Insufficient cutaneous vasoconstriction leading up to and during syncopal symptoms in the heat stressed human

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Crandall CG, Shibasaki M, Wilson TE. Insufficient cutaneous vasoconstriction leading up to and during syncopal symptoms in the heat stressed human. Am J Physiol Heart Circ Physiol 299: H1168–H1173, 2010. First published August 6, 2010; doi:10.1152/ajpheart.00290.2010.—As much as 50% of cardiac output can be distributed to the skin in the hyperthermic human, and therefore the control of cutaneous vascular conductance (CVC) becomes critical for the maintenance of blood pressure. Little is known regarding the magnitude of cutaneous vasoconstriction in profoundly hypotensive individuals while heat stressed. This project investigated the hypothesis that leading up to and during syncopal symptoms associated with combined heat and orthostatic stress, reductions in CVC are inadequate to prevent syncope. Using a retrospective study design, we evaluated data from subjects who experienced syncopal symptoms during lower body negative pressure (N = 41) and head-up tilt (N = 5). Subjects were instrumented for measures of internal temperature, forearm skin blood flow, arterial pressure, and heart rate. CVC was calculated as skin blood flow/mean arterial pressure × 100. Data were obtained while subjects were normothermic, immediately before an orthostatic challenge while heat stressed, and at 5-s averages for the 2 min preceding the cessation of the orthostatic challenge due to syncopal symptoms. Whole body heat stress increased internal temperature (1.25 ± 0.3°C; P < 0.001) and CVC (29 ± 20 to 160 ± 58 CVC units; P < 0.001) without altering mean arterial pressure (83 ± 7 to 82 ± 6 mmHg). Mean arterial pressure was reduced to 57 ± 9 mmHg (P < 0.001) immediately before the termination of the orthostatic challenge. At test termination, CVC decreased to 138 ± 61 CVC units (P < 0.001) relative to before the orthostatic challenge but remained approximately fourfold greater than when subjects were normothermic. This negligible reduction in CVC during pronounced hypotension likely contributes to reduced orthostatic tolerance in heat-stressed humans. Given that lower body negative pressure and head-up tilt are models of acute hemorrhage, these findings have important implications with respect to mechanisms of compromised blood pressure control in the hemorrhagic individual who is also hyperthermic (e.g., military personnel, firefighters, etc.).

Skin blood flow; baroreceptors; hyperthermia; orthostasis

Under heat stress conditions human skin blood flow is estimated to increase from ~300 ml/min upward to 7.5 l/min, resulting in the capacity for 50% or more of cardiac output being directed to the skin (25, 27). To maintain blood pressure in the face of pronounced increases in systemic vascular conductance associated with cutaneous vasodilation, cardiac output increases whereas vascular conductance to many noncutaneous beds decreases. Based on these values and with the use of a normothermic cardiac output of 6 l/min, cutaneous vascular conductance (CVC) represents ~5% of the systemic vascular conductance when subjects are normothermic, but with the capacity of being >50% of the systemic vascular conductance during heat stress conditions. Therefore, the neural control of CVC has minimal influence on blood pressure while heat stressed.

Combining heat and orthostatic stresses in humans leads to an increased incidence of hypotension associated with pronounced and consistent reductions in tolerance during upright tilt (18, 44), gravitational acceleration (1), and simulated hemorrhage via lower body negative pressure (LBNP) (5, 13, 14, 43). Highlighting these observations, ~85% of heat-stressed subjects were not able to tolerate 3 min of 40 mmHg LBNP without symptoms of ensuing syncope, whereas 100% of these subjects were able to tolerate this LBNP when normothermic (14, 43).

Although while heat stressed the skin serves as a large reservoir whereby vascular conductance can be decreased, the extent to which baroreflexes modulate CVC is unclear with some studies identifying large decreases in CVC, whereas other studies observe little to no changes in CVC (3, 5, 13, 15, 17, 19, 23, 29, 36, 37). The reasons for these divergent responses are not forthcoming, although Vissing et al. (36) proposed that convective skin cooling during LBNP may be a source of nonbaroreceptor-mediated cutaneous vasoconstriction. Additionally, inter- and intra-subject heterogeneity of cutaneous vasoconstrictor responses to baroreceptor unloading likely contributes to these varied responses (19, 23).

