{es}}$  and a slight change in  $T_{\text{sl}}$  (measured from the sites of SR and CVC measurement) (Fig. 2). The physiological significance of those differences is likely unimportant relative to the large changes in CVC and SR during IHG and occlusion. CVC from glabrous skin decreased during IHG and remained below preexercise levels during occlusion (Fig. 3). CVC from nonglabrous skin did not change markedly throughout the experiment, although there was a slight increase in chest CVC during IHG that reduced to preexercise levels during postexercise ische-

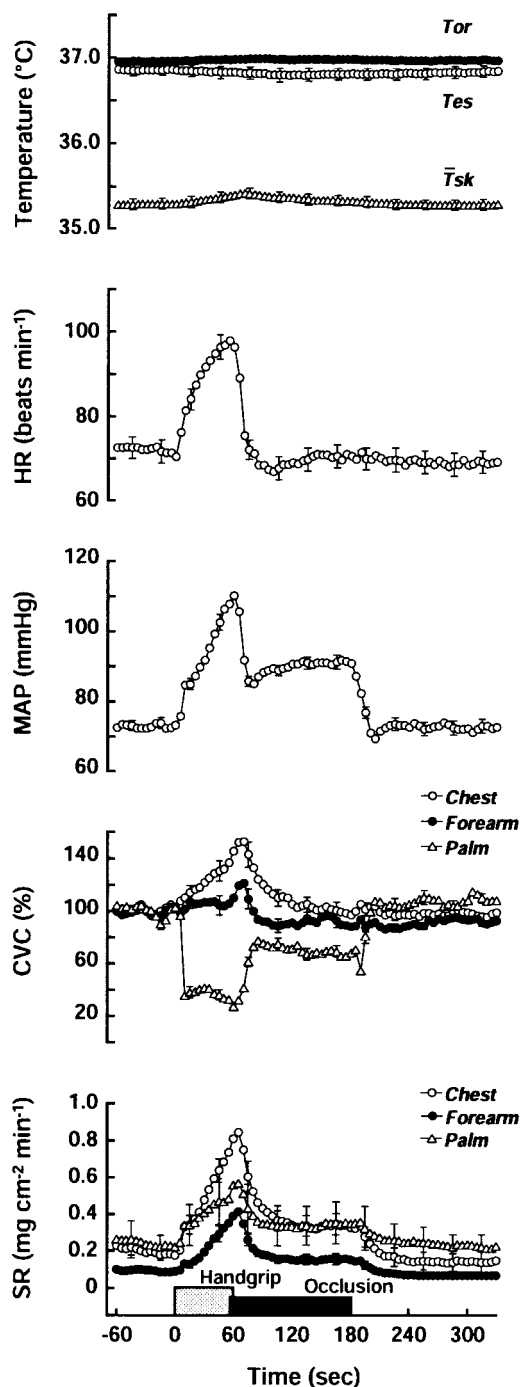


Fig. 1. Changes in esophageal temperature ( $T_{es}$ ), sublingual temperature [oral temperature ( $T_{or}$ )], mean skin temperature ( $T_{sk}$ ), heart rate (HR), mean arterial pressure (MAP), and cutaneous vascular conductance (CVC) and sweating rate (SR) from the chest, forearm, and palm in response to isometric handgrip exercise and postexercise ischemia. Data were obtained at rest, during isometric handgrip exercise for 60 s at 50% maximal voluntary contraction, during postexercise ischemia (occlusion) for 120 s, and during recovery. Values are means  $\pm$  SE for 21 subjects.

mia. SR from all areas of skin increased during IHG, decreased slightly during postexercise ischemia, and then returned to preexercise levels during the recovery period (see Figs. 1 and 3).

