

Effect of skin surface cooling on central venous pressure during orthostatic challenge

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Cui, Jian, Sylvain Durand, Benjamin D. Levine, and Craig G. Crandall. Effect of skin surface cooling on central venous pressure during orthostatic challenge. *Am J Physiol Heart Circ Physiol* 289: H2429–H2433, 2005. First published July 15, 2005; doi:10.1152/ajpheart.00383.2005.—Orthostatic stress leads to a reduction in central venous pressure (CVP), which is an index of cardiac preload. Skin surface cooling has been shown to improve orthostatic tolerance, although the mechanism resulting in this outcome is unclear. One possible mechanism may be that skin surface cooling attenuates the drop in CVP during an orthostatic challenge, thereby preserving cardiac filling. To test this hypothesis, CVP, arterial blood pressure, heart rate, and skin blood flow, as well as skin and sublingual temperatures, were recorded in nine healthy subjects during lower body negative pressure (LBNP) in both normothermic and skin surface cooling conditions. Cardiac output was also measured via acetylene rebreathing. Progressive LBNP was applied at -10 , -15 , -20 , and -40 mmHg at 5 min/stage. Before LBNP, skin surface cooling lowered mean skin temperature, increased CVP, and increased mean arterial blood pressure (all $P < 0.001$) but did not change mean heart rate ($P = 0.38$). Compared with normothermic conditions, arterial blood pressure remained elevated throughout progressive LBNP. Although progressive LBNP decreased CVP under both thermal conditions, during cooling CVP at each stage of LBNP was significantly greater relative to normothermia. Moreover, at higher levels of LBNP with skin cooling, stroke volume was significantly greater relative to normothermic conditions. These data indicate that skin surface cooling induced an upward shift in CVP throughout LBNP, which may be a key factor for preserving preload, stroke volume, and blood pressure and improving orthostatic tolerance.

thermoregulation; cardiovascular regulation; orthostatic tolerance; lower body negative pressure

ORTHOSTATIC INTOLERANCE is a common occurrence after spaceflight (2, 6), after long-term bed rest (5), and in over 500,000 Americans who suffer from idiopathic orthostatic intolerance (13, 14). We recently showed (4, 18) that skin surface cooling improves orthostatic tolerance in normothermic and heat-stressed individuals. Although increases in orthostatic tolerance with skin surface cooling are clearly a result of attenuated decreases in arterial blood pressure and cerebral blood flow velocity (4, 10, 11, 18), the mechanism(s) by which skin cooling causes these responses remains unclear. One possible mechanism is that skin surface cooling increases central blood volume and central venous pressure (CVP) and in turn elevates stroke volume, arterial blood pressure, and cerebral perfusion during orthostasis.

Raven et al. (10, 11) showed that skin surface cooling attenuates the reduction in stroke volume during progressive

lower body negative pressure (LBNP). They proposed that elevated cardiac preload was the primary mechanism for heightened stroke volumes with cooling (10, 11). However, indicators of cardiac preload (e.g., CVP) were not measured in those studies, and changes in CVP and stroke volume are not consistently well correlated (8, 17). Therefore, it is necessary to evaluate the combined effects of skin surface cooling and orthostatic stress on CVP. Such information will provide insight into mechanisms of elevated stroke volume (11) and blood pressure (4, 11, 12) and orthostatic tolerance (4) during cold stress. Therefore, we tested the hypothesis that skin surface cooling attenuates the reduction in CVP during an orthostatic challenge.

METHODS

Subjects. Nine subjects (6 men, 3 women) participated in this study. The average age was 31 ± 3 (mean \pm SE) yr, and all were of normal height (174 ± 4 cm) and weight (75 ± 5 kg). All subjects were normotensive (supine blood pressures $<140/90$ mmHg), were not taking medications, and did not have cardiovascular diseases. Subjects refrained from caffeine, alcohol, and exercise 24 h before the study. This study was approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas. A written informed consent was obtained from each subject before participation in this study.

