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PULMONARY GAS EXCHANGE, DIFFUSING CAPACITY IN NATIVES AND NEWCOMERS AT HIGH ALTITUDE

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Abstract. At high altitude, in resting conditions, no differences have been observed between High Altitude Natives (HAN) and acclimatized Sea Level Natives (SLN) in $\mathrm{AaD_{O_2}}$, $\mathrm{aAD_{CO_2}}$ or venous admixture.

In acclimatized SLN, $\mathrm{AaD_{O_2}}$ is smaller than at sea level because of:

(1) The minor effect on arterial oxygenation of the probably constant venous admixture.

(2) The reduction of $\dot{V}_A/\dot{Q}$ inequality as shown by a smaller $\mathrm{aAD_{CO_2}}$.

In HAN, $\mathrm{DL_{CO}}$ is greater than in SLN; the contribution of DM or Vc in this difference remains unsettled, mainly because of the difficulties of measurement of DM and Vc in HAN suddenly exposed to acute hyperoxia.

In SLN, in acute hypoxia, $\mathrm{DL_{CO}}$ increased transitorily. Asynchronous mechanisms of adaptation to high altitude are evoked.

Alveolar–arterial O_2 difference
High altitude natives
Lung diffusing capacity
Pulmonary diffusive conductance
Sea level natives
Ventilation/perfusion ratio

Adaptation to high altitude provokes many changes in the mechanisms of gas transport between ambient air and tissues. These changes limit the consequences of the decrease in $\mathrm{PI_{O_2}}$ for the availability of oxygen at the cellular level. However, the existence of an increased efficiency of pulmonary gas exchange is questionable in high altitude natives as well as in newcomers.

The alveolar–arterial oxygen difference ($\mathrm{AaD_{O_2}}$) reflects the efficiency of pulmonary gas exchange. Its components can be affected to a variable extent by altitude: a

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decrease of the part of the $\mathrm{AaD_{O_2}}$ caused by venous admixture and a variable increase of the part related to the pulmonary diffusing capacity may be theoretically predicted. On the other hand, the contribution of ventilation/perfusion distribution to the $\mathrm{AaD_{O_2}}$ at high altitude remains largely unknown.

Measurement of $\mathrm{AaD_{O_2}}$ in high altitude natives (HAN) at rest have given variable results, either lower than (Hurtado, 1964) or identical (Kreuzer *et al.*, 1964; Mithoefer *et al.*, 1972) to sea level native (SLN) values. For SLN, the same dispersion is observed at real or simulated high altitude as compared to sea level values: no change (Pugh *et al.*, 1964; Kreuzer *et al.*, 1964; Kreuzer and Van Lookeren Campagne, 1965; Hansen *et al.*, 1967; Reeves *et al.*, 1969; Kronenberg *et al.*, 1971; Dempsey *et al.*, 1971; Cruz *et al.*, 1975) and a decrease in $\mathrm{AaD_{O_2}}$ have been reported (Houston and Riley, 1947).

In order to evaluate changes in the $\mathrm{AaD_{O_2}}$ components, $\mathrm{AaD_{O_2}}$, $\mathrm{aAD_{CO_2}}$ and pulmonary diffusing capacity for carbon monoxide ($\mathrm{DL_{CO}}$) were studied using different $\mathrm{PI_{O_2}}$ values at sea level and high altitude, in both sea level and high altitude natives.

Subjects and methods

I. OXYGEN AND CARBON DIOXIDE ALVEOLAR-ARTERIAL DIFFERENCE AND ARTERIAL pH

Measurements were carried out at the Instituto Boliviano de Biologia de Altura (IBBA), La Paz, Bolivia (altitude 3650 m, mean barometric pressure 497 torr). Two groups of subjects were studied: 4 SLN, members of the research team sojourning at altitude for three weeks, and 10 high altitude natives, medical students, born and living permanently at this altitude (HAN 3650). All subjects were free of cardio-pulmonary disease by clinical evaluation and by chest X-ray. Informal consent was obtained from subjects before participation in the study. Physical characteristics of the subjects are given in table 1.

