Respiration Physiology (1972) **15**, 182–189; *North-Holland Publishing Company, Amsterdam*

PULMONARY GAS EXCHANGE IN ANDEAN NATIVES AT HIGH ALTITUDE[1]

J. C. MITHOEFER[2], J. E. REMMERS[3], G. ZUBIETA and M. C. MITHOEFER

Departments of Medicine and Physiology, Dartmouth Medical School, Hanover, New Hampshire 03755, U.S.A. and Instituto Bolivano de Biologio de Altura, La Paz, Bolivia

Abstract. A–a D_{O_2} at 3 levels of oxygenation and the a–A D_{CO_2} and V_D/V_T ratios during ambient air breathing were measured in 11 Andean natives at 3700 m. Six were permanent residents of this altitude, 5 had recently come from permanent residence at 4500 m. Breathing ambient air: the A–a D_{O_2} was equal to values at sea level when $P_{I_{O_2}}$ was lowered to that of 3700 m; the a–A D_{CO_2} and V_D/V_T ratio was increased indicating increased distribution of high $\dot{V}_A/\dot{Q}$; there was no evidence of increased venous admixture. At high inspired P_{O_2} (445 mm Hg) there was no evidence of increased true venous shunt. However, when $P_{I_{O_2}}$ was increased to 160 mm Hg the A–a D_{O_2} was significantly larger than at sea level. These findings differ from those previously reported.

The relatively low A–a D_{O_2} under ambient conditions, in the face of increased V_D/V_T (high $\dot{V}_A/\dot{Q}$) results from the absence of significant venous admixture and the effect of $P_{I_{O_2}}$ on A–a D_{O_2} in the presence of $\dot{V}_A/\dot{Q}$ abnormality. The significance of these findings in terms of acclimatization is discussed.

Andean natives, A–a D_{O_2} — High altitude, gas exchange
a–A D_{CO_2} — V_D/V_T

The efficiency of pulmonary gas exchange in native residents at high altitude has, in the past, been evaluated by measurement of alveolar-arterial oxygen pressure differences. The results have been conflicting; the gradient, compared to man at sea level, having been reported as low by some (Hurtado, 1964) and increased by others (Kreuzer *et al.*, 1964).

It has been suggested that this discrepancy is the result of differences in the technique of measurement of P_{O_2} (Kreuzer *et al.*, 1964). In addition, the possibility exists that the high A–a D_{O_2} found in the native miners from Morococha (Kreuzer *et al.*,

Accepted for publication 4 January 1972.

[1] This work was supported by grants from the United Health Foundations, Inc. and from the U.S. Public Health Service, National Institutes of Health, Grants HE 02888-11, HE 09130-03 and HE 05869-02.

[2] Reprint requests: J. C. Mithoefer, Cardiopulmonary Division, Dartmouth Medical School, Hanover, N.H. 03755, U.S.A.

[3] Postdoctoral Fellow and Trainee in Physiology supported by NIH Training Grant, 5TI-HE 5322-06.

1964) was the result of unrecognized pulmonary disease since clinical evaluation of the subjects was not made and chest roentgenograms were not available.

The studies summarized here were done on normal native Andean residents who were selected on the basis of a negative history of cardiopulmonary disease or heavy cigarette smoking and a normal chest roentgenogram. In addition to measurements of A–a D_{O_2}, the evaluation of pulmonary gas exchange was extended to include measurement of arterial-alveolar CO_2 pressure difference and dead space-tidal volume ratio during ambient air breathing.

Methods

The work was carried out at the Instituto Bolivano de Biologio de Altura in La Paz, Bolivia, where the altitude is 3700 m (mean barometric pressure 490 mm Hg). Studies were done on six healthy soldiers (average age 19 years), who had lived all of their lives in La Paz, and on five mine employees (average age 28 years), who had lived for at least 10 years at an altitude of 4500 m and had been in La Paz for only 1–5 days. A medical history and chest roentgenogram were obtained on each subject. Of 15 allegedly normal men who presented themselves for study, four were eliminated because of clinical and roentgenographic evidence of silicosis and, in one case, pneumonia. None admitted awareness of the existence of his disease.

