Reduced hyperthermia-induced cutaneous vasodilation and enhanced exercise-induced plasma water loss at simulated high altitude (3,200 m) in humans

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Miyagawa K, Kamijo Y, Ikegawa S, Goto M, Nose H. Reduced hyperthermia-induced cutaneous vasodilation and enhanced exercise-induced plasma water loss at simulated high altitude (3,200 m) in humans. J Appl Physiol 110: 157–165, 2011. First published November 18, 2010; doi:10.1152/japplphysiol.00950.2010.—We examined whether less convective heat loss during exercise at high altitude than at sea level was partially caused by reduced cutaneous vasodilation due to enhanced plasma water loss into contracting muscles and whether it was caused by hypoxia rather than by hypobaria. Seven young men performed cycling exercise for 40 min at 50% peak aerobic power in normoxia at (710 mmHg) 610 m, determined before the experiments, in three trials: 1) normobaric normoxia at 610 m (CNT), 2) hypobaric hypoxia [low pressure and low oxygen (LPLO)] at 3,200 m (510 mmHg), 3) normobaric hypoxia [normal pressure and low oxygen (NPLO)] at 610 m, in an artificial climate chamber where atmospheric temperature and relative humidity were maintained at 30°C and 50%, respectively. Subjects in CNT and LPLO breathed room air, whereas those in NPLO breathed a mixed gas of 14% O2 balanced N2, equivalent to the gas composition in LPLO. We measured change in PV (APV), oxygen consumption rate (VO2), mean arterial blood pressure (MBP), esophageal temperature (Tes), mean skin temperature (Tsk), forearm skin blood flow (FBF), and sweat rate (SR) during exercise. Although VO2, MBP, Tsk, and SR responses during exercise were similar between trials (P > 0.05), the sensitivity of forearm vascular conductance (FBF/MBP) in response to increased Tsk was lower in LPLO and NPLO than in CNT (P < 0.05), whereas that of SR was not, resulting in a greater increase in Tsk from minute 5 to 40 of exercise in LPLO and NPLO than in CNT (P = 0.026 and P = 0.011, respectively). APV during exercise was twofold greater in LPLO and NPLO than in CNT. These variables were not significantly different between LPLO and NPLO. Thus reduced convective heat loss during exercise at 3,200 m was partially caused by reduced cutaneous vasodilation due to enhanced PV loss. Moreover, this may be caused by hypoxia rather than by hypobaria.

hypobaric hypoxia; normobaric hypoxia; forearm vascular conductance; redistribution of blood flow

HEAT DISSIPATION DURING EXERCISE is achieved mainly by evaporative and convective heat-loss mechanisms. Regarding the relative contribution of these in a hypobaric hypoxic environment of high altitude, Gagge and Nishi (5) suggested in the physicochemical theory that the convective transfer of heat from the skin surface to the atmosphere was reduced, whereas that for evaporative heat loss was enhanced owing to lowered barometric pressure. Greenleaf et al. (7) examined the theory in human subjects exercising in a hypobaric hypoxic condition simulating 4,000 m with an artificial climate chamber, measured convective and evaporative heat loss by partitional calorimetry, and confirmed that convective heat loss contributed to body temperature regulation less than evaporative heat loss. On the other hand, to our knowledge, there have been only a limited number of studies that examined thermoregulatory responses to a hypobaric hypoxic condition (7, 16), which may further modify the heat dissipation mechanisms that are physicochemically unique in the condition (5).

During exercise of a given intensity with hypoxia, since a larger portion of cardiac output (CO) is distributed to active muscles than in normoxia (27), a greater volume of plasma water might be shifted into the active muscles, and a consequent greater decrease in plasma volume (PV) might affect the heat dissipation mechanisms (4, 17, 19). Experimentally, Takamata et al. (31) examined the effects of normobaric hypoxia attained by having subjects breathe 13% O2, equivalent to PO2 at 3,400 m, on PV during graded exercise and suggested that a decrease in PV was enhanced to twofold that in normoxia at the same absolute intensity. Regarding the mechanisms for the enhanced PV loss in hypoxia, they suggested that a greater increase in capillary pressure due to enhanced peripheral vasodilation and a greater increase in intracellular osmolality due to more accumulation of osmotic substances, lactic acid, accelerated the fluid shift out of the vascular space into the interstitial or intracellular spaces of the active muscles (29). These results suggest that a greater decrease in PV reduced venous return to the heart, lowered cardiac filling pressure, and thereby suppressed cutaneous vasodilation through baroreflexes (4, 17, 19), whereas it would have minor effects on sweating as previously suggested in a normoxic condition (15).