An indwelling needle was inserted in a brachial artery after local anesthesia. The seated subject breathed through a mouthpiece and a 2-way Hans Rudolph valve*,

TABLE 1

Physical characteristics of subjects whose alveolar and arterial values were measured

	n	Age (yr)	Weight (kg)	Height (cm)
Sea level natives	4	36.2 ± 1.7	60.7 ± 7.9	173 ± 5.7
High altitude natives (3650 m)	10	23.9 ± 1.4	61.5 ± 1.7	166 ± 1.6

Mean values (± SE) of age, weight and height.

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* Warren E. Collins, Inc., Braintree, MA.

connected by a 3-way stopcock to an inspiration bag filled with either ambient air (PI_{O_2} = 95 torr), an oxygen–nitrogen mixture (PI_{O_2} = 150 torr) or pure oxygen (PI_{O_2} = 450 torr). The expiratory side was vented to the room through a Haldane tube (length 1 m and internal diameter 2.5 cm). After a 10-min adaptation period, the subject was connected successively during 10-min periods to inspiratory bags with increasing P_{O_2}. The PI_{O_2} 150 torr gas mixture was obtained from a Tissot spirometer and checked by electrodes*. At the end of each period, 10 ml of arterial blood were withdrawn in a heparinized glass syringe, and at the same time alveolar gas was sampled from the Haldane tube close to the expiration valve with a 10-ml syringe during inspiration. Arterial blood and alveolar gas were immediately analyzed for P_{O_2}, P_{CO_2} and pH with electrodes*. The apparatus was calibrated with gases and buffer solutions of known composition. The P_{O_2} electrode correction factor for blood–gas difference had been previously determined by tonometry. All measurements were performed at 37 °C. In addition, ideal alveolar P_{O_2} was calculated using the classical alveolar gas equation, assuming that alveolar and arterial P_{CO_2} were similar. Arterial blood hemoglobin concentration was determined by the cyanmethemoglobin method.

2. PULMONARY DIFFUSING CAPACITY FOR CARBON MONOXIDE

DL_{CO} measurements were carried out in three groups of subjects, whose physical characteristics are reported in table 2: group I: 6 SLN, members of the research team; group II: 21 HAN 3650; group III: 4 high altitude natives living at 4600 m (HAN 4600).

Subjects of group III were judged to be healthy only by clinical examination; they lived in a mining town (Milluni, Bolivia) but were carefully selected for no exposure to silicosis risk. In all groups, no subject smoked more than 5 cigarettes a day, and most of them did not smoke at all.

In group I, DL_{CO} was measured at sea level (Rouen, France, altitude 20 m), with PI_{O_2} = 95, 150 and 450 torr, and again after a 3-week period of acclimatization at 3650 m. In addition DL_{CO} was measured in the same SLN group at ambient PI_{O_2},

TABLE 2

Physical characteristics of subjects whose DL_{CO} was measured

	n	Age (yr)	Weight (kg)	Height (cm)
Sea level natives	6	34.7 ± 2.8	65.7 ± 5.9	169.8 ± 3.8
High altitude natives (3650 m)	21	25.8 ± 1.0	59.2 ± 1.5	164.4 ± 1.7
High altitude natives (4600 m)	4	25.7 ± 0.8	60.7 ± 0.8	163.2 ± 2.9

Mean values (± SE) of age, weight and height.

during an 8-day sojourn at High Altitude Research Station, Jungfraujoch (Switzerland), 3500 m, 6 hours after arrival and then twice a day. Finally DL_{CO} was measured in these subjects twice an hour during a 3-hour exposure to acute hypoxia ($PI_{O_2} = 95$ torr) at sea level.

In group II, measurements were carried out at IBBA with $PI_{O_2} = 95$, 150 and 450 torr.

In group III, measurements were carried out at Milluni, with $PI_{O_2} = 80$, 150 and 380 torr.

