Effects of hyperthermia on contraction and dilatation of rabbit femoral arteries

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Effects of hyperthermia on contraction and dilatation of rabbit femoral arteries. J. Appl. Physiol. 85:6: 2205–2212, 1998.—To analyze the effect of hyperthermia on the cardiovascular response, the isometric response of isolated rabbit femoral artery segments was recorded at 37°C and hyperthermia (41 and 44°C). Contraction to potassium (5 × 10−3–5 × 10−2 M) was significantly greater at 41 and 44 than at 37°C and increased by inhibition of nitric oxide (NO) synthesis with Nα-nitro-L-arginine (L-NNA; 10−4 M) or endothelium removal at 37°C but not at 41 or 44°C. Norepinephrine (10−8–10−4 M) produced a concentration-dependent contraction greater at 41 or 44 than at 37°C and not modified by endothelium removal or L-NNA at either temperature. Phenylephrine (10−9–10−4 M) produced a contraction increased by warming to 44°C but not to 41°C. The specific α1-adrenoceptor agonist BHT-920 produced a weak contraction, reduced by the α1-adrenoceptor antagonist prazosin (10−6 M) and increased at 44°C but not at 41°C. The concentration-dependent contraction to endothelin-1 (ET-1; 10−11–10−7 M) was increased by warming to 41 and 44°C and by endothelium removal or L-NNA at 37°C but not at 41 or 44°C. Response to ET-1 was reduced by endothelin ET receptor antagonist BQ-123 (10−5 M) and ETB-receptor antagonist BQ-788 (10−5 M). In arteries precontracted with ET-1 (10−8–3 × 10−8 M), relaxation to sodium nitroprusside (10−8–10−4 M) was increased at 41 and 44°C vs. at 37°C, but that of ACh (10−8–10−4 M) or adenosine (10−8–10−4 M) was not different at all temperatures studied. Relaxation to ACh, but not adenosine, was reduced similarly by L-NNA at all temperatures studied. These results suggest that hyperthermia in muscular arteries may inhibit production of, and increase dilatation to, NO, resulting in unchanged relaxation to ACh and increased constriction to KCl and ET-1, and may increase constriction to stimulation of α1-adrenoceptors by NO-independent mechanisms.

endothelin-1; α-adrenoceptors; nitric oxide; endothelium

THE EFFECTS OF HYPERTERMHA on the cardiovascular system are little known. Hyperthermia produced by acute heating in rats induces an homeostatic response characterized by increased arterial blood pressure, heart rate, and regional vascular resistance (5, 8, 9). Failure of this adaptation may produce the pathologi- cal condition known as heatstroke, which is character- ized by marked hypertension and cardiovascular shock (13), but the pathogenesis of this disorder remains unclear. One possibility is that sympathetic activity or sympathetic vascular reactivity is altered. There is evidence that during heat stress an increased activity of perivasculare sympathetic fibers (4, 6) and raised plasmatic catecholamine levels occur (4), which probably contribute to maintain arterial pressure homeostasis by producing vasoconstriction. However, it is unclear whether reactivity of blood vessels is altered, as there are conflicting reports that elevated temperature increases (14), does not modify (16), or decreases (8, 18) the vasoconstriction to norepinephrine. Other vascular regulatory mechanisms, involving the endothelium, may be also functioning during hyperthermia. This hypothesis is based on data indicating endothelial cell damage (17) and increased plasma levels of endothelin-1 (1) in heatstroke patients, as well as excessive production of nitric oxide during hyperthermia, possibly due to endotoxemia and induction of nitric oxide synthase (6). However, more studies are required to elucidate the role of the endothelium in the vascular effects of hyperthermia.

