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Children At High Altitude Have Less Nocturnal Periodic Breathing Than Adults

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Abstract

Although children commonly travel to high altitude their respiratory adaptation to hypoxia remains elusive. We therefore recorded respiratory inductive plethysmography, pulse oximetry (SpO_2) and end-tidal PCO_2 in 20 prepubertal children (9-12y) and their fathers during a night in Zurich (490m) and two nights at the Swiss Jungfrau-Joch research station (3450m) following ascent by train within <3h. In children mean±SD nocturnal SpO_2 fell from 98±1% (490m) to 85±4% and 86±4% (nights 1 and 2, 3450m); end-tidal PCO_2 decreased from 37±6 to 32±3 and 33±4 mmHg ($P<0.05$, 3450m vs. 490m). In adults, changes in nocturnal SpO_2 and end-tidal PCO_2 at 3450m were similar to those in children. Children spent less time in periodic breathing at 3450m (8±11% and 9±13% of night 1 and 2) than adults (34±24% and 22±17%, $P<0.05$) and their apnea threshold for CO_2 was lower (27±2 mmHg, both nights) compared to adults (30±2 mmHg, both nights, $P<0.05$). SpO_2, end-tidal PCO_2, and time in periodic breathing at altitude were not correlated between children and fathers. We conclude that children revealed a similarly reduced nocturnal oxygen saturation and associated hyperventilation at high altitude as adults but their breathing pattern was more stable, possibly related to a lower apnea threshold for CO_2.

Keywords: Periodic breathing, high altitude, apnea, acute mountain sickness, hypoxia

Introduction

Many families with children travel to high mountain areas for leisure time activities, to pursue the parental professional occupation and for other reasons [1]. However, little is known about children's respiratory adaptation to hypobaric hypoxia and their tolerance of high altitude. In adults, hypobaric hypoxia increases ventilation and induces respiratory alkalosis [2-4]. This attenuates hypoxemia, but may also destabilize ventilation due to hypocapnia that triggers apnea [5]. Periodic breathing characterized by crescendo-decrescendo ventilation with hyperpnea alternating with hypopnea/apnea is typically observed in adults at high altitude. Periodic breathing causes frequent arousals from sleep [6, 7] resulting in poor sleep quality, one of the manifestations of acute mountain sickness [8, 9]. There is a considerable inter-subject variability in periodic breathing due to individual differences in autonomic control of ventilation [10]. According to feed-back control theory, susceptibility to periodic breathing depends on various factors such as on controller gain, gas exchange, the circulation time and response lags involved in the chemoreflex feedback [11]. Consistent with this theory, periodic breathing has been induced in animals by inserting a circulatory delay system between the lungs and the brain [12] or by augmenting controller gain by an increase in the gain of a servo-respirator during mechanical ventilation [13]. Furthermore, ventilatory instability and periodic breathing have been shown to depend on the proximity of the eupneic PCO_2 to the apneic and hypopneic threshold PCO_2 as well as on the ventilatory sensitivity to CO_2 below eupnea [14]. These factors may differ between children and adults and may affect ventilation, oxygenation and thereby well-being and performance at high altitude [15-17]. Since respiratory adaptation to acute altitude exposure has not been studied in detail in children, we performed unobtrusive breathing pattern recordings by calibrated respiratory inductive plethysmography and actimetry in prepubertal children and their fathers. Studies were performed at low altitude (in Zurich, 490m) and during two consecutive nights at the Jungfrau Joch high altitude research station (3450m), Switzerland. Some of the results of these studies have been reported as a case report [18].

Methods

Subjects

Twenty prepubertal children, 4 girls, Tanner stage I [19, 20], (i.e., without clinical signs of puberty) mean age ±SD 11 ±1 y (range 9 to 12 y), body mass index 16.2 ±2.0 kg/m^2, and 20 men (19 were biological fathers of participating children) age 44 ±4 y (range 36 to 57y), body mass index 23 ±1.6 kg/m^2 were recruited from lowland residents (<1000m) in Switzerland. Participants were healthy, none suffered from any sleep or breathing disorder, and they had not stayed at altitudes >2000 m in the 2 months prior to the study. No drugs other than paracetamol were allowed to treat high altitude related headaches. All participants gave informed consent, and the Institutional Ethics Committee approved the study.

Measurements

A medical history and physical examination were obtained. Acute mountain sickness (AMS) was assessed by the environmental symptoms questionnaire cerebral score with ≥0.7 points considered to indicate AMS [21]. Participants were assisted in filling out the questionnaires by an investigator.

Nocturnal polygraphic studies included calibrated respiratory inductive plethysmography, pulse oximetry, ECG, and capnography of expired air to estimate end-tidal carbon dioxide tension ($PetCO_2$) as a surrogate of $PaCO_2$ (SomnostarPT, Sensormedics, Yorba Linda, CA; CapnoSleep, Weinmann, Hamburg, Germany). The technical pulse oximeter response time from sensor disconnection to a drop in oxygen saturation was 8.5 s. The capnograph response time from beginning of the rise in CO_2 concentration to 90% of

maximal amplitude after switching from room air to a 5% CO_2 mixture was 0.6 s. The respiratory inductive plethysmograph was first calibrated by the Qualitative Diagnostic Calibration method [22], and then against the integrated output of a flowmeter during 10 to 20 breaths [23]. Validation of the calibration in the morning after sleep studies revealed a deviation of tidal volume by inductance plethysmography from corresponding flowmeter values of ≤ 20% in all instances. Wrist actigraphy was performed as an indirect measure of sleep and wakefulness (Actiwatch; Cambridge Neurotechnology; Cambridge, UK) [8, 24].

