Divergent roles of plasma osmolality and the baroreflex on sweating and skin blood flow

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Lynn AG, Gagnon D, Binder K, Boushel RC, Kenny GP. Divergent roles of plasma osmolality and the baroreflex on sweating and skin blood flow. Am J Physiol Regul Integr Comp Physiol 302: R634–R642, 2012. First published December 14, 2011; doi:10.1152/ajpregu.00411.2011.—Plasma hyperosmolality and baroreceptor unloading have been shown to independently influence the heat loss responses of sweating and cutaneous vasodilation. However, their combined effects remain unresolved. On four separate occasions, eight males were passively heated with a liquid-conditioned suit to 1.0°C above baseline core temperature during a resting isosmotic state (infusion of 0.9% NaCl saline) with (LBNP) and without (CON) application of lower-body negative pressure (–40 cmH2O) and during a hyperosmotic state (infusion of 3.0% NaCl saline) with (HYP) and without (HYP) application of lower-body negative pressure. Forearm sweat rate (ventilated capsule) and skin blood flow (laser-Doppler), as well as core (esophageal) and mean skin temperatures, were measured continuously. Plasma osmolality increased by ~10 mosmol/kgH2O during HYP and HYP + LBNP conditions, whereas it remained unchanged during CON and LBNP (P ≤ 0.05). The change in mean body temperature (0.8 × core temperature + 0.2 × mean skin temperature) at the onset threshold for increases in cutaneous vascular conductance (CVC) was significantly greater during LBNP (0.56 ± 0.24°C) and HYP (0.69 ± 0.36°C) conditions compared with CON (0.28 ± 0.23°C, P ≤ 0.05). Additionally, the onset threshold for CVC during LBNP + HYP (0.88 ± 0.33°C) was significantly greater than CON and LBNP conditions (P ≤ 0.05). In contrast, onset thresholds for sweating were not different during LBNP (0.50 ± 0.18°C) compared with CON (0.46 ± 0.26°C, P = 0.950) but were elevated (P ≤ 0.05) similarly during HYP (0.91 ± 0.37°C) and LBNP + HYP (0.94 ± 0.40°C). Our findings show an additive effect of hyperosmolality and baroreceptor unloading on the onset threshold for increases in CVC during whole body heat stress. In contrast, the onset threshold for sweating during heat stress was only elevated by hyperosmolality with no effect of the baroreflex.

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DEHYDRATION IS ASSOCIATED with decreases in plasma volume (hypovolemia) and increases in plasma osmolality (hyperosmolality), which are thought to stimulate peripheral baroreceptors and central osmoreceptors, respectively (9, 27, 38, 40). Independently, hypovolemia or baroreceptor unloading and plasma hyperosmolality have both been shown to have a significant negative influence on thermoeffector activity and therefore body core temperature regulation (8, 9, 24, 27, 33). Plasma hyperosmolality has consistently been shown to increase the core temperature at which onset threshold of sweating and increases in cutaneous vascular conductance (CVC) occur without any changes in the thermosensitivity (10, 33, 40). Similarly, baroreceptor unloading has been shown to cause a delay in the core temperature onset threshold for cutaneous vasodilation without any changes in the thermosensitivity of the response (20, 24, 27). These responses result in a greater increase in core temperature for a given level of heat stress. However, modulation of the sweating response by the baroreflex is less consistent, with some studies reporting an attenuated sweating response (8, 24, 36) and others showing no effect (6, 43, 45, 46) during baroreceptor unloading.

Although numerous studies have examined the effects of baroreceptor unloading and hyperosmolality on the heat loss responses of cutaneous blood flow and sweating, they have generally examined these conditions independently. However, in the setting of real-time heat stress, dehydration results in the convergent signals by plasma hyperosmolality and hypovolemia (4). Therefore, it remains to be determined if one of these stimuli has a predominant effect, or if both act together (i.e., synergistically or additively) in causing the observed disturbances in the heat loss mechanisms of sweating and skin blood flow while dehydrated. Furthermore, it is unknown if plasma hyperosmolality and baroreceptor unloading affect sweating and skin blood flow to a similar extent, or if one stimulus preferentially modulates either one of these heat loss responses.

