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RESEARCH ARTICLE

Plasma catecholamines and blood volume in native Andeans during hypoxia and normoxia

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Abstract Plasma catechols and blood volume were measured in 20 male, native high-altitude residents of Cerro de Pasco, Peru (4338 m), while hypoxic and subsequently while normoxic at sea level. Ten subjects were healthy controls, with hematocrits lower than 61 %, and ten had chronic mountain sickness (CMS), a syndrome of maladaptation to altitude, characterized by polycythemia (hematocrit > 61 %), profound hypoxemia, and neurologic symptoms. The main aim of the study was to evaluate the chronic effects of hypoxia on plasma catechols and on blood volume, by studying these parameters during hypoxia at high altitude (HA) and shortly after exposure to normoxia at sea level (SL). Subjects were first studied at HA in their habitual hypoxic environment, and measurements were repeated within 4 hours of arrival at SL (Lima, Peru, 150 m). All subjects had higher plasma norepinephrine (NE), dopamine (DA), and dihydroxyphenylglycol (DHPG) levels in HA (NE in controls and CMS: 414 ± 47 and 514 ± 35 pg/mL; DA: 9 ± 1 and 13 ± 1 pg/mL, DHPG: 817 ± 48 and 972 ± 77 pg/mL) than at SL (NE: 164 ± 9 and 243 ± 28 pg/mL; DA: 4 ± 0.5 and 5 ± 1 pg/mL DHPG: 502 ± 23 and 649 ± 39 pg/mL). Group differences were statistically significant only for NE in the CMS group. Plasma volume was higher in HA in both groups ($p < 0.05$); red cell volume was higher in HA only in the CMS group. The results indicate sympathetic nervous stimulation by chronic ambient hypoxia at altitude in Andean natives, independent of maladaptation to their native environment.

Key words hypoxia · catecholamines · blood volume · chronic mountain sickness

Introduction

More than 100 million people live and work in ambient hypoxia in the high mountains of the world. This model of naturally occurring chronic hypobaric hypoxia offers unique opportunities to assess effects of chronic hypoxia on human physiology.

Catecholamine systems are well known to participate in responses to hypoxia acutely and also in chronic hypoxia from pulmonary diseases [16]. Until recently it was thought that these systems functioned in a monolithic manner in response to any global emergency, such as hypoglycemia, hypoxia, or "fight-or-flight" situations. Over the past two decades, however, evidence has accrued for separate regulation of three types of peripheral cate-

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cholamine systems [11, 14]. In the adrenomedullary hormonal system, epinephrine is the primary hormone released from adrenomedullary chromaffin cells into the bloodstream. The sympathetic nervous system uses norepinephrine (NE) as the main neurotransmitter for cardiovascular regulation. In the DOPA-dopamine (DA) system, DA produced in non-neuronal cells acts as an autocrine-paracrine substance. Most of the dopamine produced and metabolized in the body does not derive from the brain, the sympathetic nervous system or the adrenal medulla, but from non-neuronal splanchnic cells draining into the portal vein [8].

Different stressors can evoke differential responses of the sympathetic noradrenergic and adrenomedullary hormonal systems [24, 35]. For instance, exposure to cold preferentially stimulates sympathoneural outflows [10], whereas hypoglycemia preferentially stimulates adrenomedullary secretion [12]. The role of locally produced dopamine in chronic adaptive responses to hypoxia remains poorly understood. The high prevalence of carotid hyperplasia and carotid body paragangliomas among high-altitude (HA) natives [3] as well as the ten times higher incidence of chemodectomas in high-altitude populations [29] might suggest a role of the DOPA-dopamine system in adaptation to chronic hypoxia.

