AMERICAN JOURNAL OF HUMAN BIOLOGY 25:151–168 (2013)

Review Article

Developmental Functional Adaptation to High Altitude: Review

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Various approaches have been used to understand the origins of the functional traits that characterize the Andean high-altitude native. Based on the conceptual framework of developmental functional adaptation which postulates that environmental influences during the period of growth and development have long lasting effects that may be expressed during adulthood**,** we initiated a series of studies addressed at determining the pattern of physical growth and the contribution of growth and development to the attainment of full functional adaptation to high-altitude of low and high altitude natives living under rural and urban conditions. Current research indicate that: (a) the pattern of growth at high altitude due to limited nutritional resources, physical growth in body size is delayed but growth in lung volumes is accelerated because of hypoxic stress); (b) low-altitude male and female urban natives can attain a full functional adaptation to high altitude by exposure to high-altitude hypoxia during the period of growth and development; (c) both experimental studies on animals and comparative human studies indicate that exposure to high altitude during the period of growth and development results in the attainment of a large residual lung volume; (d) this developmentally acquired enlarged residual lung volume and its associated increase in alveolar area when combined with the increased tissue capillarization and moderate increase in red blood cells and hemoglobin concentration contributes to the successful functional adaptation of the Andean high-altitude native to hypoxia; and (e) any specific genetic traits that are related to the successful functional adaptation of Andean high-altitude natives have yet to be identified. Am. J. Hum. Biol. 25:151–168, 2013. © 2013 Wiley Periodicals, Inc.

In 1912, Franz Boas, and others at later dates (Boas, 1912; Greulich, 1957; Hulse, 1960), demonstrated that local environmental conditions were able to modify the morphological phenotype and produce continuous variation. However, the prevailing goal in human physiology was to determine the biological/physiological features that could be used to place humans into taxonomic groups. For example, studies of thermoregulation led physiologists to classify the patterns of human adaptation to cold into three categories: *hypothermic*, *mesothermic*, and *hyperthermic* (Elsner et al., 1960; Hammel, 1963). These investigators proposed that the thermal adaptation to cold of the South American Andean natives was characterized as being mesothermic (Elsner et al., 1960; Hammel, 1963). In 1962, Baker and his family and three graduate students went to Perú to determine the extent to which the adaptation to cold of the South American Andeans natives was mesothermic. To test this hypothesis, Baker (1966) and his students conducted an experimental study of the thermoregulatory responses to cold stress of Andean natives and nonnatives. The protocol included exposure for 2 h to a temperature of 10°C and 14°C of Andean natives and nonnatives in the town of Chinchero situated at 3,500 m altitude and about 30 km north of the city of Cuzco. These investigations revealed that native Andean populations when tested under cold stress maintained high internal temperature and warm skin temperature. Hence, the Andean natives living under chronic cold stress did not fall into the hypothermic category. In fact, if they were to be classified, their response would have corresponded more closely to the hyperthermic category. The results of this study were reported at the Wenner-Gren Foundation conference in 1964 (Baker and Weiner, 1966). Furthermore, this field research revealed that the greater stress on populations living at high altitude was not low temperatures but rather the stress of low oxygen availability.

Peruvian biomedical scientists in the Central highlands of Perú demonstrated that the Andean high-altitude native, despite the hypoxic stress, is able to attain a functional adaptation comparable to that of lowland populations at low altitude. Since these studies were limited to individual samples of workers in the mining centers, they did not allow full understanding of the adaptation of Andean natives to the high-altitude environment. For this reason, Paul T. Baker realized that, to understand fully the adaptation of Andean natives to the high-altitude environment, a holistic approach was required that included evaluation of the physiological traits of children and adults within an ecological context. To achieve this goal, it was decided that a study population was needed that lived at high altitude and was relatively isolated. With this objective in mind, a research assistant (ARF) contacted a high school classmate (Victor Barreda) who came from the town of Nuñoa situated at 4,250 m above sea level and about 200 km south of Cuzco on the *altiplano*. Then, in May of 1962, Baker, along with Dr. Manuel Chavez Ballon, a Professor of Archeology from the University of Cuzco, and the two Peruvians (ARF and Victor Barreda), made a trip to Nuñoa. It was during this trip that Baker decided Nuñoa was an ideal site for future high-altitude research. Based on his 1962 experiences, Baker, along with Ellsworth Buskirk of the Department of Kinesiology at the Pennsylvania State University, developed the research program on biocultural adaptation to the high-altitude environment. The goals of the project were to: (a) determine the biocultural mechanisms of adaptation of high-altitude populations living under conditions of chronic cold stress and (b) determine the biological processes whereby sea level and high-altitude populations adapt to the chronic stress of altitude hypoxia.

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Accepted 26 November 2012
DOI: 10.1002/ajhb.22367
Published online 5 February 2013 in Wiley Online Library (wileyonlinelibrary.com).

In this article, I first summarize the fundamental processes of O_2 transport, lung function, and physiological responses presented by life at high altitude. Then, I review the various adaptive mechanisms that enable both lowland and highland natives to overcome the hypoxic stress of high altitudes and to attain physiological homeostasis under the conditions of altitude hypoxia. In doing so, I will summarize some of the studies conducted among high-altitude native and nonnative populations living the central and southern Andean regions of Perú and La Paz, Bolivia that led to advancement of the concept of developmental adaptation to account for observed population differences in functional adaptation to high altitude.

THE NATURE OF HYPOXIC STRESS

Historic background of high-altitude hypoxic stress

During their conquest of the Incas, the Spaniards were the first to notice that high-altitude environments could have adverse effects on the normal functioning of people accustomed to living at low altitudes (Kellogg, 1968). In 1590, the chronicler Jose de Acosta, in his *Historia Natural y Moral de las Indias*, gave the first clear description of mountain sickness experienced by lowland natives sojourning at high altitudes (de Acosta, 1590). Three centuries later, Jourdanet (1861) and Bert (1878) began their scientific observations of the effects on man of high altitudes and low barometric pressures. Since then, the study of the mechanisms whereby humans adapt to the pervasive effects of high-altitude hypoxia has been a major concern of both biological and social scientists. There is little doubt that man can adapt to oxygen-impoverished environments—witness the large number of populations living at high altitudes. In becoming so adapted, humans and other organisms develop a variety of coordinated mechanisms that have been investigated intensively in recent decades, both at high altitudes and in low-pressure chambers. Before I describe the various adaptive mechanisms that enable both lowland and highland natives to overcome the stress associated with the high-altitude environment, it is necessary first to evaluate the characteristics of hypoxic stress.

The low pressure of oxygen

The biological problem of adaptation to high-altitude hypoxia depends mainly upon the partial pressure of oxygen in the atmosphere, which decreases proportionately with an increase in altitude. Oxygen reaches cells through the combined functions of the respiratory, cardiovascular, and hematological systems that facilitate passage of gas molecules from the atmosphere to the tissues. When the tissues receive insufficient oxygen, a physiological condition called "hypoxia" develops. Hypoxia can be produced by any physiological, pathological, or environmental condition that interferes with the oxygen supply to the tissues. For example, certain defects in the cardiopulmonary system can produce the condition known as anemic hypoxia. Hypoxia can also be produced by atmospheric conditions, for example, contamination of the air with carbon monoxide or other gas that displace oxygen or by normal depletion of oxygen in the atmosphere such as that occurs at high altitudes.

The amount of oxygen in the atmosphere, 20.93%, remains constant up to an altitude of 110,000 m. However, because air is compressible, the number of gaseous molecules it contains is greater at low altitudes than at high altitudes and the barometric pressure, which depends upon the molecular concentration of the air, thus also decreases with an increase in altitude. This is the fundamental problem of high-altitude hypoxia: the oxygen in the air at high altitudes is less concentrated and, consequently, is at a lower pressure than it is at low altitudes. At sea level, the barometric pressure is 760 mm Hg and the partial pressure of oxygen (pO_2) is 159 mm Hg (at 20.93%). At 3,500 m (11,840 ft), the barometric pressure is reduced to 493 mm Hg and the pO_2 is 103 mm Hg; that is, at an altitude of 3,500 m, the oxygen has about 35% less pressure than at sea level. At 4,500 m, the pO_2 is decreased by as much as 40% (to 91 mm Hg) with respect to the pO_2 at sea level (see Fig. 1). Because of this decrease in pO_2 in the ambient air, the pO_2 of the air reaching the trachea and the alveoli of the lungs is also reduced, and this, in turn, reduces the amount of oxygen that is available to the tissues. The decrease in pO_2 at high altitudes causes a reduction in the oxygen saturation of the arterial blood because the proportion of oxyhemoglobin formed depends on the pO_2 in the air reaching the alveoli. Thus, if the pO_2 of the ambient air is 159 mm Hg and in the alveoli it is 104 mm Hg, as it is at sea level, the hemoglobin in the arterial blood is 97% saturated with oxygen. On the other hand, if the pO_2 of the ambient air is 110 mm Hg and in the alveoli it is 67 mm Hg, as occurs at an altitude of 3,000 m (9,840 ft), the hemoglobin in the arterial blood is only 90% saturated. This means that at an altitude of 3,000 m, there is a decrease of 10% of oxygen for each unit of blood that leaves the lungs. Between an altitude of 4,000 and 5,000 m, this decrease can reach as high as 30%.

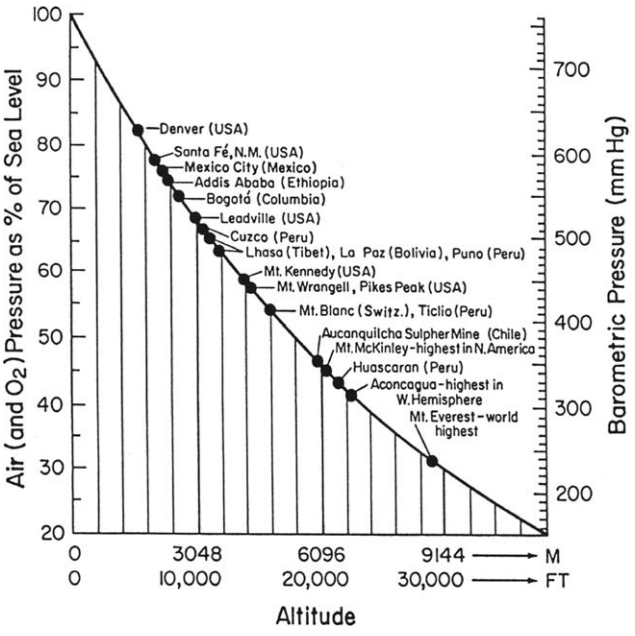

Fig. 1. Barometric pressure and oxygen pressure at high altitudes. With an increase in altitude, there is a percentage decrease in the air and oxygen pressure. (From Frisancho AR, Human adaptation and accommodation, 1993, © University of Michigan Press, reproduced by permission.)

Symptoms of high-altitude hypoxia

When there is a lack of biological adjustment to altitude-induced hypoxia, symptoms of high-altitude sickness may occur, to include shortness of breath, respiratory distress, physical and mental fatigue, rapid pulse rate, interrupted sleep, and headaches that are intensified by physical activity. There may also occur some digestive disorders and in some cases a marked loss of weight over days or weeks. In other cases, the individual may experience dyspnea, nausea, and vomiting. In very rare cases, at altitudes above 4,500 m, a diminution of visual acuteness, painful menstruation, and bleeding of the gums will occur. While some individuals appear to be predisposed to high-altitude sickness, others may feel only mild effects that can be overcome with acclimatization. Among those individuals who appear to be predisposed to mountain sickness, some may lack the ability to become acclimatized and may develop chronic mountain sickness (Monge and Monge, 1966; Rahn and Otis, 1949).

