

Skin surface cooling improves orthostatic tolerance in normothermic individuals

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Durand, S., J. Cui, K. D. Williams, and C. G. Crandall. Skin surface cooling improves orthostatic tolerance in normothermic individuals. *Am J Physiol Regul Integr Comp Physiol* 286: R199–R205, 2004; 10.1152/ajpregu.00394.2003.—Previous studies suggest that skin surface cooling (SSC) preserves orthostatic tolerance; however, this hypothesis has not been experimentally tested. Thus the purpose of this project was to identify whether SSC improves orthostatic tolerance in otherwise normothermic individuals. Eight subjects underwent two presyncope limited graded lower-body negative pressure (LBNP) tolerance tests. On different days, and randomly assigned, LBNP tolerance was assessed under control conditions and during SSC (perfused 16°C water through tube-lined suit worn by each subject). Orthostatic tolerance was significantly elevated in each individual due to SSC, as evidenced by a significant increase in a standardized cumulative stress index (normothermia 564 ± 58 mmHg·min; SSC 752 ± 58 mmHg·min; $P < 0.05$). At most levels of LBNP, blood pressure during the SSC tolerance test was significantly greater than during the control test. Furthermore, the reduction in cerebral blood flow velocity was attenuated during some of the early stages of LBNP for the SSC trial. Plasma norepinephrine concentrations were significantly higher during LBNP with SSC, suggesting that SSC may improve orthostatic tolerance through increased sympathetic activity. These data demonstrate that SSC is effective in improving orthostatic tolerance in otherwise normothermic individuals.

lower-body negative pressure; syncope; norepinephrine; blood pressure

ORTHOSTATIC INTOLERANCE can be defined as the inability of the body to maintain the upright position during orthostatic stress due to the onset of syncopal symptoms. Orthostatic tolerance is reduced by a variety of conditions, including autonomic failure, heat stress, and after actual and simulated microgravity exposure (1–4, 12). In the latter two cases, the mechanisms leading to reduced orthostatic tolerance remain unclear. Nevertheless, substantial benefit would come from the identification of a countermeasure that improves orthostatic intolerance, particularly in individuals with autonomic dysfunction, as well as after prolonged bed rest or space flight. One such countermeasure may be skin surface cooling (SSC).

Lind et al. (7) observed that during a 5-min head-up tilt test in a hot environment (45°C dry bulb/35°C wet bulb room temperature), 16 of 64 tilting procedures resulted in the subject fainting. In contrast, no subjects fainted during tilting in cool environmental conditions (room temperature 18–20°C). However, in that study orthostatic tolerance was not assessed when individuals were normothermic, and thus the effects of cooling on improving orthostatic tolerance relative to normothermic

conditions were not investigated. Later, Raven et al. (10, 11) suggested that SSC may improve orthostatic tolerance. However, in those studies orthostatic tolerance was not assessed because the highest level of lower-body negative pressure (LBNP) was limited to –50 mmHg and no subject experienced syncopal symptoms. Although insightful information was provided from those studies, it remains unknown whether orthostatic tolerance is improved by SSC. Finally, we recently demonstrated that SSC improves orthostatic tolerance in heat-stressed subjects (16). However, in that study no subject experienced presyncopal symptoms during 10 min of upright tilt either with or without SSC while otherwise normothermic. Thus we were unable to draw any conclusions regarding whether cooling of normothermic subjects improved orthostatic tolerance. Given that SSC has been suggested, but not confirmed, to improve orthostatic tolerance, the purpose of this project was to test the hypothesis that SSC improves orthostatic tolerance in otherwise normothermic individuals and to assess mechanisms of this expected outcome.

METHODS

Subjects. Eight healthy subjects (4 men, 4 women) participated in this study. Mean age, height, and weight were 33 ± 2 yr, 176.8 ± 2.6 cm, and 77 ± 5.4 kg, respectively. Subjects were free of cardiovascular, metabolic, and neurological disorders. Subjects gave their written consent to participate in this institutionally approved study.

Protocol. On different days, subjects were exposed to either normothermic or SSC presyncopal limited LBNP tolerance tests. The order of these trials was randomized. Subjects were dressed in a tube-lined suit perfusable with temperature-controlled water. Under the suit the male subjects wore only shorts while the female subjects wore shorts and a swimsuit top or sports bra. The subjects were then placed in the supine position in an LBNP device. The LBNP device was sealed at the iliac crest. At the beginning of each experiment, whatever the condition (i.e., normothermia or cooling), 34°C water was circulated through the suit. The temperature of water perfusing the suit was kept at this level for the normothermic LBNP challenge, while 16°C water was perfused through the suit throughout the SSC trial. Using our water-perfused suits and perfusion system (flow rate: ~ 1.5 l/min), 16°C water was identified in pilot experimentation to induce the largest increase in blood pressure without causing shivering over a period of 30 min (data not shown). In normothermic conditions, a 6-min baseline period of data collection preceded the onset of LBNP. For the SSC protocol, after a similar 6-min baseline period, cool water was perfused for 10 min before the onset of LBNP. The possible occurrence of shivering during the experiment was assessed via electromyography with electrodes placed on the upper part of the back (trapezius) and on one thigh (quadriceps).

