Skin cooling maintains cerebral blood flow velocity and orthostatic tolerance during tilting in heated humans

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Wilson, Thad E., Jian Cui, Rong Zhang, Sarah Witkowski, and Craig G. Crandall. Skin cooling maintains cerebral blood flow velocity and orthostatic tolerance during tilting in heated humans. *J Appl Physiol* 93: 85–91, 2002; 10.1152/japplphysiol.01043.2001.—Orthostatic tolerance is reduced in the heat-stressed human. The purpose of this project was to identify whether skin-surface cooling improves orthostatic tolerance. Nine subjects were exposed to 10 min of 60° head-up tilting in each of four conditions: normothermia (NT-tilt), heat stress (HT-tilt), normothermia plus skin-surface cooling 1 min before and throughout tilting (NT-tilt$_{cool}$), and heat stress plus skin-surface cooling 1 min before and throughout tilting (HT-tilt$_{cool}$). Heating and cooling were accomplished by perfusing 46 and 15°C water, respectively, though a tube-lined suit worn by each subject. During HT-tilt, four of nine subjects developed presyncopal symptoms resulting in the termination of the tilt test. In contrast, no subject experienced presyncopal symptoms during NT-tilt, NT-tilt$_{cool}$, or HT-tilt$_{cool}$. During the HT-tilt procedure, mean arterial blood pressure (MAP) and cerebral blood flow velocity (CBFV) decreased. However, during HT-tilt$_{cool}$, MAP, total peripheral resistance, and CBFV were significantly greater relative to HT-tilt (all $P < 0.01$). No differences were observed in calculated cerebral vascular resistance between the four conditions. These data suggest that skin-surface cooling prevents the fall in CBFV during upright tilting and improves orthostatic tolerance, presumably via maintenance of MAP. Hence, skin-surface cooling may be a potent countermeasure to protect against orthostatic intolerance observed in heat-stressed humans.

hyperthermia; heat stress; syncope; transcranial Doppler

ELEVATED ENVIRONMENTAL TEMPERATURES combined with orthostatic stress can be quite stressful to the human cardiovascular system (2, 20). Prior studies have shown that this combination of stresses decreases orthostatic tolerance during tilting (14), $+G_z$ acceleration (1), and lower body negative pressure (12). Whole body heating leads to increases in heart rate and cardiac output, with little change in mean arterial blood pressure (MAP) and stroke volume despite decreases in central venous pressure and total peripheral resistance

(13, 21). Under normothermic conditions, acute orthostatic stress also decreases central venous pressure and increases heart rate; however, in contrast to whole body heating, cardiac output and stroke volume decrease, whereas total peripheral resistance increases, resulting in little or no change in MAP (8, 22). It is likely that during orthostasis in a hyperthermic condition the combined effects of these stresses exacerbates the fall in central venous pressure and stroke volume and reduces the magnitude of increase in total peripheral resistance, and thus contributes to the reduction in arterial blood pressure and ensuing orthostatic intolerance (22).

Orthostasis-induced syncope is multifactorial in nature, which may occur via a wide variety of underlying mechanisms (3, 11, 22). During orthostasis the ability of the body to increase total peripheral resistance seems to play a pivotal role in preventing orthostatic intolerance and maintaining arterial blood pressure (4). Nevertheless, syncope during orthostatic stress will always occur if cerebral perfusion is sufficiently reduced (31). Interestingly, mild heating itself has been reported to reduced cerebral blood flow velocity (6).

Although a number of studies have demonstrated that perturbations such as heat acclimation may improve orthostatic tolerance in a hyperthermic environment (2, 25, 26), such procedures may not be a practical countermeasure because of the duration necessary to achieve that outcome. One potential countermeasure that has implications to improve orthostatic tolerance in a number of settings is rapid skin-surface cooling via a water-perfused suit. This technique has been shown to alter hemodynamic responses during orthostatic stress in normothermia (16, 17). However, these studies did not identify whether skin-surface cooling improved orthostatic tolerance in either normothermic or heat-stressed individuals. Thus implications for the use of this technique to improve orthostatic tolerance in the heated human remain unknown.

Rowell et al. (23) demonstrated that rapid skin cooling after whole body heat stress increased central venous pressure and returned heart rate and cardiac

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output back toward preheating values before observed changes in core temperature. Thus these responses occurred when the individual remained hyperthermic as indicated by the elevated core temperature. Others have reported that the application of cold packs increases cerebral blood velocity in normothermic individuals (6). Hence, rapid skin-surface cooling possibly maintains arterial blood pressure and increases cerebral blood velocity during a heat stress, thereby improving orthostatic tolerance in the heated human.

