Effect of heating on the hemodynamic responses to vasoactive agents

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Masset, Michael P., Stephen J. Lewis, and Kevin C. Kregel. Effect of heating on the hemodynamic responses to vasoactive agents. Am. J. Physiol. 275 (Regulatory Integrative Comp. Physiol. 44): R844–R853, 1998.—During hyperthermia, vasoconstrictor tone in the viscera is lost despite high levels of sympathetic neural outflow and plasma catecholamines, suggesting that vascular responsiveness to adrenergic receptor stimulation is reduced. The purpose of this study was to determine whether adrenoceptor-mediated control of vascular resistance is altered at high body core temperatures. The hemodynamic responses to adrenoceptor agonists were examined in chloralose-anesthetized rats heated to colonic temperatures (Tco) of 37, 39, and 41.5°C. Elevating Tco to 39°C did not alter the hemodynamic responses to any of these agents. Further heating to 41.5°C markedly attenuated the hemodynamic responses to α- and β-adrenergic agonists. Similarly, the regional and systemic hemodynamic responses to ANG II and endothelin were also reduced at 41.5°C. In contrast, the hemodynamic responses to endothelium-dependent and -independent vasodilator agents were unchanged or slightly reduced at 41.5°C. The blunted hemodynamic responses observed at 41.5°C indicate that vascular reactivity to vasoconstrictor agents is reduced with hyperthermia and suggest that this nonspecific change in vascular responsiveness may contribute to the circulatory collapse associated with high body temperatures.

Prolonged exposure to high ambient temperatures can lead to heat stroke and circulatory collapse (13, 24). Although the pathogenesis of heat stroke is unknown, several potential mechanisms have been proposed, including a loss of central nervous system control of thermoregulatory function and physiological failure (13). The end result in either event is an inability to maintain blood pressure homeostasis and subsequent production of a shock-like syndrome. Arterial blood pressure is maintained during hyperthermia by a series of hemodynamic adjustments that balance vasodilation in cutaneous regions with vasoconstriction in the viscera (19, 24). During the early stages of hyperthermia, vasoconstriction in the splanchnic region is well maintained; however, the ability to sustain this vasoconstriction at high body temperatures (>42°C) can be lost, marking the onset of circulatory collapse (24).

The underlying mechanism for the marked vasodilation in the mesenteric artery is unknown. However, this loss of compensatory vasoconstriction does not appear to be due to reduced efferent neural drive to the region because splanchnic sympathetic nerve activity and plasma catecholamine levels are elevated during moderate and severe hyperthermia (21, 23). Because splanchnic nerve activity and plasma catecholamine levels increase during heating yet vasoconstrictor tone is lost, it is possible to speculate that heating alters adrenergic receptor function or the signaling pathway linked to these receptors (20). Kregel and Gisolfi (20) reported that the hemodynamic responses to vasoconstrictor agents in anesthetized rats were decreased with hyperthermia and concluded that adrenoceptor function is altered with increasing body core temperature. Although some data obtained using vascular ring preparations support this conclusion (3, 32), corroborating evidence based on in vivo models is limited. Therefore, one aim of this study was to determine whether high body core temperature alters the hemodynamic responses to adrenoceptor agonists in chloralose-anesthetized rats.

In contrast to vasoconstrictor agents, little attention has been given to the effect of hyperthermia on the hemodynamic responses to vasodilator agents. A change in responsiveness to vasodilator agents during hyperthermia might provide insight into whether the responsiveness to endogenous nitric oxide is altered. Recent evidence suggests that nitric oxide is released during hyperthermia (14) and can contribute to the regional vascular adjustments to hyperthermia in rats (22, 40). Furthermore, limited data from in vitro preparations indicate that decreasing temperature alters the relaxant responses to cholinergic agonists in cutaneous and deep vessels (6, 12, 29), suggesting that the relaxation responses to endothelium-derived relaxing factors can be modulated by temperature. Enhanced responsiveness to endogenous vasodilator substances may promote the loss of vasoconstrictor tone in the splanchnic region by eliciting relaxation or by counteracting catecholamine and sympathetic nervous system-mediated vasoconstriction (26). However, the effect of heating on the cardiovascular responses to vasodilator agents is not known. Therefore, the second aim of this study was to determine whether the hemodynamic responses to endothelium-dependent and -independent vasodilator agents are altered in anesthetized rats heated to body core temperatures above 37°C by exposure to warm ambient conditions.