To the best of our knowledge, Ito et al.’s study (16) is the only one that has addressed a potential interaction between plasma hyperosmolality and baroreceptor unloading, focusing solely on the skin blood flow response. By applying lower-body negative pressure (LBNP) after 60 min of passive heating under either an isosmotic or hyperosmotic state, they examined the capacity of the baroreflex to cause reductions in forearm vascular conductance as a function of plasma osmolality. Interestingly, greater reductions in forearm vascular conductance were observed in the hyperosmotic state compared with the isosmotic state, but only at higher levels of LBNP (~40 mmHg). Although these findings suggest a potential interaction between plasma hyperosmolality and the ability of the baroreflex to reduce forearm vascular conductance, they do not provide any information as to how this interaction may affect the initiation of active vasodilation since they applied LBNP once forearm vascular conductance had attained elevated levels. Furthermore, the interactive response on sweating, the main avenue of heat loss during heat stress, was not reported. As such, it remains to be determined how the combination of baroreceptor unloading and plasma hyperosmolality influences the thermal control of sweating and cutaneous vasodilation.

Therefore, we examined the separate and combined effects of baroreceptor unloading and plasma hyperosmolality on human temperature regulation as measured by the mean body
temperature at which the onset of sweating and increases in CVC occur, as well as the thermosensitivity of these responses during whole body heating. We hypothesized that combined LBNP and plasma hyperosmolality would result in a greater delay in the mean body temperature at which sweating and increases in CVC occur, relative to the independent effects of each condition. A second hypothesis was that the thermosensitivity of each response would be unaffected by the baroreflex and plasma hyperosmolality.

METHODS

Ethical Approval

The current experimental protocol was approved by the University of Ottawa Health Sciences and Science Research Ethics Board, in accordance with the Declaration of Helsinki. Written informed consent was obtained from all volunteers before their participation in the study.

Participants

Using an effect size (>1.1) calculated from the pooled mean data from Shibasaki et al. (33), we found that a sample size of seven to nine participants would provide similar changes in plasma volume between conditions. From Shibasaki et al. (33), we found that a sample size for determining sensitivity of each response would be unaffected by the baroreflex and plasma hyperosmolality.

Experimental Protocol

All subjects volunteered for one screening visit and four experimental sessions that were separated by a minimum of 48 h. During the screening visit, participants were informed of the study protocol before written consent was obtained.

On the day before each experimental session, subjects were instructed to abstain from salty foods and drink water throughout the day. Subjects then reported to the laboratory between 0730 and 1000 h and were asked to void their bladder and provide a urine sample before weighing themselves nude. Next, an 18-gauge catheter was inserted in an antecubital vein of the right arm. Subjects were then infused with either 0.9 or 3.0% NaCl solution (Mon-a-therm Nasopharyngeal Temperature Probe; Mallinckrodt Medical, St. Louis, MO) through the participant’s nose to a depth of 40 cm past the opening of the nose. Skin temperature was measured at nine points over the body’s surface using 0.3-mm-diameter T-type (copper/constantan) thermocouples (Concept Engineering, Old Saybrook, CT). Thermocouples were attached using surgical tape (Blenderm; 3M, St. Paul, MN). Mean skin temperature was calculated using the nine skin temperatures weighted to the regional proportions as determined by Hardy and DuBois (15): head 7%, upper back 9.5%, chest 9.5%, lower back 9.5%, abdomen 9.5%, bicep 10%, quadriceps 19%, hamstring 10%, and front calf 16%. All temperature data were collected using an HP Agilent data acquisition module (model 3497A) at a sampling rate of 15 s. Data were simultaneously displayed and recorded in spreadsheet format on a personal computer with LabVIEW software (version 7.0; National Instruments).

Heart rate was monitored using a Polar-coded transmitter, recorded continuously, and stored with a Polar Advantage interface and Polar Precision Performance software (Polar Electro, Oy, Finland).

Mean arterial pressure was estimated using a Finapres (Finapres Medical Systems, Amsterdam, Netherlands) from the beat-to-beat recording of the left middle finger arterial pressure waveform with the volume-clamp method (29) and physical criteria that is used to calibrate the finger arterial size at which the finger cuff air pressure equals finger arterial blood pressure (44). For the start of measurement recording, brachial artery pressure reconstruction (13, 14) was calibrated with an upper arm return-to-flow systolic pressure detection (2). Furthermore, the left arm was supported at heart level, and a level calibration was performed.

