Blood pressure and plasma catecholamines in acute and prolonged hypoxia: effects of local hypothermia

INGE-LIS KANSTRUP,1 TROELS DIRCH POULSEN,2 JESPER MELCHIOR HANSEN,1 LARS JUEL ANDERSEN,3 MORTEN HEIBERG BESTLE,4 NIELS JUEL CHRISTENSEN,5 AND NIELS VIDIENDAL OLSEN6

Departments of 1Clinical Physiology and Nuclear Medicine, 4Anaesthesiology and Intensive Care, and 5Endocrinology, Herlev Hospital, 2Department of Anaesthesiology, Gentofte Hospital, 3Institute of Medical Physiology, and 4Institute of Pharmacology, University of Copenhagen, DK-2730 Herlev, Denmark

Kanstrup, Inge-Lis, Troels Dirch Poulsen, Jesper Melchior Hansen, Lars Juel Andersen, Morten Heiberg Bestle, Niels Juel Christensen, and Niels Vidiendal Olsen. Blood pressure and plasma catecholamines in acute and prolonged hypoxia: effects of local hypothermia. J. Appl. Physiol. 87(6): 2053–2058, 1999.—This study measured the pressor and plasma catecholamine response to local hypothermia during adaptation to hypobaric hypoxia. Eight healthy men were studied at rest and after 10 and 45 min of local cooling of one hand and forearm as well as after 30 min of rewarming at sea level and again 24 h and 5 days after rapid, passive transport to high altitude (4,559 m). Acute mountain sickness scores ranged from 5 to 16 (maximal attainable score: 20) on the first day but were reduced to 0–8 by the fifth day. Systolic blood pressure, heart rate, and plasma epinephrine increased on day 1 at altitude compared with sea level but declined again on day 5, whereas diastolic and mean blood pressures continued to rise in parallel with plasma norepinephrine. With local cooling, an increased vasoactive response was seen on the fifth day at altitude. Very high pressures were obtained, and the pressure elevation was prolonged. Heart rate increased twice as much on day 5 compared with the other two occasions. Thoracic fluid index increased with cooling on day 5, suggesting an increase in pulmonary vascular resistance. In conclusion, prolonged hypoxia seems to elicit an augmented pressor response to local cooling in the systemic and most likely also the pulmonary circulation.

acute mountain sickness; bioimpedance; healthy subjects; pulmonary vascular resistance; thoracic fluid index

IT HAS BEEN PROPOSED that acute hypoxia influences systemic blood pressure (BP) very little in humans (8, 21, 22). This point of view is, however, based on results from short-lasting hypoxia (7 min, 40 h, 1–4 days). During more prolonged hypoxia (several days) a gradual increase in systemic pressure, especially in mean arterial BP (MABP) and diastolic BP (DBP), has been reported in parallel with increases in plasma concentrations and urinary excretion rates of norepinephrine (10, 24). This suggests that cardiovascular reactions in humans in hypoxia are similar to those found in dogs (8). In the pulmonary circulation, acute hypoxia induces in most species, including humans, an immediate arteriolar constriction, leading to elevated pulmonary BP (6). An increased pulmonary vascular responsiveness to adrenergic stimuli such as local cooling has been found in hypoxemic subjects (2). In normoxia a cold pressor test produces an exaggerated systemic pressor response in hypertension-prone subjects compared with normotensive individuals (20). To date, previous studies with prolonged hypoxia have concentrated on the circulatory and pulmonary systems while subjects were at rest. It is not known whether increasing BP and catecholamine levels previously observed with prolonged hypoxia somehow alter the adrenergic responsiveness to an acute stressor relative to what is observed at sea level.

The purpose of the present study was to evaluate the systemic response, as reflected by BP, plasma catecholamines, and bioimpedance measures of pulmonary status, to an adrenergic stimulus applied as local cooling of a hand and forearm at different phases of the adaptation to hypoxia in normal subjects.