METHODS

Sixty male Sprague-Dawley rats (Harlan Labs, Indianapolis, IN) weighing 230–350 g were used for this study. 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-h light-dark schedule. All experiments were performed in accordance with guidelines approved by the Institutional Animal Use and Care Committee.
Surgery. The surgical procedures outlined below have been described in detail previously (24). Initial anesthesia was achieved via an intraperitoneal injection of methohexital sodium (Brevital, 55 mg/kg body wt). The right jugular vein was isolated and two catheters (PE-10, Clay Adams, Parsippany, NJ), one for Brevital and one for \( \alpha \)-chloralose, were inserted for infusion of additional anesthetics. Anesthesia was maintained throughout the surgery using Brevital (10 mg-kg\(^{-1} \cdot \)h\(^{-1} \)) and \( \alpha \)-chloralose (50 mg-kg\(^{-1} \cdot \)h\(^{-1} \)). A third catheter (PE-50) filled with heparinized saline was inserted into the right carotid artery for measurement of arterial blood pressure. After surgical procedures were completed, anesthesia was maintained throughout the remainder of the experiment with \( \alpha \)-chloralose.

After performing a midline laparotomy, we isolated segments of the superior mesenteric and left renal arteries and placed a Doppler flow probe (Iowa Doppler Products, Iowa City, IA) filled with ultrasonic transmission gel around each artery. The midline incision was then closed with surgical clips. An incision was also made in the left hindlimb region at the level of the inguinal fold, and the iliac artery was isolated and fitted with a Doppler flow probe. A water-filled heating pad was used to maintain body temperature between 36 and 37°C throughout the surgical period. Colonic temperature (Tco) was measured throughout the experiment using a thermistor probe (Yellow Springs Instruments, Yellow Springs, OH) inserted 6 cm past the anal sphincter into the colon.

Hemodynamic measurements. Blood pressure was determined by connecting the carotid artery catheter to a Gould P-23XL pressure transducer (Gould, Glen Burnie, MD). The signal was electronically averaged to obtain mean arterial blood pressure (MAP). Heart rate was determined using a Grass 7P4 tachograph (Grass Instruments, Quincy, MA) that was triggered by the pulsatile blood pressure signal. Mesenteric, renal, and hindlimb blood flow velocities in kilohertz Doppler shift were monitored using a pulsed Doppler flowmeter (University of Iowa, Bioengineering Resource Facility).

Experimental protocol. Three groups of rats were used for these experiments (n = 20 per group). One group of rats received injections of the adrenergic agonists phenylephrine (PE, 0.5–8.0 \( \mu \)g/kg), norepinephrine (NE, 0.1–2.5 \( \mu \)g/kg), epinephrine (Epi, 0.25–2.0 \( \mu \)g/kg), and isoproterenol (0.25–1.0 \( \mu \)g/kg). Injections of ANG II (0.1–1.0 \( \mu \)g/kg), ACh (0.1–5.0 \( \mu \)g/kg), sodium nitroprusside (SNP, 1.0–10.0 \( \mu \)g/kg), and S-nitrosothioglycine (SNC, 25–250 nmol/kg) were administered to a second group of rats. A third group received injections of endothelin-1 (ET-1, 0.1–0.1 \( \mu \)g/kg), ATP (10–200 \( \mu \)g/kg), calcitonin gene-related peptide (CGRP, 50–500 nmol/kg), and pituitary adenylate cyclase-activating polypeptide (PACAP, 0.1–2.0 \( \mu \)g/kg). Several of the agents used in these experiments were included to determine the specificity of any observed changes in receptor function. The vasoconstrictor agents ANG II and ET-1 were included as controls for the \( \alpha \)-adrenoceptor agonists. ATP and SNC served as control agents for the endothelin-dependent and -independent vasodilators ACh and SNP, respectively. CGRP and PACAP were the control agents for the \( \beta \)-adrenergic agonist isoproterenol.

