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# High Altitude Renal Syndrome (HARS)

Abdias Hurtado Arestegui,* Richard Fuquay,† Jeffrey Sirota,† Erik R. Swenson,‡ Robert B. Schoene,‡ J. Ashley Jefferson,‡ Wei Chen,§ Xue-qing Yu,§ Jackeline Pando Kelly,‖ Richard J. Johnson,† and Elizabeth Escudero*

*Division of Nephrology, Hospital Arzobispo Loayza, Cayetano Heredia University, Lima, Peru; †Division of Renal Diseases and Hypertension, University of Colorado, Aurora, Colorado; ‡Department of Medicine, University of Washington, Seattle, Washington; §Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; and ‖Cork University Hospital, Royal College of Physicians of Ireland, Cork, Ireland

## ABSTRACT

More than 140 million people live permanently at high altitude (>2400 m) under hypoxic conditions that challenge basic physiology. Here we present a short historical review of the populating of these regions and of evidence for genetic adaptations and environmental factors (such as exposure to cobalt) that may influence the phenotypic responses. We also review some of the common renal physiologic responses focusing on clinical manifestations. The frequent presentation of systemic hypertension and microalbuminuria with relatively preserved GFR coupled with the presence of polycythemia and hyperuricemia suggests a new clinical syndrome we term high altitude renal syndrome (HARS). ACE inhibitors appear effective at reducing proteinuria and lowering hemoglobin levels in these patients.

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The term high altitude is used to define living at an altitude exceeding 2400 m above sea level. Using this definition, >140 million people in the world currently live at high altitude, representing 2% of the world's population.[1] There are several major regions in the world that are situated at high altitude. The Ethiopian summits in northeast Africa consist of mountains that reach an altitude between 4600 and 4900 m above sea level. Known as the *Roof of Africa*, this region is inhabited by the Amhara ethnic group. The Himalayan Mountains in Asia are the highest range of mountains in the world, inhabited by the Sherpa in the Nepali region, as well as a variety of other ethnic groups elsewhere. The Andean region of South America constitutes a third major high altitude region, primarily inhabited by two different ethnic groups: the Quechua and Aymara. These peoples have been involved in a continuous process of racial mixing with the Spanish.

## HUMAN ORIGINS AND THE POPULATING OF HIGH ALTITUDE REGIONS

Modern humans (*Homo sapiens*) have their origin in Africa.[2] The earliest fossils of *H. sapiens* date to 200,000 years ago and were found in Ethiopia (Kibish man).[3] Studies of mitochondrial DNA, which is only inherited maternally,[4] also place the origin of humans to this same period.[5] Genetic studies of different African populations suggest an origin in southwestern Africa near the Angola and Namibia border, possibly from an ancestor of the hunter gatherer San (Bushmen) people.[6] Around 70,000 years ago, humans moved into the East African plateau of Ethiopia (2400 m) to become the first population living at high altitude.[7] Roughly at the same time (50,000 to 90,000 years ago), humans began migrating out of Africa to Asia and Europe.[8] Even later (approximately 15,000 to 22,000 years ago), the first migrations to the Americas occurred, likely over the Bering land bridge (Beringia), which in the past had connected Asia and Alaska.[9,10] Genetic studies based on mitochondrial haplotypes suggested these early peoples represented ancestral Mongolians[11,12] or perhaps the Altaian people from southern Siberia.[13] By 13,500 to 15,000 years ago, the first humans entered South America, with one of the earliest documented sites being in Monte Verde, Chile.[14]

## GENETIC ADAPTATIONS TO HIGH ALTITUDE

People living in the Ethiopian highlands, Tibet, and the Andes descend from settlers who arrived to these high altitude regions 70,000, 25,000, and 11,000 years ago, respectively.[15] Numerous differences in responses to high altitude have been described in three populations living at these

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**Correspondence:** Dr. Abdias Hurtado Arestegui, Division of Nephrology, Hospital Arzobispo Loayza, Cayetano Heredia University, Lima 27, Peru. Phone: 511 2248178; Fax: 511 3309361; E-mail: ahurtadoa@hotmail.com

altitudes (Table 1).[15] A classic hypothesis is that Tibetan inhabitants have a better adaptation to altitude than Andeans because of their longer exposure to high altitude, which allowed genetic modifications to develop.[15,16] Although not as well studied as these groups, Amharic highlanders may be even better adapted because of their longer time residence in the mountains. The better adaptations of the Tibetans and Amhara to altitude is suggested by the following observations:

