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Baroreflex control of muscle sympathetic nerve activity during skin surface cooling

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Cui J, Durand S, Crandall CG. Baroreflex control of muscle sympathetic nerve activity during skin surface cooling. *J Appl Physiol* 103: 1284–1289, 2007. First published August 2, 2007; doi:10.1152/jappphysiol.00115.2007.—Skin surface cooling improves orthostatic tolerance through a yet to be identified mechanism. One possibility is that skin surface cooling increases the gain of baroreflex control of efferent responses contributing to the maintenance of blood pressure. To test this hypothesis, muscle sympathetic nerve activity (MSNA), arterial blood pressure, and heart rate were recorded in nine healthy subjects during both normothermic and skin surface cooling conditions, while baroreflex control of MSNA and heart rate were assessed during rapid pharmacologically induced changes in arterial blood pressure. Skin surface cooling decreased mean skin temperature (34.9 ± 0.2 to $29.8 \pm 0.6^\circ\text{C}$; $P < 0.001$) and increased mean arterial blood pressure (85 ± 2 to 93 ± 3 mmHg; $P < 0.001$) without changing MSNA ($P = 0.47$) or heart rate ($P = 0.21$). The slope of the relationship between MSNA and diastolic blood pressure during skin surface cooling (-3.54 ± 0.29 units $\cdot\text{beat}^{-1}\cdot\text{mmHg}^{-1}$) was not significantly different from normothermic conditions (-2.94 ± 0.21 units $\cdot\text{beat}^{-1}\cdot\text{mmHg}^{-1}$; $P = 0.19$). The slope depicting baroreflex control of heart rate was also not altered by skin surface cooling. However, skin surface cooling shifted the “operating point” of both baroreflex curves to high arterial blood pressures (i.e., rightward shift). Resetting baroreflex curves to higher pressure might contribute to the elevations in orthostatic tolerance associated with skin surface cooling.

autonomic nervous system; baroreflex gain; thermoregulation; blood pressure regulation; baroreceptors

TOLERANCE TO ORTHOSTATIC STRESS is greatly influenced by the thermal condition of the individual. For example, humans become more susceptible to fainting during orthostatic stress or gravitation acceleration when combined with heat stress (1, 6, 7, 17, 30), whereas skin surface cooling improves orthostatic tolerance (10). Consistent with improvements in orthostatic tolerance, our laboratory have shown that skin surface cooling elevates arterial blood pressure and cerebral blood velocity (10, 30). Together these findings suggest that skin surface cooling may be a practical method to improve orthostatic tolerance during conditions in which orthostatic tolerance is known to be reduced, such as prolonged bed rest or extended duration spaceflight. However, the responsible mechanism(s) for the elevation of orthostatic tolerance associated with skin surface cooling remains unclear.

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To address this question, our laboratory previously assessed the effects of skin surface cooling on central venous pressure and found that cooling significantly increased this index of cardiac filling pressure (4), although interestingly, skin surface cooling does not consistently increase cardiac output (10, 21). In addition to that observation, cold stress has been shown to increase sympathetic activity to skin (2) and muscle (12), which could increase vascular resistance and thus blood pressure.

Increased activity from cutaneous thermoreceptors is transmitted to the hypothalamus (24), and electrical stimulation of this region can modify the baroreceptor reflex (13, 22). Given these observations, another potential mechanism by which skin surface cooling could improve orthostatic tolerance is if this perturbation increases baroreflex regulation of blood pressure. Consistent with this hypothesis, Yamazaki et al. (31, 32) reported that skin surface cooling increased the gain of baroreflex control of heart rate during spontaneous changes in blood pressure that occur with respiration. Neural control of vascular resistance is also a vital component of blood pressure regulation, and the effects of skin surface cooling on baroreflex control of sympathetic nerve activity remain unknown.

