No evidence for interstitial lung edema by extensive pulmonary function testing at 4559 m

Short title: Pulmonary function testing at high altitude

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Abstract:

**Purpose of the study:** To better understand previously reported changes in lung function at high altitude. **Methods:** Comprehensive pulmonary function testing utilizing body-plethysmography and assessed changes in closing volume (CV) at sea level and repeatedly over two days at high altitude (4559m) in 34 mountaineers. **Results:** In subjects without high altitude pulmonary edema (HAPE) there was no statistically significant difference in total lung capacity, forced vital capacity, closing volume and lung compliance between low and high altitude while diffusing capacity increased at high altitude. Bronchoconstriction at high altitude could be excluded as cause for changes in closing volume because there was no difference in airway-resistance and bronchodilator responsiveness to salbutamol. There were no significant differences in these parameters between mountaineers with and without acute mountain sickness. Mild alveolar edema on radiographs in HAPE was associated only with minor decrease in forced vital capacity, diffusing capacity and lung compliance and minor increase in closing volume. **Conclusion:** Comprehensive lung function testing provides no evidence for interstitial pulmonary edema in mountaineers without HAPE during the first two days at 4559m. Data obtained in mountaineers with early mild HAPE suggest, that these methods may not be sensitive enough for detecting interstitial pulmonary fluid accumulation.

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Introduction:

Previous investigations reported reduced forced vital capacity (FVC)\cite{1-12} and reduced forced expiratory volume in the first second (FEV1)\cite{3,7,9,10,12} as well as increased closing volume (CV)\cite{4,12,13} during the first days after ascent to altitudes between 2800 and 5300m. These findings were interpreted as being consistent with pulmonary interstitial fluid accumulation or subclinical HAPE. However, there are several other factors that could also account for or contribute to the observed changes.

Prolonged and intense exercise even at low altitude can lead to an increase in pulmonary interstitial fluid accumulation\cite{14-16} suggesting that the physical effort of mountaineering may cause a transient increase in pulmonary interstitial fluid independent of the effects of altitude. Bronchoconstriction during or after exercise in cold and dry environment\cite{17-19} frequently occurs even in asymptomatic athletes and may account for increased CV. Furthermore, hypocapnia due to hypoxia induced hyperventilation can cause mild peripheral bronchoconstriction\cite{20}. Pulmonary function testing can also be affected by fatigue or debilitating symptoms of AMS that may impair maximum effort critical to adequate pulmonary function testing and interpretation.

In an effort to gain better insight into previously reported changes in lung function we conducted a comprehensive program of pulmonary function testing by body plethysmography at sea-level and following rapid ascent to 4559m including lung volume measurements, spirometry, diffusion capacity, closing volume, lung compliance, airway resistance and assessment of bronchodilator responsiveness. If extravascular lung water accumulates to the extent proposed by these prior studies we would expect to find evidence of decreased vital capacity, decreased air flow, impaired diffusion capacity, decreased lung compliance and increased closing volume. Since AMS is associated with fluid retention\cite{21} worsened gas exchange\cite{22}, pulmonary interstitial fluid accumulation could be more
pronounced in subjects with AMS. We also included subjects with known susceptibility to HAPE as controls for measurements of these parameters in patients with clinically evident pulmonary edema.
Methods:

Study population

The study was performed according the Declaration of Helsinki and its current amendments, and was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg. Thirty-eight (32 male, six female) healthy, non-acclimatized subjects living at low-altitude were included after written informed consent. A total of 38 subjects were enrolled in the study, four of them withdrew prior to ascending to high altitude and their data is not included in the analysis. Therefore the analysis is based on the 34 subjects (5 female) who completed all of the low and high altitude testing sessions (age 37±10 years, height 178±9 cm, body weight 77±10 kg). Of those ascending to high altitude 30 subjects had been above 3000m several times. 16 were considered well trained and experienced mountaineers, eight developed symptoms of AMS frequently and six were considered HAPE susceptible because of at least one previous episode of HAPE. Three had participated in previous studies at the Margherita hut. The mean VO₂ max assessed on a bicycle ergometer in a ramp test starting at 50 Watt with an increase of 25 W/min was 52 ± 9 ml/min/kg and maximum workload in this test was 322 ± 42 W (4.2 ± 0.8 W/kg).

Study design

Health status of the subjects was evaluated and subjects with pulmonary diseases (e.g. asthma) were excluded before baseline measurements were performed at an altitude of 110m (Heidelberg, Germany; Measurement LA; barometric pressure ranged from 748 to 758 mmHg). Two to four weeks later subjects climbed from 1100 to 4559m (Capanna Margherita; barometric pressure ranged from 435 to 442 mmHg) within less than 24 h with one overnight stay at 3600m (Capanna Gnifetti). Study measurements were performed about three hours (HA1), 20 hours (HA2) and 44 hours (HA3) after arrival at the Capanna Margherita.