Cardiac output was measured noninvasively using an Innocor inert gas rebreathing unit with breath-by-breath ergospirometry option and an arterial oxygen saturation sensor (Innovisions, Odense, Denmark) that has been previously validated against the direct oxygen Fick method and thermodilution (31). For rebreathing gases, we used 5% nitrous oxide and 1% sulfur hexafluoride, diluted with atmospheric air (1, 23). The closed rebreathing system consisted of a three-way respiratory valve connecting a facemask, an antistatic rubber bag, and an infrared photoacoustic gas analyzer. Before each rebreathing maneuver, the gas mixture was filled into the bag with a previously determined volume (≤2 liters) that the participant could fully and easily empty into their lungs during each inhalation. Stroke volume was calculated as cardiac output divided by heart rate.

Forearm blood flow was estimated using laser-Doppler velocimetry maintained locally at 35°C (PeriFlux System 5000, Main control unit; PF5010 LDPM) on the left midanterior forearm. After the skin was shaved and cleaned with alcohol, the probe (Perimed integrating probe 413, Järfälla, Sweden) was placed on an area that,
superficially, appeared to be minimally vascularized. The probe was not moved from its location throughout the experimental trial. To determine maximum skin blood flow, a local heating period to 42°C for 20 min and then to 44°C for an additional 25 min was performed at the end of each experimental trial (3). CVC was subsequently calculated as laser-Doppler velocimetry output in arbitrary perfusion units divided by mean arterial pressure and expressed as a percentage of maximum.

Forearm sweat rate was estimated from a 3.8-cm² ventilated capsule placed on the left midanterior forearm. Anhydrous compressed air was passed through the capsule over the skin surface at a rate of 1 l/min. Water content of the effluent air was measured at known barometric pressure using dew point hygrometry (model 473; RH Systems, Albuquerque, NM). Sweat rate was defined as the product of the difference in water content between effluent and influent air and the flow rate and was adjusted for skin surface area under the capsule (expressed in mg·min⁻¹·cm⁻²).

Measurements of nude body weight to the nearest 0.01 kg were obtained before each experimental session using a digital high-performance weighing terminal (model CBU150X; Mettler Toledo, Mississauga, Ontario, Canada). Urine specific gravity was measured using refractometry (TS 400; Reichert, Depew, NY) before each experimental session.

Venous blood samples were collected without stasis through an indwelling plastic catheter in a superficial vein. Blood samples (~10 ml) were drawn and transferred into K2 EDTA and SST vacutainers (BD Vacutainer, Franklin Lakes, NJ) for the determination of plasma volume and osmolality, respectively. Four samples were taken throughout each experimental trial at the following time points: 1) at rest following 30 min in the seated position, 2) before the start of whole body heating, 3) following a 0.5°C increase in core temperature, and 4) at the end of heating, equal to a 1°C increase in core temperature. Hematocrit and hemoglobin concentrations were determined using the Coulter method (Coulter A²-T diff 2 analyzer; Beckman Coulter, Miami, FL). Plasma osmolality was determined by centrifuging each blood sample and storing the separated plasma frozen at ~20°C until measurement. All samples of plasma osmolality were analyzed ~48 h after collection by freezing point depression (Osmometer; Advanced Instruments). Changes in plasma volume from baseline resting were estimated from changes in hemoglobin and hematocrit using the formula proposed by Dill and Costill (7).

Statistical Analysis

To determine the effect of LBNP before the heating period, the dependent variables were analyzed at baseline (B1) and during the application of LBNP or sham pressure [baseline 2 (B2)] using a one-way repeated-measure ANOVA with the factor of treatment condition. Furthermore, to determine the effect of heating and LBNP on the dependent variables, a two-way repeated-measures ANOVA was employed with the repeated factors of increase in core temperature (levels: 0, 0.25, 0.5, 0.75, and 1°C) and treatment condition. Relative core temperature increases were determined from the 15 min of baseline data collection (B1), before the application of LBNP. Subsequently, dependent variable values were determined at core temperature increases for analysis by taking a 3-min average of data that included 1 min before and 1 min after each core temperature increase was reached.

The onset thresholds for sweating and increases in CVC are expressed as mean body temperature (0.8 × core temperature + 0.2 × mean skin temperature) to account for the relative influences of changes in skin and core temperatures on thermoeffector activity during whole body heating (12). Sweating and CVC data were plotted over time, and onset thresholds were defined as the corresponding mean body temperature at which a rapid increase in CVC and sweating occurred over three consecutive measurements (24, 39).

