Baroreflex modulation of peripheral vasoconstriction during progressive hypothermia in anesthetized humans

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Nakajima, Yasufumi, Toshiki Mizobe, Akira Takamata, and Yoshifumi Tanaka. Baroreflex modulation of peripheral vasoconstriction during progressive hypothermia in anesthetized humans. Am J Physiol Regulatory Integrative Comp Physiol 279: R1430–R1436, 2000.—Mild hypothermia is a major concomitant of surgery under general anesthesia. We examined the hypothesis that baroreceptor loading/unloading modifies thermoregulatory peripheral vasoconstriction and, consequently, body core temperature in subjects undergoing lower abdominal surgery with general anesthesia. Thirty-six patients were divided into four groups: control group (C), applied positive end-expiratory pressure (PEEP; 10 cmH₂O) group (P), applied leg-up position group (L), and a group of leg-up position patients with PEEP starting 90 min after induction of anesthesia (L + P). The esophageal temperature (Tₑₛ) and the forearm-fingertip temperature gradient, as an index of peripheral vasoconstriction, were monitored for 3 h after induction of anesthesia. Mean arterial pressure and pulse pressure did not change during the study in any group. The change in Tₑₛ at the end of the study was 0.3 ± 0.1 mmHg in C, −3.0 ± 0.5 mmHg in P, and 2.3 ± 0.4 mmHg in L (P < 0.01). The change in Tₑₛ at the end of the study was −1.7 ± 0.1 (35.1 ± 0.1°C in C, −1.1 ± 0.1 (35.7 ± 0.1°C in P, and −2.7 ± 0.1 (34.1 ± 0.1°C in L, showing significant differences (P < 0.01). The Tₑₛ threshold for thermal peripheral vasoconstriction was 35.6 ± 0.1°C in C, 36.2 ± 0.2°C in P, and 34.8 ± 0.2°C in L (P < 0.01). Excessive Tₑₛ decrease in the leg-up-position operation was attenuated by applying PEEP (L + P group; P < 0.05). Our data indicate that baroreceptor loading augments and unloading prevents perioperative hypothermia in anesthetized and paralyzed subjects by reducing and increasing the body temperature threshold for peripheral vasoconstriction, respectively.

METHODS

Subjects. This study was approved by the Review Board on Human Experiments, Kyoto Prefectural University of Medicine. Written informed consent was obtained from all subjects before the study. The subjects were 36 patients (American Society of Anesthesiologists Physical Status 1 or 2), aged 20–60 yr, scheduled for open lower abdominal surgery. No subject was obese, was taking any medication that affected cardiovascular regulation; thermoregulation; peripheral blood flow; core temperature threshold

PERIPHERAL VASOCONSTRICTION, along with increased heat production by nonshivering thermogenesis and shivering, plays a major role in the thermoregulatory response to reduced body temperature. Mild hypothermia is a major concomitant of surgery under general anesthesia, because most anesthetics are direct vasoconstrictors, and all impair normal thermoregulation by interfering with hypothalamic function and lowering the body core temperature threshold for peripheral vasoconstriction in a dose-dependent manner (9, 30). In addition, muscle relaxants prevent shivering. Thus the contribution of peripheral vasoconstriction to the thermoregulatory response should become higher.

Baroreceptor unloading by lower body negative pressure (3, 10, 15) or plasma volume reduction with diuretics (18, 19, 27) is known to attenuate thermoregulatory responses to increased body temperature by increasing the body core temperature threshold for cutaneous vasodilation and/or by suppressing the rise in cutaneous vasodilation per unit increase in body core temperature above the threshold. However, baroreflex modulation of thermoregulatory responses to decreased body temperature has not been studied sufficiently.

In the present study, we hypothesized that reduction in central blood volume should modulate the thermoregulatory responses to progressive hypothermia during surgery via baroreceptor-mediated reflexes and, consequently, modifies perioperative hypothermia. To test this hypothesis, we modified right atrial transmural pressure (RATP) by applying 10 cmH₂O positive end-expiratory pressure (PEEP; baroreceptor unloading) (20, 25, 28) and the leg-up position (baroreceptor loading) (5, 6, 8), which are known to affect baroreceptor activity, and examined the cardiovascular and thermoregulatory responses during lower abdominal surgery. Moreover, to ensure that the baroreflex reflex was engaged in this protocol, hormonal levels were measured.

