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Full Review

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Cardiovascular and renal effects of chronic exposure to high altitude

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Abstract
Over 140 million people live at high altitude, defined as living at an altitude of 2400 m or more above sea level. Subjects living under these conditions are continuously living under hypoxic conditions and, depending on the population, various adaptations have developed. Interestingly, subjects living chronically at high altitude appear to have a decreased frequency of obesity, diabetes and coronary artery disease. However, these benefits on health are balanced by the frequent development of systemic and pulmonary hypertension. Recently, it has been recognized that subjects living at high altitude are at risk for developing high-altitude renal syndrome (HARS), which is a syndrome consisting of polycythemia, hyperuricemia, systemic hypertension and microalbuminuria, but with preserved glomerular filtration rate. More studies should be performed to characterize the mechanisms and etiology of HARS; as such studies may be of benefit not only to the high-altitude population, but also to better understanding of the renal consequences of acute and chronic hypoxia.

Keywords: chronic mountain sickness; high altitude; high altitude renal syndrome; hypoxia

Introduction

The term 'high altitude' is used to define an altitude exceeding 2400 m above sea level. There are more than 140 million people living in these regions, representing 2% of the world's population [1]. One of the characteristics of these high-altitude regions is the diminished oxygen availability due to the low barometric pressure. For this reason, people living in these regions have to develop mechanisms to adapt to the hypobaric hypoxia.

Worldwide, there are several major high-altitude regions that are inhabited and they are mainly localized in Africa (in the Ethiopian summits), in Asia (in the Tibetan plateau and along Himalayan mountains) and in America (in the Andean mountains). The native dwellers of these regions have developed adaptation mechanisms that allow them to live in environments with low oxygen levels [2]. Studies done in populations living in these three regions of high altitude have shown genotypic and phenotypic differences, which suggest different adaptation levels. The Amhara ethnic groups that dwell in Ethiopia (3530 m), in spite of the low oxygen tension in which they live, have similar levels of hemoglobin and oxygen saturation to those who dwell at the sea level. This likely represents a successful adaptation [3]. In the case of the Tibetans who have lived at very high altitudes for thousands of years, normal hemoglobin levels have been found in spite of arterial hypoxemia [4]. Andean populations, who have been living at high altitudes for shorter time compared with the Ethiopians and Tibetans, show higher erythrocytosis and arterial hypoxemia. Some of these latter subjects also develop chronic mountain sickness (CMS), or Monge's disease, in which erythrocytosis is so marked (hematocrit > 75) that they develop symptoms of pulmonary hypertension and hyperviscosity [5]. While the generally greater erythrocytosis in Andean populations likely represent a poor adaptation to high altitude, recent studies suggest that those with the more severe forms of erythrocytosis carry high blood levels of cobalt, presumably from the local mines, which is known to potentiate erythrocytosis in response to hypoxia (to be discussed in more detail below) [6].

Physiological adaptations to high altitude

Significant differences in various physiological traits comprising the oxygen delivery process have been observed in the different ethnic native groups living at high altitude around the world.

Energy production

Individuals who live at the sea level and then travel to high altitude undergo several immediate adaptations, of which, one is an increase in basal metabolic rate. Nevertheless, both Andean and Tibetan highlanders have normal metabolic rate expected for their age, sex and body weight [7]. They also demonstrate a full range of

aerobic potential for activities requiring oxygen delivery as individuals at low altitude. All this implies that their functional adaptations do not entail increased basal oxygen requirements [8].

Ventilation

A study showed that the mean resting ventilation (resting ventilation, expressed as the product of tidal volume and respiratory rate) for Tibetans was >1 standard deviation (SD) higher than that observed in Andean highlanders [9]. Therefore, Tibetans inspire a larger overall volume of air during times of rest, thereby achieving a higher level of oxygen in the alveolar air and more diffusion of oxygen. Tibetans also express a normal hypoxic ventilator response 'HVR' (which is a measure to quantify the increase in ventilation induced by exposure to a standardized experimental hypoxic stress) when compared with sea-level populations in their native altitude. The average HVR of Tibetans was approximately double that of Andean high-altitude natives who have generally lower HVRs than sea-level values [10]. The implication is that the Tibetan respiratory physiology has changed from the ancestral functional response of temporary increase in ventilation and HVR to a pattern in which these responses can be sustained indefinitely [4].