Measurements. Each subject was instrumented for the measurement of sublingual temperature (T_{sl}) with a thermistor placed in the sublingual sulcus. Mean skin temperature (T_{sk}) was obtained from the electrical average of six thermocouples attached to the skin (15). Each subject was dressed in a tube-lined suit that permitted control of T_{sk} by changing the temperature of the water perfusing the suit. Under the suit male subjects wore only shorts, whereas female subjects wore shorts and a swimsuit top or sports bra. Skin blood flow was measured from dorsal forearm skin (not covered by the suit) via laser-Doppler flowmetry using integrating flow probes (Perimed, North Royalton, OH). Subjects were placed in a Plexiglas box that was sealed at the iliac crests. Suction was provided by a vacuum pump controlled with a variable transformer. The pressure difference between the LBNP chamber and atmosphere was measured with a digital manometer.

CVP was measured from a catheter inserted in the subjects' basilic vein, with the tip of the catheter advanced to the superior vena cava. The position of the catheter was confirmed by 1) distance inserted into the body, 2) appropriate pressure waveforms, and 3) rapid rise and fall in CVP by Valsalva and Mueller maneuvers, respectively. The CVP catheter was connected to a calibrated pressure transducer. Zero reference for this transducer was set at the subjects' midaxillary line. Heart rate was monitored from the electrocardiogram interfaced with a cardiometer (1,000-Hz sampling rate; CWE, Ardmore, PA). Arterial blood pressure was measured at the fourth minute of each

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Table 1. Thermal and hemodynamic responses to skin surface cooling before LBNP

| | Normothermia | Skin Surface Cooling | <i>P</i> |
|--------------------------------|--------------|----------------------|----------|
| T_{sk} , °C | 34.9±0.1 | 31.7±0.3 | ≤0.001 |
| T_{sl} , °C | 36.7±0.1 | 36.7±0.1 | 0.86 |
| SkBF, arbitrary units | 23±7 | 14±5 | 0.007 |
| SBP, mmHg | 111±3 | 119±4 | ≤0.001 |
| DBP, mmHg | 71±2 | 79±3 | 0.005 |
| MAP, mmHg | 84±2 | 92±3 | ≤0.001 |
| HR, beats/min | 61±3 | 59±3 | 0.34 |
| CVP, mmHg | 7.5±0.6 | 9.3±0.7 | ≤0.001 |
| Cardiac output, l/min | 6.05±0.36 | 5.94±0.50 | 0.53 |
| Stroke volume, ml/beat | 90±6 | 89±6 | 0.81 |
| TPR, mmHg·l ⁻¹ ·min | 12.7±0.9 | 14.8±1.5 | 0.008 |

Values are means ± SE before lower body negative pressure (LBNP). Mean arterial blood pressure (MAP) was calculated as two-thirds diastolic arterial blood pressure (DBP) + one-third systolic arterial blood pressure (SBP). T_{sk} , mean skin temperature; T_{sl} , sublingual temperature; SkBF, forearm skin blood flow; HR, heart rate; CVP, central venous pressure; TPR, total peripheral resistance.

LBNP stage by auscultation of the brachial artery (SunTech Medical Instruments, Raleigh, NC); this value is the reported blood pressure for each LBNP stage. Cardiac output was measured by a modified rebreathing technique (16), using acetylene as the soluble gas and helium as the insoluble gas, as previously described (9, 21). Adequate mixing of the rebreathing gas in the lung was confirmed from the helium measurement. Rebreath cardiac outputs were obtained at baseline and the last minute (5th min) of each stage of LBNP. Heart rate during the rebreathing procedure was used to calculate stroke volume, whereas heart rates reported in Table 1 and Fig. 2 are from nonbreathing periods. Arterial blood pressure was again measured during the cardiac output measurement. Total peripheral resistance (TPR) was calculated as (mean arterial blood pressure - CVP)·cardiac output⁻¹. The possible occurrence of shivering during skin surface cooling was assessed via electromyography with electrodes placed on the upper part of the back (trapezius) and on one thigh (quadriceps).

Protocols. All studies were conducted with the subject in the supine position in a room with an ambient temperature of 24–26°C; 34°C water was perfused through the suit during the normothermic trial, whereas 16°C water was perfused through the suit during the ensuing skin surface cooling trial. A pilot study identified that a water temperature of 16°C, with flow rates of 1.5 l/min, was sufficient to cause the greatest increases in mean arterial blood pressure (~10 mmHg) without causing shivering. Perfusing water below this temperature caused shivering in some subjects, whereas perfusing water above this temperature did not raise blood pressure in some subjects. Therefore, we used this cooling paradigm in the present study. Under

both normothermic and skin surface cooling conditions, progressive LBNP at -10, -15, -20, and -40 mmHg was applied at 5 min/stage.