The purpose of this study was to assess the effect of hyperthermia on vascular reactivity, analyzing the role of the endothelium in this effect. We hypothesize that hyperthermia may increase vasoconstriction and/or reduce vasodilatation in some vascular beds by altering the release of endothelial vasoactive factors. This effect of hyperthermia would act as a homeostatic mechanism aiming to maintain systemic arterial pressure. To analyze this hypothesis, we used isolated femoral arteries from rabbits to examine the constriction to potassium, to norepinephrine, and to endothelin-1, as well as the relaxation to the nitric oxide donor sodium nitroprusside, the nitric oxide-dependent relaxant acetylcholine, and the nitric oxide-independent relaxant adenosine. These experiments were performed in the arteries exposed to normothermia (37°C) and moderate (41°C) and severe (44°C) hyperthermia. The use of in vitro preparations may be useful in approaching this issue as they avoid complicating factors that may arise from in vivo experiments (e.g., desensitization of adrenoceptors because of prolonged sympathetic stimulation). Femoral artery was selected as it is a muscular artery, and it has been hypothesized that muscular vascular tone is a potential target of vasoconstriction as part of the integrated pattern of blood flow redistribution during heat stress (15).

METHODS

Seventy-seven New Zealand White rabbits, weighing 2–2.5 kg, were killed by intravenous injection of pentobarbital sodium (100 mg/kg). Femoral arteries (OD after dissection: 1–1.3 mm) were dissected free and cut into cylindrical segments 2 mm in length. Each segment was prepared for isometric tension recording in a 4-ml organ bath containing modified Krebs-Henseleit solution with the following composition (in mM): 115 NaCl, 4.6 KCl, 1.2 KH2PO4, 1.2 MgSO4, 2.5
CaCl₂, 25 NaHCO₃, and 11.1 glucose. The solution was equilibrated with 95% O₂-5% CO₂ to give a pH of 7.3-7.4, which was measured with a pH meter (micro pH, Crison Instruments). Briefly, the method consists of passing two fine, stainless steel pins, 150 µm in diameter, through the lumen of the vascular segment. One pin is fixed to the organ bath wall, whereas the other is connected to a strain gauge for isometric tension recording, thus permitting the application of passive tension in a plane perpendicular to the long axis of the vascular cylinder. The recording system included a universal transducing cell (UC3, Statham Instruments), a Statham microscale accessory (UL5, Statham Instruments), and a Beckman type RS recorder (model R-411, Beckman Instruments). The optimal passive tension was determined in preliminary experiments by recording the contraction to potassium chloride (10⁻⁴ M) after applying, at random sequence, different passive tensions (0.1, 0.25, 0.5, 1, 2, and 5 g) at 37 (20 segments), 41 (10 segments), and 44°C (10 segments). In these experiments it was found that the maximal response was obtained at a passive tension of 0.5 g at the three temperatures studied. Therefore, the experiments were performed in vascular segments stretched to this optimal passive tension of 0.5 and equilibrated for 60-90 min before any drug was added, renovating the solution in the baths every 30 min. In a group of experiments (n = 7) designed to study the effect of temperature on the basal tone of the arteries, the temperature was set from the beginning at 37, 41, or 44°C, and, after the equilibration period, the temperature was changed from 37 to 41 or 44°C, or from 41 or 44 to 37°C. In the experiments performed to study the response to vasoconstrictor or vasodilator stimuli, the temperature of the bath was adjusted from the beginning of the experiment at 37, 41, or 44°C, and the arteries remained at the chosen temperature throughout the duration of the experiment.

