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Lung diffusing capacity and exercise in subjects with previous high altitude pulmonary oedema

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ABSTRACT: Subjects with a history of high-altitude pulmonary oedema (HAPE) have increased pulmonary artery pressure and more ventilation-perfusion (V'_A/Q') inhomogeneity with hypoxia and exercise. We used noninvasive methods to determine whether there are differences in the pulmonary diffusing capacity for carbon monoxide ($D_{L,CO}$) and cardiac output (Q') during exercise, indicative of a more restricted pulmonary vascular bed in subjects with a history of HAPE.

Eight subjects with radiographically documented HAPE and five controls with good altitude tolerance had standard pulmonary function testing and were studied during exercise at 30 and 50% of normoxic maximal oxygen consumption (V'_{O_2}) at an inspiratory oxygen fraction of 0.14 and 0.21. $D_{L,CO}$ and Q' were measured by CO and acetylene rebreathing techniques.

HAPE-resistant subjects had 35% greater functional residual capacity than HAPE-susceptible subjects. Vital capacity and total lung capacity were also 7–10% greater. There were no differences in airflow rates or resting diffusing capacity. However, $D_{L,CO}$ in HAPE-susceptible subjects was lower in hypoxia and with exercise, and showed less increase (32 *versus* 49%) with the combined stimulus of hypoxic exercise. HAPE-susceptible subjects had smaller increases in stroke volume, Q', and ventilation during exercise.

The findings are consistent with lower pulmonary vasoconstriction, greater vascular capacitance and greater ventilatory responsiveness during exercise in subjects who are resistant to high-altitude pulmonary oedema. Their larger lung volumes suggest a constitutional difference in pulmonary parenchyma or vasculature, which may be a determinant of high-altitude pulmonary oedema resistance.
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High-altitude pulmonary oedema (HAPE) is a potentially lethal condition in which increased pulmonary artery pressure (P_{pa}) and marked pulmonary vascular constriction are found. Although the exact mechanisms of HAPE are not completely understood, elevated P_{pa}, which has been demonstrated in several previous studies [1–4], may play an important role in its development. Increasing P_{pa} in combination with regional inhomogeneous vasoconstriction may lead to hyperperfusion of lung regions with less vasoconstriction [5, 6] and more interstitial fluid formation, if not actual alveolar-capillary barrier disruption [7]. Fluid accumulation beyond the limits of local reabsorptive capacity may lead to interstitial oedema and ventilation-perfusion (V'_A/Q') inhomogeneity, the latter demonstrated by scintigraphy [6, 8] and by the multiple inert gas elimination technique [9]. During the first hours, oedema of the lung does indeed have an inhomogeneous radiographic appearance [4, 5, 10]. Before the development of clinical oedema gas exchange limitation and arterial hypoxaemia can be demonstrated in subjects susceptible to HAPE [3, 4, 11, 12]. These findings are affected both by the degree of hypoxia and the intensity and duration of concomitant exercise [13, 14].

It has been shown that P_{pa} reduction decreases the gas exchange abnormalities of HAPE and hastens its resolution, probably by reducing the formation of pulmonary interstitial oedema and redistributing blood flow to better ventilated regions [6, 15]. It has been also demonstrated, that subjects with a history of HAPE have increased P_{pa} values during exercise in hypoxia and normoxia [13, 14] and concomitantly higher V'_A/Q' mismatch [9]. Interestingly, several reports [4, 14, 16] have documented that HAPE resistant subjects have roughly 10% greater vital capacity (VC) leading ELDRIDGE *et al.* [14] to speculate that this might indicate a smaller vascular bed in subjects susceptible to HAPE.

Because measurements of P_{pa} or V'_A/Q' mismatch by scintigraphy or inert gas elimination are invasive and/or technically difficult there is a need for other less invasive techniques to identify those people who may be at risk of developing HAPE. The present study examined whether differences can be found between subjects susceptible to HAPE and those with good altitude tolerance, in noninvasive measurements of lung diffusing capacity ($D_{L,CO}$) and cardiac output ($\overline{Q}'$). If such differences exist they probably represent the greater pulmonary vascular resistance and/or

a reduced vascular bed in subjects susceptible to HAPE which may predispose climbers to earlier and clinically important interstitial oedema formation and V'_A/Q' mismatch during ascent to high altitude.