The subjects sat in a chair, the back of which was tilted posteriorly approximately 30° from the vertical position. An indwelling needle was placed in the brachial artery, following which the subject, wearing a nose clip, was connected by way of a rubber mouthpiece to a two-way valve through which he breathed ambient air for a 10 minute period for the purpose of accommodation to the apparatus. Following this, he inspired for 10 min, in random order, the following gas mixtures: ambient air ($P_{I_{O_2}} = 93$ mm Hg), 36% oxygen in nitrogen ($P_{I_{O_2}} = 160$ mm Hg) and 100% oxygen ($P_{I_{O_2}} = 443$ mm Hg). At the end of each period, end tidal alveolar gas was obtained by repetitive 5 ml sampling distal to the expiratory valve during inspiration; simultaneously an arterial blood sample was drawn anaerobically in an heparizinized syringe[4].

Immediately following alveolar sampling, expired gas was collected. The blood samples were analyzed for P_{O_2}, P_{CO_2} and pH by electrodes[5]. The oxygen and carbon dioxide electrodes were calibrated with blood from the subject equilibrated in a 250 cc tonometer at 37 °C at two levels of P_{CO_2} and P_{O_2}. Readings from the meter of the oxygen electrode system were made every 30 sec and plotted against time. The values reached a steady plateau at about three minutes and no time correction was necessary. The gas samples were analyzed for O_2 and CO_2 in duplicate with a 0.5 cc Scholander analyzer as well as by the electrodes, calibrated with gas of known

[4] At a lower altitude ($P_B = 738$ mm Hg), using this breathing apparatus and method of alveolar gas sampling in 6 normal subjects, the alveolar P_{O_2} was 97 mm Hg ($s\bar{x}$ 2.4 mm Hg) and $P_{A_{CO_2}}$ was 26 mm Hg ($s\bar{x}$ 0.9 mm Hg).

[5] Electrodes (Model 113) manufactured by Instrumentation Laboratory Inc., Watertown, Mass.

composition. There was close agreement between the two methods. Hemoglobin concentration was measured by Sahli hemoglobinometer and by photoelectric colorimeter.

Results

The age, height, weight and hemoglobin concentration for the two groups of high altitude residents are shown in table 1. The residents of 4500 m were, on the average, nine years older than the soldiers from 3700 m and their arterial hemoglobin concentration was 6.4 g% higher. The body size was similar in the two groups.

TABLE 1

	Number	Age	Height (cm)	Weight (kg)	Hgb (g%)
Residents of 3700 m (La Paz)	6	19 (0.37)	164 (2.7)	60 (3.3)	16 (0.56)
Residents of 4500 m	5	28 (3.4)	165 (0.71)	62 (4.3)	22.4 (1.2)

Standard error of the mean given in parentheses.

TABLE 2

	$P_{I_{O_2}}$ (mm Hg)	$P_{A_{O_2}}$ (mm Hg)	$P_{a_{O_2}}$ (mm Hg)	A–a D_{O_2} (mm Hg)
Residents of 3700 m	93	64 (1.2)	58 (0.6)	6 (1.0)
	160	119 (2.3)	100 (2.3)	19 (0.9)
	445	384 (10.5)	352 (8.8)	31 (1.7)
Residents of 4700 m	93	64 (0.8)	55 (1.0)	9 (1.0)
	160	120 (2.6)	101 (3.1)	19 (2.1)
	445	407 (7.8)	366 (10.6)	41 (6.8)

Standard error of the mean given in parentheses.

