Forehead versus forearm skin vascular responses at presyncope in humans

Daniel Gagnon, R. Matthew Brothers, Matthew S. Ganio, Jeffrey L. Hastings, and Craig G. Crandall

Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas and University of Texas Southwestern Medical Center, Dallas, Texas; Environmental and Autonomic Physiology Laboratory, Department of Kinesiology and Health Education, The University of Texas at Austin, Austin, Texas; Department of Health, Human Performance and Recreation, University of Arkansas, Fayetteville, Arkansas; and Veterans Affairs North Texas Health Care System, Dallas, Texas

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Facial pallor is a typical observation in humans during profound hypotension sufficient to cause presyncope. When the hypotensive challenge is accompanied by heat stress, this occurrence is particularly noticeable. The pallor observed in the face is in contrast to what is observed in other nonglabrous areas, such as the forearm. As forehead SkBF is generally greater compared with the forearm, particularly during heat stress (6, 14, 15), facial pallor may be more noticeable due to a greater decrease in facial SkBF relative to the forearm, although the mechanisms for this presumed response have not been studied. Facial pallor could result from passive reductions in SkBF secondary to the rapid and pronounced reductions in blood pressure at the point of presyncope (1, 21), from neurally mediated vasoconstriction (should this exist in forehead skin) and/or withdrawal of active vasodilation, or a combination of these mechanisms. Although the neural control of SkBF may differ between the forehead and the forearm, the passive effect of reductions in blood pressure would be expected to similarly affect the skin circulation of both regions. Therefore, it can be hypothesized that facial pallor at presyncope is associated with a greater neurally mediated reduction in forehead SkBF relative to the forearm.

The purpose of this study was to compare forehead and forearm SkBF responses during a central hypovolemic challenge performed to presyncope under normothermic, as well as heat stress conditions. Furthermore, we determined the fractional contributions by which decreases in forehead and forearm SkBF were “passive” i.e., as a result of decreases in blood pressure, or “active” i.e., due to influences on the skin vasculature, which were presumed to be of neural origin. We tested the hypotheses that 1) the magnitude of the reduction in SkBF would be greater in the forehead compared with the forearm at presyncope, while normothermic or heat stressed, which may explain facial pallor subjectively observed under such conditions, and 2) greater reductions in forehead SkBF relative to the forearm at presyncope would be due to a greater “active” component.

METHODS

Subjects. Simultaneous measurements of forehead and forearm SkBF were retrospectively analyzed from 24 subjects who underwent incremental lower body negative pressure (LBNP) to presyncope. Eleven of these subjects (three females) underwent the protocol while normothermic, and 13 subjects (six females) performed the protocol while heat-stressed. Of the 13 subjects that completed the heat stress trial, 2 of them performed the protocol twice, on separate days. The averaged data from both trials were analyzed for these two subjects.
Five of the subjects completed the protocol under both thermal conditions, although on different days. Subject characteristics are as follows: age, 37 ± 11 years; height, 172 ± 6 cm; weight, 71.1 ± 12.0 kg. All subjects were free of any known cardiovascular, respiratory, neurological or metabolic diseases. Phase of menstrual cycle was recorded, but not controlled for in female subjects. All procedures were approved by the Institutional Review Boards at the University of Texas Southwestern Medical Center and at Texas Health Presbyterian Hospital Dallas. Written informed consent was obtained from all subjects prior to their participation in the study.

