



The Young Everest Study: Effects of hypoxia at high altitude on cardio-respiratory function and general well-being in healthy children

Emma Scrase, Aidan Lavery, Johanna CD Gavlak, Samatha Sonnappa, Denny ZH Levett, Daniel Martin, Michael P W Grocott and Janet Stocks

Arch. Dis. Child. published online 23 Apr 2009;
doi:10.1136/adc.2008.150516

Updated information and services can be found at:
<http://adc.bmj.com/cgi/content/abstract/adc.2008.150516v1>

These include:

Rapid responses

You can respond to this article at:
<http://adc.bmj.com/cgi/eletter-submit/adc.2008.150516v1>

Email alerting service

Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Notes

Online First contains unedited articles in manuscript form that have been peer reviewed and accepted for publication but have not yet appeared in the paper journal (edited, typeset versions may be posted when available prior to final publication). Online First articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Online First articles must include the digital object identifier (DOIs) and date of initial publication.

To order reprints of this article go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to *Archives of Disease in Childhood* go to:
<http://journals.bmj.com/subscriptions/>

The Young Everest Study: Effects of hypoxia at high altitude on cardio-respiratory function and general well-being in healthy children

E Scrase BSc,¹ A Lavery MSc,¹ JCD Gavlak BSc,¹ S Sonnappa MD DCH MRCP FRCPCCH,² DZH Levett MA MRCP,³ D Martin BSc, MBChB, FRCA,³ MPW Grocott BSc MBBS MRCP FRCA,³ J Stocks PhD²

¹Department of Paediatric Respiratory Medicine, Great Ormond Street Hospital for Children NHS Trust, London and ²Portex Anaesthesia, Intensive Therapy and Respiratory Medicine Unit, UCL, Institute of Child Health, London, ³UCL Centre for Altitude Space and Extreme Environment Medicine, Institute of Human Health and Performance, UCL, London.

Corresponding Author: E Scrase, Respiratory Medicine, Level 6 Cardiac Wing, Great Ormond Street Hospital for Children, Great Ormond Street, London WC1N 3JH. E.Scrase@ich.ucl.ac.uk fax 0207 829 8634

Author 2: A.Lavery@ich.ucl.ac.uk Author 3: j.dingle-gavlak@ich.ucl.ac.uk Author 4: s.sonnappa@ich.ucl.ac.uk Author 5: denny.Levett@ucl.ac.uk Author 6: dan.s.martin@gmail.com Author 7: ucgbmik@ucl.ac.uk Author 8: J.Stocks@ich.ucl.ac.uk

Keywords: Hypoxia, Respiratory Physiology, Respiratory Function Tests, Altitude, Oximetry

Abstract

Objectives: To assess the effect of altitude and acclimatisation on cardio-respiratory function and well-being in healthy children.

Methods: A daily symptom diary, serial measurements of spirometry, end-tidal carbon dioxide (etCO₂) and daytime and overnight pulse oximetry (SpO₂), were undertaken at sea-level and altitudes up to 3500m in healthy children during a trekking holiday. SpO₂ at altitude was compared with that in-flight and during an acute hypoxic challenge (breathing 15% O₂) at sea-level.

Results: Measurements were obtained in nine children; 6-13 (median 8) years. SpO₂ decreased significantly during the hypoxic challenge (difference -5%, 95% CI -6;-3% p<0.01) but remained above 90% in all children. There was a significant fall both in daytime and overnight SpO₂ (95%CI -11.9;-7.5% and -12;-8 respectively) and etCO₂ (-8.5; -4.5 mmHg) as the children ascended to 3500m. There was a significant increase in SpO₂ (95%CI 1.1; 4.9%), and further drop in etCO₂ (-5.9;-0.8 mmHg) after a week at altitude, etCO₂ being negatively correlated with SpO₂. There was no correlation between SpO₂ during hypoxic challenge, in-flight or at altitude. Lung function remained within 7% of baseline in all but two children, in whom reductions of up to 23% in FVC and 16% FEV₁ were observed at altitude. The children generally remained well, but the Lake Louise Scoring system was unreliable in this age group.

Conclusions: A wide range of physiological responses to altitude are evident in healthy children. This study should inform future larger studies in children to improve understanding of responses to hypoxia in health and disease.

Introduction

Arterial hypoxaemia is a common feature of cardio-pulmonary disease and sleep disorders, which are among the commonest causes of childhood morbidity.¹ Children exposed to reductions in inspired oxygen levels as a result of air travel²⁻⁵ or altitude⁶ may be vulnerable to the pathological consequences of hypoxaemia.⁷ With increasing altitude, barometric pressure falls, ambient air at 3500m having an oxygen partial pressure equivalent to 13% oxygen at sea-level. Modern aircraft are pressurised to ~8000 feet/2438m, the equivalent to breathing 15.1% oxygen, and a hypoxic challenge is recommended in children with lung disease to assess fitness-to-fly with or without supplemental oxygen.^{4;8} There is a lack of data on the range of normal desaturation in children during air travel, and studies on healthy subjects have been recommended.^{5;9;10}

Increasing numbers of healthy, lowland children are holidaying at high altitude (above 2500m)^{7;11} and as such may experience some of the hypoxaemic-related symptoms common to children with lung disease. Although rapid exposure to low oxygen leads to hypoxaemia and, potentially, impaired physical function including acute mountain sickness (AMS), high altitude pulmonary oedema and/or cerebral oedema^{6;11-14} slow progressive exposure to hypoxia allows development of adaptive mechanisms which serve to normalise oxygen content and protect the tissues from these effects.^{13;14} Nevertheless, the increased ventilation that occurs on exposure to altitude is accompanied by marked hypocapnoea and respiratory alkalosis, which may in turn lead to disturbed sleep and periodic breathing.¹⁴

The commonly accepted definition of AMS uses the Lake Louise classification¹⁵ to rank the presence and severity of symptoms (Appendix). Although a preverbal version has been developed for very young children,^{7;16;17} there is minimal information regarding the validity of Lake Louise definitions in school-age children.¹⁸ This lack of information about effects of altitude in young children led Pollard et al. to suggest that until further evidence is obtained, children <10 years should not sleep above 3000m.⁶

Caudwell Xtreme Everest (CXE) is one of the largest field studies to investigate mechanisms underlying adaptation to hypoxia in healthy adults.^{19 20} The infra-structure for that study provided the opportunity to perform similar measurements in healthy children who were undertaking a family trek in the region at the same time.

