ERJ Express. Published on April 16, 2008 as doi: 10.1183/09031936.00166407

2. Revision of Manuscript ERJ-01664-2007

Higher pulmonary artery pressure in children than adults upon fast ascent to high altitude

Susi Kriemler[1,2], Christian Jansen[4], André Linka[4], Arnheid Kessel-Schaefer[4], Monika Zehnder[2], Tina Schürmann[4], Malcolm Kohler[3], Konrad Bloch[3], Hans Peter Brunner-La Rocca[4]

[1]Exercise and Health Sciences, University of Basel and [2]Exercise Physiology ETH-University of Zürich, [3]Pulmonary Division, University Hospital Zürich, [4]Cardiology, University Hospital Basel, Switzerland

Correspondence to:

Dr. med. Susi Kriemler
Institute of Exercise and Health Sciences
University of Basel
Brüglingen 33
4052 Basel
Switzerland

Tel +41 (0)61 377 87 68
Fax +41 (0)61 377 87 68
Email susi.kriemler@unibas.ch

Short title: Pulmonary artery pressure at high altitude

Abstract

The response of pulmonary artery pressure to high altitude in children has not been studied. It is also unknown if the individual response is hereditary. We therefore measured the response of pulmonary artery pressure to high altitude in prepubertal children in comparison to their biological fathers.

Echocardiography was performed at 450m and over 3 days at 3450m. Systolic pulmonary artery pressure was estimated from pressure gradient of tricuspid regurgitation.

The increase of pulmonary artery pressure in children was higher than in adults at day 1 of high altitude (15.5±9.1 vs. 7.9±6.4mmHg, $p<0.001$), but it returned to adult levels on day 2. The increase of pulmonary artery pressure from low to high altitude of each child correlated with the increase in his/her father ($r^2=0.41$, $p<0.003$).

Prepubertal children transiently develop greater pulmonary hypertension when exposed to high altitude than their fathers. The individual response of pulmonary pressure to high altitude seems to be at least partly hereditary.

Keywords: children, high altitude pulmonary edema, heredity, high altitude, pulmonary artery pressure

Introduction

It is increasingly popular for families to spend their vacation at high altitude, but high altitude tolerance in children is hardly known. The limited data available indicate that acute mountain sickness is equally prevalent in adults and children [1]. However, prevalence of high-altitude pulmonary edema (HAPE) may differ between adults and children, despite some contradictory notion [1]. Children resident at high altitude were more likely to develop HAPE [2, 3] when returning to high altitude after stay at lowland.

HAPE accounts for most deaths from high-altitude illness [5] and occurs in 1/10'000 in Colorado. In adults, up to 10% may be susceptible to HAPE [6]. The occurrence of HAPE depends on individual susceptibility, the rate of ascent and the altitude reached. At 4500m altitude, HAPE occurs in 4-6% after ascent within less than one day [7], and at 5500m in up to 15% of adults [8]. Although not everybody with increased hypoxia-induced pulmonary artery hypertension develops HAPE, the major pathophysiologic mechanism in adults is an exaggerated hypoxic pulmonary vasoconstriction with an abnormal increase in pulmonary artery [9] and capillary pressure, which directly corresponds to HAPE susceptibility [10].

The underlying cause of HAPE in children is little investigated. Children resident at high altitude developing HAPE after return from low altitude to high altitude may have an inherited predisposition to develop pulmonary hypertension as suggested in lowland adults [6] since their pulmonary artery pressure (PAP) rise is significantly higher compared to non-susceptible controls when breathing a hypoxic gas mixture [3]. However, in addition to pulmonary artery hypertension, other mechanisms have been suggested, such as intercurrent viral infections leading to increased permeability of the blood-gas barrier [11, 12] or a history of transient perinatal hypertension possibly as consequence of a persistent defect of nitric oxide synthesis [13].

Nevertheless, the response of PAP to acute exposure of high altitude in children born at low altitude in comparison to adults is not known. Moreover, if a significant correlation of PAP rise at high altitude existed between children and their parents, an inherited predisposition would likely be of importance. We, therefore, studied 20 lowland children and their fathers at low altitude and over three days at high altitude to evaluate whether (1) children differ from adults in their PAP response to hypoxia, and (2) whether there is a hereditary influence on the level of PAP rise under hypoxic conditions.