Measurements. SkBF, in arbitrary units (au), was measured by laser-Doppler flowmetry using integrated probes (Moor Instruments, Devon, United Kingdom; or Perimed, North Royalton, OHA) placed on forearm and forehead skin. The forearm SkBF probe was placed on the dorsal side of the forearm, in a region that visually was devoid of large veins. The forehead SkBF probe was placed at the center of the forehead. Local skin temperature at each site was not controlled and was, therefore, allowed to fluctuate freely. This approach was selected to maximize the practical validity of the obtained SkBF values. Blood pressure was continuously measured noninvasively using photoplethysmography (Finometer Pro, FMS, Amsterdam, Netherlands) and corrected to pressures obtained by auscultation of the brachial artery (Tango+; SunTech Medical, Morrisville, NC). In seven of the subjects who performed the heat stress trial, blood pressure was measured by direct cannulation of the radial artery (Baxter Healthcare, Irving, CA). Cutaneous vascular conductance (CVC) was calculated as SkBF divided by mean arterial pressure. Heart rate was obtained from an electrocardiogram (Agilent, Munich, Germany) that was interfaced with a cardiotachometer (CWE, Ardmore, PA). Internal body temperature was measured by an ingestible telemetric pill (HQ Palmetto, FL) that was swallowed by the subject upon arrival, ~2 h prior to data collection. Mean skin temperature was measured as the weighted average of six thermocouples attached to the skin surface on the abdomen, calf, chest, lower back, shoulder, and quadriceps (22).

Experimental protocol. Upon arrival to the laboratory, the subjects swallowed the telemetric pill for the measurement of internal body temperature before being dressed in a two-piece tube-lined suit that covered the entire body except for the head, hands, feet, and one forearm. While supine, the subjects were sealed at the wrist within a custom-made LBNP chamber. The subjects were then instrumented for the measurement of heart rate, blood pressure, forehead and forearm SkBF, and mean skin temperature. Following a baseline rest period, incremental LBNP to presyncope was performed for the normothermic trial, while the subjects in the heat stress trial underwent incremental LBNP to presyncope after internal body temperature had increased by ~1.4°C. The LBNP protocol began at 20 mmHg, with an increase in LBNP of 10 mmHg every 3 min until presyncope. During the normothermic condition, mean skin temperature was clamped by circulating water maintained at ~34°C through the tube-lined suit, while whole-body heat stress was achieved by circulating water at 48°C through the tube-lined suit. Once the desired increase in internal body temperature was achieved, the temperature of the water perfusing the suit was slightly reduced to 46°C to maintain internal body temperature relatively constant during the subsequent LBNP period. Criteria for the termination of the LBNP protocol included continued self-reporting by the subject of feeling faint, sustained nausea, rapid and progressive decrease in blood pressure resulting in a sustained systolic blood pressure being <80 mmHg, and/or relative bradycardia accompanied with a narrowing of pulse pressure.

Data analysis. Data were collected with data acquisition software (Biopac MP150, Santa Barbara, CA) at a minimal sampling frequency of 50 Hz. The data were analyzed at baseline rest, during heat stress prior to the initiation of LBNP, and during the final 100 s prior to the cessation of LBNP. Minute averages were performed for the baseline normothermic and heat stress data, while the data during the final 100 s of LBNP were averaged into 5-s segments. To account for differences in absolute values of SkBF and CVC between the forehead and forearm (see RESULTS section), the percent reduction in SkBF and CVC from pre-LBNP was calculated for each site. To determine the contribution by which decreases in SkBF occurred due to the decrease in blood pressure (i.e., passive), the ratio of the percent reduction in blood pressure to the percent reduction in SkBF during LBNP was calculated using the following formula: passive contribution (%) = [percent reduction in blood pressure from pre-LBNP ÷ percent reduction in SkBF from pre-LBNP] × 100. The remaining contribution (i.e., 100% − passive contribution) was considered to be due to active, presumably neurally mediated decreases in SkBF. In some instances, the percent reduction in mean arterial pressure was greater than the percent reduction in SkBF. In these cases, a value of 100% was attributed to the passive contribution, while a value of 0% was attributed to the active contribution, given that under such conditions, there was no evidence of a neurally mediated (i.e., active) vasoconstrictor response.