Oxygenation of blood

Studies have shown that the level of oxygen in the arterial blood of Tibetans living at ∼3700 m was lower than that of a sample of Andean high-altitude natives at the same altitude [10]. Hemoglobin is less saturated with oxygen among Tibetans than among their Andean counterparts and they have lower hemoglobin and erythropoietin concentrations than Andean highlanders at the same altitude [10, 11]. Together, oxygen saturation and hemoglobin concentration determine arterial oxygen content. The calculated arterial oxygen content in a sample of Tibetans is substantially lower than among Andean highlanders, who actually have higher arterial oxygen content than sea-level natives at the sea level [4]. Andean highlanders have overcompensated for ambient hypoxia according to this measure, whereas Tibetans highlanders have undercompensated. Tibetans are profoundly hypoxic and must be adapting at other points in the oxygen transport cascade to sustain normal aerobic metabolism.

Blood flow and oxygen diffusion

High-altitude hypoxia results in poor oxygenation of the entire lung and general constriction of blood vessels to the degree that it raises pulmonary blood pressure, often to hypertensive levels [12]. Andean highlanders are consistently reported as having pulmonary hypertension [13]. In contrast, most Tibetans do not have hypoxic pulmonary vasoconstriction or pulmonary hypertension and have normal or minimally elevated pulmonary artery pressure [4]. One potential reason is that Tibetans have higher rate of nitric oxide (NO) transfer out of the airway wall, thus, implicating tremendous vasodilation [14]. Although, the reaction of NO with hemoglobin greatly limits the lifetime of NO in blood, redox-activated nitrogen oxides, such as nitrite and *S*-nitrosothiols, may enable hypoxia-associated vasodilatation [15, 16]. Tibetans have relatively high blood flow that may contribute significantly to offsetting their low arterial oxygen content. Tibetans also have evidence for higher rates of diffusion of oxygen in tissues that may help overcome profoundly low arterial oxygen content as evidenced by higher capillary density in muscles when compared with Andean high-altitude natives, lowlanders as well as Tibetans born and raised at low altitude [4, 17]. No distinguishing physiological traits have been identified in high-altitude Ethiopians. Hemoglobin levels and oxygen saturation in high-altitude Ethiopians (3530 m) have been reported as similar to those in low-altitude residents in the USA [3, 18].

Genetic evidence for high-altitude adaptation

Amhara ethnic group

In this native ethnic group that dwells in the highlands of Ethiopia, genome-wide analysis has identified several genes (*CBARA1, VAV3, ARNT2, THRB*) that may be responsible for the adaptation to altitude. *CBARA1* regulates calcium uptake by the mitochondria, and is thought to play a critical role in the response to hypoxic conditions [19]. *VAV3* induces GTPase activity and is involved in angiogenesis, which is triggered by hypoxia [20]. *ARNT2* is directly involved in the HIF-1 pathway and forms a heterodimer expressed in the fetal lung, whereas *THRB* is required for HIF expression in hepatic cells, which is the primary source of erythropoietin (EPO) during fetal development [21]. These genes have not been found in other ethnic groups and two of these (*ARNT2* and *THRB*) play an important role in the HIF-1 pathway. The same study demonstrated that *PPARA* and *EPAS1* (genes involved in the HIF-1 pathway cascade that is initiated in response to hypoxic environmental conditions) contain small nuclear proteins (SNPs) with marginal associations with hemoglobin, which raises the possibility that variations at these loci may be responsible for a role in adaptation to high altitude in the Ethiopian population [18].