Methods

Study participants

Twenty healthy prepubertal children and their fathers were recruited through an announcement in the Swiss Alpine Club journal. Subjects with symptoms and signs of cardiovascular or pulmonary abnormalities, any sleeping problems by history or a sleep study at LA, previous history of perinatal pathology, and those with a recent (within 2 months) history of respiratory infections were excluded from the study. None had a history of HAPE, but the majority had not been exposed to altitudes above 4000m. Subjects were not allowed to stay at altitudes above 2000m over the two months prior to the study. The day prior and during all testing, subjects were not allowed to take any drugs other than acetaminophen. They abstained from any substances that might interfere with control of breathing such as alcohol or caffeine and they had a minimum of 8 hours of night rest prior and during the study period. A physical examination of the cardiopulmonary system was taken at low altitude and daily at high altitude to ensure a good general health. Height, weight and Tanner stage was assessed once at low altitude.

Design

Medical and physiological assessments were performed during a four hour visit to the laboratory at low altitude (450m, barometric pressure 718 mmHg) within four weeks prior to ascent and at the Jungfraujoch research station at an altitude of 3450m (barometric pressure 509 mmHg), which they reached by a train in three hours. Testing was performed 4-5 hours after arrival on day 1 (HA1), in the afternoon of day 2 (HA2) after a mountain climb of one to six hours to a maximal elevation of 4010m, and in the morning of day 3 (HA3). The experimental protocol was approved by the ethics committee of the ETH Zürich and all participants provided written informed consent.

Measurements

Heart rate was measured by heart rate monitor (Polar Vantage XL) and oxygen saturation by pulse oximetry (OxiMax N-595, Nellcor, Leuag AG, Stans, Switzerland) at the finger after a 15 min rest sitting in a comfortable chair. The mean of 5 min was taken. Systemic blood pressure was measured prior to echocardiography about 15 min after lying quietly, the mean of three consecutive measurements was calculated. Doppler echocardiography was performed with an integrated colour Doppler system using a 4.0 MHz transducer (Toshiba Aplio 80, Japan). For assessment of the peak pressure gradient between the right ventricle and the right atrium, the tricuspid valve regurgitation was first located by colour Doppler imaging in the four-chamber view or modified four chamber view, if required. The peak flow velocity of the transtricuspid regurgitant jet then was measured using continuous wave Doppler. Based on the peak velocity, the transtricuspid pressure gradient (dpTR) was calculated using the simplified Bernoulli equation ($dpTR = 4xV_{TR}^2$). Diastolic PAP was estimated from the pressure gradient across the pulmonary valve at end of diastole, after locating the pulmonary insufficiency jet in the parasternal view using colour Doppler recordings. Additionally, the pulmonary vascular resistance (PVR) was estimated using the following formular [14]

$$PVR = 10 \times {V_{TR}}/{VTI_{RVOT}} + 0.16$$

where V_{TR} is the peak velocity of tricuspid regurgitation and VTI_{RVOT} the velocity-time integral of the systolic flow in the right-ventricular outflow tract using pulse-wave Doppler recording. Finally, the acceleration time relative to ejection time was calculated as an indirect measure of mean pulmonary artery pressure [15].

All recordings were stored on magneto-optical disks and analyzed off-line by three investigators independently using the average of three consecutive heart beats. In case of disagreement (i.e. >10%), recordings were reanalyzed by the three investigators together. Consensus was found for all measurements.

Acute mountain sickness

Acute mountain sickness was assessed by a scoring system for the symptoms and signs of acute mountain sickness by the ESQ questionnaire (AMS-C-Score) [16] and also by the Lake Louise Score [17]. An AMS-C-Score of ≥0.70 and a Lake Louise Score of ≥5 were defined as diagnostic for AMS.

Statistics

Data are expressed in mean values ± SD unless otherwise stated. Changes from low to high altitude and between groups were analyzed by a two-way (low to high altitude; children versus adults) general linear model for repeated measures with post hoc testing including adjustment according to Bonferroni. The differences in the response from low to high altitude between children and adults were examined by using the interaction term (response to altitude * groups) of the above mentioned model. Comparison of individual values between groups was done using the t-test for paired samples (unadjusted for baseline measurement; adjusted for multiple comparison at high altitude). To test significant relationship of response to high altitude between children and their fathers, pairs of father and child were used as covariate in the general linear model. Correlations between variables were examined by Pearson or Spearman r, as indicated. Statistical analysis was performed with the use of the commercially available statistical package SPSS 14.0.