Thermosensitivity was defined by the slope of the linear portion of the CVC/sweating-to-mean body temperature relationship, fitted with a least-squares-linear-regression line. The independent and combined effects of baroreceptor unloading and hyperosmolality on changes in onset threshold and thermosensitivity were analyzed by comparing each condition (HYP, LBNP, and LBNP + HYP) relative to CON using paired-sample t-tests. To determine which treatment condition had the greatest effect on changes in onset threshold and thermosensitivity, each condition (HYP, LBNP, and LBNP + HYP) was subsequently compared using a one-way repeated-measures ANOVA. For all analyses, when a significant main effect of condition was observed, post hoc comparisons were carried out with paired-sample t-tests corrected for multiple comparisons using the Holm-Bonferroni procedure. The level of significance was set to an α level of P ≤ 0.05. All analyses were performed using the statistical software package SPSS 18.0 for Windows (SPSS, Chicago, IL). All results are presented as means ± SD, unless otherwise indicated.

RESULTS

No differences in hydration status as determined by total body weight (CON, 80.20 ± 8.37 kg; LBNP, 80.25 ± 8.49 kg; HYP, 80.25 ± 8.15 kg; and LBNP + HYP, 80.04 ± 8.21 kg, P = 0.889) and urine specific gravity (CON, 1.015 ± 0.008; LBNP, 1.017 ± 0.010; HYP, 1.018 ± 0.008; and LBNP + HYP, 1.017 ± 0.008, P = 0.670) were measured between conditions before the start of the experimental protocol.

Plasma Osmolality and Plasma Volume

Mean changes in plasma osmolality and plasma volume after infusion and during heat stress are presented in Fig. 1. Preinfusion osmolality did not differ between conditions (P = 0.714). Isotonic saline infusion did not change plasma osmolality in either the CON or LBNP conditions, whereas hypertonic saline infusion significantly increased plasma osmolality to a similar extent in the HYP and LBNP + HYP conditions (P ≤ 0.05). During whole body heating, plasma osmolality remained similar to preinfusion levels in the CON and LBNP conditions (P > 0.05). In contrast, plasma osmolality remained significantly elevated above preinfusion levels during whole body heating in the HYP and LBNP + HYP conditions (P ≤ 0.05).

There was no statistical effect of condition on plasma volume increases after infusion and before whole body heating (P = 0.241). Whole body heating caused a decrease in plasma volume from postinfusion values in all conditions (P ≤ 0.05), with a greater decrease observed during LBNP conditions (LBNP and LBNP + HYP) compared with sham pressure conditions (CON and HYP) (P ≤ 0.05).

Cardiovascular Responses

Baseline period. During baseline rest (B1), there were no significant differences in cardiac output (P = 0.426), heart rate (P = 0.641), stroke volume (P = 0.508), mean arterial pressure (P = 0.694), and total peripheral resistance (P = 0.253) among conditions. During the baseline period with application of LBNP or sham pressure (B2), cardiac output and stroke volume were significantly lower in the LBNP and LBNP + HYP conditions compared with the HYP condition (P ≤ 0.05, Fig. 2). Similarly, there was a main effect of condition (P < 0.001) for differences in total peripheral resistance (Fig. 3) and heart rate (Fig. 2) during B2, demonstrated by generally greater heart rate and total peripheral resistance values in the LBNP and LBNP + HYP conditions compared with the HYP and...
CON conditions ($P \leq 0.05$). There was no main effect of LBNP or sham pressure on mean arterial pressure before whole body heating ($P = 0.865$, Fig. 3). The observed differences in cardiovascular responses during the application of LBNP compared with the sham pressure conditions demonstrate that a similar level of baroreceptor unloading had been successfully induced in the LBNP and LBNP + HYP conditions before beginning the whole body heat stress period.

**Whole body heating.** During whole body heating, stroke volume and total peripheral resistance decreased as a function of increases in core temperature for all conditions ($P = 0.05$), but to a greater extent in the LBNP conditions compared with the sham pressure conditions ($P = 0.05$). Cardiac output significantly increased in the CON, LBNP, and HYP conditions ($P \leq 0.05$), but no significant change in the LBNP + HYP condition was observed ($P = 0.134$). Throughout whole body heating, cardiac output was significantly greater in the CON and HYP conditions compared with LBNP and LBNP + HYP conditions ($P \leq 0.05$). Similarly, heart rate increased during whole body heating in all conditions ($P < 0.001$), with significantly greater increases observed in the LBNP and LBNP + HYP conditions compared with CON and HYP conditions at 0.5, 0.75, and 1.0°C core temperature increases ($P \leq 0.05$). In contrast, there was no significant effect of condition ($P = 0.193$) or core temperature ($P = 0.191$) on mean arterial pressure during whole body heating. These different cardiovascular responses indicate that the baroreceptor unloading achieved before beginning the heating period was maintained throughout passive heat stress in the LBNP and LBNP + HYP conditions.