Material and methods

Subject selection

We studied 13 clinically healthy male mountaineers whose susceptibility to acute mountain sickness (AMS) and HAPE was established from previous ascents to high altitude (4,559 m). All were natives of low altitudes and climbed from 1,170 m to 4,559 m within 24 h, with an overnight stay at 3,611 m. Symptoms of AMS were determined by the AMS-C Score of the environmental symptom questionnaire (ESQ) of SAMPSON *et al.* [17] and by clinical score [12]. Subjects were considered not to be susceptible to AMS if their AMS-C Score was smaller than 0.7 and clinical score less than 3 in all examinations at high altitude. Subjects were considered susceptible to HAPE if they had at least two radiographically documented episodes of HAPE, one of which had been diagnosed by the authors at the time of illness. These subjects were drawn from a larger set of subjects reported by HOHENHAUS *et al.* [16] in whom low altitude ventilatory and pulmonary vascular responsiveness to acute hypoxia in Heidelberg, Germany (100 m) had been used to test their predictive value in determining susceptibility to AMS and HAPE. The present subset of subjects were asked to participate and came to Ulm, Germany (560 m, barometric pressure 96.2±1.0 kPa (723±7.5 mmHg)). Because it was difficult to convince subjects without past altitude illness to participate in an extensive series of experiments dealing with high altitude problems, an exact matching in age range and number of HAPE and control subjects was not possible. Examiners in Ulm were informed about the study hypothesis but were blinded to clinical status of the subjects until final data evaluation of the data was performed. The study was approved by the ethics committee of the Medical Faculty of the University of Heidelberg. All subjects gave written informed consent prior to their inclusion in the study.

Pulmonary function measurements

Resting pulmonary function data were measured in Heidelberg using a body plethysmograph with spirometer (Universal Bodytest; Jaeger, Würzburg, Germany). In addition to lung volume and flow measurements, single breath diffusing capacity of the lung for carbon monoxide ($D_{L,CO,sb}$) was also determined. The best values from three attempts (according to quality of registration and absolute values) were recorded as both absolute values and as percentages of the predicted values, based upon age and body height.

Exercise protocol and gas exchange measurements

The subjects exercised on an upright stationary cycle ergometer (Ergotest; Jaeger, Würzburg, Germany). Resting values were taken during unloaded pedalling. Following these measurements, the subjects then performed 5 min of exercise at 30% of maximal oxygen consumption ($V'_{O_2,max}$) and then at 50% $V'_{O_2,max}$. The V'_{O_2max} value of each individual in normoxia had been established 2–3 months earlier in Heidelberg, and the work (in W) necessary to attain these fractions of normoxic $V'_{O_2,max}$ in each subject were given to the investigators in Ulm. After resting for at least 30 min following the normoxic exercise bout, subjects performed hypoxic exercise by breathing air with a reduced oxygen content (inspiratory oxygen fraction (F_{I,O_2}) = 0.14, inspiratory partial pressure of oxygen (P_{I,O_2}) = 12.9±0.7 kPa (97.1±5.6 mmHg)) which was delivered from a volume-controlled gas mixing apparatus. The hypoxic gas was mixed from cylinders containing nitrogen and oxygen (purity 10^{-5}), partially humidified and warmed to ~18°C and delivered directly at atmospheric pressure to a switching valve connected *via* a tube and a y-valve to the mouth piece. Baseline measurements were taken after breathing the hypoxic gas for 20 min. The exercise protocol in hypoxia was identical to the ambient air experiment, with the subjects again exercising at 30 and 50% of their normoxic $V'_{O_2,max}$.

Subjects breathed through a mouth piece connected to a low-resistance, high-resolution ultrasonic flow-sensing device (TUBA; Medese Co., Zurich, Switzerland). For breath-by-breath analysis of gas exchange and ventilation, respired gas was sampled continuously from the mouthpiece (3 $mL \cdot s^{-1}$) at the proximal end of the flow tube. Sampled gas was analysed for O_2, CO_2 and N_2 by mass spectrometer (AMIS 2000; Innovision A/S, Odense, Denmark; Quadrupole QMA 20; Balzers AG, Balzers, Lichtenstein) with a sampling frequency of 50 Hz and a transit delay of about 300 ms. The same setup was used for the rebreathing measurements, respired gas was analyzed for $C^{18}O$, C_2H_2, He, SF_6, CO_2, O_2 and N_2 with a sampling frequency of 33 Hz. Switching between ambient or hypoxic air breathing and rebreathing bag was performed by an electromechanically controlled valve, which added a dead space of 120 mL to the setup during rebreathing.

Rebreathing measurements of $D_{L,CO}$ and cardiac output

The rebreathing manoeuvre was performed at rest and in the 5th min of exercising at 25% and 50% of $V'_{O_2,max}$. After 2 s of breath-holding in the midexpiratory position, rebreathing started and was performed for 20 s at rest and for 12 s during exercise. The test gas mixture contained 0.4% $C^{18}O$, 0.4% C_2H_2, 5% He, 5% SF_6, 5% CO_2 and 35% O_2 in N_2, gas bag volume was 60% of VC at rest and about 75% during exercise. $\overline{Q}'$, $D_{L,CO}$ and oxygen uptake (V'_{O_2}) were calculated from concentrations of acetylene, carbon monoxide and oxygen at the mouth during the re-breathing manoeuvre [18–20]. Calculations were perfor-med according to a single-alveolus one-compartment lung model [19]. Disappearance curves were calculated by the least square method applied to normalized and log-transformed data points on alveolar plateaus. Because the model that was used requires complete mixing between alveolar and bag volumes, two breaths after the end of the first inspiration were usually excluded from the analysis. Complete mixing was controlled by equilibrium of He and SF_6 curves and calculations were performed only after evidence

of equilibrium [20]. Furthermore, no more than 4–6 breaths were included in the analysis to avoid the influence of recirculation [18, 21]. Stroke volume (SV) was calculated from $\overline{Q}'$ and cardiac frequency. In our laboratory, coefficients of variation for duplicate rebreathing measurements for V'_{O_2}, $\overline{Q}'$, SV and $D_{L,CO}$ are typically: 5.24%, 3.15%, 3.81% and 8.94%. respectively [22], and there is an excellent agreement between measurements of $\overline{Q}'$ by rebreathing and by direct Fick method [23].