Under normothermic conditions, pre-LBNP cardiac outputs were measured three times, separated by a minimum of 5 min (9, 21). The mean value of these measurements was used as the baseline cardiac output. The LBNP protocol was then administered, with a single cardiac output being measured for each level of LBNP. A minimum of 30 min elapsed between the end of the normothermic LBNP protocol and the onset of skin surface cooling. For the cooling protocol, at ~15 min from onset of skin surface cooling baseline cold stress variables were measured, followed by a cardiac output measurement. Thereafter, progressive LBNP was applied with the protocol outlined above. All subjects completed both LBNP protocols without presyncopal symptoms. The order of LBNP trials was not randomized, given concerns of the effects of a prior cold stress on a subsequent normothermic LBNP trial.

Data analysis. Data were sampled at 200 Hz with a commercial data acquisition system (Biopac System, Santa Barbara, CA). During the fourth minute of each LBNP stage, mean CVP, heart rate, and arterial blood pressure were reported and analyzed for the specified stage. Cardiac output and associated calculated variables are from the fifth minute of each LBNP stage.

Statistical analyses were performed with commercially available software (SigmaStat 3.0; SPSS). Baseline values (pre-LBNP) from the control and skin surface cooling trials were compared with paired *t*-tests. Differences in LBNP-induced responses between normothermic and skin surface cooling trials were evaluated by post hoc analysis after repeated-measures two-way ANOVA. Main factors of that ANOVA were thermal condition and LBNP stage. All values are reported as means ± SE. *P* values of <0.05 were considered statistically significant.

RESULTS

The effects of skin surface cooling on thermal and hemodynamic variables are reported in Table 1. Skin surface cooling decreased T_{sk} by ~3°C relative to normothermia. No occurrence of shivering was observed in the electromyogram signal or indicated by any subject. Before LBNP, skin surface cooling decreased skin blood flow ~38% from the normothermic baseline and increased mean arterial blood pressure ~8 mmHg, but did not change heart rate. Cooling resulted in significant increases in CVP. Cardiac output and stroke volume were not significantly different from normothermia, but TPR was significantly elevated by skin surface cooling.

During progressive LBNP neither T_{sl} nor skin blood flow was altered regardless of the thermal condition, whereas T_{sk} decreased throughout LBNP during the skin surface cooling trial (Table 2). LBNP of -20 to -40 mmHg decreased mean

Table 2. Responses during progressive LBNP under both thermal conditions

| | LBNP, mmHg | | | | |
|-----------------------|------------|------------|------------|------------|------------|
| | Baseline | -10 | -15 | -20 | -40 |
| Normothermic | | | | | |
| T_{sk} , °C | 34.9±0.1 | 34.8±0.1 | 34.7±0.1 | 34.7±0.1 | 34.6±0.1 |
| T_{sl} , °C | 36.7±0.1 | 36.7±0.1 | 36.6±0.1 | 36.6±0.1 | 36.6±0.1 |
| SkBF, arbitrary units | 23.2±7.1 | 22.3±6.1 | 22.2±6.2 | 24.1±7.4 | 20.7±5.8 |
| Cooling | | | | | |
| T_{sk} , °C | 31.7±0.3† | 31.1±0.3*† | 30.6±0.3*† | 30.4±0.3*† | 30.1±0.3*† |
| T_{sl} , °C | 36.7±0.1 | 36.7±0.1 | 36.5±0.1 | 36.6±0.1 | 36.6±0.1 |
| SkBF, arbitrary units | 14.5±5.1† | 14.1±4.6† | 15.2±4.7† | 14.9±4.3† | 15.0±3.9† |

Values are means ± SE. *Significantly different from baseline (*P* < 0.05); †significantly different from normothermic condition (*P* < 0.05).

arterial blood pressure compared with baseline (pre-LBNP) under both conditions. Importantly, arterial blood pressure at each stage of LBNP during skin surface cooling was significantly greater relative to normothermia. Significant increases in heart rate during LBNP occurred at -20 and -40 mmHg LBNP in normothermia and at -40 mmHg LBNP during skin surface cooling (Fig. 1). Heart rates at -20 and -40 mmHg LBNP during skin surface cooling were significantly lower relative to normothermia (Fig. 2).