METHODS

Subjects and experimental protocol. Eight healthy men [age 26 (22–35) yr, height 185 (180–194) cm, weight 76 (67–90) kg (mean and range)] gave their informed written consent to participate in the study, which was approved by the local Ethics Committee for the county of Copenhagen. The subjects were studied at sea level (Herlev Hospital, Copenhagen, Denmark), and 24 h and 5 days after arrival at high altitude. The high altitude studies were carried out in the Capanna Regina Mageritha Hut (Mount Rosa, Italy; 4,559 m). The subjects were airlifted by helicopter. The protocols for the 3 study days were identical and were conducted at the same time of the day. Room temperature in both laboratories was 19–21°C. At altitude physical activity was kept at a minimum. At sea level, strenuous physical activity was not allowed 72 h before the experiment.

The subjects were investigated while they were in the resting supine position. A venous catheter was inserted into an antecubital vein for blood sampling. Electrocardiograph electrodes for impedance measurements were carefully positioned according to the manufacturer’s instructions, and the positions were marked to attain identical positions in all experiments. Control measurements were performed after a minimum of 30 min of rest. Then local hypothermia was applied by wrapping one hand and antebrachium in ice bags (the arm opposite to where the Venflon was placed), and measurements were repeated after 10 and 45 min of local cooling. The ice bags were then removed, and the measure-

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ments were repeated after 30 min of spontaneous rewarming in room temperature.

Measurements. Stroke volume, cardiac output, and thoracic fluid index were measured simultaneously by bioimpedance (BoMed NCCOM 3 Medical Manufacturing, Irvine, CA). BP s and heart rate were recorded with a Finapress (Ohmeda, Engelwood, CO) attached to the noncooled hand. Because the Finapress and bioimpedance recordings could not be sampled simultaneously, bioimpedance recordings were obtained for 2 min in the control situation, and then BPs and heart rate were recorded continuously onward in the control situation and into the first 10 min of hypothermia. Bioimpedance recordings were then sampled from 10 to 12 min (10-min values), and the measurements were repeated in the same order after 45 min of hypothermia and after the succeeding 30 min of gradual rewarming. During the recording times, venous plasma was sampled for the measurements of epinephrine and norepinephrine concentrations. Packed cell volume was measured in the control situation.

Oxygen saturation at high altitude was measured in the control period by a pulse oximeter (Ohmeda Biox III, Boulder, CO) with the sensor attached to the first or second finger. Body weight was measured in the morning before the experiments started. At altitude, scoring for acute mountain sickness (AMS) was registered in the morning shortly after the subjects awoke and while they were in the fasting state, according to a slight modification of the Lake Louise AMS Scoring System (18) where each of the symptoms, headache, gastrointestinal symptoms, fatigue and/or weakness, dizziness (AMS) was registered in the morning shortly after the subjects awoke and while they were in the fasting state, according to a slight modification of the Lake Louise AMS Scoring System (18) where each of the symptoms, headache, gastrointestinal symptoms, fatigue and/or weakness, dizziness/limb hypotension, and difficulty in sleeping, was assessed on a scale from 0 to 4.

Analytical methods. Bioimpedance was measured across the thorax between four electrodes placed around the basis of the neck at the level of the lung apex and four electrodes placed around the chest at the level of the xiphoid process corresponding to the level of the lung basis (25). A high-frequency alternating current of 2.5 mA at 70 kHz was sent between the two outer sets of electrodes, and the impedance signal was measured between the inner sets of electrodes. The stroke volume in milliliters was calculated by the bioimpedance equipment by using the empirical formula described by Sramek-Bernstein (19)

\[
\text{Stroke volume} = \frac{(\text{VEPT} \times \frac{dZ}{dt_{\text{max}}}) \times \text{VET}}{Z_0}
\]

where VEPT (volume of electrically participating tissue) = L^{3/4} 25, and L is a constant estimated from the subject’s height and weight by using a nomogram. Z_0 is the basal impedance (proportional to the intrathoracic fluid volume, hereafter named thoracic fluid index), \(dZ/dt_{\text{max}}\) the peak rate of change of the impedance, and \text{VET} the ventricular ejection time. With a developed software program for on-line recordings, readings of stroke volume, heart rate, cardiac output, and thoracic fluid index were obtained for each cardiac cycle, and the resultant values were calculated as the mean of 60–120 cycles.