Tibetans

In the case of Tibetans, who have lived at very high altitudes for thousands of years, normal hemoglobin levels have been found in spite of arterial hypoxemia. The genetic adaptation may be due to polymorphisms in the Endothelial PAS domain containing protein-1 (*EPAS1*) [22]. This is the gene for hypoxia-inducible factor 2α (HIF-2α) transcription factor which stimulates erythrocyte production. A significant genetic divergence in *EPAS1* was shown in Tibetans compared with the Han population that live in China. Variants in *EPAS1* have been correlated with lower hemoglobin concentrations supporting its role in maintaining a blunted erythropoietic response to lower oxygen saturation values, which is a hallmark of altitude adaptation in Tibetans. Subjects that were homozygous for the polymorphism showed 0.8 g/dL lower hemoglobin

concentration compared with the population that were heterozygote for the polymorphism [22].

Genome-wide scans of Tibetans have identified evidence of positive selection for several genes that are likely involved in adaptation to high altitude. Several haplotypes of *EGLN1* and *PPARA* are significantly associated with the decreased hemoglobin phenotype that is unique to this highland population [23]. An analysis of the human exome comparing Tibetans and Han Chinese found a significant difference in the frequency of one variant in the *EPAS1* (87 versus 9%). This dramatic difference is consistent with strong selection pressures. Nevertheless, the *EPAS1* alleles are not fixed in the Tibetans, which may mean that there are balancing selective forces that preserve some frequency of the lowland allele, that alternative compensatory strategy may be involved or that insufficient time has passed for complete assimilation of the polymorphism to have occurred. An admixture of Tibetan and Han populations could also explain this observation [24]. Several other recent genomic studies of high-altitude Andean and Tibetan population samples have also identified patterns of SNP variations in *EPAS1*, *EGLN1* and *PPARA* consistent with positive selection [23, 25, 26].

Andeans

Recently, the presence of polymorphisms of hypoxia-sensitive genes such as erythropoeitin (EPO), EPO receptor, hypoxia-inducible factor, Prolyl hydroxylase domain-1, -2, -3 and Von Hippel–Lindau was evaluated in Andean populations with and without CMS. There were no genetic differences in patients with CMS among these populations that could explain their excessive erythrocytosis (defined as a hematocrit > 65%) [27]. However, *EGLN1* and *ARNT2* have been implicated in the altitude adaptation of the Andeans [28]. The protein encoded by *EGLN1* is central to HIF-1-mediated gene expression. Variants in the gene could mediate a variety of hypoxia responses that may provide several physiological advantages. There is no evidence that *EPAS1* variants are enriched in Andean highlanders, which is consistent with what is known about the humoral physiology of this population compared with the Tibetans.

While a lack of genetic adaptation may account for one reason why severe erythrocytosis may be greater in the Andean population, there may also be environmental exposures that contribute to the high prevalence of CMS in Andean communities. One striking finding is the high prevalence of CMS in and around mining communities. Cobalt is a metal that is known to stimulate HIF-1α due to its ability to block the prolyl hydroxylase that regulates HIF-1α l levels. We reported that cobalt poisoning was common in individuals with CMS who were living in the high-altitude city of Cerro de Pasco [6]. The slag water from the mine also contained high levels of cobalt. However, none of the individuals with cobalt poisoning in our study worked in the mines. While the route of poisoning is still not known, we postulate that it may be due to the draining of the slag water into the local river with contamination of the fish.

The heart at high altitude

Acute exposure to high altitude has been recognized as a type of cardiovascular stress, and results in an immediate increase in cardiac output, with tachycardia and a transient rise in the blood pressure but without changes in the ejection fraction [29]. Nevertheless, highlanders who reside at high altitude show anatomical and physiological characteristics on their cardiovascular system that has allowed them to adapt to high-altitude chronic hypoxia. In highlanders, although the coronary flow and the oxygen supply are lower than at the sea level, the myocardium shows enhanced oxygen extraction with no evidence of anaerobic metabolism [30]. There is a preference to metabolize glucose over free fatty acids [31] and red cell levels of 2,3 diphosphate glycerate are higher, shifting the hemoglobin curve to the right, thus increasing oxygen release at the tissue level [32].

Hypoxia also triggers an increase in pulmonary vascular resistance causing moderate pulmonary hypertension, right ventricular hypertrophy and an increase in the number of smooth muscle cells in the distal branches of the pulmonary artery [13].