The effects of high-altitude hypoxia also depend on physical and biological factors. Some physiological effects may be evident at 1,500 m (4,920 ft). Under rest conditions at this altitude, there may not be any effects; but during physical activity, hypoxia effects may become evident. Between 2,000 and 3,000 m (6,500–9,840 ft), the effects of hypoxia are felt during both rest and physical activity. Above 3,000 m, the physiological effects become increasingly evident and unavoidable, and the physiological limits of human tolerance to high-altitude hypoxia appear to be reached at 8,545 m (33,000 ft).

ADAPTIVE PATHWAYS

The various adaptive mechanisms triggered by exposure to high altitudes are directed toward increasing the availability of oxygen and increasing the pressure of oxygen at the tissue level. This is accomplished through modifications in (a) pulmonary ventilation, (b) lung volume and pulmonary diffusing capacity, (c) transportation of oxygen in the blood, (d) diffusion of oxygen from blood to tissues, and (e) utilization of oxygen at the tissue level (see Fig. 2).

Pulmonary ventilation

Upon exposure to high-altitude hypoxia or within 3 to 4 days after ascent to high altitude, lowland natives show, both at rest and during exercise, a progressive increase in pulmonary ventilation that reaches as much as 100% of sea level values (Chiodi, 1957; Rahn and Otis, 1949; Reeves et al., 1967; Severinghaus et al., 1966; Torrance et al., 1970-1971). Such hyperventilation is both adaptive and nonadaptive. It is adaptive because there are increases in pO_2 at the alveolar and arterial levels and consequent increases in the diffusion gradient between the blood and the tissues (Severinghaus et al., 1966; Torrance et al., 1970-1971). It is nonadaptive because the enhanced ventilation decreases the partial pressure of carbon dioxide (pCO_2) at the alveolar level and, if this is not compensated for, it may change the pH of the blood from a normal pH (7.4) to an alkaline one (pH > 7.4) and result in alkalosis. Such alkalosis is prevented by active and rapid removal of bicarbonate from the cerebrospinal fluid (Lenfant and Sullivan, 1971) and the blood. This mechanism, which lowers the pH of medullary chemoreceptors in relation to any given pCO_2, resets the level at which the arterial pCO_2 is regulated by changing the relationship between pCO_2 and response of the medullary chemoreceptors pH. In this manner, the original homeokinetic relationship between pH of the cerebrospinal fluid and the blood is restored to sea level values. It is maintenance of this equilibrium that enables the lowland native to sustain increased ventilation at high altitude without risks of alkalosis or hypocapnia.

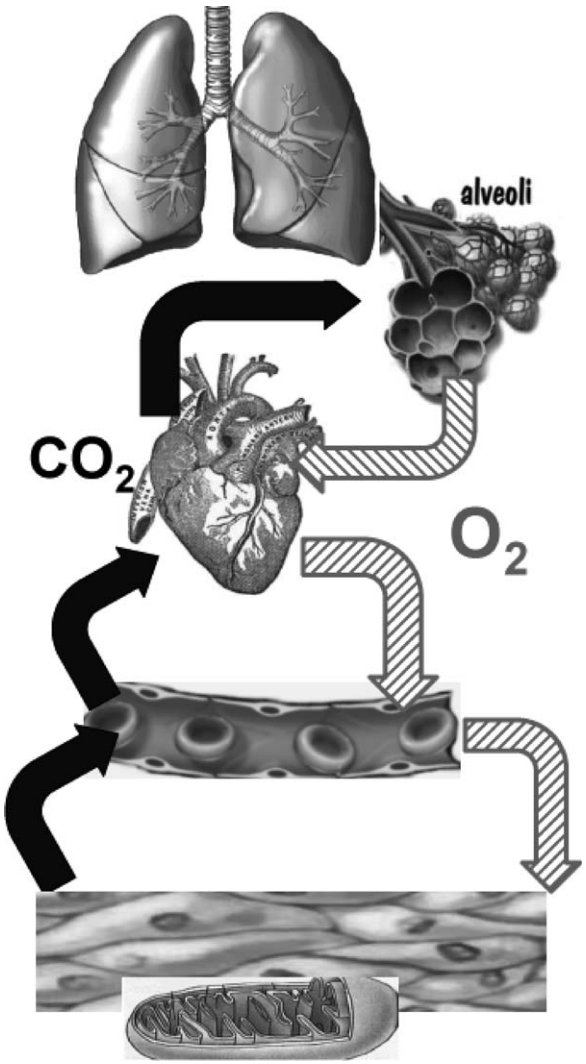

Fig. 2. Functional pathways of oxygen transport. At sea level, the delivery of oxygen from the ambient air to the cell is dependent upon the synchronized action of the respiratory, cardiovascular systems, and biochemical processes, all of which are accentuated upon exposure to high-altitude hypoxia and differs between individuals and populations. (Composite made by the author.)

In general, in both lowland and highland natives, the magnitude of the increase in pulmonary ventilation during exercise is directly proportional to the increase in altitude (Lenfant and Sullivan, 1971). However, at a given altitude, as shown in Figure 3**,** pulmonary ventilation of the lowland native (sojourning on a short-term or long-term basis at high altitudes) is invariably higher than that of the high-altitude native (Beall et al., 1997; Brutsaert et al., 2005; Frisancho et al., 1999; Hurtado, 1964).

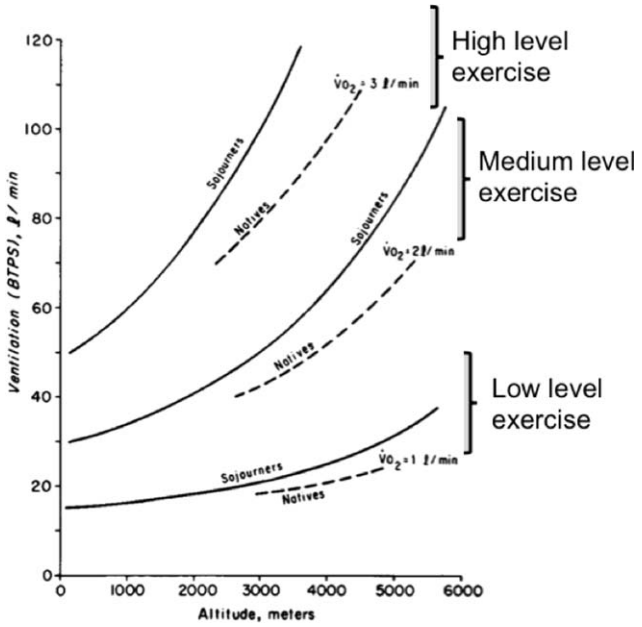

Fig. 3. Pulmonary ventilation in relation to altitude in lowland and highland natives as a function of altitude and measured at three levels of exercise. (VO_2, maximum volume of oxygen consumed.) (Modified from Lenfant C, Sullivan KN, Engl J Med, 1971, 284, 1298–1309, reproduced by permission.)

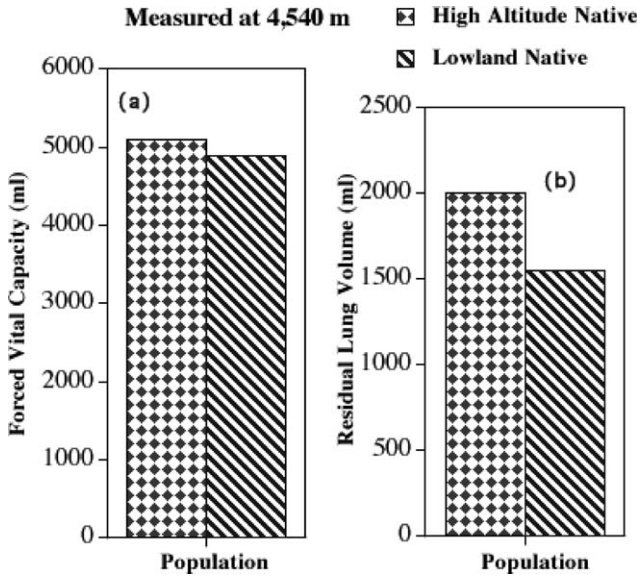

Fig. 4. Lung volume of high-altitude Andean natives. High-altitude natives differ from their low altitude counter parts by their enlarged residual lung volume. (Data from Hurtado A, Animals in high altitudes: resident man. In: Dill DB, Adolph EF, Wilber CG, editors. Handbook of physiology, vol. 4. Adaptation to the environment, 1964, ©American Physiological Society, reproduced by permission.)

Thus, acclimatization to high altitude in the lowland native is unquestionably associated with an increase in pulmonary ventilation. In the highland native, however, acclimatization to high altitude is accompanied by a smaller increase in pulmonary ventilation. Since the increase in pulmonary ventilation permits the newcomer to maintain an increase in pO_2 at the alveolar level and an increase in arterial oxygen saturation (Lenfant and Sullivan, 1971), it would appear that a hyperventilatory response is critical to the acclimatization of the newcomer. After acclimatization occurs, however, the increase in pulmonary ventilation reaches a plateau, probably reflecting the operation of other adaptive mechanisms.

Lung volume and pulmonary diffusing capacity

Upon initial exposure to high-altitude hypoxia, the volume of air exhaled after a forceful inspiration [referred to as the forced vital capacity (FVC) of the lung volume] of lowland natives is reduced. However, after about 1 month of residency at high altitudes, such subjects attain values, which are comparable to those they had at low altitudes (Frisancho et al., 1997; Hurtado, 1964). The oxygen pulmonary diffusing capacity of lowland natives remains unchanged at high altitudes when compared to the capacity attained at sea level (DeGraff et al., 1970; Kreuzer and van Lookeren Campagne, 1965). In contrast, highland natives have a larger lung volume (Fig. 4), and especially a larger residual lung volume (volume of air remaining in lungs after maximum expiration), than subjects from low altitudes, when adjustments are made for differences in body size (Frisancho et al., 1973a,b,1997; Hurtado, 1964). During childhood at low altitudes, growth in lung volume is associated with the proliferation of alveolar units and the consequent increase in alveolar surface area (Davies and Reid, 1970; Dunnill, 1962); among children raised at high altitudes, the rapid growth in lung volume is probably also associated with these factors. As a consequence of the increased alveolar formation, the pulmonary diffusing capacity of the highland native is systematically greater than that attained by lowland natives at low altitudes and those acclimatized to high altitudes (Cerny et al., 1973; DeGraff et al., 1970; Dempsey et al., 1971; Hurtado, 1964; Schoene et al., 1990; Vincent et al., 1978; Vargas et al., 1982; Wagner et al., 2002).

In summary, studies at sea level indicate that the increase in airspace volume is paralleled by an increase in capillary volume and the pulmonary diffusing capacity is related in part to the alveolar surface area. Therefore, the enhanced pulmonary diffusing capacity of the highland native is probably due to his having a greater residual lung volume and increased alveolar area and capillary volume.