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cardiovascular function or heat balance, or had a history of any cardiopulmonary disorders, thyroid disease, dysautonomia, or Raynaud’s syndrome. The patients were randomly divided into two groups: control group (C, n = 9) and PEEP group (P; at 10 cmH2O, n = 9). The patients who underwent surgery in the leg-up position were randomly assigned into groups [L (n = 9) or L + P group (n = 9), in which PEEP (10 cmH2O) was applied starting 90 min after induction of anesthesia]. Three males and six females were included in each group.

Protocol. All experiments were performed between 0800 and 1200. All patients fasted for more than 8 h before the study. They were given 0.5 mg of atropine sulfate and 50 mg of hydroxyzine intramuscularly 60 min before induction of anesthesia. The ambient temperature of the operating room was maintained at ~24°C and relative humidity at ~40%. The subjects remained in the operating room for at least 30 min to become accustomed to the environment while an 18-gauge catheter was inserted into the left antecubital vein 30 min before induction of anesthesia to administer fluid (lactated Ringer solution) delivered at the ambient temperature (~10 ml·kg−1·h−1), and a 22-gauge catheter was placed in the left radial artery for blood pressure monitoring and collecting blood samples. An epidural catheter was placed via the L1-L2 or the L2-L3 vertebral interspaces with the patient in a lateral position. Anesthesia was induced with 2 mg/kg propofol and 0.15 mg/kg vecuronium bromide and was maintained with 0.4% isoflurane and 66% nitrous oxide in oxygen, and vecuronium bromide was infused at 0.025 mg·h−1. Minute ventilation was adjusted to maintain end tidal P CO2 at 35–40 mmHg by controlled mechanical ventilation. After 7 ml of 1% lidocaine injection into the epidural catheter, 5 ml/h of 0.25% bupivacaine was continuously infused to obtain epidural analgesia. The upper and lower levels of sensory blockade produced by epidural anesthesia were confirmed after emergence from general anesthesia by cold sensation and a pin-click test. PEEP (P group) or the leg-up position (L group) was applied 10 min after induction, and these conditions were maintained for 3 h. Blood pressure, heart rate (HR), oxygen saturation, end-tidal PCO2, and end-tidal isoflurane concentrations were continuously monitored. We excluded three patients whose surgical bleeding exceeded 500 ml, because they needed cardiovascular drugs to treat hypotension.

Measurement. Thermistor probes (Mon-a-therm, Mallinkrodt, St. Louis, MO) for skin temperature measurement were attached to the right forearm halfway between the elbow and the wrist, the right index fingertip (opposite the nail bed), the 10th thoracic dermatome and caudally to the fourth lumbar dermatome after emergence from general anesthesia by cold sensation and a pin-click test. PEEP (P group) or the leg-up position (L group) was applied 10 min after induction, and these conditions were maintained for 3 h. Blood pressure, heart rate (HR), oxygen saturation, end-tidal PCO2, and end-tidal isoflurane concentrations were continuously monitored. We excluded three patients whose surgical bleeding exceeded 500 ml, because they needed cardiovascular drugs to treat hypotension.

Blood samples were collected from the radial artery in each patient three times: 20, 90, and 180 min after induction of anesthesia. Samples were immediately centrifuged at 4°C, and aliquots of the plasma were stored at −80°C until hormone assays were performed. For the determination of plasma epinephrine (E) and norepinephrine (NE), high-performance liquid chromatography (HLC-725CA, Tosco, Japan) was used with an electrochemical detector after alumina extraction. The detection limit of the assay was 8 pg/ml, and the within- and between-assay coefficients of variation (CV) were <5%. The plasma renin activity (PRA) was determined with an ANG I radioimmunoassay kit (Renin RIABEAD, Dainabot, Japan); the level of detectability was 0.1 ng·ml−1·h−1, and the within- and between-assay CV were 4.5 and 5.5%, respectively. Plasma ANG II was measured with radioimmunoassay kits (Nichols Institute, CA); the level of detectability was 3.8 pg/ml, and the within- and between-assay CV were 4.0 and 8.1%, respectively.

