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HORMONAL CHANGES IN HIGH ALTITUDE RESIDENTS

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ABSTRACT

The response of renin and aldosterone is attenuated under acute and chronic exposure to high altitude (HA); the release of atrial natriuretic peptide (ANP) in sea level (SL) natives is also modified. No data are available in HA residents in whom increased total blood volume and the pulmonary arterial hypertension may influence the hormonal release. Twenty four men residing at 3600 ± 200m, La Paz, were included either in a normocythemic group "HAN" (hematocrit, Ht <57%, n=13) or in a polycythemic group "HAP" (Ht>57%, n=11). A control group of SL residents was studied in normoxia "SLN" and at 4,350m "SLH". Plasma active renin, aldosterone, ANP, potassium and norepinephrine concentrations were measured at rest and after a maximal exercise. Pulmonary artery pressure was assessed by Doppler at rest.
In SLH, renin and aldosterone were blunted, and ANP was unchanged.
In highlanders, the renin response was normal in HAN but decreased in HAP. The exercise-induced increase in aldosterone was lower in HA natives than in SL natives. The correlation between renin and aldosterone observed in SLN and HAN was not found in the group HAP. A protective mechanism against water and salt retention in polycythemic subjects may be evoked . ANP in highlanders was lower than in SL natives. Lower ANP in HA residents in spite of higher pulmonary pressure could be an adaptation to chronic distension of atrial stretch receptors. **(Acta Andina 1996, 5:9-13)**

Keywords: renin, aldosterone, atrial natriuretic peptide, exercise, pulmonary arterial pressure.

RESUMEN

La respuesta de renina y aldosterona está atenuada en la exposición aguda y crónica a las grandes alturas; la liberación del péptico atrial natriurético (PAN) en nativos de nivel del mar también se encuestra modificada. No existen datos disponibles respecto a estas hormonas en nativos y residentes de grandes alturas, en quienes determina eritrocitosis, aumento de la masa sanguínea e hipertensión arterial pulmonar, son factores que potencialmente pueden modificar la s liberación hormonal.Se estudiaron 24 residentes de La Paz, Bolivia, distribuídos en 2 grupos según el hematocrito (Ht):"HAN" normocitémicos Ht<57%, y "HAP" policitémicos Ht>57%.Un grupo de residentes del nivel del mar constituyó el grupo control estudiado en normoxia "SLN", y en hipoxia a 4,350 m "SLH". Fueron medidas en plasma la renina, aldosterona, peptido atrial natriurético, noradrenalina, dopamina y electrolitos, en condiciones de reposo y despúes del ejercicio. La presión arterial pulmonar fué medida por Ecocardiografía - Doppler. En los grupos HAN y HAP hubo bloqueo de la renina y aldosterona y el ANS no se modificó. En los sujetos de altura, la respuesta de renina fué normal en el grupo HAN pero disminuyó en el grupo. El incremento de aldosterona inducido por ejercicio fue menor en los nativos de altura que en los de nivel del mar. La correlación entre renina y aldosterona observada en los grupos SLN y HAN no se encontrón en el grupo HAP. Puede evocarse un mecanismo protector contra la retención de salu y agua en sujetos policitémicos. La ANS en sujetos de altura fue menor que en nativos de nivel del mar. **(Acta Andina 1996, 5: 9-13).**

Palabras claves: renina, aldosterona, peptido atrial natriurético, ejercicio, hipertensión arterial pulmonar.

High altitude hypoxia blunts the renin and aldosterone response during acute and chronic exposure in sea level subjects exposed to high altitude (5,7,9,10,12). Acute mountain sickness is associated to fluid retention with increased antidiuretic hormone (16), aldosterone (2) and atrial natriuretic peptide concentration (3), particularly in pulmonary oedema (11). No study is available in healthy natives residing above 3,000m.Chronic hypoxia might interfere with these hormones since tissular hypoxia, greater volume load secondary to polycythemia, and pulmonary arterial pressure are factors that may modify the hormonal release (10). In moderate altitude natives, 2,200m, the aldosterone response has been shown to be decreased when subjects were exposed to a more severe simulated hypoxia (9,13).

The purpose of this work was to study two hypotheses: (a) residents at 3,600 m show a persistent blunting of the renin aldosterone system, and this could be an adaptive response to chronichypoxia, or (b) the renin aldosterone system is over-stimulated and impairs water and sodium excretion, suggesting a lack of adaptation.