Therefore, the purpose of this project was to test the hypothesis that skin surface cooling increases baroreflex control of muscle sympathetic nerve activity (MSNA) during pharmacologically induced changes in blood pressure. Moreover, given that prior work by Yamakazi et al. (31, 32) assessed baroreflex control of heart rate across relatively minor changes in blood pressure, a secondary purpose of this study was to test the hypothesis that skin surface cooling improves baroreflex control of heart rate during relatively larger changes in blood pressure.

METHODS

Subjects. Nine subjects (5 men, 4 women) participated in this study. The average age was 32 ± 3 (SE) yr, and all were of normal height (171 ± 5 cm) and weight (73 ± 6 kg). All subjects were normotensive (supine blood pressures $< 140/90$ mmHg), were not taking medications, and did not have cardiovascular disease. Subjects refrained from caffeine, alcohol, and heavy 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 from each subject was obtained before participation in this study.

Measurements. Each subject was instrumented for the measurement of sublingual temperature (T_{sl}) with a thermistor placed in the

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sublingual sulcus. Mean skin temperature (T_{sk}) was obtained from the electrical average of six thermocouples attached to the skin (27). 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, the male subjects wore only shorts while the 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) and chest skin (under the suit) via laser-Doppler flowmetry using integrating flow probes (Perimed, North Royalton, OH). Heart rate was monitored from the electrocardiogram interfaced with a cardiota-chometer (1,000-Hz sampling rate; CWE, Ardmore, PA). Blood pressure was recorded on a beat-by-beat basis from a finger (Finapres, Ohmeda, Louisville, CO). Resting blood pressures obtained from the Finapres were verified by auscultation of the brachial artery (SunTech, Medical Instruments, Raleigh, NC). Respiratory frequency was monitored using piezoelectric pneumography. Possible occurrence of shivering during skin surface cooling, which was avoided, was assessed via surface electromyography with electrode placed on the upper part of the back (trapezius) and on one thigh (quadriceps).

Multifiber recordings of MSNA were obtained with a tungsten microelectrode inserted in the peroneal nerve. A reference electrode was placed subcutaneously 2–3 cm from the recording electrode. The signal was amplified, filtered with a bandwidth of 500–5,000 Hz, and integrated with a time constant of 0.1 s (Iowa Bioengineering, University of Iowa, Iowa City, IA). The recording electrode was adjusted until a site was found in which muscle sympathetic bursts were clearly identified using previously established criteria (28). Mean voltage neurograms were displayed on a chart recorder. The nerve signal was also routed to an oscilloscope and a loudspeaker for monitoring throughout the study.

Protocols. Studies were conducted with the subject in the supine position in a room with an ambient temperature of $\sim 25^{\circ}\text{C}$. To assess baroreflex sensitivity, changes in arterial blood pressure were induced by bolus injections of sodium nitroprusside followed by phenylephrine HCl (11, 14) during both control and skin surface cooling conditions. These drugs were administered intravenously via a catheter placed in an antecubital vein. For the control trials, 34°C water was circulated through the suit. After a 6-min baseline period, 100 μg of sodium nitroprusside was administered, followed ~ 60 s later by 150 μg of phenylephrine HCl. These doses decreased arterial pressure 10–15 mmHg below baseline levels and then increased blood pressure 5–10 mmHg above baseline levels, respectively. Three of these challenges were performed separated by 15-min intervals. This duration was sufficient for arterial blood pressure, heart rate, and MSNA to return to predrug levels. Results from these three trials were averaged and are reported as the control trial (23).

After normothermic data collection, the tube-lined suit was perfused with 16°C water, which constitutes the skin surface cooling trial. In a pilot study, we identified this water temperature, using our perfusion system with flow rates of 1.5 l/min, was sufficient to cause stable increases in mean blood pressure of ~ 10 mmHg for ~ 40 min without causing shivering (unpublished observation). Perfusing water below this temperature caused shivering in some subjects, whereas perfusing water above this temperature did not raise blood pressure in some subjects. At ~ 10 min from onset of skin surface cooling, at which time skin temperature had decreased and blood pressure was elevated, 3 min of baseline data were obtained followed by bolus infusions of sodium nitroprusside and phenylephrine using the same time course and doses relative to the normothermic trial. After 15 min, while continuing to cool the skin, a second period of baseline data collection and subsequent pharmacological challenge were performed. Results from these two trials (including the respective baselines) were averaged and are reported as the skin surface trial.