**Thermal Responses**

**Heating time.** The time required for esophageal temperature to increase by 1°C was $54 \pm 5$, $48 \pm 6$, $67 \pm 17$, and $85 \pm 13$
mean body temperature relationship during each condition. The mean body temperature required to elicit an increase in CVC was significantly greater in the LBNP, HYP, and LBNP + HYP conditions compared with CON (P ≤ 0.05, Table 2). The mean body temperature required to initiate an increase in CVC in the LBNP + HYP condition was also significantly greater compared with LBNP (P ≤ 0.05) but not HYP (P = 0.164). These observations suggest that plasma hyperosmolality and baroreceptor unloading additively contributed to the increased CVC response during whole body heating in the LBNP + HYP condition. In contrast, there was no effect of condition on the thermosensitivity of CVC (P = 0.478).

Sweating. Figure 5 illustrates the typical response of a representative subject for the sweating-to-mean body temperature relationship during each condition. The mean body temperature threshold at which the onset of sweating occurred was significantly greater in both the HYP and LBNP + HYP conditions compared with CON and LBNP conditions (P ≤ 0.05, Table 2). The mean body temperature onset thresholds for sweating were not statistically different between isosmotic conditions (CON and LBNP, P = 0.950) nor did they differ between hyperosmotic conditions (HYP and LBNP + HYP, P = 0.459), indicating that threshold changes observed in the LBNP + HYP condition were solely the result of increases in plasma osmolality. Furthermore, there was no significant effect of condition on the thermosensitivity of sweating (P = 0.172).

**DISCUSSION**

The present study is the first to examine the separate and combined effects of baroreceptor unloading and plasma hyperosmolality on the thermal control of sweating and CVC during progressive whole body heat stress. The current results support our hypothesis that combined baroreceptor unloading and plasma hyperosmolality causes a greater attenuation in the heat loss response of cutaneous vasodilation relative to their independent effects. This is evidenced by the observation that plasma hyperosmolality and baroreceptor unloading caused the greatest delay in the onset threshold for CVC during whole body heating. However, contrary to our hypothesis, baroreceptor unloading had no effect on the onset threshold for eccrine sweating under either isosmotic or hyperosmotic conditions. In addition, once sweating and increases in CVC occurred, there were no differences in the thermosensitivity of each response between conditions. Our results suggest that alterations in skin perfusion associated with dehydration during heat stress are mediated by a combination of baroreceptor loading status and plasma hyperosmolality, whereas reductions in sweat rate are primarily mediated by changes in plasma osmolality.

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**Table 1.** $T_{sk}$ during B1, during the application of lower-body negative pressure or sham pressure (B2), and at 0.25°C increments in esophageal temperature during a passive heat stress

<table>
<thead>
<tr>
<th>Measure</th>
<th>Condition</th>
<th>B1</th>
<th>B2</th>
<th>0.25°C</th>
<th>0.5°C</th>
<th>0.75°C</th>
<th>1.0°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{sk}$,°C</td>
<td>CON</td>
<td>34.11 ± 0.31</td>
<td>34.10 ± 0.32</td>
<td>36.70 ± 0.60</td>
<td>36.92 ± 0.54</td>
<td>37.14 ± 0.53</td>
<td>37.35 ± 0.53</td>
</tr>
<tr>
<td></td>
<td>LBNP</td>
<td>33.93 ± 0.54</td>
<td>33.82 ± 0.43</td>
<td>36.41 ± 0.65</td>
<td>36.82 ± 0.48</td>
<td>37.00 ± 0.38</td>
<td>37.21 ± 0.51</td>
</tr>
<tr>
<td></td>
<td>HYP</td>
<td>34.12 ± 0.31</td>
<td>34.07 ± 0.34</td>
<td>36.82 ± 0.54</td>
<td>37.07 ± 0.51</td>
<td>37.29 ± 0.51</td>
<td>37.49 ± 0.55</td>
</tr>
<tr>
<td></td>
<td>LBNP + HYP</td>
<td>34.11 ± 0.40</td>
<td>33.80 ± 0.32</td>
<td>36.55 ± 0.63</td>
<td>36.98 ± 0.60</td>
<td>37.21 ± 0.66</td>
<td>37.28 ± 0.68</td>
</tr>
</tbody>
</table>