## DISCUSSION

The primary novel finding of this study suggests that stimulation of muscle metaboreceptors is capable of reducing CVC in glabrous skin and that decreases in CVC from glabrous skin during IHG are likely due to a combination of central command and/or muscle mechanoreceptor stimulation coupled with muscle metaboreceptor stimulation. This conclusion is based on the observation that CVC from glabrous skin decreased by 65.2% during IHG and remained 31.8% below preexercise levels during the period of postexercise ischemia when muscle metaboreceptors remained stimulated (16–17, 20–24). In a prior study, our laboratory showed that CVC from glabrous skin returns to preexercise levels after IHG without occlusion (25), and thus the sustained reduction in palm CVC during postexercise ischemia in the present study is not due to a slow recovery of CVC after IHG exercise. This point is further emphasized on looking at the abrupt stair-step pattern of CVC responses in Fig. 1. In contrast, forearm CVC did not change from baseline during IHG or postexercise ischemia, whereas chest CVC increased during IHG and returned to pre-IHG baseline during the ischemic period. Because body temperatures did not change markedly during IHG or postexercise ischemia, changes in CVC of glabrous skin and SR from glabrous and nonglabrous skin were not due to thermal factors.

Reported differences in sympathetic innervation of glabrous and nonglabrous skin (8) raises the hypothesis that muscle metaboreceptor regulation of CVC may differ between these regions of skin. Prior studies have shown that CVC of glabrous skin decreases below resting levels during IHG at 30% MVC for 2 min in normothermic conditions (19) and at 35 and 50% MVC for 1 min in mildly hyperthermic conditions (25). Findings from the present study with respect to CVC responses during IHG from glabrous skin are consistent with these prior observations. However, in those prior studies (19, 25), the mechanism(s) responsible for modulating CVC responses of glabrous skin during IHG were not investigated. Thus the primary objective of the present study was to investigate whether muscle metaboreceptor stimulation during IHG is capable of contributing to the previously observed reductions in CVC during IHG. The observation that CVC from glabrous regions remains below pre-IHG baseline during postexercise ischemia indicates that muscle metaboreceptor stimulation is capable of reducing palm CVC. However, on the cessation of IHG and the onset of postexercise ischemia, palm CVC rapidly increased toward pre-IHG baseline but stayed significantly below pre-IHG baseline (see Fig. 1). The observation that palm CVC increased toward baseline at the end of IHG suggests that some of the decrease in CVC was due to factors associated with central command and/or muscle mechanoreceptor stimulation.

In the present study, CVC from the chest increased during IHG but returned to pre-IHG levels during postexercise ischemia. This observation suggests that