DL_{CO} was measured using the steady state method ($FI_{CO} = 0.1\%$). End tidal CO concentration (FA_{CO}) was measured using a fast response infrared analyzer* insensitive to CO_2 pressures in the physiological range. The sample line was connected close to the expiratory valve. The analyzer was calibrated just before each measurement. Analyzer response when subject was breathing air (F_{CO_0}), was subtracted from FA_{CO} during inhalation of the carbon monoxide mixture. Expired minute volume ($\dot{V}E$), collected in a Douglas bag, was measured with a dry gas meter checked with a Tissot spirometer. DL_{CO} was calculated from the equation:

$$DL_{CO} = (FI_{CO} - FE_{CO}) \cdot \dot{V}E\ \text{STPD}/(PB - 47) \cdot (FA^{CO} - F_{CO_0})$$

The membrane diffusing component (DM) and pulmonary capillary blood volume (Vc) were calculated with the results of the DL_{CO} measurements at 150 and 450 or 380 torr using the Roughton and Forster (1957) equation:

$$1/DL = 1/DM + 1/\theta Vc \text{ and taking}$$
$$1/\theta = 0.0057\ P\bar{c}_{O_2} + 0.75$$

$1/\theta$ was corrected using the actual hemoglobin concentration, and $P\bar{c}_{O_2}$ was estimated as 10 torr lower than PA_{O_2}.

All the mean results were statistically compared using Student test and, when appropriate, with paired comparison.

Results

ALVEOLAR-ARTERIAL DIFFERENCE FOR OXYGEN AND CARBON DIOXIDE AND ARTERIAL pH (table 3)

No significant difference between SLN newcomers and HAN 3650 was found for AaD_{O_2} or aAD_{CO_2} at the three levels of oxygenation. As expected AaD_{O_2} increased with PI_{O_2} but in both groups was similar to values observed in SLN at sea level in the same conditions of oxygenation (Mellemgaard, 1966; Harris *et al.*, 1974). In addition, no significant difference was found between measured and ideal calculated PA_{O_2}.

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* Rubis 3000, response time = 200 ms for 90% of full deviation. Cosma, F 91430 Igny.

TABLE 3a

Mean measured alveolar and arterial values (± SE) in acclimatized SLN and HAN at 3 levels of oxygenation

	n	PI_{O_2} (torr)	PA_{O_2} (torr)	Pa_{O_2} (torr)	AaD_{O_2} (torr)	PA_{CO_2} (torr)	Pa_{CO_2} (torr)	aAD_{CO_2} (torr)	pHa	Hb (g/l)
Acclimatized		95	61.1 ± 1.7	58.6 ± 1.3	2.5 ± 1.2	27.9 ± 0.9	29.3 ± 0.7	1.4 ± 0.6	7.45 ± 0.02	160.5 ± 5.5
sea level	4	150	110.8 ± 2.4	99.0 ± 3.7	11.8 ± 1.4	28.3 ± 1.1	31.4 ± 0.4	3.2 ± 1.3	7.43 ± 0.01	
natives		450	409.0 ± 7.0	348.3 ± 22.0	60.7 ± 26.0	28.2 ± 1.7	32.8 ± 0.6	4.6 ± 1.1	7.44 ± 0.01	
High altitude		95	61.1 ± 0.9	56.1 ± 1.6	5.0 ± 1.8	30.3 ± 0.8	31.3 ± 1.1	1.0 ± 0.7	7.41 ± 0.01	174.1 ± 9.0
natives	10	150	113.3 ± 2.5	99.8 ± 2.2	13.5 ± 2.2	27.9 ± 1.1	29.9 ± 1.6	2.1 ± 0.7	7.41 ± 0.02	
(3650 m)		450	414.7 ± 3.7	377.6 ± 5.7	37.1 ± 7.4	25.9 ± 1.6	28.7 ± 1.7	2.7 ± 0.6	7.44 ± 0.02	

