ENDOCRINE TESTICULAR FUNCTION AND ADAPTATION TO HIGH ALTITUDE

International Society for Mountain Medicine Newsletter, **8** (2): 5-7 (April 1998)

INTRODUCTION

Respiratory characteristics of natives at high altitude are blunted hypoxic ventilatory response (HVR) (1), high hypercapnic ventilatory response (HCVR), and increased periodic breathing and sleep apnea (2). People living at high altitude hyperventilate with respect to natives at sea level (3). Hypoventilation, particularly during sleep, appears to be the dominant cause of hypoxemia in patients with chronic mountain sickness (3).

Both, the common respiratory dysrhythmia and the less common instances of overt sleep apnea are seen more frequently in men than women (4). Testosterone contributes to the respiratory dysrhytmias and apneas in men and women (5,6). Therefore, it is possible that testosterone may play a role in sleep apnea at high altitude.
The present article has been prepared to determine any association of serum testosterone levels with hypoxemia and adaptation to high altitude.

TESTOSTERONE AND VENTILATION

Testosterone has been related to regulation of ventilation during sleep. Testosterone depresses hypercapnic ventilatory drive during sleep (13), and it increases sleep apneas in adults (7). Sleep apnea may produce hypoventilation increasing hypoxemia. Testosterone also stimulates erythropoiesis. Both situations, hypoventilation and excessive erythropoiesis, have been advocated as causes of the clinical manifestations of mountain chronic diseases or maladaptation to high altitude life (8) through accentuation of hypoxemia and pulmonary hypertension.

The lower prevalence of chronic mountain sickness in women at reproductive ages than in men or post-menopausal women (9,10) support a role for testosterone in the mechanism of maladaptation to high altitude. Some authors have suggested that estradiol may prevent CMS (11). Therefore, it is possible that increased T/estradiol ratio may be a risk factor for CMS.

TESTOSTERONE AND ENVIRONMENTAL HYPOXIA: THE CASE OF THE NATIVE AT HIGH ALTITUDE

As shown in Table 1, a low level of serum testosterone was observed in men at high altitude, just when hematocrit level reached values over 65%. This reduction was observed irrespective of age of subjects. Subjects with high hematocrit had low serum FSH levels. These data suggest that in situation of excessive erythrocytosis, which in turn is associated with hypoxemia, the pituitary-testis axis is affected. In hypoxic male patients with stable chronic obstructive airways disease hypothalamic-pituitary-testicular axis dysfunction has been also observed (12).

Table 1.- Serum levels of testosterone, LH and FSH in adult male high altitude natives: relation to hematocrit levels.

Hematocrit %	n	Age (Years)	T ng/ml	LH ng/ml	FSH ng/ml
50-60	6	44.0 ± 3.0	7.2 ± 0.8	9.2 ± 1.3	15.1 ± 1.4
61-65	6	38.6 ± 2.9	6.3 ± 1.1	11.4 ± 3.1	15.9 ± 3.0
Ž65	6	41.3 ± 4.4	2.9 ± 0.3*	7.6 ± 1.2	8.9 ± 1.5**

Data are mean ± SD. *P<0.01;**P<0.05.

The data in table 1 suggest that testosterone is important in regulating ventilation and erythropoiesis at high altitude, but when its values increase over a treshold, accentuation of hypoventilation and erythropoiesis may occur increasing the risk to chronic mountain sickness (CMS).

If such assumption is true, we would expect a high incidence of CMS during puberty and low incidence during senescence, situations in which serum testosterone levels increase and decrease significantly (13,14). However, incidence of CMS is lower at puberty and higher at senescence (9).

Estradiol, a metabolite of testosterone, also increases significantly with puberty (15), and this hormone has been suggested to be a protector against CMS (10,11). Testosterone and estradiol (E2) act in opposition, such that the ratio T/E2 may be a better estimate of testosterone bioavailability than T alone. We have calculated T/E2 ratio at puberty from published data (15), and this was below 1.0 suggesting a protective effect of estradiol. Thus we have proposed this ratio as a marker of bioavailability of serum testosterone at high altitude as a better marker of androgen action.