The contraction to potassium chloride (5 x 10⁻³ to 5 x 10⁻² M), norepinephrine (10⁻⁹ to 10⁻⁴ M), and endothelin-1 (10⁻¹¹ to 10⁻⁷ M) was studied in the arteries under control conditions, after removal of endothelium, and after treatment with the inhibitor of nitric oxide synthase N-nitro-L-arginine (L-NNA; 10⁻⁴ M), at 37, 41, and 44°C. The response to the specific α₁-adrenergic agonist phenylephrine (10⁻⁷ to 10⁻⁴ M), the specific α₂-adrenergic agonist BHT-920 (10⁻⁷ to 10⁻⁴ M), and the specific endothelin ETA-agonist IRL-1620 (10⁻¹¹ to 10⁻⁷ M) was also analyzed in control conditions at these temperatures. In addition, the contraction to endothelin-1 was studied in the presence of the antagonist of endothelin ETA receptors cyclo D-α-aspartyl-L-propyl-D-valyl-L-leucyl-D-tryptophyl (BQ-123; 10⁻³ M) and the antagonist of ETB receptors N-[N-[(2,6-dimethyl-1-piperidinyl) carbonyl]-4-methyl-L-leucyl]-L-(methoxy carbonyl)-D-tryptophyl-D-norleucine monosodium (BQ-788; 10⁻⁵ M), the response to phenylephrine in the presence of the α₂-adrenergic antagonist yohimbine (10⁻⁶ M), and the response to BHT-920 in the presence of the α₂-adrenergic antagonist prazosin (10⁻⁶ M) at the three temperatures indicated.

The relaxation to acetylcholine (10⁻⁸ to 10⁻⁴ M), sodium nitroprusside (10⁻⁸ to 10⁻⁴ M), or adenosine (10⁻⁸ to 10⁻⁴ M) was studied in segments precontracted with endothelin-1 (10⁻⁸ to 3 x 10⁻⁸ M) at 37, 41, and 44°C. The relaxation to acetylcholine and adenosine was also recorded in the presence of L-NNA (10⁻⁴ M).

The agonists were added to the organ bath in a cumulative manner, and L-NNA, BQ-123, BQ-788, yohimbine, or prazosin was added to the bath 20 min before the concentration-response curves for the corresponding agonists was begun. Removal of the endothelium was accomplished by gently rubbing the vascular lumen with a steel rod, and the adequacy of the procedure was tested by abolition of the relaxing response to acetylcholine (10⁻⁶ M) in the arteries precontracted with endothelin-1 (10⁻⁸ to 3 x 10⁻⁸ M).

**RESULTS**

Effect of temperature changes on basal tone. At the basal tension of 0.5 g, warming from 37 to 41 or 44°C, or cooling from 41 or 44 to 37°C, did not induce any change in the tension of the vascular segments.

Contraction to potassium chloride. Potassium chloride (5 x 10⁻³ to 5 x 10⁻² M) produced concentration-dependent contraction of femoral arteries at every temperature studied. Figure 1 summarizes the results with potassium chloride, and the corresponding pD₂ values are shown in Table 1. At 41 and 44°C, both the sensitivity and maximal effect were significantly higher than at 37°C (Fig. 1A). At 37°C endothelin removal increased the sensitivity, and pretreatment with L-NNA increased both the sensitivity and maximal effect, compared with intact arteries (Fig. 1B). At 41 or 44°C, neither endothelin removal nor L-NNA pretreatment modified the contraction to potassium (Fig. 1C and D).

Contraction to adrenergic stimulation. Norepinephrine produced a concentration-dependent contraction of femoral arteries, and the sensitivity and maximal contraction were significantly higher at 41 and 44°C than at 37°C (Fig. 2A). Compared with control arteries, endothelin removal or treatment with L-NNA did not modify significantly the contraction to norepinephrine at any of the temperatures studied (Table 1).

The concentration-dependent contraction to the α₁-adrenergic agonist phenylephrine was similar at 37 and 41°C. At 44°C the sensitivity, but not the maximal contraction, was significantly greater than at 37°C (pD₂ = 6.26 ± 0.16 vs. 5.51 ± 0.22, P < 0.05) (Fig. 2B). Treatment with the α₂-adrenergic antagonist yohimbine did not modify this contraction at any temperature studied (not shown).
The α2-adrenergic agonist BHT-920 produced contraction only at high concentrations (10^-6 to 10^-4 M). The contraction was similar at 37 and 41°C, and the sensitivity, but not the maximal contraction, was higher at 44 than at 37°C (pD₂ = 5.03 ± 0.13 vs. 4.38 ± 0.09; P < 0.01) (Fig. 2C). The α1-adrenergic antagonist prazosin markedly reduced the contraction to BHT-920 at every temperature studied, and the response to this α2-agonist in the presence of prazosin was not significantly different at any of the temperatures studied (the contraction to 10^-4 M BHT-920 in the presence of prazosin was 0.61 ± 0.24, 0.69 ± 0.36, and 1 ± 0.41 g for 37, 41, and 44°C, respectively).