Transport of oxygen in the blood

The major function of the hemoglobin in the red blood cells (RBCs) is to transport oxygen from the lungs to the tissues (see Fig. 2). At high altitudes, in response to the insufficient amounts of oxygen, the bone marrow is stimulated by an erythropoietic factor to increase the production of RBCs (Reynafarje et al., 1964). For this reason, at altitudes above 4,000 m, both lowland and highland natives have normal RBC counts ranging from 5 to 8 million per cubic millimeter compared to 4.5 million at low altitudes (Hurtado, 1964; Merino, 1950). Along with the increase in the RBCs, the hemoglobin is augmented so that, at high altitudes, the averages range from 17 to 20 g/100 ml compared to the 12 to 16 g/100 ml at sea level (Hurtado, 1964; Merino, 1950) (Fig. 5). However, nonmining Andean high-altitude populations are characterized by a moderate increase in RBC and hemoglobin

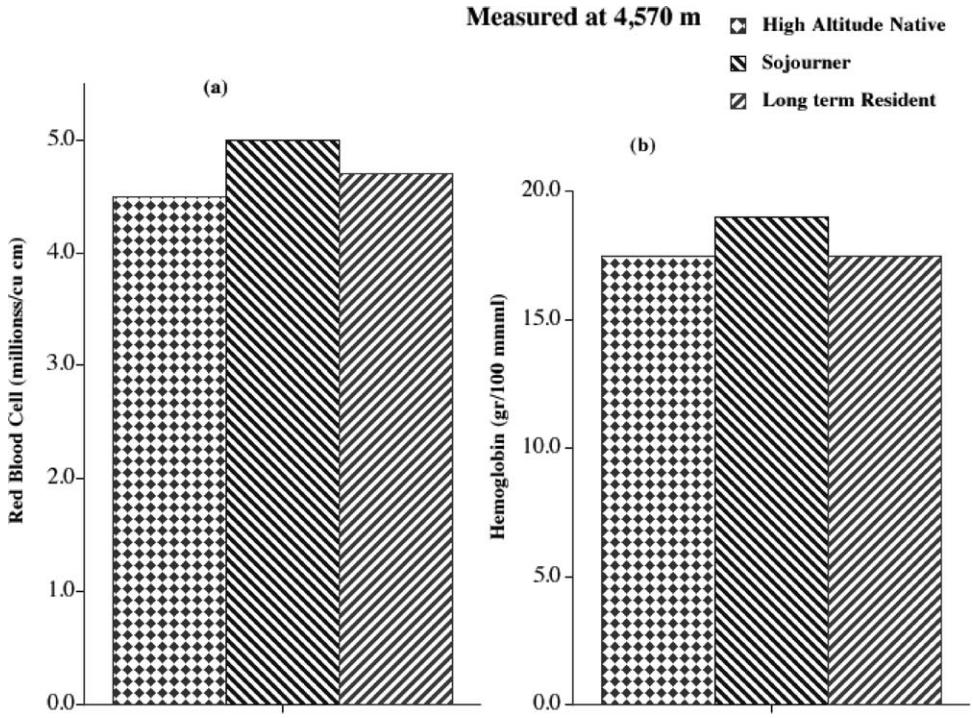

Fig. 5. Increase in red blood cell and hemoglobin concentration at high altitude. In response to the insufficient amounts of oxygen, the bone marrow is stimulated by an erythropoietic factor to increase the production of red blood cells (a) and hemoglobin concentration (b). This increase is greater in the sojourner and long-term resident than in the high-altitude natives. (Data from Hurtado A, Animals in high altitudes: resident man. In: Dill DB, Adolph EF, Wilber CG, editors. Handbook of physiology, vol. 4. Adaptation to the environment, 1964, © American Physiological Society, reproduced by permission.)

concentration that is about 10% greater than sea level norms (Frisancho, 1988; Garruto and Dutt, 1983). In this manner, in the Andean high-altitude native, without increasing blood viscosity and vascular resistance, the oxygen-carrying capacity of the blood and tissue oxygenation is increased (Calbet et al., 2002).

Diffusion of oxygen from blood to tissues

For the oxygen to be utilized, it must reach the cell mitochondria through a process of physical diffusion, and the rate of such diffusion depends on the pO_2. Because the oxygen is consumed as it goes through successive tissue layers, the pO_2 rapidly declines, and the more distance the oxygen has to travel, the greater the drop in the pO_2. At high altitude, where the pO_2 of the ambient air is already low, the organism must respond by shortening the distance the oxygen has to travel. This is accomplished by the opening up of existing and new capillaries. Through microscopic studies of experimental animals, it has been found that the number of open muscle capillaries at high altitudes is increased by more than 40% compared to the number at low altitudes (Mathieu-Costello, 2001). A very important effect of the increased capillary bed is that it increases the blood perfusion and, thus, oxygen is more readily diffused per unit time into tissue despite the lowered oxygen tension of the blood before it reaches the capillaries (Guleria et al., 1971). Since, among highland natives, the muscle myoglobin concentration is also increased (Reynafarje, 1962), this, coupled with the increased capillarization and pulmonary angiogenesis (de Bisschop et al., 2010) must certainly enhance the diffusion of oxygen at high altitudes.

Right shift in the dissociation curve for oxygen and hemoglobin

Another mechanism, which at high altitudes facilitates the diffusion of oxygen from the blood to the tissues, is that shown by a rightward shift in the dissociation curve for oxygen and hemoglobin (Lenfant et al., 1968; Torrance et al., 1970-1971). This shift results from a decrease in the hemoglobin affinity for oxygen. This decrease appears to be related to an increase in intraerythrocytic 2,3-diphosphoglycerate (Lenfant et al., 1968; Moore et al., 1972; Torrance et al., 1970-1971). At a given pO_2, the percentage of oxygen in the hemoglobin of venous blood is significantly lower at high altitudes than at sea level. Because of this difference, among lowland and highland natives, the proportion of the available oxygen that is delivered to the tissues is greater at high than at low altitudes (Moore et al., 1972; Torrance et al., 1970-1971). However, the relative effectiveness of this mechanism is not yet well defined.

Utilization of oxygen

The last step in the process of adaptation to hypoxia involves variations in the rate of oxygen utilization and generation of energy at the cellular level. On the basis of studies on guinea pigs, it has been postulated that, at high altitudes, glycolysis (anaerobic) proceeds by way of the pentose phosphate pathway rather than the Embden-Meyerhof pathway (Reynafarje, 1966). The advantage of the pentose pathway appears to be related to the fact that

no additional adenosine triphosphate is required to generate glyceraldehyde triphosphate as is necessary in the Embden-Meyerhof pathway. According to this mechanism, at high altitudes, by relying on the pentose phosphate pathway, the organism saves energy (adenosine triphosphate) or produces more chemical energy with the same oxygen consumption (Reynafarje, 1966). This finding supports the hypothesis that the activity of oxidative enzymes in the Sartorius muscles is greater at high altitudes than at sea level (Reynafarje, 1966). For example, in homogenates of whole cells, the reduced diphosphopyridine nucleotide-oxidase system, the reduced triphosphopyridine nucleotide-cytochrome c reductase, and the transhydrogenase are significantly more active in the highland than in the lowland native (Reynafarje, 1966). Thus, it appears that, among highland natives, the chemical and morphological characteristics related to energy utilization and energy production are qualitatively and quantitatively different from those of lowland natives. It is not known whether lowland natives residing for long periods at high altitudes may acquire such characteristics.

Cardiovascular traits

Pulmonary circulation. Histological studies have demonstrated that, after the first month of postnatal development, children born at high altitudes show a thickening of the muscular layer and muscularization of the pulmonary arteries and arterioles that resembles the development of the fetal pulmonary vascular tree (Peñaloza et al., 2008). These characteristics contribute to the increased pulmonary vascular resistance or pulmonary hypertension in the high-altitude resident and native (Huicho, 2007; Peñaloza and Arias-Stella, 2007; Peñaloza et al., 2008). Based on studies of steers, the hypothesis has been proposed that pulmonary hypertension at high altitudes would favor a more effective perfusion of all the pulmonary areas and, therefore, increase the effective blood–gas interfacial area of the alveoli (Grover et al., 1963). In this manner, perfusion of the entire lung coupled with an increased vascularization would enhance the diffusing capacity of the lung and should decrease the difference between the arterial and the alveolar blood. These changes would permit a more effective oxygenation of the arterial blood. However, one cannot assume that pulmonary hypertension would necessarily decrease the arterial-alveolar gradient in man, and the application of this hypothesis to the adaptation of human beings at high altitudes remains to be proven (Sylvester, 2012).

Right ventricle of the heart. As result of the increased pulmonary resistance or hypertension, the right ventricle of the heart of the high-altitude resident and native is enlarged as shown by anatomical and electro- and cardiologic studies (Peñaloza et al., 1963). The enlargement of the right ventricle may also be related to the high prevalence of patent ductus arteriosus among highland natives (Peñaloza et al., 1963). Hence, because of the pressure differential between the aorta and pulmonary artery, the work of the right ventricle of the heart may be increased. The high incidence of patent ductus arteriosus may be a consequence of fetal and newborn hypoxia and may also be one of the sources of the pulmonary hypertension. Lowland natives with patent ductus arteriosus also commonly suffer from right ventricular hypertrophy and pulmonary stenosis. Although pulmonary hypertension and right ventricular hypertrophy may occur at all ages in both highland and lowland subjects in their native environments, these characteristics are accentuated among subjects exposed to insufficient supplies of oxygen during childhood and adolescence (Huicho, 2007; Peñaloza and Arias-Stella, 2007; Peñaloza et al., 2008; Sime et al., 1963). These findings demonstrate the influence of developmental factors in the acquisition of the cardiovascular characteristics of highland dwellers.

Cardiac output. Upon initial exposure to high-altitude hypoxia, the resting pulse rate of the lowland native increases rapidly from an average of 70 beats/min to as much as 105 beats/min. This increase is associated both with a generalized increase in sympathetic activity and with an abrupt augmentation of the resting cardiac output (Klastersky, 1972; Vogel et al., 1974). With acclimatization, the cardiac output declines so that, in about a week, it equals or is below that attained at sea level (Klastersky, 1972; Moret et al., 1972; Vogel et al., 1974). This decline in cardiac output appears to be associated with a decrease in heart rate, which usually remains above sea level values (Klastersky, 1972; Moret et al., 1972; Vogel et al., 1974). The cardiac output of highland natives during rest and exercise was found to be equal to that of lowland natives at sea level (Klastersky, 1972; Moret et al., 1972; Vogel et al., 1974). Therefore, the oxygen requirements of the body appear to be met by greater oxygen extraction rather than greater blood flow at high altitude.

Systemic circulation. Various studies indicate that the systemic blood pressure in adult highland natives is lower than that is in the lowland natives at sea level (Hooper and Mellor, 2011; Richalet, 2012). Among highland natives, the frequency of systemic hypertension and ischemic heart disease is also significantly lower than among lowland natives at sea level, as well as a lowering of 10 mm Hg or more in systolic and diastolic pressures in lowland subjects who resided for a long time (2–15 years) at high altitude (Marticorena et al., 1969). Furthermore, Marticorena et al. (1969) found a lowering of 10 mm Hg or more in systolic and diastolic pressures in lowland subjects who resided for a long time (2–15 years) at high altitude.

The etiology of these differences has not been completely determined. Because exposure to high altitudes results in increased vascularization, it is possible that the prevalence of low blood pressure at high altitude may be related to the reduction in peripheral vascular resistance to blood flow. In other words, lowering of blood pressure may be considered a by-product of tissue adaptation to high-altitude hypoxia.