Values are means ± SD. $T_{sk}$, mean skin temperature; B1, baseline rest; B2, baseline 2. Conditions are isosmotic and sham pressure [control (CON)], isosmotic with lower-body negative pressure (LBNP), hyperosmotic with sham pressure (HYP), and hyperosmotic with lower-body negative pressure (LBNP + HYP).
Previous findings have shown that the baroreflex has the capacity to reduce blood flow to the cutaneous circulation during combined orthostatic challenge and heat stress, which is critical to maintain arterial blood pressure (5, 25, 30, 35). Furthermore, previous reports by Nadel et al. (27) and Mack et al. (24) have shown that isosmotic hypovolemia and baroreceptor unloading delay the onset threshold for increases in skin blood flow during cycling exercise. Consistent with these findings, we show that the application of LBNP can independently delay the onset of CVC during progressive whole body heating (Table 2 and Fig. 4). Similarly, we show an independent effect of plasma hyperosmolality in elevating the onset threshold for CVC during whole body heating (Table 2 and Fig. 4), a response consistent with previous findings (10, 33, 38, 40).

The purpose of the present study, however, was to examine the combined effects of baroreceptor unloading and plasma hyperosmolality on thermoefferent activity, since dehydration results in simultaneous plasma hyperosmolality and hypovolemia. To our knowledge, only Ito et al. (16) have investigated a potential interaction of the combined effects of baroreceptor unloading and plasma hyperosmolality, focusing solely on the capacity of the baroreflex to cause reductions in CVC in either an isosmotic or hyperosmotic state. They reported greater reductions in forearm vascular conductance during graded levels of LBNP applied under a hyperosmotic state relative to an isosmotic state during heat stress conditions. However, LBNP was only applied after 60 min of heat stress, which occurred at different levels of hyperthermia for the isosmotic and hyperosmotic conditions (i.e., core temperature increase of 0.3 and 0.9°C, respectively). Although similar levels of forearm vascular conductance were reported before the application of LBNP, it is possible that differences in the level of hyperthermia may have contributed to the greater reductions in forearm vascular conductance observed in the hyperosmotic condition, since reductions in skin blood flow are more readily evidenced as the level of heat stress increases (30). In the present study, we continuously applied LBNP before and throughout whole body heating. As such, this novel approach allowed us to examine the combined effects of baroreceptor unloading and plasma hyperosmolality on the thermal control of cutaneous vasodilation (onset thresholds and thermosensitivity) at similar levels of thermoafferent stimuli. Relative to CON, the average onset threshold for CVC in the LBNP and HYP conditions was delayed by 0.31 ± 0.13 and 0.44 ± 0.17°C, respectively, the sum of which (0.75°C) approximates the delay observed during the LBNP/HYP condition (Table 2). Therefore, our observation that combined plasma hyperosmolality and baroreceptor unloading caused the greatest delay in the onset threshold for CVC confirms the findings of Ito et al. (16) and extend them by showing that the combined influence of both stimuli appears to be additive.

It has been shown that decreases in CVC during moderate to high levels of LBNP are manifested by increases in vasoconstrictor tone without heat stress (19, 42), whereas, during heat stress, baroreceptor unloading causes a decrease in the cutaneous vascular response through withdrawal of active vasodilation (5, 19). However, work by Shibasaki et al. (35) provides evidence to suggest that the cutaneous vasoconstrictor system is capable of decreasing CVC during an orthostatic challenge while heat stressed. Therefore, the delayed-onset threshold in CVC with combined baroreceptor unloading and plasma hyperosmolality observed in the present study could be the result of a LBNP-induced baroreceptor-mediated increase in vasoconstrictor activity, a delay in active vasodilation, or a combination of both. Recently, Shibasaki et al. (33) concluded that the independent effect of hyperosmolality in elevating the internal temperature onset threshold for CVC is due to a delay in cutaneous active vasodilation, and not to increased vasoconstrictor activity. This was evidenced by similar core temperature-

**Cutaneous Vascular Conductance**

![Fig. 4. The cutaneous vascular conductance (CVC) response as a function of changes in mean body temperature during whole body heating in the LBNP (A), HYP (B), and LBNP + HYP (C) treatment conditions from a representative subject. Each condition is compared with CON. Cutaneous vascular responses are expressed as a percent of CVC_{max}. Arrows indicate the approximate onset threshold for CVC.](http://ajpregu.physiology.org/)

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ture onset thresholds for cutaneous vasodilation at treated and untreated sites with bretylium tosylate (vasoconstrictor block-ade). Therefore, it is likely that the augmented delay in the onset threshold for CVC associated with plasma hyperosmolarity and baroreceptor unloading observed in the present study is centrally mediated via a further withdrawal of the active vasodilator system. However, since we did not directly measure the responses of the vasoconstrictor and vasodilator systems, further study is warranted to evaluate this hypothesis.

