Skin-surface cooling elicits peripheral and visceral vasoconstriction in humans

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Wilson TE, Sauder CL, Kearney ML, Kuipers NT, Leuenberger UA, Monahan KD, Ray CA. Skin-surface cooling elicits peripheral and visceral vasoconstriction in humans. J Appl Physiol 103: 1257–1262, 2007. First published August 2, 2007; doi:10.1152/japplphysiol.00401.2007.—Skin-surface cooling elicits a pronounced systemic pressor response, which has previously been reported to be associated with peripheral vasoconstriction and may not fully account for the decrease in systemic vascular conductance. To test the hypothesis that whole body skin-surface cooling would also induce renal and splanchnic vasoconstriction, 14 supine subjects performed 26 skin-surface cooling trials (15–18°C water perfused through a tube-lined suit for 20 min). Oral and mean skin temperature, heart rate, stroke volume (Doppler ultrasound), mean arterial blood pressure (MAP), cutaneous blood velocity (laser-Doppler), and mean blood velocity of the brachial, celiac, renal, and superior mesenteric arteries (Doppler ultrasound) were measured during normothermia and skin-surface cooling. Cardiac output (heart rate×stroke volume) and indexes of vascular conductance (flux or blood velocity/MAP) were calculated. Skin-surface cooling increased MAP (n = 26; 78 ± 5 to 88 ± 5 mmHg; mean ± SD) and decreased mean skin temperature (n = 26; 33.7 ± 0.7 to 27.5 ± 1.2°C) and cutaneous (n = 12; 0.93 ± 0.68 to 0.36 ± 0.20 flux/mmHg), brachial (n = 10; 32 ± 15 to 20 ± 12), celiac (n = 8; 85 ± 22 to 73 ± 22 cm s–1 mmHg–1), superior mesenteric (n = 8; 55 ± 16 to 48 ± 10 cm s–1 mmHg–1), and renal (n = 8; 74 ± 26 to 64 ± 20 cm s–1 mmHg–1; all P < 0.05) vascular conductance, without altering oral temperature, cardiac output, heart rate, or stroke volume. These data identify decreases in vascular conductance of skin and of brachial, celiac, superior mesenteric, and renal arteries. Thus it appears that vasoconstriction in both peripheral and visceral arteries contributes importantly to the pressor response produced during skin-surface cooling in humans.

Doppler ultrasound; cardiac output; renal vascular conductance; splanchnic vascular conductance

SKIN-SURFACE COOLING HAS BEEN suggested as an aid in hypotensive or hypovolemic conditions and is a nonnoxious technique that decreases mean skin temperature and systemic vascular conductance and increases arterial blood pressure (13, 15, 31, 40). This decrease in systemic vascular conductance is thought to be mediated primarily by peripheral vasoconstriction, as indicated by observations of decreases in vascular conductance in the forearm, calf, and cutaneous vasculature (15, 41). Kregel et al. (20) identified that nonnoxious cooling of the skin does not alter muscle sympathetic nerve activity. Thus it appears that peripheral vasoconstriction during skin-surface cooling is confined to the skin. During normothermic and cold conditions, cutaneous vascular conductance is low, and changes in skin blood flow are not thought to contribute significantly to arterial blood pressure control. Therefore, other vascular beds must vasoconstrict and contribute importantly to the cold-induced pressor response.

Modulation of renal and splanchnic vascular tone can exert profound effects on systemic arterial blood pressure. Rowell et al. (33, 34) observed increase in splanchnic vascular conductance and mean arterial pressure during skin cooling after whole body heating. It is important to emphasize that in these studies cooling was applied after whole body heating at a time when it is possible that the high internal temperature and skin blood flows are masking skin-surface cooling responses. Additionally, Raven et al. (30) suggested, but did not measure, that prolonged cold stress may increase splanchnic vascular conductance. Thus the effects of cold stress on renal and splanchnic vascular conductance remain unclear.