RESULTS
Normothermic condition. Baseline SkBF was greater at the forehead (96.3 ± 19.7 au) compared with the forearm (16.1 ± 4.7 au, P ≤ 0.001). LBNP time and level at presyncope averaged 1,251 ± 173 s and 75 ± 9 mmHg, respectively, while in this thermal condition. Mean arterial pressure decreased during the final 100 s of LBNP (P ≤ 0.001), averaging 57 ± 7 mmHg at presyncope compared with 91 ± 5 mmHg at baseline rest (P ≤ 0.001). Relative to pre-LBNP, forehead, and forearm SkBF decreased over the final 100 s of LBNP (P ≤ 0.001, Fig. 1), with the magnitude of the reduction in SkBF over time being different between skin sites (site × time interaction; P = 0.009). At presyncope, forehead SkBF was reduced 55 ± 14% compared with 24 ± 11% at the forearm (P ≤ 0.001; Fig. 3). At the forehead, 68 ± 13% of that decrease in SkBF was attributed to decreases in blood pressure, compared with 89 ± 11% at the forearm (P = 0.031 between sites; Fig. 4). As such, 32 ± 13% and 11 ± 11% of the decrease in forehead and forearm SkBF, respectively, were active in origin (P = 0.031 between sites, Fig. 4). At presyncope, forehead CVC decreased by 31 ± 15% (P = 0.003), while forearm CVC increased by 27 ± 25% although this increase was not statistically significant (P = 0.061). The difference in CVC between the forehead and forearm at presyncope was significant (P = 0.002).

Heat stress condition. Prior to heat stress, SkBF was greater at the forehead (121.5 ± 37.5 au) compared with the forearm

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(20.6 ± 3.7 au; \( P \leq 0.001 \)). Whole body heat stress increased mean skin temperature from 34.5 ± 0.4°C to 38.9 ± 0.5°C (\( P \leq 0.001 \)) and internal body temperature by 1.42 ± 0.12°C. Forehead SkBF (311.1 ± 36.5 au) remained greater compared with the forearm (149.8 ± 33.0 au; \( P \leq 0.001 \)) with heat stress. Heat stress also increased heart rate from 63 ± 4 bpm to 110 ± 9 bpm (\( P \leq 0.001 \)) and reduced mean arterial pressure from 90 ± 5 mmHg to 82 ± 5 mmHg (\( P \leq 0.001 \)). LBNP time and LBNP level at presyncope averaged 682 ± 159 s and 47 ± 8 mmHg, respectively. Mean arterial pressure decreased over the last 100 s of LBNP during heat stress (\( P \leq 0.001 \)), averaging 57 ± 7 mmHg at presyncope (\( P \leq 0.001 \) relative to baseline). Relative to pre-LBNP, forehead and forearm SkBF decreased over the last 100 s of LBNP (\( P \leq 0.001 \), Fig. 2), with the pattern of response differing between sites (site \times \text{time} \text{interaction}; \( P = 0.003 \)). Overall, forehead SkBF decreased by 39 ± 11% during LBNP compared with a reduction in forearm SkBF of 28 ± 8% (\( P = 0.007 \), Fig. 3). At the forehead, 70 ± 13% of that decrease in SkBF was due to the decrease in mean arterial pressure, compared with 90 ± 13% at the forearm (\( P = 0.004 \) between sites, Fig. 4). As such, 30 ± 13% of the decrease in forehead SkBF and 10 ± 13% of the decrease in forearm SkBF was active in nature (\( P = 0.004 \) between sites, Fig. 4). The relative contribution of passive and active decreases in SkBF did not differ between thermal conditions at both sites (all \( P > 0.05 \)). Forehead CVC decreased by 15 ± 13% (\( P = 0.047 \)) during LBNP, while it increased 5 ± 9% at the forearm, although this change was not statistically significant (\( P = 0.334 \)). The difference in CVC between the forehead and forearm at presyncope was significant (\( P = 0.018 \)).