BIOAVAILABILITY OF TESTOSTERONE AT HIGH ALTITUDE

The bioavailability of serum testosterone may be studied under basal or stimulated conditions. The stimulated conditions may be performed after injection of gonadotrophin releasing hormone (GnRH), or human chorionic gonadotrophin (hCG). GnRH stimulates production and secretion of luteinizing hormone (LH) which in turn will increase serum testosterone levels. Human chorionic gonadotrophin (hCG) will stimulate directly Leydig cells increasing synthesis and secretion of testosterone.

Bioavailability of testosterone under basal conditions

We have proposed a marker for bioavailable testosterone by measuring serum levels of testosterone (T), the precursor, 17 -hydroxyprogesterone (17 OHP), and its metabolite 17 estradiol. The ratio of T/17 OHP has been defined as testosterone produced by anabolism ($T_{anabolism}$). The ratio $E_2/T_{anabolism}$ has been defined as estradiol by catabolism ($E_{2\ catabolism}$). The bioavailability of testosterone has been defined as the relation $T_{anabolism}/E_{2\ catabolism}$.

Analysis of our data demonstrated that ratio $T_{anabolism}/E_{2\ catabolism}$ in adult men at sea level is about 1.13. Calculation of data from others (17) shows that ratio serum T/ serum estradiol increases as puberty develops. Estradiol increases more than

testosterone during puberty. That could be the reason why incidence of CMS is lower in puberty (9).

We have calculated the ratio $T_{anabolism}/E_{2\ catabolism}$ at high altitude (4340 m), and this value resulted higher (1.6) than that observed at sea level (1.13). This suggests a high bioavailability of testosterone in adult men at high altitude.

There is a general agreement that total and free testosterone levels and testosterone production rates are lower in older men compared with young healthy men (16). At high altitude, it has been also observed that serum T levels decline with aging (17) but CMS increases with age (9). Calculation of the ratio $T_{anabolism}/E_{2\ catabolism}$ showed a value of 1.92 in older men at sea level and 2.27 in older men at high altitude, suggesting a higher availability of testosterone at high altitude. This finding may explain the higher hematocrit levels and higher prevalence of CMS observed with aging at high altitude.

There is a high prevalence of sleep apnea in the elderly at sea level (18), and it has been calculated from our data the T/E_2 ratio is higher in elderly men at sea level. As ratio is higher at high altitude than at sea level, the prevalence of sleep apneas could be higher in older men at high altitude, increasing hypoventilation and hypoxemia increasing the risk of CMS.

Bioavailability of testosterone under stimulated conditions at high altitude

Response to Gonadotrophin releasing Hormone (GnRH)
Serum testosterone response to GnRH has been studied in native men at 3400 m (19). Serum testosterone levels in men at high altitude remained high at 180 min after injection, whereas in men at sea level, their values had returned to basal levels.

This high testosterone response occurred despite the fact that serum LH levels increased in a similar magnitude at sea level and at high altitude (19).

Response to Human Chorionic Gonadotrophin (hCG)
HCG, is a hormone which acts on Leydig cells in the LH-receptors, and it is used as a test for Leydig cells reserve. A similar increase in serum testosterone with respect to basal values after injection of 1000 IU of hCG has been observed at 3400 m, whereas at 4340 m altitude, a higher response was reported (20). Therefore, it is suggested that high availability of serum testosterone after hCG stimulation may be due to a reduction of conversion to estradiol.

The ratio $T_{anabolism}/E_{2\ catabolism}$ after 48 h of hCG stimulation was 0.15 at sea level and 0.30 at high altitude (198.9% increase), confirming a higher bioavailability of testosterone at high altitude. At high altitude, there is a moderate increment in the metabolism of 17 OHP to testosterone (118.1% with respect to sea level), and a significant reduction in the metabolism of testosterone to estradiol (60.8% with respect to sea level) resulting in a ratio $T_{anabolism}/E_{2\ catabolism}$ twice at high altitude than at sea level. This is a demonstration that per unit of time, there is a high availability of peripheral testosterone, which is more evident after gonadotrophin stimulation.