The values for alveolar and arterial P_{O_2} and A–a D_{O_2} at three levels of oxygenation are shown in table 2. There was little difference between the two groups. During ambient air breathing, the younger subjects from the lower altitude (3400 m) had a slight but significantly lower alveolar-arterial oxygen pressure difference as compared to the older subjects from the higher altitude (4700 m). A comparable slight difference existed during 100% oxygen breathing. There was no difference in A–a D_{O_2} between the two groups when the inspired P_{O_2} was 160 mm Hg. Compared to man at sea level (Kreuzer *et al.*, 1964), the A–a D_{O_2} was high in both groups when the $P_{I_{O_2}}$ was 160 mm Hg, but was similar to sea level when $P_{I_{O_2}}$ was 93 or 445 mm Hg.

Alveolar and arterial P_{CO_2}, $P_{E_{CO_2}}$ and V_D/V_T are shown in table 3. The arterial-alveolar CO_2 pressure difference was increased above normal sea level values in both groups, slightly more so in residents of the higher altitude. Consistent with this finding was the increased physiological dead space as measured by the V_D/V_T ratio

TABLE 3

	$P_{A_{CO_2}}$ (mm Hg)	$P_{a_{CO_2}}$ (mm Hg)	a-A D_{CO_2} (mm Hg)	pHa	$P_{E_{CO_2}}$ (mm Hg)	V_D/V_T
Residents of 3700 m	28 (1.0)	34 (1.6)	6 (0.7)	7.44 (0.01)	22 (1.3)	0.35 (0.01)
Residents of 4700 m	27 (1.1)	35 (1.1)	8 (0.6)	7.43 (0.01)	21 (1.3)	0.40 (0.05)

Standard error of the mean given in parentheses.

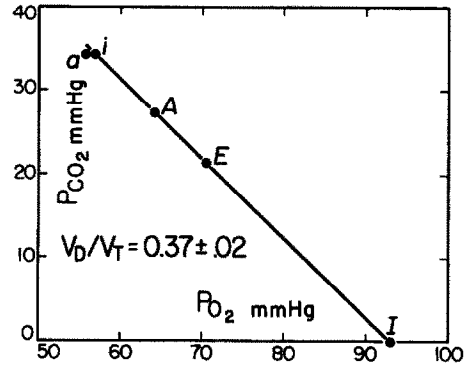

Fig. 1. Combined results from 11 high altitude natives (table 1) studied at 3700 m. I = inspired gas in mm Hg, E = measured expired gas in mm Hg, A = measured alveolar gas in mm Hg, i = calculated ideal alveolar gas in mm Hg, and a = arterial blood in mm Hg. Standard error of the mean is less than 1 mm Hg for all values.

which, using the techniques of this study normally is less than 0.3 (Karetzky and Mithoefer, 1967).

Since the results from the two groups of high altitude residents were nearly the same, some of the data are combined on an O_2–CO_2 diagram in order to give a composite picture of gas exchange during ambient air breathing (fig. 1). The inspired oxygen pressure was 93 mm Hg. The measured alveolar and expired gas points are displaced down the R line from the ideal alveolar point, calculated by the alveolar gas equation (Rahn and Fenn, 1955), as a result of increased dead space ventilation ($V_D/V_T = 0.37$), indicating an increased distribution of high $\dot{V}_A/\dot{Q}$. The arterial point, however, lies close to the ideal alveolar gas value suggesting that the A–a D_{O_2} in these subjects was not significantly contributed to by venous admixture.

In nine of these subjects the carbon monoxide diffusing capacity was also measured; the results were reported elsewhere (Remmers and Mithoefer, 1969). Both the diffusion and reaction components of the total resistance to oxygen uptake in the lung were found to be decreased, a favorable adaptation for oxygen transport at high altitudes.