HA Andean natives are descendants of populations who have resided at high altitude for thousands of years. This long history raises the possibility that they might be genetically adapted to hypobaric hypoxia. A pathologic maladaptation to high altitude is present in approximately 15 % of this population. The maladaptation syndrome is called chronic mountain sickness (CMS) [23]. CMS was first noted in 1925 by Monge [22] in a miner from Cerro de Pasco, Peru, where the present study was conducted. CMS is characterized by profound hypoxemia, polycythemia, neurologic symptoms and signs, blood vessel proliferation and prominent migrainous headache. Severe polycythemia, exceeding physiological values for the particular altitude, is the main characteristic and primary diagnostic sign of CMS. Symptoms remit within hours of exposure to normoxia at lower altitude. Lingering signs of the illness, such as engorged veins and blood vessel proliferation, disappear within 2 months, when the laboratory hallmark of the disorder, polycythemia, also disappears [2, 25].

It is well known that chronic hypoxia from altitude exposure in non-natives produces sympathoexcitation [15] as well as a decrease in plasma volume and an increase in red cell mass. Acute hypoxia produces relatively small increases in plasma norepinephrine levels [33]. High altitude natives have increased total blood volume and red cell volume and reduced plasma volume [6]. Among sojourners, after 1–3 weeks at high altitude, red cell mass increases and plasma volume decreases; the increased red cell mass is associated with elevated blood volume.

The present study was designed to evaluate the chronic effects of hypoxia on plasma catechols and blood volume, by assessing these parameters at HA and shortly after exposure to normoxia. If there were complete adaptation to chronic hypoxia, as suggested by previous studies, normoxia would not produce important changes in the variables studied. We also studied CMS patients, known to suffer from maladaptation to hypoxia. For these purposes, we measured plasma levels of epinephrine (EPI), norepinephrine (NE), dopamine (DA), and the neuronal NE metabolite, dihydroxyphenylglycol (DHPG), and blood volumes in HA Andean native controls and in HA Andean native patients with CMS (N = 10 in each group). Measurements were performed at HA in Cerro de Pasco, Peru, and repeated in the same subjects within 4 hours after arriving at sea level (SL) in Lima, Peru.

Methods

Subjects

We recruited 20 high altitude men born in Cerro de Pasco, Peru (4338 m) who had not lived elsewhere for more than 6 months. None of the subjects had traveled in the previous year to any place at a lower altitude. Ten subjects were healthy controls and ten were patients suffering from CMS. All gave written informed consent to the study, which was approved by the Institutional Review Board of the Universidad Peruana Cayetano Heredia, Lima, Peru.

All subjects were rated using a standardized CMS scale based on hematologic, cardiovascular and neurologic findings [20]. All participants were examined in Cerro de Pasco and at Lima. Subjects were diagnosed as having CMS by a CMS score ≥ 12 and hematocrit (Hto) ≥ 61 % (mean ± 20 SD of the normal distribution of the male population) [23]. Individuals not meeting these criteria were utilized as controls. The CMS score is a standard measure based on the ten most frequent symptoms and signs found in CMS. A value of zero was assigned to negative answers. Positive answers were divided as occasional (2 signs per month) and frequent (≥ 3 signs per month) and had values of two (or three) and four (or six), respectively. The sum of these assigned values constituted the CMS score.

Protocol

Subjects were studied twice, first at HA, and after 3 days measurements were repeated at SL (Fig. 1). All subjects were free of methylxanthines and were not taking any medication for at least 3 days before the study and came fasting overnight prior to the study. No special diet was indicated. At HA, subjects were asked to come to the "Laboratorio de Investigaciones de Altura" of the "Universidad Peruana Cayetano Heredia" at Cerro de Pasco. An antecubital venous catheter was placed for blood drawing, and subjects then rested supine for at least 30 min before blood was drawn. After 3 days, subjects were transported to Lima (SL), which is a 6 to 8-h trip from Cerro de Pasco (HA) on a paved road. The first 2–3 h involve a rapid ascent from the Peruvian Altiplano (3.600–4.300 m) to a high mountain pass (> 4.800 m). The last ~4–5 h involve a rapid descent. Low altitudes (< 1000 m) are reached after approximately 4–6 h from the start of the trip. Subjects arrived to SL in groups of 3–4 per day over a 5-day period. They rested in the laboratory in Lima for 2–4 h before studies were initiated. Thus, subjects were studied after no more than 4-hours of acute exposure to normobaric normoxia.

