



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

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ABSTRACT: The response of pulmonary artery pressure to high altitude has not been studied in children. It is also not known whether the individual response is hereditary. Therefore, the response of pulmonary artery pressure to high altitude was measured in pre-pubertal children in comparison to that in their biological fathers.

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

The increase in pulmonary artery pressure in children was greater than that in adults at day 1 of high altitude (15.5 ± 9.1 versus 7.9 ± 6.4 mmHg), but returned to adult levels on day 2. The increase in pulmonary artery pressure from low to high altitude of each child correlated with that in the father.

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

KEYWORDS: Children, heredity, high altitude, high-altitude pulmonary oedema, pulmonary artery pressure

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

HAPE accounts for most deaths arising from high-altitude illness [4], and occurs in one per 10,000 population in Colorado (USA). Up to 10% of adults may be susceptible to HAPE [5]. The occurrence of HAPE depends upon individual susceptibility, rate of ascent and altitude reached. At an altitude of 4,500 m, HAPE occurs in 4–6% after ascent within <1 day [6], and in up to 15% of adults at 5,500 m [7]. Although not everybody with increased hypoxia-induced pulmonary artery hypertension develops HAPE, the major pathophysiological mechanism in adults is exaggerated hypoxic pulmonary vasoconstriction with an abnormal increase in pulmonary artery

pressure (P_{pa}) [8] and capillary pressure, which directly corresponds to HAPE susceptibility [9].

The underlying cause of HAPE in children is investigated very little. Children residing at high altitude developing HAPE after returning from low to high altitude may have an inherited predisposition to the development of pulmonary hypertension, as suggested for lowland adults [5], since their P_{pa} rise is significantly greater than that of nonsusceptible 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 [10, 11] or a history of transient perinatal hypertension, possibly as consequence of a persistent defect of nitric oxide synthesis [12].

Nevertheless, the response of P_{pa} to acute exposure to high altitude in children born at low altitude in comparison to that of adults is not known. Moreover, if a significant correlation of P_{pa} rise at high altitude existed between children and their parents, an inherited predisposition would probably be of importance. Therefore, 20

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STATEMENT OF INTEREST

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lowland children and their fathers were studied at low altitude and over 3 days at high altitude in order to evaluate whether: 1) children differ from adults in their P_{pa} response to hypoxia; and 2) there is a hereditary influence on the magnitude of P_{pa} rise under hypoxic conditions.

METHODS

Study participants

In total, 20 healthy pre-pubertal children and their fathers were recruited through an announcement in the journal of the Swiss Alpine Club (Bern, Switzerland). Subjects with symptoms and signs of cardiovascular or pulmonary abnormalities, any sleeping problems revealed by history taking or a sleep study at low altitude, a previous history of perinatal pathology and a recent (within 2 months) history of respiratory infection were excluded from the study. None had a history of HAPE, but the majority had not been exposed to altitudes of >4,000 m. Subjects were not allowed to stay at altitudes of >2,000 m during the 2 months prior to the study. On the preceding day 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 had ≥ 8 h rest-night⁻¹ prior to and during the study period. A physical examination of the cardio-pulmonary system was performed at low altitude and daily at high altitude in order to ensure good general health. Height, weight and Tanner stage were assessed once at low altitude.

Design

Medical and physiological assessments were performed during a 4-h visit to the laboratory at low altitude (450 m; barometric pressure 718 mmHg) within 4 weeks prior to ascent, and at the Jungfrauoch research station at an altitude of 3,450 m (barometric pressure 509 mmHg), which they reached by train in 3 h. Testing was performed 4–5 h after arrival on day 1 (HA1), during the afternoon of day 2 (HA2) after a mountain climb of 1–6 h to a maximal elevation of 4,010 m, and in the morning of day 3 (HA3). The experimental protocol was approved by the ethics committee of the Swiss Federal Institute of Technology Zurich (Zurich, Switzerland) and all of the participants provided written informed consent.