Many autonomic stressors that elicit systemic pressor responses are mediated in part by vasoconstriction in the splanchnic and renal circulation (17, 22–24). Thus vasoconstriction of the splanchic and renal vasculatures may contribute to the cooling-induced pressor responses. Besides these implications on systemic blood pressure, cold-induced alterations in splanchnic blood flow may also provide insight into observations of intestinal ischemia during cold stress (28). Accordingly, we tested the hypothesis that skin-surface cooling induces renal and splanchic vasoconstriction in humans. Such an effect would be important to understand the integrative cardiovascular response to cold stress in humans and the mechanism by which skin-surface cooling elicits a pressor response.

METHODS

Subjects. Fourteen healthy young volunteers (6 men and 8 women) participated in the study. Male participants were a mean (± SD) age of 25 ± 3 (range: 22–31) yr, height of 180 ± 6 (173–188) cm, weight of 81 ± 12 (73–104) kg, and Dubois body surface area (AAB) of 1.99 ± 0.16 (1.85–2.30) m2. Female participants were a mean (± SD) age of 27 ± 4 (22–35) yr, height of 166 ± 5 (160–173) cm, weight of 60 ± 9 (46–77) kg, and AAB of 1.66 ± 0.13 (1.47–1.90) m2. All subjects were nonsmokers, nonobese, normotensive, and not taking any medications that would influence the results of the study. Subjects were also neither cold acclimatized nor cold habituated at the time of experimentation. The experiments were approved by the Institutional Review Board of The Pennsylvania State University College of Medicine. Procedures were verbally explained, and informed consent was obtained from all subjects.

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Experimental design. A total of 26 whole body skin-surface cooling trials were completed on the 14 subjects in the postabsorptive state (fasted for a minimum of 6 h). Twelve subjects performed two cold stress trials, and two subjects performed one cold stress trial. Skin-surface cooling consisted of perfusing 15–18°C water through a one-piece high-density tube-lined suit (Med-Eng Systems, Ottawa, ON, Canada) for 20 min. This suit covered the subject’s entire body except the left arm, right hand, feet, and head; in addition, the suit contained two-way zippers that allowed access to the chest and abdomen for Doppler measures with minimal skin exposure except directly at the measurement site. The cold stress was designed to be as cool as possible to maximize blood pressure responses without evoking shivering. If preshivering tonus was observed water temperature was increased slightly (1–3°C) to abate this response. Thermoneural conditions involved perfusing 35°C water through the same suit. Pilot data demonstrated that there were no significant differences in peripheral or visceral blood velocities in thermoneural conditions over extended durations. Subjects who underwent multiple skin-surface cooling trials repeated the cold stress after 30–60 min of quiet supine rest in thermoneutral conditions to ensure hemodynamic parameters returned to baseline (precooling) levels. Pilot studies indicated that visceral blood velocities returned to baseline values in all subjects tested within this timeframe. Multiple cold-stress trials were utilized to accommodate up to four Doppler ultrasound measures per subject. Doppler measures were not randomized; we employed two Doppler machines and thus could only make four of five measurements on a particular subject (i.e., 2 measures during the first cooling and 2 measures during the second cooling). Initial anatomic scans were performed to identify appropriate vessels and intensity of signals; in some subjects, an adequate signal could not be obtained on a particular vessel and thus these vessels’ velocities were not measured. The possible Doppler ultrasound measures on a particular subject included renal, celiac, superior mesenteric, and brachial artery blood velocity and average aortic time velocity integral for the assessment of cardiac output. All subjects were tested in the supine position and maintained this position for a minimum of 30 min before baseline data collection. Experiments were performed in a dimly lit, quiet laboratory maintained at 21–23°C.