There are few population-based studies examining the effects of chronic exposure to high altitude on systemic blood pressure. A study done in Andean highlanders living at 4300 m above the sea level showed a low prevalence of high blood pressure [33]. However, more recent studies done in Tibetan and Andean highlanders suggest that the prevalence of hypertension is similar, or higher than in people living at the sea level [34, 35]. In particular, there appears to be a dichotomy, in which hypertension at lower altitudes is associated more with obesity and classical cardiovascular risk factors, whereas at high altitude the frequency of hypertension correlates more with the presence of polycythemia and hyperuricemia [36].

Coronary heart disease at high altitude

A low prevalence of coronary disease among Andean populations living at high altitude compared with people living at the sea level was first reported in the 1960s [37]. A subsequent study of people living at altitudes between 914 and 2133 m above the sea level in the USA found a reduction in the mortality rate among men, as altitude increased [38]. In mountain regions of Greece (950 m), a decrease in total mortality and coronary mortality rates was reported in men and women compared with mortality rates at the sea level even after controlling for cardiovascular risk factors [39]. In another study performed in residents of Germany and Switzerland, there was a steady decline in ischemic heart disease (IHD) mortality and stroke as altitude of residency increased (range 259–1960 m above the sea level). Being born at high altitude also had a beneficial effect upon IHD mortality even if the residents subsequently moved to lower altitude [40]. In another study conducted in the USA, living at high altitude was associated with the reduced frequency of IHD, despite no effect on life expectancy [41].

There are several potential explanations for the positive benefit of altitude on the frequency and severity of coronary heart disease. Animal studies have demonstrated molecular changes induced by hypoxia that appear to have a cardioprotective effect, largely due to the activation of HIF-1, which is a transcriptor modulator. HIF-1 induces the expression of multiple genes such as the EPO, NO synthase, vascular endothelial growth factor (VEGF) and genes associated with anti-oxidant functions (such as heme oxygenase-1).

For example, hypoxia stimulates angiogenesis by increasing the production of VEGF [42], and subjects living at high altitude have increased number of branches and peripheral vessels in the coronary vasculature compared with those found in people who live at the sea level [43]. Similarly, an increase in cardiac capillary density has been reported in polycythemic rats [44]. The myocardium also shows an enhanced oxygen extraction and a preference to metabolize glucose over free fatty acids [30, 31]. As mentioned, high altitude is also associated with lower frequencies of obesity and diabetes, which are major risk factors for causing IHD. Nevertheless, the countering adverse effects of high altitude on systemic and pulmonary hypertension likely explain why the reduction in the frequency of coronary artery disease (CAD) is not associated with improved longevity.

The kidney at high altitude

Living at high altitude under chronic hypoxic conditions has many effects on the kidney [45]. One of the more common phenotypes presents as the combination of polycythemia, systemic hypertension, hyperuricemia and microalbuminuria and is called the high-altitude renal syndrome (HARS) [46].

Reduced renal plasma flow and increased filtration fraction

Glomerular filtration rate (GFR) is used to measure renal function, and this is determined both by renal plasma flow (RPF) and by the percentage of RPF that is filtered at the glomerulus, the filtration fraction (FF, normally around 20%). In the setting of high altitude-associated polycythemia, there is a marked decrease in RPF due to the elevation in hematocrit, yet this is associated with a relative preservation of GFR as a consequence of an increased FF. This was first shown in five men with severe polycythemia living at high altitude in Peru, in whom RPF was reduced to 52% of normal and yet GFR was only slightly reduced (11%), resulting in a corresponding increase in FF of almost 90% [47]. Another study compared men who lived at the sea level with men living at high altitude with modest polycythemia and a third group of subjects living at high altitude who had severe polycythemia and CMS. The FF was 18, 25 and 28% respectively [48].