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Methods

The normocythemic group "HAN" (n=13,33 ± 7yr), had an hematocrit <57%, and the polycythemic group "HAP" (n=11,35 ± 10yr) had an hematocrit .>57%. Subjects were born between 3,200m and 4,000m, and were residing at La Paz most of the time (3,600m, P_B=500mmHg). Polycythemic subjects were not receiving any treatment. Arterial blood gases, ventilatory mechanics and spirometric measurements were performed in HAN and HAP groups before inclusion to eliminate a respiratory disease at the I.B.B.A. A control group included 8 subjects from sea level (35±6 yr, 66±3kg studied in normoxia "SLN", and

after 4 days at 4,350m "SLH", at the Vallot's Observatory, France (4,350m, P_B=450mmHg).

Blood samples were obtained at rest and at the end of exercise. The samples were centrifuged and stored in liquid nitrogen for ulterior examination in France. Plasma active renin was measured as active renin immunologically recognized by specific monoclonal antibodies according to the IRMA technique (14); sensitivity was 10 pg/l and the intra-and interassay coefficients of variability were 4 and 6%, respectively. Plasma aldosterone concentration was measured with a radioimmunoassay (Aldosterone II RIA kit, Abbot Laboratories). Aniline-8-naphtalene-1-sulfate was used for extraction. Recovery was 106.5%. Sensitivity was 61 pmol/l and the intra-and interassay coefficients of variability were 3.7 and 4.4 %, respectively. Plasma immunoreactive-atrial natriuretic peptide was measured by a direct radioimmunological technique (7); sensitivity was 3.6 pg/ml with rabbit antiserum, and the intra-and interassay coefficients of variability were 6 and 9%, respectively. Catecholamines were measured by a high-pressure liquid chromatography method (15).

Maximal exercise, performed in a cycloergometer was limited by exhaustion. Oxygen comsumption (vO_2) was measured at the end of each stage through collection of expired gas in a Douglas bag. Expired volume was measured by a Tissot Spirometer, and expired O_2 and CO_2 concentrations were measured by Servomex 570 A and Capnograph Gould, respectively. Heart rate, systolic and diastolic arterial blood pressure and oxygen saturation were continuously monitored. Mean arterial pressure was obtained as 2/3xDBP+1/3xSBP.

Pulmonary artery pressure was assessed at rest by means of a 2.5 mHz probe (4).

Statistical analysis was performed by analysis of variance and covariance. Data are presented as means ± SD.

Results

Resting heart rate and maximal heart rate were not different between highlanders and SLN (Table 1). In SLH resting heart rate was significantly higher than in SLN whereas maximal heart rate was lower. Blood pressure did not show significant differences between the HA groups and SLN in normoxia; MBP was lower in highlanders at rest and during exercise.

Maximal oxygen consumption (VO_2) was lower in highlanders: 32±6 and 31±5 ml.kg-1.min-1 for HAN and HAP respectively, than in lowlanders, 44±4 ml.kg-1.min-1 in normoxia.

Table 1. Hematological characteristics, heart rate and blood pressure.

		SLN	SLH	HAN	HAP
SaO_2	r	97±1	92±4 **	95±2	94±4
(%)	e	97±1	89±2 **	91±4 **	90±4 **
CaO_2 (ml.100ml $^{-1}$)	r	18.8±0.8	18.4±1.0	21.2±1.0	24.7±1.2
Ht (%)	r	44±3	44±3	52±3**	62±5**
Hb(g.dl)	r	14.5±0.8	15±1.3	16.7±1.0**	19.6±1.5**
HR	r	66±7	91±8 **	57±1	69±7
(bpm)	e	182±8	164±10 **	181±12	173±12
MBP	r	95±6	97±5	91±5	91±8
(mmHg)	e	139±8	127±15	124±12	122±14

Values are mean ± SD : * p<0.05, ** p<0.001 different from SLN.
r=rest, e=exercise. SLN: sea level natives in normoxia. SLH: sea level natives in hypoxia . HAN: high altitude normocythemic natives. HAP: high altitude polycythemic natives.
Hb: hemoglobin concentration; Ht: hematocrit, SaO2: oxygen saturation; arterial oxygen content; HR: heart rate; MBP: mean systemic blood pressure.

