Vascular reactivity and baroreflex function during hyperthermia in conscious rats

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DURING ACUTE HEATING IN RATS, the autonomic nervous system mediates a series of thermoregulatory and cardiovascular adjustments to reduce the rate of rise in body core temperature and to regulate arterial blood pressure (BP) (13, 14, 16). These adjustments are characterized by increases in arterial BP, heart rate (HR), visceral and renal vascular resistances, and a decrease in cutaneous vascular resistance (14, 16). The changes in vascular resistance in the viscera and kidney are primarily due to increases in sympathetic neural output (7, 13). The magnitude of these hemodynamic responses is determined by thermosensitive areas in the preoptic and anterior hypothalamic nuclei of the hypothalamus (2) and modulated by the arterial baroreceptors (12). Removal of baroreceptor control augments sympathoexcitatory responses and decreases thermal tolerance (12), suggesting that the baroreflex exerts an inhibitory influence on sympathetic cardiovascular adjustments during a thermal challenge.

Previous work has demonstrated that the hemodynamic responses to adrenergic agonists are altered during hyperthermia in anesthetized rats (11, 18). Both the pressor and regional vasoconstrictor responses to norepinephrine and ANG II are reduced when body core temperature is elevated above 40°C. The hemodynamic changes elicited by pharmacological agents such as adrenergic agonists should evoke reflex changes in HR and regional sympathetic nerve activity. Although these reflex responses have been studied during a variety of experimental conditions (1, 9), the effect of heating on baroreflex-mediated changes in HR and regional sympathetic nerve activity is unclear. Limited evidence suggests that the baroreceptor-HR reflex is enhanced with heating (21), but this may be dependent on the directional change in BP elicited by the stimulus (5). A general increase in baroreflex sensitivity during heating could mediate augmented sympathetic withdrawal in response to acute increases in BP. This would be consistent with the role of the arterial baroreceptors in suppressing the increases in arterial BP and mesenteric vascular resistance that occur during hyperthermia in rats (12). On the basis of the blunted pressor responses to adrenergic agonists observed during heating, it is tenable to postulate that the reflex neural responses may be attenuated as well. However, there are currently no data addressing the effect of heating on reflex neural responses to acute changes in BP in rats.

Therefore, the primary aim of this study was to determine the effect of heating on the reflex sympa-
thmetic neural and HR responses to vasoactive agents. Because previous studies examining the effect of hyperthermia on the hemodynamic responses to adrenergic agonists were conducted in anesthetized rats, a secondary aim of this study was to determine the effect of increasing temperature on the cardiovascular responses to vasoactive agents in unanesthetized rats. These aims were addressed in instrumented, freely moving conscious rats by concurrently measuring splanchnic sympathetic nerve activity (SpNA) and mesenteric blood flow during bolus injections of phenylephrine and sodium nitroprusside under normothermic and hyperthermic conditions.

METHODS

Eight male Sprague-Dawley rats (270–350 g, Harlan Labs, Indianapolis, IN) were used in these experiments. All rats were housed in individual cages and allowed standard rat chow and water ad libitum before any intervention. Rats were maintained on a 12:12-h light-dark schedule. All experiments were performed in accordance with guidelines approved by the Institutional Animal Care and Use Committee.

Surgery. Surgical procedures were performed ~24 h before experimentation as detailed previously (13, 21). After induction of anesthesia with an intraperitoneal injection of pentobarbital sodium (Nembutal, 50 mg/kg ip), the right femoral vein was isolated via an inguinal incision, and a catheter (PE-10 connected to PE-50, Clay Adams, Parsippany, NJ) was inserted for drug administration. A PE-50 catheter stretched to an outer diameter of ~0.7 mm was then inserted into the femoral artery to measure arterial BP. Catheters were tunneled subcutaneously, exteriorized at the nape of the neck, and flushed with heparinized saline. The inguinal incision was closed with suture.