**DISCUSSION**

This study examined forehead and forearm SkBF responses during incremental LBNP to presyncope in both normothermic and heat-stressed humans. Regardless of the thermal condition, the relative decrease in forehead SkBF at presyncope was greater compared with that in the forearm. While the primary mechanism for these decreases in SkBF is accounted for by decreases in blood pressure, a greater proportion of actively mediated decreases in forehead SkBF (relative to forearm) was observed in both conditions. These findings provide a potential mechanism for the facial pallor commonly observed at presyncope in humans.

Previous studies have noted a lack of decrease in forehead SkBF during the local application of cold to the forehead (5), as well as during whole body cold stress (17). Furthermore, attenuated decreases in forehead SkBF relative to the forearm have been observed during hyperventilation-induced hypocapnia (4). Together, these studies suggest that the forehead skin
circulation may not be responsive to sympathetic vasoconstric-
tion stimuli. In fact, Nordin (12) performed direct microneu-
rographic recordings of cutaneous sympathetic activity in the
 supraorbital nerve and observed little background activity
when individuals rested at normal ambient temperatures and no
increase in nerve activity during body cooling. Although the
present results do not support or refute sympathetic vasocon-
strictor control of forehead SkBF, they clearly demonstrate that
forehead SkBF is capable of decreasing during a sympathoex-
citatory stimulus, regardless of whether it is performed under
normothermic or heat stress conditions. Furthermore, the rel-
ative decreases in forehead SkBF were greater compared with
those observed in the forearm. It should be noted that the
stimulus employed in the current study (i.e., LBNP) elicited
substantial reductions in blood pressure, whereas most of the
previous stimuli used to examine the control of forehead SkBF
(e.g., local application of cold, cold stress) likely resulted in
either no change or an increase in blood pressure. Given that
decreases in blood pressure were the main determinant for the
reduction in forehead SkBF under both thermal conditions, the
lack of change in forehead SkBF in previous studies could have
been due to a lack of decrease in blood pressure. To this effect,
a more recent study has reported decreases in forehead SkBF
during acute and pronounced reductions in blood pressure
under normothermic conditions (13).

Overall, reductions in blood pressure during LBNP ex-
plained the majority of the reductions in forehead and forearm
SkBF under both thermal conditions. However, a novel finding
of the current study is the greater contribution of active
influences upon the reduction in forehead SkBF relative to the
forearm. The mechanisms by which a larger fraction of fore-
head SkBF is “actively” decreased during presyncopal LBNP
include greater cutaneous vasoconstriction and/or greater with-
drawal of active vasodilation. Since active vasodilation occurs
only after core and skin temperatures have increased beyond an
onset threshold (10, 18), it is unlikely that a withdrawal of
active vasodilation can explain the greater proportion of active
influences upon the reduction in forehead SkBF during the
normothermic condition. As such, the greater actively medi-
atated reduction in forehead SkBF during the normothermic
condition was most likely driven by greater vasoconstrictor
activity, should it exist in forehead skin. Although Nordin (12)
did not report any increase in nerve activity from the supraor-
bital nerve during body cooling, it was acknowledged that
vasoconstrictor fibers supplying forehead skin may run through
other nerves than the one measured. It should also be consid-
ered that absolute values of SkBF were greater at the forehead
compared with the forearm, which could contribute to a greater
relative decrease in blood flow, since there was more “reserve”
for SkBF to decrease. This could potentially account for a
greater relative decrease in mean arterial pressure, which
exceeded that for SkBF in a few subjects. This was particu-
larly noticeable in the CVC values, as attenuated decreases in
 forearm SkBF combined with a continued decrease in mean
arterial pressure led to CVC values that indicated a vasodila-
tion (i.e., increase in conductance) in the forearm as opposed to

Fig. 3. The percent reduction in forehead and forearm skin blood flow (SkBF) at presyn-
cope, relative to the period just prior to LBNP, under normothermic and heat stress
conditions. The open circles represent individual data points, while the solid circles
represent the means ± confidence intervals.

*Significantly different from the forehead.