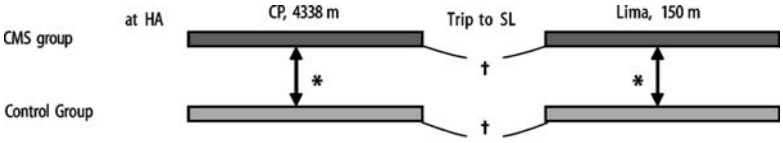

Fig. 1 Graph shows how the study was conducted and the comparisons that were made. Between group differences (*) were studied at each altitude. Differences between different altitudes (†) were studied within groups. *CMS* chronic mountain sickness patient group; *HA* high altitude study site; *SL* sea level study site; *CP* Cerro de Pasco-Perú; *Lima* Lima-Perú; *m* meters above sea level

Catecholamines and blood volumes

Blood samples were centrifuged at 4 °C and the plasma separated. At HA, plasma was immediately placed in dry ice and brought to SL, where the samples were stored at –70 °C until assayed in the Clinical Neurochemistry Laboratory of the Clinical Neurocardiology Section at the NIH. The plasma was assayed for catecholamines by high-pressure liquid chromatography with electrochemical detection after batch alumina extraction [17].

Blood volume was measured using the indicator dye-dilution principle after injection of a known amount of ^{131}I-albumin. A baseline venous blood sample was collected prior to injection of the tracer. Using a pre-filled 1 ml syringe, up to 25 μCi of ^{131}I-labeled human serum albumin (Volumex, Daxor Corporation, New York) was injected into the antecubital vein and flushed with 30 ml of normal saline. Starting at 12 min post injection, 5 ml aliquots of venous blood were collected at 6-min intervals for 30 min. Microcapillary hematocrit was measured in duplicate from each sample. Plasma radioactivity was measured in duplicate using an automated counter (BVA-100 Blood Volume Analyzer, DAXOR Corporation, New York, NY) and automated linear regression analysis. Plasma volume was determined as the volume of distribution of ^{131}I-albumin. Total blood volume was calculated from measured plasma volume and microcapillary venous antecubital hematocrit corrected for the plasma packing ratio (0.99), the ratio of mean body hematocrit to peripheral (measured) hematocrit (0.91), and the effects of heparin within the sampling syringe (0.97). Ideal blood volumes were determined for each individual based upon the height, weight, and gender of the subject. Percentages of ideal values are obtained dividing the actual values by the ideal values and expressing the result as %. This algorithm eliminates systematic errors for lean and obese individuals that arise from norms based on body weight or body surface area. Utilization of fixed ratio norms results in underprediction of normal volume in obese individuals and overprediction of normal volume in lean individuals [9].

Statistical analyses

Data were analyzed using SPSS for Windows Version 11. Differences in the measured variables among conditions (high altitude vs. sea level) were assessed by repeated measures ANOVA, with altitude as a between-subjects factor with two levels. Student's paired t or Wilcoxon's tests for related samples were used when appropriate to determine if the observed differences between the two altitudes were significant or not. Differences between groups (Controls or CMS patients) were assessed with student's t test for independent samples or Mann-Whitney U test for independent samples when appropriate. Kolmogorov-Smirnov test was applied to test for normal distribution. Statistical significance was set at $p < 0.05$. Values are expressed as mean ± SEM.

Results

One subject from the control group was not able to travel to SL, and one patient required treatment (phlebotomy and hemodilution) because of symptomatic CMS before travel to SL. Data from these subjects were excluded from the analysis. The CMS and control groups did not differ in mean age, body mass, or height (Table 1). CMS patients tended to be older than controls.

Plasma levels of dopamine (DA), norepinephrine (NE), and dihydroxyphenylglycol (DHPG) were higher at HA than at SL (Table 2). Neither plasma epinephrine (Fig. 2) nor L-DOPA varied after the descent to SL. Plasma dihydroxyphenylacetic acid (DOPAC) levels were also higher at HA, but only in CMS patients ($p < 0.05$). Plasma levels of all catechols measured tended to be higher in the CMS group compared to controls, but only NE at SL was significantly higher ($p = 0.04$). Plasma L-DOPA levels did not vary with altitude. At high altitude there was a trend toward higher values for plasma DA, DOPA, and DOPAC in the CMS group compared to controls. This trend was not observed at sea level.