Contraction to endothelin-1. Endothelin-1 (10^-11 to 10^-7 M) contracted femoral vascular segments in a concentration-dependent way, and the contraction for 10^-11 to 3 × 10^-10 concentrations was significantly higher at 41 and 44°C compared with 37°C (Fig. 3A). Compared with control arteries, endothelium removal or treatment with L-NNA increased the response to endothelin-1 at 37°C (Fig. 3B), but not at 41 (Fig. 3C) or 44°C (Fig. 3D).

Treatment with the antagonist of endothelin ETₐ receptors BQ-123 reduced the response to endothelin-1, and these blocking effects of BQ-123 were higher at 41 (P < 0.001; Fig. 4B) and 44 (P < 0.05; Fig. 4C) than at 37°C (Fig. 4A). The contraction to endothelin-1 that remained in the presence of BQ-123 was similar at the three temperatures studied.

The antagonist of endothelin ETₐ receptors BQ-788 also reduced the response, and this reduction was similar at the three temperatures assayed (Fig. 4, A-C). The contraction to endothelin-1 in the presence of BQ-788 was higher at 41 (P < 0.01) and 44 than at 37°C (P < 0.01).

The agonist of endothelin ETₐ receptors IRL-1620 produced a small contraction of femoral arteries, and this contraction was not different at 41 or 44°C compared with that obtained at 37°C (Fig. 4D).

### Table 1. pD₂ values of the contraction to endothelin-1, norepinephrine, and potassium chloride in rabbit femoral arteries in control conditions, without endothelium, or in the presence of L-NNA at 37, 41, and 44°C

<table>
<thead>
<tr>
<th>Condition</th>
<th>Endothelin-1</th>
<th>Norepinephrine</th>
<th>Potassium</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>8.54 ± 0.14</td>
<td>6.28 ± 0.25</td>
<td>1.33 ± 0.02</td>
</tr>
<tr>
<td>Without endothelium</td>
<td>9.04 ± 0.34</td>
<td>6.98 ± 0.17</td>
<td>1.25 ± 0.014†</td>
</tr>
<tr>
<td>L-NNA</td>
<td>9.42 ± 0.32†</td>
<td>7.00 ± 0.3</td>
<td>1.48 ± 0.32‡</td>
</tr>
<tr>
<td>41°C</td>
<td>9.38 ± 0.3*</td>
<td>7.27 ± 0.24*</td>
<td>1.22 ± 0.016</td>
</tr>
<tr>
<td>Without endothelium</td>
<td>8.87 ± 0.49</td>
<td>7.44 ± 0.29</td>
<td>1.24 ± 0.016</td>
</tr>
<tr>
<td>L-NNA</td>
<td>9.47 ± 0.67</td>
<td>7.77 ± 0.35</td>
<td>1.15 ± 0.026</td>
</tr>
<tr>
<td>44°C</td>
<td>9.18 ± 0.18</td>
<td>7.48 ± 0.30*</td>
<td>1.17 ± 0.0175</td>
</tr>
<tr>
<td>Without endothelium</td>
<td>8.99 ± 0.46</td>
<td>7.87 ± 0.72</td>
<td>1.21 ± 0.012</td>
</tr>
<tr>
<td>L-NNA</td>
<td>9.30 ± 0.51</td>
<td>7.97 ± 0.26</td>
<td>1.16 ± 0.015</td>
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</table>