TABLE 3b

Mean R, calculated alveolar oxygen pressure assuming $P_{A_{CO_2}} = Pa_{CO_2}$ and AaD_{O_2} in SLN and HAN at 3 levels of oxygenation

	n	$P_{I_{O_2}}$ (torr)	Ideal $P_{A_{O_2}}$ (torr)	AaD_{O_2} (torr)	R
Acclimatized sea level natives	4	95	59.3 ± 2.1	0.7 ± 1.2	0.79 ± 0.05
		150	106.1 ± 3.2	7.2 ± 2.4	0.64 ± 0.06
		450	417.1 ± 0.6	68.7 ± 22.8	
High altitude natives (3650 m)	10	95	60.1 ± 0.9	3.9 ± 1.4	0.87 ± 0.02
		150	110.4 ± 3.3	10.6 ± 2.8	0.71 ± 0.04
		450	421.3 ± 1.7	43.7 ± 5.8	

aAD_{CO_2} was small and within the range of error of the gas analyzer. This may explain why in some cases negative values were encountered especially during hypoxia. aAD_{CO_2} increased with $P_{I_{O_2}}$, but in both groups the difference was only significant when the lower and the higher $P_{I_{O_2}}$ were compared ($P < 0.05$). When $P_{I_{O_2}}$ was 95 (ambient air) or 150 torr, mean arterial pH was higher in SLN than in HAN, but this difference was not statistically significant. The arterial pH of HAN was significantly increased ($P < 0.05$) during pure oxygen breathing ($P_{I_{O_2}} = 450$ torr), in comparison with ambient air breathing.

PULMONARY DIFFUSING CAPACITY, MEMBRANE DIFFUSING COMPONENT AND PULMONARY CAPILLARY BLOOD VOLUME

In SLN sojourning for three weeks at 3650 m, DL_{CO} was identical to its sea level value (table 4). Similarly, no change was observed after 6 hours or during an 8-day sojourn at 3460 m. In contrast, DL_{CO} was significantly increased at the onset of hypoxia and decreased progressively to sea level values in approximately three hours (fig. 1). Whereas DL_{CO} was the same in SLN at sea level and after acclimatization, a non-significant increase of D_M and a significant decrease of Vc ($P < 0.05$) were found at high altitude (table 5).

In HAN 3650, DL_{CO} was greater than in acclimatized SLN ($P < 0.01$). In addition the higher the HAN lived, the higher the DL_{CO} was: the difference between HAN 3650 and HAN 4600 was highly significant ($P < 0.001$). The increase in DL_{CO} in HAN 3650 as compared to SLN was only caused by a greater D_M since Vc was the same in the two groups. In HAN 4600, the values of D_M and Vc were very scattered and not interpretable perhaps because it was impossible to measure DL_{CO} with sufficiently high $P_{I_{O_2}}$.

TABLE 4

Mean values (± SE) of DL_{CO} and hemoglobin concentration in 3 groups of subjects at different levels of oxygenation

	n	Altitude during measurement (m)	PI_{O_2} (torr)	DL (ml/mn/torr)	Hb (g/l)
Sea level natives	6	20	95	26.3 ± 2.3	151.2 ± 5.8
			150	20.2 ± 1.8*	
			450	11.8 ± 0.9	
Acclimatized sea level natives	6	3650	95	20.3 ± 1.6*	164.1 ± 5.3
			150	19.9 ± 1.9	
			450	10.4 ± 0.8	
High altitude natives (3650 m)	21	3650	95	28.6 ± 1.4*	174.1 ± 9.0
			150	26.2 ± 1.3	
			450	15.1 ± 0.7	
High altitude natives (4600 m)	4	4600	80	47.5 ± 5.8*	195.4 ± 17.5
			150	44.1 ± 8.7	
			380	21.3 ± 3.2	

Values marked * were performed breathing ambient air.