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In both thermal conditions, graded LBNP was administered as follows: LBNP began at -30 mmHg for 3 min, followed by the pressure progressively being reduced by -10 mmHg every 3 min until the occurrence of presyncopal symptoms. Presyncopal symptoms were defined as a sustained systolic blood pressure of <80 mmHg, or periodic systolic blood pressures of <80 mmHg associated with symptoms of lightheadedness, nausea, diaphoresis, and/or bradycardia.

Experiments were performed at the same time of day and were separated by a minimum of 3 days for the male subjects and by 28 days for the female subjects. The duration between tests for the female subjects was to control for the possible effects of the menstrual cycle in altering orthostatic tolerance (9). The order of experiments was randomized, with the first LBNP test being the SSC assessment for four subjects and the normothermic assessment being administered first for the other four subjects. Investigators were blinded as to the level of LBNP achieved in the first tolerance test.

Orthostatic tolerance was quantified via a cumulative stress index (6, 18). This index was calculated for each LBNP protocol by summing the product of the level of negative pressure and duration, in minutes and fraction of minutes, at each level of negative pressure (e.g., $30 \text{ mmHg} \times 3 \text{ min} + 40 \text{ mmHg} \times 3 \text{ min} + 50 \text{ mmHg} \times 3 \text{ min} \dots$) until the onset of presyncopal symptoms.

Measurements. Mean skin temperature was obtained from the average of six thermocouples attached to the skin, and sublingual temperature was recorded via a thermistor placed under the tongue. Intermittent arterial blood pressure was measured from the upper arm (Suntech, Raleigh, NC), while continuous blood pressure was obtained from a Finapres (Ohmeda, Louisville, CO). Heart rate was obtained from an electrocardiogram (SpaceLabs, Redmond, WA) with the signal interfaced with a cardiometer (CWE, Ardmore, PA). Cardiac output was measured using a standard inert gas (acetylene) rebreathing technique (15). Rebreath cardiac outputs were obtained at baseline for the normothermic and SSC trials, during baseline for the cooling period (i.e., pre-LBNP), and at -30 , -50 , and -70 mmHg LBNP. Heart rate during the rebreathing procedure was used to calculate stroke volume. Thoracic impedance (Biopac Systems, Santa Barbara, CA) was used as an index of changes in central blood volume. Mean arterial pressure and total peripheral resistance were calculated according to standard methods.

Plasma norepinephrine concentrations were measured from blood drawn from the antecubital vein at baseline (i.e., pre-LBNP for both trials), during SSC but before LBNP, at -40 mmHg LBNP, and on the presence of presyncopal symptoms. The intravenous catheter was inserted a minimum of 20 min before the first blood draw. Due perhaps to vasoconstriction, blood could not be withdrawn in three of the eight subjects during the cooling procedure. Thus the reported norepinephrine concentrations are from five subjects. For each blood sample, ~ 3 ml of blood was drawn in tubes containing K_2EDTA

(Vacutainer system, Franklin Lakes, NJ) and was immediately put in ice. Blood samples were then centrifuged and the plasma isolated. Plasma was frozen at -80°C and sent to a biochemistry laboratory for HPLC analysis (Arup Laboratory, Salt Lake City, UT).

Local forearm skin blood flow was measured via laser-Doppler flowmetry (Perimed, North Rayalton, OH). A mercury-in-Silastic strain gauge was positioned around the right calf, at the point of maximum circumference, to provide an index of the change in calf volume during LBNP. The water-perfused suit did not cover this region of the leg. Cerebral blood flow velocity was measured from the middle cerebral artery by transcranial Doppler ultrasonography (DWL Elektronische Systeme, Sipplingen, Germany). Cerebral blood flow velocity was expressed as a percent change from pre-LBNP baseline period for the normothermic trial and after 10 min of cooling, but before LBNP, for the SSC trial. The probe was held in place using a polyvinylsiloxane mold and a headband. End-tidal CO_2 was measured via nasal cannula (Oridion Medical, Needham, MA).

Statistical analysis. For baseline periods (i.e., precooling and pre-LBNP), 2 min of data were averaged and analyzed, while 1 min of data was averaged and analyzed for SSC responses before LBNP. Throughout LBNP, responses during the final 30 s of each stage were averaged and analyzed. Cerebral blood flow velocity was averaged during a 30-s window after the first minute in each LBNP stage. This time period was selected to obtain cerebral blood flow velocities before the rebreath cardiac output measures, which at times acutely altered this variable. For each thermal condition, differences in hemodynamic and temperature variables from baseline to maximal tolerated LBNP were evaluated using paired *t*-tests. The effects of LBNP between thermal conditions were evaluated using a repeated-measures two-way ANOVA followed by post hoc analyses. Main factors of that ANOVA were LBNP stage and thermal condition. For most variables, ANOVA was performed on data from -30 , -40 , and -50 mmHg LBNP, as -50 mmHg was the highest level reached by all subjects in both thermal conditions. The cumulative stress index, as well as other variables at the end of LBNP, was compared between thermal conditions by paired *t*-test. Data are reported as means \pm SE. $P \leq 0.05$ was considered statistically significant.