### Increase in Hemoglobin in Response to Hypoxia

Among the Andean populations, the hypoxia-related increase in hemoglobin is seen starting at an altitude of 1600 m above sea level. In contrast, among the Tibetan populations, who have resided at high altitude for a longer period of time, the increase of hemoglobin as a response to hypoxia is seen only in those living >4000 m above sea level.[16] In this regard, the Ethiopian Amharic population hemoglobin distribution is equivalent to the Tibetans.[17] One potential explanation for this discrepancy may relate to genetic polymorphisms in *EPAS1*, the gene coding for hypoxia inducible factor-2 (HIF-2), a known modulator of erythropoietin levels.[18] In comparison to the closely related but lower altitude dwelling Han Chinese population, Tibetans have polymorphisms in *EPAS1* that are associated with lower hemoglobin levels, suggesting a selection advantage of Tibetans to help protect high altitude dwellers against the development of severe erythrocytosis.[19,20] To our knowledge, studies of *EPAS-1* polymorphisms in the Andean and Amharic populations have not been reported.

### Prevalence of Chronic Mountain Sickness

Chronic mountain sickness (CMS) or Monge's disease results from the development of severe erythrocytosis and occurs in some people who live permanently at high altitude. It presents with symptoms such as headache, dyspnea, fatigue, palpitations, cyanosis, sleeping problems, and polycythemia (hematocrit > 65%). Studies performed in ethnic Tibetans report a CMS prevalence of 1.2%, whereas the Han ethnic group, who have resided in Tibet for a shorter period of time, have a CMS prevalence of 5.5%.[21] This suggests better genetic adaptation of the Tibetan ethnic group.[19–22] In contrast, research performed in Andean populations show a CMS prevalence of 8.5 to 15.6%.[23,24] With respect to the Amhara, whose residence at high altitude has been the longest, there have been no reported cases of CMS. Although some evidence for genetic adaptation of Andeans has been identified, particularly as it relates to polymorphisms in HIF, evidence for evolutionary modification of this general biochemical pathway has not be shown.[25] These differences could theoretically be accounted for by the shorter residence time of Andeans at high altitude compared with the Tibetan people,[15] coupled with ongoing racial mixing between Europeans and Andean, which might further decrease the genetic adaptation.[26]

### Prevalence of Low Birth Weight Newborns

Although the above studies suggest poorer adaptations in Andeans compared with Tibetans, there is also evidence for some adaptations among the Andean population compared with peoples who have lived until recently at sea level. Because chronic hypoxia causes growth retardation, birth weight modestly decreases as altitude increases.[27,28] As such, Andean populations who live at high altitude over many generations have an increased frequency of low birth weight infants. However, these newborns have an average birth weight that is higher than those from populations living at high altitude for a shorter period of time, such as Europeans.[29] Furthermore, mixed European-Andean populations have newborns with an intermediate birth weight.[29] Again, these observations suggest potential, as yet unidentified, genetic adaptations that occur with living at high altitude.

## ENVIRONMENTAL FACTORS RELATED TO HIGH ALTITUDE?

Although it is likely that there have been genetic adaptations to high altitude and that these adaptations are more pronounced in those with longer exposure to high altitude (Tibetans), there is also increasing evidence for environmental factors that may be involved. Specifically, the greater hematocrit response and the higher prevalence of CMS in Andeans may be at least partially explained by environmental exposures.[30] Most of the Andean sites where severe polycythemia and CMS have been reported occur at mining sites,[31] as is the case in the North American Rockies.[32,33] The first report of CMS was in the Andean mining community of Cerro de Pasco (4300 m altitude),[34] and CMS has been reported in other mining communities such as Chuquicamata, Chile (2800 m altitude), where the mean hemoglobin is significantly higher than in other nonmining communities that are at higher altitude (3700 and 4100 m).[35,36]

One potential explanation for the association of CMS and mining communities could be exposure to heavy metals that can stimulate erythropoiesis, such as cobalt and nickel.[37,38] Cobalt, and to a lesser extent nickel, increase erythropoietin levels by inhibiting HIF-1$\alpha$ prolyl hydroxylase, thereby preventing the ubiquitination and degradation of HIF-1$\alpha$ and HIF-2$\alpha$. This inhibition results in higher levels of HIF-1$\alpha$, potentiating erythropoietin production. Cobalt is commonly present as a contaminant in many mines, and we previously reported high concentrations in the slag water from the major open pit mine in Cerro de Pasco.[30] In our study, many of the subjects with severe polycythemia and CMS had elevated cobalt levels in their blood, and we are currently looking for the source of the cobalt. Although we could not find cobalt in the local drinking water supply, the fact that the mine water drains into the nearby San Juan River has led to the suggestion that the local fish could be a source through ingestion. We plan to study this hypothesis in the future and to determine whether *N*-acetyl cysteine, which can chelate cobalt,[39] may help treat CMS in this community. In addition, the use of chelation therapy may enhance the sensitivity for detecting cobalt poisoning and thereby resolve the discrepancy from a different study in which elevated cobalt levels could not be shown in CMS