Aims of Study

The aims of this study were to observe healthy lowland children during a trek at altitude in order to:

1. ascertain whether pulse oximetry during acute hypoxic challenge at sea level reflects that at similar oxygen levels in-flight and at equivalent altitude of 2600m
2. describe the cardio-respiratory and symptom responses to altitude
3. explore the relationship between changes in cardio-respiratory variables and reported symptoms at altitude

Subjects and Methods

Overview: Children 6 years and over, without prior exposure to high altitude, who were already booked to trek with their parents in Nepal were recruited. The study was approved by UCL Research Ethics Committee and informed written assent/consent obtained from children and their parents. No financial compensation was provided for participation. Medical screening was undertaken to ascertain

suitability for enrolment. Prior to departure, arrangements were discussed with the trek organisers to maximise the children's safety.

Protocol: The itinerary and testing schedule are summarised in Table 1. The trek was planned to minimise AMS by slow graded ascent.⁷ Measurements detailed below were undertaken in the Respiratory Laboratory (London, UK) and during a weekend trek at sea-level and repeated in Nepal at 1300m, on arrival at 3500m and after 9 days acclimatisation at 3500m. Measurements marked by an asterisk were repeated daily during the trek:

- * The Lake Louise Symptom Score (LLSS)^{11;13;14} (Appendix): completed by the children, with parental help where necessary
- Vital signs: * Peripheral oxygen saturation (SpO₂) (Minolta Pulsox300, Stowood Scientific, Oxford), *heart rate (HR), end tidal carbon dioxide (etCO₂) via nasal catheter (Tidal Wave Sp, Novamatrix), respiratory rate and blood pressure
- Spirometric lung function, according to international guidelines²¹ adapted for children,²² using an ultrasonic flowmeter (EasyONE, NDD, Zurich), independent of gas density²³ and validated for use at altitude (C Buess, pers comm)
- Hypoxic challenge (fitness-to-fly, London only);^{3;4} SpO₂ and heart rate monitored by pulse oximetry while breathing 15% O₂ in a modified body plethysmograph for 20 minutes
- In-flight monitoring of SpO₂ ~4 hours into flight, cabin pressurised to ~2430 m
- SpO₂ and heart rate at 2600m were recorded for direct comparison at an equivalent inspired oxygen with those in-flight and during fitness-to-fly assessments

Statistical Analysis

Wilcoxon non-parametric T-test was used to assess within-subject changes. Spearman Correlation was used to assess relationships between variables (SPSS 15.0 for Windows).

Results

Serial measurements at sea-level, in-flight and at altitude were obtained in nine healthy children (five boys) aged 6-13 (median eight) years.

Hypoxic Challenge: There was a significant drop in SpO₂ (difference -5.0%, IQR -6; -3% p<0.01) with marked inter-subject variability in response to the laboratory hypoxic challenge (Figure 1). No child desaturated below 90%, the cut-off for fitness-to fly without supplemental oxygen.⁸ Mean(SD) SpO₂ and HR during the test [93.4(1.7)% and 86(10) bpm respectively] were similar to those recorded at equivalent levels of inspired oxygen in-flight and at 2600m (Figure 1, Table 1), but there was marked individual variability on these three occasions.

General Well-being and Lake Louise Symptom Scores (at altitude): Despite occasional fatigue and minor injuries even the youngest children coped extremely well with the trekking regime, confirming the value of gradual ascent at altitude. When compared with either the objective physiological measures (see below) or observations by parents and investigators, the children appeared to both under- and over-report symptoms on the LLSS, average values at sea level being similar to those at altitude (Table 1).

Effect of altitude on cardio-respiratory function: On ascent to 3500m there was a small increase in resting daytime respiratory rate (Table 1). Resting HR increased gradually with increasing altitude, being on average 24 bpm faster at 3500m than at sea-level (95% CI 9; 26 bpm p<0.01). There was, on average, a 9% fall in daytime SpO₂ (95%CI -11.9; -7.5% p< 0.01), an 11% fall in overnight SpO₂ (-

12; -8% $p < 0.01$) and a 7mmHg reduction in etCO_2 (-8.5; -4.5 mmHg $p < 0.01$), when compared with baseline, with marked between-subject variability (Figure 2). At 3500m, overnight SpO_2 was significantly correlated with daytime values (R^2 0.51, $p = 0.03$), overnight values being, on average, 3% (95%CI 1.4; 5.2% $p = 0.011$) lower than those recorded during the day.

Repeat measures of SpO_2 and etCO_2 at 3500m after a week of trekking and sleeping at up to 3860m demonstrated an average 3% recovery in SpO_2 (95%CI 1.1; 4.9% $p < 0.01$), and 3mmHg further drop in etCO_2 (-5.9; -0.8mmHg, $p = 0.01$) when compared with values on arrival at this altitude. Individual changes in two children who represented the extremes of response are highlighted in Figure 2. Child H, who had the highest SpO_2 and among the lowest etCO_2 at sea-level, maintained this pattern during ascent to 3500m but showed no further changes 9 days later, suggesting rapid acclimatisation. By contrast, Child C had relatively low SpO_2 and high etCO_2 on all occasions. The reciprocal relationship between SpO_2 and etCO_2 can be seen in Figure 3. There was a marked left shift in the CO_2/O_2 relationship at altitude with further adaptation following acclimatisation. One child showed a drop in diastolic pressure at 1300m and a further decrease at 3500m, but there were no significant group changes in blood pressure.