Discussion

The alveolar-arterial oxygen pressure difference at the lowest and highest inspired oxygen pressures were similar to those of man at sea level. When $P_{I_{O_2}}$ was 160 mm Hg, however, the A–a D_{O_2} was increased suggesting an increase in the distribution of

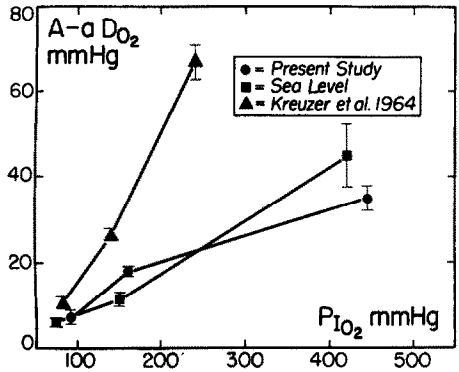

Fig. 2. Mean values in mm Hg for the effect of inspired P_{O_2} on A-a D_{O_2} from 11 high altitude natives of this study. 8 normal subjects at sea-level (Kreuzer *et al.*, 1964), and 6 native residents of 4343 m. from a previous publication (Kreuzer *et al.*, 1964). Vertical bars indicate standard error of the mean.

ventilation-perfusion inequality. This is further suggested by the demonstration of an increase in arterial-alveolar CO_2 difference and dead space-tidal volume ratio.

These values for A–a D_{O_2} differ from those previously reported where oxygen differences of only 1 mm Hg were found in native residents of Morococha breathing ambient air and only 6 mm Hg when the inspired oxygen pressure was raised to sea level values (Hurtado, 1964). These small differences were probably the result of inaccuracy introduced by the experimental technique, as has been previously discussed (Kreuzer *et al.*, 1964). In later studies which used methods of alveolar sampling and direct polarography similar to those of the present work, the A–a D_{O_2}'s at three levels of oxygenation were higher than those reported here. The results of these authors are compared to those of the present study and with values from normal subjects at sea level (Kreuzer *et al.*, 1964) in fig. 2. Since the results of the two groups of high altitude residents in the present study were nearly the same (tables 2 and 3) their values for A–a D_{O_2} are combined in this figure. They differ significantly from normal subjects studied at sea level only when the inspired oxygen pressure was raised to 160 mm Hg. The comparable results when $P_{I_{O_2}}$ was raised above 400 mm Hg indicate no difference in true venous shunting between normal subjects at sea level and high altitude residents. On the other hand, the data of Kreuzer *et al.* show values for A–a D_{O_2} which were greater than normal at all levels of inspired oxygen pressure.

An explanation for this difference is the possiblity that some of the miners from Morococha (Kreuzer *et al.*, 1964) had unrecognized pulmonary disease and that the mean values for alveolar-arterial O_2 pressure difference were high as the result of pneumoconiosis in some of the subjects. Without chest roentgenograms, it is impossible to rule out this contingency as evidenced by the fact that in the present study four of 15 subjects who volunteered were eliminated on the basis of radiological evidence of advanced pulmonary disease of which they alleged to be unaware. This possibility is further suggested by the fact that the data of Kreuzer *et al.* show that of the six high altitude natives studied, three had A–a D_{O_2}'s of 9 mm Hg or less when breathing ambient air (values comparable to those of the present study) whereas the

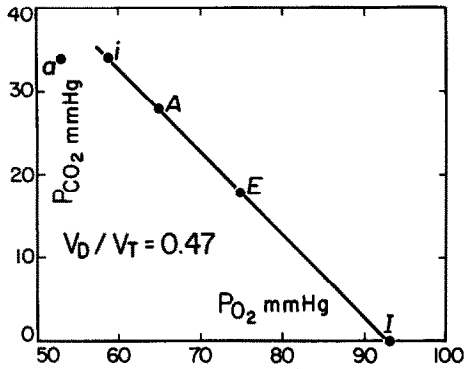

Fig. 3. Results of a study on an allegedly normal 20 year old Andean native who, in fact, had pulmonary disease demonstrated by chest roentgenogram. Note increased V_D/V_T and A-a D_{O_2} of 14 mm Hg as compared to normal high altitude natives (fig. 1); Symbols as in fig. 1.

other three had gradients above 11 mm Hg.