Plasma norepinephrine concentration increased during exercise in all groups (Table 2). Highlanders showed higher levels of norepineprine than SLN, but lower than SL(p<0.01).

Plasma active renin (PAR) decreased in SLH at rest and after exercise.Resting PAR was higher in highlanders than in SLN; the exercise-induced increase in PAR was lower in HAP (-43%) than in the other groups (Table 2); the response of aldosterone to renin was reduced in HAP as it is shown in Fig.1, where no correlation was found, conversely to the three other groups.

Table 2. Hormonal concentrations at rest and after maximal exercise.maximal exercise.

		SLN	SLH	HAN	HAP
PAR	r	21±7	12±8 *	33±17 *	41±36
pg.ml^{-1}	e	69±44	30±18 *	63±41	58±50
PAC	r	364±139	193±107 *	332±141 *	277±79 *
pmol.l^{-1}	e	903±268	363±129 **	456±157 *	444±150 *
ANP	r	56±25	38±28	16±7 *	34±40 * +
pg.ml^{-1}	e	91±32	92±41	40±5 *	66±56
NE	r	280±117	734±204 **	550±204 **	632±417 *
pg.ml^{-1}	e	1439±794	3724±1566**	2409±1264*	2486±1690*
DA	r	56±51	37±14	51±27	31±11
pg.ml^{-1}	e	31±18	157±78	143±75 *	76±60 +

Values are means ± SD r=rest, e=exercice.
*p<0.05, **p<0.01 different from SL, +p<0.05 HAP different from HAN.
PAR:plasma active renin. PAC:plasma aldosterone concentration. ANP:plasma atrail natriuretic peptide concentration. NE, DA: plasma norepinephrine and dopamine concentrations.

Resting and exercise plasma potassium concentration was not different between groups (SLN: 4.1, SLH:3.8, HAN: 4.4, and HAP: 4.6 mmol.l-1). ANP was lower in highlanders than in SL natives; it was higher in HAP than in HAN. In HA natives low ANP concentrations were associated with higher pulmonary pressure, when compared to SL natives (Fig. 2). Systolic pulmonary arterial pressure at rest in SLN was 21±5 mmHg, in HAN 26±3 and in HAP 30±5 mmHg. There was a loose correlation between ANP and pulmonary pressure in HAP (r=0.664).

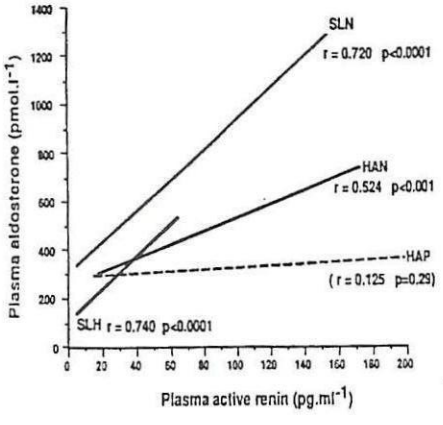

Figure 1.-Correlation between active renin and aldosterone. The aldosterone response to renin is significantly attenuated in the polycythemic group.

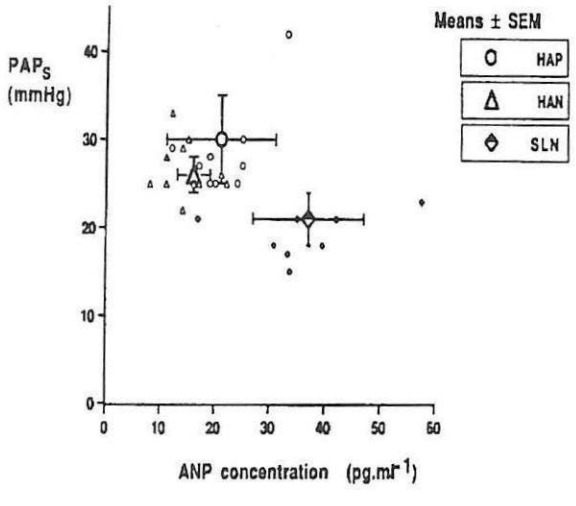

Figure 2.-Relationship between plasma atrial natriuretic peptide (ANP) and systolic pulmonary arterial pressure. Low values of ANP are observed in HA residents despite higher pulmonary pressure.