Progressive LBNP from -10 to -40 mmHg significantly decreased CVP under both thermal conditions. Importantly, CVP at each stage of LBNP under skin surface cooling conditions was significantly greater than under normothermic conditions (Fig. 3). These results indicate that skin surface cooling induced an upward shift in CVP during LBNP.

Progressive LBNP caused significant decreases in cardiac output and stroke volume in both thermal conditions (Figs. 1 and 2). However, stroke volume at -20 and -40 mmHg LBNP during skin surface cooling was significantly greater

relative to normothermia (Fig. 2). Although baseline TPR was elevated by cooling, thereafter there was no significant difference in TPR during LBNP between the two thermal conditions (Fig. 1).

DISCUSSION

The unique finding of the present study is that skin surface cooling increases CVP and this upward shift remains present during an orthostatic challenge. We speculate that elevated CVP throughout LBNP may be a factor contributing to preserving preload, stroke volume, and blood pressure and improving orthostatic tolerance.

Whole body skin surface cooling induced $\sim 38\%$ decrease in skin blood flow (see Table 1). This reduction in skin blood flow, and corresponding reduction in skin blood volume, will contribute to the observed increase in CVP and presumably central blood volume. We (4) and others (11) have shown that the increase in leg circumference during LBNP is significantly smaller with skin surface cooling compared with normothermic conditions. Similar responses have also been reported during head-up tilt with cooling (19). These data suggest that central blood volume under cooling conditions may remain relatively higher during orthostatic stress.

Adequate arterial blood pressure is the key component in the maintenance of cerebral blood flow and thus orthostatic tolerance. Before LBNP, skin surface cooling increased arterial blood pressure by ~ 8 mmHg, and blood pressure remained significantly elevated throughout LBNP, which is consistent with prior findings (4, 10, 11, 20). The mechanism(s) associated with these elevations in arterial blood pressure is not certain but can be speculated upon from the present data. Arterial blood pressure is the product of cardiac output and vascular resistance. Before LBNP, skin surface cooling increased TPR without significantly changing cardiac output, a finding consistent with others (4, 11). Stroke volume did not change with skin surface cooling before LBNP. This may seem unexpected given the elevation in filling pressure with cooling. However, an increase in filling pressure occurred in combination with an elevation in systolic blood pressure, such that increased afterload associated with cooling may have opposed Frank-Starling mechanism-induced increases in stroke volume, the outcome of which would be no change in stroke volume due to cooling. An additional hypothesis leading to this observation may be that the individual is functioning on the plateau portion of the Starling curve such that further increases in filling pressure do not increase stroke volume. Because heart rate was unaffected by cooling, cardiac output was not elevated. It is interesting to note that maintained heart rate, coupled with elevated blood pressure, suggests that cardiac baroreflexes were reset as a result of cooling. Therefore, before LBNP, the increases in TPR and perhaps baroreflex resetting are likely the main factors responsible for the elevation in arterial blood pressure during cooling.

Regardless of thermal condition, LBNP reduced CVP, arterial blood pressure, stroke volume, and cardiac output while increasing heart rate and TPR (1, 3, 7). However, skin surface cooling caused an upward offset of CVP and arterial blood pressure that remained elevated, relative to the normothermic trial, throughout LBNP. The decrease in cardiac output by LBNP was attenuated with skin surface cooling in some, but