The hemodynamic responses to bolus injections of vasoactive agents were recorded at Tco of 37, 39, and 41.5°C. Each rat was allowed to stabilize at a Tco of 37°C for 20–35 min before the initial series of injections was started. After completion of the first series of injections, Tco was elevated to 39°C and maintained at that temperature until a second series of injections was completed. Drug injections were repeated for a third time while Tco was maintained at 41.5°C. The sequence of adrenoceptor agonist administration (i.e., PE vs. NE) was randomized; however, complete dose-response data were obtained for a single drug before the next drug was administered at a given Tco.

A 250-W infrared heat lamp positioned 60 cm above the animal was used to elevate and maintain Tco. Ambient temperature was monitored during the heating period using a thermistor probe positioned between the forelimbs of the supine animal. Mesenteric, renal, and hindlimb blood flow velocities, along with MAP, heart rate, and Tco, were continuously monitored throughout the experiment (Grass model 7 polygraph, Grass Instruments). All drugs were dissolved in distilled water. ANG II was purchased from CIBA (Summit, NJ). All other agents were purchased from Sigma (St. Louis, MO). SNC was made by combining 1-ml solutions of equal concentrations (0.2 mol/l) of sodium nitrite and L-cysteine (30). All drugs were dissolved in distilled water. SNP and SNC were protected from the light during the experimental protocol.

Data analysis. Vascular resistance was calculated from MAP and the mean flow velocity signal at various time points during the experiment. The hemodynamic responses to drug administration were calculated at the peak response for each variable, and changes in response to drug injection were expressed as a percentage change from preinjection values to correct for differences in baseline values. Measured variables were allowed to return to preinjection values before the next injection and before the heating protocol was initiated or resumed.

Data were analyzed by repeated-measures ANOVA and paired \( t \)-tests. The hemodynamic responses for each agonist obtained at 37°C were compared with the responses at either 39 or 41.5°C; however, the responses at 39°C were not compared with those at 41.5°C due to missing data at different temperatures. The hemodynamic responses to heating were compared by repeated-measures ANOVA followed by a modified Student’s \( t \)-test with a Bonferroni correction for multiple comparisons. Statistical significance was set at \( P < 0.05 \).

RESULTS

Hemodynamic responses to heating. The hemodynamic variables for each stage of the heating protocol are presented in Table 1. MAP decreased when Tco was raised to 39°C and significantly increased above baseline in all groups with further heating to 41.5°C. Changes in MAP during heating were accompanied by a significant tachycardia at 39 and 41.5°C. Mesenteric and renal vascular resistances were relatively unchanged during heating in rats receiving the adrenoceptor agonists or endothelin, whereas mesenteric and renal resistances in rats receiving ANG II were significantly increased above baseline at 41.5°C. Heating to 39°C elicited a marked vasodilation in the hindlimb, which was maintained during heating to 41.5°C.

Effect of heating on hemodynamic responses to vasoconstrictor agents. \( \alpha \)-Adrenergic agonists elicited dose-dependent increases in MAP and mesenteric and renal vascular resistances at each temperature. The effect of heating on the hemodynamic responses to NE, PE, and Epi was comparable across agents. Therefore, the hemodynamic responses to NE are presented in Fig. 1 as a representative example for the adrenergic agonists. To illustrate the dose-response nature of the blood pressure responses to adrenoceptor stimulation, thepressor responses to PE and Epi at 37 and 41.5°C are shown in Table 2. Increasing Tco from 37 to 39°C
had little effect on the hemodynamic responses to any of these agents. However, a further increase in Tco to 41.5°C significantly altered the peak changes in MAP and regional vascular resistances. The pressor responses to all doses of NE, PE, and Epi were significantly attenuated at 41.5°C. Changes in mesenteric and hindlimb resistances in response to PE and Epi at 41.5°C tended to be smaller compared with responses at 37°C, but this difference was not statistically significant. Changes in renal resistance in response to the α-adrenergic agonists were not altered with increasing Tco.