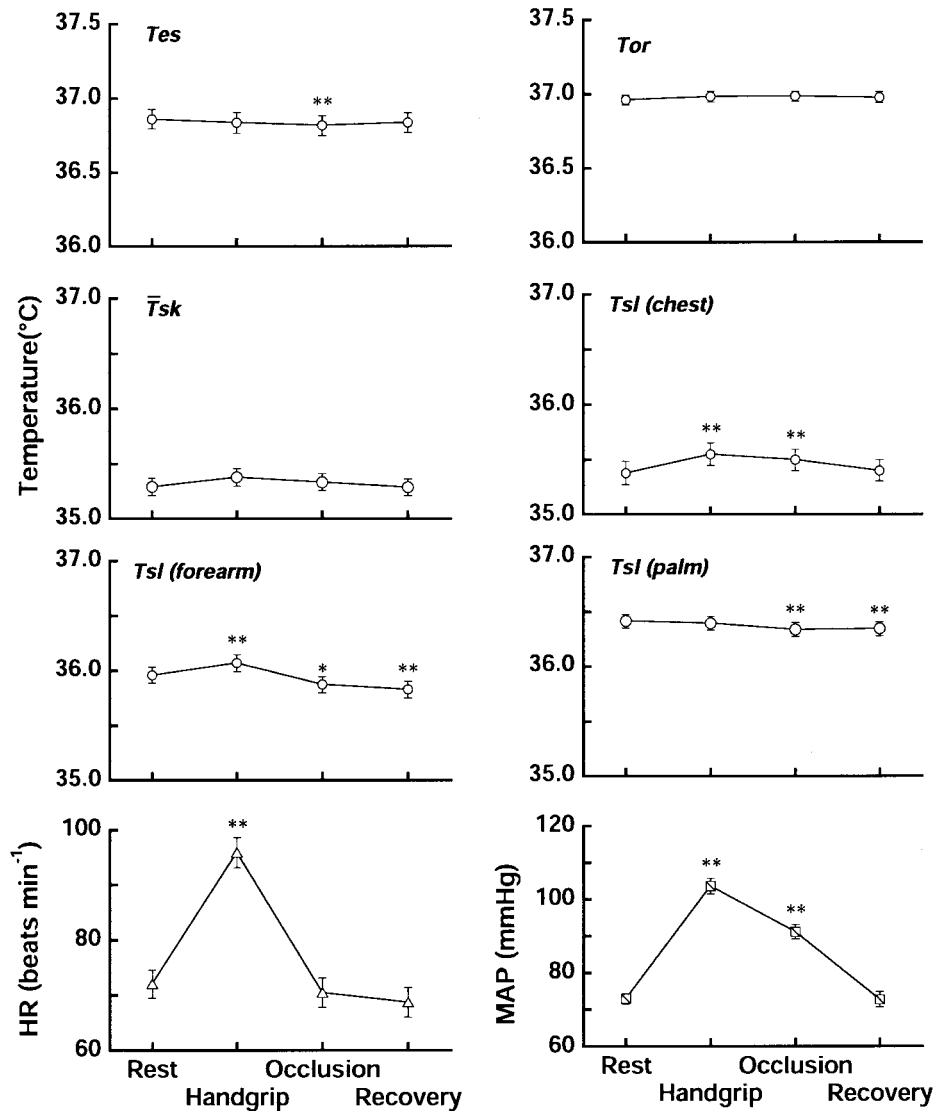


Fig. 2.  $T_{es}$ ,  $T_{or}$ ,  $\bar{T}_{sk}$ , and local skin temperature ( $T_{sl}$ ) on the chest, forearm, and palm; HR; and MAP at rest, during isometric handgrip exercise for 60 s at 50% maximal voluntary contraction, during postexercise ischemia (occlusion) for 120 s, and during recovery. Values are means  $\pm$  SE for 21 subjects. Significantly different from rest: \* $P < 0.05$ ; \*\* $P < 0.01$ .

the increase in chest CVC during IHG was unlikely to be due to muscle metaboreceptor stimulation. In the forearm, CVC did not change regardless of the perturbation. Prior studies have reported no change, slight increases, or slight decreases in CVC from nonglabrous regions during IHG exercise at different environmental conditions (2, 13, 19, 25). Taken together, it is likely that differences in nonglabrous CVC responses during IHG may be due to the thermal state of the individual during IHG and/or the region of nonglabrous skin measured.

In the present study, placing the individual in a warm environment for 60 min induced slight increases in SkBF at all sites measured. Because internal temperature did not increase markedly by this mild heat stress, it is likely that these slight increases in SkBF from nonglabrous skin were primarily due to withdrawal of the sympathetic vasoconstrictor system, as opposed to engagement of the active vasodilator system. However, we cannot exclude the possibility that a component of the increase in SkBF from nonglabrous

regions was due to engagement of the cutaneous active vasodilator system. In contrast, because glabrous skin does not possess an active vasodilator system (8), any change in SkBF from these regions of skin is likely due to modulation of the sympathetic vasoconstrictor system.

The effects of muscle metaboreflex stimulation on reducing CVC are seen only in glabrous skin. Differences in the microvascular anatomy and neural innervation (8) between glabrous and nonglabrous skin may be a reason for the different responses between these sites during IHG and postexercise ischemia. Glabrous skin has a large concentration of arteriovenous anastomoses, which causes large fluctuations in the SkBF observed in these regions (1, 14, 19). In contrast, arteriovenous anastomoses are virtually absent in nonglabrous skin (5). Moreover, glabrous skin is innervated with only an adrenergic vasoconstrictor system, whereas nonglabrous skin is innervated with both a vasoconstriction and an active vasodilator system. It remains unclear whether differences in CVC responses