Hyperuricemia and hypertension

Hypoxemia, by virtue of causing tissue ischemia, also results in the increased production of uric acid [49]. The mechanism may relate to the reduction in ATP levels with increased adenine nucleotide turnover, coupled with the activation of xanthine oxidase [50]. In addition, lactate generated with hypoxia competes with the excretion of urate at the proximal tubule, resulting in a decrease in urate clearance [51]. Polycythemia may also result in increased uric acid levels due to increased cell turnover [52].

In a small clinical study that was conducted in Peru, it was found that uric acid levels tended to increase with rising hematocrit and were significantly greater in subjects with CMS compared with those living at the sea level. Moreover, subjects living at high altitude had a low fractional excretion of uric acid in spite of the high serum levels of uric acid [53]. A large population-based epidemiological 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 [36]. The higher prevalence of hyperuricemia was associated with both the presence of microalbuminuria and systemic hypertension. The most striking finding was a marked increased prevalence of albuminuria (16.2%) and hypertension (38%), both of which were strongly associated with hyperuricemia (29%) and elevated hematocrit. However, reduced GFR (defined as eGFR < 60 mL/min/1.73 m^2) was observed in only 2% of these subjects [36]. Multivariate analysis showed that hyperuricemia, polycythemia and hypertension were independent predictors of albuminuria. These findings expand upon the laboratory finding that experimental hyperuricemia can induce systemic and glomerular hypertension and microalbuminuria in animals [54].

Microalbuminuria and proteinuria

An increased prevalence of proteinuria has been reported in subjects living at high altitude [55]. A population-based epidemiological study from Tibet found the prevalence of microalbuminuria to be 16.2% and an increasing prevalence of proteinuria with higher hematocrit values [36]. In one study, 6 out of 27 (22%) CMS patients had proteinuria >1 g/24 h [53]. The pathogenesis of the proteinuria may relate to a variety of factors, including the effects of tissue hypoxia within the kidney parenchyma, glomerular capillary hypertension, hyperviscosity and elevated right heart pressures.

Glomerular hypertrophy

Subjects living at high altitude are known to develop large glomeruli. One study reported the presence of larger glomeruli in children living at high altitude compared with those living at the sea level [56]. The mechanism is uncertain, but could relate to the effects of low birth weight at altitude (mainly secondary to placental insufficiency due to chronic hypoxia) which has been shown to cause low nephron number [57]. Hyperuricemia has also been reported to induce glomerular hypertrophy in experimental animals [58], likely mediated in part by the activation of the renin–angiotensin system and the induction of glomerular hypertension [58, 59].

Effect of altitude on dosing and response to EPO in end-stage renal disease

Tissue hypoxia, as may result from high altitude living or anemia, has a strong influence in many of the biologic pathways involved in erythropoiesis. Through activation of HIF, hypoxia increases EPO expression and regulates iron metabolism to alter iron availability [17–20]. Patients with chronic kidney disease (CKD) remain able to mount an EPO response, even with brief hypoxic exposure [60]. End-stage renal disease (ESRD) subjects living at high altitude may produce more EPO and have better response to endogenous and exogenous EPO. Altitude-induced hypoxia is associated with reduced EPO requirements in a subset of patients on hemodialysis who had treatment-refractory anemia [61]. Hypoxia is also believed to affect the dose–response relationship of EPO. A large retrospective cohort study of ESRD patients found that the population living at high altitude (>6000 feet) required smaller dose of EPO (19% less, 12.9 versus 15.9 thousand units/week) and yet maintained higher hematocrit (1.1 points) levels. The study also noted that resistance to EPO decreased with increasing elevation [62].

Summary

Subjects living at high altitude represent a special group that should be of interest to nephrologists. Living chronically under hypoxic conditions can be associated with both beneficial and detrimental effects on health. Some populations have developed protective mechanisms, especially for the Amhara people of Ethiopia and Tibetans of the Himalayas. However, the Andean population is particularly susceptible to the deleterious effects of chronic hypoxia, likely because the Andean people have lived there for <10 000 years, and also because of environmental exposure to cobalt from the local mines.

