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Pulmonary Diffusing Capacity in Young Andean Highland Children[1]

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Abstract. Lung diffusing capacities for carbon monoxide were measured in 125 highland Andean children between 4 and 6 years of age in La Paz, Bolivia (3,650 m), using a steady-state technique. Male children had a significantly lower DL_{CO} (13.2 ± 2.7) compared to females (14.2 ± 1.9; $p < 0.05$), despite similar body size Hemoglobin concentration was significantly greater than published values for low-altitude children and this also changes pulmonary diffusing capacities and supports the concept of early developmental adaptation in pulmonary function to environmental stressors as well as a sexual dimorphism in this type of adaptation.

Introduction

Pulmonary diffusing capacity for carbon monoxide (DL_{CO}) is generally accepted as being greater in adults living at high altitude than in lowland dwellers of the same genetic background [1]. This adjustment to the hypobaric hypoxic environment increases oxygen flux in the first step of oxygen transport from the environment to tissue beds, but it is not clear how and when this estimated 20–25% increase occurs. Altered chest sizes and lung volumes in Andean highland adults and children [2, 3] suggest that functional adaptations occur in pulmonary function in the early stages of childhood growth above 3,000 m, at a time when the organism is more sensitive to exogenous environmental influences. Recent studies have focused on pulmonary function in early growth [4, 5] and show that lung volumes are exponentially related to height which in turn is retarded in highland populations. Little information exists concerning the adaptive value of altered DL_{CO} in young children at high altitude, and how such adaptations may limit or affect ultimate

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growth and development. DL_{CO} is thought to represent a single functional measure of pulmonary gas exchange and may be a key part of pulmonary adaptation to high altitude.

This study was undertaken to establish normal values for DL_{CO} in 4- to 5-year-old highland children and to test the hypothesis that this adaptation to high altitude occurred at an early age.

Methods

125 children were examined at the Instituto Boliviano de Biologia de la Altura, La Paz, Bolivia (3,650 m), between August and October of 1979. Consent was obtained from the parents and local school officials. Ages were obtained from school records while height and weight measurements were performed after removal of shoes and bulky outer clothing, according to standard methods [6].

A free-flowing blood sample was collected by finger prick. Hemoglobin concentration was determined by the cyanmethemoglobin method; hematocrit and RBCs were measured by standard procedures. DL_{CO} was measured using a steady-state method [7] and in the sitting upright position. Inspired gas concentration of CO (F_ICO = 0.1%), end tidal CO (F_ACO) and expired CO (F_ECO) were measured using a fast-response infrared analyzer (Rubix 3000, Cosma), calibrated daily with a known gas concentration. A sample line (PE 200 tubing) was connected directly to the expiration side of a two-way breathing valve (single 'J') with sampled air returning to the gas collection bag after analysis. Minute ventilation ($\dot{V}_E$) was collected in a Douglas bag and the volume measured with a calibrated dry gas meter. F_IO_2 was equal to 0.21. The respiratory quotient was assumed to be equal to 1 and no correction was applied. The subject inhaled ambient air for 3–4 min during which time F_ACO was measured (back pressure). The subject then breathed the gas mixture for a 5-min period while $\dot{V}_E$, F_ECO, and F_ACO were obtained. Barometric pressure, ambient room temperature and relative humidity were recorded daily with mean values being 499 mm Hg, 19 °C, and 40%, respectively.

Body surface area was calculated using *Dubois and Dubois's* [8] formula, while percentiles of the National Center for Health Statistics were computed from the newest growth charts [9]. All children were judged to be healthy and free from respiratory diseases. Static lung volumes were not obtained. The steady-state method was well tolerated by the children and measurements were repeated if the personnel felt the child was not breathing normally and in a resting manner.