Sweating Response

Consistent with previous studies, we show that the onset threshold for sweating under a hyperosmotic state is delayed compared with the isosmotic condition (Table 2 and Fig. 5) (10, 33, 38, 40). In contrast to previous reports, however, we show that baroreceptor unloading induced by LBNP has no influence on the sweating response during whole body heating in either the isosmotic or hyperosmotic conditions (Table 2 and Fig. 5). A number of studies have demonstrated a role for baroreceptors in modulating sweating responses during heat stress. Mack et al. (24) reported an increase in the esophageal temperature onset threshold for sweating during exercise with combined LBNP. Similarly, Solack et al. (36) reported a reduction in the slope of the sweating-to-esophageal temperature relationship during simultaneous whole body heating and LBNP application. In contrast, Johnson and Park (17) found no differences in sweating during exercise and passive heating performed in the supine and upright posture. Additionally, recent work by Wilson et al. (45, 46) reported no changes in skin sympathetic nerve activity and sweat rate during multiple 30° head-up tilts throughout a 1.2°C increase in mean body temperature or during pharmacologically induced decreases in arterial blood pressure under heat stress (0.6°C increase in sublingual temperature). These later findings propose that the baroreflex does not have an efferent limb in the control of thermal sweating, although it has been shown that pharmacological and postural manipulations of blood pressure perturb baroreceptors differently compared with LBNP (11). Therefore, we are confident that the application of LBNP during the Mack et al. study had a significant influence on the determination of their sweating thresholds, since local skin cooling has been shown to decrease sweating and delay the onset threshold for sweating (28, 45). In the current study, however, a novel approach was to perform LBNP in a temperature-controlled chamber regulated at 40°C to minimize any cooling effects through the circulation of warm air. Furthermore, LBNP was continuously applied before and throughout whole body heating to avoid the inhibitory influence of negative rates of skin temperature change on sweating (47). Finally, any effect of skin cooling on the sweating response would be accounted for in our mean body temperature measurements. Therefore, after minimizing the effects of convective skin cooling associated with applying LBNP and despite a strong baroreceptor drive, a baroreceptor-mediated modulation of sweat rate was still not observed in either an isosmotic or hyperosmotic condition. Our findings, combined with more recent work on the effects of the baroreflex on sweating (6, 45, 46), provide strong evidence that unloading of baroreceptors does not modulate sweating, which is congruent with a number of recent review articles on baroreceptor unloading and the sweating response (20, 35).

Limitations

In the current study, we employed standard infusion rates that have been previously shown to elicit similar changes in plasma volume with marked differences in plasma osmolality (33, 40). However, this procedure ultimately results in different infusion volumes between the hyperosmotic and isosmotic conditions, which may influence the cardiovascular stress imposed by the application of LBNP. This is particularly important when comparing the LBNP and LBNP + HYP conditions of the current study. However, plasma volume changes were not different after infusion and remained similar between these conditions throughout the heating period. Furthermore, the cardiovascular responses to the application of LBNP between the LBNP and LBNP + HYP conditions were similar (Fig. 2). Therefore, we are confident that the application of LBNP between these conditions caused similar levels of baroreceptor unloading. Additionally, LBNP in the current study was used to simulate baroreceptor unloading that is thought to occur during dehydration-induced hypovolemia (26, 32). However, it is possible that the mechanism by which hypovolemia during thermal and/or exercise-induced dehydration perturbs baroreceptors differs from baroreceptor unloading during the application of LBNP. Moreover, the differences may be influenced in the current study by the use of saline infusion to manipulate