Data analysis. Data were sampled at 200 Hz via a commercial data acquisition system (Biopac System, Santa Barbara, CA) and analyzed using LabView software (National Instruments, Austin, TX). MSNA bursts were first identified in real time by visual inspection of data

plotted on the chart recorder, coupled with the burst sound from the audio amplifier. These bursts were further evaluated via a computer software program that identified bursts based on fixed criteria, including an appropriate latency following the R wave of the electrocardiogram (5, 8, 9). Integrated MSNA in both thermal conditions was normalized by assigning a value of 100 to the mean amplitude of the largest 10% of the bursts during the 6-min normothermic baseline period (14, 26). Normalization of the MSNA signal was performed to reduce variability between subjects attributed to factors including needle placement and signal amplification. Total MSNA was identified from burst area of the integrated neurogram that was evaluated on a beat-by-beat basis. If no MSNA burst was detected for a particular cardiac cycle, a value of zero was assigned to that cardiac cycle. Beat-by-beat systolic and diastolic blood pressures were obtained from the arterial blood pressure waveform, and R-R interval was obtained from the electrocardiogram.

Mean baseline blood pressures and MSNA, for both thermal conditions, were classified as the “operating point” of the baroreflex curves in the respective thermal conditions. The sensitivity of baroreflex control of MSNA was identified from the linear relationship between MSNA and diastolic pressure during pharmacologically induced changes in blood pressure (5, 8, 14, 23). Diastolic pressure was used because MSNA correlates closely with diastolic pressure but not with systolic pressure (25). For the linear regression analysis, MSNA values were averaged over 3-mmHg diastolic blood pressure bins. Because MSNA was often completely suppressed when blood pressure was elevated by phenylephrine, the relationship between MSNA and blood pressure was nonlinear at higher blood pressures. Only the linear portion of the data was used to calculate the slope of relationship between MSNA and diastolic pressure. Baroreflex modulation of heart rate was identified from the relationship between beat-by-beat heart rate and systolic blood pressure during pharmacologically induced changes in blood pressure. Beat-by-beat heart rates were also pooled over 3-mmHg systolic blood pressure bins, followed by linear regression analysis of these data. In addition, the relationship between R wave-to-R wave interval (RRI) and beat-by-beat systolic blood pressure during pharmacologically induced changes in blood pressure was analyzed using the same methods.

Statistical analyses were performed using commercially available software (SigmaStat 3.0, SPSS). Baseline values between control and skin surface cooling trials were compared via paired *t*-tests. The effects of the skin surface cooling on baroreflex gains, calculated from the slope of the linear regression, were compared with the control trials via paired *t*-tests. All values are reported as means \pm SE. *P* values < 0.05 were considered statistically significant.

RESULTS

After 10 min of perfusing cold water through the suit, T_{sk} decreased by $\sim 5^{\circ}\text{C}$, whereas T_{si} did not change significantly. No evidence of shivering was observed or commented on by any subject. Skin surface cooling significantly decreased skin blood flow, increased mean arterial blood pressure, but did not change heart rate (Table 1). The average MSNA responses, expressed either in burst rate or total activity, did not change due to skin surface cooling (Table 1).