A retroperitoneal flank incision was then made, and the area of the left splanchnic nerve and superior mesenteric artery was exposed. Once the nerve was identified, the mesenteric artery was isolated and a Doppler flow probe (Iowa Doppler Products, Iowa City, IA) was placed around the artery. The space between the probe and the artery was flushed with saline, and the probe was filled with ultrasonic transmission gel. After the flow probe was in position, a branch of the greater splanchnic nerve was dissected free of fat and connective tissue and placed on a bipolar platinum electrode. The quality of the nerve signal was evaluated with an oscilloscope and loudspeaker before the nerve and electrode were insulated with a small amount of silicone rubber gel. The transmission lines from the nerve electrode and the Doppler flow probe were exteriorized through a miniature connector at the animal’s neck. The flank incision was closed, and the animal was allowed to recover for 24 h. Antibiotics (chloromycetin sodium succinate, 50 mg/kg ip) were administered postoperatively, and animals were observed for resumption of eating and drinking behavior during the recovery period.

Experimental measurements. The femoral artery catheter was connected to a Gould P23XL pressure transducer to measure arterial BP. The signal was electronically averaged to obtain mean arterial blood pressure (MAP). A Grass 7P4 tachograph (Grass Instrument, Quincy, MA) triggered by the pulsatile BP signal was used to determine HR. Mesenteric blood flow velocity in kilohertz Doppler shift was monitored with the use of a pulsed Doppler flowmeter (University of Iowa, Bioengineering Resource Facility). The splanchnic nerve signal was amplified with a differential preamplifier, then rectified and integrated (time constant = 0.05 s) with the use of a nerve traffic analyzer (662C-3, University of Iowa, Bioengineering Resource Facility). Arterial BP, HR, mesenteric blood flow velocity, and raw and integrated nerve activity were continuously recorded on a computer with the use of a MacLab 8/s (ADInstruments Pty, Castle Hill, Australia) recording and analyzing system. Colonic temperature (Tco) was measured throughout the experiment with the use of a thermistor probe (YSI, Yellow Springs, OH) inserted ~6 cm past the anal sphincter into the colon and secured to the base of the tail. All rats were familiarized to the colonic probe before surgery.

Experimental protocol. Each rat was placed in an individual cage (25 × 25 × 20 cm, length × width × height) after the 24-h recovery period. Unrestrained conscious rats were attached to monitoring equipment, and the thermistor probe was inserted to measure Tco. Rats were then given 60–90 min to allow variables to stabilize. Bolus injections of phenylephrine (0.1–20.0 μg/kg iv) and sodium nitroprusside (0.1–40.0 μg/kg iv) were administered at baseline and during heating. After baseline injections were completed, rats were exposed to an ambient temperature of 43°C until Tco reached 41.5°C. During the second series of phenylephrine and sodium nitroprusside injections, Tco was maintained at 41.5°C by adjusting ambient temperature. Ambient temperature was regulated by varying the position of a 250-W infrared heat lamp located 40–50 cm above the animal. Ambient temperature was ~24°C during normothermic control periods.

The sequence of drug administration (phenylephrine vs. sodium nitroprusside) was randomized; however, complete data were obtained for a single drug before the next drug was administered. The total volume of fluid injected at each temperature was <500 μl. Hemodynamic parameters were allowed to return to preinjection values before the next injection and before initiating the heating phase of the protocol. After completing the entire protocol, a lethal injection of pentobarbital sodium was administered, and background noise from the system was recorded and subtracted from the total nerve activity.

Data analysis. MAP, HR, mesenteric blood flow, calculated mesenteric resistance, and mean integrated SpNA data that were analyzed were those obtained just before (baseline) and during the drug injections in the normothermic and hyperthermic states. Baseline values at 37 and 41.5°C were calculated as the mean of a 5-min period. MAP and mesenteric blood flow responses to drug administration were analyzed at the peak BP response during a 30-s period after drug injection. Mesenteric vascular resistance at these same time points was calculated from MAP and the mean flow velocity signal. Peak reflex HR and SpNA responses, independent of BP values, were also analyzed during a 30-s period after injection. Peak values for each variable were calculated as the mean of a 3- to 6-s period during the response. Changes in each variable were calculated with the use of preinjection and peak values for each dose.

Absolute values for HR (in beats/min) and mean integrated SpNA (in μV) were used to evaluate reflex responses in HR and SpNA to changes in MAP. Individual curves for HR and SpNA reflex responses were analyzed with the use of a sigmoidal logistic curve function (8, 23). The gain of the baroreflex curve was calculated from the first derivative of the sigmoidal logistic curve and plotted over a range of BP (8). Maximal gain was determined from this calculation.