Results

Baseline characteristics are shown in table 1. As expected, the 9- to 12-year-old children had lower blood pressure and higher heart rate at low altitude compared to their fathers. PAP did not differ significantly between the 2 groups and calculated PVR was identical. However, PAP in relation to systemic pressure was higher in children at low altitude. Oxygen saturation was slightly, though significantly higher in children.

One girl developed severe AMS and an exaggerated PAP after 4 hours of altitude expose and had to be excluded from further analysis because she was treated with dexamethasone. A boy finished measurements on day 1 and then went home with his father because of home sickness. In one child, Doppler signal across tricuspid valve was insufficient for analysis on day 3.

The increase in PAP was significantly higher in children than in adults on day 1 (absolute increase: 15.3±8.7mmHg versus 7.7±6.4mmHg, p=0.004, figure 1; relative increase 91±54% versus 45±42%, p=0.003), although the altitude induced fall in oxygen saturation did not differ between the groups (table 2). Systolic blood pressure increased in children but not in adults (p=0.03; table 2), but this increase was smaller than that of systolic PAP (p<0.01). On average, systolic PAP in relation to systolic BP on day 1 at high altitude increased more in children than in adults (0.15±0.09 vs 0.07±0.05, p=0.002). Also, diastolic PAP (5.4±3.2 vs. 1.6±2.8mmHg, p=0.04), calculated PVR (40±27 vs. 25±21dyne*s*cm^{-5}, p=0.02) increased, and acceleration time relative to ejection time of Doppler flow in the right ventricular outflow tract decreased (0.13±0.08 vs. 0.08±0.05, p=0.04) significantly more in children at high altitude, consistent with the findings of systolic PAP (table 3). Interestingly, the increase of systolic PAP from low to high altitude on day 1 of each child significantly correlated with the increase in his/her father (% increase r=0.57, p=0.009, figure 2). This relationship was also statistically significant if tested in multivariate general linear model for repeated measures (p=0.005). A similar relationship was seen regarding the calculated PVR (p=0.02), and non-

significant trends were seen regarding diastolic PAP (p=0.22) and acceleration time relative to ejection time (p=0.12). Heart rate increased significantly more in children than in adults (p=0.002; table 2). This increase in heart rate correlated significantly with the increase in systolic PAP in both groups (r=0.46, p=0.003) as did the increase in systolic BP (r=0.35, p=0.03). The decrease in oxygen saturation was also, but less correlated to the increase in PAP in the whole group (r=-0.31, p=0.05).

On day 2 and 3, systolic PAP gradually decreased in children, whereas it remained stable in adults (figure 1). Nevertheless, the overall response over the three days including only those who completed the whole study (n=17 pairs) showed a significantly different response between children and adults in general linear model for repeated measures (p=0.02) with significant correlation between related pairs (p=0.02). The relation of systolic PAP and systolic BP was persistently larger in children than in adults (table 3, $p<0.05$), with a significant relationship in related pairs (p=0.03). Also, estimated PVR remained significantly more elevated in children throughout the study as did diastolic PAP on day 2 (table 3).

At high altitude, AMS by AMS-C-Score occurred in 10 children and 6 adults, respectively (p=0.20) and 8 children and 7 adults, respectively (p=0.74), when using the Lake-Louise score. Overall, the increase in systolic PAP was higher in the subjects developing AMS when using the AMS-C-Score score and combining children and adults (15±9 versus 9±7mmHg, p=0.04), but this difference was not significant when using the Lake Louise score (14±8 versus 10±8, p=0.19). Oxygen saturation in those with and without AMS was not significantly different for the whole group (90.0±2.8 vs. 88.9±3.1%, p=0.26) nor when children and adults were analyzed separately.

Discussion

The increase of PAP was higher in children than in adults at the first day of high altitude exposure. This cannot be attributed to lower oxygen saturations as the degree of altitude-induced hypoxemia did not differ between the two groups. Systemic blood pressure and heart rate also increased more in children than adults suggesting a greater response of the sympathetic nervous system in children with exposure to hypoxia. The similar PAP at low altitude in both groups and the fact that we selected healthy children without perinatal complications suggest that the exaggerated pulmonary vasoconstrictor response was related to an adaptive rather than a structural difference. This adaptive difference was not selective to the pulmonary circulation and included also the systemic circulation, but the response of the pulmonary arterial system clearly exceeded the one of the systemic vasculature.