Values are means ± SE; n = 5–7 animals. pD₂ = -log EC₅₀. L-NNA, N⁵-nitro-L-arginine (10^-4 M). Statistically significant compared with 37°C: *P < 0.05; †P < 0.01. Statistically significant compared with its control at same temperature: †P < 0.05; ‡P < 0.01.
Relaxation to acetylcholine, sodium nitroprusside, and adenosine. The level of active tone induced with endothelin-1 $10^{-8}$ to $3 \times 10^{-6} \text{ M}$ ($3.4 \pm 0.1 \text{ g}$) was not different in any of the experimental conditions studied. In these precontracted vascular segments, acetylcholine ($10^{-8}$ to $10^{-4} \text{ M}$) (Fig. 5), sodium nitroprusside ($10^{-8}$ to $10^{-4} \text{ M}$) (Fig. 6), or adenosine ($10^{-8}$ to $10^{-4} \text{ M}$) (not shown) produced concentration-dependent relaxation. Table 2 shows the $pD_2$ values for these vasodilators at the three temperatures studied. The sensitivity to sodium nitroprusside was significantly higher at 41 or 44°C compared with 37°C, whereas the sensitivity to acetylcholine or adenosine was not significantly different at any of the temperatures studied. Maximal relaxation, relative to the tension attained with endothelin-1, at 37, 41, and 44°C was, respectively, $82 \pm 4$, $91 \pm 7$, and $90 \pm 6\%$ for acetylcholine; $93 \pm 1.4$, $98 \pm 1.4$, and $96 \pm 1.4\%$ for sodium nitroprusside; and $73 \pm 10$, $80 \pm 17$, and $88 \pm 3\%$ for adenosine, and it was not significantly different between the temperatures studied. L-NNA treatment partially reduced the relaxation to acetylcholine in a similar degree at all the temperatures studied (Fig. 5), and it did not modify the relaxation to adenosine (not shown).

**DISCUSSION**

The purpose of this study was to analyze the effects of hyperthermia on the constrictor and dilator responses of a muscular artery. Our results with sodium nitroprusside suggest that the sensitivity of the vascular smooth muscle to exogenous nitric oxide is increased during hyperthermia, and this effect may be specific for nitric oxide because the relaxation to adenosine was not modified by warming. The observations with sodium nitroprusside apparently contrast with those found with a substance that produces relaxation by releasing nitric oxide, such as acetylcholine, for which no increase in sensitivity was observed during warming. These results, however, might be reconciled if we suppose that the release of nitric oxide during cholinergic stimulation is reduced during warming, and this is compensated for by the increased sensitivity of the smooth muscle to nitric oxide. The reduction in nitric oxide production might be due to functional impairment of endothelial cells and/or of nitric oxide synthase, produced by elevated temperature. We have also found that warming from 37 to 41 or 44°C, or cooling to 37°C in segments previously warmed at 41 or 44°C, produced no changes in the basal tension of the arteries. This may be related to the lack of active tone in our vascular preparations because inhibition of the release or effects of nitric oxide may fail to induce vasoconstriction in the absence of vasoconstrictor tone (19).

On the other hand, the results with the vasoconstrictors studied suggest that during hyperthermia the arterial contraction is increased. Because cooling may inhibit and warming may enhance Ca$^{2+}$ influx in rat vascular smooth muscle (20), a facilitation of Ca$^{2+}$ entry may underlie, in part, the increased arterial contraction to potassium found during hyperthermia in the present study. This suggestion is in line with the finding that hyperthermia in the anesthetized rat increases renal vasoconstriction to membrane Ca$^{2+}$ channels opening with BaCl$_2$ (8).