The primary health benefits of living at high altitude appear to relate to reduced frequencies of obesity, diabetes and coronary heart disease, which might relate to both the effects of high altitude and differences in diet. However, the dark side of high altitude is the increased frequency of systemic and pulmonary hypertension, and the potential consequences of HARS. Further studies examining the mechanisms driving HARS may help our understanding of not only its cause, but may provide insights into the renal adaptive and maladaptive responses to a hypoxic environment.

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References

1. Moore LG. Human genetic adaptation to high altitude. *High Alt Med Biol* 2001; 2: 257–279
2. Beall CM. Andean, Tibetan, and Ethiopian patterns of adaptation to high-altitude hypoxia. *Integr Comp Biol* 2006; 46: 18–24
3. Beall CM, Decker MJ, Brittenham GM *et al*. An Ethiopian pattern of human adaptation to high-altitude hypoxia. *Proc Natl Acad Sci USA* 2002; 99: 17215–8
4. Beall CM. Two routes to functional adaptation: Tibetan and Andean high altitude natives. *Proc Natl Acad Sci USA* 2007; 104(Suppl. 1): 8655–8660
5. Monge CC, Arregui A, León-Velarde F. Pathophysiology and epidemiology of chronic mountain sickness. *Int J Sports Med* 1992; 13: S79–S81
6. Jefferson JA, Escudero E, Hurtado ME *et al*. Excessive erythrocytosis, chronic mountain sickness, and serum cobalt levels. *Lancet* 2002; 359: 407–408
7. Picon-Reategui E. Basal metabolic rate and body composition at high altitudes. *J Appl Physiol* 1961; 16: 431–434
8. Beall CM, Brittenham GM, Strohl KP *et al*. Hemoglobin concentration of high-altitude Tibetans and Bolivian Aymara. *Am J Physiol Anthropol* 1997; 104: 427–447
9. Beall CM. Adaptations to altitude: a current assessment. *Annu Rev Anthropol* 2001; 30: 423–456
10. Winslow RM, Chapman KW, Gibson CC *et al*. Different hematologic responses to hypoxia in Sherpas and Quechua Indians. *J Appl Physiol* 1989; 66: 1561–1569
11. Beall CM, Brittenham GM, Strohl KP *et al*. Hemoglobin concentration of high-altitude Tibetans and Bolivian Aymara. *Am J Phys Anthropol* 1998; 106: 385–400
12. Groves BM, Droma T, Sutton JR *et al*. Minimal hypoxic pulmonary hypertension in normal Tibetans at 3,658 m. *J Appl Physiol* 1993; 74: 312–318
13. Penaloza D, Arias-Stella J. The heart and pulmonary circulation at high altitudes: healthy highlanders and chronic mountain sickness. *Circulation* 2007; 115: 1132–1146
14. Hoit BD, Dalton ND, Erzurum SC, Laskowski D, Strohl KP, Beall CM. Nitric oxide and cardiopulmonary hemodynamics in Tibetan highlanders. *J Appl Physiol* 2005; 99: 1796–1801
15. Angelo M, Singel DJ, Stamler JS. An S-nitrosothiol (SNO) synthase function of hemoglobin that utilizes nitrite as a substrate. *Proc Natl Acad Sci USA* 2006; 103: 8366–8371
16. Janocha AJ, Koch CD, Tiso M *et al*. Nitric oxide during altitude acclimatization. *N Engl J Med* 2011; 365: 1942–1944
17. Hoppeler H, Vogt M, Weibel ER, Flück M. Response of skeletal muscle mitochondria to hypoxia. *Exp Physiol* 2003; 88: 109–119
18. Scheinfeldt LB, Soi S, Thompson S *et al*. Genetic adaptation to high altitude in the Ethiopian highlands. *Genome Biol* 2012; 13: R1
19. Perocchi F, Gohil VM, Girgis HS *et al*. MICU1 encodes a mitochondrial EF hand protein requires for Ca^{2+} uptake. *Nature* 2010; 467: 291–296
20. Zeng L, Sachdev P, Yan L *et al*. Vav3 mediates receptor protein tyrosine kinase signaling, regulates GTPase activity, modulates cell morphology, and induces cell transformation. *Mol Cell Biol* 2000*;* 20: 9212–9224
21. Semenza GL. HIF-1: mediator of physiological and pathophysiological responses to hypoxia. *J Appl Physiol* 2000; 88: 1474–1480
22. Beall CM, Cavalleri GL, Deng L *et al*. Natural selection on EPAS1 (HIF2alpha) associated with low hemoglobin concentration in Tibetan highlanders. *Proc Natl Acad Sci USA* 2010; 107: 11459–11464
23. Simonson TS, Yang Y, Huff CD *et al*. Genetic evidence for high-altitude adaptation in Tibet. *Science* 2010; 329: 72–75
24. Yi X, Liang Y, Huerta-Sanchez E *et al*. Sequencing of 50 human exomes reveals adaptation to high altitude. *Science* 2010; 329: 75–78
25. Xu S, Li S, Yang Y *et al*. A genome-wide search for signals of high altitude adaptation in Tibetans. *Mol Biol Evol* 2011; 28: 1003–1011
26. Bigham AW, Bauchet M, Pinto D *et al*. Identifying signatures of natural selection in Tibetan and Andean populations using dense genomes scan data. *PLoS Genet* 2010; 6: e1001116
27. Mejía OM, Prchal JT, León-Velarde F *et al*. Genetic association analysis of chronic mountain sickness in an Andean high-altitude population. *Haematologica* 2005; 90: 13–19