RESULTS

Assessment of orthostatic tolerance. In normothermia the index of orthostatic tolerance was 564 ± 58 mmHg \cdot min, while with SSC this value was 752 ± 58 mmHg \cdot min ($P < 0.05$ compared with normothermia), resulting in $\sim 34\%$ elevation in the cumulative stress index. All subjects increased their level of orthostatic tolerance with SSC. Five subjects attained higher levels of LBNP with SSC, while three subjects increased the duration at the final LBNP stage (Table 1).

Table 1. Maximal tolerated LBNP, duration of LBNP, and the calculated cumulative stress index during both thermal conditions for each subject

Subjects	Normothermic Conditions			Whole Body Skin Surface Cooling		
	Maximal level of LBNP, mmHg	Duration of LBNP procedure, min	Cumulative stress index, mmHg \cdot min	Maximal level of LBNP, mmHg	Duration of LBNP procedure, min	Cumulative stress index, mmHg \cdot min
1	-60	10.2	430	-80	15.5	791.3
2	-80	16.3	851.3	-90	19.2	1098
3	-70	12.7	589	-80	15.9	823.3
4	-70	12.5	573.8	-70	13.8	666
5	-70	13.5	641.5	-70	14.4	709
6	-50	7.7	294.2	-60	12	540
7	-60	11.2	491	-70	14.7	726.7
8	-70	13.4	638	-70	13.7	659

For each subject orthostatic tolerance was elevated with skin surface cooling. The duration of the lower body negative pressure (LBNP) procedure was rounded to the nearest 0.1 min, while the cumulative stress index was calculated based on the exact time of cessation of LBNP.

Table 2. Effects of skin surface cooling and LBNP on skin temperature, calf volume, and cutaneous perfusion

Variable/Condition	Baseline	Cooling (Without LBNP)	End of LBNP
Skin temperature, °C			
Normothermia	34.6±0.2		34.2±0.1*
Cooling	34.8±0.1	31.6±0.3*	29.3±0.3*
ΔCalf volume, %			
Normothermia			3.3±0.4*
Cooling		-0.7±0.3*	3.2±0.4*
Cutaneous forearm blood flow, AU			
Normothermia	10.4±1.1		8.9±1.1
Cooling	15.3±2.3	8.8±0.6*	8.4±0.9*

Values are means ± SE. Cooling, responses during skin surface cooling before LBNP. End of LBNP, responses at presyncope just before removal of negative pressure. ΔCalf volume is expressed as a percent change from baseline. AU, arbitrary units. * $P < 0.05$ from baseline.

Thermal responses. Before cooling and LBNP, baseline skin (Table 2) and sublingual (36.6 ± 0.2 vs. $36.5 \pm 0.2^\circ\text{C}$) temperatures were not significantly different between normothermic and cooling protocols, respectively. A slight, but

significant, decrease in skin temperature (-0.4°C , $P < 0.01$) was observed during the normothermic LBNP procedure. In contrast, SSC caused pronounced decreases in skin temperature. After 10 min of SSC, just before the beginning of LBNP, mean skin temperature was $31.6 \pm 0.3^\circ\text{C}$ ($P < 0.001$ vs. baseline). Skin temperature continued to decrease throughout LBNP, resulting in a mean skin temperature reduction of $\sim 5.5^\circ\text{C}$ at the end of LBNP (Table 2).

Responses to SSC before graded LBNP. Ten minutes of SSC before LBNP induced typical cutaneous vasoconstrictor responses as evidenced by a significant decrease in forearm skin perfusion (see Table 2). SSC increased mean blood pressure (from 84.1 ± 1.8 to 90.3 ± 1.6 mmHg; $P < 0.05$; Fig. 1) and stroke volume (from 100.9 to 109.5 ml, $P < 0.01$; Fig. 2), while heart rate (from 59.7 ± 4.0 to 58.0 ± 3.1 beats/min; $P = 0.41$) and cardiac output (from 7.4 ± 1.1 to 7.6 ± 1.7 l/min; $P = 0.47$) were not significantly affected by SSC. No significant change in central blood volume, as identified by thoracic impedance, was observed with SSC. SSC increased cerebral blood flow velocity by $4.4 \pm 1.5\%$ ($P < 0.05$), while no change in end-tidal CO_2 was observed (38.5 ± 1.4 vs. 37.4 ± 1.6 Torr). After 9 min of SSC, blood norepinephrine concen-