The autonomic nervous system plays an important role in mediating many of the physiological adjustments to hypoxia leading to increased heart rate and cardiac output to counterbalance the decreased oxygen availability from air [18]. Therefore, the sympathetic nervous system may also contribute to an exaggerated pulmonary pressure rise and is one of the suggested pathophysiological mechanism of hypoxia induced pulmonary hypertension and HAPE. An increased sympathetic nerve activity in skeletal muscles has indeed been shown in HAPE-susceptible subjects [19], which was directly related to PAP and occurred prior to the development of HAPE. As our study was performed at a moderate altitude of 3450m where HAPE rarely occurs in adults [20], none of our subjects developed HAPE. Nevertheless, in one child we found a rather large increase in PAP accompanied with severe AMS, both linked with the development of HAPE in adults [5], within approximately three hours after exposure to high altitude [21]. Severe AMS required immediate treatment including dexamethasone, after which she was noted to have reduced PAP. Although reduced PAP has been shown to effectively prevent the development of HAPE in adults [22], it is impossible to know if HAPE would have evolved in this girl without treatment.

Importantly, the PAP level found in the children on the first day corresponded to PAP in non-HAPE susceptible adults measured at an altitude of 4559m, i.e. more than 1000m higher than in the present study [22]. Yet, there is no evidence so far that children are more susceptible for development of HAPE than adults. Children showed gradual decrease in PAP on day 2 and 3, converging the PAP in the adults, although some of the indirect measures of pulmonary vasoconstriction remained elevated. Nevertheless, adaptation to altitude seems to occur within two to three days in children, emphasising the importance of slow ascent. This seems particularly important since rapid exposure to HA, as often done during vacation, is one of the most important risk factors for development of HAPE [8].

Another important aspect of the present study is that we found evidence of a hereditary component of the individual response of PAP to high altitude induced hypoxia. We found a significant correlation of the response of the PAP to high altitude of each child with his/her father's response which is a novel finding. However, some forms of pulmonary arterial hypertension are known to be hereditary [23] and in families with known pulmonary arterial hypertension, gene carriers exhibit a substantially larger risk of exercise induced pulmonary hypertension [24]. Given the fact that we investigated only one parent of each child (i.e. half of the genetic information), the results of this study suggest a significant hereditary determination of the individual response of the pulmonary vasculature to hypoxia, but the magnitude remains to be investigated.

Finally, this study suggests that stimulation of the sympathetic tone may contribute to the excessive pulmonary hypertensive response to hypoxia. This may be particularly important for the excessive rise in PAP in children as they showed both larger increase in heart rate and systolic blood pressure. Therefore, the increased PAP in children in this study is probably caused by a combination of increased flow, direct sympathetic vasoconstriction as shown in the animal model [25] and to a minor extent by direct hypoxia induced vasoconstriction. Disproportionate increase in sympathetic tone was described also in individuals developing

HAPE [19], but previous results have not been uniform [6]. Other factors may additionally contribute to the individual response, such as a reduced NO availability or increased endothelin-1, angiotensin II, or arachadonic acid metabolites [6]. Particularly, NO has been repeatedly suggested as an important factor [6]. Interestingly, there is some evidence that children might have reduced NO production in the pulmonary circulation compared to adults [26, 27], but the present study did not investigate potential involvement of NO and other factors. In addition, evidence of increased sympathetic tone as a potentially contributing factor is only indirect. Thus, further studies are required to address this issue in more detail.

There are some limitations that may apply to this study. Thus, mothers were not included in this study as the influence of the menstrual cycle on the pulmonary vascular response to high altitude is not well defined. In addition, it would have been difficult to recruit the majority of the mothers since only children with a very narrow age-range were included. Furthermore, all our haemodynamic measurements were obtained non-invasively, which contains a certain level of uncertainty. Finally, we did not directly measure sympathetic tone. Additional analyses such as urine catecholamines or catecholamine kinetics would have supported increased sympathetic tone.

