

# Adrenergic System in High Altitude Residents

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## Abstract

A. M. Antezana, J. P. Richalet, G. Antezana, H. Spielvogel, R. Kacimi, Adrenergic System in High Altitude Residents. *Int J Sports Med*, Vol 13, Suppl 1, pp S96–S100, 1992.

Heart rate (HR) response to isoproterenol (ISO) infusion (IP) is decreased in normal sea level (SL) natives exposed to high altitude (HA). Since norepinephrine plasma concentration is higher in HA hypoxia, a downregulation of beta-adrenoceptors ( $\beta$ AR) was evoked. We explored this phenomenon at 3600 m in a HA normal population (HAN) and in polycythemic subjects (HAP). Results are compared to SL natives in normoxia (SLN), and during chronic hypoxia at 4800 m (SLH) (*J Appl Physiol* 65: 1957–1961, 1988). ISO dose required to raise HR by 25  $\text{min}^{-1}$  (I 25) is not different in HAN or HAP group when compared to SLN. Density of  $\beta$ AR on lymphocytes was 39% and 25% lower in HAN and HAP than in SLN group, respectively. Chronotropic response to IP is similar in SL and HA subjects under their usual environmental conditions, while SL natives show a blunted response under hypoxia, probably due to a decrease in  $\beta$ AR density. No adrenergic desensitization was found in highlanders. Lower  $\beta$ AR density in HA groups could be an adaptive mechanism to chronic hypoxia. Polycythemia does not affect this responsiveness.

## Key words

Hypoxia, beta-adrenergic receptors, isoproterenol, norepinephrine

## Introduction

Altitude hypoxia stimulates the adrenergic system as indicated by the increased plasma norepinephrine concentrations (10, 12, 19). Heart rate (HR) at rest and during moderate exercise is increased in altitude; maximal HR clearly decreases above 3000 m (9, 15, 23, 26). The relationship between HR and NEp is modified in altitude with a progressive decrease in HR for the same level of plasma NEp (24). A blunted cardiac chronotropic response at high altitude (HA) has been demonstrated in animals under beta-adrenergic stimulation. In humans exposed to 4350 m during several days

a blunted response to isoproterenol infusion was found (20), supporting the hypothesis of a chronotropic refractoriness secondary to increased sympathetic activity (21). A decrease in beta-adrenoceptors ( $\beta$ AR) density was observed in rat cardiomyocytes (27) and in human lymphocytes exposed to altitude hypoxia (25). A  $\beta$ AR downregulation phenomenon was therefore evoked. However, in highlanders living under chronic hypoxic conditions no data upon adrenergic system is available. The purpose of this study was to evaluate this system in normal and polycythemic highlanders at 3600 m and to establish whether the hypoxia-induced alterations in adrenergic system observed in sea level natives exposed to acute and chronic high altitude hypoxia are also present in this population; moreover, does polycythemia influence this system? Finally some people residing at this altitude and suffering from heart diseases could also benefit from this knowledge by a rational use of beta blocker therapy. The population of high altitude residents was compared with normal sea level subjects in normoxia and under hypoxic conditions (25).

## Methods

Twenty four men, born at 3500–4000 m (Bolivia) volunteered in this study. Group 1: 13 high altitude natives (HAN), (23–40 yrs old), with hematocrit (Ht)  $\leq$  57%; Group 2: 11 high altitude natives (HAP), (16–45 yrs old), with Ht  $>$  57%. A control group included 9 sea level natives (28–50 yrs old), in normoxia (SLN) and after 21 days at 4800 m (SLH). Clinical examination, complete blood count, 12-lead electrocardiogram and echocardiography-Doppler were performed. Spirometric measurements were performed in group 2.

## Exercise testing

Experiments took place at the Instituto Boliviano de Biología de Altura (I.B.B.A.) at 3600 m (La Paz, Bolivia). Barometric pressure was 498–502 mmHg. Ambient temperature was 17–18 °C. Exercise was performed in the morning after a light breakfast. An ear oximeter was placed on ear lobe for the recording of oxygen saturation; an intravenous cannula was inserted in the left forearm for blood sampling at rest and after exercise. Heart rate and blood pressure were continuously monitored by means of an electrocardiograph and a manual sphygmomanometer. Exercise was performed on a mechanical cycloergometer until exhaustion. Ventilation was measured at the end of each work load; exhaled gas was collected in Douglas bags for maximal oxygen consumption determinations (Servomex analyser 570 A). Blood samples were drawn and centrifuged immediately for norepinephrine, epinephrine and electrolytes dosage. Plasma was stored in liquid nitrogen until analysis by a radioenzymatic assay (25).