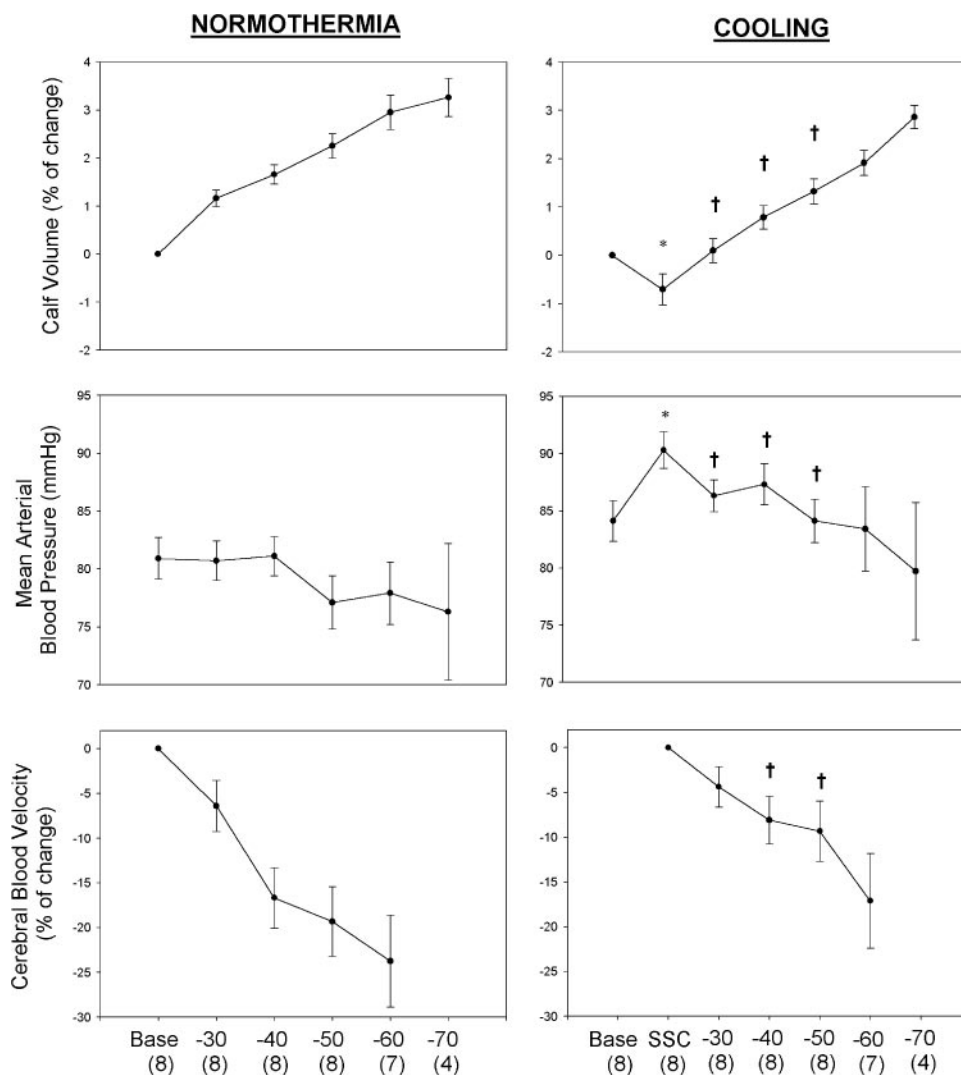


Fig. 1. Changes in calf volume (expressed as a % change from baseline), blood pressure, and cerebral blood flow velocity before and during lower body negative pressure (LBNP) in both thermal conditions. Nos. in parentheses below the LBNP level indicate no. of subjects used in the analysis at the specified LBNP level. For -70 mmHg LBNP, the reported data are from 4 subjects due to difficulties in obtaining blood pressure at this stage of LBNP in 1 subject who ended the normothermic LBNP test 30 s into the stage. Cerebral blood flow velocity responses during -70 mmHg LBNP are not reported due to technical issues associated with its measurement in 1 subject coupled with the low number of subjects exposed to this level of LBNP. Finally, data are included only if responses were obtained for the specified LBNP stage during both the normothermic and skin surface cooling (SSC) trials. Base, baseline; SSC, SSC (before LBNP). †Statistical significance ($P < 0.05$) between cooling and normothermic conditions for the specified level of LBNP. *Statistical significance ($P < 0.05$) between baseline (i.e., precooling) and the SSC period (i.e., before LBNP).