28. Bigham AW, Mao X, Mei R *et al*. Identifying positive selection candidate loci for high-altitude adaptation in Andean population. *Hum Genomics* 2009; 4: 79–90
29. Naeije R. Physiological adaptation of the cardiovascular system to high altitude. *Prog Cardiovasc Dis* 2010; 52: 456–466
30. Moret PR. Coronary blood flow and myocardial metabolism in man at high altitude. In: Porter R, Knight J (eds). *High Altitude Physiology Cardiac and Respiratory Aspects, A Ciba Foundation Symposium*. London: Churchill Livingstone, 1971, pp. 131–144
31. Hochachka PW, Clark CM, Holden JE *et al*. 31P magnetic resonance spectroscopy of the Sherpa heart: a phosphocreatine/adenosine triphosphate signature of metabolic defense against hypobaric hypoxia. *Proc Natl Acad Sci USA* 1996; 93: 1215–1220
32. Lenfant C, Torrance J, English E *et al*. Effect of altitude on oxygen binding by hemoglobin and on organic phosphate levels. *J Clin Invest* 1968; 47: 2652–2656
33. Ruiz L, Penaloza D. Altitude and hypertension. *Mayo Clin Proc* 1977; 52: 442–445
34. Sun SF. Epidemiology of hypertension on the Tibetan Plateau. *Hum Biol* 1986; 58: 507–515
35. Zhao X, Li S, Ba S *et al*. Prevalence, awareness, treatment, and control of hypertension among herdsmen living at 4,300 m in Tibet. *Am J Hypertens* 2012; 25: 583–589
36. Chen W, Liu Q, Wang H *et al*. Prevalence and risk factors of chronic kidney disease: a population study in the Tibetan population. *Nephrol Dial Transplant* 2011; 26: 1592–1599
37. Hurtado A. Animals in high altitude: resident man. In: *Handbook of Physiology: Adaptation to the Environment*. Washington, DC: American Physiological Society, 1964, pp. 843–860
38. Mortimer EA, Jr, Monson RR, MacMahon B. Reduction in mortality from coronary heart disease in men residing at high altitude. *N Engl J Med* 1977; 296: 581–585
39. Baibas N, Trichopoulou A, Voridis E *et al*. Residence in mountainous compared with lowland areas in relation to total and coronary mortality. A study in rural Greece. *J Epidemiol Community Health* 2005; 59: 274–278
40. Faeh D, Gutzwiller F, Bopp M; Swiss National Cohort Study Group. Lower mortality from coronary heart disease and stroke at higher altitudes in Switzerland. *Circulation* 2009; 120: 495–501
41. Ezzati M, Horwitz ME, Thomas DS *et al*. Altitude, life expectancy and mortality from ischaemic heart disease, stroke, COPD and cancers: national population-based analysis of US counties. *J Epidemiol Community Health* 2012; 66: e17
42. Sasaki H, Fukuda S, Otani H *et al*. Hypoxic preconditioning triggers myocardial angiogenesis: a novel approach to enhance contractile functional reserve in rat with myocardial infarction. *J Mol Cell Cardiol* 2002; 34: 335–348
43. Arias Stella J, Topilsky M. Anatomy of the coronary circulation at high altitude. In: Porter R, Knight J (eds). *High Altitude Physiology: Cardiac and Respiratory Aspects, A Ciba Foundation Symposium*. London: Churchill Livingstone, 1971, pp. 149–154