Therefore, in the present study, we hypothesized that a reduction in skin blood flow by an enhanced decrease in PV accelerates the physicochemically reduced convective heat loss due to hypobaria (5) and that sweating response being unaffected by the condition compensates for the reduced convective heat loss, resulting in acceleration of the physicochemically enhanced evaporative heat loss due to hypobaria (5). To examine these hypotheses, we compared thermoregulatory responses during exercise at 610 m (710 mmHg) in a warm environment between a hypoxic trial, attained by having subjects breathe 14% O2 gas, equivalent to 3,200 m, and a normoxic trial, attained by having them breathe 21% O2 gas. In addition, to examine any effects of hypobaria on thermoregulatory responses at high altitude (5), we measured thermoregulatory response in a hypobaric chamber simulating 3,200-m altitude (510 mmHg), while having subjects breathe 21% O2. In addition, we measured CO to estimate muscle blood flow
during exercise in hypoxia (27) by subtracting skin blood flow in the whole body, calculated from forearm skin blood flow (FBF) and the body surface area (2), from CO. Finally, we measured respiratory gas composition during exercise to evaluate any effects of hypocapnia during exercise at high altitude on cutaneous vasodilation (23, 24, 28).

**METHODS**

**Subjects**

This study was approved by the Review Board on Human Experiments, Shinshu University School of Medicine. Seven healthy young men gave written, informed consent before participating in this study. The physical characteristics of the subjects were 23 ± 4 yr of age, 173 ± 6 cm in height, 64 ± 5 kg in body weight, 2,994 ± 143 ml/min in peak aerobic power (V\(^\text{O}_2\)peak), and 3,111 ± 517 ml in PV (means ± SD).

**Protocols**

Within 1 wk after the determination of V\(^\text{O}_2\)peak and PV, the thermoregulatory response test was performed on each subject in three environmental conditions: normobaric normoxia at 610 m (CNT), hypobaric hypoxia at 3,200 m (low pressure and low oxygen (LPLO)) and normobaric hypoxia at 610 m (normobaric normoxia at 610 m (NPLO)).

**Measurements**

V\(^\text{O}_2\)peak. V\(^\text{O}_2\)peak was measured with graded exercise in a semi-recumbent position at ~25°C of Ta and ~50% of RH in 610 m. After 3-min baseline measurements at rest, subjects started pedaling at 60 cycles/min at an initial intensity of 0 W. The intensity was increased by 60 W every 3 min until 180 W was reached and, above this intensity, by 30 W every 2 min until 240 W, and then by 15 W every 2 min until subjects were not able to maintain the rhythm owing to exhaustion. V\(^\text{O}_2\) was calculated every 15 s from the oxygen and carbon dioxide fractions in the expired gas and the ventilator volume (Aeromonitor AE260, Minato, Tokyo, Japan). V\(^\text{O}_2\)peak was determined after averaging three maximal values at the end of the exercise.

HR was recorded every min from an electrocardiogram trace (Life Scope 8, Nihon Koden, Tokyo, Japan). Peak heart rate (HR\(_\text{peak}\)) was adopted at V\(^\text{O}_2\)peak.

**Blood volume.** PV was determined by the Evans blue dilution method (8). Subjects reported to the laboratory at 0630 and were normally hydrated but had fasted for 10 h before the measurement. After 60 min of resting in a sitting position at ~28°C of Ta and ~50% of RH, a control blood sample was taken, the dye was injected at 0.2 mg/kg body wt, and blood samples were taken at 10 and 20 min after the injection. The background absorbance due to plasma turbidity was corrected using the regression equation for the relationship between 620 and 740 nm (3), and the absorbance of a 10-min plasma sample was used to calculate PV.

**HR and blood pressure.** HR was recorded every minute from an electrocardiogram trace (Life Scope 8; Nihon Koden, Tokyo, Japan). SBP and DBP were measured every minute from the right upper arm at the heart level by inflating the cuff with a sonometric pickup of Korotkoff’s sound (STPB-780, Colin, Komaki, Japan). Mean arterial blood pressure (MAP) was calculated as DBP + (SBP – DBP)/3.

**Body temperature.** Ta was monitored with a thermocouple in polyethylene tubing (PE-90). The tip of the tube was advanced to a distance of one-fourth of the subject’s standing height from the external nares. Ta was monitored as Tfa = 0.25Ta + 0.43Tch + 0.32Ta (22), where Tfa, Tch and Ta are skin surface temperatures at the right forearm at 10 cm below the cubital line on the radial line, the right chest at 10 cm below the midclavicle, and the right anterior thigh at 15 cm above the patella on the middle line, respectively, which were measured with thermocouples. Tfa and Ta were recorded every 5 s and presented every minute on average.

**SR and FBF.** SR was determined by capacitance hygrometry, calculated from the relative humidity and temperature (THPB3, Shin- nei, Tokyo, Japan) of the dry air from a gas cylinder flowing out of a 12.56 cm\(^3\) capsule at a rate of 1.5 l/min at 5 cm below the left clavicle. FBF was measured by venous occlusion plethysmography with a mercury-in-Silastic tube strain gauge placed around the upper left forearm positioned above the heart level. The hand was eliminated from the circulation with a wrist cuff inflated to 280 mmHg, and venous return from the forearm was occluded with an upper arm cuff inflated to 60 mmHg (35). SR was recorded every 5 s and represented every minute on average. FBF was measured twice every minute and was represented every minute on average.