Measurements. Heart rate was derived from an electrocardiogram. Arterial blood pressure was measured every 2 min over the brachial artery via an automated sphygmomanometer (Dinamap, General Electric, Waukesha, WI). Four-site mean skin temperature was measured and calculated (0.3 chest + 0.3 arm + 0.2 thigh + 0.2 leg) according to previous reports (29). Oral temperature was measured by securing a thermistor in the sublingual sulcus; subjects were instructed not to converse and to only nasally breathe during the baseline and whole body cooling periods. Under controlled experimental conditions, oral temperature has been demonstrated to respond to systemic track internal temperature (8). Local skin blood flow was indexed by laser-Doppler flowmetry using 2-mm integrating flow probes (FlowLab, Moor Instruments, Wilmington, DE) attached to nonglabrous skin on the dorsal portion of the hand between the first and third metacarpal in an area devoid of large surface veins. In addition to brachial artery measures described below, forearm blood flow was also assessed via venous occlusion plethysmography (39). In brief, measures were made via mercury-In-Silastic strain gauges (Hokanson, Bellevue, WA) secured on the widest aspect of the forearm. Wrist cuff was then inflated to 280 mmHg to remove the hand circulation from the measure, and then an upper arm cuff was inflated to 40 mmHg and cycled every 15 s. Venous occlusion plethysmography was completed on the opposite trial from brachial and cutaneous Doppler measures.

Duplex ultrasound (model HDI 5000, ATL Ultrasound, Bothell, WA) was used to determine blood velocity in the brachial, celiac, superior mesenteric, and renal arteries and in the left ventricular outflow tract. Standard brachial artery and left ventricular outflow track measures were completed as previously described (1, 11). In brief, a 5- to 12-MHz linear transducer with a 6-MHz pulsed Doppler frequency was positioned over the brachial artery just above the antecubital fossa. The insonation angle for measuring mean blood velocity was ≤60°. To minimize overestimation of mean blood velocity, the sample volume was adjusted to cover the size of the vessel. Average mean blood velocity was obtained from the Doppler waveform post hoc via software (HDI 5000). To measure arterial diameter a longitudinal view of the artery was taken. Arterial diameter measurements were made in end-diastole (determined by ECG) by measuring the distance between the lumen-intima interface in the near wall and the intima-media interface in the far wall. A 2- to 4-MHz phased array transducer with a pulsed Doppler frequency of 2 MHz was used for the measurement of stroke volume. The left ventricular outflow tract time velocity integral was measured from the apical long-axis view just proximal to the aortic annulus. Average aortic time velocity integral was obtained from the Doppler waveform post hoc via software (HDI 5000). Velocity measurements were expressed as centimeters per second. It should be noted that blood flow is a function of mean blood velocity and vessel cross-sectional area. Therefore, accurate measurements of vessel diameter are required to determine blood flow. This was possible for brachial artery and left ventricular outflow tract measurements, but due to the limited spatial resolution of the technique for deeper seated structures, accurate measurements of renal, celiac, and superior mesenteric artery diameter are difficult to perform in humans. However, these large conduit vessels show no significant change in diameter during pharmacological flow perturbations or changes in prandial state for the renal artery and celiac and superior mesenteric arteries, respectively (3, 21). Thus, changes in mean blood velocity likely correspond to the blood flow.

Data analysis. All continuous non-Doppler ultrasound data were recorded electronically at 60 Hz (model 16SP Powerlab, ADInstruments, New Castle, Australia). Vascular conductance of the renal artery, celiac artery, superior mesenteric artery, and dorsal hand skin was indexed by dividing Doppler-ultrasound velocity or laser-Doppler flux values by mean arterial blood pressure (MAP). Brachial artery blood flow (brachial blood velocity multiplied by brachial arterial cross-sectional area and by 60) and forearm blood flow from venous occlusion plethysmography were expressed as brachial vascular conductance and forearm vascular conductance, respectively, by dividing blood flow by MAP. Stroke volume was calculated by multiplying left ventricular outflow tract time velocity integral and cross-sectional area, and once this value was obtained, multiplying by heart rate to obtain cardiac output. Systemic vascular conductance was calculated from the ratio of cardiac output and MAP. Minute averages were calculated for even minutes of skin-surface cooling for brachial, celiac, cutaneous, superior mesenteric, and renal vascular conductance, while forearm vascular conductance was calculated five times between minutes 2–4, 6–8, 10–12, 14–16, and 18–20. Vascular conductance values were normalized to baseline values and expressed as percent change.