Catecholamines were determined with a radioenzymatic assay. Five milliliters of blood were drawn into ice-chilled tubes containing 1.7 mg/ml EGTA and 1.1 mg/ml reduced glutathione. After centrifugation (for 10 min at 3,500 rpm) plasma was removed and stored initially in dry ice, and after it was returned to sea level it was stored at −80°C until analysis. Intra-assay coefficients of variation in samples containing normal basal levels have been found to be 6 and 8%, respectively, and interassay coefficients of variation were 7 and 11%, respectively (n = 10) (7).

Packed cell volume was determined in triplicate by a minicentrifuge at 2,000 rpm for 5 min.

Statistics. Values are presented as means ± SE. Statistical difference of variations between conditions was assessed by a two-way ANOVA for repeated measures. If allowed for, differences between means as well as between delta values, taking changes in baseline levels into account, were determined by paired t-tests. Simple linear regression was applied to test correlations when appropriate. The level of significance was 0.05.

RESULTS

Systemic effects. Oxygen saturation on day 1, at altitude was 79 ± 2.9% and increased on day 5 to 85 ± 2.1% (P < 0.05). Packed cell volume increased from 43 ± 1.0% at sea level to 46 ± 1.3% on day 1 (P < 0.01) and 46 ± 1.5% on day 5 (P < 0.05).

The subjects were moderately or quite severely affected by the altitude. Scorings for symptoms of AMS ranged from 5 to 16 points on the first day (mean 9.9, maximal score 20). By the fifth day the AMS score had diminished to a mean of 2.9 (range 0–8) points. There were no signs of more severe complications to the AMS. Body weight did not differ between sea level and day 1 in altitude (76.0 ± 2.7 and 76.5 ± 2.9 kg, respectively; not significant), but was decreased on day 5 (75.1 ± 2.7 kg; P < 0.05).

Cardiac and pulmonary effects of high altitude in the control situation. Cardiac output remained unchanged at high altitude. Heart rate increased at high altitude (Fig. 1) but, compared with day 1, decreased again on the fifth day. Stroke volume decreased on both days at altitude compared with sea level but with no significant differences between the altitude measurements. Thoracic fluid index remained unchanged (Fig. 2). Calculated total peripheral resistance on day 5 increased by 33% in the control situation compared with normoxia (P < 0.01) and by 23% compared with day 1 (P < 0.05).

BP in the control situation. Systolic BP (SBP) increased in all subjects on day 1 at altitude compared

\[
\text{Heart Rate with acute hypoxia (bpm)} = \begin{cases} 
75 & \text{day 1} \\
70 & \text{day 5}
\end{cases}
\]

**Fig. 1. Heart rate with acute and subacute hypoxia and response to local cooling and gradual rewarming. Values are means ± SE; n = 8 men. bpm, Beats/min. ** **P < 0.01 compared with normoxia. † P < 0.05, ‡ P < 0.01 compared with day 1 in hypoxia. §§ P < 0.01 compared with control situation on the same day.**
with sea level (Table 1, Fig. 3) but decreased again on day 5 ($P < 0.06$ compared with sea level). Both DBP and MABP also rose on day 1 and further increased on day 5. Four subjects had DBP $> 90$ mmHg on day 5. In one subject the increase was especially pronounced from $144/81$ (mean $98$) mmHg at sea level to $181/104$ (mean $125$) mmHg on day 1 and $162/106$ (mean $124$) mmHg on day 5.

Catecholamines at control. Mean norepinephrine concentration almost doubled on day 1 (Table 1, Fig. 4) and increased further to ~$300\%$ above sea-level values on day 5. Plasma epinephrine concentration significantly increased on day 1 but had returned to normoxic levels on day 5.

Effects of local hypothermia. In normoxia, local cooling immediately increased BPs (Fig. 3) and heart rate (Fig. 1). Peak BP values measured during the first 10 min of cooling increased from $134 \pm 4.4$ to $151 \pm 5.6$, from $75 \pm 3.4$ to $88 \pm 5.2$ and from $89 \pm 3.4$ to $102 \pm 5.7$ mmHg, respectively, for SBP, DBP and MABP ($P < 0.01$). Heart rate increased from $58 \pm 3.2$ to $67 \pm 3.9$ beats/min (bpm) ($P < 0.01$).