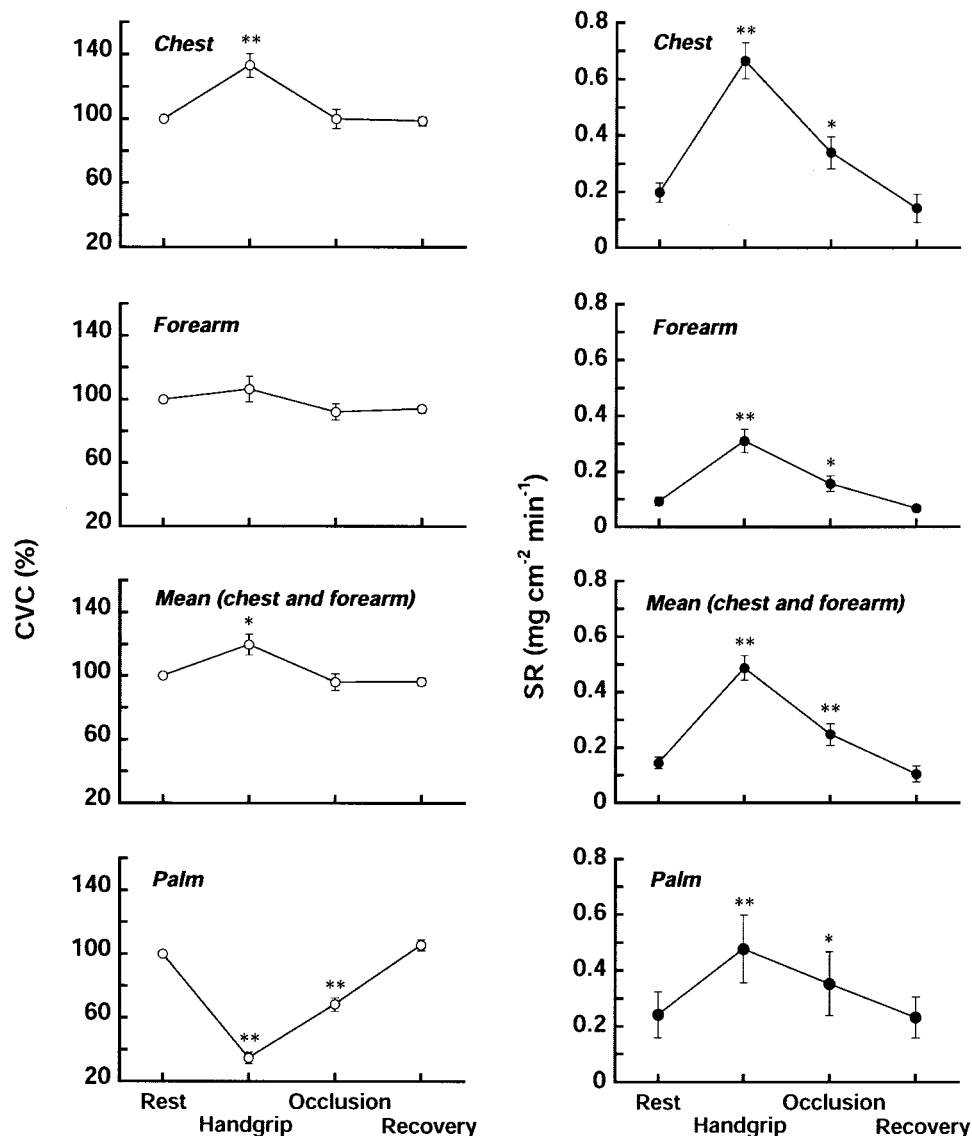


Fig. 3. Mean cutaneous vascular conductance (CVC) and SR from nonglabrous (chest and forearm) and glabrous (palm) skin at rest, during isometric handgrip exercise for 60 s at 50% maximal voluntary contraction, during postexercise ischemia (occlusion) for 120 s, and during recovery. Values are means  $\pm$  SE for 21 subjects. Significantly different from rest: \* $P < 0.05$ ; \*\* $P < 0.01$ .

during postexercise ischemia between glabrous and nonglabrous regions are due to one or both of these differences between glabrous and nonglabrous skin.