In conclusion, prepubertal children exhibit a larger increase in PAP upon high-altitude induced hypoxia than their fathers, which was transient and was limited to the first day of altitude exposure. The more pronounced pulmonary vascular response of children is in part related to a higher sympathetic tone and modulated by a hereditary component. There is no evidence, so far, that the excessive increase in PAP in children may predispose them to HAPE.

Acknowledgments

We thank all participants and especially the children for their valuable contribution to the study. We thank Toshiba, Switzerland, for providing the ultrasound equipment and Leuag, Switzerland, for providing the pulse oximeter. We also thank all team members of the High Altitude Research Station Jungfraujoch for their competent and extraordinary support. The study was supported by the Federal Council of Sports, Magglingen, Switzerland. They had no role in the design and conduct of the study, collection, management, analysis and interpretation of the data. There was no industry sponsoring.

References

1. Pollard AJ, Niermeyer S, Barry P, Bartsch P, Berghold F, Bishop RA, Clarke C, Dhillon S, Dietz TE, Durmowicz A, Durrer B, Eldridge M, Hackett P, Jean D, Kriemler S, Litch JA, Murdoch D, Nickol A, Richalet JP, Roach R, Shlim DR, Wiget U, Yaron M, Zubieta-Castillo G, Sr., Zubieta-Calleja GR, Jr. 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: 389-403.

2. Scoggin CH, Hyers TM, Reeves JT, Grover RF. High-altitude pulmonary edema in the children and young adults of Leadville, Colorado. *N Engl J Med* 1977; 297: 1269-1272.

3. Fasules JW, Wiggings JW, Wolfe R. Increased lung vasoreactivity in children from Leadville, Colorado, after recovery from high-altitude pulmonary edema. *Circulation* 1985; 72: 957-962.

4. Sui GJ, Liu YH, Cheng XS, Anand IS, Harris E, Harris P, Heath D. Subacute infantile mountain sickness. *J Pathol* 1988; 155: 161-170.

5. Hackett PH, Roach RC. High-altitude illness. *N Engl J Med* 2001; 345: 107-114.

6. Bartsch P, Mairbaurl H, Maggiorini M, Swenson ER. Physiological aspects of high-altitude pulmonary edema. *J Appl Physiol* 2005; 98: 1101-1110.

7. Maggiorini M, Buhler B, Walter M, Oelz O. Prevalence of acute mountain sickness in the Swiss Alps. *Bmj* 1990; 301: 853-855.

8. Singh I, Kapila CC, Khanna PK, Nanda RB, Rao BD. High-Altitude Pulmonary Oedema. *Lancet* 1965; 1: 229-234.

9. Scherrer U, Vollenweider L, Delabays A, Savcic M, Eichenberger U, Kleger GR, Fikrle A, Ballmer PE, Nicod P, Bartsch P. Inhaled nitric oxide for high-altitude pulmonary edema. *N Engl J Med* 1996; 334: 624-629.

10. Maggiorini M, Melot C, Pierre S, Pfeiffer F, Greve I, Sartori C, Lepori M, Hauser M, Scherrer U, Naeije R. High-altitude pulmonary edema is initially caused by an increase in capillary pressure. *Circulation* 2001; 103: 2078-2083.

11. Durmowicz AG, Noordeweir E, Nicholas R, Reeves JT. Inflammatory processes may predispose children to high-altitude pulmonary edema. *J Pediatr* 1997; 130: 838-840.

12. Das BB, Wolfe RR, Chan KC, Larsen GL, Reeves JT, Ivy D. High-altitude pulmonary edema in children with underlying cardiopulmonary disorders and pulmonary hypertension living at altitude. *Arch Pediatr Adolesc Med* 2004; 158: 1170-1176.

13. Sartori C, Allemann Y, Trueb L, Delabays A, Nicod P, Scherrer U. Augmented vasoreactivity in adult life associated with perinatal vascular insult. *Lancet* 1999; 353: 2205-2207.

14. Abbas AE, Fortuin FD, Schiller NB, Appleton CP, Moreno CA, Lester SJ. A simple method for noninvasive estimation of pulmonary vascular resistance. *J Am Coll Cardiol* 2003; 41: 1021-1027.

15. Huez S, Retailleau K, Unger P, Pavelescu A, Vachiery JL, Derumeaux G, Naeije R. Right and left ventricular adaptation to hypoxia: a tissue Doppler imaging study. *Am J Physiol Heart Circ Physiol* 2005; 289: H1391-1398.