Work capacity

During severe exercise, the metabolic requirements for oxygen increase drastically so that all the processes involved in the transport, delivery, and utilization of oxygen are required to work at their maximum. For this reason, the effects of high-altitude hypoxia are most evident

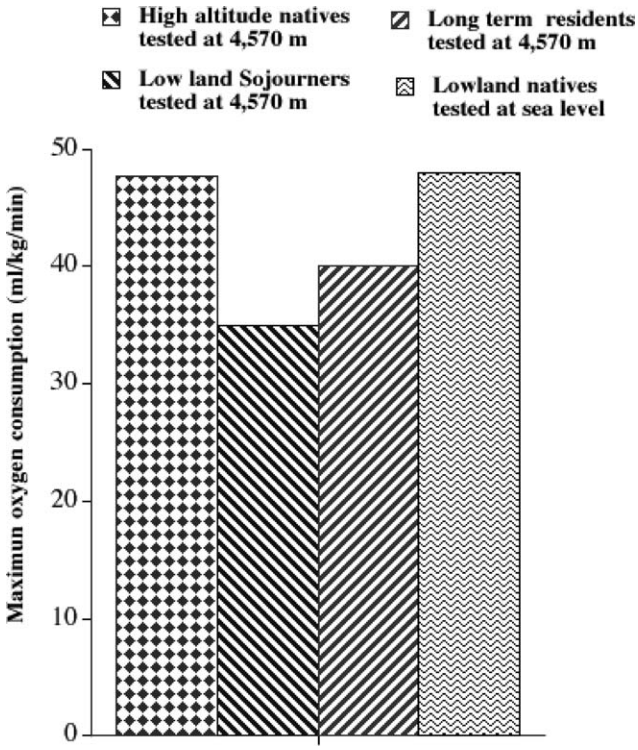

Fig. 6. Maximum aerobic capacity measured by the maximum amount of oxygen consumption at high altitude. Highland natives despite the low oxygen pressure attain similar aerobic capacity as lowland natives tested at sea level. In contrast, sojourners and long-term residents at high altitude exhibit a reduction of about 20% to 10% of aerobic capacity, respectively. (Data from Hurtado A, Animals in high altitudes: resident man. In: Dill DB, Adolph EF, Wilber CG, editors. Handbook of physiology, vol. 4. Adaptation to the environment, 1964, ©American Physiological Society, reproduced by permission.)

during periods of high levels of physical activity. Measurements of an individual's work capacity indicate the degree of success of the various adaptive responses made by the organism. It is generally agreed that the maximum oxygen intake per unit of body weight (or aerobic capacity) during maximal physical activity is a measure of the individual's work capacity because it reflects the capacity of the working muscles to utilize oxygen and the ability of the cardiovascular system to transport and deliver oxygen to the tissues. Studies of newcomers to high altitude demonstrated a reduction in aerobic capacity of from 13% to 22% (Grover et al., 1967). The aerobic capacity of fit lowland natives at high altitudes, when expressed as a percentage of the values obtained at sea level, declines by 3.2% for every 300 m (1,000 ft) ascended beyond 1,500 m (Buskirk et al., 1976; Kollias et al, 1968). In contrast, the aerobic capacity of highland natives (Fig. 6) is comparable to that attained by lowland natives at sea level (Baker, 1976; Elsner et al., 1964; Frisancho et al., 1973a, 1995; Hurtado, 1964; Mazess, 1969; Velasquez and Reynafarje, 1966; Way, 1976).

DEVELOPMENTAL FUNCTIONAL ADAPTATION

Conceptual Framework

The conceptual framework of developmental functional adaptation is that environmental influences during the period of growth and development have long lasting effects that may be expressed during adulthood. This hypothesis is based upon research that indicates that exposure to environmental stress will have its greatest long-term impact during a sensitive period of development when the organism may be the most vulnerable. Hence, the respective contribution of genetic and environmental factors on the expression of adult functional traits varies with the developmental stage of the organism, and in general, the earlier the age, the greater the influence of the environment. Previous studies indicated that Andean high-altitude natives despite the hypoxic environment are able to attain a full functional adaptation that is comparable to that reached by lowland natives at sea level. Furthermore, Andean high-altitude natives have a larger residual lung volume than low-altitude natives. Because oxygen is required for all physiological processes, I postulated that exposure to high-altitude hypoxia during the period of growth and development would have an effect on the expression of adult functional traits of populations that live at high altitude (Frisancho, 1970, 1975). To test this hypothesis, my associates and I conducted a series of investigations that included studies of: (a) growth and development of the population of Nuñoa in Southern Perú who lived between 4,150 m (13,615 ft) and 4,350 m (14,270 ft) of altitude, (b) the functional traits at high altitude in Southern Perú; and (c) the functional traits at high altitude in La Paz, Bolivia.

Pattern of growth at high altitude in Nuñoa-Puno in Southern Perú

Starting in 1964 and during 3 consecutive years, we conducted both a cross-sectional and semilongitudinal study of growth and development of a sample of 1,202 Quechua natives, aged 2 to 35 years living between 13,615 ft (4,150 m) and 14,270 ft (4,350 m) in the district of Nuñoa, Department of Puno, in the southern highlands of Perú. As summarized in Figure 7, the pattern of growth in body size and lung volume of high-altitude natives is different from those observed at sea level. At high altitudes, growth in body size and maturation is delayed and extended into the early twenties when compared to growth of low-altitude populations**.** This delayed growth is related to the combined stress of high-altitude hypoxia and limited nutritional resources (Dittmar, 1997; Frisancho and Baker, 1970; Gonzales et al., 1996; Greksa, 1988; Leonard, 1989; Pawson et al., 2001; Stinson, 1982). In contrast, the pattern of growth in lung volume and chest dimensions in high-altitude residents is more accelerated than in low-altitude populations (de Meer et al., 1995; Frisancho, 1969; Hurtado, 1932). The accelerated growth of the lungs and chest size reflect a developmental compensatory response to high-altitude hypoxia.

In summary, the pattern of growth and development at high altitude is different from that at low altitude. Given the high-energy requirements for maintaining an accelerated growth in both physical dimensions and lung volumes, the delayed growth in body size is a biological trade-off that facilitates the accelerated growth of the respiratory system that is critical for survival at high altitude. These findings provide further support for the hypothesis that growth and development at high altitude elicits strong cardiovascular responses, which in turn, contribute to the attainment of full functional adaptation to the high-altitude hypoxic environment. Continuing this

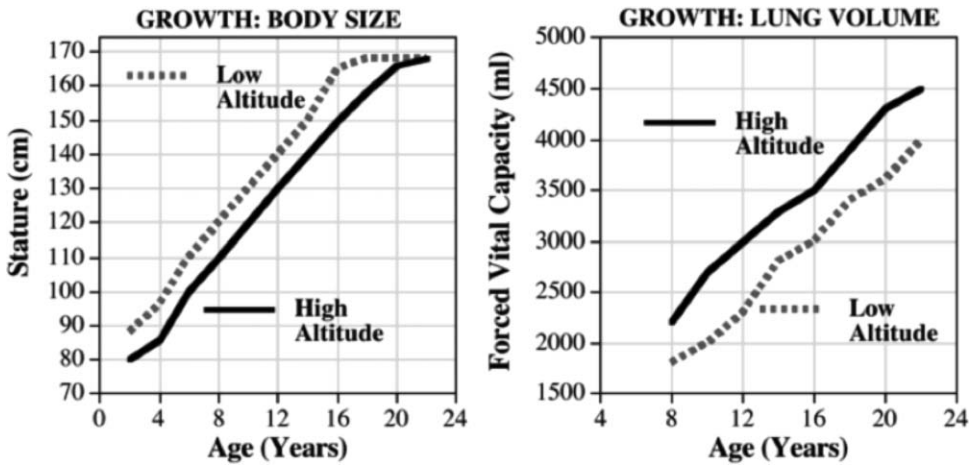

Fig. 7. Allometric growth on body size and lung volumes at high altitude. Growth in body size at high altitude is delayed while growth in lung volumes is accelerated. (Data from Frisancho and Baker, 1970; Frisancho, 1969, reproduced by permission.)

TABLE 1. Comparison of forced vital capacity (ml) and residual lung volume (ml) adjusted for age, weight, and height of subjects measured at 3,400 m and 3,840 m in Cusco, Southern Perú[a]

Forced vital capacity (ml) measured at 3,400 m		
20	Peruvian highland native	4,990.3 ± 128.6
21	Peruvian acclimatized during growth	5,055.0 ± 121.5
	Significance	NS
10	US subjects acclimatized as adults	4,573.9 ± 231.6
	Significance	$P < 0.02$
Forced vital capacity (ml) measured at 3,840 m		
40	Peruvian highland native	4,830.3 ± 69.9
13	Peruvian acclimatized as adults	4,504.6 ± 122.1
	Significance	$P < 0.02$
Residual lung volume (ml) measured at 3,840 m		
36	Peruvian highland native	1,585.1 ± 56.5
Residual lung volume (ml) measured at sea level		
69	US adults	1,301.0 ± 34.8
	Significance	$P < 0.001$

Values are means ± standard errors.
[a]Adapted from Frisancho et al. (1973b).

research direction, I developed two research projects one: in Cuzco, Perú, and one in La Paz, Bolivia. Both were addressed to studying the functional adaptation of lowland natives to high altitude.

Functional adaptation of lowland natives to high altitude in Southern Perú

In 1972–1973, my associates and I conducted a series of studies on lung function and aerobic capacity in the Cities of Cuzco situated at a mean altitude of 3,400 m) and Puno located at an average altitude of 3,850 m in Southern Perú (Frisancho et al, 1973a,b). The goals of the study were to determine:

a. If low-altitude urban natives who were acclimatized to high altitude during growth and development attained full functional adaptation to high altitude that is comparable to that of high-altitude natives.
b. If low-altitude urban natives who were acclimatized to high altitude during adulthood attained full functional adaptation to high altitude that is comparable to that of high-altitude natives.

With this purpose in mind, we studied the lung volumes and aerobic capacity in participants who had the following characteristics: (1) high-altitude adult Peruvian natives (born and raised at high altitude (above 3,400 m and 3,840 m), (2) lowland Peruvian natives who migrated, lived, and were acclimatized to high altitude (above 3,400 m) since childhood; (3) lowland Peruvian natives who migrated, lived, and were acclimatized to high altitude (above 3,400 m) as adults; and (4) lowland U.S. natives who migrated, lived and were acclimatized to high altitude (above 3,400 m) as adults. The results of these studies are summarized in Tables 1 and 2. The findings given Table 1 indicate that Peruvian sea level natives raised at high altitude since childhood attained a FVC similar to high-altitude natives, but Peruvian and U.S. sea level adult natives who migrated as adults and resided at high altitude for as long as 2 years attained a lower FVC than high-altitude natives. The residual lung volume of highland natives living above 3,840 m is significantly higher than the values obtained at sea level. Likewise, Table 2 shows that Peruvian sea level natives acclimatized at high altitude since childhood attained an aerobic capacity similar to high-altitude natives, but Peruvian and U.S. sea level adult natives who migrated as adults and resided at high altitude for as long as 2 years attained a lower aerobic capacity than high-altitude natives. Furthermore, the ventilation equivalent (given by the ratio of maximum pulmonary ventilation to maximum O_2 consumed) of the Peruvian sea level natives raised at high altitude since childhood is similar to the highland natives but significantly lower than the Peruvian and U.S. sea level adult natives who migrated as adults and resided at high altitude for as long as 2 years.