Data analysis. To quantify thermoregulatory peripheral vasoconstriction, we employed a skin surface temperature gradient, because positive forearm-fingertip temperature gradient was reported to be closely correlated with reduction in blood flow in acral regions and to be less affected by ambient temperature than fingertip temperature alone (23). Moreover, the increase in forearm-fingertip temperature gradient is known to prevent further progress of hypothermia (13). We defined the body core temperature threshold for thermal vasoconstriction as the Tm, at which a successive rapid increase in forearm-fingertip temperature gradient occurred, and the threshold was determined by an inspector blinded to the experimental conditions on an individual basis. Thermal responsiveness below the threshold was defined by the slope of the linear portion of the forearm-fingertip temperature gradient-Tm relationship below the threshold on an individual basis and was calculated by least-squares linear regression. Mean skin temperature was calculated with the following equation: mean skin temperature = 0.43 × Tchest + 0.25 × Tforearm + 0.32 × Thigh, where Tchest is chest skin temperature, Tforearm is forearm skin temperature, and Thigh is thigh skin temperature. Because the change in T_forearm was not significantly different from the change in upper arm temperature in our preliminary experiments (n = 20), we replaced the upper arm temperature in the original formula (21) with T_forearm.

The effects of the modification of RATP and time were analyzed by general linear regression model procedures for ANOVA with repeated measures (1 between factor, 1 within factor), followed by a multiple-comparison test with Fisher’s least-significant difference test. Regression equations for the relationships were calculated using least-square linear regression. P values <0.05 were considered significant.

RESULTS

Table 1 shows the morphometric values and the preinduction values of cardiovascular and thermal variables, which are expressed as average values during the 30-min period. There were no significant differences in these variables among the groups. Table 2 shows the anesthetic management during surgery and the mean level of epidural blocks extended cephalad to the 10th thoracic dermatome and caudally to the fourth lumbar dermatome after emergence from general anesthesia in each group. These parameters were not significantly different between the groups.
Mean arterial pressure (MAP) and pulse pressure (PP) did not change during the study in any experimental conditions. HR decreased gradually during the study in all groups, and the change in HR at the end of the study was similar in all groups (−16 to 20 beats/min). The change in RATP (∆RATP) after the application of stress was 0.3 ± 0.1 mmHg in C, −3.0 ± 0.5 mmHg in P, and 2.3 ± 0.4 mmHg in L (P < 0.01), and these values remained unchanged until the study ended. The change in mean skin temperature was −0.9 ± 0.2°C in the C group, −1.0 ± 0.2°C in the P group, and −0.9 ± 0.2°C in the L group, showing no significant differences among the groups.

Figure 1 shows time courses of T es and forearm-fingertip temperature gradient starting from the preinduction control under each condition. The change in T es in the P group became significantly less than that in the C group starting 55 min after induction (P < 0.05), whereas the decrease in T es in the L group became significantly greater than that in the C group starting 45 min after induction (P < 0.05). T es at 180 min after induction was 35.1 ± 0.1°C in C, 35.7 ± 0.1°C in P, and 34.1 ± 0.1°C in L, showing significant differences (P < 0.01). The induction of anesthesia reduced the forearm-fingertip temperature gradient from 3.5°C to −1°C. The increase in forearm-fingertip temperature gradient occurred earlier in P than in C, and the magnitude of the increase was significantly larger in P than in C starting 65 min after induction (P < 0.05). However, the increase in forearm-fingertip temperature gradient was delayed and became significantly smaller in L than in C starting 105 min after induction (P < 0.05).

The functional relationship between forearm-fingertip temperature gradient and T es is shown in Fig. 2. The threshold for peripheral vasoconstriction (T es threshold) was 35.6 ± 0.1°C in C, 36.2 ± 0.2°C in P, and 34.8 ± 0.2°C in L (P < 0.01). The T es threshold for vasconstriction and ∆RATP were highly negative correlated (Fig. 3, top), and the regression equation was (T es threshold) = −0.3 (∆RATP) + 35.6 (r = 0.87, P < 0.001).