Substantial benefits would come from the identification of a countermeasure to improve orthostatic tolerance after conditions such as prolonged bed rest and/or spaceflight, especially if internal temperature is elevated during the period of gravitational stress as has been observed during reentry of the space shuttle (19). To the authors' knowledge, no study has addressed the effects of rapid skin-surface cooling in the heated human to identify the potential beneficial effects of this perturbation. Such a study may be useful in furthering our understanding of the combined effects of elevated internal temperature and orthostasis on the control of cerebral blood flow and orthostatic tolerance. Therefore, the purpose of this project was to test the hypothesis that rapid skin cooling improves orthostatic tolerance of heated individuals and to identify the mechanism(s) underlying this event.

METHODS

Subjects. Nine healthy subjects (4 men, 5 women) completed each of two protocols. The participants' mean age was 32 ± 2 yr, and all were of typical height (172 ± 3 cm), weight (73 ± 5 kg), and body surface area of 1.43 ± 0.8 m^2 (7). The protocol and informed consent received institutional approval. Written informed consent was obtained from all participants before they enrolled in this study.

Measurements. Heart rate was obtained continuously from an electrocardiogram (SpaceLabs, Redmond, WA) with the signal interfaced with a cardiotachometer (CWE, Ardmore, PA). Arterial blood pressure was measured from the upper arm via electrosphygmomanometry (SunTech, Raleigh, NC). This technique involves placing a microphone over the brachial artery to gate Korotkoff sounds to the electrocardiogram. Continuous monitoring of changes in blood pressure was obtained via the Penaz method (Finapres Ohmeda, Englewood, CO); however, this measurement was used solely for monitoring purposes and was not used in the analysis of the data. Cardiac output was measured by a rebreathing technique using acetylene as the soluble gas and helium as the insoluble gas (28). Gas concentrations for this technique were measured with a mass spectrometer (Marquette Electronics, Milwaukee, WI). Stroke volume was calculated from cardiac output and heart rate obtained during the rebreathing. MAP and total peripheral resistance were calculated according to standard methods.

Local skin blood flow was measured via laser-Doppler flowmetry using integrating flow probes (Perimed, North Rayalton, OH) attached to the forearm. The arms were positioned such that the laser-Doppler flow probes remained at heart level during tilting. Cutaneous vascular conductance was indexed by dividing laser-Doppler flux values by MAP and multiplying that number by 100. Sweat rate was measured via capacitance hygrometry (Viasala, Woburn, MA) as described previously (29). Internal temperature was continuously obtained from a thermocouple placed in the sublingual sulcus (T_{sl}). In addition, in six subjects, internal temperature was obtained at 10-s intervals via an ingestible pill telemetry system (HTI Technologies, Palmetto, FL). Mean skin temperature was measured via the weighted average of six thermocouples attached to the skin (27).

Cerebral blood flow velocity was obtained from the middle cerebral artery by transcranial Doppler ultrasonography. A 2-MHz Doppler probe (DWL Elektronische Systeme, Sipplingen, Germany) was adjusted over the temporal window until an optimal signal was identified. The probe was then fixed with a mold constructed of polyvinylsiloxane impression medium and held in place by a headband. This technique has been used in our facility during orthostatic tests to presyncope (30, 31). Respiratory rate was measured by a respiration transducer (UFI, Morro Bay, CA) belted around the torso, and ventilatory end-tidal CO_2 was measured via nasal cannula (Criticare Systems, Waukesha, WI).

Protocols. Participants underwent two protocols on separate days that were randomly assigned and performed at the same time of day. One protocol consisted of performing the outlined procedures first under normothermic conditions (NT-tilt), followed by repeating the procedures after whole body heating (HT-tilt). Subjects were in the supine position (45–60 min) before the recording of baseline conditions. The subjects were then tilted from supine to 60° for 10 min. Tilting was performed by using a motorized tilt bed (Omni Technologies, Valley City, ND), that elevated the individual to 60° in ~3 s. A foot board and bed straps around torso, waist, and upper legs were used to stabilize the subject during tilting; subjects were instructed to relax and not voluntarily contract leg muscles during all procedures. Arm boards were also used to maintain forearms at heart level throughout tilting. The tilt test was discontinued if signs or symptoms of presyncope were observed (i.e., nausea, pallor, sudden decrease in heart rate and/or blood pressure, or a sustained decrease in systolic blood pressure <80 mmHg). Subjects were then returned to the supine position, and whole body heating began. After internal temperature increased 0.6–1°C, the subjects were once again tilted to 60° for 10 min. Whole body heating was performed by perfusing 46°C water through a tube-lined suit worn by the subject (Carleton Technologies, Tampa Bay, FL). The water temperature perfusing the suit was slightly reduced to 44–45°C for 10–15 min before tilting in the heat in an attempt to cause internal temperature to plateau.