The hemodynamic responses to ANG II are presented in Fig. 2. ANG II elicited pressor responses at all temperatures. These responses were significantly attenuated at a Tco of 41.5°C compared with 37°C. ANG II also caused potent vasoconstrictor responses in the mesenteric, renal, and hindlimb vascular beds. Mesen-
teric vasoconstriction was markedly attenuated at 41.5°C, whereas vasoconstrictor responses in the hindlimb were blunted at 39 and 41.5°C. Changes in renal resistance in response to ANG II were unaltered with heating. ET-1 increased MAP and regional vascular resistances in all arteries studied (Fig. 3). The pressor responses to endothelin at 37°C were unaffected by heating to 39°C but were nearly abolished at 41.5°C. The dose-dependent vasoconstrictor responses in the mesenteric artery were also reduced at 41.5°C, with the responses to the highest dose being significantly attenuated. Changes in renal resistance were comparable at all temperatures. The vasoconstrictor responses in the hindlimb tended to be smaller at 41.5°C compared with responses at 37°C; however, there were no statistically significant differences among responses in the hindlimb.

Effect of heating on hemodynamic responses to vasodilator agents. The vasodilator agents isoproterenol, ACh, SNP, and SNC elicited depressor and vasodilator responses at all temperatures (Figs. 4–6). The hemodynamic responses to the β-adrenergic agonist isoproterenol are presented in Fig. 4. Isoproterenol elicited dose-dependent decreases in MAP and regional vascular resistances, which were markedly reduced at 41.5°C but not at 39°C.

The hemodynamic responses to the endothelium-dependent vasodilator ACh are shown in Fig. 5. Bolus injections of ACh decreased MAP in a dose-dependent manner. The maximum decrease in MAP was comparable across temperatures (40–50%). ACh also elicited vasodilator responses in the mesenteric artery and hindlimb. These responses were not altered by heating to 39 or 41.5°C. In the renal artery, the vasodilator response to ACh was relatively constant across doses. ACh-evoked vasodilation in this artery was significantly enhanced at 41.5°C compared with 37°C (Fig. 5).

### Table 2. Percent changes in blood pressure in response to bolus injections of PE and Epi given at colonic temperatures of 37 and 41.5°C

<table>
<thead>
<tr>
<th></th>
<th>37°C</th>
<th>41.5°C</th>
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<tr>
<td>PE, µg/kg</td>
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<tr>
<td>0.5</td>
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<td>1.0</td>
<td>13±2</td>
<td>2±1*</td>
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<td>4.0</td>
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<td>6.0</td>
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<td>8.0</td>
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<td>18±3*</td>
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<tr>
<td>Epi, µg/kg</td>
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<td>0.25</td>
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<tr>
<td>2.0</td>
<td>26±4</td>
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Values are means ± SE; n = 5–6 per drug. Changes were calculated from preinjection and peak values at each temperature. PE, phenylephrine; Epi, epinephrine; Δ, change. *P < 0.05 compared with 37°C.
Fig. 3. Effect of heating on percent changes in MAP and regional vascular resistance in response to bolus injections of endothelin-1 (0.1–1.0 µg/kg). Injections were administered to chloralose-anesthetized rats at colonic temperatures of 37, 39, and 41.5°C (n = 6–8). Values are means ± SE. *P < 0.05 compared with 37°C.

Fig. 4. Effect of heating on percent changes in MAP and regional vascular resistance in response to bolus injections of isoproterenol (0.125–1.0 µg/kg). Injections were administered to chloralose-anesthetized rats at colonic temperatures of 37, 39, and 41.5°C (n = 6–8). Values are means ± SE. *P < 0.05 compared with 37°C.
The changes in MAP and regional vascular resistances in response to SNP are shown in Fig. 6. SNP, an endothelium-independent vasodilator, decreased MAP and regional vascular resistances in a dose-dependent manner. Heating to 39°C had little effect on the depressor and vasodilator responses to SNP. At 41.5°C, the decreases in MAP were slightly less than at 37°C. The hemodynamic responses also tended to be smaller at 41.5°C compared with responses at 37°C, but these differences did not reach statistical significance.