**CO.** CO was measured at 10 min before and at 5 (Ex5), 10 (Ex10), and 40 min (Ex40) after the start of exercise by the transcutaneous indocyanine green (ICG) dilution method (12, 26). Briefly, ICG (Daiichi, Tokyo) dissolved in 0.9 ml of saline (5 mg/ml) was mounted in a 1-ml syringe and transferred and filled in an extension tube connected to the Teflon catheter placed in

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the right antecubital vein via a three-way stopcock. The dye was then injected with 20 ml of saline solution by swiftly pushing the inner cylinder of a 20-ml syringe connected to the stopcock so as not to leave the dye in the extension tube. Several seconds after injection, the transient change in ICG concentration in arterial blood was monitored transcutaneously with a detector placed on the left nostril, and the trace was printed out by the instrument. CO was calculated after correction for the injected amount of ICG and hemoglobin concentration ([Hb]; g/dl, cyanomethemoglobin) in blood samples taken before the dye injection. Stroke volume (SV) was calculated from CO and HR measured at the same time.

The reproducibility of this measurement, examined in another group of young subjects during graded cycle ergometer exercise, was confirmed to be 0.4 – 0.9 l/min of 95% confidence limit over the range of 3.3 – 22.8 l/min, covering the range in the present study (21).

SPo2. Pulse arterial O2 saturation (SPo2) was continuously measured transcutaneously with a probe placed on the left index finger by near-infrared spectrometry (DDG-2001).

Blood properties

Blood samples were taken at rest and at Ex5, Ex10, Ex20, and Ex40 after the start of exercise during thermoregulatory response test. Two of 12 ml of a sampled blood aliquot was used to determine Hct (% microcentrifuge) and [Hb]. An aliquot of 3 ml of blood was placed in a chilled and heparinized tube, centrifuged at 4°C, and the plasma was stored at −85°C until assayed. The plasma was used to determine PaO2 by freezing-point depression (1-10 Osmometer, Fisk, MA) and plasma lactate concentration ([Lac]p) using an enzyme electrode (YSI 2300 Stat Plus, YSI, Yellow Springs, OH).

The remaining 7 ml of the aliquot at rest and at Ex10, Ex20, and Ex40 in five of seven subjects was placed in a chilled tube [EDTA (2Na) 1.5 mg/ml] that was centrifuged at 4°C, and the plasma was stored at −85°C until assayed. The plasma was used to determine plasma adrenaline ([Ad]p) and noradrenaline ([NA]p) concentrations by HPLC (model HPLC-725CA; Toso, Tokyo, Japan). The respective intra-assay coefficients of variation for the measurements of [Ad]p and [NA]p were 7.19 and 6.79% at the levels of 249 and 258 pg/ml, and they were 9.27 and 10.1% at the levels of 876 and 886 pg/ml. We measured plasma catecholamine concentrations in five of seven subjects because a part of samples in two subjects was lost while stored.

Data analyses

ΔPV. Change in PV (in ml) during exercise was calculated by multiplying PV at baseline by percentage change of PV from baseline determined from changes in Hct and [Hb] (8).

FVC. Forearm vascular conductance (FVC) was calculated as FBF/MBP in the unit of ml·100 m-1·min-1·100 mmHg-1. SR and FVC responses to increased Tes. The Tes vs. FVC relationship in each subject was fitted with three regression equations using standard Y-minimized regression analysis as described by Takeno et al. (52). The first equation was determined visually from the first sharp increase in Tes before the rapid increase in FVC, the second was determined from the rapid increase in FVC, and the third was determined from the measurements after the second component. The Tes threshold for an increase in FVC (THFVC) was determined from the point where the first and second regression lines crossed. The slope of increase (Δ) in FVC (ΔFVC) at a given ΔTes (ΔFVC/ΔTes) was from the slope of the second regression. THFVC and ΔFVC/ΔTes were determined by three separate investigators familiar with the methods, and the three values were averaged. The Tes threshold for an increase in SR (THSR) and ΔSR/ΔTes were also determined by the same methods. These determinations were performed with the experimental designs blinded to the investigators.