TABLE 5

Mean values (± SE) of DM and Vc in SLN and HAN

	Sea level natives (20 m)	Sea level natives acclimatized to 3650 m	High altitude natives (3650 m)
DM (ml/mn/torr)	51.5 ± 8.6	158.9 ± 71.2	101 ± 23.9
Vc (ml)	54 ± 5	35.4 ± 3.6	54.3 ± 2.9

Discussion

1. ALVEOLAR ARTERIAL OXYGEN DIFFERENCE

AaD_{O_2} obtained either with calculated PA_{O_2} or with measured PA_{O_2} is always lower than values observed in the literature (table 6). This can be explained in part by the fact that, in this different works, conditions of measurement were different.

TABLE 6

Alveolar–arterial oxygen tension gradient according to other published work

Authors		SLN		HAN	
		Altitude (m)	$\mathrm{AaD_{O_2}}$ at rest (torr)	Altitude (m)	$\mathrm{AaD_{O_2}}$ at rest (torr)
Houston and Riley	(1947)	4300–6500	2		
Terman and Newton	(1964)	3800–4300	12		
Kreuzer *et al.*	(1964)	4600	5.8	4600	10.5
Kreuzer and Van Lookeren Campagne	(1965)	4560	7.2		
Hansen *et al.*	(1967)	4300	8		
Reeves *et al.*	(1969)	5000	7–12		
Raymond and Severinghaus	(1971)	4000	7.4		
Dempsey *et al.*	(1971)	3100	5–8	3100	5
Mithoefer *et al.*	(1972)			3700	6
				4500	9
Weiskopf and Severinghaus	(1972)	4670	4.3–6.1		
Cruz *et al.*	(1975)	4350	11.5	4350	6

Furthermore, when $\mathrm{AaD_{O_2}}$ components are analyzed, it seems little consistent to observe elevated values of $\mathrm{AaD_{O_2}}$ in high altitude.

2. $\mathrm{AaD_{O_2}}$ COMPONENTS

(a) *Venous admixture*

Our $\mathrm{AaD_{O_2}}$ values during pure oxygen inhalation ($\mathrm{PI_{O_2}}$ 450 torr) are similar to those reported by Kronenberg *et al.* (1971), by Raymond and Severinghaus (1971) in acclimatized SLN, and by Mithoefer *et al.* (1972) in HAN. In contrast, they are smaller than those measured by Cruz *et al.* (1975) in HAN and SLN at both low and high altitudes, but these latter values seem unusually high when compared to those commonly observed at low altitude. In the present work, $\mathrm{AaD_{O_2}}$ values are larger in SLN than in HAN but more scattered, and the difference is not significant. Assuming an arterio-venous oxygen difference of 5 vol.%, the calculated venous admixture (Finley *et al.*, 1960) would be 2.2 and 3.6% of the cardiac output for HAN and SLN, respectively. These results are close to those observed at sea level in SLN (Mc Ilroy, 1967).

(b) *Ventilation-perfusion ratio* ($\dot{V}\mathrm{A}/\dot{Q}$)

The magnitude of $\dot{V}\mathrm{A}/\dot{Q}$ inequality at high altitude in both SLN and HAN is controversial, and the larger $\mathrm{AaD_{O_2}}$ values have been attributed to these inequalities. Few $\mathrm{aAD_{CO_2}}$ measurements at high altitude are available, and the observations of negative difference have been considered as technical errors. However decreases of $\mathrm{aAD_{CO_2}}$ at altitude have been reported by several authors (Kreuzer *et al.*, 1964;