Results

The children were divided into two groups by sex (table I) and are nearly identical in anthropometric characteristics. No significant differences exist between these groups and mean values are in good agreement with previously reported anthropometry in 4- to 5-year-old highland children [3, 9]. Hematological data (table II) reflect a significant, but relative polycythemia com-

Table I. Anthropometric means ± SD for 4 to 5-year-old Andean highland children (3,650 m)

	Males (n=67)[a]	Females (n=58)
Weight, kg	17.7 ± 2.0	17.1 ± 1.7
Height, cm	108.2 ± 12.2	107.1 ± 5.5
BSA, m^2	0.726 ± 0.056	0.730 ± 0.061
Weight/age, %tile NCHS[b]	48.4 ± 27.0	52.3 ± 22.9
Height/age, %tile NCHS	37.2 ± 25.0	49.7 ± 32.0
Weight/height, %tile NCHS	52.6 ± 24.0	55.7 ± 26.0

[a] No significant differences were observed between sexes [9].

[b] Percentile of National Center for Health Statistics [9].

Table II. Means and SD for DL_{CO}, DL_{CO} values corrected for hemoglobin concentration, and hematological parameters in male and female highland children

Diffusion capacity	Males (n=63)	Females (n=54)
DL_{CO}, ml/min×mm Hg	13.41 ± 2.67	13.94 ± 1.88
DL_{CO} corrected[a] ml/min/mm Hg/g Hb	13.18 ± 2.70[b]	14.20 ± 1.9
DL_{CO} of lowlanders[c] ml/min×mm Hg	7.7 ± 2.0	7.1 ± 1.8
Hematology		
Hemoglobin, g/dl blood	14.6 ± 1.0	14.1 ± 1.9
Hematocrit, %	44.0 ± 2.1	42.6 ± 1.9
RBC, cells × $10^6/cm^3$ blood	4.69 ± 0.23	4.50 ± 0.33

[a] Correction formula used from *Dinkara* [11]; corrected $DL_{CO} = \frac{\text{uncorrected } DL_{CO}}{0.06965 \times Hb}$.

[b] Significant difference between males and females by Student's t test ($t=2{,}82$; $p < 0.05$).

[c] Data derived from plots of *DeMuth and Howatt* [5] for children of 100 cm in height.

pared to low-altitude standards and show a nearly 20% increase in oxygen-carrying capacity. Extensive nutritional assessments were not performed but the absence of anemia in this sample was documented by distribution analysis techniques.

The consistent hematological differences between boys and girls are not significant except for their effect when utilized to correct DL_{CO} [10] for hemoglobin concentration.

Uncorrected DL_{CO} is slightly greater in females versus males despite similar body sizes. However, diffusing capacity is significantly greater in females when corrected for differences in hemoglobin concentration (table II).

Children of the same age, height, weight and hemoglobin showed less than a 5% variation in measured DL_{CO}. The contribution was corrected according to published methods [11]. This correction increased the male versus female differences in DL_{CO} by approximately 1 ml/min/mm Hg.

Multiple-regression and correlation analysis using transformed and untransformed variables showed no statistically significant relationships between anthropometric variables and DL_{CO}. This may be attributed to a very narrow data base without any physiological implications. $\dot{V}_E$ was similar between the groups and represented resting breathing.

Discussion

Several reports in the last 20 years have documented the physiologically important lung adjustments that occur when early growth and development take place under hypobaric hypoxic conditions [12, 13]. There is an increased chest size, total lung capacity and a proportionately larger residual volume. The latter does not imply more molecules in highland children but is attained in early and rapid growth phases. A rapid proliferation of alveolar units and surface area during early growth [14] suggests that DL_{CO} keeps pace with overall growth and is responsive to exposure to hypobaric hypoxia. Studies in adults [15–17] consistently show a 20–25% increase in DL_{CO} in highland natives versus lowlanders. Growth at high altitude seems to be required for this adaptation to be elicited. The hypothesis that this increase in DL_{CO} is attained in early childhood is given support by recent studies [18–20] that show an influence of hypoxia on alveolar surface area, capillary blood volume and pulmonary membrane surfaces.