Given the large potential for the cutaneous vasculature to assist in blood pressure regulation in the hyperthermic human, insufficient cutaneous vasoconstriction during pronounced baroreceptor unloading may be a primary mechanism by which heat stress impairs blood pressure regulation leading to heat syncope. However, little is known regarding the extent to which the cutaneous vasculature constricts leading up to and at the onset of syncopal symptoms in heat-stressed subjects. Understanding the effect of acute hypotension under such conditions on neural control of the cutaneous vasculature has important implications with respect to the mechanisms of compromised blood pressure control in the hemorrhagic individual who is also hyperthermic (e.g., military personnel, firefighters, etc.). Thus the primary objective of this investigation was to test the hypothesis that under heat-stressed conditions, the magnitude of cutaneous vasoconstriction leading up to and during syncopal symptoms is inadequate relative to the hypotensive challenge.
RESULTS

Whole body heat stress increased internal temperature 1.25 ± 0.3°C relative to when subjects were normothermic (range, 0.69 to 1.97°C; *P* < 0.001), resulting in an increased heart rate (58 ± 10 to 90 ± 16 beats/min; *P* < 0.001) without altering mean arterial pressure (83 ± 7 to 82 ± 6 mmHg). At the point of termination due to syncopal symptoms, mean arterial pressure was reduced to 57 ± 9 mmHg (Fig. 1). At this same time point, heart rate had decreased from a peak of 121 ± 21 beats/min during the orthostatic challenge to 96 ± 28 beats/min (*P* < 0.001; Fig. 2).

While normothermic, CVC was 29 ± 20 CVC units and increased approximately fivefold to 160 ± 58 CVC units (*P* < 0.001) during the heat stress but before the orthostatic challenge. At test termination due to syncopal symptoms, CVC decreased to 138 ± 61 CVC units relative to CVC just before the orthostatic challenge, representing a reduction of 15 ± 21% (Fig. 3). Importantly, CVC at the end of the orthostatic challenge was well above CVC when subjects were normothermic (*P* < 0.001). A visual analysis of CVC throughout the orthostatic challenge and a statistical analysis of CVC during the period just before ending the orthostatic challenge did not reveal evidence of paradoxical cutaneous vasodilation (see Fig. 3).

The magnitude by which LBNP or head-up tilt reduced CVC was not related to the increase in internal temperature (range of 0.65 to 1.97°C) when the cutaneous vascular response was expressed either as an absolute (*r* = 0.04; *P* = 0.77) or a relative change in CVC (*r* = 0.1; *P* = 0.52).

A subsequent analysis was performed to evaluate CVC responses in six subjects (1 female) who had a high tolerance to LBNP (final LBNP of at least 50 mmHg; average, 60 ± 9 mmHg) with seven subjects (4 females) who had a low tolerance to LBNP (final LBNP was not >20 mmHg). Immediately

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**Fig. 1.** Mean arterial pressure at normothermia, heat stress, and the final 100 s during the orthostatic challenge. At test termination due to syncopal symptoms, CVC was reduced approximately fivefold to 160 ± 58 CVC units (*P* < 0.001) during the heat stress but before the orthostatic challenge. At test termination due to syncopal symptoms, CVC decreased to 138 ± 61 CVC units relative to CVC just before the orthostatic challenge, representing a reduction of 15 ± 21% (Fig. 3). Importantly, CVC at the end of the orthostatic challenge was well above CVC when subjects were normothermic (*P* < 0.001). A visual analysis of CVC throughout the orthostatic challenge and a statistical analysis of CVC during the period just before ending the orthostatic challenge did not reveal evidence of paradoxical cutaneous vasodilation (see Fig. 3).