Protocol

Pairs of a child and its father underwent baseline examinations in Zurich (490 m). Two to four weeks later they ascended to the Jungfrau Joch research station (3450m) by a <3h train ride and stayed there for 48h. Nocturnal polygraphic recordings were performed during one night at 490 m and during the two nights at 3450 m. The nocturnal rest period lasted for approximately 8 hours from 10 pm to 6 am. Clinical examination and assessment of AMS were performed in the evenings and mornings.

Data analysis and statistics

Polygraphic recordings were analyzed from lights-off in the evening to lights-on in the morning. This period was defined as time in bed (TIB). Breathing pattern variables derived from respiratory inductive plethysmography were measured breath by breath and mean values computed for TIB [23]. Periodic breathing was defined as a pattern of waxing and waning of ventilation with periods of hyperventilation alternating with central apneas/hypopneas for at least 3 successive cycles with hypopneas showing a >50% amplitude reduction of the inductive plethysmographic tidal volume signal compared to the previous 2 min baseline for >5 sec (figure 1) [5, 8, 25]. The number of periodic breathing cycles, their length (the cycle time), and the fraction of TIB spent with periodic breathing were determined. Occasional apneas/hypopneas that were not part of periodic breathing were defined as a reduction of the inductive plethysmographic tidal volume signal to <50% of the preceding 2 minutes baseline during ≥10 s in adults and during ≥5 s in children [26, 27]. Obstructive apneas/hypopneas were differentiated from central events by rib cage-abdominal asynchrony [23] and by continued chest wall excursions in the absence of $PetCO_2$ deflections. The apnea/hypopnea index was defined as the number of apneas/hypopneas (including periodic breathing cycles) per hour TIB. Oxygen desaturations ≥4% per hour of TIB were determined as the oxygen desaturation index (ODI). Sighs were defined as large breaths with tidal volumes >2 times the previous stable tidal volume amplitude [28]. The CO_2 apnea threshold was defined as the value of $PetCO_2$ of the last breath before an apnea occurred [29]. The CO_2 reserve ($\Delta PetCO_2$) was calculated as the difference in $PetCO_2$ during eupnea and the CO_2 apnea threshold. The lung-to-finger circulation time was measured as the time from the end of an apnea to the subsequent nadir of arterial oxygen saturation as an estimate of the circulatory delay from the lungs to the peripheral chemoreceptors [29]. To evaluate whether there were differences in circulation time between children and adults independent of body size, the circulation time was also expressed as seconds divided by height. We placed oximeter probes at the finger rather than at the ear lobe since this was found less disturbing by the children. Mean CO_2 apnea threshold and circulation time from 3 consecutive apnea/hyperpnea cycles were measured every 15 min if applicable. Activity and rest periods were derived from actigraphy with dedicated software. The acceleration level below which sleep is assumed was graphically assigned [24]. Time with acceleration below threshold was defined as rest time, and estimated sleep efficiency as rest time in per cent of TIB.

Results are expressed as mean ±SD. Measurements at different altitudes and between children and fathers were compared by ANOVA followed by Newman-Keuls tests if appropriate. A probability of $p<0.05$ was assumed as significant.

Results

Seventeen of the 20 children, and 19 of the adults completed the entire protocol. One child returned home with its father after the first night at 3450 m because of homesickness; one child was withdrawn from the study when it developed severe AMS [18]; in one child, the cardiorespiratory sleep study in the second night at 3450 m could not be analysed because of technical failure.

Results of polygraphic studies are summarized in table 1. In children and adults mean nocturnal oxygen saturation was significantly reduced by 11 to 13% during the first and second night at 3450m when compared to baseline at 490m. This was associated with a significant increase in minute ventilation that was similar in children and adults when expressed in percent of the corresponding baseline value at 490m although absolute values in L/min were higher in adults. Consistent with an increased respiratory center drive that induced hyperventilation, mean inspiratory flow (V_T/T_I) at 3450m was increased by 22% to 45% above baseline values at 490m while $PetCO_2$ was decreased. These changes were similar in children and adults (table 1). Children achieved their increased minute ventilation mainly by increasing the breath rate, whereas adults increased both the breath rate and the tidal volume. Compared to adults, heart rate in children was higher already at baseline and increased even more at high altitude. Actigraphic recordings revealed that rest time and estimated sleep efficiency decreased significantly in the first night at high altitude in children and adults (table 1).

The analysis of transient respiratory events is summarized in table 2. In children and adults the observed apneas and hypopneas were nearly exclusively of the central type (>99%) and occurred as part of a periodic breathing pattern. Therefore, central and obstructive apneas/hypopneas are not reported separately. At 490m, apneas/hypopneas were rarely detected. In contrast, at 3450m, periodic breathing with central apneas/hypopneas was common in children and adults. However, children had less apnea/hypopnea at 3450m and during the first night they spent less than one fourth of the time with periodic breathing compared to adults (Table 2, Figure 2). In the second night at 3450m, adults had a slight reduction in the apnea/hypopnea index compared to the first night but their apnea/hypopnea index was still higher than that of children which spent less than one half of the time in periodic breathing compared to adults. Children had less cyclical oxygen desaturations than adults, but their swings in oxygen saturation tended to be more pronounced than in adults although these differences were not statistically significant (table 2).