AMS or HAPE were treated according to the general recommendations[23] Subjects with clinical and radiographic signs of HAPE were given nifedipine and supplemental oxygen.
Headache was treated with acetaminophen (500 mg) or ibuprofen (400 mg). One subject with severe AMS received dexamethasone (4 mg) during the second night at high altitude. Final measurements were performed prior to treatment of HAPE or severe AMS and the study was terminated thereafter. In addition to the data reported in this paper studies on the pulmonary circulation\cite{24}, and on oxidative stress were performed and will be reported separately.

*Pulmonary function testing*

Subjects were familiarized with the procedures in a separate session before collection of baseline measurements. Flow and pressure sensors, the cabin of the body plethysmograph and gas analysers, were calibrated before each measurement. Tests were performed according to the guidelines of the American Thoracic Society (ATS) for pulmonary function testing\cite{25}. In all measurements performed during normal tidal breathing, breathing frequency was guided by a metronome set at a frequency of 10/minute. The sequence of measurements was the same at each time point. Special attention was paid to obtain maximum efforts by constant strenuous and repeated verbal direction.

*Spirometry and body plethysmography*

Lung volumes, diffusing capacity and airway resistance were obtained using a standard body plethysmograph equipped with a pneumotachograph (Jäger MasterScreen Body, VIASYS Healthcare GmbH, Hoechberg, Germany). Airway resistance and intra-thoracic gas volume (ITGV) were determined during tidal breathing. At least five typical breathing cycles served for determination of airway resistance. ITGV was measured at least three times. Reported values are the mean of three measurements. Thereafter a forced vital capacity maneuver was performed. Measurements were accepted if forced vital capacity and peak expiratory flow in three different measurements differed by less than 200ml and 0.5l/s, respectively. Reported values are maximum values of the acceptable measurements. FEF-values are taken from the trial with the highest sum of FVC and FEV1.
For determination of the alveolar-to-arterial oxygen difference (AaDO$_2$), alveolar PO$_2$ (P$_A$O$_2$) was calculated from the alveolar gas equation: 

$$P_{A\text{O}_2} = (P_B - 47) \cdot F_{I\text{O}_2} - P_A \cdot CO_2 \cdot [F_{I\text{O}_2} + (1 - F_{I\text{O}_2})/R]$$

with $P_B$ as barometric pressure, $F_{I\text{O}_2}$ as inspired oxygen fraction. Alveolar PCO$_2$ (P$_A$CO$_2$) was assumed to be equal to the arterial PCO$_2$ (P$_a$CO$_2$) and the respiratory exchange rate (R) was assumed to be 0.85 and body temperature was assumed to be 37.0°C. The arterial PO$_2$ (P$_a$O$_2$) was measured in arterial blood sampled through a radial artery catheter which was also used for another study$^{[24]}$ (Rapidlab 840, Bayer Diagnostics, Sudbury, UK). On HA3 AaDO$_2$ was calculated from an arterialized capillary blood sample (ear lobe), since arterial lines were removed on HA2. Diffusing capacity for carbon monoxide (DL$_{CO}$) was measured by the single-breath CO rebreathing method. Values were adjusted to the lower PO$_2$ at altitude according the formula given in the guidelines of the ATS/European Respiratory Society (ERS)$^{[26]}$: 

$$DL_{CO,\text{Alt}} = DL_{CO,\text{measured}}/(1 + 0.0031 \cdot (P_{I\text{O}_2} - 150))$$

where DL$_{CO,\text{Alt}}$ and DL$_{CO,\text{measured}}$ are the values of the single-breath DL$_{CO}$ corrected for altitude and measured, respectively, P$_{I\text{O}_2}$ is the P$_{I\text{O}_2}$ at altitude and 150 mmHg is the assumed P$_{I\text{O}_2}$ at sea level.

**Compliance measurement**

Lung compliance was calculated from transpleural pressure differences in relation to volume changes measured by an esophageal balloon and body plethysmography respectively. Dynamic compliance was determined during normal tidal breathing, while static compliance was determined at every 200ml of exhaled volume in the first half of a slow vital capacity maneuver. Reported values are mean values of at least three measurements.