Statistics

Values are represented as means ± SE for seven subjects except when noted. One-way ANOVA [one between (trial)] for repeated measures was used to examine any significant differences in thermoregulatory response between trials (CNT, LPLO, and NPLO) (Table 1). One-way ANOVA [one within (time)] for repeated measures was used to examine any significant differences in the trend changes of variables during thermoregulatory response test in each trial (Tables 2–5). Two-way ANOVA [two within (trial × time)] for repeated measures was used to examine any significant differences in variables during thermoregulatory response test between trials (Figs. 1 and 3; Tables 2–5). Using this model, we examined any significant interactive effect of [trial × time] on Tes, HR, CO, and SV during exercise so that we assessed whether their changes from Ex5 to Ex10 and Ex40 were significantly different between trials (Fig. 4). For Tables 2 and 4, the analyses were performed every minute, although the values are presented at rest, Ex5, Ex10, Ex20, and Ex40 to avoid complicating the tables. Subsequent post hoc tests to examine any significant differences in the various pairwise comparisons were performed by Fisher’s least squares difference test. The null hypothesis was rejected at the level of P < 0.05.

RESULTS

Figure 1 shows FVC and SR during thermoregulatory response test in three trials. There were no significant differences in FVC at rest and for the first 10 min after the start of exercise between trials; however, thereafter, FVC was ~30% lower (P < 0.05) in the hypoxic trials than in the CNT trial. In contrast, there was no significant difference in SR during thermoregulatory response test (P > 0.9). On the other hand, none of FVC and SR was significantly different between the hypoxic trials.

Figure 2 shows FVC and SR responses to increased Tes during thermoregulatory response test in three trials. As summarized in Table 1, ΔFVC/ΔTes was lower in the hypoxic trials than in the CNT trial (P < 0.05), but with no significant differences between the hypoxic trials (P = 0.235). In contrast, there were no significant differences in THFVC, THSR, and ΔSR/ΔTes between trials (P = 0.089, P = 0.190, and P = 0.499, respectively).

Table 1. THFVC and THSR, ΔFVC/ΔTes, and ΔSR/ΔTes during thermoregulatory response test

<table>
<thead>
<tr>
<th></th>
<th>THFVC, °C</th>
<th>THSR, °C</th>
<th>ΔFVC/ΔTes, Units/°C</th>
<th>ΔSR/ΔTes, mg·min⁻¹·cm⁻²/°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNT</td>
<td>36.86 ± 0.12</td>
<td>36.85 ± 0.10</td>
<td>37.19 ± 5.29</td>
<td>1.98 ± 0.15</td>
</tr>
<tr>
<td>LPLO</td>
<td>36.92 ± 0.10</td>
<td>36.86 ± 0.09</td>
<td>22.35 ± 1.88*</td>
<td>1.72 ± 0.20</td>
</tr>
<tr>
<td>NPLO</td>
<td>37.00 ± 0.09</td>
<td>36.93 ± 0.12</td>
<td>26.81 ± 4.70*</td>
<td>1.96 ± 0.29</td>
</tr>
</tbody>
</table>

Values are means ± SE for 7 subjects. THFVC, esophageal temperature (Tes) threshold for increasing forearm skin vascular conductance (FVC); THSR, Tes threshold for increasing chest sweat rate (SR); ΔFVC/ΔTes and ΔSR/ΔTes, slopes of the second regression equation between Tes and FVC and between Tes and SR, respectively, in Fig. 1; CNT, normobaric normoxia at 610 m; LPLO, hypobaric hypoxia at 3,200 m; NPLO, normobaric hypoxia attained by having subjects breathe mixed gas of 14% O2 and balanced N2 at 610 m. *Significant differences from CNT (P < 0.05).
Table 2 shows minute expiratory volume (\(\dot{V}E\); l/min) in BTPS, respiratory frequency (\(f\); breaths/min), \(\dot{V}O_2\), carbon dioxide production rate (\(\dot{V}CO_2\); ml/min), and SPO2 during thermoregulatory response test in three trials. \(\dot{V}E\) in the hypoxic trials (LPLO and NPLO) was 45% higher than in the CNT trial during exercise (\(P < 0.0001\)). The \(f\) at rest was not significantly different between trials, but after Ex5 it was higher in NPLO than in the CNT (\(P = 0.007\)). Although \(\dot{V}O_2\) at rest and during exercise was not significantly different between trials (\(P > 0.4\)), \(\dot{V}CO_2\) was higher in the hypoxic trials than in the CNT trial (\(P < 0.05\)). SPO2 was ~14% lower in the hypoxic trials than in the CNT trial at rest and during exercise (\(P < 0.0001\)). On the other hand, none of these variables was significantly different between the hypoxic trials throughout the test.

Table 3 shows Hct, [Hb], Posmol, and [Lac]p during thermoregulatory response test in three trials. Hct increased after the start of exercise (\(P < 0.0001\)); however, the increase was
greater only in NPLO than in the CNT trial with significant differences from Ex10 to Ex40 ($P < 0.05$). Although $[\text{Lac}^-]_p$ increased significantly after the start of exercise in all trials ($P < 0.0001$), the increase was significantly greater in the hypoxic trials than in the CNT trial from Ex10 to Ex40 (all, $P < 0.0001$). There were no significant differences in $[\text{Hb}]$ and $P_{\text{osmol}}$ between trials throughout the test.