To evaluate potential mechanisms responsible for the greater stability of ventilation in children their apnea threshold for CO_2 was compared to that in adults. This analysis revealed a lower apnea threshold in children (table 2). Since the mean $PetCO_2$ was similar in children and adults, this suggested a greater CO_2 reserve in children during both nights at 3540m. Moreover, children had a significantly shorter lung to finger circulation time than adults (table 2), and the cycle time in children was also shorter than the corresponding value in adults.

We did not find symptoms or signs of high altitude pulmonary oedema, ataxia or impaired consciousness that would have suggested impending high altitude cerebral edema in any of the participants (apart from the child excluded because of severe AMS (15)). Nevertheless, 10 of the 20 children (50%) and 6 of the 20 adults (30%, Chi-square P=0.1) fulfilled the criteria for AMS according to the ESQ criteria (AMS-C $\geq$ 0.7) at least once during their stay at 3450m. AMS-C scores of children were not statistically different from corresponding values in adults (table 3). There was no significant correlation for both nights at high altitude between AMS-C scores and minute ventilation (R=0.24 children, R=0.03 adults), oxygen saturation (R=0.05 children, R=0.14 adults), end-tidal CO_2 (R=0.06 children, R=0.13 adults), and percent time with periodic breathing (R=0.14 children, R=0.08 adults) (P=NS for all

analyses). Multiple regression analysis revealed no association of minute ventilation, oxygen saturation, end-tidal CO_2, and percent time with periodic breathing in night 1 and 2 at 3450m with AMS-C scores in the following morning in children (R^2=0.09, P=NS) or adults (R^2=0.07, P=NS).

To evaluate a potential genetically determined component of ventilatory adaptation to hypoxia, changes in minute ventilation, oxygen saturation, end-tidal CO_2 and percent time in periodic breathing from baseline at 490m to the first and second night at 3450m were correlated among each of the 19 pairs of a child and its father. Multiple regression analysis did not reveal any statistically significant relationship of physiologic variables within families (data not shown).

Discussion

This is the first study which provides detailed data on the nocturnal breathing pattern and ventilation in children acutely exposed to high altitude. Using calibrated respiratory inductive plethysmography and other unobtrusive monitoring techniques during 2 successive nights at 3450m we found that children had a similar degree of hypoxemia and a proportional increase in mean ventilation at altitude as their accompanying fathers. In contrast, periodic breathing was much less pronounced in children than in adults. The greater stability of breathing in children was related to a lower apnea threshold for CO_2 , a larger CO_2 reserve and a shorter circulation time compared to adults. Half of the children and 30% of the adults suffered from acute mountain sickness during their stay at 3450m. Therefore, the greater stability of ventilation in children did not translate into a clinically superior tolerance of high altitude.

Acute exposure to hypobaric hypoxia at 3450m resulted in a similar degree of hypoxemia in children and adults with a mean arterial oxygen saturation of 84 to 86% (table 1) which is comparable to the mean nocturnal oxygen saturation of 86% we had observed previously in healthy adults at 3605m [8], but it is lower compared to the value of 91% recorded at 3109m in children 3-36 months of age [30]. According to the expected ventilatory stimulation at altitude [2], minute ventilation and mean inspiratory flow, which reflects respiratory center drive [31], were proportionally increased by 22% to 42% in children and adults, while end-tidal PCO_2, our surrogate of $PaCO_2$, was decreased to 31 to 33 mmHg indicating a similar degree of hypoxic induced hyperventilation in children and adults (table 1).

Although altitude exposure resulted in high counts of central apneas/hypopneas which occurred as part of a periodc breathing pattern in children and adults, this was significantly less pronounced in children (table 2). Their shorter cycle length of periodic breathing additionally contributed to a much lower fraction of their night-time spent with periodic breathing, i.e., less than 10%, compared to 22% to 34% in adults which is similar to the corresponding value of 25% we observed in adults at 3650m [8]. To evaluate potential mechanisms responsible for the greater stability of ventilation in children we applied the concepts described by Dempsey [32], Nakayama et al.[14] and Xie et al.[33] as illustrated in figure 4. We measured the apnea threshold for CO_2 and found that it was 3 mmHg lower in children than in adults, i.e., 27 mmHg vs. 30 mmHg in both nights at 3450m (table 2, figure 1 and 4). Since the mean nocturnal end-tidal PCO_2 was not significantly different between children and adults, this indicated that the CO_2 reserve, i.e., the difference between baseline PCO_2 and the apnea threshold was reduced more in adults which explains their greater susceptibility to ventilatory instability. These findings principally agree with those of Xie et al. [29, 33] who observed a reduced CO_2 reserve during hypoxia compared to normoxia in healthy adults hyperventilated by pressure support ventilation until central apnea occurred. Although our estimation of the apnea threshold and the CO_2 reserve cannot be directly compared to the cited studies that used face masks, mechanical ventilation and sedation [29,

33], we believe that our results obtained in a more natural setting with unobtrusive techniques reflect relevant physiologic mechanisms. In adults, periodic breathing was further promoted by an only modestly increased heart rate at altitude associated with a long circulation time (table 2) that additionally impaired a stable control of ventilation [11] and contributed to the longer hyperpnea duration and cycle time of periodic breathing compared to children. These findings are similar to the differences among patients with central sleep apnea associated with heart failure compared to those with normal cardiac function [34]. Thus, a higher heart- and breath rate, and a shorter circulation time even when corrected for height (table 2) allows children a more dynamic cardio-respiratory adaptation to high altitude compared to adults, and in combination with a greater CO_2 reserve reduces their propensity to periodic breathing. These concepts are consistent with a greater response of heart – and breath rate and ventilation during a hypoxic challenge, as well as with a lower apnea threshold for CO_2 in children compared to adults as reported by Marcus et al.[15].