Blood and alveolar gas pressures

Arterial oxygen tension (P_{a,O_2}), carbon dioxide tension (P_{a,CO_2}) and oxygen saturation (S_{a,O_2}) were estimated from capillary blood from the hyperaemized earlobe (OSM3 and ABL500; Radiometer, Copenhagen, Denmark) in the last 10 s before rebreathing. Additionally, haemoglobin (Hb) and carboxyhaemoglobin (HbCO) were measured in capillary blood by multiwavelength spectroscopy (OSM3; Radiometer, Copenhagen, Denmark) after each rebreathing procedure. These values and any calculated from them are designated "cap" to distinguish them from true arterial values. Tests were terminated for safety reasons if HbCO values higher than 6% and $S_{a,O_2,cap}$ values lower than 70% were measured.

Alveolar oxygen tension (P_{A,O_2}) was evaluated manually as "mean" P_{A,O_2}, from the expirogram of O_2 at 50% of tidal volume (V_T) [24]. The alveolar-capillary oxygen difference is the difference between these alveolar values and capillary blood.

Statistical analysis

Group differences were tested with Student's t-test for normally distributed data and, if not applicable, with the nonparametric Wilcoxon signed rank test for paired data and the Mann Whitney test for unpaired data. Values are expressed as means and standard deviations. Values were also compared by multifactor analysis of variance (ANOVA) for normally distributed data with the Newman-Keuls modification for range tests. Analysis was performed with covariates, if their use was appropriate. For all tests, the assumed level of significance for differences was equal to or less than 0.05.

Results

HAPE and AMS history

Table 1 gives the clinical data of both groups at an altitude 4559 m. The AMS-C and clinical scores differed significantly between the HAPE and the control group, and show that the subjects control group were healthy and not susceptible to HAPE or significant AMS at this altitude. The subjects of the HAPE group had experienced two to four episodes of radiographically and clinically documented HAPE and, not surprisingly, more AMS.

Table 1. – High-altitude pulmonary oedema (HAPE) and acute mountain sickness (AMS) history

	HAPE (n=8)	Control (n=5)
HAPE episodes n	2.7	0
AMS Score+	1.3±0.95	0.43±0.02*
Clinical Score+	5.43±1.8	2.61±0.6

Values are presented as mean±SD. *: p<0.05 *versus* HAPE; +: at 4559 m altitude.

Baseline anthropometric, lung function and $V'_{O_2,max}$ *data*

Table 2 shows the characteristics of both groups. There were no significant differences in age and weight, but the height and body surface area of the HAPE group were smaller and their mean age higher, although, body mass index was not different. HAPE susceptible subjects had smaller total lung capacity (TLC) and VC than the controls (p=0.005 and 0.001), but as a consequence of their smaller height and greater age these did not reach the traditional statistical significance level of 0.05 when expressed as a percentage of the predicted value (p=0.126 and 0.135, respectively). There were no differences in residual volume, either in absolute or percentage predicted values. However, there was a significant 35% greater functional residual capacity (FRC), both in absolute and percentage predicted values (p=0.001) in the control group, although the FRC in both groups was still within normal limits. There were no significant differences in air flow rates. $D_{L,CO,sb}$ was slightly higher in the control subjects, but when the data were presented as percentage predicted, these differences were nonsignificant. There was no difference in normoxic $V'_{O_2,max}$ between the groups.

Cardiac output and $D_{L,CO}$ *during normoxic and hypoxic exercise*

The submaximal exercise $\overline{Q}'$ and $D_{L,CO}$ values are shown in table 3. $\overline{Q}'$ was slightly lower in the HAPE susceptible group at both exercise levels. The corresponding

Table 2. – Lung function and maximal oxygen consumption ($V'_{O_2,max}$)