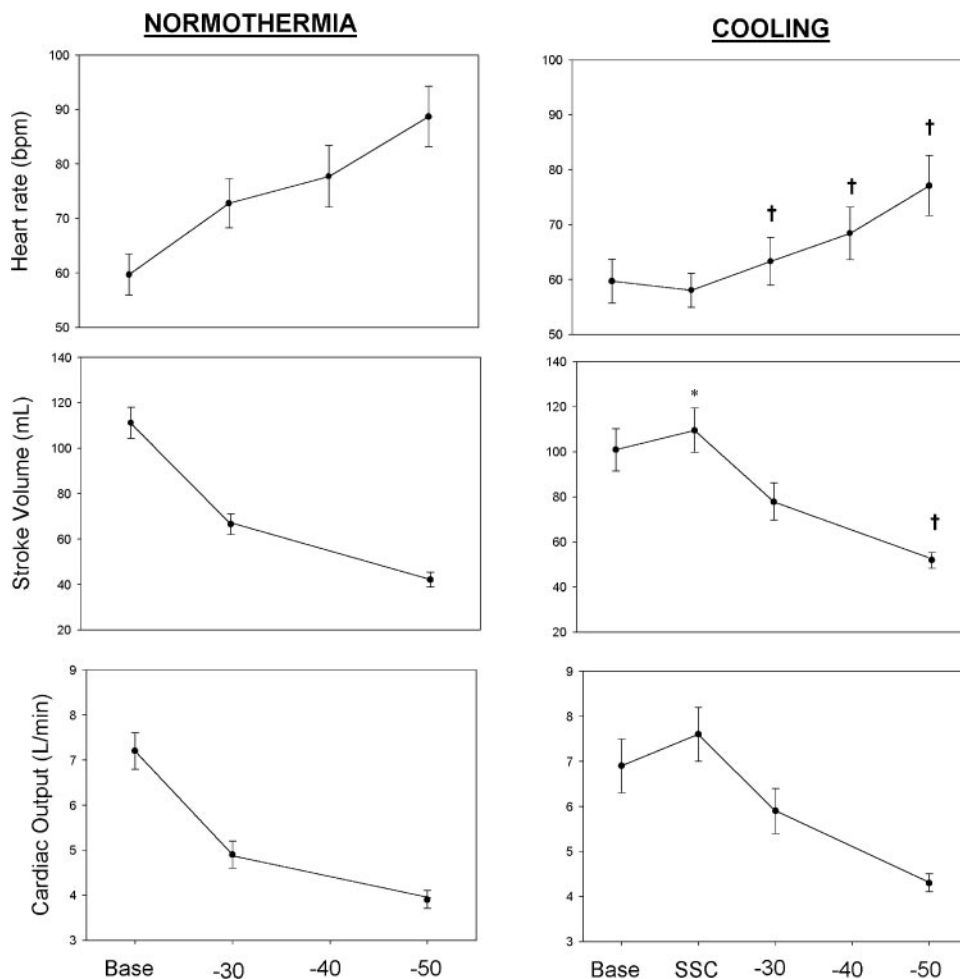


Fig. 2. Changes in heart rate, stroke volume, and cardiac output before and during LBNP in both thermal conditions. †Statistical significance ($P < 0.05$) between cooling and normothermic conditions for the specified level of LBNP. *Statistical significance ($P < 0.05$) between baseline (i.e., precooling) and the SSC period (i.e., before LBNP). bpm, Beats/min.

tration significantly increased from 180 ± 18 to 316 ± 37 pg/ml ($P < 0.01$, Fig. 3).

Responses to graded LBNP with or without SSC. Analysis of EMG revealed no episodes of shivering throughout SSC. For

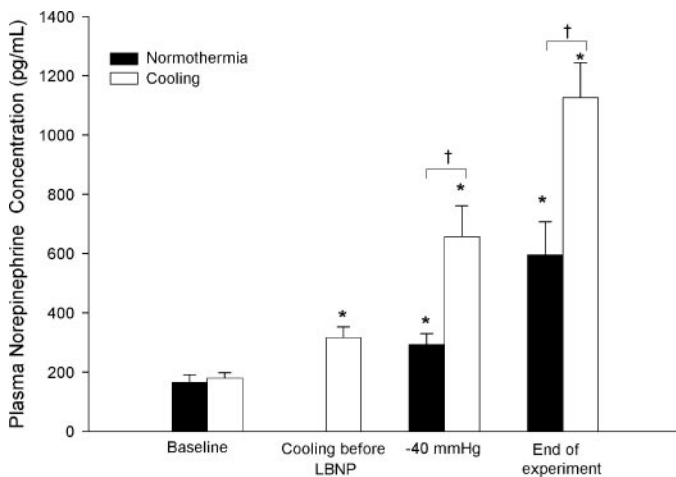


Fig. 3. Plasma norepinephrine concentrations in normothermia and during skin surface cooling during baseline, after skin cooling but before LBNP, at -40 mmHg LBNP, and at maximally tolerated LBNP. *Significant differences ($P < 0.01$) between baseline and the indicated stage. †Significant differences ($P < 0.05$) between normothermic and cooling conditions.

several variables, SSC exerted a protective effect on cardiovascular responses to LBNP. Indeed, at each level of LBNP (to -50 mmHg) calf volume was significantly lower (i.e., less pooling) during the SSC trial (Fig. 1). However, this response did not translate into differences in thoracic impedance as the increase in thoracic impedance due to LBNP was unaffected by SSC. The elevation in heart rate during LBNP was significantly greater during the normothermic trial (Fig. 2). SSC during LBNP attenuated the reduction in stroke volume at -50 mmHg LBNP, resulting in stroke volume being significantly elevated relative to this level of LBNP in normothermia (normothermia 42.1 ± 3.3 ml; SSC 51.9 ± 3.5 ml; $P < 0.05$). At -30 mmHg LBNP there was a tendency for stroke volume to be elevated during the SSC trial (normothermia 66.5 ± 4.6 ml; SSC 77.9 ± 8.3 ml; $P = 0.067$; Fig. 1). Similarly, a tendency for an elevation in cardiac output during the SSC trial was observed at -30 mmHg (normothermia 4.9 ± 0.3 l/min; SSC 5.9 ± 0.5 l/min; $P = 0.058$) and -50 mmHg (normothermia 3.9 ± 0.2 l/min; SSC 4.3 ± 0.2 l/min; $P = 0.065$). Finally, during the SSC trial, mean blood pressure was significantly higher for the first three levels of LBNP (-30 mmHg: 80.7 ± 4.7 vs. 86.3 ± 4.1 mmHg; -40 mmHg: 81.1 ± 4.8 vs. 87.3 ± 5.1 mmHg; -50 mmHg: 77.1 ± 6.5 vs. 84.1 ± 5.3 mmHg, normothermia vs. SSC respectively, each $P < 0.05$, Fig. 1), although the increase in total peripheral resistance was similar for each level of LBNP between thermal conditions.