16. Sampson JB, Cymerman A, Burse RL, Maher JT, Rock PB. Procedures for the measurement of acute mountain sickness. *Aviat Space Environ Med* 1983; 54: 1063-1073.

17. Roach RC, Bartsch P, Hackett PH, Oelz O. The Lake Louise acute mountain sickness scoring system. *In:* Sutton JR, Houston CS, Coates G, eds. Hypoxia and Molecular Medicine. Queens City Press, Burlington, Canada, 1993; pp. 272-274.

18. Seals DR, Johnson DG, Fregosi RF. Hypoxia potentiates exercise-induced sympathetic neural activation in humans. *J Appl Physiol* 1991; 71: 1032-1040.

19. Duplain H, Vollenweider L, Delabays A, Nicod P, Bartsch P, Scherrer U. Augmented sympathetic activation during short-term hypoxia and high-altitude exposure in subjects susceptible to high-altitude pulmonary edema. *Circulation* 1999; 99: 1713-1718.

20. Sophocles AM, Bachman J. High-altitude pulmonary edema among visitors to summit county, Colorado. *J Fam Pract* 1983; 17: 1015-1017.

21. Kriemler S, Kohler M, Zehnder M, Bloch KE, Rocca HB-L. Successful treatment of severe acute mountain sickness and excessive pulmonary hypertension with dexamethasone in a prepubertal girl. *High Alt Med Biol* 2006; pp. 256-261.

22. Maggiorini M, Brunner-La Rocca HP, Peth S, Fischler M, Bohm T, Bernheim A, Kiencke S, Bloch KE, Dehnert C, Naeije R, Lehmann T, Bartsch P, Mairbaurl H. Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema: a randomized trial. *Ann Intern Med* 2006; 145: 497-506.

23. McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. *Circulation* 2006; 114: 1417-1431.

24. Grunig E, Janssen B, Mereles D, Barth U, Borst MM, Vogt IR, Fischer C, Olschewski H, Kuecherer HF, Kubler W. Abnormal pulmonary artery pressure response in asymptomatic carriers of primary pulmonary hypertension gene. *Circulation* 2000; 102: 1145-1150.

25. Shirai M, Matsukawa K, Nishiura N, Kawaguchi AT, Ninomiya I. Changes in efferent pulmonary sympathetic nerve activity during systemic hypoxia in anesthetized cats. *Am J Physiol* 1995; 269: R1404-1409.

26. Buchvald F, Baraldi E, Carraro S, Gaston B, De Jongste J, Pijnenburg MW, Silkoff PE, Bisgaard H. Measurements of exhaled nitric oxide in healthy subjects age 4 to 17 years. *J Allergy Clin Immunol* 2005; 115: 1130-1136.

27. Avital A, Uwyyed K, Berkman N, Bar-Yishay E, Godfrey S, Springer C. Exhaled nitric oxide is age-dependent in asthma. *Pediatr Pulmonol* 2003; 36: 433-438.

TABLE 1 Subjects' characteristics at low altitude

	children	**adults**
Age yrs	10.7 ± 1.1	44.0 ± 4.0
Height cm	143 ± 8	179 ± 7
Weight kg	33 ± 6	74 ± 7
Systolic BP mmHg	94 ± 7	125 ± 13*
Diastolic BP mmHg	46 ± 7	65 ± 9*
Heart rate bpm	73 ± 9	61 ± 8*
Systolic PAP mmHg	21.9 ± 3.2	24.1 ± 4.5
Diastolic PAP mmHg	6.9 ± 1.4	7.6 ± 2.3
PVR dyne* cm^{-5}*s	114 ± 19	113 ± 15
Oxygen saturation %	98.0 ± 1.0	97.3 ± 1.0*

Values are means ± SD. BP denotes blood pressure, PAP pulmonary artery pressure, PVR pulmonary vascular resistance, bpm beats per minute

*$p<0.05$ for comparison between groups

TABLE 2 Effect of high altitude on systemic artery pressure, heart rate and oxygen saturation