Children tended to have more pronounced swings in oxygen saturation during periodic breathing than adults (9% vs. 7 to 8%, table 2) although these differences were not statistically significant. As the minimal oxygen saturation was 80 to 82% (table 2) and the mean saturation 84 to 85% (table 1) this indicated that the oxygen saturation oscillated around the mean value, dropping from baseline during desaturations and overshooting during resaturations (figure 3). Hypoxic ventilatory stimulation during rapid and pronounced drops in oxygen saturation in children might have contributed to their shorter apnea duration (table 2). Since adults did not desaturate more than children despite longer apneas they might have had larger oxygen stores in relation to oxygen consumption.

Actigraphic recordings suggested a similar total sleep duration of children and adults but we could not assess potential differences in sleep-wakefulness transitions and sleep stage distribution which might also have influenced the breathing pattern at high altitude since previous studies have shown that periodic breathing in hypoxia occurred less frequently in REM compared to NREM sleep [5, 35], and children are known to spend a higher proportion of their total sleep time in REM sleep. Differences in the ventilatory response to hypoxia and hypercapnia in children and adults may have further influenced the prevalence of periodic breathing [15].

Children sighed significantly more frequently during the nights than adults, and their number of sighs increased with ascent from low to high altitude (table 2). Although sighs have been described during sleep in infants [36] and in adults [28] their physiologic significance is not well understood. Some data in infants suggest a role of sighs in restoration of lung mechanics [37] and in resetting the neuro-respiratory control system [36] or as a trigger of arousals during sleep [38]. Sighs in prepubertal children have not been investigated in detail. Since we found an increase in sigh frequency at altitude in children but not in adults (table 2) they may represent a specific response of children to hypobaric hypoxia. Although the transient hypocapnia and neuromechanical inhibition (lung stretch reflex)[39] following sighs may trigger central apnea, the prevalence of periodic breathing in children was significantly lower than in adults despite their higher number of sighs. This further corroborates the greater stability of their respiratory control system (figure 2).

Half of the children and 30% of adults experienced significant symptoms of AMS (defined by $\geq$0.7 points in the environmental symptoms questionnaire cerebral score) during their stay at 3450m (table 3). For comparisons, all of 6 children, 0.5-4 y, and 5 of 10 teenagers, 13-18y, had significant symptoms of AMS (defined by $\geq$3 points in the Lake Louise questionnaire after one night at Putre (3500m) (very young children were evaluated with a modified questionnaire)[16]. Since we found no statistical correlation among AMS scores and measures of periodic breathing in the current study an interaction between periodic

breathing and severity of AMS symptoms seems unlikely or weak. This is in agreement with our observations in adults ascending to Capanna Regina Margherita (4559m) [8].

We did not identify any significant correlation among corresponding breathing pattern characteristics in children and their fathers but as our study may not have been appropriately powered and did not include mothers we might have failed to detect potential genetically determined properties of ventilatory control.

In summary, our analysis of nocturnal breathing patterns in children and adults during acute high altitude exposure revealed a similar degree of hypoxemia and hyperventilation but significantly less periodic breathing in children compared to adults. This suggests a more stable control of ventilation in children than in adults at high altitude, which is related to their lower apnea threshold for CO_2, a larger CO_2 reserve and a shorter circulation time.

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Figure legends

Figure 1

Nocturnal polygraphic recording obtained at 3450m in a 43 year old father (left panel) and his 11 year old son (right panel). The inductive plethysmographic signals reflect the volume of the ribcage (RC), the abdomen (AB) and their sum, the lung volume. The end-tidal carbon dioxide tension ($PetCO_2$), arterial oxygen saturation by pulse oximetry (SpO_2) and heart rate measured by ECG are also shown. There is a periodic breathing pattern associated with fluctuations in arterial oxygen saturation and heart rate. This was extraordinarily pronounced in this child. The apnea threshold for CO_2 is lower in the child (25 mmHg, horizontal arrow) than in his father (30 mmHg, horizontal arrow). The circulation time measured as the time from the end of an apnea to the corresponding nadir in arterial oxygen saturation (vertical arrows) is shorter in the boy (12 s) compared to the father (19 s).