Associated with the aforementioned differences in blood pressure between trials, the decrease in cerebral blood flow velocity was greater during the normothermic trial for -40 mmHg LBNP (normothermia $-16.7 \pm 3.4\%$; SSC $-8.1 \pm 2.7\%$, $P < 0.05$; Fig. 1) and -50 mmHg LBNP (normothermia $-19.3 \pm 3.9\%$; SSC $-9.3 \pm 3.4\%$, $P < 0.05$; Fig. 1). No difference in cerebral blood flow velocity was observed between trials at -30 mmHg (normothermia $-6.4 \pm 2.9\%$, SSC $-4.4 \pm 2.3\%$, $P = 0.4$). Cerebral vascular conductance decreased in normothermia at -40 and -50 mmHg LBNP [baseline: $0.73 \pm 0.03 \text{ cm}\cdot\text{s}^{-1}\cdot\text{mmHg}^{-1}$; -40 mmHg: $0.61 \pm 0.04 \text{ cm}\cdot\text{s}^{-1}\cdot\text{mmHg}^{-1}$; -50 mmHg: $0.62 \pm 0.04 \text{ cm}\cdot\text{s}^{-1}\cdot\text{mmHg}^{-1}$ (both $P < 0.05$ vs. baseline)]. In contrast, during the SSC trial, cerebral vascular conductance did not change through -50 mmHg LBNP. LBNP reduced end-tidal CO_2 for both normothermic and SSC trials. There were no significant differences in this variable between thermal conditions for any level of LBNP. That said, at -40 and -50 mmHg LBNP, end-tidal CO_2 during the normothermic trial tended to be lower compared with the SSC trial (both $P = 0.06$).

Immediately before the cessation of LBNP, the following hemodynamic responses were not significantly different between normothermic and SSC trials: increase in calf volume (normothermia $3.3 \pm 0.4\%$; SSC $3.2 \pm 0.4\%$), heart rate (normothermia 111.4 ± 8.0 beats/min; SSC 112.5 ± 8.1 beats/min), stroke volume (normothermia 24.3 ± 3.3 ml; SSC 25.9 ± 2.9 ml), cardiac output (normothermia 2.6 ± 0.3 l/min; SSC 2.7 ± 0.2 l/min), and cerebral blood flow velocity (normothermia 41.9 ± 2.5 cm/s; SSC 38.0 ± 3.0 cm/s).

Before LBNP and SSC, norepinephrine concentrations were similar between trials, while SSC significantly increased plasma norepinephrine concentrations (Fig. 3). Norepinephrine concentrations increased during LBNP for both trials; however, the increase in this variable was significantly greater during the SSC trial relative to the normothermic trial (Fig. 3). This increase in norepinephrine concentration during the combination of SSC and LBNP was not due solely to an increase in baseline norepinephrine concentrations associated with SSC.

DISCUSSION

Previous reports suggested that SSC improves orthostatic tolerance in normothermic subjects; however, the present study is the first to confirm this hypothesis. Indeed, we observed a 34% improvement in the cumulative stress index with SSC. Although the mechanisms resulting in improved orthostatic tolerance with SSC are not readily apparent, this response is likely related to the elevation in blood pressure at most levels of LBNP. In addition, improvements in orthostatic tolerance may be related to pronounced elevations in plasma norepinephrine concentrations with SSC, although total peripheral resistance was not significantly different between normothermic and SSC trials.

The onset of presyncopal symptoms during an orthostatic challenge is an indicator of inadequate cerebral perfusion in response to orthostatically induced reductions in blood pressure (6, 18). Previously we showed that SSC of heat-stressed subjects attenuates the decrease in cerebral blood flow velocity and improves orthostatic tolerance (16). However, there are two important distinctions between the present and our prior study. First, the prior study assessed orthostatic responses to a

10-min upright tilt test in heat-stressed subjects with and without SSC immediately before tilting. Thus internal temperature was significantly elevated during both tilt tests in the prior study. This is in contrast to the present study in which subjects were not heat stressed. Second, in the prior study the objective was not to assess orthostatic tolerance and no subject experienced presyncopal symptoms during the SSC tilt test. This is in contrast to the present study in which presyncopal symptoms were observed in each subject during both normothermic and SSC challenges.

Yamazaki et al. (17) recently reported that the magnitude of increase in calf area during head-up tilt was reduced during cooling compared with responses during the normothermic tilt test. They suggested that the volume of blood shifted to the legs during orthostatic stress was minimized by SSC. We identified similar findings in the present study, as leg circumference was significantly smaller during LBNP with SSC (Fig. 1). However, it is interesting to note that despite smaller calf volumes during the SSC trial we did not observe differences in thoracic impedance between trials as would be expected if more blood pooled in the legs during the normothermic trial. We are unsure whether these apparently contradictory findings are related to differences in sensitivity between the thoracic impedance device, as an index of changes in blood volume, and plethysmographic measures of changes in calf volume, or whether other mechanisms are in place that preserve central blood volume during LBNP despite differences in the amount of blood pooled in the legs. Nevertheless, in the present protocol, stroke volume was significantly greater during SSC at -50 mmHg, while there was a strong tendency for stroke volume to be elevated at -30 mmHg LBNP ($P = 0.067$) as well as cardiac output to be elevated at -30 mmHg ($P = 0.058$) and -50 mmHg ($P = 0.065$) LBNP during the SSC trial. A possible mechanism for these elevated responses during LBNP with SSC is less pooling of blood in the legs and sustained central blood volume during the orthostatic challenge despite the absence of differences in thoracic impedance between trials.