Figure 3 shows change in PV from the baseline at rest ($\Delta$PV) during thermoregulatory response test in three trials. Although PV decreased significantly after the start of exercise in all trials ($P < 0.0001$), the decrease was $\sim 200$ ml greater in the hypoxic trials than in the CNT trial with significant differences from Ex10 to Ex40 (all, $P < 0.05$) but with no significant differences between the hypoxic trials.

Table 4 shows $T_{\text{es}}$, $T_{sk}$, HR, CO, SV, and MBP during the thermoregulatory response test in three trials. All variables except for $T_{sk}$ increased immediately after the start of exercise in all trials (all, $P < 0.0001$). Although there were no significant effects of [trial] on other variables except for HR, we found a significant interactive effect of [trial] × time on $T_{es}$, CO, and SV during exercise ($P < 0.0001, P = 0.047, P = 0.024$, respectively), suggesting that their responses to exercise were significantly different among trials; therefore, we compared the changes in $T_{es}$, HR, CO, and SV from Ex5 at Ex10 and Ex40 between trials as shown in Fig. 4. As in the figure, we found that the increase in $T_{es}$ from Ex5 to Ex40 was $\sim 0.1^\circ C$ greater in the LPLO and NPLO trials than in the CNT trial ($P = 0.026$ and $P = 0.011$, respectively). In addition, we found that $\Delta CO$ was significantly higher in the hypoxic trials than in the CNT trial at Ex40 in the LPLO and NPLO trials ($P = 0.049$ and $P = 0.012$, respectively), and, similarly, $\Delta SV$ was significantly higher in the LPLO and NPLO trials than in the CNT trial at Ex40 ($P = 0.034$ and $P = 0.010$, respectively).

Table 5 shows $[\text{Ad}[_p]$ and $[\text{NA}][_p]$ during thermoregulatory response test in five subjects. Both increased after the start of exercise in all trials ($P < 0.05$); the increases were comparatively higher in the hypoxic trials than in the CNT trial with significant differences in $[\text{NA}][_p]$ at Ex5 in the LPLO trial and Ex10 and Ex40 in both hypoxic trials ($P < 0.026$).

**DISCUSSION**

The major findings in the present study were as follows: 1) an increase in FVC during exercise was suppressed, whereas an increase in SR was not in the hypoxic trials (NPLO and LPLO) compared with those in the CNT trial; 2) the sensitivity of cutaneous vasodilation response to increased $T_{es}$ during exercise was suppressed, whereas that of sweating response remained unchanged in the hypoxic trials; 3) a reduction in PV at the same absolute exercise intensity was greater in the hypoxic trials than in the CNT trial; 4) an increase in CO during exercise was greater in the hypoxic trials than in the CNT trial with a greater increase in HR; and 5) there were no significant effects of hypobaria on these variables.

**Thermoregulatory and cardiovascular responses**

As shown in Fig. 2 and Table 1, the sensitivity of cutaneous vasodilation response to increased $T_{es}$ was reduced in the hypoxic trials compared with that in the CNT trial. There have been many studies suggesting that a reduction in venous return to the heart, such as by PV loss (4, 19), posture change from...
Table 4. $T_{es}$, $T_{sk}$, HR, CO, SV, and MAP during thermoregulatory response test