Data are presented as means ± SE. Hemodynamic data were compared by repeated-measures analysis of variance followed by a modified Student’s t-test with a Bonferroni correction for multiple comparisons. Baroreflex curve param-
RESULTS

Table 1 shows the values for each variable before (baseline) and during (preinjection) drug administration during normothermia and hyperthermia. Heating to 41.5°C significantly increased baseline MAP, HR, mesenteric resistance, and SpNA. Mesenteric blood flow decreased significantly during heating. Preinjection values for MAP, HR, and mesenteric resistance remained significantly elevated during drug administration at 41.5°C, however, mesenteric blood flow and SpNA drifted toward control (37°C) levels over this same time period.

Mean group data for the hemodynamic and neural responses to bolus injections of phenylephrine at 37 and 41.5°C are presented in Fig. 1. Phenylephrine elicited dose-dependent increases in MAP and mesenteric resistance at 37 and 41.5°C. Heating significantly attenuated the pressor responses to phenylephrine for the four highest doses administered. The increases in mesenteric resistance were also attenuated for the three highest doses administered. HR and SpNA decreased in a dose-dependent manner at 37°C. Reflex bradycardia to phenylephrine was almost eliminated during heating despite an elevated HR. The reflex decreases in SpNA during heating were greater for every dose of phenylephrine; however, this difference was not statistically significant.

The hemodynamic responses to sodium nitroprusside are presented in Fig. 2. Sodium nitroprusside elicited dose-dependent changes in all variables at 37°C. The depressor responses to sodium nitroprusside were significantly attenuated during heating. In contrast, the decreases in mesenteric resistance were comparable at 37 and 41.5°C. Reflex tachycardia associated with sodium nitroprusside injections was significantly attenuated at 41.5°C compared with responses at 37°C for all doses. SpNA increased in response to bolus injections of sodium nitroprusside, although heating had no significant effect on the reflex neural responses to sodium nitroprusside.

The calculated parameters for the baroreflex curves are illustrated graphically in Fig. 3. Baroreflex and gain curves for HR at 37 and 41.5°C are presented in Fig. 4. Heating significantly altered several components of the MAP-HR baroreflex curve. The curve was...
shifted to the right, and the minimal HR or lower plateau \( (P_L) \) was significantly elevated at 41.5°C (Table 2). The reflex range was also markedly reduced at 41.5°C due to reductions in the maximal bradycardic \( (HR-P_L) \) and tachycardic \( (P_U-HR) \) responses. Maximal gain was reduced at 41.5°C \( (-2.63 \pm 0.57 \text{ beats/mmHg}) \) compared with 37°C \( (-4.69 \pm 0.97 \text{ beats/mmHg}) \).

Fig. 2. The effect of hyperthermia on the cardiovascular and splanchnic sympathetic neural responses to bolus injections of sodium nitroprusside (0.1–40.0 \( \mu \text{g/kg iv} \)) in conscious, unrestrained rats \( (n = 8) \). Injections were administered during normothermia (37°C) and hyperthermia (41.5°C). Values are expressed as a change from preinjection values. * \( P < 0.05 \) compared with 37°C.

Fig. 3. Graphic representation of sigmoidal MAP-effector response [heart rate (HR) or SpNA] curve describing baroreflex parameters calculated with the use of exponential sigmoid curve analysis (23). \( BP_{50} \), MAP at midpoint of the blood pressure range; \( P_U \) and \( P_L \), upper and lower plateaus for effector response variable; range, difference between \( P_U \) and \( P_L \); \( T_U \) and \( T_L \), upper and lower reflex thresholds for MAP; \( G_{\text{ave}} \), average gain of the linear portion of the curve. The responses to changes in MAP were related with the use of the following: HR or SpNA = \( P_L + \text{range}/(1 + e^{(\text{MAP} - BP_{50})}) \), where \( A = \left(-4.56G_{\text{ave}}/\text{range}\right) \), \( T_U = (BP_{50} - 1.317 \times \text{range})/(4.56/G_{\text{ave}}) \), and \( T_L = (BP_{50} + 1.317 \times \text{range})/(4.56/G_{\text{ave}}) \).

Fig. 4. Average MAP-HR baroreflex curves (A) and gain of baroreflex control of HR with variation in MAP (B) for conscious male Sprague-Dawley rats at 37 and 41.5°C. The single point in each curve represents the average \( BP_{50} \) before and during heating \( (n = 6) \).
beats/mmHg), whereas the average gain or slope (Gav) of the MAP-HR baroreflex curve was reduced by 45% during heating (Fig. 4 and Table 2).

