Developmental Responses to High Altitude Hypoxia

A. ROBERTO FRISANCHO
Center For Human Growth and Development and Department of Anthropology, University of Michigan, Ann Arbor, Michigan

ABSTRACT From a review of published literature on developmental responses to high altitude, three major conclusions are derived. First, the small birth weight of high altitude native populations are adaptive responses to reduce the oxygen requirements, while the relative increase in the placental weight is a compromise mechanism to increase the volume and surface area for a better oxygenation. Second, the small stature of the high altitude native is due to slow prenatal and postnatal growth. Third, the enlarged chest size, increased lung volumes and predominance of the right ventricle of the heart are due to accelerated development during childhood and adolescence. However, there is not adequate information to determine whether or not the developmental responses of the high altitude native are population-specific, based on a genetic structure different from that of sea level populations. Hence, the need for further study of developmental factors is emphasized.

In recent years there has been increasing interest in the study of responses by man to high altitude hypoxia. The interest of human biologists in studying human populations at high altitudes lies not only in the investigation of how man reacts to environmental extremes, but also in finding out the mechanisms whereby a population adapts to such an environment. The mechanisms may be genetic, developmental or short-term adjustments. Considering that the period of growth and development consists of more than a quarter of the average person's lifetime, and the major selective forces operate prior to reproductive age, the developmental responses of a population must be viewed as one of the most important sources of inter-population variations in physiological and morphological adaptation to environmental stress. The purpose of this paper, therefore, is to evaluate the major morphological and physiological responses to the stress of high altitude hypoxia during the prenatal and postnatal development of man.

Prenatal responses

Birth weight and placental morphology. Because of resistance offered to oxygen tension by the tissue barrier separating maternal and fetal blood, and because of the intrinsic oxygen consumption of the tissues (Anselmino and Hoffman, '30; Eastman, '30; Barcroft, '33), the fetus at sea level develops in a hypoxic environment. Thus, despite various adaptive responses, such as high fetal hematocrit and higher oxygen affinity, the margin of safety of the fetus with respect to its oxygen supply, is limited. Therefore, the fetus at high altitudes would most likely be subject to even greater stress than at sea level unless adaptive responses were made. The responses could be physiological or morphological, or a combination of both.

Since the early 1950's, Peruvian investigators have demonstrated that high altitude populations tend to have low birth weights and relatively greater placental weights than their sea level counterparts (Vilchez, '54; Jara, '61; Sanchez, '63; Chabes et al., '66). A summary of these data is presented in table 1. At high altitudes there is an 18% reduction in birth weight, while the weight of the placenta relative to the weight of the neonate is about 25% greater than at sea level.

These findings have recently been confirmed by McClung ('67). As shown in table 2, this study consisted of Quechua samples residing at sea level and at 3300 m (11,000 feet). The data clearly indicate that at high altitudes there is a 7% reduction in birth weight and a 12% increase in the placental weight/birth weight ratio. The reductions in measurements of body size and subcutaneous fat (sum of skinfolds) are proportional to the decrease in birth weights. Analysis of the maternal anthropometric measurements demonstrates

TABLE 1

Placental weight, birth weight, placental weight/birth weight rate at sea level altitudes in Peruvian populations from various sources

Altitude	Location	N	Placental weight		Birth weight		Placental weight birth weight ratio	
			Mean	S.D.	Mean	S.D.	Mean	S.D.
m			*gm*		*gm*			
203	Lima[1]	490	544	83	3612	425	0.15	0.02
203	Lima[2]	100			3297	511		
203	Lima[3]	100	582	108	3540	550	0.17	0.03
Sea level weighted mean[5]			550	87	3555	455	0.15	0.02
3880	La Oroya[2]	186			3039	420		
4340	Cerro Pasco[4]	100	568	94	2730	350	0.20	0.04
High altitude weighted mean[5]			588	94	2934	395	0.20	0.04
Per cent difference[5]			4		18		25	

[1] Vilchez ('54).
[2] Jara Velarde ('61).
[3] Cuellas ('62).
[4] Sanchez ('63).
[5] Calculated by Frisancho.