Whatever the thermal condition, graded LBNP induced a progressive decrease in arterial blood pressure, which was associated with a decrease in cerebral blood flow velocity until the occurrence of presyncopal symptoms (Fig. 1). The decrease in arterial blood pressure with LBNP was similar between normothermia and SSC trials. However, since arterial blood pressure was elevated before LBNP as a result of SSC, for -30 through -50 mmHg LBNP stages, blood pressure was significantly elevated during the SSC orthostatic challenge. After -50 mmHg LBNP, no differences in blood pressure were identified between trials. However these data, as well as corresponding brain blood flow velocity data, must be viewed with caution since at these higher levels of orthostatic stress subject numbers are reduced. It is also important to emphasize that in Fig. 1 at the higher levels of LBNP, for comparative purposes, data during the SSC trial are excluded if the subject did not reach the specified level of LBNP in the normothermic trial. For example, at -70 mmHg LBNP, data were obtained from only four subjects during the normothermic trial, whereas during the SSC trial data were obtained from seven subjects (see Table 1). However, in Fig. 1, during -70 mmHg LBNP, data are depicted only from the four subjects from whom data were obtained during both normothermic and SSC trials.

It is not clear from the present data whether the elevation in arterial blood pressure during the SSC trial was due to elevated cardiac output and/or elevated vascular resistance. The present data do not show a difference in total peripheral resistance with SSC compared with normothermia, which is similar to findings reported by Raven et al. (10, 11). Even though cardiac output tended to be elevated during each level of LBNP with SSC, there were no statistically significant differences in this variable between thermal conditions as well. It is unclear whether this slight, but nonsignificant, increase in cardiac output was the primary mechanism resulting in elevated arterial blood pressures with SSC and associated elevated blood pressure during most LBNP levels. It is likely that higher levels of SSC (i.e., lower water temperature) would have caused greater increases in arterial blood pressure and perhaps elevated cardiac output and vascular resistance during LBNP, as well as greater improvements in orthostatic tolerance. However, our experience is that lower water temperatures are quite uncomfortable to the subject and in most cases lead to shivering within 15–30 min.

LBNP unloads baroreceptors, resulting in the activation of the sympathetic nervous system, leading to increases in peripheral vascular resistance (8, 14). Consistent with this chain of events, plasma norepinephrine concentrations progressively increased with LBNP in both thermal conditions. However, the elevation in plasma norepinephrine concentrations was substantially greater during LBNP with SSC. At -40 mmHg LBNP, and at the onset of presyncopal symptoms, plasma norepinephrine concentrations were approximately twofold greater during the SSC trial relative to the normothermic trial (Fig. 3). These elevated plasma norepinephrine concentrations were not simply due to elevated concentrations associated with SSC before LBNP. In fact, there was a synergistic effect of combined SSC and LBNP such that for the same orthostatic stress the increase (i.e., delta) in plasma norepinephrine concentration was significantly greater for the SSC trial. It is unlikely that the elevated plasma norepinephrine concentration during LBNP with SSC was a result of greater baroreceptor unloading during the LBNP trial given the elevated blood pressures during the SSC trial. Sympathetic nerve activity to muscle was not measured in this study, and therefore we do not know if the elevated plasma norepinephrine concentrations were related to increased sympathetic activation and/or other mechanisms such as reduced norepinephrine reuptake. Thus mechanisms leading to augmented increases in plasma norepinephrine concentration during LBNP with SSC could not be identified in this study.

Before LBNP, SSC caused significant increases in cerebral blood flow velocity. This response was primarily due to elevated blood pressures as calculated cerebral vascular resistance was not different relative to the period before cooling. Given this finding, we hypothesized that cerebral blood flow velocity would remain elevated during LBNP with SSC. Such a response was observed only at -40 and -50 mmHg LBNP. However, except for the period just before the onset of presyncopal symptoms, cerebral blood flow velocity was higher during SSC for most subjects despite the absence of statistical significance at LBNP levels greater than -50 mmHg. For the first three levels of LBNP, cerebral vascular conductance was unchanged during the SSC LBNP. This is in contrast to the

normothermic trial wherein cerebral vascular conductance was significantly reduced at -40 and -50 mmHg LBNP. The mechanism responsible by which SSC preserves cerebral vascular conductance during LBNP is unclear. One possibility for this observation may be related to a tendency ($P = 0.06$) for end-tidal CO_2 to be lower during -40 and -50 mmHg LBNP during the normothermic trial compared with the SSC trial. Together, these observations suggest that for most subjects the effects of SSC on minimizing the decrease in cerebral blood flow velocity and cerebral vascular conductance may have contributed to an improvement in orthostatic tolerance.