**Closing Volume**

Closing volume was determined according to the single breath nitrogen washout method as described by West$^{[27]}$, using a custom-designed spirometric device (ZAN600, ZAN Messgeräte GmbH, Oberthulba, Germany). Briefly, after a single breath of 100% oxygen taken to total lung capacity (TLC) a slow vital capacity maneuver with an exhaled air flow of
approximately 0.5l/s was performed. Visual feedback of measured exhalation rate helped the subjects to maintain the air flow within 0.4 – 0.6l/s without superimposing a resistance device. Special care was also taken to achieve complete expiration. Therefore, as air flow fell below 0.4l/s subjects were verbally encouraged to keep exhaling as long as possible to obtain maximum exhalation. The nitrogen concentration during exhalation was recorded and the onset of airway closure was identified as the point of intersection between slopes of phase III and IV of the expirogram. Closing volume was defined as the difference between onset of airway closure and complete exhalation. The linear fitting for phase III and phase IV was performed in random order by two examiners blinded to the subjects’ data. Measurements were only accepted if the difference in closing volume between the two examiners was less than 100ml. Three values of the closing volume measurement (one at LA and two at HA1) and five closing volume values from the bronchodilation test (one at LA, three at HA2 and one at HA3) had to be excluded. Reported values are mean values of the measurements with an intraobserver difference of less than 100ml.

**Diagnosis of HAPE and AMS**

The diagnosis of HAPE was based on chest radiography as previously described\[28\]. Daily chest radiographs were performed in all subjects, radiographs were analyzed in random order by a radiologist blinded to the clinical and experimental data. AMS was assessed by the Lake Louise Score\[29\] and the AMS-C score of the Environmental Symptom Questionnaire\[30\]. AMS was diagnosed if subjects had a Lake-Louise Score of >4 points and an AMS-C score of ≥0.70 in the morning of the second day at 4559m. If both scores were below these cut off values subjects were considered not to have AMS while diagnosis of AMS was uncertain, if one score was above and the other below the cut off value.

**Bronchodilator testing**
To test for evidence of bronchoconstriction body plethysmography and closing volume measurements were repeated 10 minutes after administration of 200µg Salbutamol (2 hubs of Sultanol N®) by inhalation.

Missing values

Due to bad weather the equipment could not be set up completely in time and therefore no data from body plethysmography at HA1 could be obtained in the first three subjects, which included one subject who developed HAPE. In one further subject body plethysmography did not meet quality criteria at HA2 (premature termination of exhalation). These results were excluded from analysis.

Statistics

A power analysis based on the closing volume data reported by Cremona et al.[13] indicated that a group size of 30 would yield a statistical power of 0.80 at a significance level of 0.05 for detecting a difference of 25 % between groups. Statistics were performed to identify differences between low and high altitude and over time at altitude as well as between subjects with and without AMS by one-way and two-way repeated measures ANOVA. Post hoc testing was performed using a paired t-test for the effect of time and a Student’s t-test for the effect of group. P<0.05 was considered statistically significant. Statistical analyses were performed using the SigmaStat® software package (SPSS Inc.). We did not perform statistical analysis on the data obtained in subjects with HAPE because there were only four cases.
Results:

34 Subjects ascended to the Margherita hut. Of these 14 subjects developed AMS and 10 subjects had no AMS. In six subjects the diagnosis of AMS was uncertain since one of the two scores (Lake Louise score or AMS-C score) was below the required criterion score. They were excluded from the comparison between subjects with and without AMS. Four subjects developed HAPE, all others had no signs of interstitial or alveolar pulmonary edema in any of the chest radiographs. Their data were analyzed separately.

Data of all subjects without HAPE

The 30 subjects without sings pulmonary edema were classified as “No HAPE”. Among these subjects without HAPE (table 1) there were no changes in TLC or FVC between low and high altitude when either expressed as absolute values or as percentage of the predicted values. Average TLC was 7.6±1.2 L at LA and during all measurements at altitude. Closing volume also did not change (p=0.61) from low to high altitude and during the 48 h at altitude. Individual values over the study period are shown in figure 1. There was a statistically non-significant increase in static pulmonary compliance between low and high altitude (p=0.07). Inspiratory muscle strength was significantly reduced at high altitude form 11.5±2.8 kPa to 10.6±2.6 kPa (p<0.001) at HA1 and 10.8±2.4 kPa (p=0.001) at HA2. Despite this small reduction of inspiratory muscle strength, maximum voluntary ventilation (MVV) increased at high versus low altitude by 20% (HA1, p<0.001) and 19% (HA2, p<0.001), respectively.

FEV1 expressed in absolute values and as percentage of FVC (table 2) as well as peak expiratory flow (PEF; data not shown) and mean expiratory flow between 25 and 75% of FVC (FEF_{25-75%}) significantly increased from LA to HA1 (for each parameter p<0.001) with a statistically non-significant decrease during the stay at altitude. Airway resistance during tidal breathing (R_{ef} and SR_{TOT}) did not change significantly throughout the study.
Arterial oxygen saturation (\(\text{SaO}_2\)) showed the expected decrease at high altitude (table 3). Diffusing capacity significantly increased at high versus low altitude and there was a non-significant trend towards base line levels over two days at high altitude. AaDO\(_2\) did not change from low to high altitude and showed a tendency to decrease during the stay at altitude (\(p<0.15\)).