To identify possible differences in vascular conductance and temperature across the entire 20-min whole body cold stress, a repeated-measures ANOVA was utilized and Student-Newman-Keuls post hoc analysis was employed if significant main effects were observed. Other study variables (i.e., cardiac output, heart rate, stroke volume, and systemic vascular conductance) were compared between baseline and end cold stress using a paired t-test. No significant differences were noted between men and women in cold-induced changes in
arterial blood pressure ($P = 0.29$) or any of the visceral vascular conductances (range: $P = 0.45$ to 0.92), and thus these gender data were collapsed for analysis purposes. There were 12 multiple measurements of internal and mean skin temperature and arterial blood pressure within the 14 subjects, but blood velocity parameters were independent (i.e., 1 velocity measurement per subject per vessel). A significance level of $P < 0.05$ was used for all tests. Results are presented in text and figures as means ± SD.

RESULTS

Whole body skin-surface cooling significantly decreased mean skin temperature without influencing oral temperature (Fig. 1). The 20-min period of cooling increased systolic blood pressure, diastolic blood pressure, and MAP (all $P < 0.001$; Fig. 1). Cardiac output ($n = 8$; $4.088 \pm 561$ and $4.129 \pm 663$ ml/min; $P = 0.683$), heart rate ($n = 26$; $57 \pm 8$ and $57 \pm 6$ beats/min; $P = 0.358$), and stroke volume ($n = 8$; $74 \pm 14$ and $73 \pm 11$ ml/beat; for normothermia and 20 min of cooling, respectively; $P = 0.224$) were unchanged by cooling. Skin-surface cooling decreased systemic vascular conductance ($n = 8$; $53 \pm 9$ and $47 \pm 6$ ml·min$^{-1}$·mmHg$^{-1}$; for normothermia and 20 min of cooling, respectively; $P < 0.005$).

During the 20-min cooling, peripheral vasconstriction occurred (Fig. 2) as evidenced by significant reductions in brachial artery (normothermic baseline vascular conductance = $32 \pm 15$ cm·s$^{-1}$·mmHg$^{-1}$) and dorsal hand skin vascular conductance (normothermic baseline vascular conductance = $0.93 \pm 0.68$ flux units/mmHg). Forearm vascular conductance (assessed via venous occlusion plethysmography) decreased early during cooling and remained at this reduced value throughout the entire 20-min period of cooling ($n = 12$; $4.0 \pm 2.4, 2.5 \pm 1.0, 2.2 \pm 0.8, 2.1 \pm 0.82, 2.3 \pm 0.8$, and $2.1 \pm 0.8$ ml·min$^{-1}$·dl$^{-1}$·mmHg$^{-1}$ for normothermia, 2–4, 6–8, 10–12, 14–16, and 18–20 min of cooling, respectively; $P < 0.005$). Visceral vasconstriction occurred during cooling as evidenced by significant decreases in celiac, superior mesenteric, and renal artery vascular conductance indexes during cooling (Fig. 3). Normothermic baseline vascular conductances were $85 \pm 22, 55 \pm 16$, and $74 \pm 26$ cm·s$^{-1}$·mmHg$^{-1}$ for celiac, superior mesenteric, and renal arteries, respectively.

DISCUSSION

The findings from this study provide insight into the integrative circulatory responses to nonnoxious skin-surface cooling in humans. Specifically, we identified significant visceral (celiac, superior mesenteric, and renal vascular conductance indexes) and peripheral (brachial artery, total forearm, and cutaneous vascular conductance) vasconstrictor responses to skin-surface cooling in young healthy adults. This vasconstriction of both peripheral and visceral vascular beds leads to a pronounced and sustained pressor response that occurs independent of changes in heart rate or cardiac output.