Table 1 Heart rate, oxygen saturation and oxygen consumption at exercise.

n		SLN 9	SLH 9	HAN 12	HAP 11
	age (yrs)	35 ± 4	35 ± 4	31 ± 7	34 ± 9
	Ht (%)	45 ± 5	57 ± 4	52 ± 3	61 ± 5* +
	HR (min <sup>-1</sup> )				
	rest	75 ± 7	86 ± 8	72 ± 8	70 ± 10
	exer	180 ± 8	171 ± 13	181 ± 12	173 ± 11.6
	SaO <sub>2</sub> (%)				
	rest	97 ± 3	85 ± 4*	94 ± 2	94 ± 4
	exer	95 ± 3	80 ± 7*	91 ± 4*	90 ± 4*
	CaO <sub>2</sub> (ml/dl)	18.0 ± 0.8	20.0 ± 1.2*	21.1 ± 0.7*	24.4 ± 1.1* +
	VO <sub>2</sub> max	40 ± 5	35 ± 5	32 ± 6*	31 ± 6*

Ht = hematocrit, HR = heart rate, SaO<sub>2</sub> = arterial oxygen saturation, CaO<sub>2</sub> = calculated arterial O<sub>2</sub> content. VO<sub>2</sub>max = maximal O<sub>2</sub> consumption (ml · kg<sup>-1</sup> · min<sup>-1</sup>), SLN = sea level natives in normoxia, SLH = sea level natives in hypoxia, HAN = high altitude normocythemic natives, HAP = high altitude polycythemic natives.

\*p < 0.001 diff. from SLN, + p < 0.001 diff. between HAP and HAN.

Table 2 βAR density and catecholamines.

n		SLN 9	SLH 9	HAN 8	HAP 9
	Bmax (fmol · mg <sup>-1</sup> prot)	49 ± 18	23 ± 7*	30 ± 14*	37 ± 17
	Kd (pM)	23.5 ± 9.2	14.3 ± 13.1	18.4 ± 8.3	9.7 ± 6.8
	NEp (pg · ml <sup>-1</sup> )	770 ± 109	1740 ± 760*	544 ± 224	556 ± 362
	Ep (pg · ml <sup>-1</sup> )	83 ± 26	100 ± 58	36 ± 28	42 ± 27

Bmax = βAR density, NEp = norepinephrine, Ep = epinephrine.

SLN, SLH, HAN, HAP: see legend of Table 1.

\*p < 0.05 diff. from SLN.

### Response to isoproterenol

Isoproterenol (ISO) infusion was performed in groups HAN (n = 8) and HAP (n = 10). Doses of ISO were adjusted according to body weight; a sequence of 0.02, 0.04 and 0.06 μg · kg<sup>-1</sup> · min<sup>-1</sup> of the ISO solution was infused during 5 minutes each, without interruption between doses. Hematocrit and hemoglobin were measured on whole blood sample; arterial oxygen saturation, blood pressure and heart rate were continuously monitored during the test. Heart rate for each dose was taken as the mean heart rate during the last 30 seconds of each period. Chronotropic sensitivity to ISO was evaluated by the dose of ISO required to raise heart rate by 25 min<sup>-1</sup> (I 25), and by the increase in HR for the highest dose (ΔHR). Systolic (SBP) and diastolic blood pressure (DBP) were measured at the end of each infusion period; mean arterial blood pressure (MBP) was calculated by MBP = 2/3 · DBP + 1/3 SBP. Pulse pressure (PP) was calculated by PP = SBP - DBP. Calculated arterial oxygen content was given by CaO<sub>2</sub> = 1.34 × Hb × SaO<sub>2</sub>. Control sea level group followed this protocol at sea level (Paris) and after 3 days at 4800 m (25).

### Beta-adrenoceptor density

Fifty ml of blood were drawn at rest from a forearm vein for lymphocytes isolation and preparation. Ficoll-Hypaque procedure was used. A buffer solution was used for dilution: D glucose anhydride 0.1% CaCl<sub>2</sub>, MgCl<sub>2</sub>, KCl, Tris, then Ficoll was added. Centrifugation at 400 g during 40 min was made at -18 °C. The layer containing the lymphocytes was withdrawn and washed twice with a saline buffer and then centrifuged at 200 g for 20 min. Lymphocytes were counted before storage in liquid nitrogen until binding assays with the <sup>125</sup>I-Iodocyanopindolol (ICYP) technique.