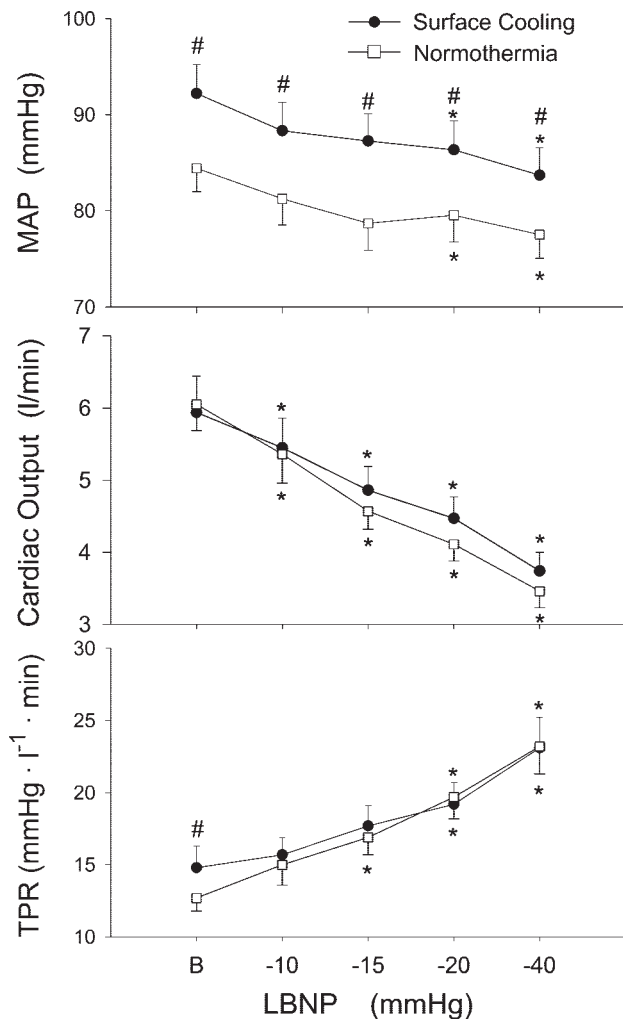
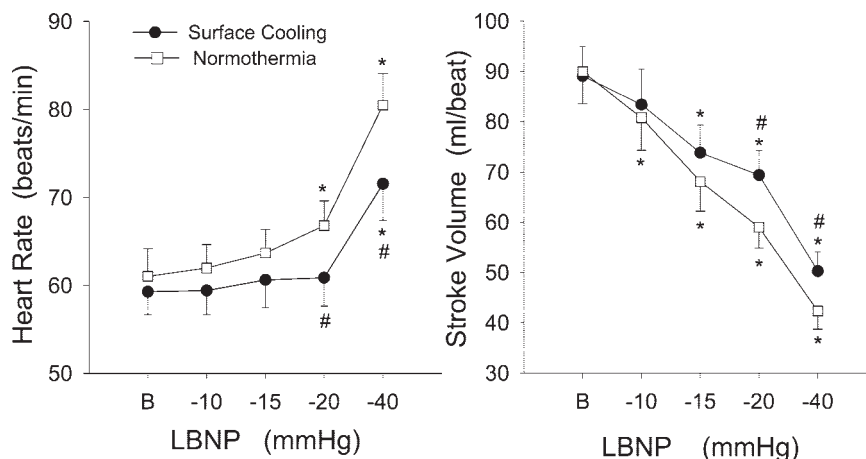


Fig. 1. Effect of skin surface cooling on mean arterial blood pressure (MAP), cardiac output, and total peripheral resistance (TPR) in response to progressive lower body negative pressure (LBNP). MAP at each stage of LBNP during skin surface cooling condition was significantly greater relative to normothermia. * $P < 0.05$ compared with baseline (B) before LBNP for the specified thermal condition; # $P < 0.05$ compared with normothermia.

Fig. 2. Stroke volume and heart rate in response to progressive LBNP under normothermic and skin surface cooling conditions. * $P < 0.05$ compared with baseline before LBNP for the specified thermal condition; # $P < 0.05$ compared with normothermia.



not all, subjects. At higher levels of LBNP (e.g., -20 and -40 mmHg LBNP), the reduction in stroke volume was significantly attenuated by cooling relative to normothermic conditions. This preservation of cardiac filling led to an attenuation of LBNP-induced tachycardia during the cooling LBNP challenge, probably due to a preservation of blood pressure relative to normothermia (see Figs. 1 and 2). In contrast to the relative effect on stroke volume, the higher baseline TPR induced by skin surface cooling was overwhelmed by the large rise in TPR during LBNP. Thus at each level of LBNP there was no significant difference in TPR between thermal conditions, which is consistent with previous observations (4, 10, 11). In summary, the present data indicated that the effects of skin surface cooling on cardiac output and vascular resistance vary as a function of LBNP as well as varying among individuals. Thus in some subjects cooling had a relatively stronger effect on increasing TPR, whereas cardiac output was relatively

lower. This response was more common before LBNP and during the initial stages of LBNP. In other subjects, cooling had a greater effect on stroke volume and cardiac output, whereas the increase in TPR was less.