Lung Function: On ascent to 3500m there was a fall in forced expired volume in 1 second (FEV_1) (difference [95% CI] -5% [-12; 0.7], $p = 0.04$), and in forced vital capacity (FVC) (-3% [-19.6; 1.0], $p = 0.07$). FEV_1 and FVC remained within 7% of baseline in all but two children, who showed decreased FEV_1 (12% and 16%) and FVC (20% and 23%) at altitude (Figure 4).

Table 1 Effect of Altitude on Vital Signs, Lung Function and Symptom Scores in Children

	Sea-level	Kathmandu <i>Day 1</i>	Phakding <i>Day 3</i>	Namche Bazaar <i>Day 5</i>	Namche (repeat) <i>Day 14</i>
Altitude					
Metres	30	1300	2600	3500	3500
Feet	98	4265	8530	11483	11483
Barometric Pressure mmHg	760	652	560	503	503
PiO₂ mmHg	150	127	108	96	96
Equivalent FiO₂	0.21	0.18	0.15	0.13	0.13
Resp rate/min	21 (4)	NA	NA	23 (5)	22 (5)
Heart rate/min	78 (13)	86 (12)	89 (14)	99 (14)	98 (14)
BP mmHg systolic/diastolic	100(8) / 61(7)	96(7) / 55(12)	NA	98(6) / 57(16)	NA
etCO₂ mmHg	42.5 (2.8)	NA	NA	35.8 (2.5)	32.7 (1.8)
SpO₂ %	98.5 (0.9)	95.9 (1.05)	93.2 (2.2)	88.9 (2.4)	91.8 (1.5)

Overnight SpO₂ %	96.8 (0.8)	94.1 (1.8)	NA	85.8 (3.3)	NA
Lake Louise*					
Total Score	1 (0-4)	1 (0-2)	1 (0-3)	0 (0-5)	NA
Headache	0 (0-1)	0 (0-1)	0 (0-2)	0 (0-1)	NA
Gastro intestinal	0 (0)	0 (0-1)	0 (0)	0 (0-1)	NA
Sleep Quality	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	NA
Fatigue	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-2)	NA
Dizziness	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	NA

Results are expressed as mean (SD) except for *Lake Louise Score expressed as median (range).
BP: Blood Pressure (Results only presented for 7 children due to missing data at 3500m).

Discussion

These results suggest that healthy children demonstrate a cardio-respiratory response to high altitude similar to that described in adults, with a fall in SpO₂ and etCO₂, increase in heart rate, and small reduction in FVC.¹³ The children responded to continued exposure to the reduced inspired oxygen at altitude with further increases in ventilation, indicated by further reductions in etCO₂, and some recovery of oxygenation levels. There was, however, marked individual variability in hypoxic response which warrants further investigation.

There were minimal changes in lung function in all but two children. Although these changes were not accompanied by respiratory symptoms, these two children displayed the most marked falls in SpO₂ and higher etCO₂ levels on arrival at 3500m, suggesting a slower hypoxic ventilatory response. To our knowledge, the effect of altitude on spirometric lung function has not been reported previously in children, but similar results have been found in adults. Senn et al reported an average fall in FVC and FEV₁ of 6% and 5% respectively, with marked individual variation.²⁴ These authors concluded that changes in pulmonary function after rapid ascent to high altitude (4559m) were consistent with sub-clinical interstitial fluid accumulation, although respiratory muscle weakness and fatigue could not be excluded.

The greatest potential weakness of this study was the limited number of children studied. Given the lack of prior evidence regarding safety and the most relevant tests to undertake, it was considered unethical to recruit young children purely for scientific research. Since these children had already booked a trekking holiday there were no ethical concerns regarding either financial remuneration or exposure to unnecessary risks.^{6;25} Furthermore, by utilising the existing CXE infrastructure we had a unique opportunity to perform a wide range of tests on a limited number of children.

Fitness-to-Fly Assessments

There are limited published data with which to compare these results, although the mean SpO₂ recorded in-flight is similar to that previously reported in healthy adults and children.^{26;27} A recent review of the risks of air travel in children confirmed the poor relationship between desaturation levels during fitness-to-fly tests and that during flights or at altitude,⁴ and recent studies have suggested that the cut-off for fitness-to-fly in young children should be adjusted to SpO₂ ≥ 85% during hypoxic challenge.^{28;29} Although the acute hypoxia test is frequently used to assess Hypoxic Ventilatory Response (HVR) in climbers before going to altitude,¹³ it is possible that pCO₂ remains normal over such a short exposure, and that variability in response may reflect not only differences in HVR but

also those in the oxygen-haemoglobin dissociation curve. Interpretation of fitness-to-fly would have been facilitated by simultaneous measurements of transcutaneous CO₂, which we would recommend for future studies. It has also been suggested that adaptation of this test to ascertain the extent to which desaturation is related to ventilation–perfusion mismatch rather than shunt, may be more predictive.³⁰