A trend toward higher blood volumes and lower plasma volumes was observed among CMS patients, but it did not reach statistical significance. At SL, blood volume in CMS patients was higher than in controls ($p = 0.021$). CMS patients both at HA and SL had higher red cell volumes ($p = 0.004$ and 0.03), hematocrits, and CMS scores (Tables 1 and 3). In both groups blood volume was significantly increased at SL ($p = 0.043$ for controls and 0.008 for CMS). Plasma volume was significantly higher than at SL, for both CMS patients ($p = 0.011$) and controls ($p = 0.05$). The interaction of altitude and subject group was not statistically significant.

Table 1 Demographic data in control subjects and in patients with chronic mountain sickness (CMS)

	Control	CMS
HA (Cerro de Pasco)		
Age (years)	36.0±2.7	43.0±2.0
Weight (kg)	62.9±1.3	63.2±2.8
Height (m)	1.6±0.0	1.6±0.0
Hematocrit	55.2±1.1	70.0±0.9*
O2 Saturation	89.0±1	88.0±1
CMS score	11.0±2.3	19.0±2.2*
SL (Lima)		
Hematocrit	52.1±1.2	68.9±1.1*
O2 Saturation	98.0±0.4	96.1±0.5
CMS score	2.8±0.5	9.2±0.8*

HA High altitude; *SL* Sea level. Data are expressed as mean ± SEM

Table 2 Plasma catecholamines in control subjects and in patients with chronic mountain sickness (CMS)

	Controls (n = 9)	CMS (n = 9)	p*
Dopamine (pg/mL)			
HA	8.7 ± 1.33	12.6 ± 1.44	0.062
SL	4.4 ± 0.48	5.0 ± 0.89	0.536
p†	† 0.008	† 0.004	
Norepinephrine (pg/mL)			
HA	414.1 ± 46.88	514.3 ± 34.63	0.113
SL	163.8 ± 8.62	242.6 ± 28.25*	0.040
p†	† 0.008	† 0.008	
Epinephrine (pg/mL)			
HA	15.2 ± 2.94	21.1 ± 4.28	0.273
SL	15.3 ± 3.73	19.6 ± 3.92	0.436
p†	0.987	0.593	
DHPG (pg/mL)			
HA	816.9 ± 47.97	971.8 ± 76.70	0.106
SL	592.1 ± 22.76	649.5 ± 41.54	0.243
p†	† 0.002	† 0.000	
DOPA (mg/mL)			
HA	1334.0 ± 63.62	1416.1 ± 56.03	0.347
SL	1366.1 ± 71.86	1335.6 ± 58.61	0.746
p†	0.500	0.263	
DOPAC (mg/mL)			
HA	673.0 ± 60.50	878.8 ± 136.53	0.297
SL	555.1 ± 26.06	590.3 ± 45.92	0.605
p†	0.051	† 0.011	

p*, p values for the differences between CMS and controls; * indicates a p value < 0.05; p†, p values for within group differences between high altitude (HA) and sea level (SL)