If one examines the published studies and prediction equation relating growth to pulmonary function, it becomes obvious that high altitude exposure has had a profound effect on DL_{CO} (fig. 1). DL_{CO} is significantly greater than low altitude DL_{CO} values in size-matched children and exceed their predicted capacities by 25% or more. This significant increase was true for both sexes and was not related statistically to body size. The relationships between pulmonary function, lung volumes, and growth were initially determined by the longitudinal studies of *DeMuth and Howatt* [5] and cross-sectional investigations of *Giammona and Doly* [4]. They contain prediction equations for pulmonary function based on biometric variables. Unfortunately, we were unable to either collect data on lowland children brought up to high altitude or to measure lowland children with this method. It is, however, identical in location, technique and equipment to that of *Vincent* et al. [21] and *Pasquis* et al. [22] in which native highlanders were found to be different from lowlanders. Theoretically, a comparison can be made in which children of the same age and size as this sample had a DL_{CO} = 7.5, a $\dot{V}_C$ = 40ml, and a computed D_M = ml/min/mm Hg [4]. If we also assume that $\dot{V}_C$ does not change with altitude and that the $\frac{1}{\theta}$ relationship to F_AO_2 [23] is valid, hen lowland children would be expected to have a DL_{CO} = 13.0 ml/min/mm Hg at 3,700 m of altitude. This

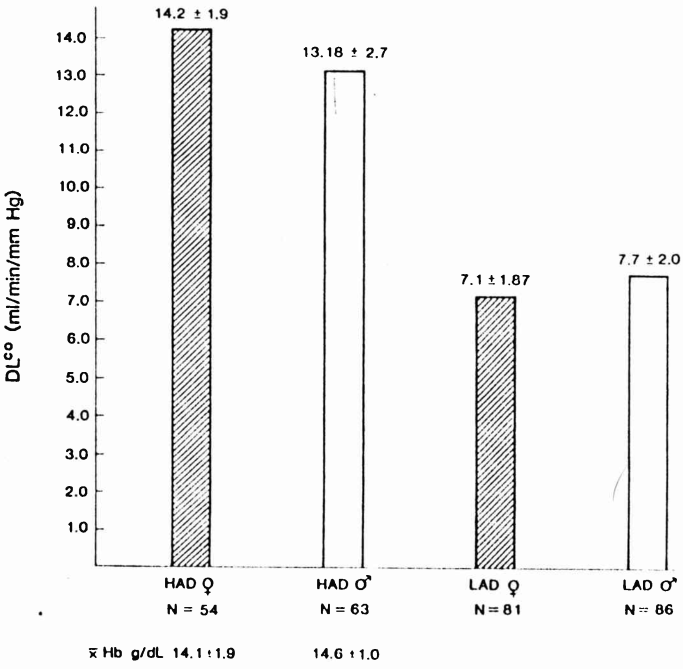

Fig. 1. Means for DL_{CO} corrected for hemoglobin concentration in lowland (LAD) and highland (HAD) male and female children. All HAD children were from La Paz, Bolivia; altitude 3,650 m (12,300 ft); PB = 496 mm Hg.

means that highland-lowland differences might be as low as 10% given our observed variation of 5% and differences in methodology. Low-altitude relationships of growth to lung function [4, 5], however, may not be valid at high altitude given published data on growth velocities in highland children [13, 24].

In addition to probable increases in DL_{CO}, there is a pronounced rise in red cell mass of the same order of magnitude as in adults [25]. Correction of the diffusing capacity for this increase in oxygen-carrying capacity shows that females have a significantly greater DL_{CO} than males. This has recently been demonstrated in Andean natives [26] and may be related to regional effects of high altitude on lung perfusion and altitude-related reactive pulmonary hypertension [27]. It is interesting to note that this difference in diffusing capacity is seen at a time when body size is nearly identical between sexes. Additionally, this difference is opposite to data reported at low altitude [4, 5] where males had higher diffusing capacities than females. The lowland studies, however, did not correct for hemoglobin concentration and hence may be in agreement with these results when this correction has been performed.

These data suggest that a proliferation of alveolar surface exchange area occurs when hypoxic stress occurs in early life [13]. Furthermore, it demonstrates that a relative polycythemia exists in very early life and may contribute significantly to the sexual dimorphism in diffusing capacities that we have observed. It is, however, only one measurement of lung functions in a narrow age range and indicates that more complete and extensive assessments of lung function in young children are warranted.

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