Our results with norepinephrine and phenylephrine suggest that warming may increase the contraction to activation of $\alpha_1$-adrenoceptors, which may be predominant in the adrenergic contraction of rabbit femoral arteries (3). Although BHT-920 produced some contraction in this preparation, this response may be due to unspecific activation of $\alpha_1$-adrenoceptors by this agonist because this response was reduced by prazosin. The small contraction to BHT-920 in the presence of prazosin was not modified by warming, further supporting the hypothesis that hyperthermia facilitates the response to activation of $\alpha_1$-, but not $\alpha_2$-adrenoceptors.
Regarding the effects of endothelin-1, we found that the endothelin ET\textsubscript{A}-antagonist BQ-123 shifted to the right the concentration-response curve to this peptide, suggesting that the response to endothelin-1 is mediated mainly by ET\textsubscript{A} receptors in our preparation. A smaller participation of endothelin ET\textsubscript{B} receptors may also be present because the endothelin ET\textsubscript{B}-agonist BQ-788 inhibited slightly the contraction to endothelin-1, and the endothelin ET\textsubscript{B} agonist IRL-1620 produced a small contraction. During hyperthermia, the contraction induced by low concentrations of endothelin-1, but not that by IRL-1620, was increased, and the blockade produced by BQ-123, but not that by BQ-788, was also greater during hyperthermia than at 37°C.

**Fig. 3.** Contraction of rabbit femoral arteries to endothelin-1 at 37, 41, and 44°C (A) and after endothelium removal and pretreatment with L-NNA at 37 (B), 41 (C), and 44°C (D). Values are means ± SE; n = 7 animals. *Statistically significant (P < 0.05) compared with 37°C. †Statistically significant (P < 0.05) compared with control at same temperature.

**Fig. 4.** Contraction of rabbit femoral arteries to endothelin-1 at 37 (A), 41 (B), and 44°C (C) in arteries nontreated or treated with endothelin ETA-receptor antagonist BQ-123 or with ETB-receptor antagonist BQ-788 (n = 7 animals). D: contraction of rabbit femoral arteries to IRL-1620 at 37, 41, and 44°C (n = 7 animals). Values are means ± SE. Statistically significant compared with control: *P < 0.05; **P < 0.01.
These observations suggest that hyperthermia may increase the sensitivity and/or effects of endothelin ETA receptors but not those of endothelin ETB receptors. This phenomenon may be due to an increased sensitivity and/or concentration of endothelin ETA receptors or to a facilitation of postreceptor mechanisms by warming.

Interestingly, although hyperthermia increased the vasoconstrictor response, the characteristics of this increase varied depending on the vasoconstrictor used. In the case of phenylephrine, hyperthermia increased sensitivity (pD2 values) but not maximal contraction, whereas with potassium and norepinephrine both the sensitivity and the maximal effect were significantly increased by hyperthermia. The reason for these differences is not apparent, but it might be related to the existence of different levels of receptor reserve for the different vasconstrictors. It may be hypothesized that a lower receptor efficacy at 37°C compared with hyperthermia would result in lower maximal effects for those agonists with no receptor reserve and a parallel shift for those with high receptor reserve.

At 37°C, inhibition of nitric oxide synthesis or endothelium removal increased the response of the rabbit femoral artery to potassium and endothelin-1 but did not modify significantly the response to norepinephrine. Thus, at normal temperature, the vascular contraction to potassium and endothelin-1 may be modulated by endothelial nitric oxide, and this phenomenon may not occur in the contraction to norepinephrine. Although the response to norepinephrine has been shown

Table 2. pD2 values of the relaxation to acetylcholine, sodium nitroprusside, and adenosine in femoral arteries precontracted with endothelin-1 at 37, 41, and 44°C