TABLE 2

Neonatal and placental dimensions of Peruvian Quechua samples at high altitude and at sea level[1]

Characteristics	3300 m Cuzco N = 80		Sea level Lima N = 88		Level of significance	Per cent difference[2]
	Mean	S.D.	Mean	S.D.		
Placental weight (gm)	603.00	97.00	594.00	124.50	$p < 0.05$	+1.45
Birth weight (gm)	3092.00	457.60	3311.50	479.60	$p < 0.01$	−7.00
Placental weight/ birth weight ratio	0.18	0.03	0.15	0.03	$p < 0.01$	+12.00
Total infant length (cm)	49.61[3]	1.60	48.92	1.81	$p < 0.05$	+0.01
Crown-rump length (cm)	32.11	1.41	33.23	1.44	$p < 0.01$	−3.30
Arm length (cm)	19.51	1.00	20.20	1.00	$p < 0.01$	−3.50
Head circumference (cm)	34.15[3]	1.20	34.15[4]	1.25	N.S.	0.00
Chest circumference (cm)	32.63[3]	1.41	33.21[4]	1.43	$p < 0.05$	−1.80
Sum of eight skinfold sites (mm)[2]	35.41[3]	7.30	38.04[4]	7.19	$p < 0.01$	−7.10

[1] Adapted from McClung ('67).
[2] Calculated from original data by Frisancho.
[3] N, 68.
[4] N, 85.

that high altitude and sea level mothers have equal stature. But the high altitude mother is considerably fatter than her sea level counterpart.

Morphological studies of the placenta of Peruvian populations indicate that at high altitudes the frequency of "irregular-shape" rather than the usual round or oval placentas, is three times greater than at sea level (Rendon, '64; Sanchez, '63). As shown in table 3 these findings have been confirmed by Chabes and associates (Chabes et al., '68). These investigations also point out that "irregular-shape" placentas are thinner and are associated with much greater levels of cord hemoglobin than those at sea level.

The experimental studies of Barron and associates (Barron et al., '64) on pregnant ewes suggest that prenatal adjustment to altitude hypoxia involves three mechanisms: (1) increasing surface area available for diffusion of oxygen transfer between maternal and fetal bloods, (2) decreasing resistance of the placental barrier to transfer of oxygen, or (3) a combination of both. Furthermore, placental surface area is highly correlated with placental capillary area and with the capacity of the placenta to nourish and oxygenate the

TABLE 3

Placental shape at high altitude and at sea level[1]

Altitude	Irregular		Oval		Round		Total	
	N	%	N	%	N	%	N	%
Sea level	8	8.0	42	42.0	50	50.0	100	100.0
High altitude (3800 m)	28	25.7	51	46.8	30	27.5	109	100.0

[1] Adapted from Chabes et al. ('68).

fetus (Aherne and Dunnill, '66). Taking these factors into account, it appears that the relative increase in placental weight and greater frequency of thinner and "irregular-shape" placentas are compromise mechanisms to increase the volume and surface area, and to diminish the placental barrier for oxygen transfer. The low birth weights may be viewed as an adaptation to reduce oxygen requirements in a hypoxic environment.

In the United States, Lichty et al. ('57) and Howard et al. ('57) indicate that in Lake County, Colorado, there is a significant reduction in birth weights when compared to birth weights in Denver. This difference may be attributed to high altitude hypoxic effects, a hypothesis which appears to be corroborated by the statistical analysis of Grahn and Kratchman ('63). However, these studies did not control for variations due to early induced labor or racial factors, and therefore any conclusions must await further experimental data.

Postnatal responses

Cardiovascular. At sea level, the right ventricle of the heart is slightly larger in size than the left ventricle at birth (Rosen and Gardberg, '57; Emery and Methal, '61); during adulthood the left ventricle becomes larger than the right. In contrast, among high altitude populations, the right ventricle is considerably larger than the left (Rotta, '38; '47; Miranda and Rotta, '44; Rotta and Lopez, '59). These findings have been confirmed by the studies of Peñaloza and associates (Peñaloza et al., '60; Peñaloza et al., '61; Peñaloza et al., '64). Furthermore, through electrocardiographic and anatomical studies, it has been found that the predominance of the right ventricle begins immediately after the fourth month of postnatal development. This right ventricular enlargement appears to be due to excessive growth in the basal zone (Arias-Stella and Recavarren, '62; Recavarren and Arias-Stella, '62).

