Role of plasma osmolality in the delayed onset of thermal cutaneous vasodilation during exercise in humans

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Takamata, Akira, Kei Nagashima, Hiroshi Nose, and Taketoshi Morimoto. Role of plasma osmolality in the delayed onset of thermal cutaneous vasodilation during exercise in humans. Am. J. Physiol. 275 (Regulatory Integrative Comp. Physiol.: 44): R286–R290, 1998.—To elucidate the role of increased plasma osmolality (P_results), which occurs during exercise in the regulation of cutaneous vasodilation (CVD) during exercise, we determined the relationship between the change in esophageal temperature (ΔTes) required to elicit CVD (ΔTes threshold for CVD) and P_results during light and moderate exercise (30 and 55% of peak oxygen consumption, respectively) and passive body heating. Then we compared the relationship with the data obtained in our previous study [A. Takamata, K. Nagashima, H. Nose, and T. Morimoto. Am. J. Physiol. 273 (Regulatory Integrative Comp. Physiol.: 42): R197–R204, 1997], in which we determined the relationships during passive body heating following isotonic (0.9% NaCl) or hypertonic (2 or 3% NaCl) saline infusions in the same subjects. P_results values at 5 min after the onset of exercise were 287.5 ± 0.9 mosmol/kg H2O during light exercise and 293.0 ± 1.2 mosmol/kg H2O during moderate exercise. P_results just before passive body heating was 289.9 ± 1.4 mosmol/kg H2O. The ΔTes threshold for CVD was 0.09 ± 0.05°C during light exercise, 0.31 ± 0.09°C during moderate exercise, and 0.10 ± 0.05°C during passive body heating. The relationship between the ΔTes threshold for CVD and P_results was shown to be on the same regression line both during exercise and during passive body heating with or without infusions [A. Takamata, K. Nagashima, H. Nose, and T. Morimoto. Am. J. Physiol. 273 (Regulatory Integrative Comp. Physiol.: 42): R197–R204, 1997]. Our data suggest that the elevated body core temperature threshold for CVD during exercise could be the result of increased P_results induced by exercise and is not due to reduced plasma volume or the intensity of the exercise itself.

Cutaneous circulation is primarily controlled by thermal drive or body temperature, and a couple of nonthermal factors are known to modify this thermoregulatory response (6). Exercise has been known to modify thermoregulatory cutaneous vasodilation (CVD) by elevating the body core temperature threshold for CVD (6, 8). Several studies have reported that the effect of exercise is intensity dependent: low-intensity exercise does not alter thermoregulatory CVD, whereas high-intensity exercise shifts the body core temperature threshold for CVD (10, 15, 18). Kellogg et al. (7) reported that the shifted esophageal temperature (Tes) threshold for CVD was not abolished with sympathetic adrenergic blockade by bretylium tosylate and concluded that the shifted body temperature threshold for CVD is not due to increased vasoconstrctor tone but rather to reduced active vasodilator outflow. However, the stimulus that induces an exercise-induced shift in the body temperature threshold for CVD remains unknown (6, 8).

Dehydration is another factor that modifies thermoregulatory CVD (1, 6, 11). Recently, we have shown that an increase in plasma osmolality (P_results) linearly elevates the difference in Tes (ΔTes) threshold for CVD (17). In addition, an increase in P_results in response to exercise intensity occurs in a fashion similar to the increase in ΔTes threshold for CVD (2, 13). From these facts, we hypothesized that the exercise-induced shift in the threshold for CVD is due to an exercise-induced increase in P_results.

The purpose of the present study was to elucidate the role of the exercise-induced increase in P_results in the regulation of CVD during exercise. We determined the relationship between the change in Tes required to elicit CVD (ΔTes threshold for CVD) and P_results during light (~30% of peak oxygen consumption; V̇O2peak) and moderate (~55% V̇O2peak)-intensity exercise and passive body heating. Then we compared these relationships with those found during passive body heating following isotonic or hypertonic saline infusions obtained in our previous study in the same subjects (17) to account for the role of the intensity of exercise itself and the exercise-induced reduction in plasma volume (PV).

METHODS

Subjects

This study was approved by the Review Board on Human Experiments, Kyoto Prefectural University of Medicine. Six healthy male subjects gave their written informed consent before participating in the study. The subjects who participated in this study were the same as in our previous study (17). The experiments were conducted 1 mo after our previous study, and the subjects did not participate in any exercise training program during this period. Thus we assumed that any changes in the state of their training and acclimation from the previous study were minimal. Their age was 26 ± 3 yr (mean ± SE); body weight, 67.9 ± 6.9 kg; and peak aerobic power (V̇O2peak) measured with a cycle ergometer in a recumbent position before the experiments, 47.6 ± 4.4 ml·min⁻¹·kg body wt⁻¹.