The slope of the forearm-fingertip temperature gradient-T es relationship below the T es threshold (thermoresponsiveness) was 17.4 ± 4.3 in the P group, which was significantly higher than that in the L group (3.0 ± 0.9; P < 0.01) but was not significantly different from that in the C group (10.8 ± 2.3). There was a highly negative correlation between the thermoresponsiveness and ∆RATP (Fig. 3, middle). The regression equation was (thermoresponsiveness) = −3.9 (∆RATP) + 11.3 (r = 0.75, P < 0.005).

A highly negative correlation was also observed between the final T es (180 min after induction of anesthesia) and ∆RATP (Fig. 3, bottom), and the regression equation was (Final T es) = −0.3 (∆RATP) + 34.9 (r = 0.91, P < 0.001).

Figure 4 shows hormonal response during the study. Plasma NE was significantly higher in P than in C and L at 180 min (P < 0.05). PRA and plasma ANG II were significantly higher in P than in C at all three time points (P < 0.05). PRA and plasma ANG II were slightly lower in L than in C.

Figure 5 shows T es and forearm-fingertip temperature gradient in the L + P group. The decrease in T es was at least partly prevented by applying PEEP starting 90 min after induction of anesthesia (P < 0.05).

**DISCUSSION**

We examined the interaction between baroreceptor-mediated blood pressure regulation reflexes and ther-

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**Table 1. Patient demographics**

<table>
<thead>
<tr>
<th></th>
<th>C Group</th>
<th>P Group</th>
<th>L Group</th>
<th>L + P Group</th>
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</thead>
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<tr>
<td>Age, yr</td>
<td>45 ± 3</td>
<td>47 ± 3</td>
<td>44 ± 4</td>
<td>42 ± 5</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>58 ± 4</td>
<td>59 ± 4</td>
<td>59 ± 4</td>
<td>55 ± 6</td>
</tr>
<tr>
<td>Height, cm</td>
<td>159 ± 3</td>
<td>158 ± 5</td>
<td>159 ± 4</td>
<td>154 ± 7</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>3/6</td>
<td>3/6</td>
<td>3/6</td>
<td>3/6</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>86 ± 2</td>
<td>91 ± 3</td>
<td>90 ± 3</td>
<td>85 ± 5</td>
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<td>Pulse pressure, mmHg</td>
<td>51 ± 1</td>
<td>53 ± 3</td>
<td>54 ± 2</td>
<td>50 ± 3</td>
</tr>
<tr>
<td>Central venous pressure, mmHg</td>
<td>5.6 ± 0.5</td>
<td>5.2 ± 0.6</td>
<td>5.4 ± 0.7</td>
<td>4.9 ± 0.7</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>84 ± 2</td>
<td>87 ± 2</td>
<td>83 ± 4</td>
<td>82 ± 5</td>
</tr>
<tr>
<td>Esophageal temperature, °C</td>
<td>36.8 ± 0.1</td>
<td>36.9 ± 0.2</td>
<td>36.8 ± 0.1</td>
<td>36.7 ± 0.1</td>
</tr>
<tr>
<td>Mean skin temperature, °C</td>
<td>33.8 ± 0.2</td>
<td>33.9 ± 0.2</td>
<td>33.8 ± 0.2</td>
<td>33.7 ± 0.3</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE of 9 subjects except that values of central venous pressure are of 5 subjects. C, control; P, positive end-expiratory pressure (PEEP); L, leg-up position; L + P, leg-up position with PEEP starting 90 min after induction of anesthesia.