TESTOSTERONE AND ADAPTATION TO ALTITUDE

The possibility that variation in the normal physiological range of testosterone concentration modulates men's adaptation to hypobaric high-altitude hypoxia through stimulating haemoglobin production and/or causing respiratory disturbances and exacerbated hypoxaemia during sleep had also been suggested by Beall et al (21). altitude. Our analysis relating testosterone to estradiol levels demonstrated that testosterone availability is higher in older men at high altitude and this may explain the higher haemoglobin production and greater hypoxaemia during sleep, all factors contributing to the CMS.

Sleep apneas are observed in high altitude natives (7), and the longest apneas and the highest number of oscillations of arterial oxygen saturation are found in the polycythemic highlanders (2). It is possible that higher bioavailability of testosterone during many years at high altitude is responsible for the sleep apnea at high altitude resulting in hypoventilation, greater hypoxemia, and excessive erythrocytosis, as it has been suggested by Sime (8). All of these may contribute to the etiopathogenesis of CMS. Periodic breathing with apnea has also been observed in high altitude newcomers (22). Similarly, serum T levels are increased after acute exposure to high altitude (13).

During senescence at sea level and at high altitude a reduction in ventilation (8) and an increase in sleep apneas may be observed (20). The ratio T_{anab}/E_{2catab} is significantly higher in the elderly (age: 65 ± 2.00 years, mean ± SEM) than in young adults (age: 21 ± 0.62 years) under basal and post- hCG conditions. In adults, the ratio $T_{anab}/E_{2\ catab}$ is near one, that is, per unit of testosterone there is a unit of estradiol; this ratio is higher in the elderly, and the highest value was observed in the elderly at high altitude. These findings may explain the high prevalence of CMS with aging.

TESTICULAR ENDOCRINE FUCTION IN MEN WITH CHRONIC MOUNTAIN SICKNESS

In CMS, there is a low basal level of serum testosterone and an absent response of Leydig cells to hCG stimulation, whereas serum LH and FSH levels are similar to controls. Men with CMS have been also observed low urinary excretion of testosterone (23). Failure in hypohyso-testicular axis seems to be secondary to CMS, and it is probably a mechanism for preventing deletereous effect of high androgen activity observed in men at high altitude on ventilation.

The reduction in serum testosterone levels in severe grades of hypoxemia could be a feedback mechanism to reduce testosterone effects on ventilation.

Which mechanisms may be postulated for these observations?. The persistent higher availability of T/E_2 increases sleep apneas, producing hypoventilation and hypercapnia. These will increase hypoxemia and decrease oxygen saturation. This situation may be aggravated in the elderly, in whom bioavailability of testosterone (higher T/E_2 ratio) is higher, increasing erythrocytosis further. If hypoxemia reaches a threshold level, CMS is produced. An unknown negative signal eventually causes a reduction in serum testosterone level and its response to Lh/hCG stimulation, as negative feedback. However, CMS is not relieved, probably because the T/E_2 ratio is stays high, or possibly because of a loss of the hormonal negative feedback control

of hemoglobin concentration.
According to our data of higher bioavailability of testosterone in the elderly at high altitude, it has been suggested that native men at high altitude are not adequately adapted to live at high altitude. To be adapted, they probably require to have T/E_2 ratio near to 1 as it happens at sea level.

Gustavo F. Gonzales
Instituto De Investigaciones De La Altura And Department Of Physiological Sciences. Universidad Peruana Cayetano Heredia.