In summary, these findings supported the hypothesis that the relatively high aerobic capacity and large lung volume of the high-altitude Peruvian native is the result of a developmental adaptation to altitude hypoxia (Frisancho, 1975). However, since among the Peruvian population there has been a great deal of admixture, an enduring question is the extent to which non-Andeans can attain full functional adaptation to high altitude.

TABLE 2. Comparison of aerobic capacity of Peruvian and US subjects during work on a bicycle ergometer tested at an altitude of 3,400 m in Cusco, Southern Perú[a]

Peruvian Highland native, $N = 20$	Peruvian acclimatized young, $N = 23$	Peruvian acclimatized as adults, $N = 10$	US subjects acclimatized as adults, $N = 10$
Maximum volume of O_2 consumed (ml kg/min)			
46.3 ± 5.0	46.0 ± 6.3	38.0[b] ± 5.2	38.5[b] ± 5.8
51.2 ± 5.8[c]	50.1 ± 5.4[c]	42.3[b] ± 5.0[c]	41.6[b] ± 5.61[c]
Maximum pulmonary ventilation (l/min)[d]			
138.5 ± 22.4	139.7 ± 17.9	165.0[b] ± 17.2	175.3[b] ± 25.5
Ratio of maximum pulmonary ventilation to maximum O_2 consumed			
51.3 ± 6.5	50.7 ± 5.4	64.4[b] ± 7.2	75.5 ± 7.9
Maximum heart rate (beat/min)			
196.1 ± 6.6	193.2 ± 6.5	192.6[b] ± 6.0	187.2[b] ± 7.9
Volume of O_2 consumed per heart beat (ml/beat)			
13.9 ± 1.8	14.4 ± 1.7	11.1 ± 0.6	14.6 ± 2.4[d]

Values are means ± standard errors.
[a]Adapted from Frisancho et al. (1973a).
[b]Significantly different from highland native at $P < 0.01$ level.
[c]Related to fat-free weight.
[d]Corrected for body temperature and pressure, saturated (BTPS).

TABLE 3. Aerobic capacity of male high-altitude rural natives (HARN), high-altitude urban natives (HAUN), Bolivians of foreign ancestry acclimatized to high altitude since birth (AHAB), Bolivians of foreign ancestry acclimatized to high altitude during growth (AHAG), and foreigners acclimatized to high altitude during adulthood (AHAA) studied at 3,750 m in La Paz, Bolivia[a]

Variables *N*	High-altitude rural native (HARN), mean ± SE 39	High-altitude urban native (HAUN), mean ± SE 32	Acclimatized since birth (AHAB), mean ± SE 33	Acclimatized during growth (AHAG), mean ± SE 25	Acclimatized during adulthood (AHAA), mean ± SE 15
SaO_2 (%)	91.00 ± 0.24	90.10 ± 0.34	88.38 ± 0.50[b]	88.44 ± 0.52[b]	88.88 ± 0.65[b]
Heart rate (beats/min)	167.28 ± 2.16	183.59 ± 1.83[b]	179.76 ± 1.96[b]	178.84 ± 2.96[b]	171.75 ± 2.61[b]
VE_{BTPS} (l/min)	119.35 ± 3.10	122.65 ± 3.26	122.26 ± 4.62	123.93 ± 3.50	132.29 ± 6.05[b]
$\dot{V}O_{2STPD}$ (l/min)	2.81 ± 0.05	2.39 ± 0.05[b]	2.49 ± 0.08[b]	2.73 ± 0.06	2.55 ± 0.12[b]
$\dot{V}O_{2STPD}$ (ml/min/kg)	48.24 ± 0.95	40.00 ± 0.75[b]	40.43 ± 0.83[b]	42.95 ± 1.21[b]	36.69 ± 1.54[b]
$\dot{V}O_{2STPD}$ (ml/min/kg-LBM)	56.21 ± 1.11	48.92 ± 0.90[b]	48.63 ± 1.04[b]	52.90 ± 1.26	44.97 ± 1.62[b]
$\dot{V}CO_{2STPD}$ (l/min)	2.81 ± 0.09	2.73 ± 0.06	2.82 ± 0.09	2.87 ± 0.09	2.75 ± 0.13
$\dot{V}CO_2$ (ml/min/kg)	48.10 ± 1.29	45.64 ± 1.02	45.58 ± 1.00	45.06 ± 1.52	39.80 ± 2.22[b]
RQ	1.01 ± 0.03	1.14 ± 0.02[b]	1.13 ± 0.02[b]	1.05 ± 0.03	1.10 ± 0.04[b]
VE_{BTPS}/VO_2	42.81 ± 1.17	49.81 ± 1.23[b]	49.49 ± 1.39[b]	45.57 ± 1.17	52.78 ± 1.81[b]
VO_2/HR (beats/min)	16.88 ± 0.37	13.04 ± 0.32[b]	13.90 ± 0.51[b]	15.39 ± 0.46[b]	15.17 ± 0.81[b]

[a]Adapted from Frisancho et al. (1995).
[b]Significantly ($P < 0.05$) different from HARN.

Functional adaptation of lowland natives to high altitude in La Paz, Bolivia.

From 1993–1997, to determine if low-altitude urban natives of non-Andean ancestry of both genders can attain full adaptation to high altitude, my associates and I studied functional adaptation of samples of the population that differed in their length of residence at high altitude. This research was conducted in La Paz, Bolivia (mean altitude, 3,750 m) on subjects of different ethnic composition (Frisancho et al., 1995, 1997). The criteria for defining functional adaptation were based on measurements of aerobic capacity and lung function. The research strategy was to evaluate participants belonging to five population groups: (1) high-altitude rural male natives (HARNs); (2) high-altitude urban natives (HAUNs); (3) Bolivians of foreign ancestry acclimatized to high altitude since birth (AHAB); (4) Bolivians of foreign ancestry acclimatized to high altitude during growth (AHAG); and (5) foreigners acclimatized to high altitude during adulthood (AHAA).

Aerobic capacity. Tables 3 and 4 and Figure 8 summarize the results of these studies. From these data, three observations are evident. First, in rural males, using as reference either weight or lean body mass, those acclimatized to high altitude since birth or during growth attained similar values of aerobic capacity as that of HAUNs. However, those acclimatized to high altitude during adulthood had a significantly lower aerobic capacity than all other population groups. On the other hand, the HARNs had a significantly higher aerobic capacity than all the other samples. In females, Table 4 shows that those acclimatized to high altitude since birth or during growth attained similar values of aerobic capacity as did HAUNs, but the samples acclimatized to high altitude during adulthood had significantly lower aerobic capacity than all the samples. Second, the ventilation equivalent (given by the ratio of maximum pulmonary ventilation to maximum O_2 consumed or $\dot{V}E_{BTPS}/\dot{V}O_2$) of the non-Bolivians acclimatized to high altitude during adulthood was significantly higher than the other population groups. This indicates that the population groups acclimatized to high altitude since birth, during growth, or the HAUNs each extract more oxygen with lower pulmonary ventilation than those acclimatized during adulthood. The present findings suggest that the hypoventilation that characterizes the Andean high-altitude native can, to a certain extent, be acquired during growth and development at high altitude.

TABLE 4. Aerobic capacity of female high-altitude urban natives (HAUN), Bolivians of foreign ancestry acclimatized to high altitude since birth (AHAB), Bolivians of foreign ancestry acclimatized to high altitude during growth (AHAG), and foreigners acclimatized to high altitude during adulthood (AHAA) studied at 3,750 m in La Paz, Bolivia[a]

Variables *N*	High-altitude rural native (HARN), mean ± SE 36	High-altitude urban native (HAUN), mean ± SE 25	Acclimatized since birth (AHAB), mean ± SE 24	Acclimatized during growth (AHAG), mean ± SE 18
SaO_2 (%)	90.97 ± 0.42	89.94 ± 0.62	89.68 ± 0.70	88.78 ±0.76[b]
Heart rate (beats/min)	173.74 ± 2.62	179.25 ± 2.34	172.28 ± 2.93	164.39 ± 3.34[b]
VE_{BTPS} (l/min)	78.75 ± 2.55	77.92 ± 2.87	83.78 ± 2.68	88.86 ± 5.88[b]
$\dot{V}O_{2STPD}$ (l/min)	1.66 ± 0.06	1.60 ± 0.06	1.78 ± 0.07	1.60 ± 0.08
$\dot{V}O_{2STPD}$ (ml/min/kg)	30.60 ± 1.04	30.15 ± 0.94	31.68 ± 1.09	27.53 ± 0.93
$\dot{V}O_{2STPD}$ (ml/min/kg-LBM)	41.98 ± 1.34	41.69 ± 1.19	41.82 ± 1.32	35.66 ± 1.12[c]
$\dot{V}CO_{2STPD}$ (l/min)	1.87 ± 0.05	1.76 ± 0.07	1.93 ± 0.09	1.66 ± 0.09
$\dot{V}CO_2$ (ml/min/kg)	34.45 ± 0.99	33.36 ± 1.05	34.33 ± 1.45	28.67 ± 1.34[c]
RQ	1.13 ± 0.02	1.11 ± 0.01	1.08 ± 0.02	1.04 ± 0.04[b]
VE_{BTPS}/VO_2	48.14 ± 1.37	49.55 ± 1.55	47.71 ± 1.42	55.99 ± 3.16[b]
VO_2/HR (beats/min)	9.63 ± 0.37	8.97 ± 0.40	10.49 ± 0.52	9.80 ± 0.56

[a]Adapted from Frisancho et al. (1995a).
[b]Significantly ($P < 0.05$) different from HAUN.
[c]Significantly ($P < 0.01$) different from HAUN.

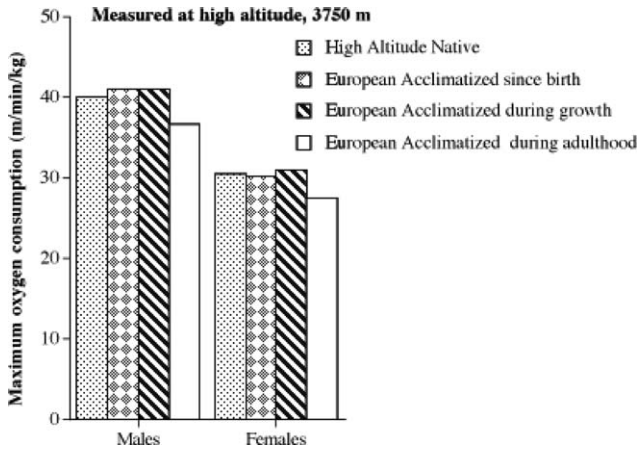

Fig. 8. Developmental adaptation and the attainment of full functional adaptation at high altitude. In both males and females, Europeans who were born or migrated to high altitude during growth had an aerobic capacity similar to that of the high-altitude native. (Adapted from Frisancho et al., 1995.)

Aerobic Capacity and Occupational Activity. Tables 5 and 6 compare the aerobic capacity by occupational activity level for males and females. These data show that, in both males and females, there is a direct relationship between occupational activity level and aerobic capacity so that the higher the occupational activity level, the *higher* is the aerobic capacity.

Developmental Response and Occupational Activity.