Fig. 4. The relative contribution of passive
(i.e., due to reductions in blood pressure, gray
bars) and active (i.e., presumably neurally
mediated, open bars) reductions in forehead
and forearm SkBF at presyncope in normo-
thermic and heat stressed subjects. Values are
expressed as means ± confidence intervals.
*Significantly different from the forehead for
the indicated contribution.
vasoconstriction (i.e., a decrease in conductance) in the forehead at presyncope. Although this possibility may especially be true for the normothermic condition, nonetheless, we observed a greater relative decrease in forehead SkBF during the heat stress condition when forearm SkBF was substantially elevated, thereby minimizing any potential for its decrease to be limited.

Minor reductions in forearm CVC at presyncope have been reported previously during heat stress (1). The cutaneous vasculature represents the greatest reservoir from which blood volume, as well as vascular conductance, can be drawn upon to maintain blood pressure during a central hypovolemic challenge under heat stress conditions. However, heat stress itself adversely affects the responsiveness of the forehead cutaneous vasculature to constrict to adrenergic agonists (23), in part, because of an inhibitory effect of nitric oxide (2, 19, 20). As such, the current results in the forearm support previous observations of minimal reductions in forearm CVC at the point of presyncope in heat-stressed humans and suggest that the reductions in SkBF that do occur are primarily passive in nature due to the decrease in blood pressure. In contrast, the current results suggest that active influences contribute to the relatively greater decrease in forehead SkBF during LBNP to presyncope in heat-stressed humans. Since the forehead cutaneous vasculature is under the control of the active vasodilator system (3), the greater actively mediated reduction in forehead SkBF during the heat stress condition could be due to a greater cutaneous vasoconstriction and/or a greater withdrawal of active vasodilation. Regardless of the potential mechanism(s), the results of the current study suggest that facial pallor observed at presyncope is associated with relatively greater decreases in forehead SkBF (compared to the forearm), which are primarily related to the decreases in blood pressure, as well as with an added active influence upon the cutaneous vasculature.

Limitations. Hyperventilation-induced hypocapnia commonly occurs during LBNP performed to presyncope under both normothermic and heat stress conditions (16). Although hypocapnia itself has been shown to reduce forehead but not forearm SkBF during heat stress (15), these reductions were small (~5%) relative to the decreases in SkBF observed at presyncope in the current study (~39%). Furthermore, Fuji et al. (4) reported that hypocapnia (~20 mmHg reduction in end-tidal CO₂) induced by voluntary hyperventilation similarly affected the forehead and forearm cutaneous circulations during passive heat stress sufficient to elevate internal body temperature by 1°C. Therefore, it is unlikely that the greater decreases in forehead SkBF observed in the current study can be attributed to regional differences in the sensitivity of the cutaneous vasculature to hypocapnia. Further work is needed to determine the exact mechanism by which forehead SkBF decreases to a greater extent compared with forearm SkBF during LBNP performed to presyncope. Potential mechanisms could be addressed by the application of drugs (e.g., via microdialysis, intradermal injection, iontophoresis, etc.) that block the sympathetic vasoconstrictor (8) and active vasodilator (9, 19) systems. For cosmetic reasons, we chose to refrain from using such techniques and rather sought to first identify whether differences in forehead and forearm SkBF responses exist, prior to seeking cosmetically favorable approaches to investigate more mechanistic answers. It should also be noted that the current study only examined forehead SkBF, and therefore, the results might not be applicable to SkBF in other areas of the face, particularly those that are considered glabrous in nature (e.g., ears, nose, lips, etc.).

In conclusion, the results of the current study show that relative decreases in SkBF are greater in the forehead compared with the forearm during incremental LBNP to presyncope in normothermic and heat-stressed humans. Although reductions in blood pressure explain the majority of the decrease in SkBF at both skin sites, a significantly greater proportion of actively mediated decreases in forehead SkBF was observed under both thermal conditions. Overall, these results suggest that the forehead cutaneous vasculature is more responsive relative to that of the forearm during incremental LBNP, which could explain the commonly observed facial pallor in individuals at the point of presyncope.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


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