No changes in FVC, FVC\%, TLC and TLC\% were noted following inhalation of 200µg salbutamol at low and high altitude. Although salbutamol led to significant but small (3-5%) increases in FEV1 and percent predicted FEV1, and 8-18% increases in mid-expiratory flow rates, none of these met standard criteria for bronchodilator responsiveness. These changes were of the same magnitude at low and high altitude (figure 2). Accordingly, airway resistance decreased (\(R\_\text{eff}\) and \(S\_\text{tot}\)) significantly with salbutamol (\(p<0.01\)). The effect of salbutamol was of the same magnitude in all subjects, independent of the presence of AMS or HAPE.

Comparison between subjects with and without AMS

Subjects with AMS had lower airway resistance than subjects without AMS at HA2 and HA3 (table 2). Furthermore, subjects with AMS showed a non-significant trend toward smaller lung volumes (table 1), lower \(\text{SaO}_2\) and higher AaDO\(_2\) (table 3) at HA2 and HA3 compared to those without AMS. The differences were, however, not statistically significant. All other parameters measured in this study were almost identical between subjects with and without AMS.

Findings in HAPE

HAPE occurred in the morning of HA2 in two subjects, during the night between HA2 and HA3 in one subject and in the morning of HA3 in another subject. Two subjects had alveolar edema in two quadrants and the other two in one quadrant of the lung. The average radiographic score\(^{[28]}\) was 7.8±3.9. A further decrease of \(\text{SaO}_2\) and an increase in AaDO\(_2\)
and DL$_{CO}$/VA demonstrate impaired gas exchange. The slight decrease of FVC, CV and lung compliance compared to measurements obtained at HA1 prior to the development of HAPE also are suggestive of increased extravascular lung water at the time of diagnosis of HAPE (table 4).
Discussion:

Comprehensive pulmonary function testing using body plethysmography performed at an altitude of 4559m showed no changes in total lung capacity, forced vital capacity, bronchodilator responsiveness, lung compliance and closing volume while parameters of air flow increased compared with base line values obtained near sea level. Development of AMS had no impact on these measurements. In summary, we found no evidence by comprehensive pulmonary function testing suggestive for pulmonary interstitial fluid accumulation in non-acclimatized mountaineers with and without AMS within the first two days after rapid ascent to high altitude. In four subjects with early mild HAPE we found small changes in several parameters consistent with increased lung water accumulation.

Lung volumes:

The finding of unchanged lung volumes (TLC, FVC) in all subjects irrespective of AMS is in accordance with three other studies\cite{13,31,32} but at variance with multiple previous studies showing significant reduction in forced vital capacity after ascent to altitudes above 4000m\cite{4,6-12,33,34}. Differences in statistical power, methodology, subject selection, ascent or time of examination may account for the discrepancies between studies. These factors are discussed in more detail below.

Insufficient statistical power of our study with regard to FVC is an unlikely explanation since the largest investigation performed on 197 mountaineers at the same location in a similar setting reported virtually unchanged FVC in subjects without clinical sings of high altitude pulmonary edema\cite{13}. Furthermore, seven studies\cite{4-9,12} reporting decreased FVC had between four and 26 subjects, i.e. had less statistical power than the present study.

It is also unlikely that the using a body plethysmography and pneumotachograph in our study accounts for discrepancies with other investigations since Gauthier used the same typ of equipment and found a decrease of FVC\cite{5}. The specified range of ambient pressures for our
equipment includes the altitude of 4559 m at which it was used. Measurements by both the bodyplethysmograph and the pneumotachograph are based on pressure differences and therefore independent of the absolute pressure in a wide range. Calibration of both devices was performed regularly before a subject was measured. Control measurements of the pneumotachograph after calibration always showed the exact volume of the calibration syringe (3 L) at different flow rates. Therefore we exclude the possibility that erroneous measurements account for our finding of unchanged lung volumes at 4559 m.

Since measurements of FVC and TLC are effort dependent, slight differences in the level of effort could contribute to discrepancies between studies. Strenuous exercise preceding the measurements and symptoms of AMS might affect subjects if they are not acclimatized to the altitude and could result in slightly reduced effort by the subject. The data reported by Cogo et al. [8] fit well with this assumption. In the same setting in which we performed our study this group found decreased lung volumes on day 1 after arrival which returned to base line levels or even above on the following three days [8]. Similarly, the reduction of FVC on day 1 at 5300 m [11] was twice as high as on day 3 [35]. Two studies which report predicted values [12] or data that allow calculation of predicted values [7] and also show a reduction in FVC of 8 and 7% report vital capacities of 87 to 96% of the predicted value. Since we were aware of these discrepancies we paid careful attention to provide the greatest encouragement of maximal efforts. An average FVC of 115–117% and TLC of 110–111% of predicted value, suggests that we indeed obtained maximal efforts at each examination. Some of the previous studies may have paid less attention to this issue. Therefore, differences in the level of effort could be a factor contributing to discrepant findings between studies.