Table 7 presents the aerobic capacity of Bolivians of foreign ancestry acclimatized to high altitude before the age of 9 years versus those who were acclimatized after the age of 10 years from the same (high) occupational activity level. These data show that the individuals who maintained a high occupational activity level had a higher aerobic capacity if they were acclimatized to high altitude before the age of 9 years than if they had been acclimatized after the age of 10. That is, maintaining a high level of occupational activity does not overcame the effect of arriving to high altitude after the age of 10 years. In other words, if the activity level is the same, the effect of growth and development at high altitude are clearly expressed in higher levels of aerobic capacity.

In summary, these findings support the hypothesis that exposure to high altitude since birth or during growth contributes to the attainment of high aerobic capacity. Variability in aerobic capacity is highly related to differences in occupation activity level, but maintaining a high level of occupational activity does not fully modify the expression of developmental adaptation.

Lung volumes. Table 8 and Figure 9 present age-adjusted means and standard errors for vital capacity and residual and total lung volume for males and females expressed as milliliter per square meter of body surface area. From these data, the following points are evident. The vital capacity among AHAB, AHAG, HAUN, and AHAA are quite similar. The AHAB and AHAG attained similar residual lung volumes as that of HAUN but lower than that of HARN. In contrast, residual lung volumes of AHAA are significantly ($P < 0.05$) lower than residual volumes of all other groups. The HARNs have significantly higher values for FVC than all other groups, but the residual lung volume is similar to the groups acclimatized since birth (AHAB) or during growth (AHAG). Among females, the only noticeable difference is a lower residual lung volume of AHAA when compared to HAUN. The findings suggest that, in males, the large residual lung volume is, to a large extent, the result of developmental acclimatization to high altitude (Frisancho and Greksa, 1989; Frisancho et al., 1973b).

Lung Volumes and Occupational Activity. Tables 9 and 10 show that, in both male and females, differences in levels of occupational activity in all samples influence the attainment of FVC, so that higher the occupational activity level, higher the FVC level. On the other hand, the residual lung volume in both sexes and in all five groups does not appear to be related to occupational activity level. These findings suggest that, to some extent, variability in occupational activity has a greater influence on the attainment of vital capacity than of residual lung

TABLE 5. Aerobic capacity by occupational activity level among five male samples studied at 3,750 m in La Paz, Bolivia[a]

Occupational activity level	High-altitude rural native (HARN), mean ± SE, $N = 39$	High-altitude urban native (HAUN), mean ± SE, $N = 32$	Acclimatized since birth (AHAB), mean ± SE, $N = 33$	Acclimatized during growth (AHAG), mean ± SE, $N = 25$	Acclimatized during adulthood (AHAA), mean ± SE, $N = 25$
$\dot{V}O_{2STPD}$ (l/min)					
Low	–	2.01 ± 0.09	2.25 ± 0.12	2.73 ± 0.07	1.85 ± 0.25
Medium	2.63 ± 0.12	2.39 ± 0.05	2.47 ± 0.10	2.88 ± 0.17	2.55 ± 0.10
High	2.86 ± 0.06	2.67 ± 0.09	2.78 ± 0.16	2.68 ± 0.07	3.01 ± 0.15
Significance	$P < 0.05$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$
$\dot{V}O_{2STPD}$ (ml/min/kg)					
Low	32.41 ± 1.49	34.31 ± 0.65	37.48 ± 1.81	25.38 ± 2.37	
Medium	41.88 ± 0.80	39.68 ± 0.41	40.09 ± 0.49	38.23 ± 1.76	37.32 ± 0.79
High	50.14 ± 0.97	46.59 ± 0.83	47.26 ± 0.87	45.30 ± 1.35	43.53 ± 0.31
Significance	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$
$\dot{V}O_{2STPD}$ (ml/min/kg-LBM)					
Low	40.18 ± 1.24	42.24 ± 1.10	47.91 ± 1.44	35.70 ± 3.96	
Medium	48.70 ± 1.23	48.36 ± 0.65	49.21 ± 1.22	50.24 ± 2.93	44.95 ± 1.07
High	58.46 ± 1.11	56.28 ± 1.47	53.81 ± 1.74	54.56 ± 1.50	51.17 ± 1.07
Significance	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$

[a]Adapted from Frisancho et al. (1995).

TABLE 6. Aerobic capacity by occupational activity level among four female samples studied at 3,750 m in La Paz, Bolivia[a]

Occupational activity level	High-altitude rural natives (HARN), mean ± SE, $N = 36$	Acclimatized since birth (AHAB), mean ± SE, $N = 32$	Acclimatized during growth (AHAG), mean ± SE, $N = 24$	Acclimatized during adulthood (AHAA), mean ± SE, $N = 18$
$\dot{V}O_{2STPD}$ (l/min)				
Low	1.45 ± 0.07	1.39 ± 0.04	1.56 ± 0.06	1.16 ± 0.14
Medium	1.64 ± 0.06	1.54 ± 0.03	1.74 ± 0.10	1.59 ± 0.12
High	1.96 ± 0.17	2.00 ± 0.21	1.86 ± 0.10	1.75 ± 0.09
Significance	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$
$\dot{V}O_{2STPD}$ (ml/min/kg)				
Low	24.12 ± 0.85	25.30 ± 0.47	26.92 ± 1.50	21.57 ± 2.04
Medium	30.71 ± 0.52	29.21 ± 0.40	30.69 ± 1.16	26.38 ± 0.25
High	38.45 ± 2.08	38.53 ± 1.51	33.38 ± 1.89	30.29 ± 0.87
Significance	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$
$\dot{V}O_{2STPD}$ (ml/min/kg-LBM)				
Low	35.65 ± 1.68	36.59 ± 1.33	37.87 ± 0.15	28.25 ± 2.61
Medium	42.37 ± 1.22	41.04 ± 1.20	39.31 ± 1.66	34.73 ± 0.94
High	49.07 ± 3.47	49.72 ± 2.33	44.78 ± 2.02	38.75 ± 0.92
Significance	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$

[a]Adapted from Frisancho et al. (1995).

TABLE 7. Developmental response inferred from comparison of aerobic capacity of Bolivians of foreign ancestry acclimatized to high altitude before the age of 9 years and those who were acclimatized after the age of 10 years from the same (high) occupational activity level studied at 3,750 m in La Paz, Bolivia[a]

Males			Females		
Age (years) of arrival to high altitude	N	Mean ± SE	Age (years) of arrival to high altitude	N	Mean ± SE
$\dot{V}O_2$ (l/min)					
2–9	7	2.91 ± 0.10[b]	1–9	7	2.01 ± 0.13[b]
10–16	10	2.52 ± 0.03	10–14	5	1.65 ± 0.14
$\dot{V}O_2$ (ml/min/kg)					
2–9	7	49.04 ± 2.17[b]	1–9	7	36.83 ± 2.24[b]
10–16	10	42.69 ± 1.22	10–14	5	28.55 ± 1.75
$\dot{V}O_2$ (ml/min/kg)					
2–9	7	60.19 ± 1.11[b]	1–9	7	48.85 ± 2.33[b]
10–16	10	50.61 ± 1.41	10–14	5	39.09 ± 1.25

[a]Adapted from Frisancho et al. (1995).
[b]$P < 0.01$.

volume. In other words, once the residual lung volume is established, it is probably not easily modified by activity levels.

In summary, these findings support the hypothesis that exposure to high altitude since birth or during development contributes to the attainment of a large residual lung volume. Accordingly, it is postulated that the enlarged residual lung volume of the high-altitude native must have been acquired during the period of growth and development at high altitude and is not the result of high

TABLE 8. Lung volumes of high-altitude rural natives (HARN), high-altitude urban natives (HAUN), Bolivians of foreign ancestry acclimatized to high altitude since birth (AHAB), Bolivians of foreign ancestry acclimatized to high altitude during growth (AHAG), and foreigners acclimatized to high altitude during adulthood (AHAA) studied at 3,750 m in La Paz, Bolivia[a]

Variables	High-altitude rural native (HARN), mean ± SE	High-altitude urban native (HAUN), mean ± SE	Acclimatized since birth (AHAB), mean ± SE	Acclimatized during growth (AHAG), mean ± SE	Acclimatized during adulthood (AHAA), mean ± SE
Males					
N	36	69	45	30	23
VC/SA (ml/m^2)	3,348.3 ± 57.1	3,056.2 ± 38.0[b]	2,981.1 ± 46.1[b]	2,984.6 ± 56.1[b]	2,988.4 ± 65.7[b]
RV/SA (ml/m^2)	1,095.1 ± 41.6	1,030.4 ± 27.7	1,004.6 ± 33.6	989.61 ± 40.9	884.0 ± 47.9[b]
TLV/SA (ml/m^2)	4,443.4 ± 83.7	4,086.6 ± 55.7[b]	3,985.7 ± 67.6[b]	3,974.2 ± 82.3[b]	3,872.5 ± 96.4[b]
RV/TLV (%)	24.5 ± 0.7	25.0 ± 0.1	24.9 ± 0.5	24.9 ± 0.7	22.9 ± 0.8[d]
Females					
N		56	40	33	23
VC/SA (ml/m^2)		2,560.7 ± 31.6	2,507.7 ± 38.1	2,458.1± 41.4	2,492.5 ± 56.2
RV/SA (ml/m^2)		850.8 ± 18.3	844.2 ± 22.2	873.8 ± 24.1	800.1 ± 32.7[e]
TLV/SA (ml/m^2)		3,411.5 ± 41.5	3,351.8 ± 50.2	3,331.9 ± 54.5	3,292.3 ± 74.0
RV/TLV (%)		24.9 ± 0.4	25.3 ± 0.5	26.12 ± 0.5	24.3 ± 0.7

[a]Adapted from Frisancho et al. (1995).
[b]Significantly different from HARN ($P < 0.01$).
[c]Significantly different from HARN, HAUN, AHAB and AHAG ($P < 0.05$).
[d]Significantly different from HARN, AHAB, and AHAG ($P < 0.05$).
[e]Significantly different from HAUN, AHAB, and AHAG ($P < 0.05$).

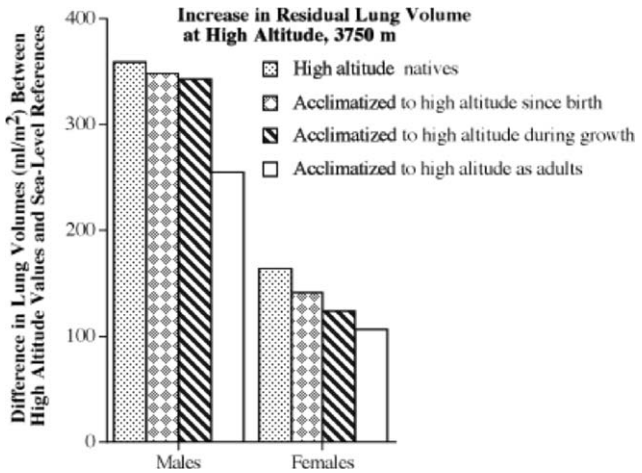

Fig. 9. Developmental adaptation and the attainment of large residual lung volume at high altitude. In both males and females, Europeans who were born or migrated to high altitude during growth had a large residual volume similar to that of the high-altitude native and higher that those who migrated as adults. (Adapted from Frisancho et al., 1997.)

levels of physical activity. This inference is supported by the fact that growth in lung volumes follows an allometric pattern, whereby growth in residual lung is established by about age 10 to 12 years after birth (Burri, 2006; Calogero and Sly, 2010; Polgar, 1979; Polgar and Weng, 1979; Stocks and Quanjer, 1995) (see Fig. 10). In contrast, vital capacity is influenced by environmental factors that produce significant changes during the transitions between childhood, adolescence, and adulthood (Miller et al., 1972; Polgar, 1979; Polgar and Weng, 1979; Sieverdes et al., 2011). These studies also indicate that the size of residual lung volume (see Fig. 11) is directly proportional to the size of the alveolar surface area and the degree of gas exchange (Zeman and Bennett, 2006), which plays a key role in the pulmonary diffusion of oxygen from blood to tissues. A recent study by Kiyamu et al. (2012) of Peruvian females born and raised at low altitude (Lima 150 m) and born and raised at high altitude Cerro de Pasco (4,338 m) and with different degrees of genetic admixture indicate that the majority of the variability for FVC and total lung capacity was explained by developmental factors.