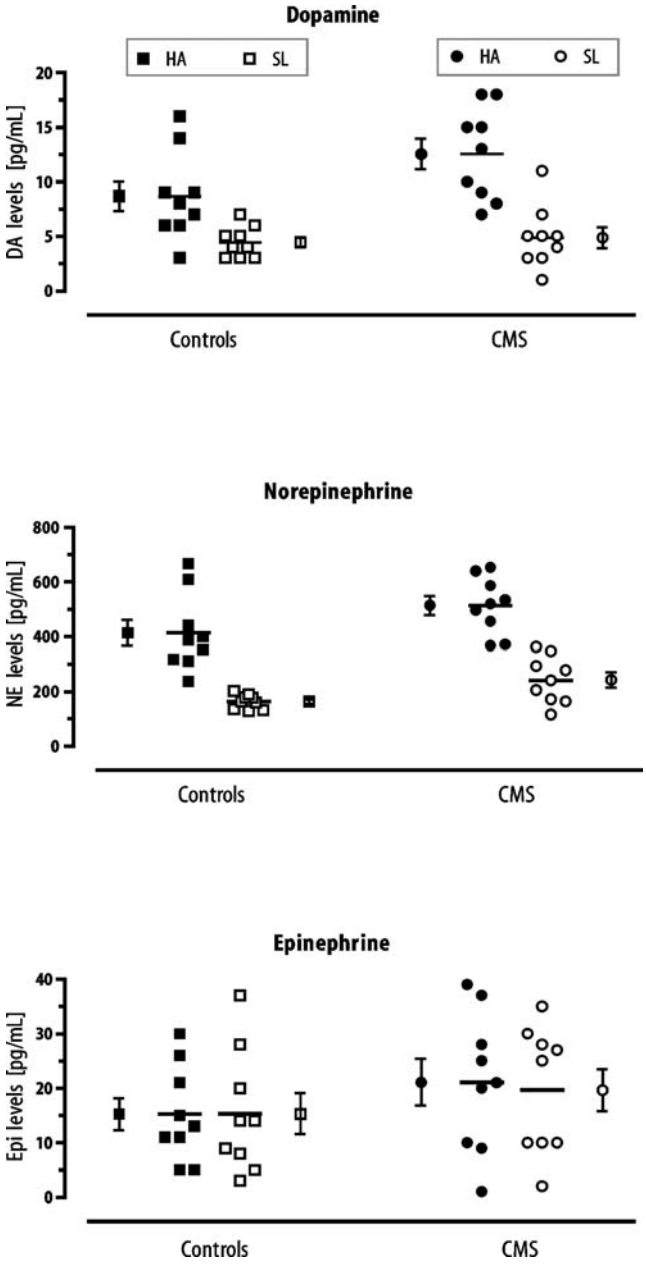

Fig. 2 **Top** – Dopamine plasma levels (pg/mL) at high altitude (CP, 4338 m) filled symbols, and at sea level (SL) non-filled symbols. Control subjects are represented by squares, and chronic mountain sickness patients (CMS) are represented by round symbols. **Middle** – Norepinephrine plasma levels. **Botto**m – Epinephrine plasma levels

Discussion

We found that Andean natives had higher plasma levels of catecholamines at altitude than at sea level. Both norepinephrine and dopamine plasma levels at sea level were near normal in these subjects when compared to previously published values [13]. Even in patients with CMS, the increases in plasma norepinephrine levels at altitude were smaller than those associated with cold exposure or exercise in sea level natives. High altitude chronic exposure in non-natives produces clear sympathoexcitation [15], increasing both norepinephrine and epinephrine plasma levels to values even higher than the observed for high altitude natives in the present study [4]. This finding may suggest that genetic, developmental, or adaptive changes are important to limit plasma norepinephrine responses to manipulation of oxygen levels in ambient air in high altitude natives.

In healthy volunteers at sea level, acute hypoxia alone produces relatively small increases in plasma norepinephrine levels [28, 33, 34]. Skeletal muscle sympathetic activity, measured by peroneal microneurography, usually does increase [27, 32, 33]. The difference between the plasma norepinephrine and sympathetic microneurography results may relate partly to increased plasma norepinephrine clearance in hypoxia [21].

Dopamine is present in cells of the carotid bodies, which are well known to be a major site for chemosensation of blood oxygen tension. The exact functions of dopamine-containing cells of the carotid bodies remain to be elucidated; however, it is known that carotid body

Table 3 Blood volume indices in control subjects and in patients with chronic mountain sickness (CMS)