Hypoxic Ventilatory Response

The HVR is mediated by the carotid body, with wide inter-subject variability in response.^{12;13} Adults respond to altitude-induced hypoxia by increasing minute volume to improve oxygenation, a similar response recently being noted in children.³¹ Increases in haemoglobin concentration can compensate for the fall in SpO₂ such that oxygen content of the blood can be maintained up to 7000m.²⁰ Our findings that neither the fitness-fly-test nor a low SpO₂ at altitude predicted symptoms of altitude illness in these children is consistent with data from adults, which suggest that, despite a weak negative correlation between SpO₂ and symptoms, this is rarely helpful clinically.³² Similar nocturnal reductions in SpO₂ and etCO₂ have been reported in pre-pubertal children and adults.³¹ The major value of SpO₂ appears to be monitoring sudden changes within individuals, especially if accompanied by an increase in symptoms. The marked inter-subject variability in response to hypoxaemia at altitude, which has also been reported in adults,²⁰ may reflect both genetically and environmentally determined differences.³³ In addition to known variations in the HVR,²⁰ differences in the shape of the oxyhaemoglobin dissociation curve and the balance of conflicting effects of shifts to the left with alkalosis versus the right shift with increased 2,3-DPG might contribute to observed variability. Assessment of urine pH in future studies may help to clarify such contributions.

Symptoms

The incidence of AMS is unclear in younger subjects, since children may report similar symptoms when travelling at sea-level due to travel or disruption to daily routine.³⁴ The LLSS has been adapted for pre-verbal children,^{16;17} but such adaptations have yet to be applied in older children. The combination of apparent under- and over-reporting, with no relationship to either physiological assessments or subjective observations rendered the Lake Louise score relatively meaningless in this study. These findings are in keeping with a report published after completion of our study.³⁵ The need for further adaptation and validation of the LLSS in children has been highlighted as an urgent priority, as it can be challenging to differentiate behavioural changes in children from potentially more serious underlying medical problems.^{6;25} It is therefore essential that parents are acquainted with the symptoms of altitude illness and its management prior to altitude travel and aware of their child's reactions during travel, irrespective of altitude.⁷

Clinical Relevance

One of the aims of this study was to relate changes in cardio-respiratory responses to altitude-induced symptoms, but the lack of overt symptoms in these children, even in those with quite marked changes in SpO₂ and lung function precluded such conclusions. This lack of symptoms probably reflects the slow ascent deliberately adopted for the trek, as more marked symptoms of altitude sickness have been reported during rapid ascent.^{31;36} While full interpretation of these data will not be possible until all results from the CXE project are available,^{19;37} the data reported here contribute to the sparse physiological evidence available from children at altitude. These results also describe the normal acute and adaptive responses to hypoxaemia in children without the confounding elements of disease process that occur in subjects with cardio-respiratory disease or undergoing intensive care.³⁷ Since tissue hypoxia is a universal phenomenon among children who are critically ill, and is frequently due to arterial hypoxaemia, useful insights may be gained by examining the biophysiological responses of healthy children exposed to low levels of environmental oxygen.

Conclusions

Results from this study suggest that, with sufficient preparation and vigilance, healthy children as young as 6 years can be taken to altitudes of 3500m without major adverse effects and that such children are willing and able to undertake a wide range of physiological assessments. While the hypoxic challenge did not predict the degree of desaturation in-flight or at altitude, among this small group of healthy children, it correctly classified all as 'fit-to-fly'. Cardio-respiratory responses to both acute exposure to altitude and subsequent acclimatisation appear similar in children and adults. A more reliable method of monitoring symptoms of AMS is required for children. Evidence from this study will help the design of future larger studies of children at altitude, as well as clarifying the extent to which results from adults can be extrapolated to younger age ranges.

Figure 1: Baseline Oxygen Saturation and Heart Rate compared with that recorded during an acute Hypoxic Fitness-to-Fly (FTF) Challenge at sea level, and at equivalent inspired levels of Oxygen (PiO_2) in-flight and at altitude.

Legend: Bars are mean with SD, dark bars SpO_2 % and pale bars heart rate bpm.

Figure 2. Alterations in A) end tidal CO_2 and B) SpO_2 on ascent to altitude in healthy children and following acclimatisation. Legend: Mean is indicated in bold. Child C and Child H represent the two extremes of response. These data show that during the transition from sea level to 3500m (day 5), a 7mmHg reduction in $etCO_2$ in child C was accompanied by a 12% fall in SpO_2 , whereas in child H, a 9mm Hg reduction in $etCO_2$ was only associated with a 9% fall in SpO_2 . After acclimatisation (day 14) at altitude, there was no further change in Child H, but increased hyperventilation in Child C resulted in a 12 mmHg reduction in $etCO_2$ compared with that recorded at sea level and an improvement in SpO_2 to only 6% lower than that at sea level. See text for further discussion.

Figure 3: Relationship between change in end-tidal CO_2 and SpO_2 on ascent to altitude in healthy children.

Legend: \times sea-level, \blacktriangle 3500m, \triangle 3500m + 9 days. These data illustrate the reciprocal relationship between $etCO_2$ and SpO_2 which was significant on all measurement occasions: ($R^2=0.31$, $p=0.12$ at sea level; $R^2=0.67$, $p=0.007$ on arrival at 3500m; $R^2=0.53$, $p=0.026$ after 9 days at 3500m)

Figure 4: Effect of altitude on Lung Function.

Legend: Percent change in FEV_1 and FVC (3500m – baseline) is shown for each child, together with fall in daytime and overnight SpO_2 on arrival at 3500m compared with sea level. The two children with the largest reductions in lung function also had some of the most marked drops in both day and night time SpO_2 at altitude.

Acknowledgements

We should like to thank:

The children and families who participated in this study, all of whom generously contributed their time for this study without any financial compensation;

The members and sponsors of the Caudwell Xtreme Everest team (www.xtreme-everest.co.uk);

Kalsang Sherpa and Susie Sherpa Baer (The Walking and Climbing Company) and all the Sherpas who accompanied us on the trek and who ensured we had a safe and enjoyable trek, while carefully transporting medical equipment between locations;

Smiths Medical for financial support;

NDD for lending us the Easyone Spirometers without charge;

Dr Donald Urquhart for undertaking physical examination and medical screening of the children prior to departure; and

Professor Monty Mythen for professional support and scientific advice.