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Ex5</th>
<th>Ex10</th>
<th>Ex40</th>
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</thead>
<tbody>
<tr>
<td>$T_{es}$, °C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNT</td>
<td>36.37 ± 0.06</td>
<td>36.65 ± 0.09</td>
<td>37.08 ± 0.11</td>
<td>37.84 ± 0.09</td>
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<tr>
<td>LPLO</td>
<td>36.34 ± 0.08</td>
<td>36.63 ± 0.09</td>
<td>37.12 ± 0.08</td>
<td>37.95 ± 0.09</td>
</tr>
<tr>
<td>NPLO</td>
<td>36.36 ± 0.03</td>
<td>36.61 ± 0.08</td>
<td>37.11 ± 0.08</td>
<td>37.96 ± 0.12</td>
</tr>
<tr>
<td>$T_{sk}$, °C</td>
<td>33.86 ± 0.10</td>
<td>33.41 ± 0.21</td>
<td>33.39 ± 0.23</td>
<td>34.46 ± 0.20</td>
</tr>
<tr>
<td>LPLO</td>
<td>34.13 ± 0.19</td>
<td>33.37 ± 0.30</td>
<td>33.35 ± 0.21</td>
<td>34.44 ± 0.19</td>
</tr>
<tr>
<td>NPLO</td>
<td>33.89 ± 0.17</td>
<td>33.47 ± 0.23</td>
<td>33.43 ± 0.16</td>
<td>34.59 ± 0.08</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>64 ± 3</td>
<td>124 ± 3</td>
<td>130 ± 3</td>
<td>148 ± 4</td>
</tr>
<tr>
<td>LPLO</td>
<td>71 ± 2*</td>
<td>144 ± 3*</td>
<td>150 ± 3*</td>
<td>166 ± 2*</td>
</tr>
<tr>
<td>NPLO</td>
<td>70 ± 3*</td>
<td>137 ± 5*</td>
<td>146 ± 4*</td>
<td>164 ± 5*</td>
</tr>
<tr>
<td>CO, l/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNT</td>
<td>5.1 ± 0.5</td>
<td>17 ± 1.4</td>
<td>15 ± 0.8</td>
<td>16.4 ± 1.2</td>
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<tr>
<td>LPLO</td>
<td>5 ± 0.5</td>
<td>15.3 ± 1.8</td>
<td>17.1 ± 2.2</td>
<td>19.4 ± 1.9</td>
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<tr>
<td>NPLO</td>
<td>5.8 ± 0.7</td>
<td>14.7 ± 0.8</td>
<td>18.2 ± 1.4</td>
<td>20.1 ± 2.2</td>
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<tr>
<td>SV, ml/beat</td>
<td>80 ± 6</td>
<td>136 ± 11</td>
<td>115 ± 5</td>
<td>110 ± 6</td>
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<tr>
<td>LPLO</td>
<td>71 ± 5</td>
<td>105 ± 11</td>
<td>113 ± 13</td>
<td>116 ± 11</td>
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<tr>
<td>NPLO</td>
<td>83 ± 9</td>
<td>107 ± 5</td>
<td>126 ± 12</td>
<td>124 ± 16</td>
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<td>MBP, mmHg</td>
<td>5 ± 3</td>
<td>107 ± 3</td>
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<td>100 ± 5</td>
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<td>CNT</td>
<td>89 ± 2</td>
<td>112 ± 5</td>
<td>108 ± 6</td>
<td>100 ± 4</td>
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<tr>
<td>LPLO</td>
<td>84 ± 2</td>
<td>112 ± 5</td>
<td>108 ± 6</td>
<td>100 ± 4</td>
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<tr>
<td>NPLO</td>
<td>85 ± 3</td>
<td>107 ± 5</td>
<td>107 ± 6</td>
<td>99 ± 6</td>
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</table>

Values are means ± SE for 7 subjects. $T_{es}$, esophageal temperature; $T_{sk}$, mean skin temperature; HR, heart rate; CO, cardiac output; SV, stroke volume; MBP, mean arterial blood pressure. *Significant differences vs. CNT ($P < 0.05$).

supine to upright position (13), and lower body negative pressure (17), reduced the sensitivity of cutaneous vasodilation in normobaric normoxia. Fortney et al. (4) examined the effects of acute BV loss of 300 ml on cutaneous vasodilation response at 60% $V_{O2}^{peak}$ at 35°C and suggested that the sensitivity of the response decreased by 20%. Recently, Kamijo et al. (15) performed a similar experiment and suggested that PV loss of ~300 ml decreased FVC by 30% during 30 min of exercise at 60% $V_{O2}^{peak}$ at 30°C of Ta and 50% of RH. In the present study, we found that an increase in total vascular resistance decreased by 20% in hypovolemia with no prominent increases in plasma catecholamine concentrations. Ikegawa et al. (11) recently measured CO and HR in subjects with hypovolemia by 300 ml who exercised at 65% $V_{O2}^{peak}$ in the similar environmental condition as in the CNT trial and suggested that CO and SV during exercise were both reduced by 10–20% in hypovolemia compared with those in normovolemia. Thus SV decreased in normoxic hypovolemia with no prominent increases in plasma catecholamine concentrations.

On the other hand, in the present study, we found in the hypoxic trials that the increase in HR was enhanced by ~20 beats/min throughout exercise, and moreover, the increase in $[\text{NA}]_p$ was significantly enhanced compared with that in the CNT trial (Table 5). According to the Guytonian preload-CO relationship model (9), cardiac filling pressure and SV are determined by the cross point of cardiac contractility and venous return curves. A greater decrease in PV such as in the hypoxic trials causes a leftward shift of the venous return curve by decreasing the mean circulatory filling pressure. If the cardiac contractility curve remains unchanged or even increases insufficiently, SV would decrease with a decrease in cardiac filling pressure. On the other hand, if the slope of cardiac contractility curve is increased by enhanced sympathetic nerve activity, the cross point of the curves moved in the upper-left direction, resulting in an increase in SV despite a further decrease in cardiac filling pressure, which might accelerate the suppression of cutaneous vasodilation by the unloading of mechanoreceptors in the cardiac wall.