### Membrane preparation

Cells were centrifuged 30,000 g for 15 min; pellet was incubated in a buffer (2 mM Tris HCl, 1 mM EDTA) for 20 min at 0 °C, homogenized with 10 strokes at 1000 rpm and centrifuged at 30,000 g for 15 min. The pellet was suspended in 75 mM Tris-HCl, 25 mM MgCl<sub>2</sub>, pH 7.4, and assayed for binding activity.

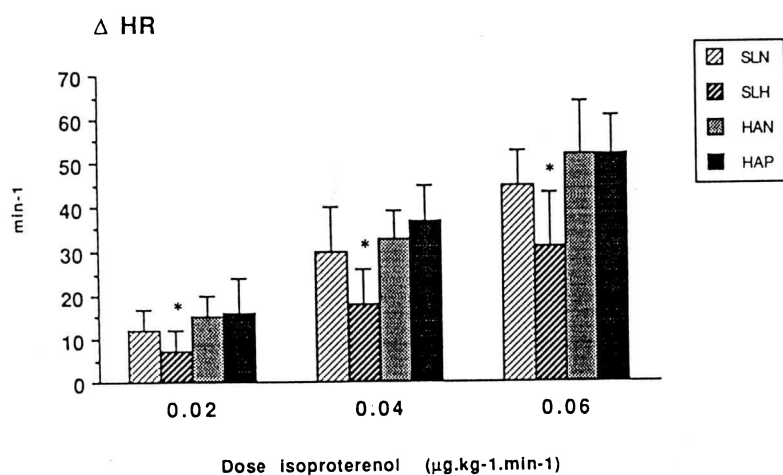
### Binding technique

Aliquots of membrane were incubated with varying concentrations of ICYP, from 1 nM to 0.03 nM, during 60 minutes at 37 °C. Reaction was stopped by adding ice cold. The incubation mixtures were filtered through Whatman glass fiber filters under vacuum and washed with buffer solution. The radioactivity of the filters was determined with a gamma counter LKB. The data were analyzed by Scatchard analysis; the density of receptors (B max) in fmol/mg protein, and the dissociation constant of ICYP (Kd) were calculated.

Statistical significance between groups was assessed by analysis of variance.

### Results

No significant difference was found between polycythemic and normocythemic subjects concerning HR at rest and during exercise; maximal heart rate was not lower in high altitude HA natives when compared to SL group in normoxia. Systolic and diastolic blood pressure during exercise raised normally in HA groups, without any difference from SL subjects (results not shown). Norepinephrine plasma concentrations (NEp) at rest were slightly but not significantly higher in HA natives when compared to sea level SL natives at



**Fig. 1** Variation in heart rate ( $\Delta$ HR) during ISO infusion.

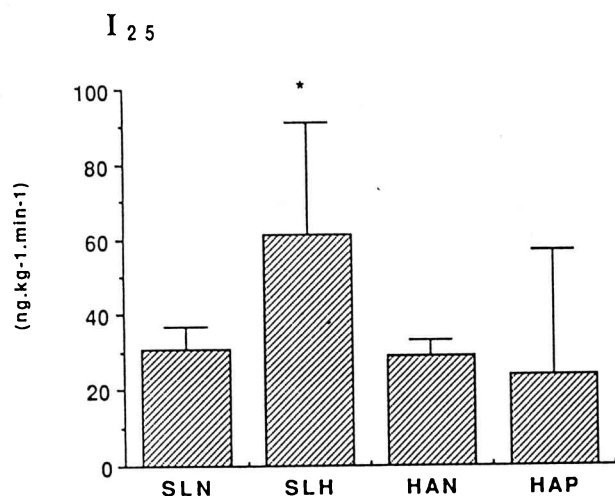
SLN = sea level natives in normoxia.

SLH = sea level natives in hypoxia.

HAN = high altitude normocythemic natives.

HAP = high altitude polycythemic natives.

\* $p < 0.001$  diff. from SLN.



**Fig. 2** Dose required to increase heart rate by  $25 \text{ min}^{-1}$  (I 25).

SLN, SLH, HAN, HAP: see legend of Fig. 1.