**Table 1.** Comparisons of Tibetans, Andeans, and Ethiopians in responses to high altitude

| | Tibetans | Andeans | Ethiopians |
|---|---|---|---|
| Basal metabolic rate | Normal | Normal | Unknown |
| Maximum oxygen consumption | Normal | Normal | Unknown |
| Ventilation (L/min) | 15 | 10.5 | Unknown |
| Hypoxia ventilatory response | Higher | Lower | Unknown |
| Oxygen saturation of hemoglobin | Lower | Higher | Highest |
| Hemoglobin | Lower | Higher | Lower |
| Arterial oxygen content | Lower | Higher | Highest |
| Pulmonary artery pressure | Lower | Higher | Lower |
| Pulmonary nitric oxide production | Higher | Lower | Higher |
| Peripheral capillary density | Higher | Lower | Unknown |
| Oxygen dissociation | Normal | Normal | Normal |
| CMS (prevalence) | 1.2% | 8 to 15% | No reports |

Adapted from refs. 15, 17, and 69.

**Table 2.** Common renal findings at high altitude

| Serum Findings |
|---|
| Polycythemia (excessive erythrocytosis) |
| Hyperuricemia |
| Hemodynamic findings |
| elevated systemic BP |
| elevated renal vascular resistance |
| elevated pulmonary artery pressure |
| Reduced renal plasma flow |
| preserved GFR (elevated FF) |
| Renal pathology findings |
| glomerulomegaly |
| Urinary findings |
| microalbuminuria |

We suggest the designation high altitude renal syndrome to characterize the combination of polycythemia, systemic hypertension, hyperuricemia, and microalbuminuria.

subjects from the same city.[40] Interestingly, by stimulating HIF-1$\alpha$, cobalt will also increase levels of vascular endothelial growth factor, which is a key factor for angiogenesis, especially for the placenta and fetus. Thus, cobalt exposure could potentially explain the slightly larger babies in Andeans compared with Europeans moving to the Andean regions.

## RENAL ADAPTATION IN INDIVIDUALS CHRONICALLY LIVING AT HIGH ALTITUDE

Living at high altitude under hypoxic conditions has many effects on the kidney.[41] Some of the more salient findings are discussed below (Table 2).

### Reduced Renal Plasma Flow and Increased Filtration Fraction

The kidney receives 25% of the cardiac output. The GFR is used to measure renal function, and this is determined both by renal plasma flow (RPF) and the percentage of RPF that is filtered at the glomerulus, the filtration fraction (FF; normally around 20%).

In the setting of polycythemia at altitude, studies show a marked decrease in RPF with a relative preservation of GFR as a consequence of an increased FF. The first study evaluating this finding was performed in five men with severe polycythemia living at high altitude in Peru, in whom GFR was slightly reduced (11%), and RPF was reduced to 52% of normal, with a corresponding increase in the FF of 89%.[42] A later Peruvian study performed evaluated kidney function in three different groups of patients: The first group included men who lived at sea level, the second was done in men living at high altitude who presented with moderate polycythemia, and the third group included men living at high altitude who developed CMS. The FF was 18, 25, and 28%, respectively.[43] It was felt that the hypoxia-related increase in hematocrit led to a decrease in total plasma volume and an increase in blood viscosity, producing a decrease in RPF, thereby increasing FF. The increased FF is presumably caused by efferent arteriolar vasoconstriction, although the exact mediators are unclear, because the renin angiotensin system is not consistently activated.[44]

### Microalbuminuria and Proteinuria

An increased prevalence of microalbuminuria and proteinuria has been reported in subjects living at high altitude.[45] For example, in a recent study in Tibet, we found that 15% of Tibetans had microalbuminuria.[46] Proteinuria increases with higher hematocrit. In one study, 6/27 (22%) of CMS patients had proteinuria $>1$ g/24 h.[47] The pathogenesis of the proteinuria may relate to a variety of factors, including the effects of tissue hypoxia within kidney parenchyma, glomerular capillary hypertension, hyperviscosity, and elevated right heart pressures. The proteinuria may also relate to the hyperuricemia commonly observed at high altitude (see below).[46]