Protocol

Control period. Subjects reported to the laboratory at 1000. They had refrained from heavy exercise for 24 h and from salty food, alcohol, and caffeine for 17 h before arriving at the laboratory. They were allowed to eat breakfast and drink water if they desired. On reporting to the laboratory they were provided with 200 ml of water to avoid dehydration. Then the subjects sat on a chair for 1 h during the control period. At the end of the control period, a blood sample was taken.
Exercise/passive body heating. In the exercise protocol, subjects were asked to exercise with a cycle ergometer in a semirecumbent position at intensities of ~30% \(V_{O_2\text{peak}}\) (light exercise) or at ~55% \(V_{O_2\text{peak}}\) (moderate exercise) for 40 min after a 10-min resting period at a room temperature of 28°C. In the passive heating protocol, the subjects immersed their lower legs in water at 42°C with a room temperature of 28°C for 40 min following a 10-min preheating control period. Blood samples were taken just before (0 min) and at 5, 20, and 40 min after the onset of exercise and just before and at 20 and 40 min after the onset of passive body heating.

Measurements

\(T_{es}\) was measured with a copper-constantan thermocouple placed in polyethylene tubing (PE-90). The tip of the probe was advanced at a distance of one-fourth of the subject’s standing height from the external nares. Skin blood flow was measured with a laser Doppler flowmeter on the chest, with the assumption that the chest skin response represents the whole body skin response (Advance ALF 21). The site of the probe placement on the chest skin was always the same for each subject. These data were collected by a computer through an analog-to-digital converter every 1 s, and mean values of every 30 s were used for further analyses. Heart rate (HR) was continuously monitored from electrocardiograph record and, blood pressure was measured every 1 min with an R-wave gated automated sphygmomanometer (Colin STBP-780). Mean arterial pressure (MAP) was calculated as \(\frac{1}{3}(SBP - DBP) + DBP\), where SBP is systolic blood pressure and DBP is diastolic blood pressure. Cutaneous vascular conductance (CVC) was calculated as the laser-Doppler flowmeter voltage output divided by MAP and shown as a percentage of the mean value of pre-exercise or preheating control (\(\Delta CVC\)).

Blood samples were drawn without stasis, and an aliquot for measurement of \(P_{osmol}\) was immediately transferred into the tube containing heparin and centrifuged. The separated plasma was stored in the freezer at −20°C until measurement. Blood for the determination of hematocrit and hemoglobin concentration was processed immediately. \(P_{osmol}\) was measured by the freezing-point depression (Fiske one-tenth osmometer), hematocrit by microhematocrit tube centrifugation, and hemoglobin concentrations by the cyanmethemoglobin method (Sigma hemoglobin kit).

Data Analyses

We defined the body core temperature threshold for CVD as the \(\Delta T_{es}\) required to elicit a rapid increase in \(\Delta CVC\) (\(\Delta T_{es}\) threshold for CVD), characterized by an increase in \(\Delta CVC\) over three consecutive measurements. We employed the \(\Delta T_{es}\) threshold for CVD in each condition in each subject. \(\Delta T_{es}\) required for CVD during moderate exercise was higher than that of exercise compared with during passive body heating or light exercise. We determined the threshold for sweating and CVD, but the \(\Delta T_{es}\) required to elicit these responses were not influenced by these shifts (5, 16). Thus to examine the effect of exercise and plasma osmolality and to eliminate day-to-day variation, we determined the \(\Delta T_{es}\) required for CVD instead of absolute \(T_{es}\) thresholds.

Percent change in PV was calculated from hematocrit and hemoglobin concentration using the following equation

\[
\Delta PV(\%) = 100 \times \left(\frac{Hb_{B}/Hb_{A}}{1 - (Hct_{A}/100)}\right) - 100\times \left(1 - (Hct_{A}/100)\right)
\]

where \(\Delta PV\) is percent change in PV, \(Hb\) is hemoglobin concentration, and \(Hct\) is hematocrit. Subscription B indicates before (control) and A, after (experiment).

The values were shown as mean and SE of six subjects. The effects of exercise intensity or time were determined by ANOVA with repeated measures. The differences between data of specific interest were determined by Fisher’s least-significant difference test. A P value < 0.05 was considered to indicate statistical significance. Regression analysis was performed using standard least-squares test.

**RESULTS**

Table 1 shows \(P_{osmol}\) and \(\Delta PV\) during the experiment. \(P_{osmol}\) just before passive body heating was 289.9 ± 1.4 mosmol/kgH\(_2\)O. \(P_{osmol}\) values at 5 min after the onset of light and moderate exercise were 287.5 ± 0.9 and 293.0 ± 1.2 mosmol/kgH\(_2\)O, respectively. \(\Delta PV\) at 5 min after the onset of light and moderate exercise were −1.7 ± 1.5 and −4.9 ± 0.9%, respectively.