The high FVC and TLC measured in the present study may suggest that we examined a selected population resistant to acute high altitude illnesses since large lung volumes had been reported in HAPE resistant controls [36-39]. Although there was no selection with
recruitment we cannot exclude that our study population had larger lung volumes by chance and that our subjects might have been more resistant to develop early interstitial pulmonary edema due to the supra normal lung volumes, which could explain the lack of changes observed in our study. However, this notion is not supported by the fact that subjects who developed HAPE during the study had even larger lung volumes than the other groups. Furthermore no correlation was found between lung size and changes in spirometric parameters, CV, or compliance. Training status, which was not assessed, is also an unlikely explanation since (endurance)training has no influence on lung volumes\[40,41\].

Different rates or modes of ascent and time of exposure at altitude could also contribute to discrepancies between studies. In addition to having an impact on effort through fatigue as discussed above rapid ascent and associated strenuous exercise at altitude could cause interstitial pulmonary edema\[16,42\] while the effects of altitude on the interstitial fluid accumulation and lung volumes are less clear. A study reporting an increase of lung volumes approaching sea level values over time at altitude\[8\] does not help to explain why we found no decrease on the first and second day at high altitude.

Diffusing Capacity
Diffusing capacity for carbon monoxide is a sensitive, although non-specific, measurement of pulmonary impairment in many diseases, including those that associated with extravascular lung water accumulation. As a result of mild elevations in pulmonary artery pressure and cardiac output with acute hypoxia at high altitude there is pulmonary vascular recruitment that increases diffusing capacity\[36\]. We found that the diffusing capacity at high altitude is elevated equally in subjects with and without AMS and there was no correlation between AMS scores and changes in diffusing capacity. These improvements in diffusing capacity are consistent with our other measures of lung function in providing no evidence to support the presence of interstitial edema. The only other study that examined diffusing capacity in subjects with AMS at 4,700 m reported that diffusing capacity did not rise on average and
across all subjects there was an inverse correlation of AMS scores with changes in diffusing capacity\textsuperscript{[29]}. The reductions in diffusing capacity were interpreted as evidence for interstitial edema in those with moderate to severe AMS. We have no ready explanation for the marked difference in our study with that of Ge and colleagues, except that we studied lowland Caucasian subjects climbing from very low altitude to 4,559 m over 2 days in contrast to the latter study in which Han Chinese subjects already acclimated to 2,700 m drove by automobile to 4700 m over three days. How these differences in baseline resident altitude, ascent rate, total elevation gain, smoking habits, salt intake, and ethnicity might explain the discrepancy between the studies is not clear. Greater insight into these differences with AMS might be gained by studying the membrane and capillary blood volume components of diffusing capacity either with nitric oxide or several levels of inspired oxygen.

Air flow rates

FEV1 and MEF\textsubscript{25-75} values increased significantly in all examinations at high altitude with highest values on day 1 while resistance did not change significantly. These findings can be explained by reduced air density and they are in agreement with the results of previous studies\textsuperscript{[5,13,33,43]}. Despite normal airway resistance and FEV1, both improved somewhat by salbutamol, but this improvement was below that considered to be a significant bronchodilator response and was independent of altitude and preceding exercise. This finding demonstrates that cold air, hypocapnia or exercise during ascent did not cause bronchoconstriction.

Closing Volume

Two studies later reported an increase of CV at the location of our study after comparable ascent rates to our study\textsuperscript{[12,13]}. Both groups interpreted increased CV as indicative of interstitial pulmonary fluid accumulation and subclinical HAPE. We could not reproduce the finding of increase of CV and our measurements of CV were about 60% higher compared to those previously reported by these groups. While differences in methodology discussed
earlier and below might account for these discrepancies we wish to point out that – in addition to unchanged CV – all other measurements performed in this study such as lung volumes, air flow, lung compliance, diffusing capacity at rest and AaDO2 do not provide any evidence for the hypothesis that acute exposure to 4559m causes interstitial pulmonary fluid accumulation.

Senn et al.[12] and the present study measured CV by the single breath nitrogen washout method for which a slow and complete exhalation with a rate of about 0.5l/min is crucial[27]. Both groups used different commercially available devices which help the subjects control the rate of exhalation by visual feedback. The system used by Senn et al.[12] employs a valve with a considerably smaller diameter compared with the device used in the present study. A smaller valve diameter has the advantage of more easily holding the expiratory flow constant by superimposing a small resistance during exhalation. This results in a slight positive end expiratory pressure which keeps the small airways open to somewhat lower lung volumes and decreases air trapping[44] resulting in lower values for the closing volume. With reduced air density at high altitude this resistance decreases and may account for an increase of CV. The results of Gray[45] who reported the first CV measurements obtained at high altitude are in accordance with this hypothesis. They also used a method without increased expiratory resistance and found no changes in CV at 5300 m in 12 subjects. It is important to note, however, that several of their subjects were on acetazolamide and that measurements were performed on day 7. Finally, maximum verbal encouragement to achieve complete exhalation may contribute to the higher CV values measured at both altitudes in our study.