By 10 min, BP and heart rate had fallen again to the control level, and at this time there were no significant changes in any of the other measured variables. After 45 min of cooling, however, SBP and MABP had again increased to $148 \pm 6.7$ and $100 \pm 6.1$ mmHg, respectively ($P < 0.05$ compared with the control situation), whereas DBP was unchanged ($83 \pm 5.6$ mmHg; $P <$

Table 1. Control values

<table>
<thead>
<tr>
<th></th>
<th>Sea Level</th>
<th>Hypoxia Day 1</th>
<th>Hypoxia Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output, l/min</td>
<td>$7.5 \pm 0.54$</td>
<td>$7.9 \pm 0.52$</td>
<td>$6.7 \pm 0.46$</td>
</tr>
<tr>
<td>Thoracic fluid index, $\Omega$</td>
<td>$24.41 \pm 1.01$</td>
<td>$23.98 \pm 1.31$</td>
<td>$23.59 \pm 1.30$</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>$58 \pm 3.2$</td>
<td>$87 \pm 4.0$</td>
<td>$73 \pm 3.3$†‡</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>$131 \pm 9.6$</td>
<td>$92 \pm 8.1$†</td>
<td>$94 \pm 8.3$†</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>$134 \pm 4.4$</td>
<td>$153 \pm 6.9$†</td>
<td>$145 \pm 5.5$</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>$75 \pm 3.4$</td>
<td>$85 \pm 3.7$*†</td>
<td>$92 \pm 3.2$†</td>
</tr>
<tr>
<td>MABP, mmHg</td>
<td>$89 \pm 3.4$</td>
<td>$103 \pm 4.2$†</td>
<td>$107 \pm 3.2$†</td>
</tr>
<tr>
<td>Norepinephrine, ng/ml</td>
<td>$0.08 \pm 0.01$</td>
<td>$0.15 \pm 0.03$</td>
<td>$0.23 \pm 0.03$‡</td>
</tr>
<tr>
<td>Epinephrine, ng/ml</td>
<td>$0.02 \pm 0.00$</td>
<td>$0.03 \pm 0.00$*†</td>
<td>$0.02 \pm 0.00$</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SE for 8 men. bpm, Beats/min; SBP, systolic blood pressure; DBP, diastolic blood pressure; MABP, mean arterial blood pressure. *$P < 0.05$, †$P < 0.01$ compared with normoxia. ‡$P < 0.05$, §$P < 0.01$ compared with hypoxia day 1.
rate rose from 87 DBP and MABP were less pronounced (Fig. 3). Heart period either.

On the first day of hypoxia, local cooling led to similar increases in peak values of SBP and heart rate as in normoxia during the initial 10 min, but the increases in DBP and MABP were less pronounced (Fig. 3). Heart rate rose from 87 ± 4.0 to 98 ± 2.2 bpm (Fig. 1). By 10 min BP and heart rate had returned to control levels but were still elevated compared with the corresponding situation in normoxia (P = 0.07 for DBP). The other parameters remained unaffected by cooling as in normoxia. After 45 min of cooling, BPs were further reduced and reached normoxic levels (P < 0.05 compared with the 10-min values), heart rate was unchanged, but stroke volume was further reduced compared with the control situation on the same day. Plasma norepinephrine reached a significant elevation in comparison with the corresponding normoxic situation. In recovery, heart rate had dropped compared with 45 min of cooling, and cardiac output was slightly reduced in comparison with the control value.

On the fifth day of hypoxia, peak values for BP increased almost equally during cooling as in normoxia in the presence of elevated basic levels compared with normoxia. This means that the augmentations in DBP and mean BP were more pronounced than on day 1 in altitude. Thus the absolute pressures were very high, increasing from 145 ± 5.4 to 169 ± 6.0, from 92 ± 3.2 to 105 ± 4.2, and from 107 ± 3.2 to 123 ± 4.3 mmHg, respectively (Fig. 3). The relative increases were of the same magnitude as in normoxia, except for a significant higher increase in SBP at 10 min (P < 0.05). Peak heart rate increased even more than earlier, i.e., 21 bpm from 73 ± 3.3 to 94 ± 3.4 bpm (P < 0.05), whereas the preceding increments had been ~10 bpm on both occasions. BP values after 10 and 45 min cooling remained very high, whereas heart rate fell to control levels. The sum of the areas of the BP increases above the actual base levels during cooling was significantly increased on day 5. The highest value for plasma norepinephrine was obtained after 10 min of hypo-thermia, but the increase was not significant (the value increased in 6 of 8 subjects but decreased in 1). Stroke volume was still reduced compared with that at sea level and, as with cardiac output, was not influenced by cooling. Thoracic fluid index, however, increased slightly (2%; P < 0.05) with cooling and remained elevated during recovery.