44. Rakusan K, Cicutti N, Kolar F. Cardiac function, microvascular structure, and capillary hematocrit in hearts of polycythemic rats. *Am J Physiol Heart Circ Physiol* 2001; 281: H2425–H2431
45. Luks AM, Johnson RJ, Swenson ER. Chronic kidney disease at high altitude. *J Am Soc Nephrol* 2008; 19: 2262–2271
46. Arestegui AH, Fuquay R, Sirota J *et al*. High altitude renal syndrome (HARS). *J Am Soc Nephrol* 2011; 22: 1963–1968
47. Becker EL, Schilling JA, Harvey RB. Renal function in man acclimatized to high altitude. *J Appl Physiol* 1957; 10: 79–80
48. Lozano R, Monge C. Renal function in high-altitude natives and in natives with chronic mountain sickness. *J Appl Physiol* 1965; 20: 1026–1027
49. Schoutsen B, De Jong JW, Harmsen E *et al*. Myocardial xanthine oxidase/dehydrogenase. *Biochim Biophys Acta* 1983; 762: 519–524
50. Hare JM, Johnson RJ. Uric acid predicts clinical outcomes in heart failure: insights regarding the role of xanthine oxidase and uric acid in disease pathophysiology. *Circulation* 2003; 107: 1951–1953
51. Johnson RJ, Kang DH, Feig D *et al*. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension* 2003; 41: 1183–1190
52. Denman M, Szur L, Ansell BM. Hyperuricaemia in polycythaemia vera. *Ann Rheum Dis* 1966; 25: 340–344
53. Jefferson JA, Escudero E, Hurtado ME *et al*. Hyperuricemia, hypertension, and proteinuria associated with high-altitude polycythemia. *Am J Kidney Dis* 2002; 39: 1135–1142
54. Sanchez-Lozada LG, Tapia E, Avila-Casado C *et al*. Mild hyperuricemia induces glomerular hypertension in normal rats. *Am J Physiol Renal Physiol* 2002; 283: F1105–F1110
55. Rennie D, Marticorena E, Monge C *et al*. Urinary protein excretion in high-altitude residents. *J Appl Physiol* 1971; 31: 257–259
56. Naeye RL. Children at high altitude: pulmonary and renal abnormalities. *Circ Res* 1965; 16: 33–38
57. Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure. Less of one, more the other? *Am J Hypertens* 1988; 1: 335–347
58. Nakagawa T, Mazzali M, Kang DH *et al*. Hyperuricemia causes glomerular hypertrophy in the rat. *Am J Nephrol* 2003; 23: 2–7
59. Mazzali M, Kanellis J, Han L *et al*. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. *Am J Physiol Renal Physiol* 2002; 282: F991–F997
60. Bosman DR, Osborne CA, Marsden JT *et al*. Erythropoietin response to hypoxia in patients with diabetic autonomic neuropathy and non-diabetic chronic renal failure. *Diabet Med* 2002; 19: 65–69
61. Brookhart MA, Bradbury BD, Avorn J *et al*. The effect of altitude change on anemia treatment response in hemodialysis patients. *Am J Epidemiol* 2011; 173: 768–777
62. Brookhart MA, Schneeweiss S, Avorn J *et al*. The effect of altitude on dosing and response to erythropoietin in ESRD. *J Am Soc Nephrol* 2008; 19: 1389–1395

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