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**METHODS**

Previously, obtained data were queried to identify subjects who experienced signs and symptoms of syncope while heat stressed during either LBNP or head-up tilt, requiring a termination of the test. Data were analyzed from 41 subjects who were exposed to heat stress LBNP and from 5 subjects who were exposed to heat stress 70° head-up tilt. Subject characteristics of age, height, and weight (means ± SD) were 34 ± 10 yr, 173 ± 11 cm, and 73 ± 15 kg, respectively, and all subjects were free of any known cardiovascular, neurological, or metabolic diseases. The phase of the menstrual cycle was not controlled for in the 19 female subjects. The heat stress was imposed by perfusing warm water (46–50°C) through a two-piece tube-lined suit worn by each subject. The suit covered the entire body surface with the exception of the head and face, hands and feet, and one forearm. The two-piece design permitted the LBNP chamber to be sealed directly to the subject’s skin, thereby reducing convective skin cooling during LBNP (36). The criteria for test termination during the orthostatic challenges were the following: continued self-reporting by the subject of feeling faint, sustained nausea, rapid and progressive decrease in blood pressure resulting in sustained systolic blood pressure being <80 mmHg, and/or relative bradycardia accompanied with a narrowing of pulse pressure. Each study protocol from which these data were obtained received institutional approval from the University of Texas Southwestern Medical Center, Texas Health Presbyterian Hospital Dallas, and/or the University of Copenhagen. All subjects signed an approved informed consent form.

**Subject instrumentation.** The following variables were obtained while subjects were normothermic, during whole body heating, and during LBNP or upright tilt while heat stressed: forearm skin blood flow was indexed via laser-Doppler flowmetry using integrating probes (Moor Instruments, Devon, UK; or Perimed, North Royalton, OH), heart rate was obtained via a cardiograph from the ECG signal, and arterial pressure was obtained either via direct cannulation of the brachial artery (Baxter Healthcare, Irvine, CA) or via a Finometer (FMS, Amsterdam, The Netherlands), while internal temperature was measured from pulmonary artery blood temperature, esophageal temperature (probe inserted to one fourth subject’s height), sublingual sulcus temperature, or via an ingestible telemetric temperature pill located in the intestines (HQ, Palmetto, FL). Mean arterial pressure was obtained by integration of the arterial pressure waveform. Finometer-derived arterial pressure data were corrected to arterial pressure obtained from auscultation of the brachial artery (Suntech, Tango, Morrisville, NC). If multiple laser-Doppler flow probes were place on the forearm skin, data from those probes were averaged. In all cases, including upright tilting, the location of the laser-Doppler probes and pressure transducers remained at heart level. CVC was calculated from the ratio of the index of skin blood flow and mean arterial pressure × 100.

**Data analysis.** Data were obtained via 16-bit analog-to-digital conversion (Biopac MP150, Santa Barbara, CA) with a minimal sampling frequency of 50 Hz. The aforementioned data were analyzed while subjects were normothermic, during heat stress just before the onset of LBNP or head-up tilt, and during the final 2 min of LBNP or head-up tilt preceding test termination due to the onset of syncopal symptoms. Data during the final 2 min of the orthostatic challenge were averaged into 5-s segments, whereas data during normothermia and heat stress but before LBNP/head-up tilt were averaged into segments of at least 1 min. The differences in responses (e.g., CVC, arterial pressure, and heart rate, etc.) between normothermia, heat stress before the orthostatic challenge, and at presyncope were analyzed via one-way repeated-measures ANOVA, followed by a pairwise multiple comparison procedure (Holm-Sidak) if a significant main effect was identified. The α-level of statistical significance was set at 0.05. Data are presented as means ± SD.
before LBNP, there were no differences between groups in the elevation in internal temperature (low tolerant, 1.3 ± 0.3°C; and high tolerant, 1.5 ± 0.1°C; P = 0.2), skin blood flow, CVC, or heart rate to the heat stress. At the highest common LBNP between groups (20 mmHg), the reduction in mean arterial pressure, and thus baroreceptor unloading stimulus, was greater in the low-tolerant group (-26 ± 8 mmHg) relative to the high-tolerant group (-2 ± 9 mmHg; P < 0.001). Consistent with this greater baroreceptor unloading stimulus, the decrease in CVC at 20 mmHg was also greater for the low-tolerant group (-18 ± 22 CVC units) relative to the high-tolerant group (+1 ± 13 CVC units; P = 0.05). However, at the point of test termination due to syncopal symptoms, when the reduction in arterial pressure and thus baroreceptor unloading status were similar between groups, regardless of LBNP, the magnitude of the reduction in CVC was not different (low tolerant, -18 ± 22 CVC units; and high tolerant, -12 ± 38 CVC units; P = 0.3).