As pointed out earlier our study was designed to have sufficient statistical power for detecting changes of CV reported by Cremona et al.[13] although we could not come near the power of the latter study. Furthermore, discrepant results compared to the studies of Cremona et al.[13] and Senn et al.[12], cannot be attributed to different ascent rate since they were very similar or identical in all three investigations. The time of examination may,
however, explain the apparent difference with Cremona et al who measured CV one hour after arrival at the Margherita hut while we performed measurements three, 20 and 44 hours after arrival. It is conceivable that strenuous exercise at altitudes between 3611 and 4559 m cause mild pulmonary edema\cite{16,46} that resolves rapidly at rest and may thus not be detectable any more after three and particularly 20 or 44 hours. In addition Cremona et al.\cite{13} determined CV using recordings of the intrabreath respiratory exchange ratio (RER). This method is completely different from the classical single breath nitrogen washout method and has never been tested in the same subjects to demonstrate equivalence. It is therefore unknown whether closing volume values determined by these different methods are directly comparable. They may be differentially affected by conditions unique to high altitude such as a different span of regional alveolar pO$_2$ and pCO$_2$ values compared to sea level and in the case of the single breath nitrogen washout method, the influence of a sudden rise in oxygen tension throughout the lung.

AMS:

To have a clear distinction between individuals who felt well and those who had AMS six subjects with questionable scores were excluded from this analysis. There were no significant differences in lung volumes, air flow rates, CV and lung diffusing capacity at rest between mountaineers with and without AMS except for a significantly lower airway resistance on day 2 and 3 at 4559m in those with AMS. This difference might be attributed to higher plasma levels of epinephrine in AMS, a finding that has been reported from a similar study at the same location\cite{21}. In accordance with previous studies\cite{37} we observed a tendency to lower AaDO$_2$ and higher SaO$_2$ at the second and third day at altitude in all subjects with somewhat higher AaDO$_2$ and lower SaO$_2$ values in the AMS group. Based on these data we conclude that that standard clinical pulmonary function testing might not be sensitive enough to detect the small degree of interstitial fluid accumulation that might cause impaired gas exchange in AMS. One possibility that has not been tested is whether AMS leads to impaired regulation of local regional ventilation and perfusion, such as a change in
the degree of hypoxic pulmonary vasoconstriction. We also need to point out that body
temperature was not measured when blood gas analysis was performed. AMS is associated
with as slight increase in body temperature of about 0.4°C\textsuperscript{[47]}, which leads to an
overestimation of AaDO\textsubscript{2} by about 3%. Thus impairment of gas exchange and the postulated
underlying interstitial pulmonary edema may be minimal.

HAPE:
Four subjects developed HAPE during the study. Their data at low altitude, on day 1 at
4559m and at the time of HAPE are shown in table 4. Two had alveolar edema in one and
two had alveolar edema in two lung quadrants on the radiographs\textsuperscript{[28]}. SaO\textsubscript{2} was decreased
and AaDO\textsubscript{2} increased in these patients. FVC, DL\textsubscript{CO}/VA, and lung compliance were all slightly
decreased and CV increased somewhat in the HAPE patients. These changes are
compatible with an increase in lung water but they are rather small compared with degree of
deterioration of gas exchange and the extent of the radiographic findings. The discrepancy
between alterations in gas exchange or on radiographs and changes in lung function
demonstrate that the latter are not sensitive methods for detecting mild interstitial lung
edema or subclinical HAPE rather than the overt disease.

In summary we found no evidence for interstitial pulmonary edema by body plethysmography
and measurements of CV and lung compliance in 30 mountaineers with and without AMS
over two days at 4559m following rapid ascent to this altitude. Data obtained in mountaineers
with early mild HAPE suggest, moreover, that these methods are not very sensitive in
detecting interstitial fluid accumulation in the lungs.
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References:


Figure Legends:

**Figure 1**

Closing volume (CV) values over the study period for subjects with (AMS) or without (No AMS) AMS, uncertain diagnosis of AMS (AMS uncertain) and those who developed HAPE during the study. In HAPE at HA 3 there was only one subject still without therapy, therefore no data point is given.
Figure 2

Average flow-volume-curve at low altitude (LA) and at the second day at 4559 m (HA2) for the forced exhalation before and 10 minutes after inhalative administration of 200 µg of salbutamol. The curve represents the average values of all subjects without HAPE (n = 30) with standard deviations for peak (PEF) and mean expiratory flow at 75%, 50% and 25% of vital capacity (FEF75, FEF50, FEF25).
Table 1: Spirometric data and lung compliance

Spirometric data (TLC = total lung capacity, FVC = forced vital capacity both expressed as percentage of predicted values and CV = closing volume in liter) and static lung Compliance (Complstat) for all subjects without HAPE (All) and the subgroups of subjects who clearly remained healthy (NoAMS) and those who suffered from acute mountain sickness (AMS). Values are given at baseline (LA) and during the stay at high altitude (HA1 = 4 h after arrival, HA2 = morning of day 2 and HA3 = morning of day 3).