The scoring for AMS on day 1 was significantly correlated to the sea-level SBP (r² = 0.63, P < 0.05) and MABP (r² = 0.53, P < 0.05), whereas no correlation was found between the severeness of AMS and the obtained BP in high altitude (neither in absolute values nor in increments). AMS score and the increments in norepinephrine were significantly correlated (r² = 0.65, P < 0.05 for day 1; r² = 0.76, P < 0.05 for day 5).

DISCUSSION

Our data emphasize the gradual development of increased systemic BPs, especially MABP and DBP, with time in altitude concomitantly with increasing levels of p-norepinephrine. This was also found in other studies with subjects spending several days in hypoxia (9, 10, 14, 24) but was only discussed in details by Mazzeo et al. (10) and Wolfel et al. (24). Wolfel et al. reported a significant correlation between MABP and urinary norepinephrine excretion from control to day 2, day 8, and day 17 in altitude (r = 0.68, P < 0.001). We found a similar correlation between plasma norepinephrine and MABP with r = 0.56 (P < 0.01). In hypertensive subjects, BP has been reported to change little with exposure to hypoxia, but the sparse measurements were performed just a few hours after arrival to 2,500-m altitude (13) or 3,460-m altitude (16). Thus with time in high altitude more pronounced changes may be foreseen. This points to the need of more attention being given to the response in hypoxia (and also to the advice given to trekkers) and to the control of people with existing systemic hypertension traveling in high altitude. It is especially of concern that some individuals may develop very high pressure elevations over time in altitude.

Common to the studies cited above is that the subjects were passively and in a short time (by car or helicopter) brought to altitude and performed little physical activity. Thus the results were not influenced by strenuous performances, temperature differences, hyphdration, and so forth. The abrupt exposure to hypoxia makes the subjects more susceptible to AMS, the development of which might be considered to influence the severeness of the BP. Symptoms of AMS were not classified in the studies referred to above but were mentioned by Richalet et al. (14) to be of various degrees of severity. Our subjects were moderately affected by AMS with high scores on the first day, but as expected symptoms gradually declined with time, and on day 5 only slight affection remained. AMS scores and the increments in norepinephrine were significantly correlated, suggesting that a connection between the factors eliciting AMS and the activation of the sympathethic nervous system is likely. However, because the increase in BP (and norepinephrine) is maintained for
weeks or even months (24), other factors may contribute as well. In rats, hypoxia-induced hypertension is associated with a transient rise in plasma endothelin and a depressed production of nitric oxide (12), but the role of this response for a sustained systemic pressure elevation is at present unknown.

The finding in our study of a reinforced vasoactive response to local cooling with time in high altitude in connection with elevated basic levels of norepinephrine and MABP is remarkable. The often-applied cold pressor test where a hand is immersed in ice water for 1–2 min induces an immediate and very marked rise in systemic BP because both a cold stimulus and pain are evoked (20). This test has been shown to produce excessive systemic pressor responses in hypertension-prone subjects (20). A slight increase (0–14%) in pulmonary vascular resistance has also been found at sea level (11). In subjects with increased vasoreactivity as in vasospastic angina or systemic hypertension, the cold pressor test induces a higher rise in pulmonary vascular resistance (1, 5, 11, 17). In our study the aim was to simulate an accidental local hypothermia, and local cooling consisted of wrapping the forearm and hand in plastic bags with crushed ice so that a direct contact with the ice was avoided. Severe pain was not reported in any of the subjects. In normoxia this local cooling led to an immediate increase in BPs and heart rate, but by 10 min of cooling the values had returned to basic levels. After 45 min of cooling, SBP and MABP increased again, whereas heart rate remained unchanged, and no change could be measured in venous catecholamine concentrations. We have no explanation for this late increase, but the changes were so modest that no measurable increases in plasma catecholamines would be expected. The pressure increases by cooling, which reached higher absolute levels and were longer lasting, were not accompanied by significant increments in plasma catecholamine concentrations, although a trend toward an increase in norepinephrine was seen on day 5.