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**Table 2. Anesthetic management during surgery**

<table>
<thead>
<tr>
<th></th>
<th>C Group</th>
<th>P Group</th>
<th>L Group</th>
<th>L + P Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambient temperature, °C</td>
<td>24.3 ± 0.2</td>
<td>24.2 ± 0.3</td>
<td>24.4 ± 0.4</td>
<td>24.5 ± 0.4</td>
</tr>
<tr>
<td>Blood loss at 180 min, g</td>
<td>244 ± 26</td>
<td>253 ± 21</td>
<td>259 ± 15</td>
<td>220 ± 39</td>
</tr>
<tr>
<td>Fluid replacement at 180 min, ml</td>
<td>2,333 ± 173</td>
<td>2,342 ± 171</td>
<td>2,371 ± 179</td>
<td>2,359 ± 201</td>
</tr>
<tr>
<td>End-tidal isoflurane, %</td>
<td>0.4 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>0.4 ± 0.1</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE of 9 subjects.
more regulatory control by modifying RATP during surgery. The most significant finding of this study was that the baroreceptor-mediated reflexes modified the thermoregulatory peripheral vasoconstrictor response to decreased body temperature during surgery; baroreceptor unloading by PEEP attenuates and baroreceptor loading by the leg-up position exaggerates perioperative hyperthermia by enhancing and attenuating thermoregulatory peripheral vasoconstriction in anesthetized patients (Figs. 1 and 2).

Modulation of RATP altered both the $T_{es}$ threshold and thermoresponsiveness below the $T_{es}$ threshold for thermal vasoconstriction (Fig. 2). Mack et al. (15) reported that baroreceptor unloading with lower body negative pressure shifted the threshold for thermal cutaneous vasodilation upward and reduced thermal responsiveness of the cutaneous vasodilation in exercising humans in a hot environment. Therefore, cutaneous circulation may be required to respond to competing signals from thermal or blood pressure-regulating reflexes. These findings suggest that baroreceptor unloading shifts the body core temperature threshold for both hyperthermia-induced cutaneous vasodilation and hypothermia-induced peripheral vasoconstriction to higher body core temperature. In contrast, baroreceptor unloading decreases thermal sensitivity for hyperthermia-induced cutaneous vasodilation but increases the sensitivity for hypothermia-induced peripheral vasoconstriction.

MAP and PP did not change significantly in any group during the study. Pulmonary stretch receptors or abdominal low-pressure baroreceptors may have complicated the effect of PEEP in the P group in peripheral vasoconstrictor response, because PEEP ventilation causes lung inflation and/or venous congestion. Sellden et al. (25) reported that these reflexes are

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**Fig. 1.** Esophageal temperature ($T_{es}$) and forearm-fingertip temperature gradient ($T_{forearm} - T_{fingertip}$) after induction of anesthesia. Positive end-expiratory pressure (PEEP; P) or the leg-up position (L) was applied 10 min after induction of anesthesia. Values are shown as means ± SE of 9 subjects. *Significant difference compared with the control (C) group.

**Fig. 2.** The functional relationship between $T_{forearm} - T_{fingertip}$ and $T_{es}$. Data are represented as means ± SE ($n = 9$ in each group) of every 5 min.

**Fig. 3.** The $T_{es}$ threshold for thermal peripheral vasoconstriction, thermoresponsiveness (gain), and the final $T_{es}$ (180 min after induction) as functions of the change in right atrial transmural pressure ($\Delta$RATP). Data were obtained from 5 patients in C, P, and L. ●, individual patients; ■, mean ± SE under each condition.
negligible compared with the effect of cardiopulmonary baroreceptors. Cardiac deafferentation after orthotopic cardiac transplantation strongly supports the interpretation that forearm vascular response to baroreceptor unloading is mediated mainly by cardiopulmonary baroreceptors (16). However, the possibility of the involvement of aortic and carotid baroreceptors cannot be ruled out in this study, because recent studies have shown that aortic pulse area (29) and carotid arterial diameter (14) were changed even though arterial pressure and PP were unchanged. Taken together, these data suggest that cardiopulmonary and/or arterial baroreceptors are involved in the modulation of hypothermia-induced peripheral vasoconstriction.