	HAPE (n=8)	Control (n=5)	p-value
Age yrs	45±8.4	38.2±11.4	0.238
Weight kg	74.1±5.0	77.8±8.5	0.173
Height cm	171.3±3.0	183.8±6.6	0.030
BSA cm^2	1.86±0.07	2.00±0.13	0.046
BMI $kg \cdot cm^{-2}$	23.1±2.37	25.3±2.10	0.110
TLC L	6.88±0.73	8.52±0.52	0.005
TLC % pred	102.9±11.2	111.8±7.9	0.126
FVC L	4.85±0.44	6.26±0.29	0.001
FVC % pred	106.4±8.1	113.4±12.4	0.135
FRC L	2.96±0.63	4.46±0.41	0.001
FRC % pred	90.1±18.1	124.0±9.8	0.001
$D_{L,CO,sb}$ % pred	35.1±5.3	41.0±7.2	0.125
$D_{L,CO,sb}$ $mL \cdot mmHg^{-1} \cdot min^{-1}$	115.9±14.3	114.6±14.6	0.880
FEV1/FVC %	80.2±4.1	75.7±3.9	0.172
$V'_{O_2,max}$ $mL \cdot min^{-1} \cdot kg^{-1}$	45.1±5.0	50.1±8.4	0.374

Values are presented as mean±SD. HAPE: high-altitude pulmonary oedema; BSA: body surface area; BMI: body mass index; TLC: total lung capacity; % pred: percentage of predicted value, corrected for age, gender, height and weight for a Middle European population; FVC: forced vital capacity; FRC: functional residual capacity; $D_{L,CO,sb}$: single-breath diffusing capacity of the lung for carbon monoxide; FEV1: forced expiratory volume in one second; FVC: forced vital capacity.

Table 3. – Haemodynamic and gas exchange values during exercise

	Normoxia			Hypoxia		
	Rest	Exercise		Rest	Exercise	
		30% $V'_{O_2,max}$	50% $V'_{O_2,max}$		30% $V'_{O_2,max}$	50% $V'_{O_2,max}$
$V'_{O_2,max}$ mL·min^{-1}·kg^{-1}						
HAPE	7.6±2.5	15.4±4.3	23.7±7.2	7.2±1.5	15.0±2.4	24.6±5.4
Control	7.9±2.4	16.8±3.3	26.9±4.8	7.9±2.1	17.5±1.9	25.3±5.8
$D_{L,CO}$ mL·min^{-1}·kg^{-1}						
HAPE	26.7±5.5	28.6±6.4	32.1±7.0	28.1±6.0	31.2±7.9	35.2±6.6
Control	29.4±6.4	35.4±5.7*	38.7±7.8*	38.7±6.8	45.3±13.6*	47.2±10.5*
$\overline{Q}'$ L·min^{-1}						
HAPE	6.2±1.5	8.2±1.3	10.6±1.9	6.2±1.9	8.5±1.6	12.1±2.3
Control	6.9±1.4	11.1±1.4*	12.9±1.4*	7.3±1.7	11.2±2.3*	15.8±4.4*
Stroke volume mL						
HAPE	83±19	86±13	90±12	74±14	78±18	88±13
Control	87±14	121±28*	117±30*	89±22	110±22*	123±33*
f_C beats·min^{-1}						
HAPE	75±13	95±17	118±20	83±18	107±16	137±18
Control	77±12	92±11	110±17	82±13	102±15	128±9

Values are presented as mean±SD. HAPE: high altitude-pulmonary oedema; V'_{O_2}: oxygen consumption; $V'_{O_2,max}$: maximal V'_{O_2}; $D_{L,CO}$: pulmonary diffusing capacity of the lung for carbon monoxide; $\overline{Q}'$: cardiac output; f_C: cardiac frequency. *: p<0.05 *versus* HAPE. Inspiratory partial pressure of oxygen was 19 kPa (143 mmHg) in normoxia was 13 kPa (97 mmHg) in hypoxia.