Funding: The Young Everest Study received funding from Smiths Medical. Research at the Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust benefits from R&D funding received from the NHS Executive.

Competing Interests: The authors have no competing interests

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in Archives of Disease in Childhood editions and any other BMJ PGL products to exploit all subsidiary rights, as set out in our licence.

"What is already known on this topic?"

- There is a lack of data on the range of normal desaturation in children during air travel, and studies on healthy subjects have been recommended.
- There are limited published data about effects of altitude in young children.

"What this study adds"

- This study suggests an acute hypoxic challenge, as administered during the fitness-to-fly test, does not predict individual responses either during flight or at altitudes with an equivalent inspired oxygen.
- Cardio-respiratory responses during gradual ascent to 3500m and subsequent acclimatisation to altitude appear similar in children and adults, although there is much individual variability.
- This study helps to clarify the extent to which results from adults can be extrapolated to younger age ranges.

Appendix: Lake Louise Scoring of AMS³⁸;

AMS is classified as a total score of three or more following recent ascent to altitude, but only if headache and at least one other symptom is present (i.e. poor sleep, fatigue and reduced appetite scores 3 but is not AMS; likewise, a severe headache alone scores 3 and is also not AMS).

Symptom	Scoring
1. Headache	0 None at all 1 Mild headache 2 Moderate headache 3 Severe headache, incapacitating
2. Gastro-intestinal symptoms	0 Good appetite 1 Poor appetite or nausea 2 Moderate nausea or vomiting 3 Severe, incapacitating nausea and vomiting
3. Fatigue and/or weakness	0 Not tired or weak 1 Mild fatigue/weakness 2 Moderate fatigue/weakness 3 Severe fatigue/weakness
4. Dizziness/light-headedness	0 None 1 Mild 2 Moderate 3 Severe headache, incapacitating
5. Difficulty sleeping	0 Slept as well as usual 1 Did not sleep as well as usual 2 Woke many times, poor night's sleep 3 Could not sleep at all

Reference List

- (1) Chernick V, Boat TF, Wilmott RW, Bush A. Kendig's disorders of the respiratory tract in children. 7th ed. Philadelphia,USA: Elsevier; 2006.
- (2) Samuels MP. The effects of flight and altitude. Arch Dis Child 2004; 89(5):448-455.
- (3) Buchdahl RM, Babiker A, Bush A, Cramer D. Predicting hypoxaemia during flights in children with cystic fibrosis. Thorax 2001; 56(11):877-879.
- (4) Bossley C, Balfour-Lynn IM. Taking young children on aeroplanes: what are the risks? Arch Dis Child 2008; 93(6):528-533.
- (5) Buchdahl R, Bush A, Ward S, Cramer D. Pre-flight hypoxic challenge in infants and young children with respiratory disease. Thorax 2004; 59(11):1000.

- (6) Pollard AJ, Niermeyer S, Barry P, Bartsch P, Berghold F, Bishop RA et al. Children at high altitude: an international consensus statement by an ad hoc committee of the International Society for Mountain Medicine, March 12, 2001. *High Alt Med Biol* 2001; 2(3):389-403.
- (7) Yaron M, Niermeyer S. Travel to high altitude with young children: an approach for clinicians. *High Alt Med Biol* 2008; 9(4):265-269.
- (8) Managing passengers with respiratory disease planning air travel: British Thoracic Society recommendations. *Thorax* 2002; 57(4):289-304.
- (9) Hall GL, Verheggen M, Stick SM. Assessing fitness to fly in young infants and children. *Thorax* 2007; 62(3):278-279.
- (10) Mohr LC. Hypoxia during air travel in adults with pulmonary disease. *Am J Med Sci* 2008; 335(1):71-79.
- (11) Hackett PH, Roach RC. High-altitude illness. *N Engl J Med* 2001; 345(2):107-114.
- (12) Peacock AJ. ABC of oxygen: oxygen at high altitude. *BMJ* 1998; 317(7165):1063-1066.
- (13) West JB, Schoene RB, Milledge JS. *High Altitude Medicine and Physiology*. 4th ed. London, UK: Hodder Arnold; 2007.
- (14) Nussbaumer-Ochsner Y, Bloch KE. Lessons from high-altitude physiology. *Breathe* 2008; 4(2):123-132.
- (15) Roach JM, Muza SR, Rock PB, Lyons TP, Lilly CM, Drazen JM et al. Urinary leukotriene E4 levels increase upon exposure to hypobaric hypoxia. *Chest* 1996; 110(4):946-951.
- (16) Yaron M, Waldman N, Niermeyer S, Nicholas R, Honigman B. The diagnosis of acute mountain sickness in preverbal children. *Arch Pediatr Adolesc Med* 1998; 152(7):683-687.
- (17) Yaron M, Niermeyer S, Lindgren KN, Honigman B. Evaluation of diagnostic criteria and incidence of acute mountain sickness in preverbal children. *Wilderness Environ Med* 2002; 13(1):21-26.
- (18) Imray CH, Kennedy CH, Pattinson K, Brearey S, Wright A. Self-assessment of acute mountain sickness in adolescents: a pilot study. *Wilderness Environ Med* 2004; 15(3):202-206.
- (19) Grocott M, Richardson A, Montgomery H, Mythen M. Caudwell Xtreme Everest: a field study of human adaptation to hypoxia. *Crit Care* 2007; 11(4):151.
- (20) Grocott MP, Martin DS, Levett DZ, McMorrow R, Windsor J, Montgomery HE. Arterial blood gases and oxygen content in climbers on Mount Everest. *N Engl J Med* 2009; 360(2):140-149.
- (21) Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A et al. Standardisation of spirometry. *Eur Respir J* 2005; 26(2):319-338.