Heating also altered the position of the MAP-SpNA baroreflex curve (Fig. 5), but it did not significantly change the sensitivity of the baroreflex (Fig. 5 and Table 3). The baroreflex curve was shifted to the right, indicating the reflex was operating at a higher BP. The P_U was shifted to a higher value and P_L was shifted downward, with P_L at 41.5°C being significantly smaller than the value at 37°C. The changes in P_L and P_U resulted in a significant increase in the reflex response range at 41.5°C compared with that at 37°C. The changes in P_U and P_L were also reflected in the maximal reflex responses to increasing and decreasing MAP. The differences between baseline SpNA and P_U (P_U-SpNA) and P_L (SpNA-P_L) increased comparably during heating (11–14 μV), but only the change in P_U-SpNA was statistically significant. In contrast to the MAP-HR baroreflex, the Gav (Fig. 5 and Table 3) and maximal gain (−1.4 ± 0.5 vs. −1.7 ± 0.5 μV/mmHg) of the MAP-SpNA baroreflex curve tended to increase with heating, but they were not significantly different from the values during normothermia.

**DISCUSSION**

The aim of this study was to determine the effect of hyperthermia on the cardiovascular and splanchnic sympathetic neural responses to bolus injections of phenylephrine and sodium nitroprusside in conscious, unrestrained rats. There are three major findings from this study. First, the systemic and regional hemodynamic responses to phenylephrine and the BP and HR responses to sodium nitroprusside were blunted during hyperthermia (41.5°C) compared with responses at 37°C. Second, the baroreflex control of HR was significantly attenuated during hyperthermia. Third, heating did not significantly alter the gain of the baroreflex control of SpNA, but it increased the reflex response range. These findings indicate that the hemodynamic responses to vasoactive agents are attenuated during hyperthermia in conscious rats. Furthermore, these data indicate that heating has differential effects on baroreflex control of HR and peripheral sympathetic nerve activity.

Bolus injections of phenylephrine and sodium nitroprusside elicited dose-dependent changes in arterial BP, HR, and mesenteric resistance at 37°C. The sys-

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**Table 2. Values of the parameters for the baroreflex-HR curves in conscious, unrestrained Sprague-Dawley rats at 37 and 41.5°C**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>37°C</th>
<th>41.5°C</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>P_L, beats/min</td>
<td>301 ± 22</td>
<td>409 ± 11</td>
<td>108 ± 19</td>
</tr>
<tr>
<td>P_U, beats/min</td>
<td>503 ± 13</td>
<td>494 ± 11</td>
<td>−10 ± 20</td>
</tr>
<tr>
<td>Range, beats/min</td>
<td>202 ± 27</td>
<td>85 ± 16</td>
<td>−117 ± 27</td>
</tr>
<tr>
<td>BP_{50}, mmHg</td>
<td>117 ± 2</td>
<td>146 ± 3</td>
<td>29 ± 4</td>
</tr>
<tr>
<td>Gav, beats·min^{-1}·mmHg^{-1}</td>
<td>−4.1 ± 0.8</td>
<td>−2.3 ± 0.5</td>
<td>1.8 ± 0.4</td>
</tr>
<tr>
<td>T_L, mmHg</td>
<td>99 ± 4</td>
<td>133 ± 2</td>
<td>34 ± 6</td>
</tr>
<tr>
<td>T_U, mmHg</td>
<td>135 ± 5</td>
<td>158 ± 5</td>
<td>23 ± 8</td>
</tr>
<tr>
<td>HR-P_L, beats/min</td>
<td>113 ± 22</td>
<td>42 ± 7</td>
<td>−71 ± 18</td>
</tr>
<tr>
<td>P_U-HR, beats/min</td>
<td>89 ± 6</td>
<td>43 ± 11</td>
<td>−47 ± 13</td>
</tr>
</tbody>
</table>

Values are means ± SE. Δ, difference between values at 41.5 and 37°C; P_U-HR, difference between preinjection HR and lower plateau (P_L); P_U-HR, difference between upper plateau (P_U) and preinjection HR; Range, difference between P_U and P_L; BP_{50}, MAP at midpoint of the blood pressure range; Gav, average gain of linear portion of the curve; T_L and T_U, upper and lower reflex thresholds for MAP; n = 6. *P < 0.05.