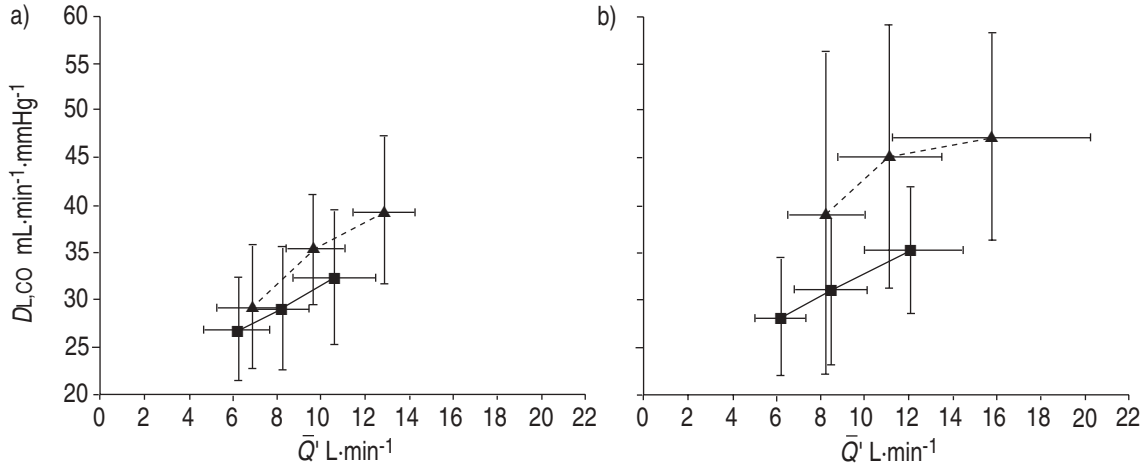

Fig. 1. – a) Diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) as a function of cardiac output ($\overline{Q}'$) in normoxia (barometric pressure (P_{bar}) 96.2 kPa (723 mmHg), inspiratory partial pressure of oxygen (P_{I,O_2}) (143 mmHg) and inspiratory oxygen fraction (F_{I,O_2}) 0.21). b) $T_{L,CO}$ as a function $\overline{Q}'$ in hypoxia (P_{bar} 96.2 kPa (723 mmHg), P_{I,O_2} 12.9 kPa (97 mmHg) and F_{I,O_2} 0.14. Values are presented as mean±SD, for eight subjects with prior high-altitude pulmonary oedema (HAPE; —■— : and five control subjects (----▲----).

values of $\overline{Q}'$ and $D_{L,CO}$ are depicted in figure 1 for normoxia and hypoxia. $D_{L,CO}$ showed an attenuated increase in HAPE susceptible subjects compared to the increase of $\overline{Q}'$ induced by the stimuli of exercise and hypoxia. Moreover, stroke volume was lower in HAPE susceptible subjects during exercise compared to controls, in both normoxia and hypoxia, and the difference was significant with ANOVA (F=13.0, p<0.05), when adjusted with $\overline{Q}'$ as a covariate. There was no statistical difference in cardiac frequencies, although at both levels of exercise, the control subjects had lower values.

Rebreathing $D_{L,CO}$ was higher in the control group at all exercise measurements and the differences were statistically significant (ANOVA, F=3.0, p<0.05) and remained so after adjustment for both age and $\overline{Q}'$ (F=5.8, p<0.05), factors which are known to affect the measurement [21, 22, 25]. With regard to the influence of body size, which was lower in the HAPE Group, $D_{L,CO}$/BSA was also lower in these subjects (ANOVA, F=4.0, p<0.05, adjusted for cardiac index and age). To eliminate the potential confounding influence of differing body sizes and ages between groups, the data also reveal that control subjects had a 49% increase in $D_{L,CO}$ with the combined stimulus of hypoxic exercise (rest-normoxia *versus* 50% $V'_{O_2,max}$-hypoxia) in contrast to the 32% increase observed in the subjects susceptible to HAPE (p=0.03).

Ventilation and blood gas data

Selected ventilation and blood gas data are presented in table 4. During exercise in normoxia and hypoxia, ventilation was lower in HAPE (ANOVA, F=10.1, p<0.05). The lower ventilation was affected by both lower V_T and respiratory frequency in the HAPE-susceptible group, consequently, carbon dioxide tensions were higher in the HAPE susceptible group, but the differences were not significant, in part because the control group had slightly higher V'_{O_2}, and, thus, higher CO_2 production. There were no significant differences between the HAPE and control groups for

Table 4. – Ventilation and blood gas data during exercise

	Normoxia			Hypoxia		
	Rest	Exercise		Rest	Exercise	
		30% $V'O_{2,max}$	50% $V'O_{2,max}$		30% $V'O_{2,max}$	50% $V'O_{2,max}$
V' L·min^{-1}						
HAPE	18.8±10.6	26.2±8.5	40.6±9.9	13.4±6.1	25.5±6.2	50.0±7.8
Control	19.3±11.4	33.3±6.0*	55.5±9.9*	16.5±3.7	39.5±7.6*	63.9±19.9*
f_R breaths·min^{-1}						
HAPE	16.9±4.2	15.3±3.8	17.4±3.4	15.4±2.2	13.7±2.2	18.7±4.7
Control	18.6±4.0	15.7±6.1	19.2±4.5	17.3±0.6	20.6±3.9*	21.7±2.6*
V_T L						
HAPE	1.38±0.45	1.76±0.70	2.29±0.47	0.80±0.30	2.00±0.60	2.70±0.44
Control	1.15±0.36	2.34±0.92	3.06±1.18	1.10±0.50	2.00±0.70	3.04±1.17
$P_{a,O_2,cap}$ mmHg						
HAPE	82.2±6.0	79.3±3.1	81.0±7.4	47.6±6.2	41.7±6.2	38.8±4.8
Control	82.5±8.7	83.5±2.7	81.5±9.4	50.3±11.3	43.2±14.6	44.4±12.4
$S_{a,O_2,cap}$ %						
HAPE	96.1±1.2	95.8±0.5	95.3±1.4	86.8±5.9	78.6±5.6	77.9±5.0
Control	96.1±0.5	95.2±1.0	95.2±1.0	84.7±7.3	76.6±11.4	77.8±10.1
$P_{a,CO_2,cap}$ mmHg						
HAPE	36.9±3.4	39.4±2.7	39.2±4.0	32.6±4.4	34.6±3.7	34.9±2.2
Control	36.9±1.5	38.5±2.7	37.6±1.0	30.8±3.8	30.9±5.7	31.6±6.5
$P_{A\text{-}c,O_2}$						
HAPE	26.2±3.5	19.2±8.8	18.9±5.4	14.3±5.5	17.3±4.1	21.3±5.2
Control	24.3±4.7	15.4±3.8	17.8±1.7	14.2±3.4	13.6±5.3	13.6±3.1*