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<td>5.5 ± 0.9</td>
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<td><strong>VC [% pred.]</strong></td>
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<td>0.87 ± 0.27</td>
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<td>0.90 ± 0.32</td>
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<td>0.29</td>
<td>0.98</td>
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<td>3.7 ± 1.4</td>
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<tr>
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<td>3.7 ± 1.6</td>
<td>3.9 ± 1.8</td>
<td>0.13</td>
<td>0.29</td>
<td>0.98</td>
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<tr>
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<td>3.2 ± 0.8</td>
<td>3.7 ± 1.3</td>
<td>3.7 ± 1.4</td>
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</table>
HA3 = morning of day 3) as mean ± SD. P values from ANOVA are given for the effect of time (P\text{Time}) group (P\text{Group}) and time x group (P\text{Time \times Group}), respectively. There are no significant differences between low and high altitude and no group differences for any of the parameters.
<table>
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<th>HA 1</th>
<th>HA 2</th>
<th>HA 3</th>
<th>P_{Time}</th>
<th>P_{Group}</th>
<th>P_{Time x Group}</th>
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<td><strong>FEV1 [% VC]</strong></td>
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<td>All</td>
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<tr>
<td>NoAMS</td>
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<td>74 ± 10</td>
<td>78 ± 8 ***</td>
<td>75 ± 9 **</td>
<td>76 ± 9 **</td>
<td>&lt;0.001</td>
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<tr>
<td>AMS</td>
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<td>76 ± 8</td>
<td>79 ± 7 ***</td>
<td>78 ± 6 **</td>
<td>78 ± 5 **</td>
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<tr>
<td><strong>FEF_{25-75%} [L/s]</strong></td>
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<td>All</td>
<td>N=30</td>
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<td>3.8 ± 1.4 **</td>
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<td>3.9 ± 1.5 ***</td>
<td>3.7 ± 1.2 **</td>
<td>3.7 ± 1.1 **</td>
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<tr>
<td><strong>R_{eff} [kPa·s/L]</strong></td>
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<td>NoAMS</td>
<td>N=10</td>
<td>0.14 ± 0.09</td>
<td>0.12 ± 0.06</td>
<td>0.18 ± 0.06 **</td>
<td>0.18 ± 0.06 **</td>
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<td>0.13 ± 0.06</td>
<td>0.12 ± 0.04</td>
<td>0.13 ± 0.05 **</td>
<td>0.14 ± 0.04 **</td>
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<tr>
<td><strong>SR_{tot} [kPa·s/L]</strong></td>
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<tr>
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<td>NoAMS</td>
<td>N=10</td>
<td>0.79 ± 0.43</td>
<td>0.70 ± 0.27</td>
<td>0.89 ± 0.34 **</td>
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<tr>
<td>AMS</td>
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<td>0.71 ± 0.20</td>
<td>0.61 ± 0.14</td>
<td>0.65 ± 0.11 **</td>
<td>0.69 ± 0.12</td>
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Table 2: Air flow and resistance