The adaptive significance of the right ventricular predominance in high altitude populations appears to be related to high pulmonary blood pressure. Arias-Stella and Saldana ('62, '63) through histological studies demonstrate that among people born and living at high altitudes, after the first month of postnatal development there is a muscularization and thickening of the muscular layer of the pulmonary arteries and arterioles resembling the fetal pulmonary vascular tree. These muscularizations along with high blood viscosity due to polycythemia, results in an increased pulmonary resistance or pulmonary hypertension in children and adults at high altitudes. Sime and associates (Sime et al., '63; Peñaloza et al., '63) as shown in table 4, have confirmed these findings. Moreover, they point out that the changes are accentuated in infants and children.

Another factor which may contribute to the enlargement of the right ventricle at high altitudes is probably related to the high prevalence of patent ductus arteriosus. According to Marticorena and associates (Marticorena et al., '62) 72% of 5000 school children of both sexes born at high altitudes had patent ductus arteriosus, compared to 4% at sea level (Richards et al., '55). It should be noted that during intra-uterine development, blood flows from the pulmonary artery to the aorta through the ductus arteriosus. After birth, with the interruption of umbilical circulation and expansion of the lungs leading to increased systemic blood pressure and lowering of the pulmonary pressure, the flow of blood is reversed, i.e. the direction is now from aorta to pulmonary artery (Barron, '44; Assali et al., '62). Thus, if the

TABLE 4

Pulmonary blood pressure in children and young adults born and living at sea level and at high altitude [1]

Altitude	Pulmonary artery: Pressures (m.m.h.g.)				Mean
	Age	N	Systolic	Diastolic	
	years				
Sea level	2.5–19	30	19.0 ± 2.9	8.0 ± 2.2	13.0 ± 2.6
	21.0	25	22.0 ± 3.4	6.0 ± 2.3	12.0 ± 2.2
High altitude (14,900 feet)	1–5	7	58.0 ± 17.1	32.0 ± 17.5	45.0 ± 16.6
	6–14	25	41.0 ± 10.0	18.0 ± 9.6	28.0 ± 10.2
	22.0	38	41.0 ± 13.4	15.0 ± 7.6	28.0 ± 10.5

[1] Adapted from Sime et al. ('63) and Peñaloza et al. ('63).

ductus arteriosus remains open it acts as a shunt from the aorta to the pulmonary artery where pressure is lower; harder work of the right ventricle results.

The adaptive significance of high pulmonary blood pressure is not clear. Grover et al. ('63) through experimental studies on steers at high altitudes have advanced the hypothesis that high pulmonary blood pressure may facilitate better blood perfusion in the lungs and thus greater oxygenation at the alveolar level. On the other hand, the patency of ductus arteriosus, according to Peñaloza et al. ('64), may be a functional response to the high pulmonary pressure associated with high altitude hypoxia.

Lung volume. At high altitudes, the most easily recognizable change, with respect to respiratory function, is increased lung volumes in all compartments. The investigations of Hurtado ('64a) demonstrate clearly that the high altitude native despite his small stature (158.0 cm) has considerably greater lung volumes than his taller (166.0 cm) sea level counterpart. As shown in table 5, the high altitude native exceeds the sea level resident in all lung compartments, but the striking differences are in the volume of air remaining in the lung at the end of a normal expiration (functional residual capacity) and that remaining after a forced expiration (residual volume). Thus, the total lung capacity as well as forced vital capacity are also significantly increased at high altitude.

These findings have recently been confirmed by a study of pulmonary function of 150 boys living at high altitudes, aged 10 to 20 years (Frisancho, '69), where it has been shown that increased lung volumes of adult high altitude populations are due to accelerated development during childhood and adolescence.

Furthermore, through stepwise multiple regression analysis, it was demonstrated that chest circumference at maximum inspiration is a better predictor of forced expiratory lung volumes than stature, weight, or surface area, contrary to what occurs in sea level populations (Frisancho, '69). These findings suggest that under hypoxic conditions, lung size is a function of chest size rather than stature; the adaptive significance of such characteristic is obvious.