The second protocol involved identical procedures to those mentioned above (i.e., normothermia followed by whole body heating); however, rapid skin-surface cooling was performed 1 min before the tilt procedure in both normothermic (NT-tilt$_{cool}$) and heat-stressed (HT-tilt$_{cool}$) conditions. Skin-surface cooling was performed by circulating 15°C water through the water-perfused suit. This method of cooling decreases skin temperature with little effect on core temperature for the duration of the tilt test (see RESULTS).

Data analysis. Hemodynamic data, with the exception of cardiac output, stroke volume, and auscaltatory measurements of blood pressure, were continuously acquired throughout all experimental procedures. One-minute data segments obtained either immediately before each cardiac output measurement or the last minute of stable cardiovascular values (if subjects were unable to stand for the full 10 min) were statistically analyzed.

In each of the four conditions (i.e., NT-tilt, HT-tilt, NT-tilt$_{cool}$, and HT-tilt$_{cool}$), the change in response from supine to tilt of the hemodynamic variables (e.g., cardiac output, stroke volume, heart rate, MAP, and cerebral blood flow velocity)

were analyzed via a one-way repeated-measures ANOVA. If a significant main effect was identified, post hoc analyses were performed (Bonferroni corrected paired t-tests) to identify paired differences. All values are reported as means ± SE. The α-level for all statistical analyses was set at 0.05.

RESULTS

Thermal and sweating responses to heating and cooling. Whole body heating significantly increased T_{sl} (~0.8°C; $P < 0.001$) and telemetry-obtained temperature (~0.9°C; $P < 0.001$). Skin-surface cooling did not alter T_{sl} or telemetry-obtained temperature for either NT-tilt$_{cool}$ or HT-tilt$_{cool}$ (all $P > 0.05$; see Table 1). As expected, mean skin temperature increased with whole body heating (~4.0°C; $P < 0.001$) and decreased during skin-surface cooling ($P < 0.001$). The magnitude of the decrease in mean skin temperature with skin-surface cooling was greater during whole-body heating (9.1°C) relative to normothermia (5.9°C) because of the higher mean skin temperature before cooling with whole body heating (see Table 1). During the heat stress, forearm sweat rate increased (~0.81 mg·min^{-1}·cm^{-2}; $P < 0.001$) and then returned to preheat stress levels with the application of skin-surface cooling during the HT-tilt$_{cool}$ procedure. Upright tilting during the heat stress (i.e., HT-tilt) did not have a measurable effect on sweat rate (see Table 1), suggesting that baroreceptor unloading via tilting did not alter sweat rate. Cutaneous vascular conductance increased with heating (~120 CVC units; $P < 0.001$) and significantly decreased during HT-tilt and HT-tilt$_{cool}$ (see Table 1).

Central and cerebral hemodynamic responses to tilt and temperature. MAP was unchanged ($P > 0.05$) before tilting and cooling in any condition and was reduced by tilting in both NT-tilt and HT-tilt conditions (Fig. 1A). However, when tilting occurred in combination with skin-surface cooling (i.e., NT-tilt$_{cool}$ and HT-tilt$_{cool}$), MAP was significantly greater than MAP during NT-tilt and HT-tilt (Fig. 1A). Before tilting, whole body heating significantly increased heart rate by ~30 beats/min. The elevation of heart rate during HT-tilt was significantly greater than the elevation in heart rate during NT-tilt (Fig. 1B). The elevation in heart rate during NT-tilt$_{cool}$ was significantly attenuated relative to during NT-tilt. In contrast to the heart rate responses under the NT-tilt, HT-tilt, and NT-tilt$_{cool}$ conditions, heart rate significantly decreased during HT-tilt$_{cool}$ (Fig. 1B).

Cardiac output significantly increased with heating (~1.7 l/min; $P < 0.001$) and decreased with tilting in all conditions. However, the decrease in cardiac output during HT-tilt$_{cool}$ was significantly greater than during NT-tilt$_{cool}$, whereas the decreases in cardiac output between HT-tilt and HT-tilt$_{cool}$ were similar (see Fig. 2A). Stroke volume was unchanged with heating. The tilt-induced decrease in stroke volume was significantly attenuated during NT-tilt$_{cool}$ compared with NT-tilt (Fig. 2B). It is interesting to note that for the heated conditions, absolute stroke volume was significantly greater at the end of tilting with skin-surface cooling (HT-tilt$_{cool}$: 73 ± 6 ml) compared with absolute stroke volume at the end of tilting when skin-surface cooling was not applied (HT-tilt: 45 ± 6 ml). Before tilting, whole body heating significantly decreased total peripheral resistance (~3 mmHg·ml^{-1}·min; $P < 0.05$), whereas tilting increased total peripheral resistance in all conditions. However, total peripheral resistance increased significantly more with HT-tilt$_{cool}$ compared with HT-tilt and NT-tilt$_{cool}$ (Fig. 2C).