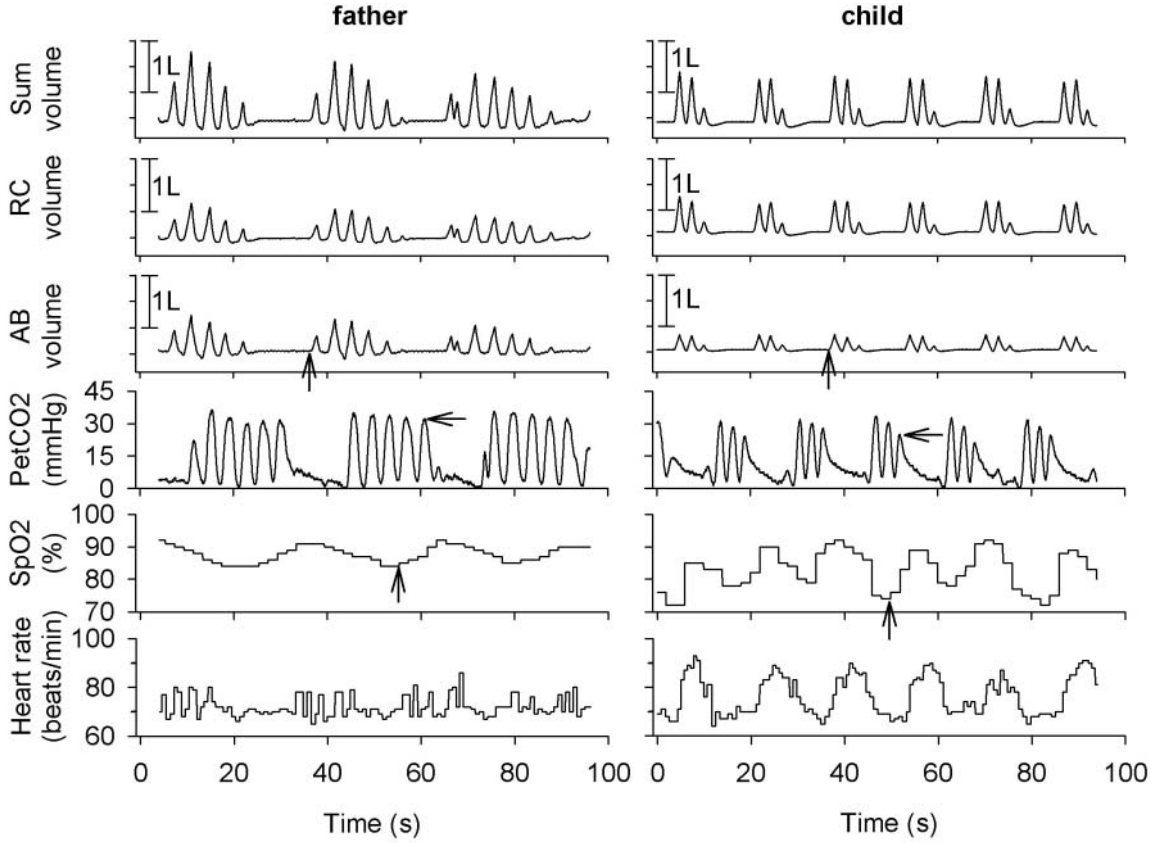


Figure 2

The percent of the night-time spent with periodic breathing was classified into 3 groups: 1) <10%, 2) 10-30%, 3) >30%. Most of the children spent less than 10% of the night-time with periodic breathing. In contrast, almost all adults spent more than 10% of the night-time in periodic breathing.