**Table 2.** \( T_b \) threshold for CVC and sweating, the sensitivities of CVC and sweating with respect to \( T_b \) (slope), and \( \Delta T_b \) from preheating to the onset of CVC and sweating in CON, LBNP, HYP, and LBNP + HYP conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Threshold, °C</th>
<th>Slope, mg · min⁻¹ · cm⁻²/°C</th>
<th>( \Delta T_b ), °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>CON</td>
<td>36.77 ± 0.36</td>
<td>1.29 ± 0.47</td>
<td>0.46 ± 0.26</td>
</tr>
<tr>
<td>LBNP</td>
<td>36.77 ± 0.29</td>
<td>1.37 ± 0.54</td>
<td>0.50 ± 0.18</td>
</tr>
<tr>
<td>HYP</td>
<td>37.19 ± 0.32*†</td>
<td>1.70 ± 0.62</td>
<td>0.91 ± 0.37*†</td>
</tr>
<tr>
<td>LBNP + HYP</td>
<td>37.25 ± 0.42*†</td>
<td>1.37 ± 0.54</td>
<td>0.94 ± 0.40*†</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>( \text{Threshold}, °C )</th>
<th>( \text{Slope}, %\text{CVC}_{\text{max}}/°C )</th>
<th>( \Delta T_b ), °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>CON</td>
<td>36.56 ± 0.27</td>
<td>80.93 ± 34.1</td>
<td>0.28 ± 0.23</td>
</tr>
<tr>
<td>LBNP</td>
<td>36.83 ± 0.25*</td>
<td>71.24 ± 31.0</td>
<td>0.56 ± 0.24*</td>
</tr>
<tr>
<td>HYP</td>
<td>36.97 ± 0.31*</td>
<td>61.63 ± 24.4</td>
<td>0.69 ± 0.36*</td>
</tr>
<tr>
<td>LBNP + HYP</td>
<td>37.18 ± 0.32*†</td>
<td>73.17 ± 21.1</td>
<td>0.88 ± 0.33*†</td>
</tr>
</tbody>
</table>

Values are means ± SD. \( T_b \), mean body temperature; CVC, cutaneous vascular conductance; \( \Delta T_b \), increase in \( T_b \). \( P \leq 0.05 \), significantly different from CON (*) and significantly different from LBNP (†) conditions.
plasma osmolality. Although these factors may limit the practical applicability of our results, they do provide important information about the mechanisms mediating altered thermoafferent control of sweating and skin blood flow during thermal dehydration. Finally, it might be expected that the time to reach a 1°C increase in esophageal temperature in the LBNP and LBNP + HYP conditions (85 ± 13 and 67 ± 17 min) would be shorter compared with the CON condition (54 ± 5 min), since we show an effect of LBNP on the control of skin blood flow. However, the longer time required to reach a 1°C increase in esophageal temperature during the LBNP conditions compared with the CON condition does not reflect the inhibition of thermoregulatory function and is likely due to redistribution of blood caused by the application of LBNP (18).

**Perspectives and Significance**

Dehydration associated with prolonged heat exposure has been well documented to result in a progressive attenuation of skin perfusion and sweating, and a concomitant increase in the level of thermal strain. Because heat-induced dehydration leads to both hyperosmolality and hypovolemia (4), central osmoreceptors and peripheral baroreceptors have been implicated as nonthermal modulators of thermoeffector activity during combined dehydration and heat stress. Before the current study, however, it remained unknown whether one of these stimuli preferentially caused the observed alterations in temperature regulation during dehydration, or if the combination of both mediated the reductions in heat loss responses. Furthermore, it was unknown if both skin blood flow and sweating were affected to a similar extent by both nonthermal stimuli. Collectively, the results of the current study suggest the activation of osmoreceptors and baroreceptors has divergent effects on the skin blood flow and sweating responses. In addition, most previous studies examining the effects of plasma hyperosmolality or baroreceptor unloading on skin blood flow and sweating responses have done so in the supine posture (5, 6, 24, 30, 33, 34, 36, 40, 43, 45). In the current study, however, we studied these effects in the upright posture and therefore provide novel insight into the interaction of osmoreceptors and the baroreflex in the control of heat loss responses as it pertains to the upright human. Specifically, we show that, despite being in a relative state of baroreceptor unloading (i.e., the upright posture), the baroreflex maintains the ability to attenuate increases in cutaneous blood flow during further baroreceptor unloading through the application of LBNP. In contrast, no measurable effect was observed in the control of sweat rate with the combination of the upright posture and further baroreceptor unloading with LBNP. Speculatively, an additive effect of hyperosmolality and baroreceptor unloading on the skin blood flow response could enhance the control of blood pressure during combined dehydration and orthostatic stress (i.e., upright posture), whereas a preferential effect of plasma hyperosmolality on the sweating response could serve to prevent further reductions in plasma volume, therefore maximizing sweat rate and the control of core temperature in such scenarios.

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**DISCLOSURES**

The authors declare that they have no conflict of interest, financial or otherwise.
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