Mean cerebral blood flow velocity significantly decreased during whole body heating, as well as during both NT-tilt and HT-tilt. However, cerebral blood flow velocity was preserved by skin-surface cooling during both NT-tilt$_{cool}$ and HT-tilt$_{cool}$ compared with during NT-tilt and HT-tilt (Fig. 3A). At the end of the whole body heating tilt tests, absolute mean cerebral blood flow velocity was significantly greater when the tilting occurred in combination with skin-surface cooling (HT-tilt$_{cool}$: 59 ± 4 cm/s) relative to when tilting occurred without skin-surface cooling (HT-tilt: 42 ± 4 cm/s). No differences were observed in the change in calculated cerebral vascular resistance between the four conditions (see Fig. 3B).

Tilting caused slight reductions in end-tidal carbon dioxide levels (supine: 40 ± 2, tilt 37 ± 2 Torr; $P <$

Table 1. *Effect of skin-surface cooling on variables before and during tilt in both thermal conditions*

Variable	Condition	Normothermic Supine	Normothermic Tilt	Heat Stress Supine	Heat Stress Tilt
Sublingual temperature, °C	No cooling	36.4 ± 0.1	36.5 ± 0.1	37.2 ± 0.1*	37.2 ± 0.1
	Skin-surface cooling	36.3 ± 0.1	36.3 ± 0.1	37.1 ± 0.1*	36.9 ± 0.1
Core temperature (via telemetry) °C	No cooling	37.0 ± 0.1	37.1 ± 0.1	37.9 ± 0.1*	38.0 ± 0.1
	Skin-surface cooling	36.8 ± 0.1	37.0 ± 0.1	37.7 ± 0.1*	37.6 ± 0.1
Mean skin temperature, °C	No cooling	34.4 ± 0.3	34.1 ± 0.3	38.0 ± 0.2*	38.1 ± 0.2
	Skin-surface cooling	34.2 ± 0.3	28.3 ± 0.9†	38.7 ± 0.3*	29.6 ± 0.7†
Forearm sweat rate, mg·min^{-1}·cm^{-2}	No cooling	0.03 ± 0.01	0.03 ± 0.01	0.81 ± 0.09*	0.78 ± 0.08
	Skin-surface cooling	0.03 ± 0.01	0.03 ± 0.00	0.87 ± 0.10	0.09 ± 0.01†
Forearm cutaneous vascular conductance, CVC units	No cooling	31 ± 6	36 ± 6	177 ± 25*	129 ± 17
	Skin-surface cooling	24 ± 5	15 ± 2	122 ± 22*	50 ± 24†

Values are means ± SE. Data under normothermic and heat-stress supine conditions for skin-surface cooling are values before the application of skin-surface cooling. Data under normothermic and heat-stress tilt conditions for skin-surface cooling are values during the combination of skin-surface cooling and upright tilt. *Significant difference between heat-stress and normothermic supine data, $P < 0.01$. †Significant differences relative to the same perturbation but without skin-surface cooling (i.e., no cooling), $P < 0.01$
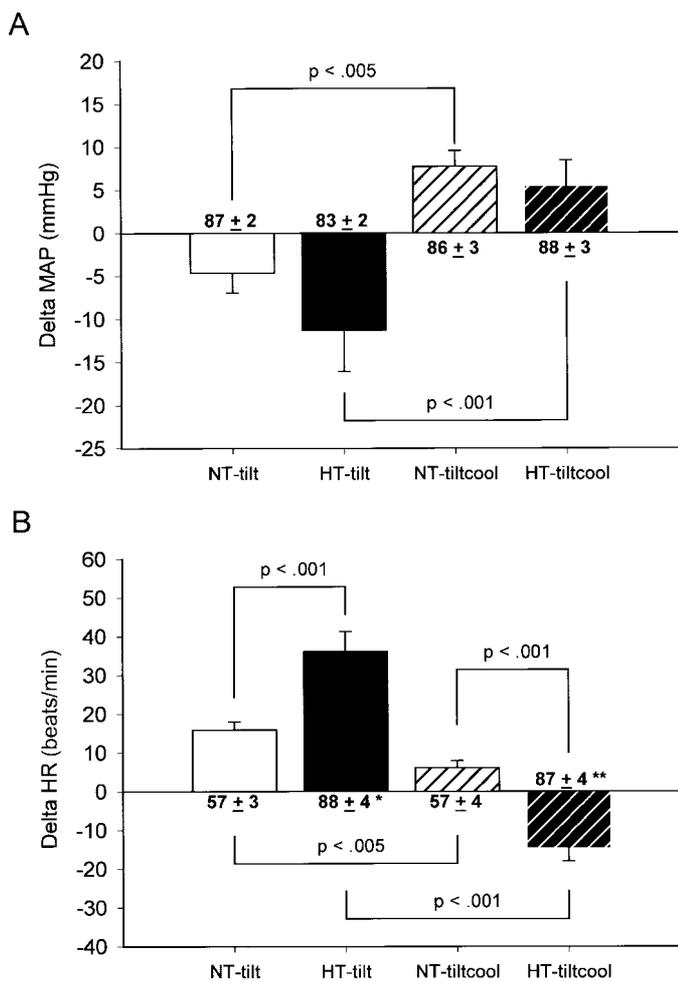
Fig. 1. Effects of tilting with and without cooling on mean arterial blood pressure (MAP; *A*) and heart rate (HR; *B*). Bars are the change (delta) in the variables between supine baseline and tilted conditions for normothermia (NT-tilt), heat stress (HT-tilt), normothermia + skin-surface cooling (NT-tilt$_{cool}$), and heat stress + skin-surface cooling (HT-tilt$_{cool}$). Numerical values associated with each bar are the values before tilting and skin cooling for that experimental condition. Values are means ± SE. *Significant differences between supine values before tilting, $P < 0.001$. **Significant differences between supine values before tilting and cooling, $P < 0.001$. Brackets indicate significant differences in the response that occurred with tilting, as well as the P value for that comparison.