The depressor responses to SNC at 37 and 41.5°C are presented in Table 3. SNC caused dose-dependent decreases in MAP and regional vascular resistances at a given Tco. The hemodynamic responses to SNC were comparable at 37 and 39°C. At 41.5°C, the depressor responses to SNC were significantly attenuated compared with responses at 37°C. The vasodilator responses to SNC were also smaller at 41.5°C, with the responses in the mesenteric artery being significantly attenuated compared with responses at 37°C.

The hemodynamic responses to the dilator agents ATP, CGRP, and PACAP were generally unaffected by heating; therefore, only the depressor responses at 37 and 41.5°C are presented in Table 3. Injections of ATP decreased MAP and mesenteric and hindlimb resistance and increased renal resistance. However, the depressor and vasodilator responses in the mesenteric artery tended to be smaller at 41.5°C compared with responses at 37°C. The vasoconstrictor responses in the renal artery were variable and unchanged with heating to 39 or 41.5°C.

CGRP and PACAP decreased MAP and regional vascular resistances in all vascular beds studied. The depressor responses to CGRP were not affected by heating to 39°C, but the responses to the two highest doses of CGRP were attenuated at 41.5°C (Table 3). Heating had a variable effect on the vasodilator responses to CGRP in renal arteries and no effect on the vasodilator responses in the hindlimb. In the mesenteric artery, the vasodilator responses to CGRP were blunted or converted to vasoconstriction at 41.5°C.

PACAP decreased MAP in a dose-dependent manner that was not altered by heating (Table 3). Vascular resistances in the mesenteric artery and hindlimb decreased in response to PACAP, whereas the vasodilator response in the renal artery was relatively constant. During heating, the vasodilator responses to PACAP in the mesenteric and renal arteries were somewhat variable; however, these responses were not different from those at 37°C. Vasodilator responses in the hindlimb were less variable but also not changed during hyperthermia.

**DISCUSSION**

The purpose of this study was to determine the effect of heating on the hemodynamic responses to adrenoceptor agonists. The major findings of this study are that 1) the hemodynamic responses to α- and β-adrenoceptor agonists are blunted by heating to a Tco of 41.5°C but not to 39°C; 2) the effect of heating on vascular responsiveness is not specific for adrenoceptor agonists, as...
evidenced by the blunted hemodynamic responses to ANG II and ET-1 at 41.5°C, suggesting that postreceptor signaling may be altered at high body temperatures; and 3) heating does not significantly affect the hemodynamic responses to endothelium-dependent and -independent vasodilator agents. Overall, these results demonstrate that heating causes a nonselective loss of vascular responsiveness to vasoconstrictor agents, which may contribute to the loss of compensatory vasoconstriction in the mesenteric region during hyperthermia.

The hyporesponsiveness to adrenoceptor agonists during hyperthermia observed in this study support and extend the findings of Kregel and Gisolfi (20) and Rogers et al. (33). Kregel and Gisolfi (20) reported that the responses to single doses of NE or ANG II were attenuated in anesthetized rats over a range of body temperatures from 40 to 42°C. Rogers et al. (33) also demonstrated that heating from 23 to 47°C caused a progressive decline in responsiveness to electrical stimulation and catecholamines in perfused canine mesenteric arteries. Collectively, these data indicate that the blunted responsiveness to adrenergic receptors is temperature dependent and may be related to the duration of heating or the autonomic cardiovascular and thermoregulatory adjustments that occur as Tco approaches 40–41°C.