Growth. The author conducted an intensive study of growth in a high altitude Peruvian Quechua population. The study consisted of both cross-sectional and semi-longitudinal samples of 1300 subjects, aged one to 35 years of age, from the district of Nuñoa, Puno, located at a mean altitude of 4200 m (14,000 feet). Detailed results of this investigation have been given elsewhere (Frisancho, '66, '68, '69; Baker, Frisancho and Thomas, '66; Frisancho and

TABLE 5

Per cent increase in lung volumes of high altitude natives with regard to sea level residents [1]

	Liters	Liters/ m^2	Liters/ stature
	per cent	*per cent*	*per cent*
Total lung capacity	12	20	15
Vital capacity	4	13	10
Inspiratory capacity	1	8	3
Function residual capacity	23	33	25
Expiratory capacity	10	20	9
Residual volume	38	49	44

[1] Calculated from tables given by Hurtado, A. ('64a). Animals in high altitudes: resident man. In: Handbook of Physiology, Section IV. Adaptation to the Environment. D. B. Dill, E. F. Adolph and K. G. Wilber, eds. American Physiological Society, Washington, D.C.

Baker, '70). The overall results of this study indicate that the pattern of growth of Nuñoa *indigenes* is characterized by (1) late sexual dimorphism in body size, (2) slow and prolonged growth period in body size, (3) late and poorly defined adolescent stature spurt in both males and females, and (4) accelerated development of chest size and lung volumes, when compared to Peruvian samples at sea level and at 2500 m (Frisancho, '69). The dietary surveys conducted in Nuñoa indicate that both on a household basis and based upon individual intakes by age and sex, the diet was found to be adequate by Peruvian and U. S. standards (Mazess and Baker, '64; Gursky, '69). Furthermore, the socioeconomic factors associated with rural-urban and altitude differences appear to be reflected in a greater deposition of fat and greater weight, but do not seem to influence the development of stature (Frisancho and Baker, '70).

Taking these factors into consideration, it was suggested that the patterns of growth of this population is related to the hypoxic effects of high altitude. The hypothesis that high altitude affects body growth is supported by recent experimental studies on animals. Krum ('57) and Timeras and co-workers (Timeras '62; Timeras and Woolley, '66) point out that rats raised under hypoxic conditions with adequate diets exhibit rather severe retardation in normal body growth and that such slow development becomes accentuated in successive generations. Furthermore, the subnormal rate of growth in size of animals born at high altitudes appears to be irreversible, even after a prolonged sojourn at sea level (Timeras, '62).

CONCLUSIONS

The most distinctive morphological and physiological characteristics of the adult high altitude Peruvian native are: (1) small stature, (2) increased lung volumes, (3) enlarged chest size, and (4) predominance of the right ventricle of the heart. The evidence suggests that the mechanisms whereby these features are established result from adjustments during prenatal and postnatal development. Thus, the small stature of Andean man appears to result from slow prenatal (low birth weight) and postnatal growth, while his large chest size and increased lung volumes result from accelerated rather than slow growth. The enlarged right ventricle and pulmonary blood pressure also appear to be developmental responses to the stress of high altitude hypoxia.

Studies on work performance, as measured by maximum oxygen uptake, indicate that the high altitude native exhibits a greater work capacity than the acclimatized newcomer (Schilling et al., '55; Hurtado et al., '56; Elsner et al., '63; Hurtado, '64a,b; Reynafarge and Velasques, '66). Similarly, both the aerobic and anaerobic cost of exercise is less in Adean Indians than in either newcomers or lowlanders (Hurtado, '64a; Velásques, '66; Baker, '69). Furthermore, these studies also indicate that the high altitude natives, when compared to samples from sea level, perform exercise with greater pulmonary ventilation, less oxygen consumption per kilogram of body weight and work load, lower pulse, and smaller increase in systemic blood pressure.

Inasmuch as the studies on newcomers were based upon adult subjects who resided at high altitudes for periods of one or two years, these differences in physiological performance at high altitudes may reflect the inherent genetic characteristics of Andean man, or the results of growth and development under chronic hypoxic stress. Considering that the major morphological and physiological characteristics of the high altitude native evolve during prenatal and postnatal growth, the evidence would favor, then, a developmental explanation. However, there is not adequate information to determine whether or not the developmental responses of the high altitude native are population-specific, based on a genetic structure different from that of sea level populations. Hence, the need for further study of developmental factors is emphasized.

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