Measurements

Cardiac frequency was measured using a cardiac frequency monitor (Polar Vantage XL; Polar, Kempele, Finland) and arterial oxygen saturation by pulse oximetry (OxiMax N-595; Nellcor, Leuag, Stans, Switzerland) of the finger after a 15-min rest sitting in a comfortable chair. The mean of each over a 5-min period was taken. Systemic blood pressure (BP) was measured prior to echocardiography after ~15 min of lying quietly; the mean of three consecutive measurements was calculated. Doppler echocardiography was performed by means of an integrated colour Doppler system using a 4.0-MHz transducer (Toshiba Aplio 80; Toshiba, Oetwil am See, Switzerland). For assessment of the peak pressure gradient between the right ventricle and right atrium, 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 (V_{TR}) then was measured using continuous-wave Doppler. Based on the peak velocity, the transtricuspid

pressure gradient (DP_{TR}) was calculated using the simplified Bernoulli equation ($DP_{TR}=4V_{TR}^2$). Diastolic P_{pa} 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, pulmonary vascular resistance (PVR) was estimated using the following formula [13]:

$$PVR = \frac{10V'_{TR}}{VTIRVOT} + 0.16 \quad (1)$$

where $VTIRVOT$ is the velocity–time integral of 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 P_{pa} [14].

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

Acute mountain sickness

AMS was assessed by means of a scoring system for its symptoms and signs using the Environmental Symptoms Questionnaire (cerebral symptoms of AMS (AMS-C) score) [15] and also the Lake Louise score [16]. An AMS-C score of ≥ 0.70 and a Lake Louise score of ≥ 5 were defined as diagnostic for AMS.

Statistics

Data are presented as mean \pm SD unless otherwise stated. Changes from low to high altitude and between groups were analysed using 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 using the interaction term (response to altitude groups) of the above-mentioned model. Comparison of individual values between groups was performed using the t-test for paired samples (unadjusted for baseline measurement; adjusted for multiple comparisons at high altitude). In order to test a 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 using Pearson's or Spearman's r , as indicated.

RESULTS

The baseline characteristics of the subjects are shown in table 1. As expected, the 9–12-yr-old children exhibited a lower BP and higher cardiac frequency at low altitude than their fathers. P_{pa} did not differ significantly between the two groups and the calculated PVR was identical. However, P_{pa} relative to systemic pressure was higher in children at low altitude. Arterial oxygen saturation was slightly, although significantly, higher in children.

One female child developed severe AMS and an exaggerated P_{pa} after 4 h of altitude exposure and had to be excluded from further analysis because of treatment with dexamethasone. A

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*
Cardiac frequency beats·min ⁻¹	73±9	61±8*
Systolic P _{pa} mmHg	21.9±3.2	24.1±4.5
Diastolic P _{pa} mmHg	6.9±1.4	7.6±2.3
PVR dyn·cm ⁻⁵ ·s	114±19	113±15
Sa _a O ₂ %	98.0±1.0	97.3±1.0*

Data are presented as mean±sd. BP: blood pressure; P_{pa}: pulmonary artery pressure; PVR: pulmonary vascular resistance; Sa_aO₂: arterial oxygen saturation.
*: p<0.05 versus children.

male child completed the measurements on day 1 and then went home with their father because of home sickness. In one child, the Doppler signal across the tricuspid valve was insufficient for analysis on day 3.

The increase in P_{pa} was significantly greater in children than in adults on day 1 (absolute increase 15.3±8.7 versus 7.7±6.4 mmHg, respectively, p=0.004, fig. 1; relative increase 91±54 versus 45±42%, p=0.003), although the altitude-induced fall in arterial oxygen saturation did not differ between the groups (table 2). Systolic BP increased in children but not in adults (p=0.03; table 2), but this increase was smaller than that in systolic P_{pa} (p<0.01). On average, systolic P_{pa} relative to systolic BP on day 1 at high altitude increased more in children than in adults (0.15±0.09 versus 0.07±0.05, p=0.002). In addition, diastolic P_{pa} (5.4±3.2 versus 1.6±2.8 mmHg, p=0.04) and calculated PVR increased (40±27 versus 25±21 dyn·s·cm⁻⁵, p=0.02), and acceleration time relative to the ejection time of Doppler flow in the right ventricular outflow tract decreased significantly more in children at high altitude (0.13±0.08 versus 0.08±0.05, p=0.04), consistent with the findings of systolic P_{pa} (table 3). Interestingly, the increase in systolic P_{pa} from low to high altitude on day 1 of each child correlated significantly with the percentage increase of their father (r=0.57, p=0.009, fig. 2).