An example of how unrecognized pulmonary disease can influence the results is shown in fig. 3. These data are from a study, in this series, done on a 20 year old soldier, resident of 3400 m, who presented himself as a normal subject unaware of pulmonary disease. A chest roentgenogram was made on the morning that the data shown in fig. 3 were collected, but was not seen until after the study had been completed; it showed consolidation in the lower lobe of the right lung. In this subject the dead space-tidal volume ratio was increased above that found in the other high altitude residents and the A–a D_{O_2} was 14 mm Hg indicating an increase in physiological dead space and venous admixture. The alveolar-arterial oxygen pressure difference was well above those found in the other subjects but comparable to three of the high altitude residents previously reported (Kreuzer *et al.*, 1964).

The significant difference in A–a D_{O_2} observed in the high altitude natives, as compared to normal subjects at sea level, when the $P_{I_{O_2}}$ was 160 mm Hg is of interest in the light of recent calculations based upon a computer model (West, 1969). It was shown that with increasing degrees of $\dot{V}_A/\dot{Q}$ inequality, the maximal A–a D_{O_2} due to $\dot{V}_A/\dot{Q}$ disturbance occurs at progressively higher alveolar oxygen pressures. Figure 4 shows a rearrangement of West's data to indicate how the magnitude of the distribution $\dot{V}_A/\dot{Q}$ inequality influences the alveolar oxygen pressure at which the A–a D_{O_2} will be maximal. Distribution of $\dot{V}_A/\dot{Q}$ is plotted as the logarithm of its standard deviation. As the $\dot{V}_A/\dot{Q}$ abnormality increases, the $P_{A_{O_2}}$ at which maximal A–a D_{O_2} will occur as a result of distribution effect also increases, but in an alinear fashion. This phenomenon may explain the finding of an alveolar-arterial O_2 pressure difference during ambient air breathing which, in the face of increased distribution of $\dot{V}_A/\dot{Q}$ inequality was no greater than that of normal sea level residents breathing comparable inspired oxygen concentrations but which increased significantly when inspired P_{O_2} was raised. Further evidence for an increase in the distribution of ventilation-perfusion inequality in the Andean natives was seen in the increased arterial–alveolar carbon dioxide difference and dead space-tidal volume ratio (table

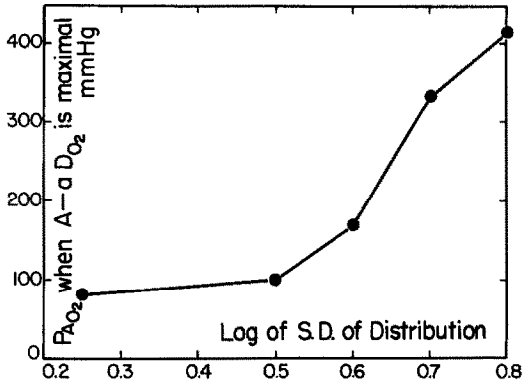

Fig. 4. Effect of ventilation-perfusion inequality (expressed as the long of the standard deviation of distribution) on the $P_{A_{O_2}}$ at which the A-a D_{O_2} is maximal. Data are taken from West (1969).

3). Progressive changes in the distribution of $\dot{V}_A/\dot{Q}$ also develop with acute exposure to high altitude as evidenced by an increase in A–a D_{O_2} and V_D/V_T (Haab, Held and Farhi, 1967; Reeves *et al.*, 1969; Kronenberg *et al.*, 1971).

In acute experiments at sea level, hyperventilation and its associated respiratory alkalosis have been shown to increase alveolar dead space when the subject is in the sitting position (Raine and Bishop, 1964). This effect, presumed to be the result of decreased perfusion of the upper portions of the lung, could be prevented by abolishing the respiratory alkalosis through the addition of CO_2 to the inspired gas, by the assumption of the supine position and in some subjects by pharmacological induction of hypertension. The applicability of these observations to the increased distribution of $\dot{V}_A/\dot{Q}$ inequality of man in the semi-recumbent position at high altitude is not known. The conditions do not appear to be comparable, particularly because of the known presence of pulmonary hypertension in high altitude natives (Penaloza *et al.*, 1963).