Treatment with angiotensin converting enzyme (ACE) inhibitors is beneficial in reducing proteinuria in subjects living at high altitude. In a study in Bolivia, high altitude residents administered an ACE inhibitor showed significant reductions in proteinuria and hemoglobin.[48] The ability of ACE inhibitors to lower hemoglobin may relate to both improvements in renal medullary blood flow and direct effects to block angiotensin II–mediated erythropoiesis.[49]

In addition, chronic acetazolamide treatment reduces both hematocrit[50] and proteinuria[51] observed in subjects at high altitude, because of improvement in arterial oxygenation and perhaps by improving renal blood flow.[52]

### Glomerular Hypertrophy

Subjects living at high altitude are known to develop large glomeruli. For example, one study reported the presence of larger glomeruli in children living at high altitude compared with children living at sea level.[53] Similar findings have been reported in children with hypoxia secondary to cyanotic heart disease.[54] The mechanism is uncertain, but could relate to the effects of low birth weight that has been shown to cause low nephron number.[55,56] Hyperuricemia can also induce glomerular hypertrophy in experimental animals,[57] likely mediated in part by activation of the renin angiotensin system and the induction of glomerular hypertension.[58,59] Clearly more studies are

needed to identify the underlying mechanism.

### Hyperuricemia and Hypertension

Hypoxemia, when associated with tissue ischemia, leads to increased production of uric acid.[60] The mechanism may relate to the reduction in ATP levels with increased adenine nucleotide turnover coupled with activation of xanthine oxidase.[61] In addition, lactate generated with hypoxia will compete with the excretion of urate at the proximal tubule, resulting in a decrease in urate clearance.[62] Polycythemia may also result in increased uric acid levels caused by increased cell turnover.[63] It is thus not surprising that subjects living at high altitude frequently have hyperuricemia.

The first description of hyperuricemia in high altitude populations was reported in 1968.[64] In a small clinical study we conducted in Peru, we found that uric acid levels tend to increase with rising hematocrit and are significantly greater in subjects with CMS compared with those living at sea level.[47] A large epidemiologic study in Tibet also found a significant increased prevalence of hyperuricemia in Tibetans compared with prior studies performed among Han Chinese people living in Guangzhou.[46] Moreover, subjects living at high altitude also have a low fractional excretion of uric acid despite the high serum levels of uric acid[47]; similar findings have been described in congenital cyanotic heart disease.[65]

Interestingly, the higher prevalence of hyperuricemia associates with both the presence of microalbuminuria and systemic hypertension.[46] For example, in our study of Tibetans, 38% of subjects had hypertension, 29% had hyperuricemia, and 16% had albuminuria (including microalbuminuria). However, reduced GFR (defined as estimated GFR $<60$ ml/min per 1.73 $m^2$) was observed in only 2% of these subjects.[46] Multivariate analysis showed that hyperuricemia, polycythemia, and hypertension were independent predictors of albuminuria. These findings expand on the laboratory finding that experimental hyperuricemia can induce systemic and glomerular hypertension and microalbuminuria in animals.[57,59,66] Taken together, these observations suggest a new clinical syndrome that we propose to call high altitude renal syndrome, comprising the constellation of high altitude polycythemia, hyperuricemia, systemic hypertension, and microalbuminuria. Consistent with this finding, of the 16% of subjects with albuminuria, 50.9% had hypertension, 39.4% had hyperuricemia, and 31.7% had high hematocrit (defined as hematocrit $>50\%$ in men and $>48\%$ in women). Pulmonary hypertension is also a very common finding in those with CMS[67] and might be considered another defining feature of high altitude renal syndrome, caused in part by uric acid–mediated suppression of pulmonary vascular endothelial cell NO production and breakdown of arginine, the nitrogenous substrate for NO formation.[68]

## CONCLUSIONS

There are a significant number of people living at high altitude worldwide. The adaptation of these people to high altitude is likely determined by both genetic and environmental factors. Compared with high altitude Tibetans, the Andean population is more vulnerable than the Tibetan population to the effects of high altitude and the development of CMS, possibly because of their shorter time span at high altitude and certain heavy metal exposures. High altitude is also associated with increased risk for the development of microalbuminuria, hypertension, and hyperuricemia, with relative preservation of GFR and with an increased FF. Some studies suggest ACE inhibitors may be helpful for high altitude proteinuria. The possibility that some subjects at high altitude with CMS may have heavy metal poisoning from cobalt or nickel also has to be considered.

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## DISCLOSURES

None.

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