High-altitude pulmonary edema (HAPE) has been proposed to develop due to an extensive, but uneven, vasoconstriction, which increases the shear stress on some of the capillaries and may result in a leakage of protein, erythrocytes, and fluid into the alveoli (6). Thus the thoracic fluid index is an interesting parameter to monitor over time in altitude, because HAPE and possibly also AMS are connected with increased fluid accumulation in the lungs. In critical care patients, the transthoracic electrical bioimpedance method has been useful to monitor changes in the amount of thoracic fluid (15). Zerahn et al. (25) found an increase in thoracic fluid index of 2.3 Ω/l/ aspirated thoracic fluid in patients with pleural effusions. However, changes were different in patients with cancer and with heart failure as elicitor of the pathological condition, pointing to methodological differences. For instance, the method cannot discern between intravascular and extravascular fluid. Changes in thoracic fluid index, however, can be used as a relative measure of changes in overall intrathoracic fluid accumulation. We found that the mean control values tended to decline with time in altitude, but changes were not significant. Day-to-day measurements should be interpreted with caution because the electrodes were not kept in place. The coefficient of variation has been found to 4.3% in measurements separated by 1 wk (19). With local cooling, thoracic fluid index increased by 2% on day 5, whereas thoracic fluid index remained unchanged on the other two occasions. The rise in thoracic fluid index is probably an expression of an increased vasoconstriction also in the pulmonary arteries. The reduced fluid content would be ~0.3 liters (25). This agrees with earlier results showing an increased pulmonary reactivity to cold in longer lasting hypoxia (2, 3).

The present findings of gradual increases in systemic pressure in hypoxia and reinforced vasoactive responses to local cooling draw the attention to a possible role of this response for the development of HAPE and high-altitude cerebral edema (HACE). It has been proposed that local cooling or exhaustion in cold environments could promote the development of HAPE (2) or HACE (4). In healthy high-altitude (3,700 m) residents, a pronounced response to local facial cooling has been reported, because pulmonary vascular resistance increased by 23% (at a mean arterial PO2 of 53 Torr) (3). Bedu et al. (2) found a 15% increase in pulmonary vascular resistance in seven subjects with chronic obstructive pulmonary disease (COPD) and reduced arterial oxygen content at 2,650-m altitude as a response to 10 min of facial cooling. At sea level, six subjects with COPD and reduced arterial oxygen pressure (arterial PO2 <50 Torr) had a pronounced increase in pulmonary vascular resistance (24%) and mean pulmonary pressure (8%) after facial cooling, whereas 13 subjects with COPD and higher oxygen pressures showed no changes. They concluded that moderate and localized cold exposure could aggravate the pathophysiological consequences of hypoxia. Our findings of increased pressure responses with local cooling in prolonged hypoxia are in line with these results.

In conclusion, prolonged hypoxia for 5 days increases systemic BPs, especially MABP and DBP, in parallel with increased circulating norepinephrine concentration. Furthermore, a reinforced vasoactivity to an adrenergic stimulus, such as local cooling, was rendered probable in the systemic and most likely also in the pulmonary circulation with time in altitude, pointing to a possible mechanism behind the development of HAPE and HACE.

The study was supported by the Danish Council for Sports Research; the Danish Hospital Foundation for Medical Research: Regions of Copenhagen, the Faeroe Islands and Greenland; the Simonsen & Weel Foundation; and Meda.

Address for reprint requests and other correspondence: I.-L. Kanstrup, Dept. of Clinical Physiology and Nuclear Medicine, Herlev Hospital, Univ. of Copenhagen, DK-2730 Herlev, Denmark (E-mail: ilka@herlevhosp.kbhamt.dk).

Received 4 March 1999; accepted in final form 2 August 1999.

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