There are several potential mechanisms underlying the attenuated hemodynamic responses observed in this study. For example, evidence from isolated vascular smooth muscle and membrane preparations suggests that heating alters adrenergic receptor affinity (3, 32, 39). However, the observation in the current study that heating had comparable effects on the pressor responses to all of the vasoconstrictor agents,

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<th>Δ Blood Pressure, %</th>
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Values are means ± SE; n = 5–6 per drug. Changes were calculated from preinjection and peak values at each temperature. *P < 0.05 compared with 37°C.
together with the data of Kregel and Gisolfi (20), suggests that this change in receptor function during heating is not selective for adrenergic receptors. This postulate is further supported by the data of Vanhoutte and colleagues (36, 37), who demonstrated that warming depressed the contractile responses to several vasoconstrictor agents and electrical stimulation in canine venous smooth muscle. Changes in temperature have also been shown to uncouple G proteins from β-adrenoceptors (11), decrease the number of functional cell surface receptors in rat parotid glands (11), and alter the efficiency of receptor-response coupling in vascular smooth muscle (7, 8).

In contrast to the results obtained in this study, several investigators have reported that heating to temperatures above 37°C either had no effect on (34) or increased (18, 31) the contractile responses to NE in isolated vessels. These in vitro data imply that receptor-response coupling and affinity are not altered by heating. Additional data from in vitro preparations indicate that the contractile responses to receptor-independent agents such as potassium chloride are facilitated by heating (3, 32, 37). Because potassium chloride elicits constriction by causing depolarization (16) and is not dependent on receptor activation, this potentiation is considered to be a direct effect of heating on vascular smooth muscle contractility. The limited evidence from in vivo models supports the suggestion that contractility is maintained during heating to 42°C (20). Therefore, the attenuated hemodynamic responses observed in this study are not likely due to a decrease in vascular smooth muscle contractility. The disparate results between in vivo and in vitro data imply that the release of a local or systemic factor(s) may be necessary to observe the change in responsiveness to vasoactive agents during heating.

The rise in T° during heating is accompanied by progressive increases in sympathetic neural outflow and plasma catecholamine levels (21, 23). As suggested by the attenuated hemodynamic responses to both α- and β-adrenoceptor agonists at 41.5°C, these elevated levels of circulating catecholamines could contribute to a temperature-dependent desensitization of adrenergic receptors. Desensitization of α- and β-adrenoceptor receptors in vivo and in vitro is generally observed after prolonged exposure to physiological or pharmacological levels of adrenergic agonists (4, 11, 15, 38). However, functional desensitization of β-adrenoceptors has been reported after a single bout of exercise in humans (5) and dogs (9). Furthermore, a single exposure to immobilization or open field stress was associated with β-adrenergic receptor redistribution and downregulation in rats (4), suggesting that a stress-induced elevation of circulating catecholamines can alter adrenergic receptor function. Taken together, these data suggest that functional desensitization of adrenergic receptors can occur in vivo under physiologically relevant conditions.

Receptor desensitization after exposure to high concentrations of adrenergic agonists is not limited to β-adrenoceptors. Lefkowitz and colleagues (2, 25) reported that short-term desensitization of α1- and β2-adrenoceptors in DDT1 MF-2 smooth muscle cells can occur after exposure to NE, isoproterenol, or bradykinin for <30 min. Limited evidence also suggests that “cross-system” phosphorylation by protein kinase A (PKA) and protein kinase C can occur between α1- and β2-adrenoceptors (2). Receptor desensitization due to prolonged exposure to an agonist is generally associated with receptor redistribution and a decrease in receptor number (4, 11, 15). In contrast, short-term desensitization is thought to occur subsequent to receptor phosphorylation (2, 15, 25). Phosphorylation of β-adrenergic receptors by PKA, which can uncouple the receptor from the regulatory G protein, is associated with activation of peripheral receptors by circulating catecholamines (15). On the basis of these reports, it is possible to speculate that the attenuated hemodynamic responses to α- and β-adrenoceptor agonists observed in this study are due to receptor desensitization subsequent to heating-induced increases in circulating catecholamines and sympathetic neural outflow. However, our data do not provide direct evidence for this. Receptor binding studies and measurements of GTPase activity and receptor phosphorylation would be necessary to confirm this postulate.