Bolus injection of nitroprusside and phenylephrine elicited a sequential fall and rise in blood pressure, respectively, that provoked reflex changes in heart rate and MSNA in both thermal conditions. A strong linear relationship between MSNA and diastolic blood pressure was seen for each subject (mean $r^2 = 0.80 \pm 0.02$ for normothermia, mean $r^2 = 0.81 \pm 0.02$ for the skin surface cooling). Figure 1 shows the relationship between MSNA and diastolic blood pressure for a subject during the modified Oxford procedures in normothermic and skin surface cooling conditions. The operating point of the

Table 1. Thermal and hemodynamic responses to skin surface cooling

	Normothermia	Skin Surface Cooling	P Value
\bar{T}_{sk} , °C	34.9±0.2	29.8±0.6*	≤0.001
T_{sk} , °C	36.6±0.1	36.7±0.1	0.20
SBP, mmHg	112±3	123±4*	≤0.001
DBP, beats/min	71±2	79±3*	0.005
MAP, beats/min	85±2	93±3*	≤0.001
HR, beats/min	63±3	60±3	0.21
MSNA, bursts/min	20.7±2.4	20.8±2.8	0.66
MSNA, bursts/100 heartbeats	34.0±4.4	34.1±4.4	0.99
Total MSNA, units/min	351±45	392±40	0.47
Forearm SkBF, units	18.6±3.7	13.2±2.6*	0.04
Chest SkBF, units	47.0±6.3	34.2±6.3*	≤0.001

Values are means ± SE of baseline values before nitroprusside and phenylephrine administration. Mean arterial blood pressure (MAP) was calculated as two-thirds diastolic blood pressure (DBP) plus one-third systolic blood pressure (SBP), which were measured by auscultation of the brachial artery. T_{sk} , sublingual temperature; \bar{T}_{sk} , mean skin temperature; HR, heart rate; SkBF, skin blood flow. *Significantly different from normothermia, $P < 0.05$.

baroreflex curve was shifted rightward by cooling as evidenced by a significant increase in blood pressure without a corresponding reduction in MSNA (also see Table 1). The change in the slope of the relationship between blood pressure and MSNA across thermal conditions varied among the subjects. With cooling, four subjects showed clear decreases in the slope of this relationship, two subjects show clear increases in the slope, whereas the remaining three subjects did not exhibit a clear change in the slope. These varied responses resulted in an average slope of the relationship between blood pressure and MSNA during skin surface cooling (-3.54 ± 0.29 units·beat⁻¹·mmHg⁻¹) that was not different from normothermia (-2.94 ± 0.21 units·beat⁻¹·mmHg⁻¹; $P = 0.19$; Fig. 2). These data indicate that as a group skin surface cooling does not alter baroreflex regulation of MSNA during pharmacologically induced changes in arterial blood pressure around the operating point.

Figure 3 shows a representative relationship between heart rate and systolic blood pressure for a subject during the modified Oxford procedures in normothermic and skin surface cooling conditions. The operating point of the relationship between the heart rate and systolic blood pressure was also shifted to the right, reflecting the higher blood pressures during skin surface cooling (also see Table 1). However, the mean slope of the relationship between heart rate and systolic blood pressure was similar (Fig. 2; $P = 0.57$) between the skin surface cooling (-0.63 ± 0.08 units·beat⁻¹·mmHg⁻¹) and control trials (-0.71 ± 0.08 units·beat⁻¹·mmHg⁻¹). Like that observed in the MSNA analysis, for the heart rate analysis individual responses varied to pharmacologically induced changes in blood pressure. Of the nine subjects, one showed clear decreases in the slope of the heart rate-systolic blood pressure relationship with skin surface cooling, four showed clear increases in this slope, whereas the remaining four subjects did not exhibit any change in the slope. The mean slope of the relationship between RRI and systolic blood pressure was also similar ($P = 0.86$) between the skin surface cooling (9.6 ± 1.0 ms/mmHg) and control trials (9.4 ± 0.7 ms/mmHg). These results suggest that as a group skin surface cooling does not alter the sensitivity of baroreflex regulation of heart rate but

shifts the baroreflex operating point to accommodate the elevation in blood pressures that occurs with the cooling paradigm.