0.05) regardless of whether tilting was preceded by cooling. Importantly, this decrease in end-tidal carbon dioxide levels was not significantly different between conditions (i.e., NT-tilt, NT-tilt$_{cool}$, HT-tilt, or HT-tilt$_{cool}$). Thus tilting caused similar absolute decreases in end-tidal carbon dioxide levels regardless of the thermal conditions.

Orthostatic tolerances. For both normothermic tilt tests (i.e., NT-tilt and NT-tilt$_{cool}$), all subjects were able to tolerate 10 min of tilting regardless of whether skin-surface cooling was employed. In contrast, signs of presyncope were observed in four of the nine subjects during the HT-tilt test, resulting in the test being terminated at the times of 5:05, 5:10, 5:50, and 6:55 min:s for those subjects. No signs of presyncope were observed in any subject when skin-surface cooling pre-
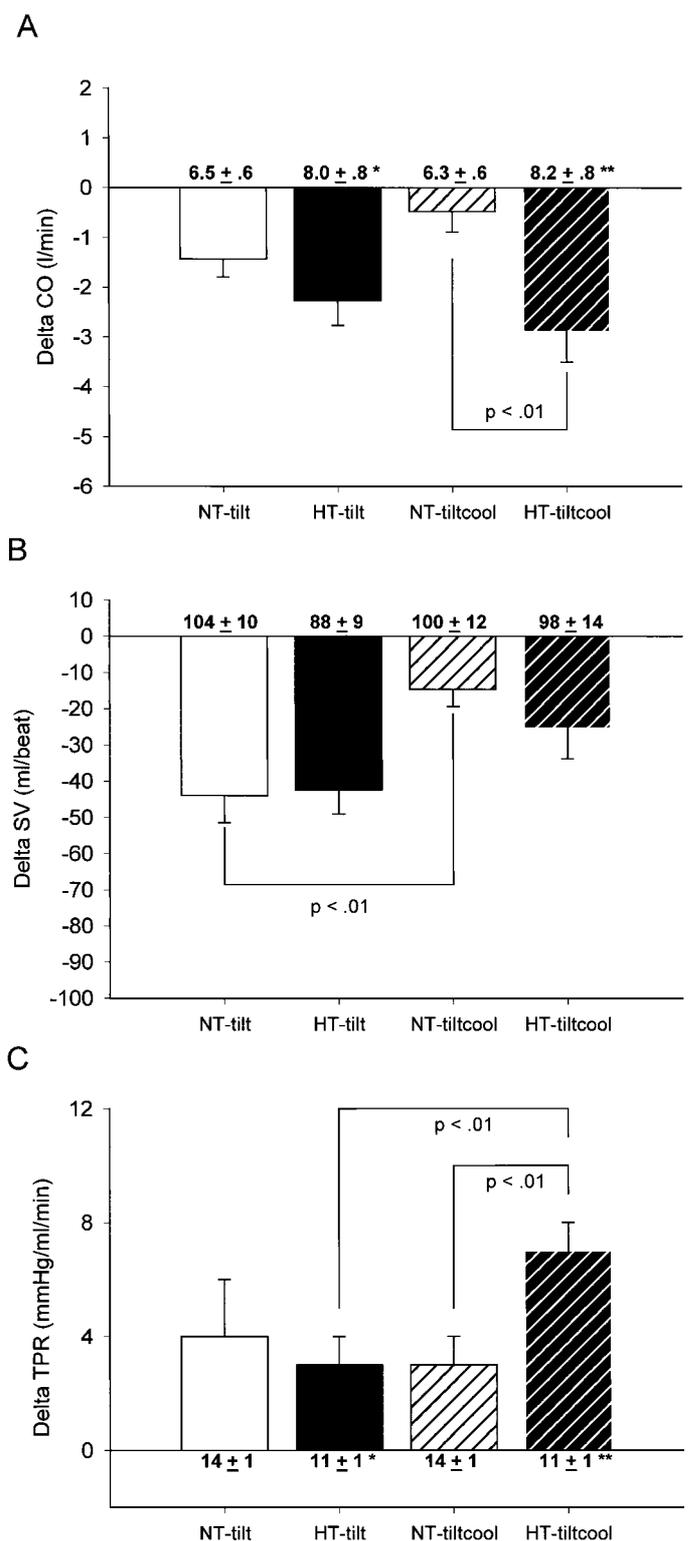