**Table 3. Values of the parameters for the baroreflex-SpNA curves at 37 and 41.5°C in conscious, unrestrained Sprague-Dawley rats**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>37°C</th>
<th>41.5°C</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>P_L, μV</td>
<td>17.3 ± 2.2</td>
<td>9.7 ± 2.2</td>
<td>−7.6 ± 2.4</td>
</tr>
<tr>
<td>P_U, μV</td>
<td>49.5 ± 8.8</td>
<td>66.7 ± 15.7</td>
<td>17.1 ± 9.4</td>
</tr>
<tr>
<td>Range, μV</td>
<td>33.3 ± 7.5</td>
<td>58.1 ± 14.2</td>
<td>24.8 ± 8.7</td>
</tr>
<tr>
<td>BP_{50}, mmHg</td>
<td>109 ± 3</td>
<td>133 ± 4</td>
<td>24 ± 7</td>
</tr>
<tr>
<td>Gav, μV/mmHg</td>
<td>−1.2 ± 0.4</td>
<td>−1.5 ± 0.4</td>
<td>0.3 ± 0.6</td>
</tr>
<tr>
<td>T_L, mmHg</td>
<td>95 ± 6</td>
<td>115 ± 9</td>
<td>21 ± 11</td>
</tr>
<tr>
<td>T_U, mmHg</td>
<td>123 ± 5</td>
<td>151 ± 5</td>
<td>27 ± 9</td>
</tr>
<tr>
<td>SpNA-P_L, μV</td>
<td>12.1 ± 2.7</td>
<td>23.3 ± 7.8</td>
<td>11.2 ± 7.6</td>
</tr>
<tr>
<td>P_U-SpNA, μV</td>
<td>20.2 ± 6.0</td>
<td>33.7 ± 6.9</td>
<td>13.6 ± 3.1</td>
</tr>
</tbody>
</table>

Values are means ± SE. SpNA-P_L, difference between preinjection SpNA and P_L; P_U-SpNA, difference between P_U and preinjection SpNA; n = 7. *P < 0.05.
temic and regional hemodynamic responses to phenylephrine and the depressor and tachycardic responses to sodium nitroprusside were attenuated at 41.5°C. In contrast, the SpNA responses during heating were increased or unchanged compared with responses at 37°C. These results provide experimental evidence that heating alters the hemodynamic and reflex sympathetic neural responses to vasoactive agents in conscious, unrestrained rats and confirm previous findings of attenuated hemodynamic responses in anesthetized rats (11, 18). However, data obtained from isolated vascular smooth muscle preparations indicate that adrenoceptor and contractile functions are not attenuated at temperatures above 37°C (17). Therefore, the hemodynamic responses to vasoactive agents during heating are likely due to local or systemic factors not present in in vitro preparations.

Because the regional hemodynamic and BP responses to vasoactive agents are attenuated during hyperthermia and the changes in BP should elicit baroreflex-mediated changes in HR and regional sympathetic neural outflow, HR and SpNA responses were analyzed to determine whether baroreceptor reflex function is altered during heating. Both the HR and SpNA baroreflex curves were shifted to the right and exhibited equivalent changes in MAP, MAP at the midpoint of the blood pressure range (BP50), and the upper and lower thresholds at 41.5°C. These changes reflect the increase in BP that occurs during heating. Hyperthermia also modified several other parameters related to the baroreflex control of SpNA and markedly altered baroreflex control of HR. The changes in baroreflex control of HR during heating were manifested in the MAP-HR curve by changes in the operating range, $P_L$, and the gain of the curve. The reflex response range was reduced during heating, primarily due to the inability to decrease HR in response to phenylephrine. However, the ability to increase HR in response to sodium nitroprusside was also attenuated at 41.5°C. Collectively, these data suggest that the ability to elicit reflex bradycardia and tachycardia is impaired during hyperthermia and further imply that the buffering capacity of the baroreceptor-HR reflex is diminished at 41.5°C. In addition, the maximal gain and $G_{ave}$ of the MAP-HR curve decreased by ~50%, suggesting that the sensitivity of the HR baroreflex is reduced during hyperthermia.