TABLE 2 Effect of high altitude (HA) on systemic (systolic) blood pressure (BP), cardiac frequency (fc) and arterial oxygen saturation (Sa_aO₂)

Day	Sa _a O ₂ %		Systolic BP mmHg		fc beats·min ⁻¹	
	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 [#]
HA1	89.4±3.1*	89.7±2.8*	123±11	99±9* [#]	66.2±8.9*	90.4±9.9* [#]
HA2	90.4±2.6*	90.1±1.8*	124±11	108±11* [#]	71.5±9.5*	98.2±14.1* [#]
HA3	91.0±2.3*	90.8±2.0*	126±14	105±10* [#]	67.8±9.0*	85.7±13.8* [#]

Data are presented as mean±sd. LA: low altitude. *: p<0.05 versus baseline; [#]: p<0.05 versus adults.

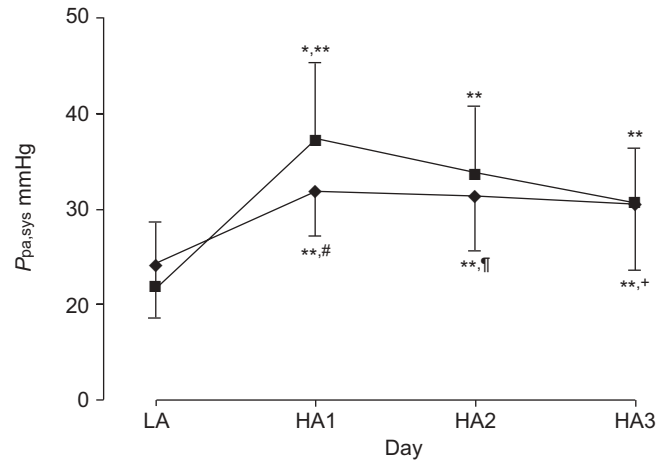


FIGURE 1. Effect of high altitude (HA; 3,450 m) exposure on systolic pulmonary artery pressure (P_{pa,sys}) in children (■) and adults (◆) on days 1, 2 and 3 of HA. Data are presented as mean±sd. In both groups, hypoxia induced a significant increase in P_{pa,sys} compared with normoxia. LA: low altitude (450 m). *: p<0.05 versus adults; **: p<0.01 versus normoxia; #: p=0.009; †: p=0.03; ‡: p=0.30 versus children's response from baseline (change in P_{pa,sys}).

This relationship was also significant if tested using a multivariate general linear model for repeated measures (p=0.005). A similar relationship was seen regarding the calculated PVR (p=0.02), and nonsignificant trends were seen regarding diastolic P_{pa} (p=0.22) and acceleration time relative to ejection time (p=0.12). Cardiac frequency increased significantly more in children than in adults (p=0.002, table 2). This increase in cardiac frequency correlated significantly with the increase in systolic P_{pa} 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 arterial oxygen saturation also, but to a lesser extent, correlated with the increase in P_{pa} in the whole group (r= -0.31, p=0.05).

On days 2 and 3, systolic P_{pa} gradually decreased in children, whereas it remained stable in adults (fig. 1). Nevertheless, the overall response over the 3 days including only those who completed the whole study (n=17 pairs) showed a significantly different response between children and adults in the general linear model for repeated measures (p=0.02), with significant correlation between related pairs (p=0.02). The relationship of systolic P_{pa} and systolic BP was persistently greater in children than in adults (p<0.05, table 3), with a