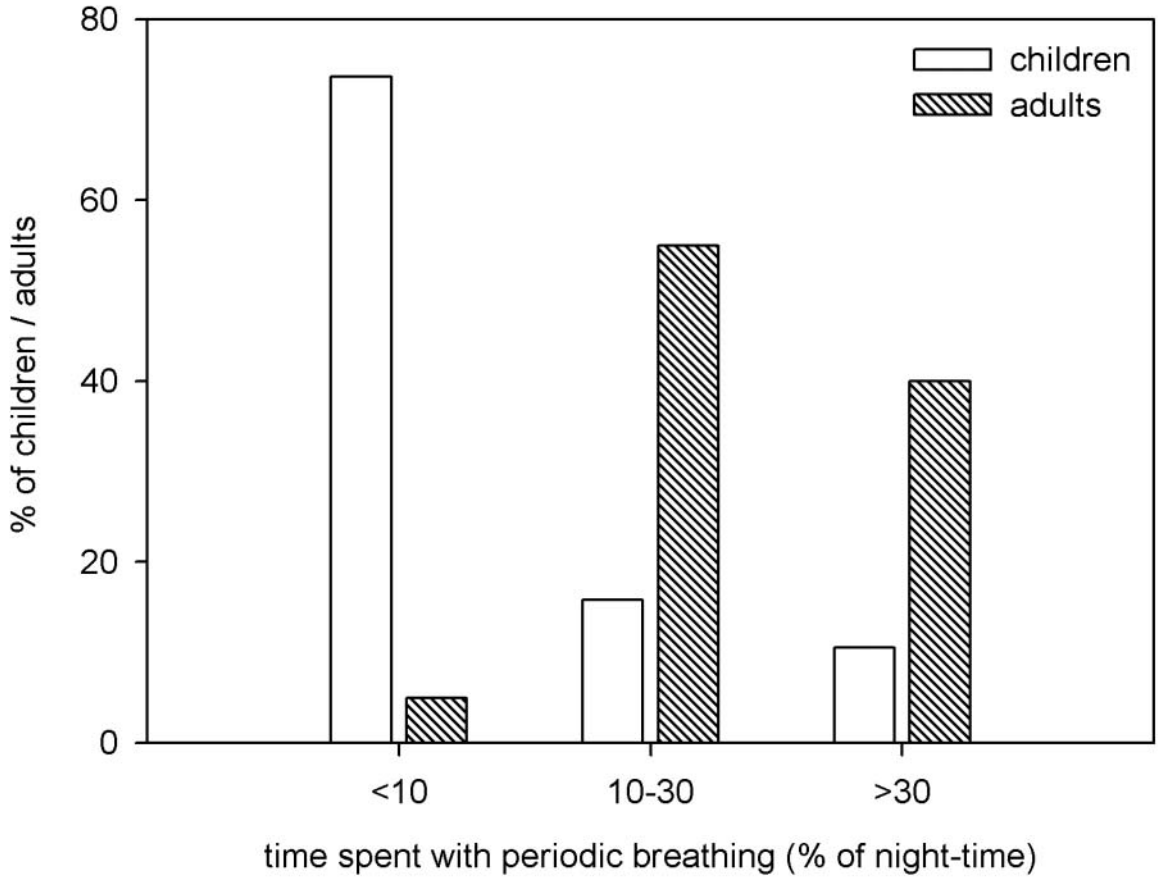
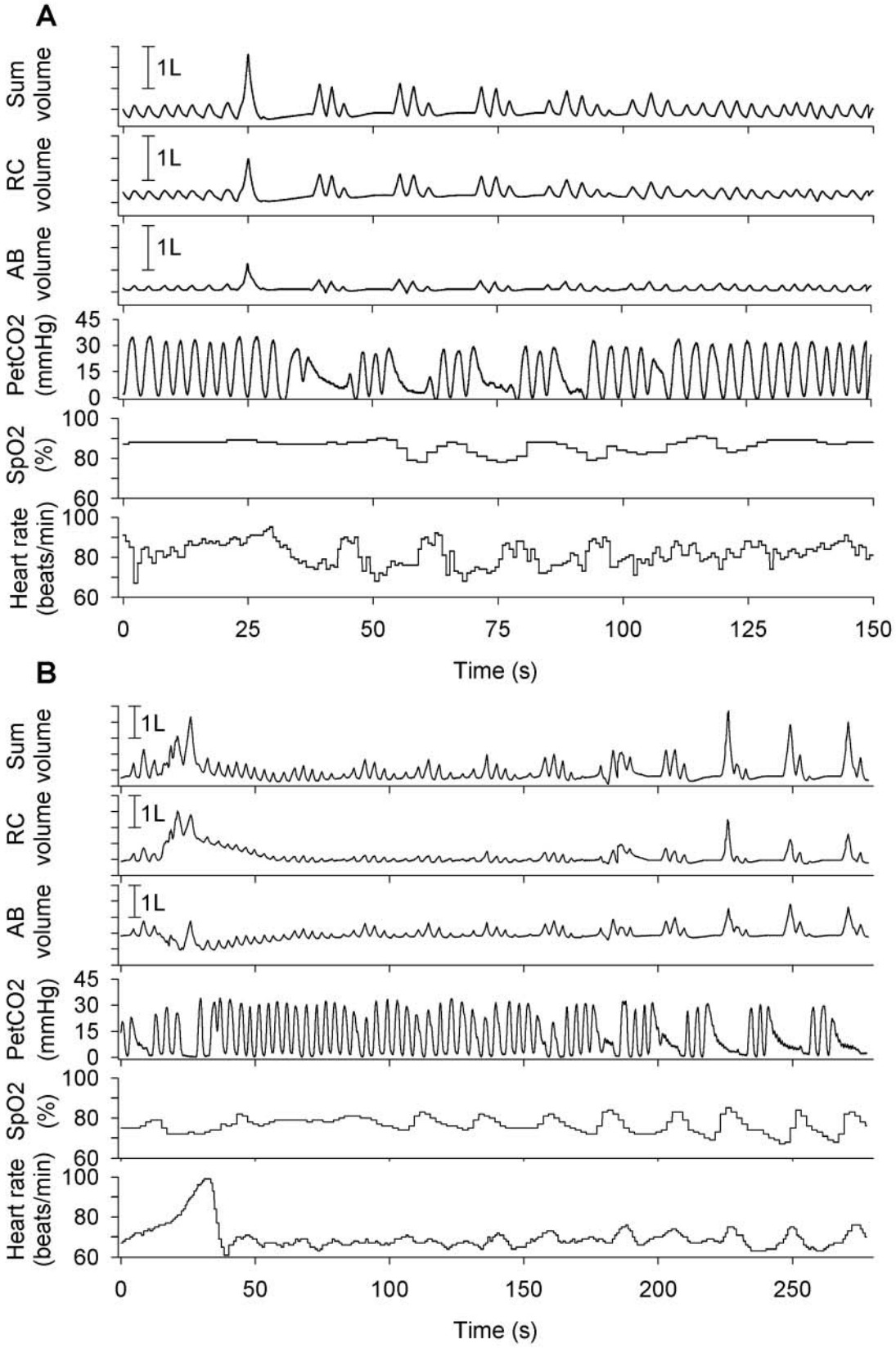


Figure 3

Time series of inductive plethysmographic recordings of the rib cage volume (RC), abdominal volume (AB), and lung volume (sum) along with end-tidal carbon dioxide tension ($PetCO_2$), arterial oxygen saturation (SpO_2) and heart rate obtained at 3450m. The upper panel (A) illustrates a short sequence of periodic breathing of a child beginning with a sigh as the initial disturbance. The breathing pattern normalizes after only four cycles of periodic breathing consistent with a stable respiratory control system. In the lower panel (B), a recording obtained in an adult reveals irregular, large breaths that trigger periodic breathing with progressively increasing fluctuations in amplitude suggesting instability of the respiratory control system.