**DISCUSSION**

The present findings are in agreement with most prior studies that report reductions in CVC in heat-stressed subjects during hypotensive gravitational stress but in the absence of syncopal symptoms (3, 5, 13, 17, 29). In the present study, leading up to and during syncopal symptoms, the magnitude of cutaneous vasoconstriction was quite small, with a CVC reduction of only 15 ± 21% relative to peak cutaneous vasodilation just before the orthostatic challenge. Finally, there was no evidence of paradoxical cutaneous vasodilation associated with the onset of syncopal symptoms, unlike what is often identified in the limbs (likely muscle) of normothermic subjects (7, 11). Given that an upward to 50% of cardiac output can be directed toward the skin in heat-stressed subjects (25, 27), coupled with the relatively small reduction in CVC leading up to and during presyncope, suggests that an inadequate cutaneous vasoconstriction may be a primary mechanism by which heat stress compromises the control of blood pressure during a hypotensive stimulus.

The present approach is in contrast to prior experimental designs in which the assessment of cutaneous vascular responses associated with syncopal symptoms was not the objective of the investigation (2–4, 12, 13, 17, 20, 29, 35). That said, one study reported data from three individuals who experienced syncopal symptoms during LBNP while heat stressed (13). In these individuals venous occlusion plethysmography measures of forearm vascular conductance (inclusive of muscle and skin vascular beds), at the point of presyncope, remained well above pre-heat stress vascular conductance. This observation is consistent with the present findings, although the magnitude of the reduction in forearm vascular conductance in the cited study was greater than that observed in the skin of the present study.

The extent of the reduction in CVC during syncopal symptoms is comparable with CVC responses during moderate LBNP in heat-stressed subjects not experiencing syncopal symptoms (3, 17, 19). For example, in the present study CVC decreased ~15%, whereas Crandall et al. (3) reported ~17% reduction in CVC to 30 mmHg LBNP (3) and Kellogg et al. (17) reported a 23% reduction in CVC during 40 mmHg LBNP in heat-stressed subjects. Nevertheless, reductions in CVC during orthostatic stress in heat-stressed subjects are not consistently observed (19, 23). In the present study, despite an overall significant reduction in CVC to LBNP or head-up tilt, CVC in six subjects increased 5% or more at the end of LBNP (data not shown), indicating there is some heterogeneity in this response.

Prior studies report reductions in muscle sympathetic nerve activity along with parallel increases in limb vascular conductance leading up to and at the point of vasovagal presyncope/syncpe (7, 11). Typically, these responses occur near the final minute or two before the onset of syncopal symptoms (11). However, it was unknown whether paradoxical cutaneous vasodilation contributed to the rapid reduction in blood pressure leading up to syncopal symptoms in the heat-stressed subjects. To evaluate this question, CVC responses were ana-
lyzed at 5-s increments during the 2-min period preceding the cessation of the orthostatic challenge. Counter to the proposed hypothesis, and unlike that observed in the whole limb of normothermic subjects (7, 11), the evidence does not support a generalized increase in CVC leading up to and during syncopal symptoms (Fig. 3).

Orthostatic stress decreases cardiac output in both normothermic and heat stress conditions. If, for example, cardiac output increased from 6 to 10 l/min because of a heat stress, which is a typical increase in cardiac output for the present level of heating (22, 39), and then was reduced during an orthostatic stress back to 6 l/min, despite cardiac output being “normal” relative to when the subject was normothermic (i.e., at 6 l/min), to maintain blood pressure, the systemic vascular conductance would need to decrease by 40% to appropriately respond to the orthostatic challenge. However, because the renal, splanchnic, and perhaps muscle vascular beds are already in a vasoconstricted state due to the heat stress before the orthostatic challenge (21, 25–28), there is a limited reserve by which these beds can further vasoconstrict to accommodate this needed reduction in systemic vascular conductance. Thus, to accommodate a 40% reduction in cardiac output in the heat-stressed human during an orthostatic challenge, whole body CVC would need to decrease ~30–40% (depending on the vasoconstrictor reserve of the splanchnic, renal, and muscle vascular beds) to maintain blood pressure. Given the relatively small reduction in CVC leading up to and at the onset of syncopal symptoms, the present data suggest that inadequate cutaneous vasoconstriction and/or inadequate reductions in cutaneous active vasodilation are primary mechanisms by which heat stress impairs blood pressure control during an orthostatic challenge.