Fig. 2. Effects of tilting with and without cooling on cardiac output (CO; *A*), stroke volume (SV; *B*), and total peripheral resistance (TPR; *C*). Bars are the change in the variables between supine baseline and tilted conditions for NT-tilt, HT-tilt, NT-tilt$_{cool}$, and HT-tilt$_{cool}$. Numerical values associated with each bar are the values before tilting and skin cooling for that experimental condition. Values are means ± SE. *Significant differences between supine values before tilting, $P < 0.01$. **Significant differences between supine values before tilting and cooling, $P < 0.005$. Brackets indicate significant differences in the response that occurred with tilting, as well as the P value for that comparison.
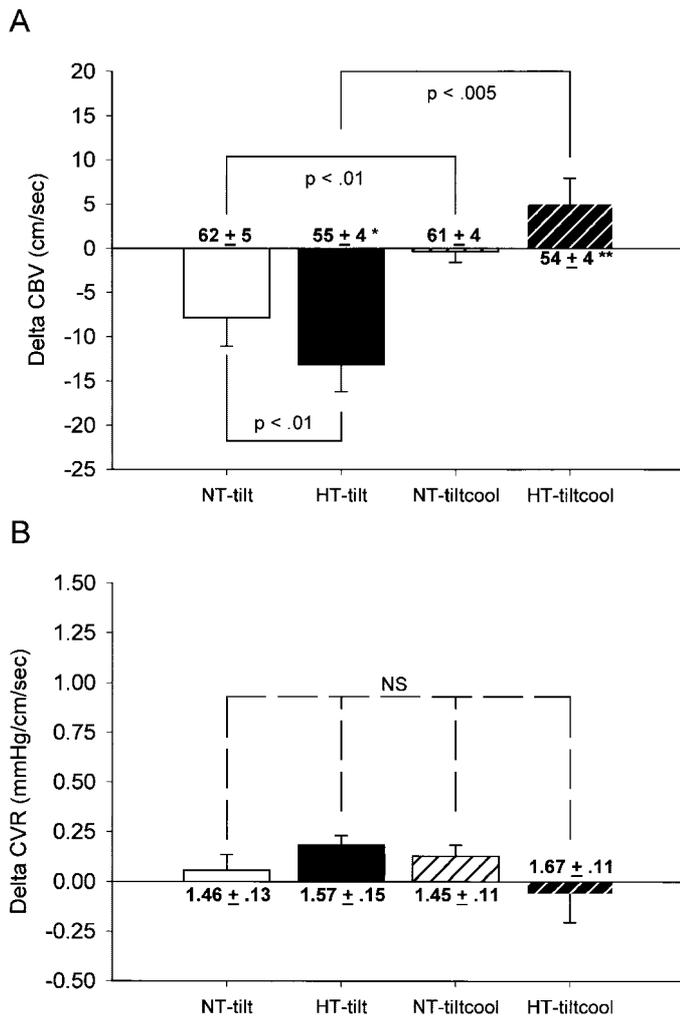
A

B

Fig. 3. Effects of tilting with and without cooling on cerebral blood flow velocity (CBV; A) and cerebral vascular resistance (CVR; B). Bars are the change in the variables between supine baseline and tilted conditions for NT-tilt, HT-tilt, NT-tilt$_{cool}$, and HT-tilt$_{cool}$. Numerical values associated with each bar are the values before tilting and skin cooling for that experimental condition. Values are as means $\pm$ SE. *Significant differences between supine values before tilting, $P < 0.01$. **Significant differences between supine values before tilting and cooling, $P < 0.05$. Brackets indicate significant differences in the response that occurred with tilting, as well as the P value for that comparison. NS, not significant.

ceded the tilt test in the heat-stressed condition (i.e., HT-tilt$_{cool}$).