Another possible mechanism for increased cutaneous vasodilation in hypoxia would be an increase in relative exercise intensity in hypoxia. Smolander et al. (30) assessed the effects of relative exercise intensity on the cutaneous vasodilation response during graded cycle ergometer exercise at 25°C and suggested that $T_{HFVC}$ increased and $\Delta FBF/\Delta T_{es}$ increased with increasing...
relative exercise intensity. In the present study, relative exercise intensity increased from 50% \( V_{\text{O}_2}\text{peak} \) in the CNT trial to \( \sim 60\% \ V_{\text{O}_2}\text{peak} \) in the hypoxic trials when estimated from the HR response at Ex5, assuming that \( HR_{\text{peak}} \) in the hypoxic trials was not different from the CNT trial. Mitono et al. (18) assessed the mechanisms and suggested that the upward shift of THFVC with increasing relative exercise intensity was abolished when a concomitant increase in \( P_{\text{osmol}} \) was reduced by hypotonic saline infusion, suggesting that the increase in \( P_{\text{osmol}} \) was a major factor in increasing THFVC with a rise in relative exercise intensity. Recently, Goto et al. (6) suggested that \( \Delta FVC/\Delta T_{es} \) increased as \( V_{\text{O}_2}\text{peak} \) and PV increased after 5-day aerobic training, and, furthermore, Ikegawa et al. (11) suggested that the increase in \( \Delta FVC/\Delta T_{es} \) after training was abolished when the increased PV after training was acutely reduced to the pretraining level by administration of a diuretic. These results suggest that an increase in THFVC with increasing relative exercise intensity is caused in part by a concomitant increase in \( P_{\text{osmol}} \) and, moreover, a decrease in \( \Delta FVC/\Delta T_{es} \) with increasing relative exercise intensity is caused in part by a concomitant decrease in PV. In the present study, we found that \( \Delta FVC/\Delta T_{es} \) decreased in the hypoxic trials with a greater decrease in PV than in the CNT trial with a rise in relative exercise intensity, whereas THFVC remained unchanged with no significantly greater increase in \( P_{\text{osmol}} \).

Finally, the reduced sensitivity of cutaneous vasodilation would be caused by the local vasoconstrictive effect of hypocapnia due to hyperventilation (27). Experimentally, when we calculated the arterial \( CO_2 \) pressure during exercise using the alveolar ventilation equation by assuming that the dead space was 150 ml (34), the pressure was 26–27 Torr in the hypoxic trials, 8–9 Torr lower than \( \sim 35 \) Torr in the normoxic trial. Robinson and King (23) examined the effects of hypocapnia during hyperventilation on hand blood flow in normoxic resting subjects and suggested that hand blood flow was decreased with a reduction in end-tidal \( CO_2 \) pressure by \( \sim 15 \) Torr with an \( \sim 20 \) l/min increase in \( V_e \), almost equivalent to the differences in \( V_e \) and estimated arterial \( CO_2 \) pressure between the hypoxic and CNT trials in the present study. However, Simmons et al. (28) examined the local effects of hypoxia and hypocapnia on cutaneous vasodilation in nonacral area by laser Doppler flowmetry and suggested that cutaneous vasodilation was enhanced by 20% when arterial \( O_2 \) saturation was reduced to 80% and by 11% when end-tidal \( CO_2 \) pressure was increased by 9 Torr. In the present study, since arterial \( O_2 \) saturation was \( \sim 80\% \) (Table 2), it appeared to be sufficient to cancel the vasoconstrictive effect of hypocapnia, assuming that there were no interactive effects of arterial \( O_2 \) and \( CO_2 \) pressures on cutaneous vasodilation and that the sensitivity of skin vessel response to change in arterial \( CO_2 \) pressure was linear in the range of the change. Moreover, hypoxia and hypocapnia in the hypoxic trials appeared to reach the equilibrium state before the rapid cutaneous vasodilation occurred after Ex10. These results suggest that the effects of hypocapnia on the suppression of cutaneous vasodilation in the hypoxic trials were minimal, if any.

The sensitivity of SR response to increased \( T_{es} \) in the hypoxic trials was not different from that in the CNT trial with no differences between the NPLO and LPLO trials, suggesting no effects of hypobaria and hypoxia on the sensitivity. On the other hand, Kolka et al. (16) examined the effects of graded hypobaria hypoxic conditions [770 Torr (sea level), 552 Torr (2,596 m), and 428 Torr (4,575 m)] on SR during exercise at 60% of their altitude-specific \( V_{\text{O}_2}\text{peak} \) at 30°C of Ta and 30% of RH and suggested that the sensitivity was reduced in the hypobaria hypoxic trials compared with that at sea level but with no differences between the hypobaric hypoxic trials. The detailed reasons for this discrepancy between their study and the present study remain unknown. However, the lower heat production due to lower absolute exercise intensity in the hypobaric hypoxic trials might have influenced their results.