This is the first report, to our knowledge, to identify renal vasconstriction during nonnoxious nonhypothermic cold stress in humans. This renal vasconstrictor response occurred within the first 4 min and was sustained throughout skin-surface cooling. Previous work in humans and rats noted decreases in renal blood flow during hypothermia (9, 25). However, hypothermia-related changes cannot be dissociated from decreases in cardiac output, MAP, and metabolic rate (37), and thus the role of vasconstrictor responses during hypothermia is not clear. Noxious cooling of the face or hand also causes increases in arterial blood pressure and decreases in renal vascular conductance (6, 16). Local cooling of the hand to 7°C or below increases MAP, but temperatures above this value do not alter arterial blood pressure (20). The water temperatures used in this study did not approach this threshold,
and thus it is unlikely that cold pain elicited the elevations in arterial blood pressure. Although the stimulus in skin-surface cooling is not related to cold pain, it is likely that the autonomic-induced vasoconstriction is mediated through nonnoxious cutaneous thermoreceptors known to be operable within the skin temperatures observed in this study (18, 27).

We also observed decreases in indexes of both celiac and superior mesenteric artery vascular conductance. These decreases in vascular conductance began at 4 min for the celiac artery and at 2 min for the superior mesenteric artery. These decreases persisted throughout the remainder of the 20-min skin-surface cooling trial. Again, we believe this time course is indicative of an autonomic vasoconstrictor reflex possibly mediated via cutaneous thermoreceptors. The celiac artery becomes the common hepatic, left gastric, and splenic arteries, whereas the superior mesenteric artery feeds portions of the small (jejunum and iliac) and large (ascending and transverse) intestine. Although we observed decreases in vascular conductance of the celiac and superior mesenteric arteries, it is not possible to determine whether there was preferential vasoconstriction of various downstream arteries. Previous research has identified splanchnic vasoconstriction during whole body heating and vasodilation during unspecified whole body cooling performed immediately after heating (34). Our data contrast the previous study. However, it is difficult to determine the precise effect of the whole body cold stress because of a previous heat-stress condition, because in many circumstances a previous heat stress can alter responses to a subsequent cold stress (12). Brauer et al. (7) summarized data indicating that an estimate of splanchnic blood flow decreased during hypothermia (dog colonic temperatures decreased to 30 and 23°C) and that liver vascular conductance decreased during hypothermia (rat liver temperatures decreased to 30 and 20°C). Clearly, there are many differences between these severe cold stresses and this study’s mild cold stress, but it is interesting that similar trends can be observed even during a mild cold stress before an observable change in internal temperature. Thus it is possible that skin-surface cooling may be able to be used as a model for testing questions related to such issues as cold-induced intestinal ischemia.

The visceral vasoconstriction observed in this study is of lower magnitude than that observed in peripheral tissues. However, it must be emphasized that during normothermic, resting, and fasting conditions, the renal and splanchnic circulations may account for ~20% and ~25% respectively, whereas the cutaneous circulation only receives ~4–5% of cardiac output. Thus even small changes in the conductance of the renal and splanchnic vascular beds may exert a significant hemodynamic impact. We observed a ~40% decrease in brachial vascular conductance and an over 50% decrease in cutaneous vascular conductance during cold stress. Our use of Doppler ultrasound to assess brachial artery blood flow during whole body cooling confirms the observations in the present study and those of previous studies during cooling via venous occlusion plethysmography methodology (2, 5, 10). Using similar whole body cooling methodology, Durand et al. (15) reported similar magnitude of decreases in cutaneous vascular conductance to the present observations. It is likely that this decrease in cutaneous vascular conductance in dorsal hand skin during cold stress is mediated via increases in skin sympathetic nerve activity during whole body cooling (4, 14, 35). However, it is possible that areas under the tube-lined suit also experienced locally mediated vasoconstriction (19).