DISCUSSION

Skin surface cooling improves orthostatic tolerance in heat stress (30) and normothermic individuals (10), but the precise mechanism(s) responsible remain elusive. Raven et al. (20, 21) reported that blood pressure and stroke volume were elevated during lower body negative pressure when individuals were cooled relative to normothermia. Consistent with this observation, we recently found that central venous pressure remains elevated during cooling throughout an orthostatic challenge relative to when the individuals were normothermic (4). Despite these observations, the effects of cooling on baroreceptor control of important neural responses associated with blood pressure regulation (e.g., MSNA) remained unknown. The main finding of present study is that the mean slopes of the relationship between MSNA and diastolic blood pressure and between heart rate and systolic blood pressure, within the operating range affected by the pharmacological perturbation, were not altered by skin surface cooling. However, skin cooling shifted the operating point to the right (i.e., higher blood pressures), evidenced by a significant increase in blood pressure without a corresponding reduction in MSNA or heart rate.

In contrast to the present results, Fagius et al. (12) demonstrated that mean MSNA was significantly elevated when subjects were exposed to low ambient temperatures. Moreover, they reported that the increase in blood pressure was positively correlated with the increase in MSNA during this exposure (12), thereby concluding that the increase in MSNA contributed to the elevation in blood pressure. The most likely expla-

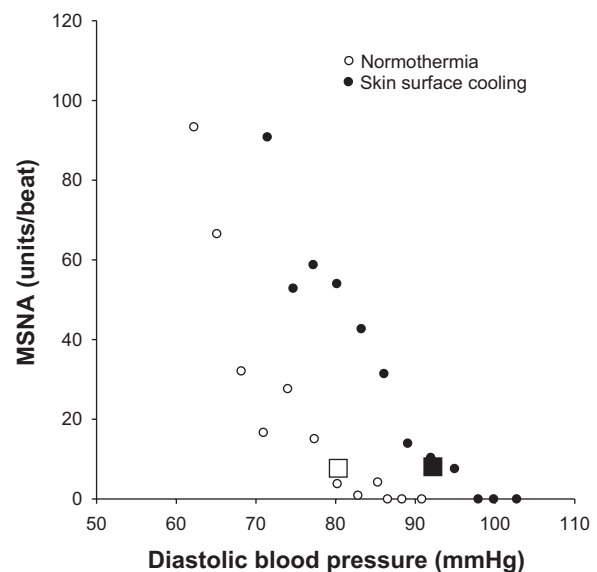


Fig. 1. Example of the relationship between muscle sympathetic nerve activity (MSNA) and diastolic blood pressure (DBP) for a representative subject. Only the linear portion of the data was used for the regression analysis during both control and skin cooling trials. Skin surface cooling induced a shift in the operating point (□, normothermia; ■, cooling) toward a higher blood pressure. However, there was no clear difference in the slope relating the change in MSNA relative to the change in DBP for this subject or for the mean response of the group of subjects.