Table 5. [Ad]p and [NA]p during thermoregulatory response test

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Ex5</th>
<th>Ex10</th>
<th>Ex40</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Ad]p pg/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNT</td>
<td>34 ± 10</td>
<td>60 ± 19</td>
<td>92 ± 32</td>
<td>189 ± 56</td>
</tr>
<tr>
<td>LPLO</td>
<td>55 ± 19</td>
<td>127 ± 42</td>
<td>240 ± 73</td>
<td>663 ± 375</td>
</tr>
<tr>
<td>NPLO</td>
<td>52 ± 18</td>
<td>87 ± 25</td>
<td>166 ± 41</td>
<td>358 ± 99</td>
</tr>
<tr>
<td>[NA]p pg/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNT</td>
<td>213 ± 22</td>
<td>521 ± 65</td>
<td>805 ± 176</td>
<td>1255 ± 308</td>
</tr>
<tr>
<td>LPLO</td>
<td>192 ± 26</td>
<td>726 ± 87</td>
<td>1084 ± 127</td>
<td>1670 ± 293</td>
</tr>
<tr>
<td>NPLO</td>
<td>189 ± 6</td>
<td>628 ± 59</td>
<td>1008 ± 149</td>
<td>1685 ± 257</td>
</tr>
</tbody>
</table>

Values are means ± SE for 5 subjects. Adrenaline [Ad]p and noradrenaline [NA]p concentrations in plasma. *Significant differences from CNT (\( P < 0.05 \)).
Alternatively, the lower relative humidity, 30% in their study vs. 50% in the present study, might have influenced the results. In the present study, we had subjects perform exercise at the same intensity while confirming that there were no significant differences in \( \text{VO}_2 \) during exercise (Table 2) and found that SR was similar between trials with no influence of hypobaria.

We found no significant differences in \( T_s \) between the hypoxic trials, suggesting no influence of hypobaria on the variables in a hypoxic condition. We calculated the change in the heat conductances for convection and evaporation in hypobaria using the equations for paritional calorimetry provided by Gagge and Nishi (5) and found that the heat conductance for convection decreased by \( \sim 20\% \), whereas that for evaporation increased by \( \sim 20\% \). Furthermore, although respiratory water loss during exercise increased more in the hypoxic trials than in the CNT trial by enhanced ventilation volume, it was only below 20 g for 40 min, negligible compared with total sweat loss during this period. Thus the reciprocal changes of the conductances might have canceled the effects of hypobaria on heat dissipation in the present study.

**Significance of redistribution of blood flow**

We estimated skin blood flow in the whole body from FBF and the body surface area (2). In addition, we estimated muscle blood flow by subtracting skin blood flow from CO. We found that skin blood flow was \( \sim 1 \text{l/min} \) lower, whereas muscle blood flow was \( \sim 4 \text{l/min} \) higher in the hypoxic trials than in the CNT trials at Ex40, suggesting that \( \sim 25\% \) of muscle blood flow was redistributed from the skin to muscle, which might be advantageous for supplying more oxygen to the active muscles, although at the cost of heat dissipation. In the present study, we suggest that the redistribution was caused by unloading of baroreceptors due to the greater PV loss.

**Limitations**

We measured FBF as an index of skin blood flow in the present study. However, hypocapnia by voluntary hyperventilation was suggested to evoke forearm muscular vasodilation (23, 24). Moreover, the forearm muscular conductance response to lower body negative pressure was suggested to be attenuated in hypoxia (10). These results suggest that FBF or FVC measured in the hypoxic trials included more muscle blood flow than in the CNT trial, and, therefore, the suppression of cutaneous vasodilation in the trials might have been underestimated; however, hypocapnia and hypoxia in the hypoxic trials seemed to reach the steady state before the prominent increase in FVC occurred, followed by the significant suppression of FVC thereafter. Thus the effects of hypocapnia and hypoxia on FBF and FVC measurements in the hypoxic trials might be minimal if any.

In the present study, the increase in [NA]p was significantly higher in the hypoxic trials than in the CNT trial, suggesting that the suppression of cutaneous vasodilation was caused by enhanced active vasoconstrictor (14, 33). On the other hand, Kamijo et al. (15) suggested that cutaneous vasodilation during exercise was suppressed in normoxic hypovolemia, whereas [NA]p was similar to that in normovolemia. Thus the efferent path for the suppression of cutaneous vasodilation in the hypoxic trials, enhanced active vasoconstrictor or attenuated active vasodilator systems, remains unknown.

In the present study, since we did not perform a hypobaric normoxic trial, the mere effects of hypobaria without hypoxia on thermoregulatory response remains unknown; however, since we did not find any prominent differences in the responses between the hypoxic trials, the effects would be minor in the condition of this study, although assuming that the effects of hypobaria and hypoxia were independent of each other with no interactive effects.

Taken together, these results suggest that the cutaneous vasodilation response to increased \( T_s \) was reduced by enhanced exercise-induced PV loss due to hypoxia, which might strengthen the heat dissipation mechanisms that are physiochemically unique in hypobaria at high altitude (5).

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

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