DISCUSSION

The major findings of the present study are 1) rapid skin-surface cooling during tilting improved orthostatic tolerance in heat-stressed individuals, and 2) skin-surface cooling prevented tilt-induced decreases in cerebral blood flow velocity in both in normothermia and heat-stressed conditions. The maintenance of cerebral blood flow velocity during tilting with skin-surface cooling was primarily due to the maintenance of arterial blood pressure, rather than changes in cerebral vascular resistance.

In the heated condition, humans experience a greater incidence of orthostatic intolerance (20, 22). In the present study, four of nine individuals were unable to tolerate the 10-min tilt test after whole body heating. This is a similar incidence of orthostatic intolerance to that seen in other studies with heating in humans (2, 14). In contrast, the tilt test was well tolerated under normothermic and skin-surface cooling conditions. In two previous studies, skin-surface cooling was used to address hemodynamic responses to progressive levels of lower body negative pressure under normothermic conditions (16, 17). Those studies hinted at the possibility that skin-surface cooling might improve orthostatic tolerance; however, the maximum level of lower body negative pressure (i.e., -50 mmHg) used in those studies did not elicit presyncopal symptoms in any subject. Moreover, those studies were not conducted on heat-stressed individuals.

In the present study, no significant changes were observed in T_{sl} or telemetry pill temperature during HT-tilt$_{cool}$ and NT-tilt$_{cool}$. Therefore, HT-tilt$_{cool}$ represents a unique physiological situation in which internal temperature is elevated (~ 0.8–0.9°C) but mean skin temperature is reduced (~ 4.5°C) compared with normothermic values. A lack of change in internal temperature during NT-tilt$_{cool}$ is contrary to a previous observation (16). However, in that study, the duration of skin cooling was substantially longer and the temperature of the water was cooler relative to the present study.

Whole body heating caused increases in heart rate without changing MAP. Typical cardiovascular changes associated with skin cooling of normothermic subjects via decreasing ambient temperature include increases in MAP with minimal changes in heart rate (15, 18). However, few studies have investigated cardiovascular responses to skin cooling in heated individuals (23). In the present study, regardless of the prior thermal status, during tilting MAP decreased without skin-surface cooling (i.e., NT-tilt and HT-tilt) and increased when skin-surface cooling was employed (i.e., NT-tilt$_{cool}$ and HT-tilt$_{cool}$). These higher MAP values associated with skin-surface cooling likely maintained cerebral perfusion pressures compared with conditions without skin-surface cooling. Heart rate typically increases during an orthostatic stress (8, 22). In the present experiment, during HT-tilt, heart rate increased dramatically compared with NT-tilt and HT-tilt$_{cool}$. The probable mechanism for this large increase in heart rate during HT-tilt is due to baroreflexes associated with the large decrease in blood pressure during HT-tilt. During NT-tilt$_{cool}$, skin-surface cooling attenuated the rise in heart rate in response to tilting, which has also been observed by others (16). One novel observation of the current experiment was the decrease, rather than increase, in heart rate during HT-tilt$_{cool}$ (see Fig. 1B). The specific mechanism for this paradoxical heart rate response is unclear, although it is doubtful that this observation is a baroreflex-mediated response to elevated blood pressure because similar elevations in blood pressure during NT-tilt$_{cool}$ did not cause bradycardia. Moreover, Rowell et al. (23) showed that rapid skin cooling of hyperthermic individuals also

causes a rapid decrease in heart rate. Thus the decrease in heart rate observed during HT-tilt$_{cool}$ is likely related to skin cooling despite orthostasis and maintenance of elevated internal temperature.

Increases in internal and mean skin temperatures associated with whole body heating increased cardiac output, decreased total peripheral resistance, and did not significantly change stroke volume or MAP (13, 21). Cardiac output decreased during tilting in all conditions, although the decrease in cardiac output was attenuated during NT-tilt$_{cool}$. In contrast, during HT-tilt$_{cool}$, the decrease in cardiac output was of a similar magnitude to that observed during NT-tilt and HT-tilt. The lack of a maintenance of cardiac output during HT-tilt$_{cool}$, despite cooling, is likely due to a combination of decreases in cardiac output associated with orthostasis and the return of cardiac output toward pre-heat stress values with skin-surface cooling (21). In the present study, the decrease in stroke volume was attenuated during NT-tilt$_{cool}$ compared with NT-tilt, which is consistent with previous observations (16). Although there were no significant differences in the decrease in stroke volume between HT-tilt and HT-tilt$_{cool}$ conditions, absolute stroke volume was significantly greater during HT-tilt$_{cool}$ (73 $\pm$ 6 ml/beat) than during HT-tilt (45 $\pm$ 6 ml/beat). These data suggest that skin-surface cooling during tilting of heat-stressed individuals preserves absolute stroke volume during orthostasis, which likely contributes to the maintenance of blood pressure in this condition.