What is the mechanism(s) resulting in inadequate reductions in CVC during the imposed orthostatic challenges? With one exception (8), we and others have not observed changes in skin sympathetic nerve activity during brief or sustained reductions in blood pressure in heat stressed individuals (5, 6, 36, 40, 42). Consistent with this observation, electrical stimulation of the carotid sinus nerve (innervating the carotid baroreceptors) in normothermic subjects did not change skin sympathetic nerve activity, despite appropriate decreases in muscle sympathetic nerve activity (38). Thus one possibility for relatively minor cutaneous vasoconstriction during baroreceptor unloading may be an inadequate neural response to the skin relative to the hypotensive perturbation. However, one has to cognize that the multiunit skin sympathetic recordings likely contain neural signals leading to cutaneous vasoconstriction, sweating, and perhaps cutaneous active vasodilation, and thus it may be that one is unable to distinguish changes in the particular component of the integrated skin sympathetic nerve recording responsible for the slight reductions in CVC.

Substances associated with active cutaneous vasodilation may attenuate the responsiveness of the cutaneous vasoconstrictor system, analogous to functional sympatholysis observed in the exercising muscle (24, 30). In support of this possibility, we showed attenuated cutaneous vasoconstrictor responsiveness to exogenous norepinephrine when subjects were moderately heat stressed, relative to when they were normothermic (41). Consistent with that observation, when the cutaneous active vasodilator limb was blocked via intradermal botulinum toxin administration, the reduction in CVC to LBNP and whole body cooling were significantly greater relative to unblocked sites (32, 33). Further studies suggest that nitric oxide, which is purported to be involved in cutaneous active vasodilation (16, 31), may be one of the factors that attenuate cutaneous vasoconstriction (9, 10, 33, 34). Finally, minimal cutaneous vasoconstriction leading up to and during syncopal symptoms in heat-stressed subjects may be due to an interaction, or perhaps competition, between cutaneous vasodilation for heat dissipation and cutaneous vasoconstriction for blood pressure control, with the former taking precedence over the latter. These, and perhaps other mechanisms, may be responsible for a relatively small reduction in CVC during profound hypotension.

Potential limitations to the interpretation of the findings. The purpose of the study was to evaluate CVC responses leading up to and during syncopal symptoms, and thus only subjects who experienced syncopal symptoms during the gravitational stress were included in the analysis. This study design may be viewed as being biased toward intolerant subjects, despite that every individual will experience syncopal symptoms if a sufficient gravitational challenge is imposed. To address the possibility that differences in individual tolerance may affect these data, the magnitude of the reduction in CVC between seven low-tolerant subjects (unable to complete more than 20 mmHg during a ramped LBNP while heat stressed) were compared with six high-tolerant subjects (able to asymptotically withstand 50+ mmHg LBNP while heat stressed). At 20 mmHg LBNP, the reduction in arterial pressure and CVC was greater for the low-tolerant group compared with the high-tolerant group. However, at test termination because of the onset of syncopal symptoms, regardless of the level of LBNP, there were no differences in the magnitude of the reduction in arterial pressure or CVC between low- and high-tolerant groups. Similar reductions in CVC at the onset of syncopal symptoms between groups, regardless of LBNP, suggest that the mechanism by which the high-tolerant group was better able to withstand greater LBNPs was unlikely due to greater cutaneous vasoconstriction; thus other mechanisms are likely responsible for these individuals’ ability to withstand this hypotensive challenge. Nevertheless, these observations do not discount the hypothesis that should the skin constrict to a greater extent during a hypotensive challenge while heat stressed, that the capacity to withstand that hypotensive challenge would be improved.

With the level of heating used in the present study, mean skin temperature under the water-perfused suit is typically ~38°C. This is in contrast to skin temperature at the uncovered sites where skin blood flow was evaluated. It is possible that cutaneous vascular responses to the hypotensive challenges may be different between skin covered by the water-perfused suit relative to uncovered skin. However, given that local heating impairs cutaneous vasoconstriction (41), perhaps through a nitric oxide-dependent mechanism (34, 45), the magnitude of cutaneous vasoconstriction would be even more attenuated under the water-perfused suit relative to at the exposed forearm where skin blood flow measurements were made.

Because these data were obtained from differing protocols (i.e., LBNP and head-up tilt), with the starting LBNP and duration of each LBNP stage not controlled, the value of reporting the average LBNP associated with syncopal symptoms, which was 34 ± 8 mmHg, is questionable. However, this does not adversely affect the interpretation of the data, given that the purpose of the study was to evaluate the reduction in
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