- (22) Kirkby J, Welsh L, Lum S, Fawke J, Rowell V, Thomas S et al. The EPICure study: Comparison of School Spirometry with that Performed in the Lung Function Laboratory. *Pediatr Pulmonol*. In press 2008.
- (23) Pollard AJ, Mason NP, Barry PW, Pollard RC, Collier DJ, Fraser RS et al. Effect of altitude on spirometric parameters and the performance of peak flow meters. *Thorax* 1996; 51(2):175-178.
- (24) Senn O, Clarenbach CF, Fischler M, Thalmann R, Brunner-La RH, Egger P et al. Do changes in lung function predict high-altitude pulmonary edema at an early stage? *Med Sci Sports Exerc* 2006; 38(9):1565-1570.
- (25) Pollard AJ, Murdoch DR, Bartsch P. Children in the mountains. *BMJ* 1998; 316(7135):874-875.
- (26) Humphreys S, Deyermond R, Bali I, Stevenson M, Fee JP. The effect of high altitude commercial air travel on oxygen saturation. *Anaesthesia* 2005; 60(5):458-460.
- (27) Lee AP, Yamamoto LG, Relles NL. Commercial airline travel decreases oxygen saturation in children. *Pediatr Emerg Care* 2002; 18(2):78-80.
- (28) Martin AC, Verheggen M, Stick SM, Stavreska V, Oostryck J, Wilson AC et al. Definition of cutoff values for the hypoxia test used for preflight testing in young children with neonatal chronic lung disease. *Chest* 2008; 133(4):914-919.
- (29) Resnick SM, Hall GL, Simmer KN, Stick SM, Sharp MJ. The hypoxia challenge test does not accurately predict hypoxia in flight in ex-preterm neonates. *Chest* 2008; 133(5):1161-1166.
- (30) Jones JG, Bakewell SE, Heneghan CP, Jones SE, Snape SL. Profound hypoxemia in pulmonary patients in airline-equivalent hypoxia: roles of VA/Q and shunt. *Aviat Space Environ Med* 2008; 79(2):81-86.
- (31) Kohler M, Kriemler S, Handke E, Brunner-Larocca H, Zehnder M, Bloch KE. Children at high altitude have less nocturnal periodic breathing than adults. *Eur Respir J* 2008.
- (32) O'Connor T, Dubowitz G, Bickler PE. Pulse oximetry in the diagnosis of acute mountain sickness. *High Alt Med Biol* 2004; 5(3):341-348.
- (33) Tasker RC. Oxygen and living at altitude. *Arch Dis Child* 2009; 94(1):1-2.
- (34) Theis MK, Honigman B, Yip R, McBride D, Houston CS, Moore LG. Acute mountain sickness in children at 2835 meters. *Am J Dis Child* 1993; 147(2):143-145.
- (35) Southard A, Niermeyer S, Yaron M. Language used in Lake Louise Scoring System underestimates symptoms of acute mountain sickness in 4- to 11-year-old children. *High Alt Med Biol* 2007; 8(2):124-130.

- (36) Bloch J, Duplain H, Rimoldi SF, Stuber T, Kriemler S, Allemann Y et al. Prevalence and Time Course of Acute Mountain Sickness in Older Children and Adolescents After Rapid Ascent to 3450 Meters. *Pediatrics* 2009; 123:1-5.
- (37) Grocott M, Montgomery H, Vercueil A. High-altitude physiology and pathophysiology: implications and relevance for intensive care medicine. *Crit Care* 2007; 11(1):203.
- (38) Roach RC, Bärtsch P, Oelz O, and Hackett PH. The Lake Louise acute mountain sickness scoring system. In: *Hypoxia and Molecular Medicine*. J.R.Sutton, C.S. Houston, and G. Coates, editors. Burlington: Queen City Press; 2003. 272-274.