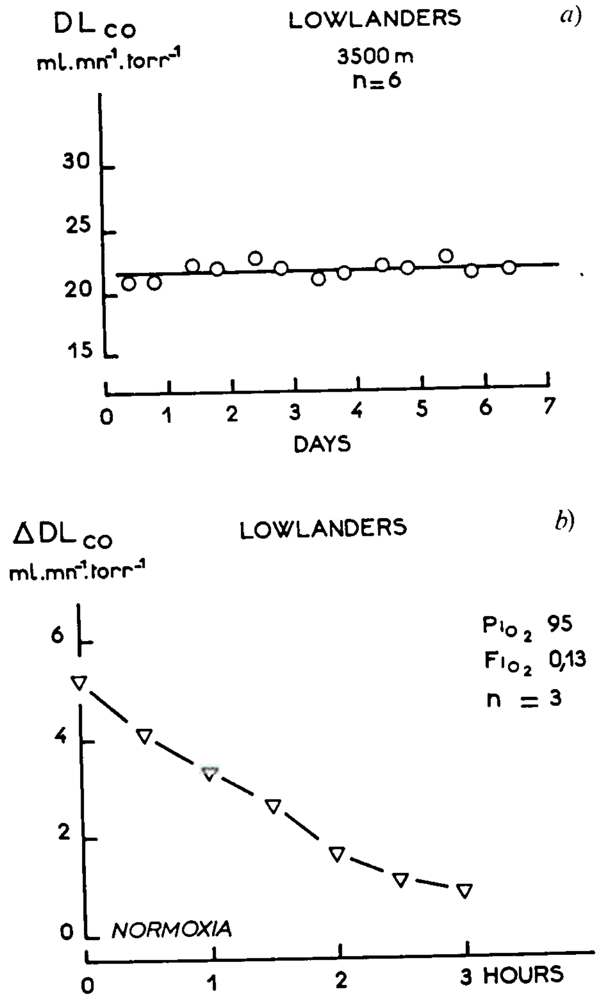

Fig. 1. (A) Values of $D_{L_{CO}}$ in 6 SLN during a 7-day sojourn at 3350 m ($P_{I_{O_2}}$ = 95 torr): (B) $D_{L_{CO}}$ at 30-min intervals after exposure to hypoxia ($P_{I_{O_2}}$ = 95 torr).

Terman and Newton, 1964). On the other hand, Haab *et al.* (1969) observed no modification for aAD_{N_2} and aAD_{CO_2} after five days at 3500 m, and from theoretical considerations they concluded that $\dot{V}_A/\dot{Q}$ inequalities must have increased. Since no significant change in venous admixture have been found in our subjects at high altitude, the observed reduction of aAD_{CO_2} at 3650 m can be interpreted as an improvement in $\dot{V}_A/\dot{Q}$ distribution. Discrepancies between the above results may be due to different timing in experimentation. During altitude acclimatization, circulatory, ventilatory and hematologic adaptations are not synchronous. The increase of ventilation is progressive over several days (Lefrançois *et al.*, 1972) whereas the cardiac output increases abruptly and then returns to sea level values

(Klausen, 1966). Hemoglobin concentration increases progressively. The increase in pulmonary arterial pressure should improve lung perfusion especially in the sitting or upright position (Dawson and Grover, 1974). From the above adaptations, reduced $\dot{V}_A/\dot{Q}$ inequalities can be expected (Lenfant and Sullivan, 1971).

The significant decrease in AaD_{O_2} observed when subjects breathed ambient air ($P_{I_{O_2}} = 95$ torr) instead of the relatively hyperoxic mixture ($P_{I_{O_2}} = 150$ torr) suggests that the distribution component in the gradient is small; it has been shown that hypoxia changes the distribution component of the AaD_{O_2} to a very small extent (West, 1965; Riley and Permutt, 1973). In addition, a small contribution of $\dot{V}_A/\dot{Q}$ inequality to the AaD_{O_2} at high altitude is suggested by the small value of aAD_{CO_2}: 1.4 torr in SLN and 1.0 torr in HAN, both of which are lower than in relative hyperoxia ($P_{I_{O_2}} = 150$ torr). Once more, this is probably caused by an increase in pulmonary arterial pressure during hypoxia (Larson and Severinghaus, 1962; Askrog, 1966; Lenfant, 1966).