A
Sum volume
RC volume
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PetCO2 (mmHg)
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0
SpO2 (%)
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Heart rate (beats/min)
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125
150
Time (s)
B
Sum volume
RC volume
AB volume
1L
PetCO2 (mmHg)
45
30
15
0
SpO2 (%)
100
80
60
Heart rate (beats/min)
100
80
60
0
50
100
150
200
250
Time (s)

Figure 4

The factors responsible for the greater stability of ventilation in children compared to adults are illustrated by a diagrammatic representation of the relationship between alveolar ventilation (V'_A) and alveolar PCO_2 (P_ACO_2), i.e. the isometabolic line according to the relation $V'_A = K^* V'CO_2 / P_ACO_2$ [32]. V'_A is expressed in percent of the value during eupnea (% V'_A eupnea) since its absolute value is not known and varies between children and adults. Although CO_2 production ($V'CO_2$) and the constant K have different values for children and adults this has no effect on the metabolic line if V'_A is expressed in percent V'_A at eupnea and as $K^* V'CO_2$ remains constant within individuals during stable resting conditions. During the first night at 3540m, the eupneic $PetCO_2$ (the surrogate for P_ACO_2) at 100% V'_A was 32 mmHg in both children and adults (table 1). The apneic threshold $PetCO_2$ was 27 mmHg in children, and 30 mmHg in adults (table 2). The lines connecting the point on the metabolic line corresponding to the eupneic P_ACO_2 at 100% V'_A and the apneic threshold P_ACO_2 at V'_A =0 reflect the ventilatory responsiveness for PCO_2 below eupnea ($\Delta V'_A/\Delta P_ACO_2$=100% V_A eupnea/CO_2 reserve). The mean value of $\Delta V'_A/\Delta P_ACO_2$ is 2.5 times greater in adults (50% V'_A eupnea per mmHg P_ACO_2) than in children (20% V'_A eupnea per mmHg P_ACO_2). The increase in V'_A required to drive P_ACO_2 from the eupneic level to the apneic threshold is much smaller in adults (7%) than in children (19%) (horizontal arrows).