Subjects did not experience either overt shivering in our study or changes in cardiac output. If subjects experienced pronounced preshivering tonus, the water temperature perfusing the suits was increased slightly (1–3°C) to abate this response before any measurements were made. Previous whole body cooling studies using similar magnitude and durations of cold stress to this study did not cause an observable increase in multiple-site electromyography indicative of shivering (15). It is likely that previous studies that have observed increases in cardiovascular variables such as cardiac output may have resulted because of the increase in muscle contractions associated with shivering (30, 32). We did not observe significant differences in cardiac output or heart rate with whole body cooling in the supine position. This observation is often reported but is highly variable between reports (36, 38). It is possible that there is a temperature-dependent change in cardiac output and systemic vascular conductance that relates to shivering response during cooling. Shivering is associated with muscle contraction and increases in metabolic rate, which can be as much as a threefold increase in resting metabolic rate (42). Thus it is likely that cold stress without shivering does not increase cardiac output and can maintain decreases in systemic conductance and vasoconstriction.
vasculature, whereas during cold-induced shivering cardiac output is elevated and systemic vascular conductance may increase from the initial vasoconstricted state to supply blood flow to these working muscles. These observations of skin-surface cooling follow reports from Muza et al. (26), who observed and assimilated that ventilatory and cardiovascular responses to air or water cold stresses are related to the degree that metabolic rate is increased and thus related to the degree to which internal temperature is changed. Skin-surface cooling, which is a milder cold stress, did not significantly alter internal temperature or cardiac output but did result in significant increases in arterial blood pressure and decreases in systemic vascular conductance.

Body composition data were not collected on study subjects. In addition to potential limitations of these measures, we do not believe that the percent body fat would have a profound effect on the data for multiple reasons. First, the vasoconstrictor responses of peripheral and visceral arteries observed in this study occurred within the first few minutes of skin-surface cooling, indicating more of a sympathetic reflex rather than a hypothermic response (or dramatic internal heat loss). Second, cutaneous vasoconstriction (as indexed by laser-Doppler flowmetry) and vasoconstriction to peripheral tissues (as indexed by brachial Doppler and venous occlusion plethysmography) provides the prime indicators of adjustable tissue insulation and thus the ability to change the core to skin temperature gradient (38).

Recently, whole body skin-surface cooling has been utilized as a countermeasure to increase orthostatic tolerance in humans (15, 40). Some of the mechanisms proposed for this preservation of cerebral blood velocity and tolerance include increases in central venous and arterial blood pressure (13, 40). Studies have also observed less of an increase in calf volume with skin cooling (15, 41), indicating less blood pooling in central venous and arterial blood pressure (13, 40). Studies have also observed less of an increase in calf volume with skin cooling (15, 41), indicating less blood pooling during orthostasis. Currently, it is not known whether the splanchnic and renal vasoconstriction observed in this study would contribute to the increase in arterial pressure during orthostatic stress during whole body cooling. Head-up tilt and lower body negative pressure increase splanchnic and renal vascular resistance (24, 33). Thus the data in the present study may provide an additional mechanism whereby skin-surface cooling augments systemic vascular resistance by further constricting both peripheral and visceral vascular beds during orthostatic stress.

Summary. This study identified reductions in indexes of vascular conductance in celiac, superior mesenteric, and renal arteries during skin-surface cooling, indicating vasoconstriction of these vessels. Peripheral vasoconstriction was also observed in brachial artery, total forearm, and cutaneous vasculature during skin-surface cooling. The vasoconstrictor responses occurred in the absence of significant alterations in heart rate, stroke volume, and cardiac output. Therefore, the integrative cardiovascular response to skin-surface cooling includes visceral and peripheral vasoconstriction, which occur independent of changes in cardiac output. Collectively, these hemodynamic responses are likely to contribute importantly to the observed pressor response to skin-surface cooling.

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