The blunted tachycardic responses are consistent with the findings of Gorman and Propppe (5). Although the mechanism for these attenuated responses is unclear, limited evidence suggests that $\beta$-adrenoceptor function is altered by heating (4, 18, 25). On the basis of these data, it is tenable to postulate that reflex tachycardia may be blunted during heating due to a decrease in $\beta$-adrenoceptor function. However, the attenuated tachycardic responses observed in the present study and by Gorman and Propppe (5) are probably due to the heating-induced increase in baseline HR and the concomitant decrease in parasympathetic nerve activity (6, 24).

Although a shift in baseline HR can partially explain the blunted tachycardic responses, the attenuated reflex bradycardia observed in this study cannot be attributed to this mechanism. As reported by Gorman and Propppe (5), an increase in baseline HR would be expected to facilitate reflex bradycardia. Parasympathetic withdrawal contributes significantly to the tachycardia during hyperthermia (6, 24). Therefore, one possible mechanism for the loss of reflex bradycardia could be due to an inability to increase vagal efferent nerve activity during heating in response to acute increases in BP. Alternatively, heating may alter cholinergic receptor function at the sinus node, thereby reducing the effector response to a similar neural input. However, the effects of heating on cholinergic receptor function and reflex vagal efferent nerve activity in conscious or anesthetized animals have not been reported.

In addition to altering the efferent pathways, hyperthermia may also modulate the central processing of baroreflex afferent signals. This is suggested by the change in gain of the MAP-HR baroreflex curve (9). The decrease in gain observed in this study connotes that the ability to compensate for transient disturbances in BP by changing HR is attenuated during heating. A centrally initiated change in baroreflex control of HR implies that hyperthermia, either directly or indirectly through other regulatory pathways, modifies the central processing of baroreceptor afferent signals. Activation of thermoreceptors, cardiopulmonary baroreceptors, posterior hypothalamic nuclei, and increased ventilation can modulate baroreflex control of HR (1). Although our data cannot confirm that hyperthermia alters baroreflex control of HR via a central mechanism, a centrally mediated change in baroreflex function due to interactions between thermoregulatory and nonthermoregulatory pathways is plausible.

In contrast to the current study, Stauss et al. (21) reported that heating increased the sensitivity of the baroreceptor-HR reflex in 12-mo-old Fischer rats. Although the results of the present report and those of Stauss et al. (21) appear to be contradictory, several important differences exist between the two studies. First, the rats used in the current study were younger and of a different strain than those used by Stauss et al. (21). Therefore, the difference between studies may be related to the age and strain of the rats used in each study. Comparisons between these studies are further complicated by differences in the methodology used to determine baroreflex sensitivity and the body temperature at which the measurements were made. The results from both studies indicate that body temperature has a significant effect on baroreflex control of HR. However, the changes in the sensitivity of the baroreceptor-HR reflex reported by Stauss et al. (21) were determined at body temperatures ranging between 37 and 41°C, whereas in the present study the MAP-HR baroreflex curves were assessed only at 37 and 41.5°C. Furthermore, Stauss et al. (21) reported that the sensitivity of the baroreceptor-HR reflex in 12-mo-old Fischer rats increased during heating up to 40°C and...
remained stable or slightly decreased with continued heating to 41°C. However, it is unclear from their data how baroreflex sensitivity might change at higher temperatures. In addition, the changes in BP analyzed by Stauss et al. (21) were relatively small and thus may not be representative of the entire baroreflex curve (9). Therefore, their results do not directly contradict the findings reported in the present study. In contrast to observations made in rats (the present study and Ref. 21), Gorman and Proppe (5) reported that heating to 39.5°C did not alter the sensitivity of the MAP-HR baroreflex curve in baboons. Although species differences may contribute to the discrepancy among the findings of Gorman and Proppe (5) and those of Stauss et al. (21) and the present study, these differences may also be related to the lower body temperature used by Gorman and Proppe. For example, heating anesthetized rats to 39°C also has no effect on the hemodynamic responses to vasoactive agents, whereas continued heating to 41.5°C significantly affects the responses to these agents (18), suggesting that changes in vascular responsiveness may be temperature dependent. Similarly, the effect of heating on the sensitivity of baroreflex control of HR may also be temperature dependent, with the greatest change occurring at higher body temperatures; however, the temperature dependence of these changes remains unclear due to limited data and methodological differences in the literature.