Discussion

The purpose of the present study was to determine the response of the renin-aldosterone system and the natriuretic peptide under chronic hypoxia. An attenuated response would account for an adaptive phenomenon; an excessive release of these hormones would account for a lack of adaptation as occurs in acute mountain disease. Comparisons of our results should be interpreted with caution, since groups were exposed to a different hypoxic stimulus: 4,350m for SL natives vs 3,600m for bolivians.

Higher resting renin concentrations were observed in four normocythemic subjects, and in one polycythemic subject; aldosterone levels in these subjects were normal. Higher renin secretion may occur when renal perfusion pressure decreases, but mean blood pressure was not lower in these subjects. Also hypohydration and low sodium intake may be responsible for increased renin and aldosterone secretion (13,16) but this was unlikely in our groups. A higher norepinephrine secretion may explain a higher resting renin in those subjects. The higher norepinephrine levels in highlanders were within normal physiological ranges. A blunting in the renin-aldosterone system was observed in the SL subjects exposed to 4,350 m; this agrees with previous studies (16,17). A downregulation of peripheral beta-adrenoceptors, renal beta-receptors, secondary to the sympathetic hyperactivity has been evoked to explain this feature. Those residents from group HAN who showed high levels of NE did not show any attenuation of the renin system; the correlation between NE and PAR was only slightly decreased in HAN.

A positive relationship between renin and aldosterone was observed in SL groups and in HAN, but not in HAP. Higher resting renin concentrations were observed in four normocythemic subjects, and in one polycythemic subject; aldosterone levels in these subjects were normal. Higher renin secretion may occur when renal perfusion pressure decreases, but mean blood pressure was not lower in these subjects. Also hypohydration and low sodium intake may be responsible for increased renin and aldosterone secretion (13,16) but this was unlikely in our groups. A higher norepinephrine secretion may explain a higher resting renin in those subjects. The higher norepinephrine levels in highlanders were within normal physiological ranges, suggesting a blunted response of aldosterone to the renin stimulation in this polycythemic group. Besides a lower exercise induced increase of aldosterone was observed in HAP. Factors which may inhibit the aldosterone secretion are hypokalemia, simultaneous and great ANP release, increase dopamine release and low tissular PO_2 in the adrenal cortex (9,16). None

of these factors could explain the aldosterone attenuation in HAP. Nevertheless, a lower synthesis secondary to a lower tissue PO_2 in the adrenal cortex particular during exercise could happen, since an inhibition of 18-hydroxylase under hypoxia has been described (16).

Resting plasma ANP concentration was lower in highlanders than in SL natives. ANP release is stimulated by atrial distension, increased central blood volume, increased heart rate, hypoxia and cold (19). Heart work, assessed by the double product HR x BP, and work load were equivalent in both SL and HA groups, so the intensity of the exercise was the same. A rise in pulmonary arterial pressure triggers ANP release during exercise (1,3,11); for technical reasons pulmonary pressure was assessed only at rest. Moderate polycythemia could also account for an increased blood volume and for a greater ANP release in HAP when compared to HAN.

In conclusion, renin was not blunted in HA natives. The higher concentration of active renin could result from a higher sympathetic tone in some subjects. A lesser exercise induced increase in aldosterone observed particularly in polycythemic subjects, could be interpreted as a protective adaptive mechanism from water and salt retention and central overload; nevertheless, a deeper adrenal hypoxia is not excluded. These results are in agreement with those observed in moderate-altitude residents (6), in which water and salt retention are probably also avoided by an aldosterone blunting. The low values of ANP in the HA groups in spite of higher pulmonary arterial pressures could be due to an adaptive phenomenon of overstimulated arterial stretch receptors. A progressive distension of these receptors at later stages could be associated to higher ANP concentrations, desensitization of peripheral receptors to ANP, and development of pulmonary hypertension, with no more pulmonary vasodilation and with impairement of renal function. Studies including renal function, hemodynamics and biological markers are needed to better understand the processus of decompensation in some high altitude residents.

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References

1.-Baertschi, A. J., Jiao, J. H., Carlson, D.E., Campbell, R.W., Teague, W.G. Neural control of ANF release in hypoxia and pulmonary hypertension. Am.J.Physiol. 259 (Heart Circ. Physiol.28): 735-744, 1990.