Because α-adrenergic, ANG II, and ET-1 receptors are linked to a common intracellular signaling pathway (27, 35), the blunted hemodynamic responses to ANG II and endothelin imply that receptor desensitization is not specific for adrenergic receptors. Alternatively, the responses to ANG II and endothelin can be modulated by their interaction with the sympathetic nervous system (1, 10). Therefore, the attenuated responses to these agents could be related to a loss of adrenoceptor function and not directly to heating-induced changes in ANG II and endothelin receptor function. Similarly, CGRP and PACAP receptors share a common second messenger system with β-adrenergic receptors. These agents exert their effects via activation of G protein-coupled receptors which activate adenylyl cyclase (15, 17, 28). However, the hemodynamic responses to CGRP and PACAP were unchanged or slightly reduced during heating compared with the marked attenuation of the responses to isoproterenol. Although these observations argue against heterologous desensitization as a potential mechanism for our results and imply that heating may have a specific effect on α- and β-adrenoceptors, the blunted responses to ANG II and ET-1 indicate that heating causes a nonspecific decrease in vascular responsiveness to vasoconstrictor agents.

In contrast to the responses to vasoconstrictor agents, heating did not significantly alter the hemodynamic responses to endothelium-dependent and -independent vasodilator agents. On the basis of in vitro data (12, 29, 37), the general lack of an effect of heating on the responses to ACh and ATP is contrary to the expected results. The majority of the experiments conducted on isolated vascular smooth muscle indicate that changing temperature alters the relaxant responses to ACh. In cutaneous vessels, cooling to 24°C facilitates the relaxation responses to ACh (12, 29) and methacholine (6) and augments nitrite production (6). The opposite
effects are observed in deep vessels (6, 12, 29), except for the rat aorta, where responses to carbachol are augmented by cooling (18). Furthermore, cooling augments the constrictor responses to ATP in canine cutaneous veins (37). Collectively, these data imply that heating should enhance the vasoconstrictor responses to ACh and ATP in deep vessels, namely the mesenteric, renal, and femoral arteries. Aside from responses to ACh in the renal artery, responses in the other vascular beds showed a trend for smaller changes during heating, suggesting that nitric oxide release in response to endothelium-dependent vasodilator agents is not altered during hyperthermia. In contrast, the responses to SNP and SNC were slightly reduced during heating. These data are in agreement with observations made by Karaki and Nagase (18), who reported that heating reduces and cooling augments relaxation responses to SNP in rat thoracic aorta. The responses to ACh and ATP, combined with the hemodynamic responses to SNP and SNC, demonstrate that hyperthermia does not alter the sensitivity to endogenous (ACh and ATP) or exogenous (SNP and SNC) nitric oxide. Therefore, these results imply that the loss of compensatory vasoconstriction in the mesenteric artery during severe hyperthermia is not due to an enhanced sensitivity of the smooth muscle to endothelium-derived relaxing factors.

In summary, the results from this study demonstrate that the hemodynamic responses to vasoconstrictor agents are blunted by raising body temperature to 41.5°C. In general, the hemodynamic responses were not altered at 39°C, suggesting a temperature-dependent loss of responsiveness. Furthermore, responses to α- and β-adrenergic agonists and nonadrenergic vasoconstrictor agents were equally affected, indicating that this attenuation may not be specific for adrenergic receptors. Because the receptors for these agents are coupled to the same intracellular pathway, any effect of heating on receptor function in this scenario is likely due to a change in postreceptor events, such as receptor coupling or phosphorylation. In contrast, heating did not significantly alter the hemodynamic responses to endothelium-dependent and -independent vasodilator agents, suggesting that increased stimulated release or augmented sensitivity to nitric oxide does not contribute to the loss of vasoconstrictor tone in the viscera during severe hyperthermia. Thus the findings from this study and others (20, 33) indicate that heating alters α- and β-adrenoceptor function. These data further suggest that a temperature-dependent and general loss of responsiveness to vasoconstrictor agents may contribute to the loss of compensatory vasoconstriction in the mesenteric region that precedes the onset of circulatory collapse during severe hyperthermia.

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