Values are presented as mean±SD. *: p<0.05 *versus* HAPE. V': ventilation; f_R: respiratory frequency; V_T: tidal volume; $P_{a,O_2,cap}$, $P_{a,CO_2,cap}$ and $S_{a,O_2,cap}$: arterial oxygen tension, arterial carbon dioxide tension and arterial oxygen saturation, respectively, measured from capillary blood from hyperaemized earlobe; $P_{A\text{-}c,O_2}$: arterial-capillary partial pressure difference for oxygen measured from capillary blood from hyperaemized earlobe. Inspiratory partial pressure of oxygen was 19 kPa (143 mmHg) in normoxia and 13 kPa (97 mmHg) in hypoxia. For further definitions, see table 3.

arterial oxygenation, capillary oxygen tension and alveolar-capillary partial pressure difference for oxygen at rest or during exercise.

Discussion

Among subjects, with previous identical high-altitude exposure and documentation of susceptibility or resistance to HAPE, we found that those who had developed HAPE had lower functional residual capacity, but no statistically significant differences in air flow rate, residual volume or resting transfer factor of the lung. With normoxic and hypoxic exercise to 50% of normoxic $V'O_{2,max}$, HAPE-prone subjects had smaller increases in pulmonary diffusing capacity, cardiac output, stroke volume and ventilation.

Resting pulmonary function: volumes and flow rates

The resting pulmonary function data revealed significant differences between the groups in TLC, VC, FRC, forced expiratory volume in one second (FEV1), but not in FEV1/VC or $T_{L,CO}$. With regard to the differences in lung volumes, in common with VISWANATHAN *et al.* [4] and PODOLSKY *et al.* [9], we found that subjects with a history of HAPE had approximately 10% smaller maximal lung volumes, assessed either as TLC or VC. In the larger set of subjects studied by HOHENHAUS *et al*. [16], from which the subjects for this study were recruited, TLC and VC were also similarly larger in control subjects when expressed relative to body surface area. However, due to the smaller subset of HAPE susceptible subjects and control subjects in the present study, the only lung volume difference that remained statistically significant when expressed as a percentage of the predicted value was FRC. The likeliest ex-planation is that our smaller sample size leaves open the possibility of a beta or type II error for TLC and VC differences, namely falsely rejecting a true difference that is seen when sample sizes are larger and more homogeneous.

Although still within the normal percentage predicted range, the FRC of HAPE-susceptible subjects (90%) in the present study is considerably lower than in normal subjects (124%). Although we cannot exclude a subtle effect of different body configuration on FRC, the body mass index did not differ between the groups (table 2). Furthermore, the unreported FRC data of the larger group of 10 HAPE susceptible and 10 control subjects studied by HOHENHAUS *et al*. [16], in whom there were no differences in body size and height, show the same striking differences in FRC (3.19±0.53 *versus* 4.49±0.80 L; and 97±14 *versus* 128±22% pred). Since it is doubtful that differences in chest wall compliance or respiratory muscle stren-gth exist between groups, the finding of greater FRC in HAPE-resistant subjects suggests that there may be an intrinsic difference in lung compliance and parenchymal composition between groups, which can be reflected in differences in maximal lung volumes when studied in a larger number of subjects [4, 9, 16]. It is of interest to note that Tibetans, a high-altitude population representing a group in whom natural selection has enhanced certain ad-aptive features, have larger lung volumes relative to body size [26] and a tenfold lesser incidence of HAPE when re-turning to high altitude [27] than their low altitude neighbours, the Chinese Han.

Although we cannot rule out that differences in FRC and other lung volumes might also be a consequence of HAPE, the relatively noninflammatory nature of HAPE and its quick resolution with descent and/or oxygen [10] speak against this possibility. Further suggestive of lesser

lung compliance are the somewhat greater FEV1/VC values in the HAPE-susceptible group, a statistically significant finding noted by Viswanathan *et al*. [4] in their large study of nearly 100 subjects, and approaching statistical significance in the data of Podolsky *et al.* [9] and Hohenhaus *et al.* [16].

Pulmonary diffusion capacity and gas exchange at rest and exercise

Despite the above differences in resting lung volumes, HAPE-susceptible subjects had equivalent single breath and rebreathing diffusing capacities, both in absolute terms and percentage predicted, as the controls at rest. In the larger set of subjects studied by Hohenhaus *et al*. [16] it was reported that HAPE-susceptible subjects had a slight-ly higher diffusing capacity when expressed as $D_{L,CO}$ per alveolar volume (VA). This indicates that at least no persistent pulmonary membrane defect existed in subjects with previous history of HAPE, because diffusion per unit alveolar volume was not altered. However, if these data were given as $D_{L,CO}$, the differences no longer remained. Although not universally agreed upon, absolute values of diffusing capacity rather than those normalized to alveolar lung volume better reflect the functional alveolar-capillary surface area available for gas exchange [28].