Limitations to the interpretation of the data. Transcranial Doppler was used to measure flow velocity from the middle cerebral artery to estimate changes in cerebral blood flow. Changes in velocity are proportional to changes in flow if the diameter of the middle cerebral artery remains unchanged by LBNP. Consistent with this statement, previous studies report that a variety of stimuli, including LBNP, did not significantly change the diameter of the middle cerebral artery (5, 13). Thus the assumption of the present protocol is that changes in cerebral blood flow velocity reflect changes in cerebral blood flow.

In conclusion, findings from the present study clearly show that SSC is effective in improving orthostatic tolerance in normothermic subjects during LBNP. Although mechanism(s) responsible for this improvement are unclear, this response is likely related to reduced pooling of blood in the lower extremities, increased blood pressure, and perhaps greater sympathetic activation during LBNP with SSC. Regardless of the mechanism, these data demonstrate that SSC may be an effective countermeasure against reduced orthostatic tolerance known to occur after prolonged bed rest and space flight (2, 18).

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REFERENCES

1. **Blomqvist CG and Stone HL.** Cardiovascular adjustments to gravitational stress. In: *Handbook of Physiology. The Cardiovascular System. Peripheral Circulation and Organ Blood Flow.* Bethesda, MD: Am. Physiol. Soc, 1983, sect. 2, vol. III, pt. 2, chapt. 28, p. 1025–1063.
2. **Buckey JC Jr., Lane LD, Levine BD, Watenpaugh DE, Wright SJ, Moore WE, Gaffney FA, and Blomqvist CG.** Orthostatic intolerance after spaceflight. *J Appl Physiol* 81: 7–18, 1996.
3. **Fritsch-Yelle JM, Whitson PA, Bondar RL, and Brown TE.** Subnormal norepinephrine release relates to presyncope in astronauts after space flight. *J Appl Physiol* 81: 2134–2141, 1996.
4. **Harms MP, Collier WN, Wieling W, Lenders JW, Secher NH, and van Lieshout JJ.** Orthostatic tolerance, cerebral oxygenation, and blood velocity in humans with sympathetic failure. *Stroke* 31: 1608–1614, 2000.
5. **Huber P and Handa J.** Effect of contrast material, hypercapnia, hyperventilation, hypertonic glucose and papaverine on the diameter of the cerebral arteries. *Invest Radiol* 2: 17–32, 1967.
6. **Levine BD, Giller CA, Lane LD, Buckey JC, and Blomqvist CG.** Cerebral versus systemic hemodynamics during graded orthostatic stress in humans. *Circulation* 90: 298–306, 1994.

7. **Lind AR, Leithead CS, and McNicol GW.** Cardiovascular changes during syncope induced by tilting men in the heat. *J Appl Physiol* 25: 268–276, 1968.
8. **Mancia G and Mark AL.** Cardiopulmonary baroreflexes in humans. In: *Handbook of Physiology. The Cardiovascular System. Peripheral Circulation and Organ Blood Flow.* Bethesda, MD: Am. Physiol. Soc, 1983, sect. 2, vol III, pt. 2, chapt. 21, p. 795–813.
9. **Minson CT, Halliwill JR, Young TM, and Joyner MJ.** Sympathetic activity and baroreflex sensitivity in young women taking oral contraceptives. *Circulation* 102: 1473–1476, 2000.
10. **Raven PB, Pape G, Taylor WF, Gaffney FA, and Blomqvist CG.** Hemodynamic changes during whole body surface cooling and lower body negative pressure. *Aviat Space Environ Med* 52: 387–391, 1981.
11. **Raven PB, Saito M, Gaffney FA, Schutte J, and Blomqvist G.** Interactions between surface cooling and LBNP-induced central hypovolemia. *Aviat Space Environ Med* 51: 497–503, 1980.
12. **Rowell LB.** *Human Cardiovascular Control.* Oxford, UK: Oxford Univ. Press, 1993.
13. **Serrador JM, Picot PA, Rutt BK, Shoemaker JK, and Bondar RL.** MRI measures of middle cerebral artery diameter in conscious humans during simulated orthostasis. *Stroke* 31: 1672–1678, 2000.
14. **Sundlof G and Wallin BG.** Effect of lower body negative pressure on human muscle sympathetic nerve activity. *J Physiol* 278: 525–532, 1978.
15. **Triebwasser JH, Johnson RL, Burpo RP, Cambell JC, Reardon WC, and Blomqvist CG.** Noninvasive determination of cardiac output by a modified acetylene rebreathing procedure utilizing mass spectrometer measurements. *Aviat Space Environ Med* 48: 203–209, 1977.
16. **Wilson TE, Cui J, Zhang R, Witkowski S, and Crandall CG.** Skin cooling maintains cerebral blood flow velocity and orthostatic tolerance during tilting in heated humans. *J Appl Physiol* 93: 85–91, 2002.
17. **Yamazaki F, Okumo C, Nagamatsu S, and Sone R.** Effects of whole-body and local thermal stress on hydrostatic volume in the changes in the human calf. *Eur J Appl Physiol* 88: 61–66, 2002.
18. **Zhang R, Zuckerman J, Pawelczyk JA, and Levine BD.** Effects of head-down-tilt bed rest on cerebral hemodynamics during orthostatic stress. *J Appl Physiol* 83: 2139–2145, 1997.