	Arterial oxygen saturation (%)		**Systemic (systolic) blood pressure (mmHg)**		**Heart rate (bpm)**	
	adults	**children**	**adults**	**children**	**adults**	**children**
LA	97.0 ± 1.1	98.0 ± 1.1†	125 ± 13	94 ± 7†	61.0 ± 8.5	73.2 ± 8.9†
HA day1	89.4 ± 3.1*	89.7 ± 2.8*	123 ± 11	99 ± 9*†	66.2 ± 8.9*	90.4 ± 9.9*†
HA day2	90.4 ± 2.6*	90.1 ± 1.8*	124 ± 11	108 ± 11*†	71.5 ± 9.5*	98.2 ± 14.1*†
HA day3	91.0 ± 2.3*	90.8 ± 2.0*	126 ± 14	105 ± 10*†	67.8 ± 9.0*	85.7 ± 13.8*†

Values are means ± SD. LA denotes low altitude, HA high altitude

*$p<0.05$ for comparison with baseline

†$p<0.05$ for comparison between groups

TABLE 3 Effect of high altitude on Doppler echocardiographic parameters of pulmonary haemodynamics

	Calculated PVR (dyn*s*cm^{-5})		**dP PI (mmHg)**		**AcT / ET**		**Systolic PAP / systolic BP**	
	adults	**children**	**adults**	**adults**	**children**	**children**	**adults**	**children**
LA	113 ± 15	114 ± 19	3.6 ± 2.3	2.9 ± 1.4	0.45 ± 0.05	0.46 ± 0.06	0.19 ± 0.03	0.24 ± 0.04†
HA day1	138 ± 18*	155 ± 22*†	6.2 ± 4.2	7.6 ± 3.2*	0.37 ± 0.06*	0.33 ± 0.07*	0.26 ± 0.04*	0.38 ± 0.09*†
HA day2	138 ± 25*	163 ± 32*†	4.7 ± 3.1	7.8 ± 4.7*	0.33 ± 0.05*	0.32 ± 0.08*	0.25 ± 0.05*	0.31 ± 0.07*†
HA day3	141 ± 33*	154 ± 38*	4.4 ± 3.1	5.7 ± 2.6	0.34 ± 0.06*	0.33 ± 0.06*	0.24 ± 0.06*	0.29 ± 0.04*†

Values are means ± SD. LA denotes low altitude, HA high altitude, PVR pulmonary vascular resistance, dP PI pressure gradient across pulmonary valve at end diastole, AcT acceleration time and ET ejection time in right ventricular outflow tract, PAP pulmonary artery pressure, BP blood pressure