A key finding of the present study is that CVP was elevated by skin surface cooling and this upward offset persisted throughout LBNP. Elevated CVP, coupled with relatively higher stroke volumes and attenuated elevations in heart rates at the higher levels of LBNP, will provide a greater reserve by which CVP and stroke volume could be further reduced, and heart rate further elevated, during an orthostatic stress before the onset of syncopal symptoms.

Study limitations. The duration of skin cooling was ~ 35 min (15 min before LBNP and 20 min during LBNP). The objective of this protocol was not to clamp T_{sk} to a fixed level while assessing responses during LBNP, because in doing so the subject would have been exposed to an inordinately prolonged period of cooling if the requirement was for T_{sk} to reach a steady-state level before LBNP. Such a protocol was not performed, given the concern that at the selected water temperature this duration would likely have caused the subject to shiver. Thus from the onset of LBNP until the end of LBNP, T_{sk} further decreased $\sim 1.6^\circ\text{C}$ (see Table 2), and it is possible that hemodynamic responses to higher levels of LBNP may have been influenced by this lower T_{sk} relative to pre-LBNP and early LBNP responses. Nevertheless, persistent decreases in T_{sk} during LBNP will not alter the key finding of an attenuated reduction in CVP with skin surface cooling.

Prior studies reported that skin surface cooling reduces heart rate ~ 8 beats/min (10, 11). A change in heart rate to cooling was not observed in the present protocol. It is likely that the relatively short duration of cooling before LBNP in the present protocol (i.e., 15 min), relative to the cited protocols (i.e., 20–25 min), is the reason for this discrepancy.

To minimize the duration of cooling, cardiac output was measured only once before LBNP in this thermal condition. Ideally, at least three cardiac output measures would have been obtained. However, because a minimum of 5 min is required between subsequent cardiac outputs, this would result in ~ 30 min of cooling before the onset of LBNP. Thus we cannot exclude the possibility that variability in the cardiac output measure may have contributed to the absence of a significant difference in stroke volume and cardiac output between ther-

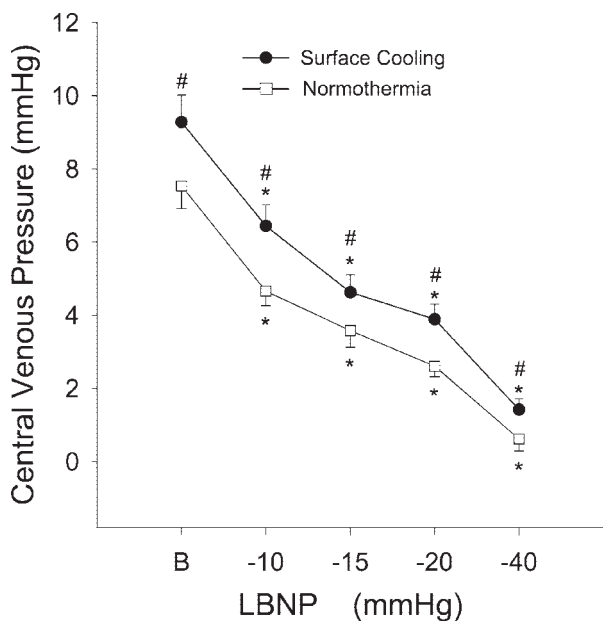


Fig. 3. Central venous pressure during progressive LBNP under normothermic and skin surface cooling conditions. Central venous pressure at each stage of LBNP during skin surface cooling condition was significantly greater relative to normothermia. * $P < 0.05$ compared with baseline before LBNP for the specified thermal condition; # $P < 0.05$ compared with normothermia.

mal conditions before LBNP. Nevertheless, Raven et al. (10, 11) also did not observe increases in cardiac output or stroke volume during their skin surface cooling protocols before LBNP.

In conclusion, this study is the first to identify that skin surface cooling increases baseline CVP and this upward offset in CVP persists during an orthostatic challenge in otherwise normothermic individuals. Elevated cardiac filling pressure may have an important role in attenuating decreases in stroke volume during an orthostatic stress. Thus elevated CVP with skin surface cooling may be a primary mechanism by which skin surface cooling improves orthostatic tolerance. Such a cooling protocol may be beneficial in protecting against orthostatic intolerance after spaceflight, after prolonged bed rest exposure, and in individuals with idiopathic orthostatic intolerance.

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