A prior study showed that forearm CVC (nonglabrous skin) can be reduced during IHG and remain reduced during postexercise ischemia in pronounced heat-stressed individuals (2, 3). These responses occurred primarily through modulation of the cutaneous active vasodilator system because the responses were preserved when adrenergic neurotransmission was inhibited. The prior findings are in contrast to the present findings of either an increase in CVC or an absence of a change in CVC during IHG from nonglabrous skin. Two reasons may explain differences between the present and prior findings. First, in the present study, internal temperature did not change markedly due to 60-min exposure in a warm environment. This is in contrast to the objective in the prior studies (2, 3) in which the goal was to increase internal temperature to specifically look at CVC responses mod-

ulated by cutaneous active vasodilator activity. Second, in the prior studies, consistent decreases in CVC were observed only after repeated bouts of IHG from the same hand, suggesting that fatigue may have contributed to observed responses (2, 3). In contrast, in the present study, each person performed only one bout of IHG per hand and thus fatigue would not have been an issue.

Cutaneous vascular responses may be influenced by baroreflexes at rest (2, 7, 10, 18) and during dynamic exercise (10, 15). During postexercise occlusion, carotid and aortic baroreceptors are loaded because MAP remains significantly above baseline level during this period. However, it is doubtful that the decrease in CVC from glabrous skin during IHG and postexercise ischemia is a consequence of arterial baroreceptor loading because it would be expected that increases in arterial baroreceptor loading would reduce sympathetic vasoconstrictor activity, leading to an increased CVC, not the observed decreased CVC from glabrous skin.

Saito et al. (20) did not observe changes in either SkBF (measured via laser-Doppler flowmetry) or calculated skin vascular resistance when measured from glabrous skin (sole of foot) during 2 min of 30% MVC isometric handgrip exercise in a normothermic environment (23°C). In contrast, in the present study, palm CVC clearly decreased during IHG and remained below baseline during postexercise ischemia (Fig. 3). It is unclear whether differences between these studies are due to differences in environmental conditions (23 vs. 35°C) or due to differences in location of skin blood flow measurement (sole of foot vs. palm of hand). However, similar to the present findings, Saad et al. (19) recently reported that the CVC of glabrous skin of both the palm of the hand and sole of the foot decreased significantly from baseline during IHG conducted under thermoneutral conditions. Thus it is unlikely that different thermal conditions and/or different responses on the soles of the feet relative to the palms of the hands during IHG explain differences in findings between the present results and those of Saito et al. (20).

During postexercise ischemia, SR from glabrous skin remained above baseline levels, whereas CVC at the same site remained below baseline (Fig. 3). These results suggest that the influence of muscle metaboreceptor stimulation differs between sweating responses and cutaneous vascular responses in glabrous skin and that vasomotor and sudomotor systems on the palm are capable of being independently controlled in humans.

The sustained elevation in SR during postexercise ischemia from glabrous skin is different from what our laboratory previously reported (13). In that study, palm SR returned toward pre-IHG levels during postexercise ischemia; although there was a strong tendency for SR to be elevated above baseline during this period, it did not reach statistical significance. The number of subjects in the present study (21 subjects) is substantially higher relative to the cited study (8 subjects), and thus the power of the statistical design is greater in the present study. Also, in the cited study, IHG exercise was performed at 45% of MVC, whereas in the present study the workload was 50% of MVC. Thus, in addition to increased statistical power, a slightly greater muscle metaboreceptor stimulation might be required to sustain sweating responses from glabrous skin during postexercise ischemia.

In conclusion, during postexercise ischemia in mildly heated humans, CVC of glabrous skin (palm of hand) remained significantly below baseline, whereas CVC of nonglabrous skin (chest and forearm) remained at baseline during this period. Body temperatures did not change appreciably during the experiments. These results suggest that in mildly heated humans the control of blood flow in glabrous skin can be modulated by afferent signals from muscle metaboreceptors, whereas this same degree of metaboreceptor stimulation has no effect on the control of SkBF in nonglabrous skin.

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