2.-Bartsch, P., Maggiorini, M.,Schobersberger, W., Shaw, S., Rascger, W.,Girard, J., Weidmann, P., Oelz, O. Enhanced exercise-induced rise of aldosterone and vasopressin preceding mountain sickness.J.Appl.Physiol. 71(1): 136-143,1991.

3.-Bartsch, P.,Shaw, S., Francioli, M.,Gnadinger, M.P., Weidmann. P. Atrial natriuretic peptide in acute mountain sickness. J.Appl. Physiol. 65: 1929-1937,1988.

4.-Berger , M.,Haimowitz, A.,Van Tosh, A., Berdoff, R., Goldberg, E. Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. J.Am.Coll. Cardiol. 6:359-65, 1985.

5.-Bouissou, P.,Richalet, J.P., Galen, F.X., Lartigue, M., Larmignat, P.,Devaux, F., Dubray C.,Keromes, A. Effect of beta-adrenoceptor blockade on renin-aldosterone and alpha-ANF during exercise at altitude. J.Appl. Physiol. 67: 141-146, 1989.

6.-Colice, G. L., Lawrason, J., Munsef, A., Bittle, P., Dietz, J., Ramirez, G. Hormonal response to exercise in high altitude natives and COPD patients. Aviat. SpaceEnviron. Med. 64:512-516, 1993.

7.-Gutkowska. J. G., G. Thibault, P. Januszewicz, M.Cautin, J. Gluest. Direct radioimmunoassay of atrial natriuretic factor. Biophys. Res.commun. 122: 593-596, 1984.

8.-Hackett, P.H., Forsling, M.L., Miledge, J.S., Rennie, I.D. Release of vasopressin in man at altitude. Horm. Metab.Res. 10: 571, 1978.

9.-Heyes, M.P., Farber, M. O., Manfredi, F., Robertshaw, D., Weinberger, M. Acute effects of hypoxia on renal and endocrine function in normal humans. Am. J.Physiol. 243 (Reg.Int.Comp. Physiol. 12): R265-R270, 1982.

10.-Hogan, R.P., Kotchen, T.A., Boyd, A.E., Hartley, L.H. Effect of altitude on renin aldosterone system and metabolism of water and electrolytes. J.Appl. Physiol. 35: 385-390, 1973.

11.-Kawashima, A., Kubo, K., Matsuzawa, Y.,

Kobayashi, T., Sekiguchi, M. Hypoxia induced ANP secretion in subjects susceptible to high altitude pulmonary edema. Respir. Physiol. 89: 309-317, 1992.

12.-Maher, J.T., Jones, L.G., Hartley, L.H., Williams, G.H., Rose, L.I. Aldosterone dynamics during graded exercise at sea level and high altitude. J. Appl. Physiol. 39: 18-22, 1975.

13.-Maresh, C.M., Noble, B.J., Robertson, K.L., Seip, R.L. Adrenocortical responses to maximal exercise in moderate-altitude natives at 447 Torr. J.Appl.Physiol.56:482-488, 1984.

14.-Menard, J.,T.T. Gayenne, P.Corvol, B.Pau, D.SImon, R.Roucucci. Direct immunometric assay of active renin in human plasma. J. Hypertens. 3 Suppl. 3:275-278, 1985.

15.-Morier E., R.Ripps. A new technique for

16.-Raff, H. The renin-angiotensin-aldosterone system simultaneous assay of biogenic amines and their metabolites in unpurified mouse brain. J.Liquid Chromatogr. 5:151-164, 1982.system during hypoxia. In: "Response and Adaptation to Hypoxia". Organ to Organelle. p212-222, 1991.

17.-Richalet, J. P, Galen, F.X.,Bouissou, P.,Lartigue M., Rutgers, V., Kéromés, A. Secretion of active and inactive renin franctions at exercise in high altitude hypoxia. Canad.J.Sport Sciences. 13: 29 P,1988.

18.-Richalet et al. Physiological factors in the survival at extreme altitude. In: "Hypoxia and molecular Medicine". Sutton, Houston, Coates, eds. Queen City Printers, Burlington, pp 235-251,1993.

19.-Schmidt, W., Brabant, G., Kroger, C., Strauch, S., Hilgendorf, A. Atrial natriuretic peptide during and after maximal and submaximal exercise under normoxic and hypoxic conditions. Eur. J.Appl. Physiol. 61:398-407, 1990.