\* $p < 0.001$  diff. from SLN.

SL; these concentrations increased during exercise in a higher (but not significant) proportion when compared to SL subjects in normoxia. Chronotropic response to ISO, evaluated by  $\Delta$ HR and I 25, was similar in HA groups and SL natives in normoxia, I 25 was significantly higher and  $\Delta$ HR was significantly blunted in SL natives exposed to HA (Figs. 1 and 2); no difference appeared within HA groups when considering hematocrit values or age. As expected, SBP and PP increased during ISO infusion in normocythemic group; a significant lower increase was observed in polycythemic group, as in SL natives in hypoxia. DBP decreased in highlanders as in SL natives in normoxia. MBP in polycythemic group is significantly lower during ISO, when compared to the normocythemic group. Beta-adrenoceptors density on lymphocytes appeared lower in HA groups, significantly for HAN (Table 2).

### Discussion

This study was performed to evaluate the cardiac chronotropic response to physiological and pharmacological sympathetic stimulation in high altitude natives. First, maximal HR is not blunted in HA natives at 3600 m. We obtained values of maximal oxygen consumption comparable to

other Bolivian reports for this population (11). Under resting conditions no exacerbation of sympathetic tone is present in normal highlanders; at maximal exercise NEp concentrations are similar to those of SL natives in normoxia. A long term overstimulation of sympathetic system could contribute to increase systemic vascular resistance and renin-angiotensin system in a pejorative manner by increasing overload and altering cardiac function (4); it is actually known that systemic blood pressure in highlanders is definitely lower (2, 17, 18) probably reflecting low systemic vascular resistance and a low sympathetic tone. Left ventricular contractility and diastolic function evaluated by the ultrasounds method (data not shown) were normal in these groups. No argument for pulmonary hypertension was found. ISO infusion, a reproducible method to explore cardiac chronotropic properties in humans, has previously demonstrated a desensitization to IP in SL natives after acute and chronic exposure to hypoxia; this phenomenon was explained by a downregulation mechanism of  $\beta$ AR face to an increased adrenergic activity, reversible with return to normoxia. In fact a diminished  $\beta$ AR density is found on lymphocytes under hypoxia (26). For the first time a HA normal population was studied using this test at 3600 m. Heart rate increment during ISO infusion was similar in both HA natives subgroups; the degree of polycythemia in the HAP group was not severe, and may explain the weak differences between groups. Response to ISO was equivalent to that in SL subjects in normoxia. Thus, chronotropic function in well adapted highlanders appears normal. The downregulation phenomenon of  $\beta$ AR observed in SL natives exposed to HA could be considered as a protective mechanism limiting myocardial oxygen consumption by reducing maximal heart rate. The lack of overstimulation of sympathetic nervous system and the lack of desensitization of cardiac  $\beta$ AR in healthy highlanders might be considered rather as an adaptive response; whether  $\beta$ AR play a role in chronic adaptation is still unknown since studies in SL subjects after long periods at HA are not available. We found a slightly lower  $\beta$ AR density in HA groups, when compared to SL subjects in normoxia; this value could be considered the real value for this normal population and the difference found in polycythemic subjects should point out our attention. If one compares the values for SL natives in normoxia and HA residents the difference could be interpreted as a partial loss in  $\beta$ AR number with a normal physiological response, leading to an adaptive phenomenon. The underlying mechanisms are complex; besides receptors number, one must consider the Gs-effector coupling, the adenylate cyclase activity

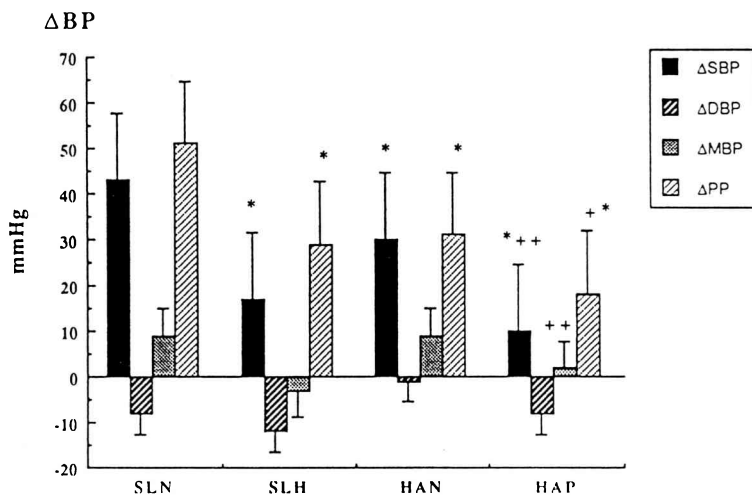


Fig. 3 Variation in blood pressure for the highest dose of ISO.