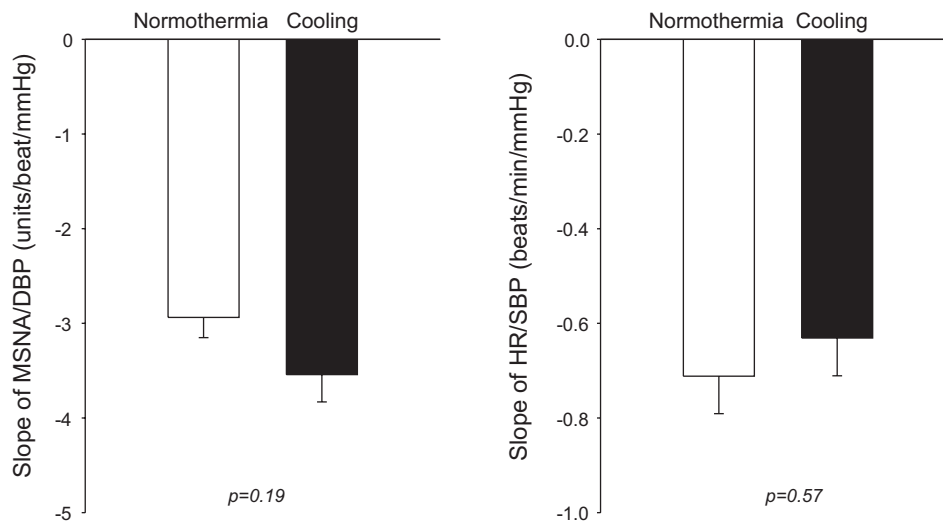


Fig. 2. *Left*: average slopes from the linear regression between MSNA and DBP for control (Normothermia) and skin surface cooling (Cooling) conditions. *Right*: average slopes from the linear regression between heart rate (HR) and systolic blood pressure (SBP). Skin surface cooling did not significantly alter baroreflex control of these variables as indicated by the absence of a difference in the slopes between control and skin surface cooling conditions.

nation for differing MSNA responses during cooling between these studies may be related to the method and intensity of cooling employed. In the study by Fagius et al., subjects were placed in a box that was cooled for at least 30 min using an air temperature between 14 and 10°C. The entire subject's body was placed in this box, including the subject's face, with the exception of the limb from which MSNA was obtained. This approach, particularly including cooling of the face and perhaps hands, are likely reasons for differences in MSNA responses between the present and their study, given that exposing these areas to a cold stimulus is a strong stimulator of MSNA (16). The magnitude of cooling may also be different between these studies, although this is difficult to confirm given that skin temperatures were not reported in that study. These contrasting observations suggest that sympathetic responses to cooling are dependent on the intensity and perhaps

populations of thermal and/or pain receptors stimulated by the cooling paradigm.

Mean heart rate did not change as a result of cooling. Others report similar findings or observe slight reductions in heart rate with cooling (4, 10, 20, 21, 31). Yamazaki et al. (31, 32) previously assessed the effects of cooling on carotid and systemic baroreflex control of heart rate. Although the maximal gain of carotid baroreflex control of heart rate was not affected by the cooling paradigm, they reported an increased gain of the heart rate-to-systolic blood pressure relationship when these values were assessed across spontaneous changes in blood pressure. This observation is in contrast to the present observation of an absence of an effect of cooling on baroreflex control of heart rate (Fig. 2), regardless of whether this response is expressed as beats per minute or as RRI. These conflicting finding may be due to the magnitude of cooling and/or methodology of assessing baroreflex sensitivity. For example, Yamazaki et al. assessed baroreceptor control of heart rate during spontaneous fluctuations in blood pressure via the sequencing technique. This technique typically induces much smaller changes in blood pressure and heart rate relative to the pharmacological technique employed in the current study, and thus the range from which the baroreflex is assessed is likely to be greater in the present study relative to the cited study. Secondly, the cooling paradigm used by Yamazaki et al. was more pronounced, resulting in a mean T_{sk} that was $\sim 3^{\circ}\text{C}$ lower in that study than present study. Our experience is that cooling to this level frequently causes the subject to shiver, which is in contrast to the present protocol in which the cooling paradigm was selected such that shivering would not occur. Nevertheless, these investigators found that cooling did not alter carotid baroreceptors control of heart rate (31). Thus the differences in the cooling condition, methodology, and perhaps the baroreceptors population assessed likely contributed to differing findings between the present and prior findings.

MSNA and heart rate are primarily under baroreflex control resulting in elevations in MSNA and heart rate when blood pressure is reduced and reductions in these variables when blood pressure is elevated (25, 29). Given these observations, it is interesting to note that skin surface cooling elevates blood pressure without altering mean MSNA or heart rate. This event