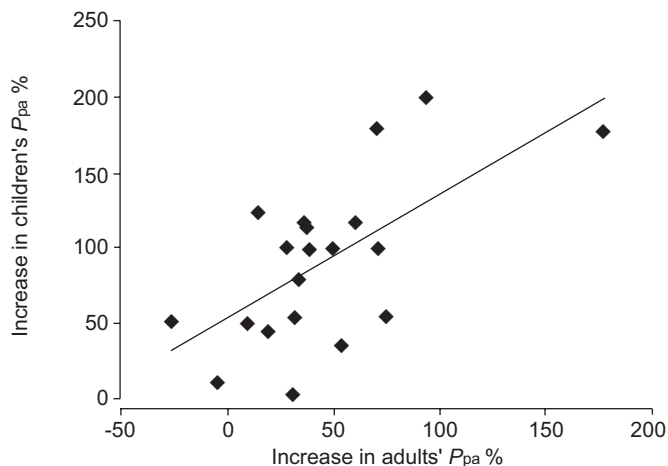


FIGURE 2. Relationship between the increase in systolic pulmonary artery pressure (P_{pa}) from low altitude to day 1 of high altitude of each child with that of the father. —: line of best fit. Spearman's $r=0.57$; $p<0.009$.

significant relationship in related pairs ($p=0.03$). In addition, the estimated PVR remained significantly more elevated in children throughout the study, as did diastolic P_{pa} on day 2 (table 3).

At high altitude, AMS by AMS-C score occurred in 10 children and six adults ($p=0.20$), and in eight children and seven adults ($p=0.74$) when using the Lake Louise score. Overall, the increase in systolic P_{pa} was greater in the subjects who developed AMS using the AMS-C score and combining children and adults (15 ± 9 versus 9 ± 7 mmHg, $p=0.04$), but this difference was nonsignificant when using the Lake Louise score (14 ± 8 versus 10 ± 8 mmHg, $p=0.19$). Arterial oxygen saturation in those with and without AMS did not differ significantly for the whole group (90.0 ± 2.8 versus $88.9\pm 3.1\%$, $p=0.26$) nor when children and adults were analysed separately.

DISCUSSION

The increase in P_{pa} was greater in children than in adults on the first day of high altitude exposure. This cannot be attributed to lower arterial oxygen saturations since the degree of altitude-induced hypoxaemia did not differ between the two groups. Systemic BP and cardiac frequency also increased

more in children than in adults, suggesting a greater response of the sympathetic nervous system in children with exposure to hypoxia. The similar P_{pa} at low altitude in both groups and the fact that healthy children without perinatal complications were selected suggest that the exaggerated pulmonary vasoconstrictor response was related to an adaptive rather than a structural difference. This adaptive difference was not selective of the pulmonary circulation and also included the systemic circulation, but the response of the pulmonary arterial system clearly exceeded that of the systemic vasculature.

The autonomic nervous system plays an important role in mediating many of the physiological adjustments to hypoxia, leading to increased cardiac frequency and cardiac output to counterbalance the decreased oxygen availability from air [17]. Therefore, the sympathetic nervous system may also contribute to an exaggerated pulmonary pressure rise, and is one of the suggested pathophysiological mechanisms of hypoxia-induced pulmonary hypertension and HAPE. Increased sympathetic nerve activity in skeletal muscles, which is directly related to P_{pa} and occurs prior to the development of HAPE, has indeed been shown in HAPE-susceptible subjects [18]. Since the present study was performed at a moderate altitude of 3,450 m, at which HAPE rarely occurs in adults [19], none of the present subjects developed HAPE. Nevertheless, a rather large increase in P_{pa} accompanied by severe AMS, both linked to the development of HAPE in adults [4], was found in one female child within ~ 3 h following exposure to high altitude [20]. The severe AMS required immediate treatment including dexamethasone, after which the child was noted to show a reduced P_{pa} . Although reduced P_{pa} has been shown to effectively prevent the development of HAPE in adults [21], it is not possible to know whether HAPE would have developed in this child without treatment.

Importantly, the P_{pa} found in the children on the first day corresponded to that measured in HAPE-insusceptible adults at an altitude of 4,559 m, *i.e.* $>1,000$ m higher than in the present study [21]. However, there is no evidence to date that children are more susceptible to the development of HAPE than adults. The children showed a gradual decrease in P_{pa} on days 2 and 3, converging with the P_{pa} in the adults, although some of the indirect measures of pulmonary vasoconstriction remained elevated. Nevertheless, adaptation to altitude seems

TABLE 3 Effect of high altitude (HA) on Doppler echocardiographic pulmonary haemodynamic parameters