<table>
<thead>
<tr>
<th></th>
<th>Acetylcholine</th>
<th>Sodium Nitroprusside</th>
<th>Adenosine</th>
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<tbody>
<tr>
<td>37°C</td>
<td>6.47 ± 0.11</td>
<td>5.92 ± 0.13</td>
<td>5.28 ± 0.14</td>
</tr>
<tr>
<td>41°C</td>
<td>6.41 ± 0.16</td>
<td>6.72 ± 0.15*</td>
<td>5.76 ± 0.52</td>
</tr>
<tr>
<td>44°C</td>
<td>6.54 ± 0.26</td>
<td>7.04 ± 0.22</td>
<td>5.55 ± 0.36</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 5–7 animals. Endothelin-1 concentration, 10^{-8}–3 × 10^{-8} M. *Statistically significant (P < 0.01) compared with 37°C.
to be modulated by nitric oxide (10), this phenomenon was not observed in our results, which might be due to absence of $\alpha_2$-adrenoceptors in our experimental preparation. During warming at 41 or 44°C, inhibition of nitric oxide synthesis did not modify the increased contraction to potassium, endothelin-1, and norepinephrine, thus suggesting that during hyperthermia the response to these vasoconstrictors is not modulated by nitric oxide. This suggests that hyperthermia by itself may inhibit the release of nitric oxide in response to potassium and endothelin-1 and might explain, at least in part, the elevated vasoconstriction to these two substances during warming. However, the increased response to norepinephrine may be related to mechanisms distinct to changes in release of nitric oxide.

There is little information in the literature concerning the effect of temperature changes in vascular production of nitric oxide. Hall et al. (6) have found in rats that hyperthermia increases blood levels of nitric oxide, probably due to endotoxemia resulting from damage of intestinal mucosa. Ryan and Gisolfi (16) observed in rat mesenteric arteries that the contraction to norepinephrine and the relaxation to acetylcholine were not significantly modified during exposure of these arteries to 42 and 43°C. On the other hand, in rat cremaster muscle arterioles, the relaxation to acetylcholine and sodium nitroprusside is reduced during local heat treatment, suggesting that warming can change production and efficacy of nitric oxide in this vascular bed (11). Our results may suggest a relatively reduced release of nitric oxide during warming, which may be compensated for in part by an increased sensitivity of smooth muscle to nitric oxide. Changes in temperature might affect the production of nitric oxide in a different way depending on vascular beds. In this sense, we have previously reported that cooling decreases the production of nitric oxide in rabbit femoral arteries, whereas it increases its production in rabbit ear arteries (2, 12).

Heatstroke is characterized by profound hypotension and cardiovascular failure (13), and it has been found that during heatstroke in rats there is a marked vasodilation in the splanchnic circulation when central temperature increases above 41–42°C, a vasodilation that may be responsible for the fall in arterial pressure (9). This hypotension might be due, at least in part, to increased sensitivity in some vascular beds to nitric oxide, as suggested by the present results in the rabbit femoral artery, where warming increased the vasodilation to exogenous nitric oxide. However, during heatstroke, vasoconstriction may be present in other vascular beds, as evidenced by flow reductions in rat tail (7, 9), iliac (9), and renal (7) arteries. This vasoconstriction present in some vascular beds (7, 9) may be an attempt at compensating splanchnic vasodilation and preventing arterial hypotension. Our results with potassium, norepinephrine, and endothelin-1 in the rabbit femoral artery are in line with those found in other vascular beds (7, 9), and they may be consistent with this compensatory mechanism. The increase in the response to vasoconstrictors, such as catecholamines and endothelin-1, in some vascular beds (e.g., muscular) during hyperthermia may be of relevance to counteract the increased vasodilation in other vasculatures (e.g., splanchnic). However, when hyperthermia is severe and/or prolonged, this increased vasoconstriction may be insufficient to maintain arterial pressure, thus resulting in severe hypotension and cardiovascular failure.

In summary, the present study suggests that in muscular arteries hyperthermia 1) decreases the production of, and increases the dilation to, nitric oxide and 2) increases the responses to potassium chloride, norepinephrine, and endothelin-1. The potentiation of vasoconstriction to potassium and endothelin-1 may be due, at least in part, to a reduced release of nitric oxide during this condition, whereas the potentiation to norepinephrine may be independent of nitric oxide.

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