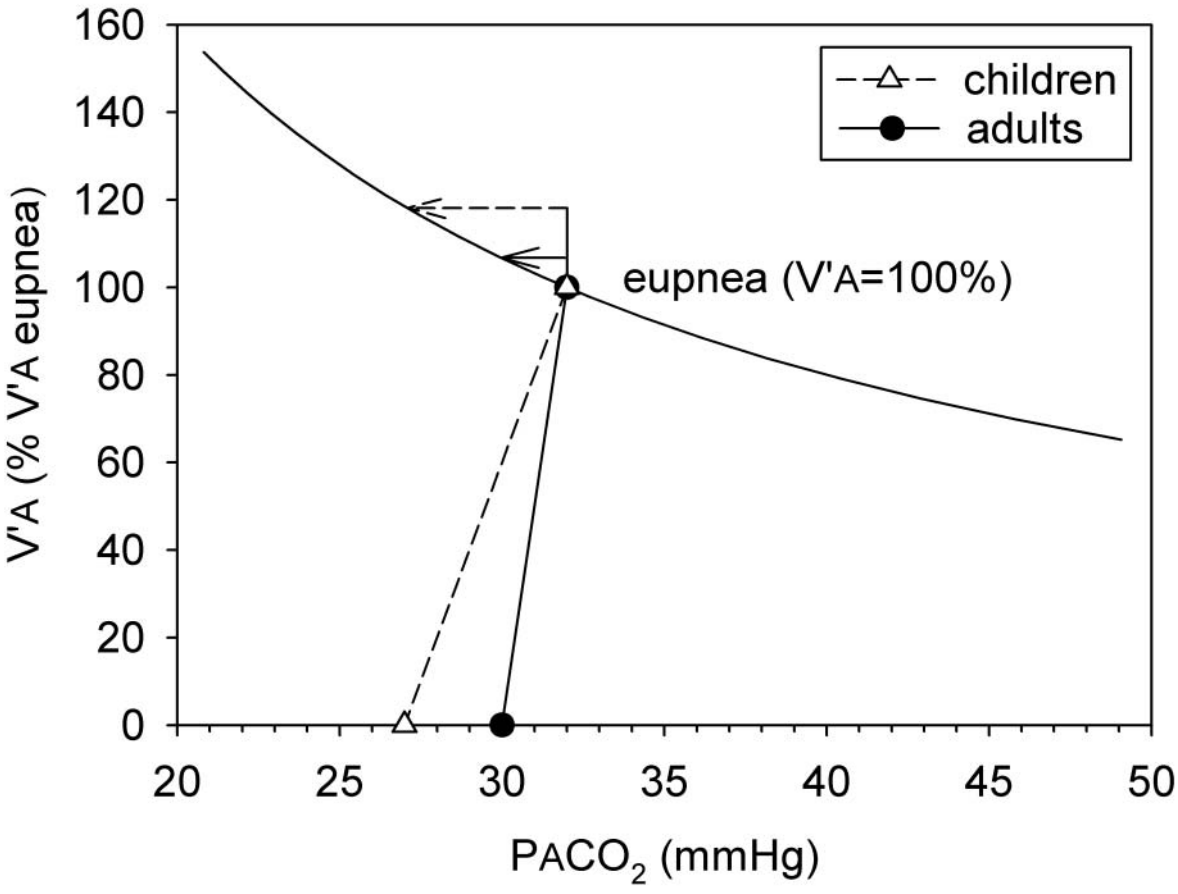

Table 1. Nocturnal polygraphic recordings in children and adults

	Children			Adults		
	490m baseline n=20	3450m day 1 n=19	3450m day 2 n=17	490m baseline n=20	3450m day 1 n=19	3450m day 2 n=19
Time in bed, min	519±52	484±44*	506±29§	515±56	462±23*	495±37§
Ventilation, L/min	3.2±0.6¶	4.4±0.7*¶	4.1±0.8*¶	6.3±1.4	8.1±1.1*	7.4±1.1*§
% baseline	100	142±38*	128±38*	100	135±27*	123±27*
Tidal volume, L	0.20±0.05¶	0.23±0.05¶	0.22±0.05¶	0.41±0.09	0.48±0.07*	0.45±0.09*§
% baseline	100	120±38	110±42	100	122±21*	111±19*§
Breath rate, 1/min	16.2±2.1	19.6±3.0*	19.3±2.8*	15.4±2.1	17.2±2.2*	17.0±2.3*
% baseline	100	121±20*¶	121±16*¶	100	112±12*	111±7*
VT/TI, L/s	0.13±0.03¶	0.17±0.03*¶	0.16±0.03*¶	0.22±0.06	0.31±0.05*	0.27±0.04*§
% baseline	100	137±40*	122±37*	100	145±32*	125±29*§
SpO_2, %	98±1	85±4*	86±4*	96±1	84±3*	85±4*
$PetCO_2$, mmHg	37±6	32±3*	33±4*	37±6	32±2*	31±2*
Heart rate, 1/min	68±6¶	88±10*¶	86±9*§¶	56±10	67±9*	63±7*§
% baseline	100	131%±12*	126±9%*¶	100%	120±15%*	112±11%*§
Rest time, min	478±56	426±62*	456±36§	483±61	406±45*	439±48*
Estimated sleep efficiency, %	92±4	88±7*	90±5	94±4	88±8*	89±5*

Means±SD. VT/TI: Tidal volume/inspiratory time=mean inspiratory flow; SpO_2: oxygen saturation by pulse oximetry; $PetCO_2$: end-tidal carbon dioxide partial pressure; Estimated sleep efficiency: rest-time measured by actigraphy in % of time in bed.

*p<0.05 vs 460m; §p<0.05 vs day 1; ¶p<0.05 vs adults.

Table 2. Nocturnal periodic breathing and transient respiratory events

	Children			Adults		
	490m baseline n=20	3450m day 1 n=19	3450m day 2 n=17	490m baseline n=20	3450m day 1 n=19	3450m day 2 n=19
Oxygen desaturation index (≥4%), per h TIB	5.3±2.6	34.7±26.1*¶	36.0±31.9*	2.3±1.6	56.6±25.7*	43.2±26.9*§
Drop in SpO_2 during desaturations, %	NA	9±2	9±3	NA	8±2	7±2§
Minimal SpO_2 during desaturations, %	NA	81±4	81±4	NA	80±3	82±4§
Apnea/hypopnea index, per h TIB	7.1±2.8	32.5±24.6*¶	32.5±26.8*	3.5±2.3	54.1±26.2*	39.5±23.9*§
Time with periodic breathing, % of TIB	0±0	8±11*¶	9±13*¶	0±0	34±24*	22±17*§
Cycle length, s	NA	17.0±2.1¶	18.5±4.1¶	NA	28.0±5.1	31.5±7.7
Apnea duration, s	8.5±1.5¶	7.4±0.8¶	7.9±0.9¶	12.0±1.4	11.6±3.2	11.9±2.0
Hyperpnea duration, s	NA	9.4±2.0¶	10.5±4.1¶	NA	16.5±5.5	19.7±8.1
CO_2 apnea threshold, mmHg	NA	27±2¶	27±2¶	NA	30±2	30±2
CO_2 reserve (Δ $PetCO_2$)	NA	4.6±3.5¶	6.4±3.1¶	NA	1.7±2.5	1.2±1.4
Circulation time (s)	NA	11.8±1.2¶	11.6±0.8¶	NA	22.2±4.1	21.6±1.9
Circulation time (s/body height in m)	NA	8.3±0.9¶	8.1±0.7¶	NA	12.4±2.2	12.0±0.9
Sighs during TIB	41±17	54±23*¶	42±26¶	24±13	29±22	18±11

Means ±SD; TIB: time in bed; NA: not applicable because no periodic breathing was detected; SpO_2: oxygen saturation by pulse oximetry; the CO_2 reserve ($\Delta PetCO_2$) was calculated as the difference between eupneic end-tidal carbon dioxide partial pressure and the CO_2 apnea threshold;

*$p<0.05$ vs 460m; §$p<0.05$ vs day 1; ¶$p<0.05$ vs adults

Table 3. Symptoms of acute mountain sickness

	Children		Adults	
AMS-C scores	Mean ± SD	Subjects n ≥ 0.7§	Mean ± SD	Subjects N ≥ 0.7§
3450 m day 1 evening	0.49 ± 0.77	5	0.45 ± 0.59	4
3450 m day 2 morning	0.46 ± 0.57	6	0.30 ± 0.34	3
3450 m day 2 evening*	0.23 ± 0.34	2	0.06 ± 0.08	0
3450 m day 3 morning*	0.10 ± 0.17	0	0.12 ± 0.18	0

Means ±SD; * on day 2, evening, only 19 children and fathers and on day 3, morning, only 18 children and 19 fathers were evaluated. P=NS children vs fathers for all comparisons;
§ 10 of the 20 children (50%) and 6 of the 20 adults (30%) had a score ≥0.7 at least once during their stay at 3450m, the difference in prevalence was not statistically significant