It has been implied in the past that the exclusion of a decreased alveolar-arterial oxygen pressure difference from the acclimatization process is unfortunate from the standpoint of effective gas exchange at the reduced inspired oxygen pressures of high altitude. This is certainly true, but the results of the present investigation, interpreted in terms of recent evidence (West, 1969) suggest an important and effective interaction between the increased distribution of $\dot{V}_A/\dot{Q}$ inequality, existing for unknown reasons in high altitude natives, and the magnitude of the effect of this distribution disturbance on the A–a D_{O_2}. The high altitude residents, in spite of $\dot{V}_A/\dot{Q}$ abnormality, have the same A–a D_{O_2} at their ambient pressure as sea level residents do at theirs, or that the latter have when their inspired oxygen pressure is lowered at sea level to reproduce high altitude conditions. This is an interaction most favorable to the adaptive process in which the lowered inspired oxygen pressure itself suppresses the deleterious effects of $\dot{V}_A/\dot{Q}$ abnormality on oxygen transport. The adaptive process is further favored by the apparent absence of significant venous admixture in normal high altitude residents and by the fact that true venous shunting is minimal.

References

Haab, P. E., D. R. Held and L. E. Farhi (1967). Readjustments of ventilation-perfusion relationships in the lung at altitude. In: Exercise at Altitude, ed. by R. Margaria. Amsterdam, Excerpta Med. Found., pp. 108–111.

Hurtado, A. (1964). Animals in high altitudes: resident man. In: Handbook of Physiology. Section 4. Adaptation to the Environment, ed. by D. B. Dill. Washington, D. C., American Physiological Society, pp. 843–860.

Karetzky, M. S. and J. C. Mithoefer (1967). The cause of hyperventilation and arterial hypoxia in patients with cirrhosis of the liver. *Am. J. Med. Sci.* 254: 797–804.

Kreuzer, F., S. M. Tenney, J. C. Mithoefer and J. Remmers (1964). Alveolar-arterial oxygen gradient in Andean natives at high altitude. *J. Appl. Physiol.* 19: 13–16.

Kronenberg, R. S., P. Safar, J. Lee, F. Wright, W. Noble, E. Wahrenbrock, R. Hickey, E. Nemoto and J. W. Severinghaus (1971). Pulmonary artery pressure and alveolar gas exchange in man during acclimatization to 12,470 ft. *J. Clin. Invest.* 50: 827–837.

Penaloza, D., F. Sime, N. Banchero, R. Gamboa, J. Cruz and E. Marticorena (1963). Pulmonary hypertension in healthy men born at high altitudes. *Am. J. Cardiol.* 11: 150–157.

Rahn, H. and W. O. Fenn (1955). A Graphical Analysis of the Respiratory Gas Exchange. American Physiological Society, Washington, D.C.

Raine, J. M. and J. M. Bishop (1964). Alterations in ventilation-perfusion relationships in the lung after breathing inert dust or bronchoconstrictor aerosols and after short periods of voluntary hyperventilation. *J. Clin. Invest.* 43: 557–570.

Reeves, J. T., J. Halpin, J. E. Cohn and F. Daoud (1969). Increased alveolar-arterial oxygen difference during simulated high altitude exposure. *J. Appl. Physiol.* 27: 658–661.

Remmers, J. E. and J. C. Mithoefer (1969). The carbon monoxide diffusing capacity in permanent residents at high altitudes. *Respir. Physiol.* 6: 233–244.

West, J. B. (1969). Ventilation-perfusion inequality and overall gas exchange in computer models of the lung. *Respir. Physiol.* 7: 88–110.