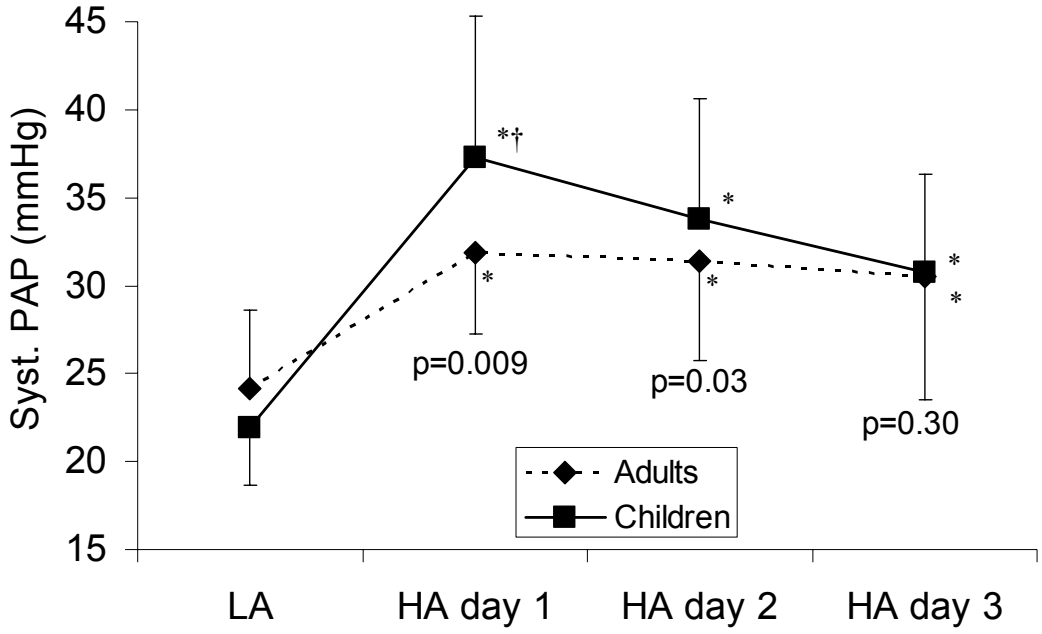
*$p<0.05$ for comparison with baseline

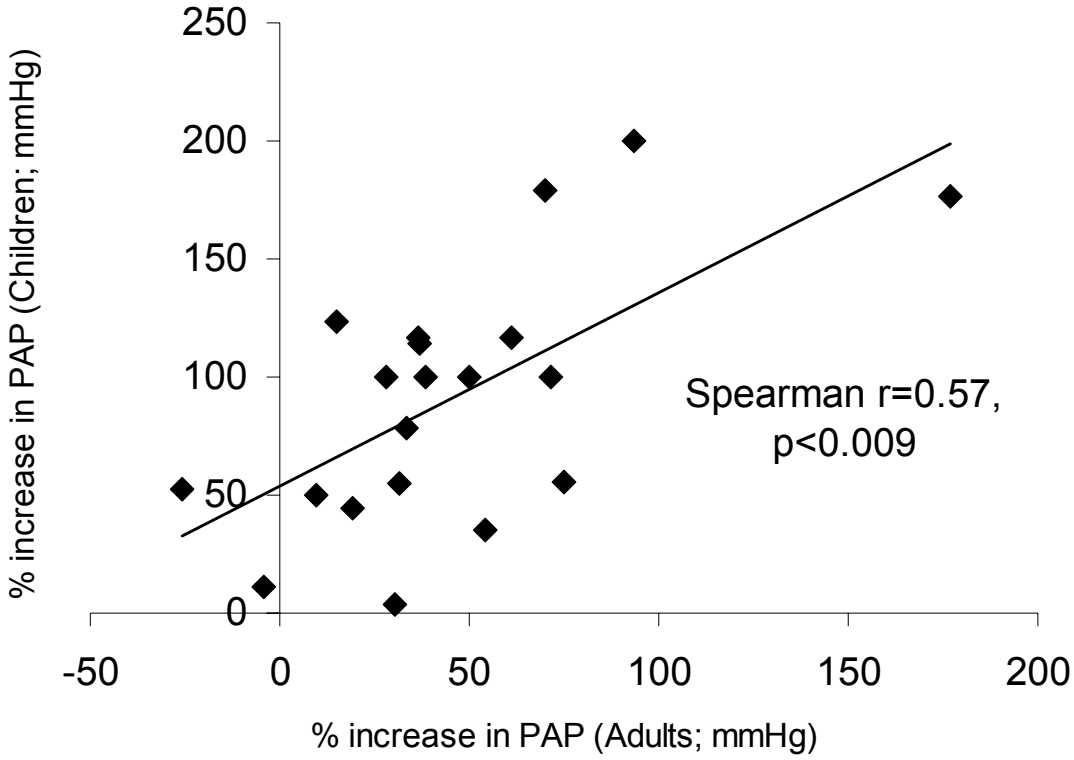
$^{\dagger}p<0.05$ for comparison between groups

Figure legends

FIGURE 1 Effect of high altitude exposure (3450m) on systolic pulmonary artery pressure in children and adults, respectively, on day1, day2 and day3 of high altitude expressed in means ± SD, LA denotes low altitude (450m), HA high altitude (3450m). In both groups, hypoxia induced a significant increase in systolic pulmonary artery pressure when compared to normoxia. P-values indicate response from baseline in children compared to adults, indicating significantly enhanced in children on day 1 and 2. *$p<0.01$ compared with normoxia; $^{\dagger}p<0.05$, children versus adults.

FIGURE 2 Relationship between the increase in systolic pulmonary artery pressure (PAP) from low to day1 of high altitude of each child with those in his/her father. Each child's relative change of pulmonary artery pressure is plotted against the relative change in pulmonary artery pressure in the corresponding father.


Syst. PAP (mmHg)
45
40
35
30
25
20
15
*†
*
*
*
*
p=0.009
p=0.03
p=0.30
Adults
Children
LA
HA day 1
HA day 2
HA day 3


250
200
150
100
50
0
-50
0
50
100
150
200
% increase in PAP (Children; mmHg)
% increase in PAP (Adults; mmHg)
Spearman r=0.57,
p<0.009