FIGURE 1

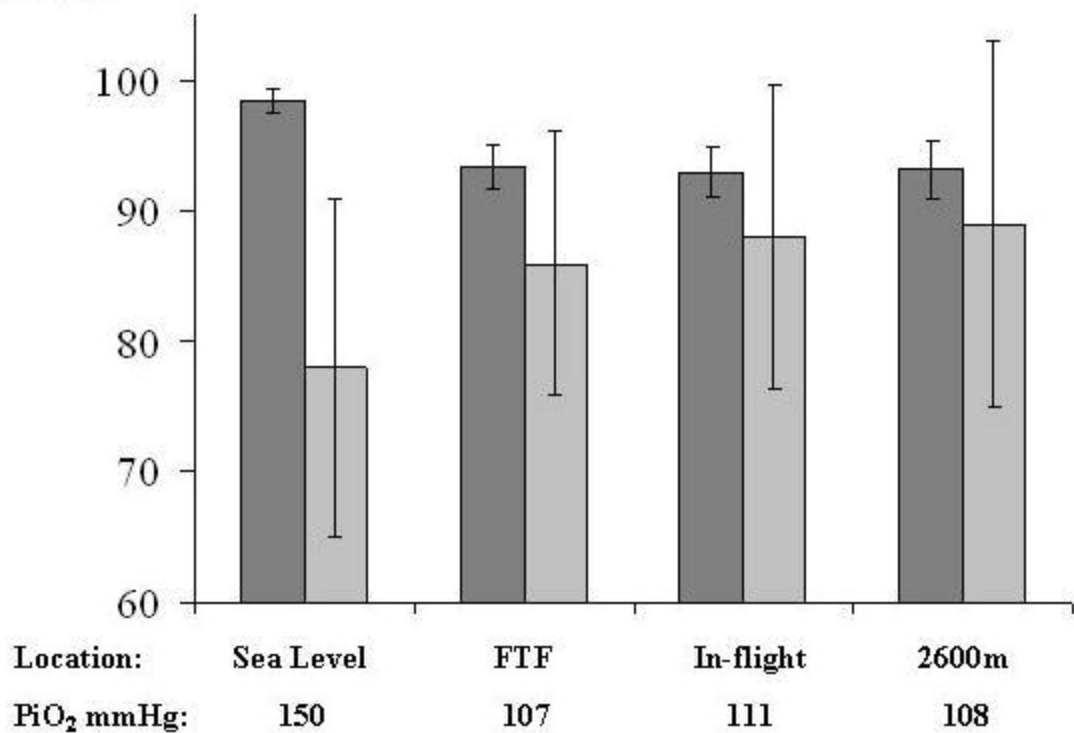


FIGURE 2A

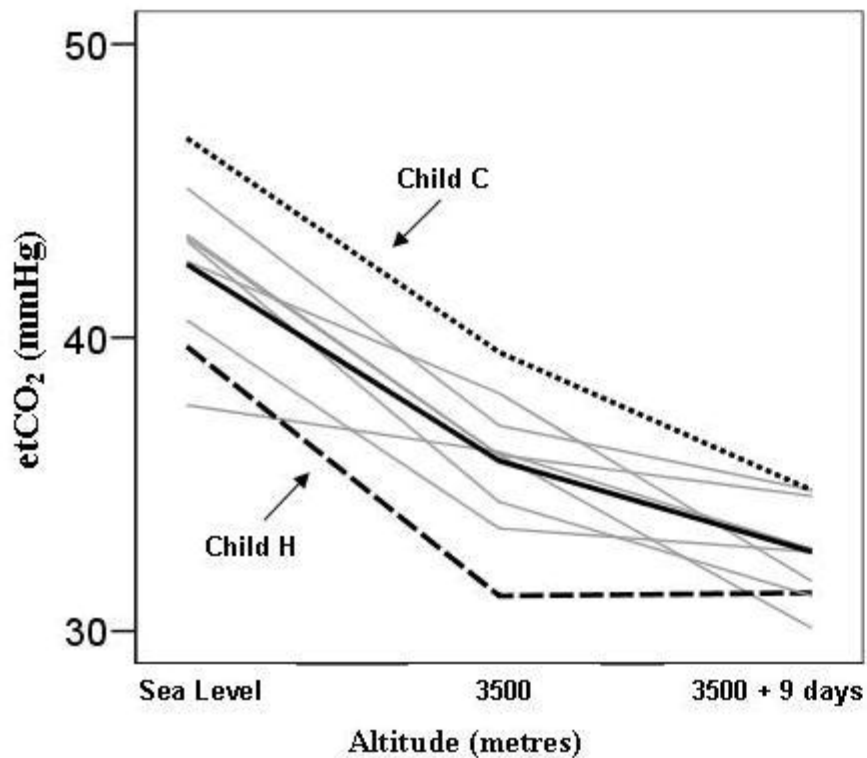


FIGURE 2B

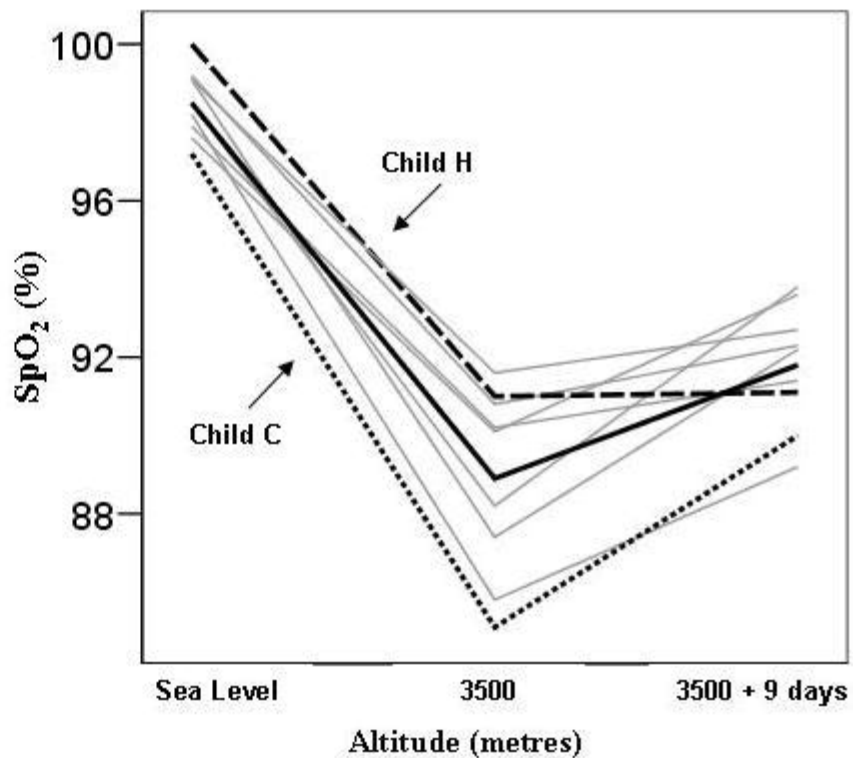


FIGURE 3