ΔSBP, ΔDBP, ΔMBP, ΔPP, respectively, variation in systolic, diastolic, mean and pulse blood pressure. LN, SLH, HAN, HAP: see legend of Fig. 1.

\*p < 0.05 diff. from SLN. Diff. between HAN and HAP: + p < 0.05, ++ p < 0.001.

which have not been evaluated in this study (8). In SL subjects exposed to HA the perturbed mechanism settles and probably remains stable insuring a blunted but constant physiological responsiveness, until a new state of acclimatization takes place at a superior level, i.e. restitution of  $\beta$ AR mRNA levels, new synthesis of protein, enhanced enzymatic activity and phosphorylation, or other mechanisms altered during desensitization (8, 16). Although cardiac  $\beta$ 1 and lymphocyte  $\beta$ 2 receptors might have different characteristics, coherent results have been obtained in both systems (5, 6). Lymphocyte receptors functionality may vary depending on the cellular subset purified and probably one should specify this fact; B cells have more  $\beta$ AR than T cells, with an adenylate cyclase less active (13).

Concerning vascular response to ISO a particular profile is observed in polycythemic subjects; pulse pressure at the maximal ISO dose is significantly lower when compared to HA normocythemics and to SL natives in normoxia, related to the slight increase in SBP, while the decrease in diastolic pressure was normal. MAP is also decreased in polycythemic subjects after ISO.

The difference in adrenoceptors density between HAN and HAP subgroups may be of interest since natural history in polycythemic subjects is the potential loss of adaptation involving right ventricular hypertrophy and pulmonary hypertension; the increased Bmax in HAP group could be a marker of a right overload development, as a compensation of enzymatic dysfunction. Complementary tests of the adenylate cyclase activity and regulation of gene expression are necessary to understand this finding (1, 3, 8). In conclusion, chronotropic response to an agonist  $\beta$  adrenergic agent is preserved in highlanders.  $\beta$ AR density is found slightly decreased in these subjects, in a lesser degree when compared to SL natives under HA hypoxia; nevertheless altitude was lower for HA natives than for SL natives, which could influence our results. Despite downregulation observed on lymphocytes  $\beta$ AR in highlanders, no desensitization, concerning chronotropic function, was found. This could be an evidence of an adaptatory mechanism to chronic hypoxia: partial increase in  $\beta$ AR number, with enhanced enzymatic activity, normal phosphorylation, restitution at the transcriptional  $\beta$  receptor level, leading to a complete functional recovery. Further studies in this HA population and in SL subjects living

for long periods at HA are needed to confirm this hypothesis. Loss of adaptation to chronic hypoxia could be detected by following up this system before clinical signs settle down, and some cardiac patients living at this high altitude could benefit from these observations.

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## Nutritional Aspects of Health and Performance at Lowland and Altitude

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### Abstract

*F. Brouns*, Nutritional Aspects of Health and Performance at Lowland and Altitude. *Int J Sports Med*, Vol 13, Suppl 1, pp S100–S106, 1992.

One of the most important nutritional goals amongst athletes is to maintain adequate energy and fluid balance, since these are subject to relatively rapid changes and are directly related to performance and health. This may especially be the case when exercise intensity is high. Furthermore, when due to exercise and environmental stress food and fluid intake become depressed. In such conditions there may be a dramatic increase in the utilization of carbohydrate (CHO), fluid, and in some instances protein. These increased requirements may then not be covered. In-

sufficient replacement of CHO may lead to hypoglycemia, altered protein metabolism, central fatigue and exhaustion. Large sweat losses may pose a risk to health by inducing severe dehydration, impaired blood circulation and heat transfer, leading to heat exhaustion and collapse. Inadequate CHO and protein intake leads to a negative nitrogen balance, which over the long term will lead to a loss of muscle mass. In the scope of this presentation we will refer to the most important nutritional factors which are known to affect performance over a short term, at sea level and altitude.

### Key words

Performance, food intake, fluid, electrolytes, carbohydrate, protein, fat, altitude