1. Lahiri S, Edelman NH, Cherniak NS, Fishman AP. Blunted hypoxic drive to ventilation in subjects with life-long hypoxemia. Fed. Proc. 28: 1289-1295, 1969.
2. Normand H, Vargas E, Bordachar J, Benoir O, Raynaud J. Sleep apneas in high altitude residents (3800 m). Int J Sports Med 13: S40-S42, 1992.
3. Kryger MH, Grover RF. Chronic Mountain Sickness. Sem. Resp. Med. 5: 164-168, 1983.
4. Block AJ, Bouysen PG, Wynne JW, Hunt LA. Sleep apnoea, hypopnoea, and oxygen desaturation in normal subjects. N Engl J Med 300:513-7, 1979.
5. Schneider BK, Pickett CK, Zwillich CW, Weil JV, McDermott MT, Santen RJ, Varano LA, White DP. Influence of testosterone on breathing during sleep. J. Appl. Physiol. 61: 618-623, 1986.
6. Mohamed G, Lopata M, Kukreja J, Schraufnagel ID. Androgen levels in women with sleep apnea syndrome (Abstract). Am. Rev. Respir. Dis. 127: 237, 1983.
7. Matsumoto AM, Sandblom RE, Schoene RB, Lee KA, Giblin EC, Pierson DJ, Bremmer WJ. Testosterone replacement in hypogonadal men: effects on obstructive sleep apnea, respiratory drives, and sleep. Clin Endocrinol. 22: 713-721, 1985.
8. Sime F. Dormir en los Andes: Contribución del sueño en la etiopatogenia de la enfermedad de Monge. Acta Andina 4: 13-24, 1995.
9. Arregui A, León-Velarde F, Valcárcel M. Salud y Minería: El riesgo del mal de montaña crónico entre mineros de Cerro de Pasco. Asociación Laboral para el Desarrollo. Lima, Perú. 127 pp, 1990.
10. Leon-Velarde F, Ramos MA, Hernandez JA, De Idiaquez D, Munoz LS, Gaffo A, Cordova S, Durand D, Monge C. The role of menopause in the development of chronic moountain sickness. Am J Physiol. 272: R90-R94, 1997.
11. Ou LC, Sardella GL, Leiter JC, Brinck-Johnsen T, Smith RP. Role of sex hormones in development of chronic mountain sickness in rats. J Appl Physiol 77: 427-433, 1994.
12. Semple PD, Beastall GH, Watson WS, Hume R. Hypothalamic-pituitary dysfunction in respiratory hypoxia. Thorax 36: 605-609, 1981.
13. Gonzales GF. Endocrinología en las grandes alturas. Revista de la AN-BIOP. 2(1): 9-66, 1983.
14. Coyotupa J, Llerena LA. Maduración sexual en Cerro de Pasco (4340 m) y Lima (150 m). Arch. Biol. Andina 12:52-66, 1983.

15. Cemeroglu AP, Barkan AL, Kletter GB, Beitins IZ, Foster CM. Changes in serum immunoreactive and bioactive growth hormone concentrations in boys with advancing puberty and in response to a 20-hour estradiol infusion. J Clin End Metab. 82: 2166-2171, 1997.
16. Morley JE, Perry HM III, Kaiser FE et al. Effects of testosterone replacement in old hypogonadal males: a preliminary study. Am J Geriatr Soc. 41: 149-152, 1993.
17. Kaneku L, Coyotupa J, Crespo I, Guerra-García R, Gonzales GF. Función endocrina testicular en jóvenes y ancianos de Lima (150 m) y Cerro de Pasco (4340 m). Acta Andina 2: 93-99, 1992.
18. Shore ET, Millman RP, Silage DA, Chung D-C C, Pack AI. Ventilatory and arousal patterns during sleep in normal young and elderly subjects. J Appl Physiol 59: 1607-1615, 1985.
19. Garmendia F, Castillo O, Valdivia H, Ugarte N, Garmendia A. Sensibili-dad hipófiso-testicular del nativo normal de altura a la administración de hormo-na liberadora de gonadotropinas. Archivos de Biología Andina. 13: 207-211, 1984.
20. Gonzales GF, Kaneku L, Góñez C. Fisiología y patología de la reproduc-ción en las grandes alturas. Acta Andina 1: 3-16, 1992.
21. Beall CM, Worthman CM, Stallings J, Strohl KP, Brittenham GM, Barragan M. Salivary testosterone concentraction of Aymara men native to 3600 m. Ann Hum Biol. 19: 67-78, 1992.
22. Goldenberg F, Richalet JP, Onnen I, Antezana AM. Sleep apneas and high altitude newcomers. Int J Sports Med 13: Sup. 1): S34-S36, 1992.
23. Guerra-García R, Llerena LA, Garayar D, Ames R. Función endocrina testicular en nativos de altura y en pacientes con mal de montaña crónico. V Jornadas Peruanas de Endocrinología. Cusco, Perú. Res. 22, 1973.

 Last modified 20-Nov-2002