The effect of hyperthermia on the maximal reflex changes in SpNA to increases and decreases in BP was opposite to that observed for the baroreflex control of HR. On the basis of the barocurve parameters, reflex excitation of SpNA was augmented, and the total response range was significantly increased at 41.5°C (Fig. 5 and Table 3). The results presented in Figs. 1 and 2 also indicate that the changes in SpNA at 41.5°C are greater than or equal to the changes in SpNA at 37°C for a given change in BP. Although the majority of these changes was not statistically significant, the data suggest that the ability to buffer acute increases or decreases in BP is enhanced during heating. Although Gave and maximal gain did not significantly increase during heating, the parameters tended to be greater at 41.5°C.

The significant differences and/or trends observed in the changes in mesenteric vascular resistance and SpNA were apparent despite some variability in the baseline data during heating and drug injections. The hemodynamic and SpNA responses to hyperthermia were appropriate, but mesenteric blood flow and SpNA drifted toward baseline (37°C) during drug injections at 41.5°C. The reason for this drift is unclear. However, this change in baseline during drug injections at 41.5°C does not significantly affect the interpretation of the data because the values tended to decline over time rather than increase. Therefore, the lower preinjection values during heating, coupled with the attenuated hemodynamic responses, lend support to our hypothesis that increasing temperature per se is affecting the hemodynamic and baroreflex changes observed in this study.

The trend toward an increase in baroreflex-buffering capacity during hyperthermia suggests that tight regulation of BP is important for maintaining both cardiovascular and thermoregulatory function. Presumably, increased ability to raise SpNA in response to acute decreases in BP would help maintain visceral vasoconstriction during hyperthermia. An inability to elicit or maintain an adequate degree of vasoconstriction in the viscera severely impairs thermal tolerance (10). Similarly, thermal tolerance can also be reduced when sympathetic nervous system-mediated increases in BP and regional vasoconstriction are not regulated properly (12). Therefore, augmented reflex sympathoinhibition may counterbalance the sympathoexcitatory influence of increasing body core temperature (7, 13) by limiting transient increases in BP and regional (e.g., splanchnic) vascular resistance.

**Perspectives**

The results of the present study suggest that heating has differential effects on the baroreflex control of HR and peripheral sympathetic nerve activity. Although this is a novel finding with regard to hyperthermia, dissociation between baroreflex control of HR and peripheral sympathetic nerve activity has been observed in response to other physiologically relevant stimuli (1, 9, 15, 19, 20). For example, exogenous and endogenous ANG II can inhibit baroreflex bradycardia, while preserving baroreflex control of renal sympathetic nerve activity (15, 19). Hyperthermia also elicits a nonuniform pattern of sympathetic neural discharge to several vascular beds to maximize heat loss, while maintaining arterial BP (3, 20). In general, the dissociation between the control of HR and regional sympathetic nerve activity may contribute to the maintenance of arterial BP during stress. For example, a change in baroreflex function may become significant during hyperthermia in an attempt to offset the loss of compensatory vasoconstriction in the splanchnic region and subsequent circulatory collapse that occurs at high body temperatures (10, 11, 14, 16). Under these conditions, the loss of reflex bradycardia may contribute to the maintenance of arterial BP by preserving cardiac output at high body temperatures (3, 22). This adjustment alone is generally not sufficient to maintain arterial BP during heating (10). However, it may complement increases in regional sympathetic nerve activity and vascular resistance in other vascular beds in an attempt to compensate for the loss of vasoconstriction in the splanchnic region and delay the onset of circulatory collapse (7, 10, 16, 21).

In summary, heating significantly blunted the hemodynamic responses to bolus injection of phenylephrine and sodium nitroprusside in conscious, unrestrained rats. These hemodynamic changes were accompanied by increased or unchanged reflex responses in SpNA. Reflex changes in HR and SpNA were also analyzed to assess baroreflex function during heating. Hyperther-
emia significantly decreased the operating range and the gain of the MAP-HR baroreflex. In contrast, baroreflex control of SpNA was shifted to a higher BP, and the operating range of the reflex was increased, but the sensitivity of the MAP-SpNA baroreflex was not significantly altered during heating. These data suggest that heating has differential effects on baroreflex control of HR and SpNA. This may be due to a specific effect of heating on cholinergic receptors or the parasympathetic nervous system; however, further studies are required to support this postulate.

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REFERENCES