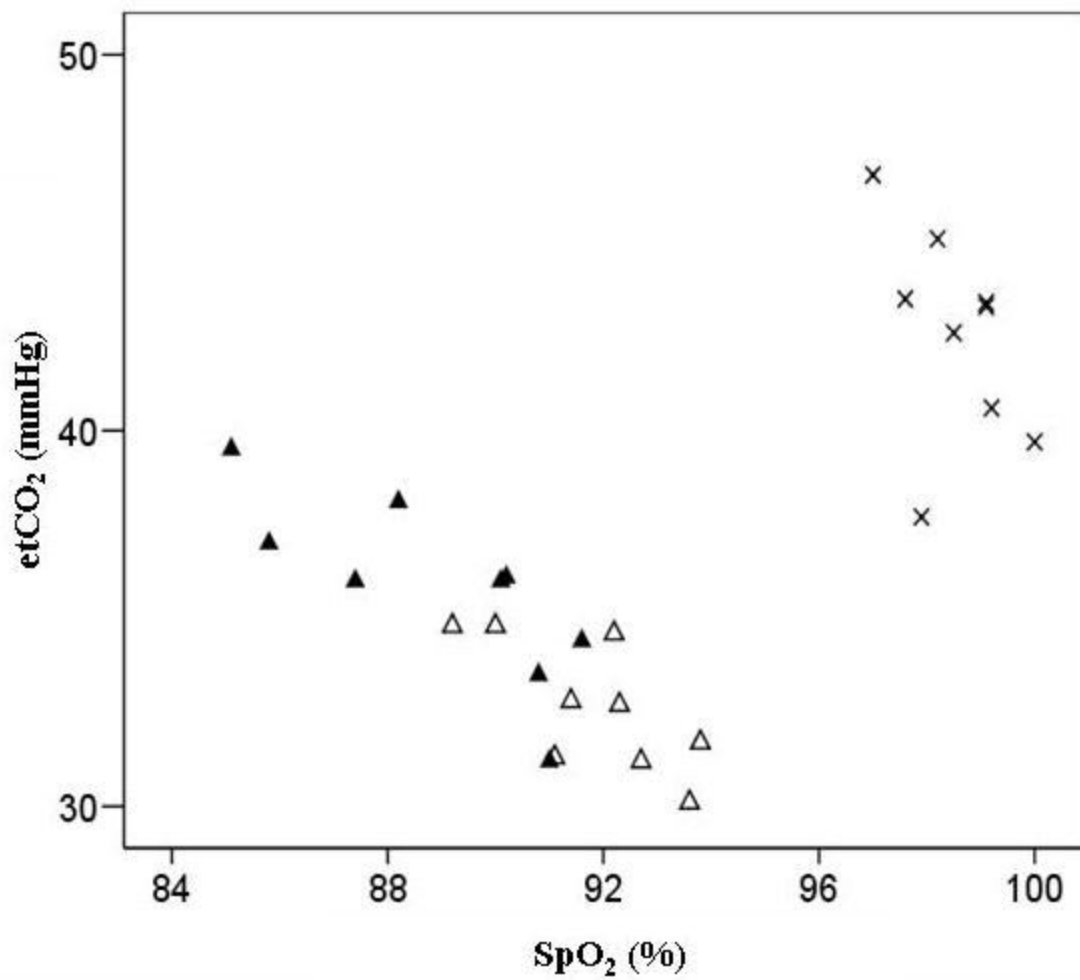
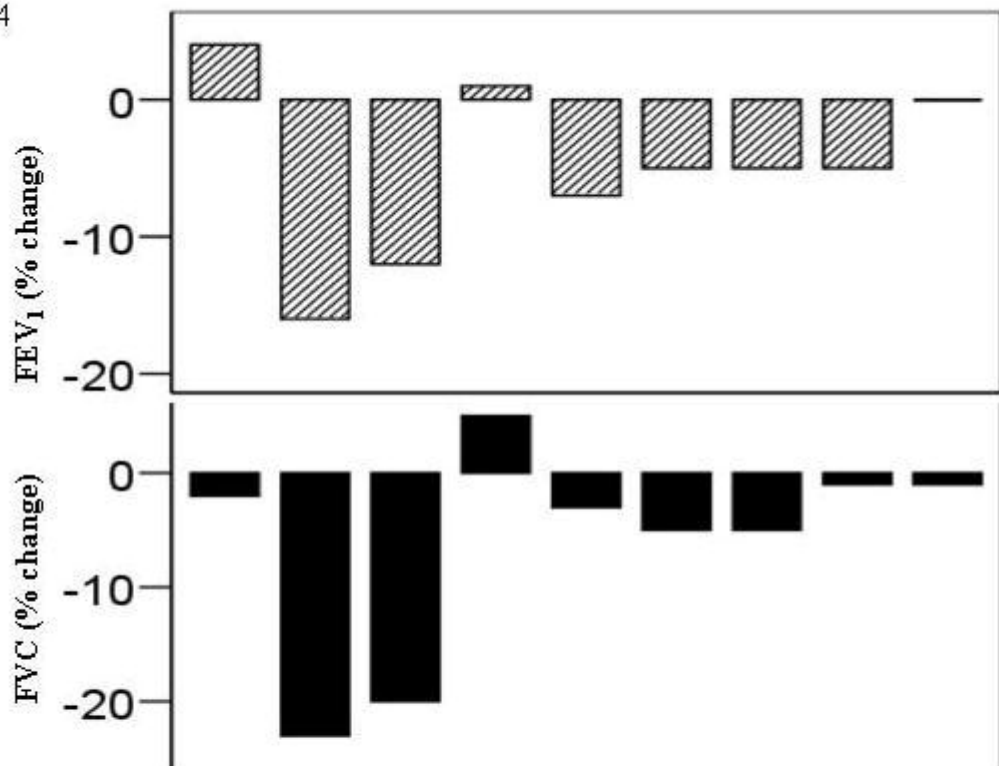


FIGURE 4



Subject	A	B	C	D	E	F	G	H	I
Fall in day SpO ₂ (%)	10	12	12	8	8	12	8	9	8
Fall in night SpO ₂ (%)	8	12	19	11	9	12	11	8	9