TABLE 9. Lung volumes (expressed as ml/m^2 of surface area) by occupational activity level among five male samples studied in La Paz, Bolivia (3,750 m)[a]

Occupational activity level	High-altitude rural native (HARN), mean ± SE (N = 37)	High-altitude urban natives (HAUN), mean ± SE (N = 69)	Acclimatized since birth (AHAB), mean ± SE (N = 45)	Acclimatized during growth (AHAG), mean ± SE (N = 30)	Acclimatized during adulthood (AHAA), mean ± SE (N = 25)
Vital capacity (m/m^2)					
Low	–	2,864.44 ± 59.19	2,778.57 ± 72.48	2,739.62 ± 179.33	2,369.67 ± 80.57
Medium	3,079.05 ± 80.07	3,118.29 ± 52.23	3,035.14 ± 68.83	2,903.67 ± 35.84	3,042.62 ± 115.61
High	3,337.15 ± 53.90	3,170.48 ± 39.06	3,200.53 ± 85.97	3,190.29 ± 107.39	3,042.97 ± 112.15
Significance	$P < 0.03$	$P < 0.01$	$P < 0.01$	$P < 0.02$	$P < 0.05$
Residual volume (m/m^2)					
Low	–	954.62 ± 85.07	955.76 ± 85.41	965.89 ± 224.87	869.41 ± 45.42
Medium	1,164.82 ± 93.37	1,044.58 ± 58.58	980.57 ± 45.35	920.38 ± 52.29	900.04 ± 61.72
High	1,117.24 ± 31.65	986.97 ± 34.05	1,069.67 ± 92.35	983.24 ± 51.08	927.95 ± 21.29
Significance	NS	NS	NS	NS	NS
Residual volume/total lung volume × 100 (%)					
Low	–	24.54 ± 1.56	25.24 ± 1.58	24.84 ± 3.54	25.09 ± 0.75
Medium	27.21 ± 1.34	24.67 ± 0.90	24.22 ± 0.60	23.92 ± 1.09	22.70 ± 1.17
High	25.04 ± 0.51	23.61 ± 0.61	24.71 ± 1.28	23.54 ± 0.93	23.47 ± 0.79
Significance	NS	NS	NS	NS	NS

[a]Adapted from Frisancho et al. (1997).

TABLE 10. Lung volumes by occupational activity level among four female samples studied at 3,750 m in La Paz, Bolivia[a]

Occupational activity level	High-Altitude urban natives (HAUN), mean ± SE, $N = 56$	Acclimatized since Birth (AHAB), mean ± SE, $N = 40$	Acclimatized during growth (AHAG), mean ± SE, $N = 33$	Acclimatized During adulthood (AHAA), mean ± SE, $N = 22$
Vital capacity (m/m^2)				
Low	2,405.15 ± 47.56	2,365.31 ± 47.93	2,347.50 ± 41.49	2,198.88 ± 123.17
Medium	2,585.25 ± 36.78	2,574.27 ± 54.40	2,445.38 ± 53.86	2,494.92 ± 81.15
High	2,805.39 ± 49.13	2,654.82 ± 85.47	2,564.90 ± 64.75	2,458.57 ± 51.27
Significance	$P < 0.01$	$P < 0.02$	$P < 0.06$	$P < 0.06$
Residual volume (m/m^2)				
Low	820.37 ± 29.59	823.89 ± 22.51	827.42 ± 56.79	755.27 ± 52.36
Medium	871.61 ± 19.71	811.98 ± 21.41	878.15 ± 55.13	774.14 ± 80.50
High	855.42 ± 50.84	892.77 ± 30.77	871.88 ± 45.71	813.29 ± 63.52
Significance	NS	NS	NS	NS
Residual volume/total lung volume × 100 (%)				
Low	25.41 ± 0.72	25.86 ± 0.66	25.88 ± 1.18	25.62 ± 1.40
Medium	25.20 ± 0.39	24.04 ± 0.59	26.22 ± 0.96	23.21 ± 1.58
High	23.23 ± 0.96	25.18 ± 0.40	25.31 ± 0.99	24.70 ± 1.54
Significance	NS	NS	NS	NS

[a]Adapted from Frisancho et al. (1997).

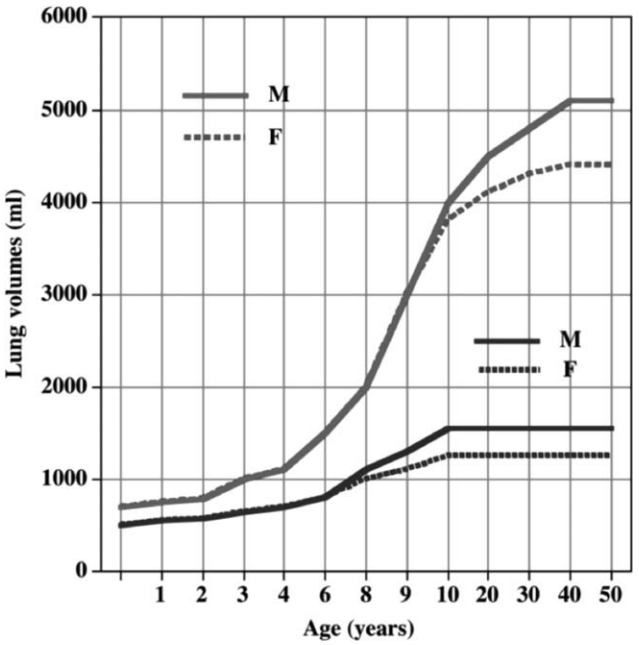

Fig. 10. Allometric growth of lung volumes. The residual lung volume grows mostly through childhood, while the forced vital capacity grows during both childhood and adulthood. (Data from Stocks and Quanjer, 1995; Polgar, 1979; Calogero and Sly, 2010, reproduced by permission.)

In conclusion, these studies together demonstrate that HARNs have significantly greater lung volumes especially residual lung volume than all other groups studied, whether it is the HAUNs or those raised at high altitude. The present research also indicates that the degree of increase in FVC at high altitude is influenced by occupational activity level, while the attainment of an enlarged residual lung volume seems to be related more to developmental acclimatization than differences in occupational activity level.

Animal experimental research and developmental lung function

Various studies have demonstrated that, after prolonged exposure to high-altitude hypoxia (>3,100 m), young rats, guinea pigs, and beagles exhibited an accelerated proliferation of alveolar units and accelerated growth in alveolar surface area and lung volume (Bartlett, 1972; Bartlett and Remmers, 1971; Burri, 2006; Burri and Weibel, 1971a,b; Cunningham et al., 1974; Johnson et al., 1985; Yilmaz et al., 2007) (see Figs. 12 and 13). In contrast, after prolonged exposure to high-altitude hypoxia, adult rats and beagles did not show changes in quantity of alveoli and lung volume (Bartlett and Remmers, 1971; Cunningham et al., 1974; Johnson et al., 1985) (see Figs. 12 and 13). The increase in size of gas exchange units was evenly distributed between alveoli and ducts in young animals but involved alveolar ducts more than alveoli in adult animals. In other words, in immature rats, lung growth was hyperplasic with regard to functional units but, in adult animals, reflecting a limited potential for cell proliferation at the alveolar level, lung growth was hypertrophic. In terms of gas exchange, hyperplasic growth is more efficient than hypertrophic growth. Studies of foxhounds demonstrate that the developmental adaptation induced by high-altitude residence (3,800 m) from 2.5 to 7.5 months of age enhances lung diffusing capacity for oxygen that persists at least 2.5 years after returning to sea level (Hsia et al., 2005, 2007; McDonough et al., 2006; Ravikumar et al., 2009).

These experimental studies clearly indicate that exposure to hypoxic conditions during growth and development influence the size of the residual lung volume and alveolar area of adults.

Developmental functional adaptation and Andean historical background

Current research has demonstrated that while Andeans natives are characterized by having a low pulmonary ventilation and moderate level of hemoglobin concentration, Tibetans exhibit high pulmonary ventilation and lower hemoglobin concentration. The sources of these differences have been attributed to three factors. First, there are prehistoric differences in the length of residence at high altitude. Various estimates based on archeological evidence suggest that Tibetans have migrated to and lived permanently at high altitude about 13,000 to 23,000 years ago (Bratingham et al., 2007; BaoYin et al., 2007; Madsen et al., 2006), while Andeans have lived at high altitude for

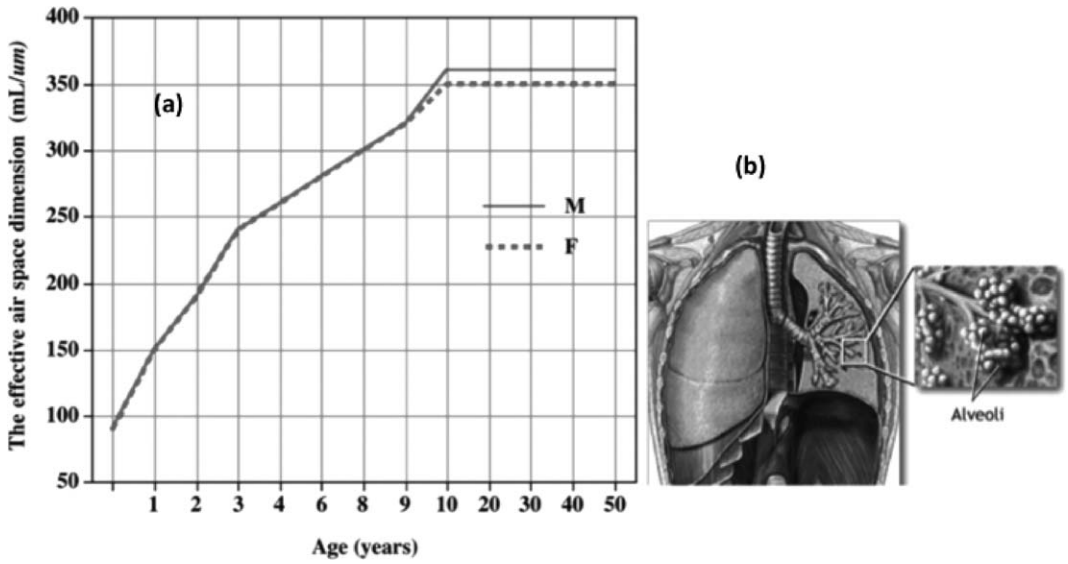

Fig. 11. Growth of the alveolar area measured by the effective air space dimension. Growth in the alveolar area is directly proportional to the size of the residual volume of the lung and the size of the alveolar area plays an important function in the supply of oxygen and getting rid of carbon dioxide [Source: (a) from data of Zeman and Bennett, 2006; and (b) from noncopyright internet sources)].