It is not surprising that the diffusing capacities at rest were similar in the two groups, since diffusing capacity at rest and normoxia does not measure the full potential capacity of the alveolar-capillary surface for gas exchange. To detect a putative difference in the vascular capacity requires a stress sufficient to recruit the pulmonary capillary bed.

During normoxic and hypoxic exercise, rebreathing $D_{L,CO}$ was lower at all time points in subjects with a prior history of HAPE compared to controls. The resting rebreathing $D_{L,CO}$ values found in this study are in the range of previously reported studies using comparable rebreathing methods [21, 22] despite the slight anticipatory hyperventilation and increased $\dot{Q}'$ before the start of exercise. We chose to measure rebreathing $D_{L,CO}$ since it is less affected by pulmonary inhomogeneities and incomplete gas mixing than single breath measurements. Furthermore, the rebreathing technique permits more reliable measurements during exercise [23] since uncomfortable or intolerable breathholding is not necessary and $\dot{Q}'$ is less affected by rebreathing than by a long breath hold at TLC.

Lung volume itself affects the diffusing capacity measurement so that, in an individual, $D_{L,CO}$ will be larger when measured at a greater volume over a range from FRC to TLC [29–31]. Since the HAPE-susceptible subjects had on average a 1.5 L smaller FRC than the HAPE-resistant group, we might ask how such a 1.5 L difference in operating lung volume alone could contribute to the measured differences in $D_{L,CO}$. The data of Stam *et al.* [29], Lipscomb *et al*. [30] and Frans *et al*. [31] in resting seated young healthy persons show that a 1.5 L increase in inspired lung volume could account for a 1.2–2.5 $mL \cdot min^{-1} \cdot mmHg^{-1}$ greater $D_{L,CO}$. We must assume that the above measured $D_{L,CO}$-lung volume dependence can be applied to rebreathing $D_{L,CO}$ measurements and that with exercise and hypoxia no significant differences from baseline in mean lung volume occur either due to dynamic hyperinflation or the development of a restrictive process. If these assumptions may be made, we calculate that, in the present subjects, lung volume differences alone could account for the 10% difference in $D_{L,CO}$ at normoxic rest, but not the 21–45% differences between groups at all other measurement points (table 3).

With the combined stimulus of hypoxia and exercise to 50% $V'_{O_2,max}$, HAPE-susceptible subjects showed a markedly attenuated increase in lung diffusing capacity compared to the control group (32 *versus* 49%; $p<0.03$, see also figure 1). Similarly, at rest these subjects showed only a slight increase in resting lung diffusing capacity with hypoxia in contrast to the control group (5 *versus* 31%; $p<0.01$). Both groups had equal increases in lung diffusing capacity from rest to 50% $V'_{O_2,max}$ in hypoxia (25 *versus* 22%, see also figure 1). The only comparable data is that of Podolsky *et al.* [9], who calculated pulmonary diffusing capacity for oxygen (D_{L,O_2}) and reported no statistically significant differences during hypoxic exercise at 35–85% $V'_{O_2,max}$ in subjects susceptible to HAPE and in controls. The lack of difference in the $D_{L,CO}$ response during hypoxic exercise between groups, in contrast to that seen in normoxic exercise may be due to the much greater rise in $D_{L,CO}$ and vascular recruitment that had already occurred with hypoxia at rest in the control group. Although, in principle, the V'_A/Q' mismatch that develops in high-intensity exercise and hypoxia [9, 32, 33] may contribute to the lower exercise $D_{L,CO}$ found in HAPE subjects, it is more likely that a difference in vascular capacity is the greater factor since the differences in V'_A/Q' mismatch between HAPE susceptible and control subjects are not large [9].

Consistent with differences in $D_{L,CO}$ between groups, we found a trend toward lower $P_{a,O_2,cap}$ but not to lower $P_{A\text{-}c,O_2}$ or $S_{a,O_2,cap}$ in the HAPE-susceptible subjects. Podolsky *et al.* [9], likewise, were unable to detect signifi-cant differences in $P_{A\text{-}c,O_2}$ (using arterial blood gas samp-ling) between HAPE-susceptible and control subjects with normoxic and hypoxic exercise, despite the higher $V'_{O_2,max}$ their subjects attained (85 *versus* 50%) and the greater V'_A/Q' mismatch noted in the HAPE-susceptible group in both normoxic and hypoxic exercise. The reasons for the disparity between respiratory blood gases or inert gas data, and diffusing capacity data are not clear, although differences in total ventilation, $\dot{Q}'$ and acid-base status in the groups may be relevant. Furthermore, at least in the present study, capillary blood sampling in lieu of arterial sampling may not be sufficiently sensitive to mirror these changes in lung diffusing capacity and $V'_A/\dot{Q}'$ mismatch.