Figure 1 shows the relationship between \(\Delta CVC\) and \(\Delta T_{es}\). The relationship shifted rightward during moderate exercise compared with during passive body heating or light exercise. We determined the threshold for CVD in each condition in each subject. \(\Delta T_{es}\) threshold for CVD was 0.10 ± 0.05°C during passive body heating, 0.09 ± 0.05°C during light exercise, and 0.31 ± 0.09°C during moderate exercise. The \(\Delta T_{es}\) threshold for CVD during moderate exercise was higher than that

**Table 1.** \(P_{osmol}\) and \(\Delta PV\) during the experiment

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>5 min</th>
<th>20 min</th>
<th>40 min</th>
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</thead>
<tbody>
<tr>
<td>(P_{osmol}), mosmol/kgH(_2)O</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Passive heating</td>
<td>289.9 ± 1.4</td>
<td>292.0 ± 1.2†</td>
<td>293.0 ± 1.6†</td>
<td></td>
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<tr>
<td>Light exercise</td>
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<td>287.5 ± 0.9†</td>
<td>286.3 ± 0.9†</td>
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</tr>
<tr>
<td>Moderate exercise</td>
<td>286.4 ± 0.8*</td>
<td>293.0 ± 1.2†</td>
<td>294.9 ± 0.8†</td>
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<tr>
<td>(\Delta PV), %</td>
<td></td>
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<tr>
<td>Passive heating</td>
<td>0</td>
<td>−0.3 ± 0.8</td>
<td>−1.6 ± 0.7</td>
<td></td>
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<tr>
<td>Light exercise</td>
<td>0</td>
<td>−1.7 ± 1.5</td>
<td>−2.1 ± 1.3†</td>
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<tr>
<td>Moderate exercise</td>
<td>0</td>
<td>−4.9 ± 0.9†</td>
<td>−8.1 ± 1.2†</td>
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</table>

Values are means ± SE of 6 subjects. \(P_{osmol}\), plasma osmolality; \(\Delta PV\), change in plasma volume. *Significantly different from passive heating at each time period (values at 5 min after onset of exercise were compared with those just before onset of passive body heating). †Significantly different from baseline values in each condition (P < 0.05).
during passive body heating, but the \( \Delta T_{\text{es}} \) threshold for CVD during light exercise was not different from that found during passive body heating.

In Fig. 2, we compared the relationship between the \( \Delta T_{\text{es}} \) threshold for CVD and \( P_{\text{osmol}} \) during exercise and passive body heating with those during passive body heating following hypertonic (2 or 3% NaCl) or isotonic (0.9% NaCl) saline infusion that were obtained in our previous study (17). \( P_{\text{osmol}} \) values of exercise experiments were those at 5 min after the onset of exercise. \( P_{\text{osmol}} \) values of passive body heating experiments (with or without infusion) were those just before the onset of passive body heating (17). The data both during exercise and passive body heating with or without infusions were shown to be on the same regression line (Fig. 2). The regression equation determined in the present study \( (y = 0.40x - 11.39) \), including the data during exercise and passive body heating with and without infusions, was not different from that determined during passive body heating with and without infusions in our previous study \( (y = 0.44x - 12.69) \).

**DISCUSSION**

Exercise increases body temperature threshold for CVD in an exercise intensity-dependent manner (6). Moderate to heavy exercise elevates the \( T_{\text{es}} \) threshold for CVD, whereas light exercise does not influence the \( T_{\text{es}} \) threshold for CVD (10, 18). However, the stimulus that induces the shift in body temperature threshold for CVD still remains unknown (6, 8). Because \( P_{\text{osmol}} \) increases during exercise and the pattern of the increase in \( P_{\text{osmol}} \) and body temperature threshold for CVD in response to exercise intensity are similar (2, 10, 13), we examined the involvement of increased \( P_{\text{osmol}} \) in the elevated body temperature threshold for CVD. To account for the role of exercise-induced reduction in PV and exercise intensity itself, we compared the relationship between the \( \Delta T_{\text{es}} \) threshold for CVD and \( P_{\text{osmol}} \) during exercise of different intensities with those found during passive body heating and during passive body heating with isotonic or hypertonic saline infusion (17).