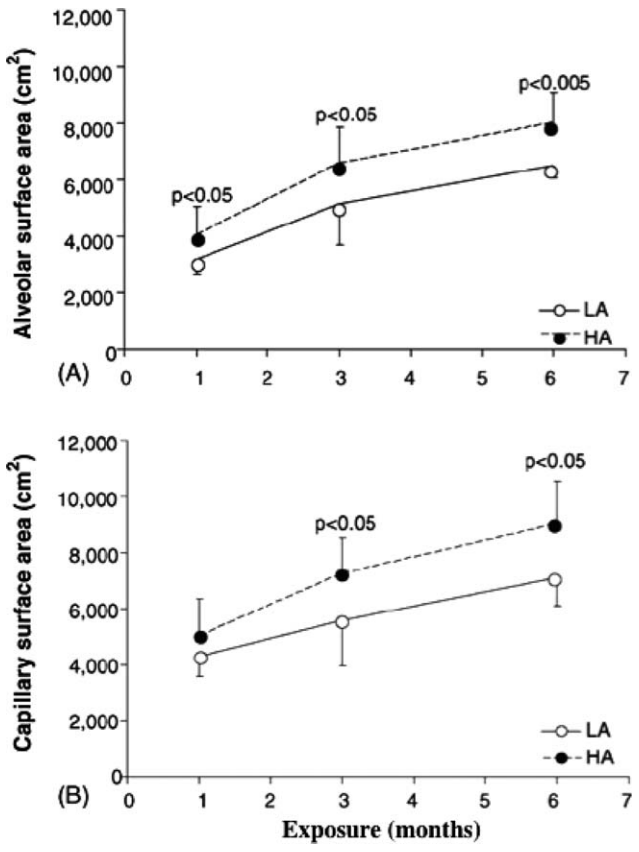

Fig. 12. Enhanced alveolar growth and remodeling in Guinea pigs raised at high altitude. The increase in alveolar surface area of the lung was greater in those exposed during development (before maturity) than those exposed during adulthood. (Data from Hsia et al., 2005, reproduced by permission.)

only about 8,000 to 10,000 years (Aldenderfer, 1999; Lynch, 1990; MacNeish, 1971; Steele and Politis, 2009). Second, there is now evidence for a specific genetic adaptation. It is assumed that the longer residence at high altitude and the relative isolation of Tibetans (Gayden et al., 2007) might have increased the possibilities of developing a specific genetic adaptation. In fact, Beall et al. (2004) do find higher offspring survival among Tibetan women with high oxygen saturation genotypes residing at 4,000 m. They also find a high frequency of DNA sequences indicating genetic evidence for high-altitude adaptation in Tibetan highlanders (Beall et al., 2010; Gu et al., 2012; Simonson et al., 2012).

In contrast, no specific genetic trait associated with high-altitude adaptation has been identified in Andean high-altitude natives (Bigham et al., 2009, 2010; Scheinfeldt and Tishkoff, 2010). The lack of high-altitude adaptation-associated unique genetic traits among high-altitude natives is related to two factors. First, Andean high-altitude natives have not been isolated during pre-Hispanic times from lowland populations. Prior to the arrival of the Spaniards to Perú, the Incas in the so-called "mitimaes" program relocated entire villages from low to high altitudes to support the building and political structure of the Inca empire (Cieza de León, 2010). Second, the Andean populations did maintain traditionally an economic continuous exchange with low-altitude populations in a program referred to as "vertical ecology" (Murra, 1980).

In summary, even though there is evidence that, among high-altitude populations, indigenous Quechua ancestry is associated with higher birth weights (Bennett et al., 2008; Julian et al., 2009; Wilson et al., 2007) and lower ventilation (Brutsaert et al., 2005) and chest shape (Greska, 1988), it appears that successful functional adaptation to high altitude of Andean natives is related to developmental acclimatization. However, it is quite possible that the expression of developmental functional

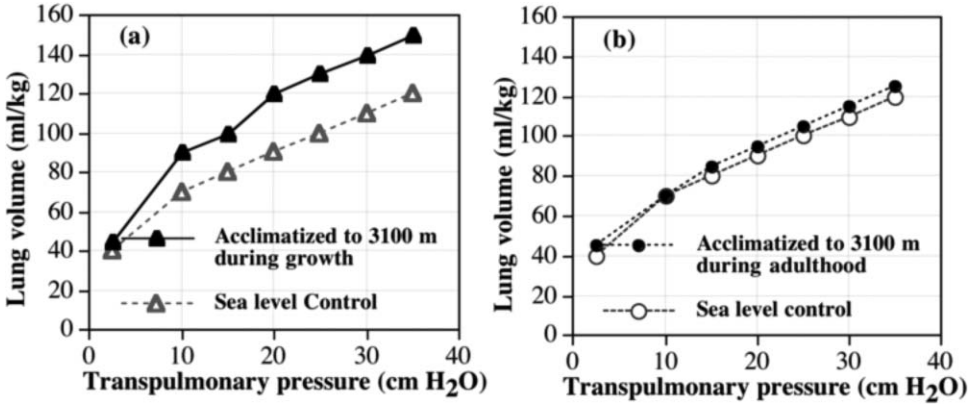

Fig. 13. Developmentally enhanced lung volume in beagles acclimatized to high altitude during growth and adulthood. Compared to sea level controls, the increase in lung volume was greater in those acclimatized to high altitude during development (a) than those acclimatized during adulthood (b). (Data from Johnson et al., 1985; McDonough, et al., 2006, reproduced by permission.)

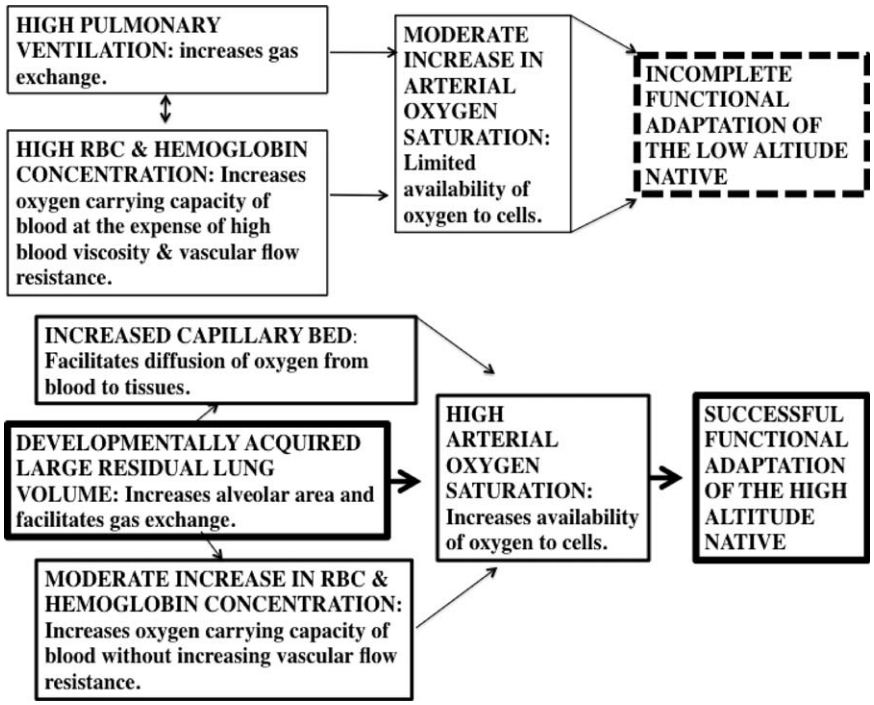

Fig. 14. Schematization of the physiological pathways elicited by high-altitude hypoxia. The lowland native responds mostly through increase in pulmonary ventilation and increase in oxygen carrying capacity of the blood. In contrast, the highland native attains a full functional adaptation through increase in capillary bed, a developmentally acquired large residual lung volume and moderate increase in red blood cells. It is postulated here that the developmentally acquired enlarged residual volume and its concomitant increase in alveolar area because its critical role in gas exchange along with the increased tissue capillarization and moderate increase in red blood cell and hemoglobin concentration contributes to the successful functional adaptation to the hypoxic environment of the of the Andean high-altitude native.

adaptation is also mediated by specific genetic traits that are yet to be identified.

CONCLUSIONS

The various adaptive mechanisms that enable both lowland and highland natives to overcome the stress of high-altitude hypoxia are summarized in Figure 14. In both lowland and highland natives, adaptation to the low availability of oxygen at high altitudes results in the operation of a variety of coordinated mechanisms oriented toward increasing the supply of oxygen to the tissue level. However, lowland natives use different pathways than highland natives to acclimatize to high altitudes. The low-altitude natives rely mostly on an increase in pulmonary ventilation and a modest increase in RBC and hemoglobin concentration, which have a moderate positive effect on arterial oxygen concentration. The net effect of these

responses is that adaptation to high altitude is not completely successful as judged by the inability to attain an aerobic capacity comparable to that attained at low altitudes.

By contrast, the high-altitude native does attain a functional adaptation comparable to that attained at low altitudes. Both experimental studies on animals and comparative human studies of groups residing at high altitudes indicate that exposure to high altitude during the period of growth and development results in the attainment of a large residual lung volume. Since the size of the residual volume is established prior to adulthood and plays a major role in the supply of oxygen and the excretion of carbon dioxide, it is postulated here that it contributes to the full functional adaptation that characterize high-altitude natives. The enhanced functional adaptation of the high-altitude native is also due to the augmented tissue capillarization that facilitates gas exchange and delivery of oxygen. Furthermore, by maintaining a moderate increase in RBC and hemoglobin concentration, the nonmining high-altitude natives decrease blood viscosity and vascular resistance, which together lead to good tissue oxygenation. The net effect of these responses is that the high-altitude native attains a functional adaptation to high altitude that is comparable to that achieved at low altitudes. Thus, it is suggested that the differences between the highland and the lowland Andean native in physiological performance and morphology are partly due to adaptations acquired during the developmental period.

ACKNOWLEDGMENTS

The author is grateful to his wife, Hedy G. Moscoso, with whom he started the high altitude field work and continued the research on developmental adaptation that is summarized in this article. The author acknowledges the invaluable collaboration and assistance of his colleagues Dr. Anthony B. Way of Texas Tech University Health Sciences Center, Lubbock, Texas; Dr. R. Brooke Thomas of the Department of Anthropology, University of Massachusets; Dr. Tulio Velasquez and Dr. Emilio Pico-Reategui of the "Instituto de Biologia Andina" of the School of Medicine of the University of San Marcos of Lima, Perú; Dr. Jorge Sanchez and Dr. Danilo Pallardel of the Department of Anthropology of the University of San Antonio Abad of Cusco, who were instrumental in conducting the research in Peru. Dr. Enrique Vargas, Dr. Mercedes Villena, Dr. Hilde Spielvogel, and Dr. Rudy Soria and the Laboratory Technitians Ms. Esperanza Cáceres, Anna Maria Alarcón, and Cristina Gonzales from the Instituto Boliviano Biologia de Altura made possible the research about developmental adaptation in La Paz. Bolivia. Finally, the author is grateful to all the participants in this session who under the leadership of Michael Little and Ralph Garruto have produced such interesting symposium.

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