Forced expiratory volume in the first second (FEV1), mid expiratory flow between 75 and 25% of forced vital capacity (FEF_{75-25%}) and airway resistance (R_{eff}, SR_{tot}) for all subjects without HAPE (All) and the subgroups of subjects who clearly remained healthy (NoAMS) and those who suffered from acute mountain sickness (AMS). Values are given at baseline (LA) and during the stay at high altitude (HA1 = 4 h after arrival, HA2 = morning of day 2 and HA3 = morning of day 3) as mean ± SD. P values from ANOVA are given for the effect of time (P_{Time}), group (P_{Group}) and time x group (P_{Time x Group}), respectively. Significant differences from baseline (LA) are indicated by *, significant changes at altitude to HA1 are indicated by # (one symbol p < 0.05, two symbols p < 0.1, three symbols p < 0.001). There were no significant differences between HA2 and HA3.
<table>
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<th>L A</th>
<th>H A 1</th>
<th>H A 2</th>
<th>H A 3</th>
<th>P Time</th>
<th>P Group</th>
<th>P Time x Group</th>
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</thead>
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<td><strong>SaO₂ [%]</strong></td>
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</tr>
<tr>
<td>All N=30</td>
<td>98 ± 1</td>
<td>72 ± 6 ***</td>
<td>77 ± 4 ***</td>
<td>80 ± 5 ***</td>
<td>&lt;0.001</td>
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<td></td>
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<tr>
<td>NoAMS N=10</td>
<td>98 ± 1</td>
<td>72 ± 7 ***</td>
<td>78 ± 4 ***</td>
<td>82 ± 3 ***</td>
<td>&lt;0.001</td>
<td>0.45</td>
<td>0.75</td>
</tr>
<tr>
<td>AMS N=14</td>
<td>98 ± 1</td>
<td>72 ± 5 ***</td>
<td>76 ± 5 ***</td>
<td>79 ± 6 ***</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>DLCO/VA [mmol/min/Pa/L]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>All N=30</td>
<td>1.71 ± 0.17</td>
<td>1.49 ± 0.16 ***</td>
<td>1.43 ± 0.16 ***</td>
<td>1.41 ± 0.17 ***</td>
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<td>1.73 ± 0.22</td>
<td>1.46 ± 0.22 ***</td>
<td>1.45 ± 0.24 ***</td>
<td>1.40 ± 0.21 ***</td>
<td>&lt;0.001</td>
<td>0.99</td>
<td>0.23</td>
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<tr>
<td>AMS N=14</td>
<td>1.72 ± 0.14</td>
<td>1.53 ± 0.11 ***</td>
<td>1.42 ± 0.10 ***</td>
<td>1.40 ± 0.14 ***</td>
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<tr>
<td><em><em>AaDO₂</em> [mmHg]</em>*</td>
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<tr>
<td>All N=30</td>
<td>10.5 ± 8.4</td>
<td>10.8 ± 3.4</td>
<td>9.0 ± 4.1</td>
<td>7.0 ± 3.2</td>
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<td>NoAMS N=10</td>
<td>11.9 ± 9.3</td>
<td>10.8 ± 3.8</td>
<td>6.8 ± 3.4</td>
<td>5.7 ± 2.1</td>
<td>0.20</td>
<td>0.62</td>
<td>0.54</td>
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<td>AMS N=14</td>
<td>11.7 ± 8.5</td>
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<td>10.2 ± 4.3</td>
<td>8.0 ± 3.4</td>
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</table>

Table 3: Gas exchange

Oxygen saturation (SaO₂), diffusion capacity (DLCO/VA) and alveolar to arterial oxygen difference (AaDO₂) for all subjects without HAPE (All) and the subgroups of subjects who clearly remained healthy (NoAMS) and those who suffered from acute mountain sickness (AMS). †AaDO2 was calculated from arterial blood samples at LA, HA1 and HA2 and from arterialized capillary blood samples at HA3. Values are given at baseline (LA) and during the stay at high altitude (HA1 = 4 h after arrival, HA2 = morning of day 2 and HA3 = morning of day 3) as mean ± SD. P values from ANOVA are given for the effect of time (P_{Time}) group (P_{Group}) and time x group (P_{Time x Group}), respectively. Significant differences to baseline (LA) are indicated by *, significant changes at altitude to HA1 are indicated by # and significant differences between HA2 and HA3 by † (one symbol p < 0.05, two symbols p < 0.1, three symbols p < 0.001). There are no significant group differences.
<table>
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<th>HAPE</th>
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<tr>
<td>TLC [L]</td>
<td>7.6 ± 1.9</td>
<td>7.8 ± 2.1</td>
<td>7.6 ± 2.0</td>
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<tr>
<td>[% pred.]</td>
<td>112 ± 8</td>
<td>115 ± 8</td>
<td>113 ± 8</td>
</tr>
<tr>
<td>FVC [L]</td>
<td>5.8 ± 1.6</td>
<td>5.7 ± 1.5</td>
<td>5.5 ± 1.3</td>
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<tr>
<td>[% pred.]</td>
<td>127 ± 10</td>
<td>126 ± 12</td>
<td>121 ± 9</td>
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<td>FEV1 [%FVC]</td>
<td>75 ± 5</td>
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<td>77 ± 8</td>
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<td>CV [L]</td>
<td>0.85 ± 0.41</td>
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<td>SaO2 [%]</td>
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<td>67 ± 7</td>
<td>48 ± 7</td>
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<td>AaDO2 [mmHg]</td>
<td>6.3 ± 5.9</td>
<td>8.9 ± 6.5</td>
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<td>DLCO/V A [mmol/min/Pa/L]</td>
<td>1.7 ± 0.2</td>
<td>1.9 ± 0.3</td>
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<td>2.7 ± 0.5</td>
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<td>3.2 ± 0.8</td>
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</table>

Table 4: Subjects developing HAPE

Total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), closing volume (CV), oxygen saturation (SaO2), alveolar to arterial oxygen difference (AaDO2), diffusion capacity (DLCO/V A), and static lung compliance (Complstat) and in subjects with HAPE (HAPE). Values are given as mean ± SD at baseline (LA) and 4 h after arrival at high altitude (HA1) and when HAPE was diagnosed (HAPE).