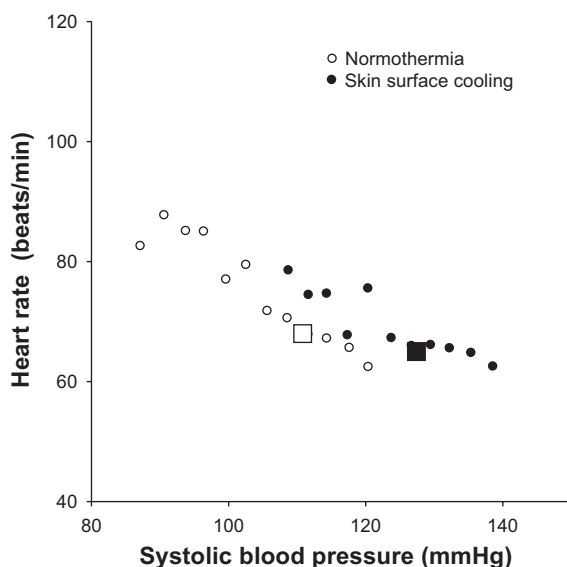


Fig. 3. Example of the linear regression between HR and SBP for a representative subject. Skin surface cooling induced a shift in the operating point (\square , normothermia; \blacksquare , cooling) toward a higher blood pressure. However, there was no clear difference in the slope relating the change in HR relative to the change in SBP for this subject or for the mean responses of group of subjects.

indicates that the operating point of baroreflex control of MSNA and heart rate is reset to the elevated blood pressure. This resetting may contribute to improved orthostatic tolerance during cooling given that in the absence of such resetting, MSNA and heart rate would decrease in the face of elevated blood pressure and thereby buffer cooling induced increases in blood pressure. In contrast, the maintenance of higher arterial blood pressures during cooling will provide a larger buffer by which arterial blood pressure could decrease during an orthostatic challenge before ensuing syncopal symptoms. The mechanisms causing the rightward shift of these baroreflex operating points remain unknown.

Study limitation. The modified Oxford technique to assess baroreflex control of MSNA and heart rate has been used extensively in various studies (3, 5, 8, 11, 14, 15, 18, 19, 23). Some of these studies identified conditions and/or perturbations in which clear and significant changes in baroreflex sensitivity were observed, whereas other studies showed that a particular perturbation did not change baroreflex sensitivity. For those studies not identifying a change in baroreceptor sensitivity, including the present study, it is possible that the absence of such a change is due to a type II statistical error. In the present study, the effects of skin cooling on baroreflex control of MSNA resulted in a *P* value of 0.19, suggesting the possibility of a type II error. However, analysis of individual responses are not consistent with such an error given that four subjects showed clear increases in baroreflex gain with skin cooling, two subjects showed obvious decreases in baroreflex gain, whereas no clear change was observed in the remaining three subjects. Nevertheless, it is recognized that the statistical paradigm is underpowered in that to statistically confirm that the observed changes in baroreflex gain of MSNA was not affected by skin surface cooling with a statistical power of 80%, using the present data for the source of variance, 39 subjects would need to participate in this study.

Because the modified Oxford technique evaluates baroreflex responses within a blood pressure range of ± 10 –15 mmHg around the operating point, we cannot exclude the possibility that surface cooling may improve baroreflex control of MSNA and heart rate had baroreflex function been evaluated across a wider blood pressure range. However, performing such a procedure may raise ethical concerns given the large changes in arterial blood pressure that would be necessary to evaluate baroreflex function across a wider blood pressure range.

Female subjects were not studied at a fixed phase of the menstrual cycle. Thus it is recognized that subjects likely came in during different stages of the menstrual cycle. Because each subject served as her own control and each subject's data were obtained on the same day, the absence of controlling for the menstrual cycle would not be a limitation unless there is an interaction between the menstrual cycle and baroreflex responsiveness specifically to skin surface cooling. To our knowledge, no such interaction has been identified, although it is recognized that using similar techniques on normothermic subjects baroreflex control of MSNA but not heart rate can be affected by phases of the menstrual cycle (18).

In conclusion, skin surface cooling does not induce significant changes in the gain of baroreflex control of MSNA or heart rate. However, this perturbation reset the baroreflex operating points to the prevailing elevated arterial blood pressure associated with cooling. Such a shift enables adequate

baroreflex-mediated buffering if blood pressure was further elevated while subjects are cooled. In addition, resetting baroreflex operating points to higher pressure may contribute to the elevations in orthostatic tolerance associated with skin surface cooling.

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