In the awake condition, tonic thermoregulatory vasoconstriction maintains a temperature gradient between the core and periphery of 2–4°C, resulting in a constant body core temperature. Diminished peripheral vasoconstrictor response due to the direct vasodilator effect and impairment of centrally thermoregulatory peripheral vasoconstriction induced by general anesthetics result in heat transfer from the body core to the periphery. Thus a larger decrease in body core temperature (1–1.5°C) should be due to the redistribution of heat, especially within the first hour after induction. This large decrease in body core temperature was followed by a gradual decline during the next 3–4 h due to heat loss to the environment, eventually reaching a plateau when arteriovenous-shunt tone is reestablished (9, 13, 30). The difference in $T_{es}$ between the three groups became significant starting 45 min after induction of anesthesia (Fig. 1), indicating that the baroreceptor-mediated reflex modulated both the heat redistribution from the core to the periphery and the heat loss to the environment by modulating peripheral skin blood flow.

Measurements of skin blood flow would have been useful as opposed to the forearm-finger temperature gradient, which may not reflect responses in nonacral regions. However, the shift in the core temperature threshold for peripheral skin vasoconstriction clearly plays a major role in modulation of perioperative hypothermia (13, 30). The difference in $T_{es}$ was well explained by the difference in forearm-fingertip temperature gradient among the groups.

Mean skin surface temperature contributes 20% to control of the thermoregulatory response during body core cooling, whereas the remaining 80% is responsible for the body core temperature (2). As the change in mean skin temperature did not show a significant difference among the groups in this study, this factor should be minor in the thermoregulatory response among the groups.

Plasma NE, PRA, and plasma ANG II responses were significantly different between C and P. On the other hand, although PRA and ANG II in L were slightly lower than in C, no significant differences were observed between C and L. Although previous studies have indicated that sympathetic nerve activity (SNA)
plays the dominant role in controlling skin blood flow (4, 7), plasma ANG II or other vasoactive agents may modify the response of cutaneous vasculature to SNA (22, 24). Alternatively, plasma NE is a crude marker for overall sympathetic nervous system activity, and selective decreases in sympathetic discharge to forearm vascular beds, for which the selective connection between the cardiopulmonary receptors and sympathetic nervous system activity is well established, could have occurred (1).

In the present study, data were obtained from the patients under general and epidural anesthesia in a clinical setting. General anesthesia and/or epidural anesthesia are known to affect the $T_{es}$ during surgery by lowering the threshold for thermal vasoconstriction in a dose-dependent manner (9, 30). Epidural anesthesia would also sympathectomize the lower extremities and limit the amount of skin and muscle vasoconstriction in response to the fall in body core temperature (9). However, we used a fairly low dose of volatile anesthetics by using epidural anesthesia, which suppressed the baroreceptor reflex activity minimally (17), and baroreceptor-mediated vasoconstriction of upper extremities and hormonal responses were well preserved (Figs. 1 and 4). In fact, the absence of change in blood pressure by modifying RATP, which presumably changes cardiac output, implies some increase or decrease in peripheral resistance. Use of atropine sulfate (0.5 mg) 60 min before induction of anesthesia to eliminate excessive vagal reflex during tracheal intubation was minimal and would not likely affect the baroreceptor reflex during surgery. Moreover, atropine sulfate does not affect thermoregulatory vasoconstriction (11). In any case, in the present study, as shown in Table 2, endtidal isoflurane concentration, epidural block levels after emergence from anesthesia, and anesthetic management were not significantly different among the groups, so the contribution of anesthetics to the difference in peripheral vascular responses between groups could be eliminated.

In summary, these results suggest that cardiac filling pressure or the level of baroreceptor loading influences the core temperature during surgery by modifying thermoregulatory peripheral vasoconstriction, and this is the first study that showed nonthermoregulatory modulation of peripheral vasoconstriction to decreased body core temperature.

**Perspectives**

Several studies have suggested that cutaneous circulation in humans subserves not only thermoregulatory but also nonthermoregulatory functions, such as baroreflexes, osmoregulation, and exercise during heat stress (3, 10, 15, 18, 19, 26). The limitations of cutaneous vasodilation during procedures known to unload baroreceptors in heat stress is not prevented by $\alpha_1$-adrenergic blockade (12) or local treatment of the skin with the antiadrenergic drug bretylium tosylate (10, 11), and the sweating response is also attenuated by baroreceptor unloading (15). The site of the integration of the thermoregulatory and cardiovascular systems during cold stress should be addressed.

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