The \( \Delta T_{\text{es}} \) threshold for CVD increased during moderate exercise compared with passive body heating, with an increased \( P_{\text{osmol}} \) and a reduced PV (Fig. 1, Table 1). Neither the \( \Delta T_{\text{es}} \) threshold for CVD, \( P_{\text{osmol}} \), or PV were changed by light exercise (Fig. 1, Table 1). The increase in \( P_{\text{osmol}} \) and the shift in \( \Delta T_{\text{es}} \) threshold for CVD were comparable with the results obtained in other studies (2, 10, 13). The relationship between \( \Delta T_{\text{es}} \) threshold for CVD and \( P_{\text{osmol}} \) during exercise was similar to that obtained in passively heated subjects with infusions (17), and the data both during exercise and passive body heating with or without infusions were shown to be on the same regression line (Fig. 2). The \( \Delta T_{\text{es}} \) threshold for CVD correlated linearly with \( P_{\text{osmol}} \) regardless of exercise intensity or PV level (Fig. 2). PV just before the onset of passive body heating in infusion studies increased by \( \sim 10\% \) (17). Thus the present data are consistent with our hypothesis that the primary factor responsible for the shift of the body temperature threshold for CVD during exercise is increased \( P_{\text{osmol}} \) and not reduced PV or the intensity of the exercise itself.

Mack et al. (9) reported that baroreceptor unloading with a lower body negative pressure of \( -40 \text{ mmHg} \) increased the body temperature threshold for CVD during exercise. Thus baroreceptor unloading has an impact on body temperature threshold for CVD. Nose et al. (12) reported that the right atrial pressure increased...
at the onset of exercise in a semirecumbent position. Reeves et al. (14) reported that pulmonary wedge pressure and right atrial pressure increased during upright cycle exercise. Arterial pressure increased immediately after the onset of exercise, and PV expansion by infusion did not influence the relationship between $\Delta T_{es}$ threshold for CVD and $P_{osmol}$ (Fig. 2). In addition, the effect of exercise intensity on the $\Delta T_{es}$ threshold for CVD in supine position was similar to that in our study (10). Taken together, the involvement of baroreceptor unloading itself could be excluded. Although it is unknown whether the resetting of baroreflex plays a role, exercise did not shift the relationship between $\Delta T_{es}$ threshold for CVD and $P_{osmol}$, suggesting that exercise-induced resetting of baroreflex is probably not involved in the exercise-induced shift in body temperature threshold for CVD.

We determined the relationship between the $\Delta T_{es}$ threshold for CVD against the $P_{osmol}$ obtained 5 min after the onset of exercise in the exercise experiments. The increase in $P_{osmol}$ in response to exercise intensity was similar to those found in other studies (2). In addition, a blood sample was taken before CVD occurred in our present study and $P_{osmol}$ was assumed to have reached a plateau by this time (4) and remained constant throughout the exercise period thereafter (Table 1). Thus our analysis is reasonable for a determination of the relationship between $\Delta T_{es}$ threshold for CVD and $P_{osmol}$ during exercise. The $P_{osmol}$ before passive body heating was higher than at 5 min after the onset of light exercise. This may reflect the difference of hydration status between the experiments. However, because we analyzed the relationship between $\Delta T_{es}$ threshold for CVD and $P_{osmol}$, this difference did not influence our analysis.

$P_{osmol}$ gradually increased during passive body heating and became similar to that during moderate exercise at the end of experiment (Table 1), but the relationship between $\Delta CVC$ and $\Delta T_{es}$ during the passive body heating did not shift rightward during the experiment with the increase in $P_{osmol}$ (Fig. 1). Fortney et al. (3) reported that hypertonic saline infusion during exercise did not alter forearm blood flow response. This result was different from their previous study (4), in which they found hypertonic saline infusion before exercise shifted the $T_{es}$ threshold for forearm blood flow. In addition, they failed to increase forearm blood flow by infusion of hypotonic saline during exercise (3). Taken together, we postulate that increased $P_{osmol}$ has an effect on the onset of CVD but that it does not influence the relationship between CV and body core temperature once CVD has occurred. Because the increase in forearm blood flow had already occurred when they started infusions in the later study by Fortney et al. (3), the contradictory results could be explained by our hypothesis, although further study is required.

It still remains unknown whether osmotic inhibition of CVD is the result of reduced active vasodilator outflow or increased vasoconstrictor tone (6). Kellogg et al. (7) reported that the shifted esophageal temperature threshold for CVD during exercise was not abolished with sympathetic adrenergic blockade by bretylium tosylate and concluded that the shifted body temperature threshold for CVD is not due to increased vasoconstrictor tone but rather reduced active vasodilator outflow. Thus, if the exercise-induced shift in the $\Delta T_{es}$ threshold for CVD is mediated by increased $P_{osmol}$ caused by exercise, the efferent pathway that shifts the $\Delta T_{es}$ threshold for CVD, found in our previous study, can be attributed to the reduced active vasodilator outflow. An experiment to examine the efferent mechanism of osmotic inhibition of CVD is expected to be performed.

In summary, we confirmed that exercise inhibits thermoregulatory CVD in an exercise intensity-dependent fashion by elevating the body temperature threshold. Our results were consistent with our hypothesis that the increased body temperature threshold for CVD during exercise is due to the increased $P_{osmol}$ that occurs during exercise. In addition, this inhibitory effect seems to be acting on the onset of CVD specifically.

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