	Controls (n = 9)	CMS (n = 9)	p*
Blood volume (mL)			
HA	4353.4 ± 508.2	5174.9 ± 365.1	0.208
SL	5440.6 ± 181.7	6872.9 ± 531.7*	0.021
p†	† 0.043	† 0.008	
% of ideal blood volume			
HA	1.022 ± 0.105	1.210 ± 0.098	0.209
SL	1.313 ± 0.032	1.567 ± 0.090*	0.018
p†	† 0.029	0.003	
Red cells volume (mL)			
HA	2013.9 ± 228.7	3175.3 ± 320.5*	0.004
SL	2446.2 ± 128.9	3815.3 ± 389.3*	0.003
p†	0.075	0.139	
% of ideal red cells volume			
HA	1.17 ± 0.12	1.82 ± 0.18*	0.007
SL	1.45 ± 0.06	2.13 ± 0.16*	0.003
p†	† 0.039	0.130	
Plasma volume (mL)			
HA	2339.6 ± 284.8	2099.6 ± 176.3	0.605
SL	2994.0 ± 86.6	3057.8 ± 236.3	0.387
p†	† 0.049	† 0.011	
% of ideal plasma volume			
HA	0.92 ± 0.10	0.83 ± 0.09	0.730
SL	1.22 ± 0.03	1.18 ± 0.09	0.113
p†	0.051	† 0.015	

p*, p values for the differences between CMS and controls; * indicates a p value < 0.05; p†, p values for within group differences between high altitude (HA) and sea level (SL); † indicates a p value < 0.05

tumors arise from uncontrolled growth of dopaminergic cells [7, 31]. Type I, oxygen-sensitive cells of the carotid bodies release dopamine in response to decreased arterial oxygen, and carotid body enlargement in high altitude Andean natives results from hyperplasia of Type I cells. Despite these considerations, in the present study, plasma dopamine levels were within the normal range, even among CMS patients, who are severely hypoxic during sleep and have marked enlargement of carotid bodies resulting from hyperplasia of dopamine-containing Type I cells.

At sea level, headache is a prominent symptom of polycythemia vera, a clonal stem cell disorder in which headache and other neurologic symptoms respond to phlebotomy, which reduces blood viscosity. CMS patients at high altitude also benefit from phlebotomy, the only known effective treatment for the headache. In the present study, headache disappeared after short-term exposure to the lower altitude in Lima, even though blood volume and blood viscosity remained increased (Table 3). Thus, the prevailing hypoxia in Cerro de Pasco, not increased blood viscosity or blood volume, seems to be the main trigger of the headache.

The results from the present study are in accordance with previous studies that have shown relatively low plasma volume among high altitude residents, so that increased blood volume results from increased red cell volume [18, 30]. This is similar to the situation observed in polycythemia vera. At high altitude, all subjects in this study had approximately the same plasma volume as reported in previous studies of sea level natives after chronic exposure to high altitude [19] or long-term intermittent hypoxia [26]. Shortly after exposure to normoxia in Lima, there was a significant increase in plasma volume in both subject groups; the change in red cell volume was not statistically significant. The results in the present study are in discordance with a previous study [5]. In the study by Claydon et al. plasma volume was determined by Evans Blue dye dilution, and no differences for plasma or blood volumes after descending were found. However, a slight, but non-significant, difference for plasma volumes after descending to sea level in both CMS and control group was observed. The difference in plasma volumes in the mentioned study were 4.1 and 1.4 mL/kg for controls and CMS patients, respectively (values calculated by the authors from references 5 and 6). In the present study, the increases in plasma volumes were found to be higher (10.9 ± 4.1 and 12.3 ± 4.8 mL/kg, for HA and CMS, respectively). This difference was statistically significant. Such discrepancy could be attributed to the different techniques used. The use of radioisotopes could have different accuracy compared to the dye dilutin method. The increase in plasma volume after return to sea level seen in the present study could be attributed to one or several factors regulating water balance. Since we did not assess any of these factors, we cannot exclude the possibility of a decline in diuresis, a decrease in evaporative water loss, change in water intake, or decreased vasomotor tone.

In Andeans with CMS and profound hypoxia, expression of splicing variants of vascular endothelial growth factor (VEGF-165–189) have been found [1]. These splicing variants are not present in Andean controls at the same altitude. Altered gene expression of vascular growth factors might affect endothelial function and contribute to abnormal volume changes in Andean natives.

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