Syncope associated with orthostatic stress, although multimechanistic in nature (3, 11, 22), will ultimately occur if cerebral perfusion is sufficiently reduced (31). To the authors' knowledge, the present investigation is the first to observe the effects of a pronounced heat stress on cerebral blood flow velocity during orthostasis. It is interesting to note that increasing core temperature 0.8–0.9°C, independent of orthostatic stress, significantly decreased cerebral blood flow velocity by ~12%. This decrease in cerebral blood flow velocity is somewhat higher than the previously reported decrease of 6.9% during minor heating via application of hot packs sufficient to increased T$_{sl}$ by 0.2°C (6). Comparison of physiological responses between these studies is difficult because of different magnitudes of heating, different modes of heating, and the lack of reporting of efferent responses (i.e., skin blood flow and sweat rate) in the prior study (6). Nevertheless, the mechanism responsible for the reduction in cerebral blood flow velocity is unclear; however, heat-induced alterations in perfusion pressure cannot be excluded.

The present study demonstrated that tilting decreases cerebral blood flow velocity, thereby confirming previous findings of decreases in cerebral blood flow velocity with lower body negative pressure (10, 30, 31). In the present study, cerebral blood flow velocity decreased with tilting regardless of the thermal status of the individual; however, tilting in the heat (HT-tilt) caused a greater decrease in cerebral blood flow velocity relative tilting in a normothermic condition (NT-tilt). Cooling immediately before the tilt test maintained cerebral blood flow velocity during tilting in both the normothermic and heat-stressed trials (i.e., NT-tilt$_{cool}$ and HT-tilt$_{cool}$). Although an absolute cerebral blood flow that will result in syncope is not known, the observation that cerebral blood flow velocity is preserved during tilt with skin-surface cooling (primarily via maintenance of perfusion pressure) suggests that the cooling protocol increases the functional reserve of cerebral blood flow before this lower limit is reached. This hypothesis is supported by the finding that four of the nine individuals experienced presyncopal symptoms during HT-tilt, whereas no presyncopal symptoms were observed in the HT-tilt$_{cool}$ condition.

There was no difference in the magnitude of change in calculated cerebral vascular resistance during tilting regardless of the thermal status (see Fig. 3B). This finding suggests that arterial blood pressure, not a change in cerebral vascular tone, was the primary mechanism resulting in the aforementioned changes in cerebral blood flow velocity during tilt. However, the present findings do not exclude the possibility of altered cerebral vascular autoregulation during heating or during the combination of heating and orthostatic stress in contributing to the increased incidence of orthostatic intolerance. In support of this hypothesis, a recent study has reported alterations in an index of cerebral vascular autoregulation during heat stress in humans (5).

Limitations to the interpretation of the results. During HT-tilt, four subjects were unable to stand for the full 10 min. For these subjects, every effort was made to obtain 1 min of stable cardiovascular data. However, cardiac outputs could not be obtained during HT-tilt from two of the four subjects because these subjects experienced presyncopal symptoms before these data were obtained. Thus reported cardiac output data, as well as data calculated from cardiac output (i.e., stroke volume and total peripheral resistance), for the HT-trial do not include data from the two subjects who were unable to complete the cardiac output measurement. However, for these subjects, all other variables, including cerebral blood flow velocity, were included in the analysis. We expect that had cardiac output been obtained from these subjects, mean cardiac output and stroke volume would have been even lower during HT-tilt than that depicted in Fig. 2.

The use of skin surface cooling 1 min before tilt precludes the assessment of the effects of cooling independent from tilting. Thus the presented data are a result of an interaction between cooling and upright tilting. Nevertheless, skin surface cooling was clearly an effective countermeasure to improve orthostatic tolerance of heat-stressed individuals.

In the present study, cerebral blood flow velocity of the middle cerebral artery, accessed through the temporal cranial window, was used as an index of cerebral blood flow. We recognize that velocity is representative of flow, only if the diameter of the vessel is unchanged. In support of this concept, investigators directly measured the middle cerebral artery diameter in humans and found that the diameter of this large vessel either was not

changed or was only minimally affected by changes in MAP and end-tidal carbon dioxide (9, 24). Thus it is likely that changes in velocity reported in the present investigation reflect changes in cerebral blood flow.

In conclusion, findings from the present study demonstrate that skin-surface cooling prevents the fall in cerebral blood flow velocity during tilting in both normothermic and heat-stressed conditions. The maintenance of cerebral blood flow velocity is likely due to the elevation of MAP during skin-surface cooling, rather than changes in cerebral vascular resistance. Importantly, rapid skin-surface cooling improved orthostatic tolerance in the presence of elevated internal temperatures. Therefore, skin-surface cooling may be an effective countermeasure to protect against orthostatic intolerance previously observed in hyperthermic conditions.

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