Day	Calculated PVR $\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5}$		DPPI mmHg		AcT/ET		Systolic P_{pa} /BP	
	Adults	Children	Adults	Children	Adults	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	$0.24\pm 0.04^{\#}$
HA1	$138\pm 18^*$	$155\pm 22^{*,\#}$	6.2 ± 4.2	$7.6\pm 3.2^*$	$0.37\pm 0.06^*$	$0.33\pm 0.07^*$	$0.26\pm 0.04^*$	$0.38\pm 0.09^{*,\#}$
HA2	$138\pm 25^*$	$163\pm 32^{*,\#}$	4.7 ± 3.1	$7.8\pm 4.7^*$	$0.33\pm 0.05^*$	$0.32\pm 0.08^*$	$0.25\pm 0.05^*$	$0.31\pm 0.07^{*,\#}$
HA3	$141\pm 33^*$	$154\pm 38^*$	4.4 ± 3.1	5.7 ± 2.6	$0.34\pm 0.06^*$	$0.33\pm 0.06^*$	$0.24\pm 0.06^*$	$0.29\pm 0.04^{*,\#}$

Data are presented as mean \pm SD. PVR: pulmonary vascular resistance; DPPI: pressure gradient across pulmonary valve at end diastole; AcT: acceleration time in right ventricular outflow tract; ET: ejection time in right ventricular outflow tract; P_{pa} : pulmonary artery pressure; BP blood pressure; LA: low altitude. *: $p<0.05$ versus baseline; #: $p<0.05$ versus adults.

to occur within 2 or 3 days in children, emphasising the importance of slow ascent. This seems particularly important since rapid exposure to high altitude, as is often the case during holidays, is one of the most important risk factors for the development of HAPE [7].

Another important aspect of the present study is that evidence was found of a hereditary component of the individual response of P_{pa} to high-altitude induced hypoxia. There was significant correlation of the response of the P_{pa} to high altitude of each child with that of their father, which is a novel finding. However, some forms of pulmonary arterial hypertension are known to be hereditary [22], and, in families with known pulmonary arterial hypertension, gene carriers exhibit a substantially greater risk of exercise-induced pulmonary hypertension [23]. Given the fact that only one parent of each child (*i.e.* half of the genetic information) was investigated, the results of the present study suggest significant hereditary determination of the individual response of the pulmonary vasculature to hypoxia, but the magnitude remains to be investigated.

Finally, the present study suggests that stimulation of sympathetic tone may contribute to the excessive pulmonary hypertensive response to hypoxia. This may be particularly important for the excessive rise in P_{pa} in children since they showed larger increases in both cardiac frequency and systolic BP. Therefore, the increased P_{pa} in children in the present study is probably caused by a combination of increased flow, direct sympathetic vasoconstriction, as shown in the animal model [24], and, to a minor extent, direct hypoxia-induced vasoconstriction. A disproportionate increase in sympathetic tone has also been described in individuals developing HAPE [18], but previous results have not been uniform [5]. Other factors may additionally contribute to the individual response, such as a reduced nitric oxide (NO) availability or increased endothelin 1, angiotensin II or arachidonic acid metabolites [5]. NO, in particular, has been repeatedly suggested as an important factor [5]. Interestingly, there is some evidence that children might exhibit reduced NO production in the pulmonary circulation compared with adults [25, 26], but the present study did not investigate the potential involvement of NO and other factors. In addition, the evidence of increased sympathetic tone as a potentially contributory factor is only indirect. Thus further studies are required in order to address this issue in more detail.

There are some limitations that may apply to the present study. Mothers were not included 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 within a very narrow age range were included. Furthermore, all of the haemodynamic measurements were obtained noninvasively, giving rise to some level of uncertainty. Finally, sympathetic tone was not directly measured. Additional analyses, such as urine catecholamine levels or catecholamine kinetics, would have supported the increased sympathetic tone.

In conclusion, pre-pubertal children exhibit a greater increase in pulmonary artery pressure upon high-altitude induced hypoxia than do their fathers, an effect which was transient and limited to the first day of altitude exposure. The more

pronounced pulmonary vascular response of children is, in part, related to greater sympathetic tone and modulated by a hereditary component. There is no evidence to date that the excessive increase in pulmonary artery pressure in children may predispose them to high-altitude pulmonary oedema.

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