(c) *Diffusion*

From the above discussion concerning the contribution of $\dot{V}_A/\dot{Q}$ inequality and venous admixture, the diffusing component must be small since the AaD_{O_2} is smaller at altitude. Weiskopf and Severinghaus (1972) have computed a theoretical diffusion component of 1.1 torr in SLN after three days at 4670 m. In HAN this component is probably less because their $D_{L_{CO}}$ is 40% greater than that of acclimatized SLN. Similar results concerning $D_{L_{CO}}$ have been observed in subjects of different ethnic origin (Cerny *et al.*, 1973; De Graff *et al.*, 1965; Kreuzer and Van Lookeren Campagne, 1965; Guleria *et al.*, 1971; West, 1962; Remmers and Mithoefer, 1969). In HAN, the greater their dwelling altitude, the greater is $D_{L_{CO}}$: in HAN 4600, $D_{L_{CO}}$ is 66% higher than in HAN 3650. This observation does not agree with the results of Remmers and Mithoefer (1969), but in this latter work subjects were studied at 1000 m lower than their actual living altitude. In our case, several mechanisms can be suggested to explain the higher $D_{L_{CO}}$ observed in HAN 3650 as compared to acclimatized SLN (8.3 ml/mn/torr). (1) HAN 3650 were 9 years younger and their height was 5 cm smaller than that of SLN. According the prediction equation for $D_{L_{CO}}$ at sea level (Pasquis *et al.*, 1973), these differences can only account for a 1.1 ml/mn/torr increase in $D_{L_{CO}}$ in HAN 3650. (2) At 3650, the hemoglobin concentration was 10 g/l higher in HAN 3650 than in acclimatized SLN. With such a difference, assuming a $P\bar{c}_{O_2}$ of 90 torr and using the D_M and Vc values calculated in the present work, $D_{L_{CO}}$ would be only 1.3 ml/mn/torr higher in HAN 3650 than in SLN. (3) $D_{L_{CO}}$ measurement in the steady state is influenced by pulmonary ventilation (Guleria *et al.*, 1971), but this factor cannot provide an explanation since acclimatized SLN had a higher pulmonary ventilation than HAN 3650. (4) A significant correlation exists between steady state $D_{L_{CO}}$ and Functional Residual Capacity (FRC). FRC is slightly larger in HAN than in SLN (Cruz *et al.*, 1975), and this difference is too small to account for the larger $D_{L_{CO}}$ in HAN. Since the larger HAN $D_{L_{CO}}$ cannot be entirely explained by the above factors, it is usually attributed to a morphologic adaptation of the lung to early life in hypoxic conditions (Burri and Weibel, 1971).

This larger DL$_{CO}$ may be the consequence of an increase in DM and/or Vc. So far, measurements of these two factors have yielded too many contradictory results to permit confident interpretation. As compared to SLN, DM in HAN has been found both unchanged (Guleria *et al.*, 1971) or increased (Remmers and Mithoefer, 1969), and Vc unchanged (Guleria *et al.*, 1971; Remmers and Mithoefer, 1969) or increased (De Graff *et al.*, 1965) in HAN. In the present work, increased DL$_{CO}$ seems to be caused only by an increased DM.

These ambiguous results with respect to DM and Vc are in contrast with the good agreement concerning DL$_{CO}$ in altitude natives. Several factors can be considered: a large scattering in DM and Vc data and the poor reproducibility in these measurements have been emphasized (Krumholz, 1966, Castillon du Peron *et al.*, 1976). Other important factors concern the doubt about value of θ, which is related to the hemoglobin affinity for oxygen, the possible interaction with CO_2 pressure (Forster and Crandall, 1976) and the pulmonary capillary hematocrit. Finally, Vc and DM are calculated from measurements carried out with different levels of oxygenation; it is generally assumed that these conditions do not modify Vc or DM (Roughton and Forster, 1957). However the increase observed in SLN DL$_{CO}$ during acute *versus* prolonged hypoxia (30%, $P < 0.01$) makes this assumption questionable especially in HAN, born and living in hypoxia and suddenly exposed to acute hyperoxia.

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