Ventilation

During exercise, ventilation was lower in HAPE susceptible subjects than in control subjects. This may be in part due to the lower lung volumes and a possible reduced lung compliance in HAPE-susceptible subjects discussed above, but is more likely to have been due to the lower hypoxic ventilatory responsiveness at rest and during exercise that we found in the present group [16] and which has been reported by others [34, 35]. Podolsky *et al.* [9] did not find statistically different ventilation during exercise between HAPE-susceptible and normal subjects al-though a trend in this direction was evident in their data at all exercise intensities.

Relationship between pulmonary circulation, diffusing capacity and lung volumes in subjects susceptible to HAPE

It is well documented that subjects with history of HAPE have increased pulmonary artery pressures during exercise in hypoxia and normoxia [13, 14] and that the increased pulmonary vascular pressures probably play an important role in the pathogenesis of HAPE [10, 36, 37]. It is not known whether the greater pulmonary pressor responses to exercise and hypoxia in HAPE-susceptible subjects are simply differences in dynamic hypoxic pulmonary vasoconstriction or also represent intrinsic differences in vascular capacitance.

The major factors that could influence the differences in $D_{L,CO}$ between groups, if one assumes no differences in V'_A/Q' mismatch, are: 1) the blood flow and pressure, which determine the capillary volume and thus surface area for gas exchange; 2) alveolar-capillary membrane characteristics; and 3) the capacitance for CO, primarily the Hb and haematocrit. Since the latter two factors probably do not differ between groups, it is probably the differences in haemodynamics that are most important. However, in this study it cannot be determined whether the differences in $D_{L,CO}$ are just a passive consequence of dissimilar cardiac outputs (*e.g*. stroke volumes) or $\overline{Q}'$ is affected by differences in the vascular bed which may be mirrored in the differences in $D_{L,CO}$. In support of the latter interpretation we found that the $D_{L,CO}$ differences are still statistically significant after adjustments for the $\overline{Q}'$ differences in ANOVA testing.

With respect to the latter idea of different vascular capacity, ELDRIDGE *et al.* [14] hypothesized that a lower cross-sectional area of the pulmonary vascular bed related to lower lung volumes is one determinant of the augmen-ted pulmonary arterial pressures across all levels of in-spired oxygen and work rates in subjects susceptible to HAPE. The present study supports this hypothesis by showing similar absolute differences in maximal lung volumes (TLC and VC) but more impressively, and for the first time. much larger differences in FRC. Consistent with smaller resting or unstressed lung volumes indicating potential differences between groups in pulmonary vascular capacity, we now show that HAPE-susceptible subjects have lower lung diffusing capacity, $\overline{Q}'$ and stroke volume during exercise. Similar findings were reported by ELDRIDGE *et al*. [14] and PODOLSKY *et al*. [9] over a greater exercise intensity with direct intravascular Fick measurements and calculations of D_{L,O_2}, but were not found to be statistically different.

The manner in which such differences in lung volume and FRC in particular could affect or mirror vascular capacity and resistance can only be speculated upon at present. If HAPE-resistant subjects have less muscularization of their pulmonary arteriolar bed, this could, in principle, decrease the tissue content of lung, leading to greater compliance. In this regard HAPE resistant subjects may occupy the opposite end of a continuum of pulmonary vascular resistance - lung volume relationship from those with primary pulmonary hypertension. In these patients a *forme-frust* "restrictive-like" pattern of pulmonary function values is indeed observed [38], and some subjects have lung volumes <90% pred but with lung diffusing capacity within the normal range at rest.

On the other hand, if differences in lung volume stem not from primary differences in the pulmonary vascular tree, but rather from differences in the parenchyma itself, then a larger vascular capacitance in HAPE-resistant subjects could simply reflect the well-known influence of lung volume on pulmonary vascular resistance [39]. Studies in isolated dog lungs show that pulmonary vascular resistance is minimal at 50% of total lung volume and increases to either side [40]. Interestingly, the HAPE-resistant subjects have an FRC/TLC ratio of 0.52 while in HAPE-susceptible subjects the ratio is 0.42.

The full relevance of our findings and those of VISWANATHAN *et al*. [4], PODOLSKY *et al*. [9] and ELDRIDGE *et al.* [14] in understanding the aetiology of high-altitude pulmonary oedema will require further study and, in particular, development of techniques to quantify lung water and interstitial oedema formation concurrently with gas exchange and haemodynamic measurements. Of addition-al importance will be quantitative measurements of lung compliance and, ideally, of lung histology. Nevertheless, the repeated findings of greater lung volumes and consistent haemodynamic and gas exchange measurements indicating a possible greater pulmonary vascular bed in those who are resistant to high-altitude pulmonary oedema point to a constitutional difference in the lungs and control of the vascular bed in these persons, which may be critical in their resistance to the development of interstitial and alveolar oedema in high-altitude pulmonary oedema.

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