Name of research institute or organization:

Exercise Physiology, ETH-University of Zürich

Title of project:

Short-term acclimatization to high altitude in children

Project leader and team:

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Project description:

Background:
There is very little known about the short-term adaptation of children to high altitude, despite the fact that more and more children travel to those altitudes for recreational reasons such as skiing or trekking. The physiological characteristics at rest and exercise in a child are different from those in an adult mainly due to smaller body dimensions, hormonal and metabolic differences. Upon acute exposure to high altitude, the body adapts through different mechanism to the lower partial pressure of oxygen, a process called acclimatization, but very few data exist in children. Based on the different physiological characteristics in children at low altitude, we also expect differences in acclimatization between children and adults.

The general *objectives* of this study were therefore to determine short-term (3-day exposure) altitude-related (3450m above sea level) 1. changes of pulmonary, cardiovascular functions at rest, during exercise and sleep, and 2. the tolerance of altitude and occurrence of AMS of prepubescent children. Specifically, we compared function between low altitude (LA) and day 1-3 in high altitude (HA) among the children, and in comparison to their fathers.

Methods:
Clinical examinations. Each subject had a physical examination of the cardio-pulmonary system at LA and daily at HA to ensure a good general health. Tanner stage and height was assessed once at LA, weight was measured at LA and daily at HA.

Acute mountain sickness score. In 1991, the Lake Louise Consensus Committee agreed on diagnostic criteria and a scoring system for the symptoms and signs of acute mountain sickness (Roach et al. 1993). It consists of a short self-report questionnaire, which is sufficient in itself, and to which an additional clinical assessment may be added, consisting of three signs: mental status, ataxia and peripheral edema. A diagnosis of AMS is based on a recent gain in altitude, at least several hours at the new altitude, and the presence of at least 5 score points. At LA and in the evenings and mornings of each day at HA, a questionnaire regarding symptoms and signs of AMS was filled out by each subject. Signs of AMS were evaluated by the investigator. One of the limitations in comparing prevalence and incidence of AMS among the studies is the fact, that there were different criteria in definition of the diagnosis. We therefore also included an ESQ questionnaire (Sampson et al. 1983) which was previously used to be able to compare AMS scores with the adult data from previous studies.

Resting pulmonary function. Pulmonary function testing was performed at LA and on each day at HA. Each subject performed at least three forced expiratory maneuvers in a sitting position (Vmax 2900, SensorMedics, Yorba Linda, CA, USA). The trial with the largest vital capacity is used to determine functional vital capacity (FVC), forced vital capacity in 1 sec (FEV_1), peak expiratory flow (PEF), single breath diffusion capacity (DL_{CO}), and closing volume by single breath nitrogen washout tests (CV) according to standard technique. For DLCO, unadjusted values, and those adjusted for altitude and alveolar ventilation are reported. Calibration of the flow meter and the gas analyzers was performed several times per day. Values will be compared to reference values (Sherill et al. 1992) and expressed as measured values and in percent change compared to LA.

Doppler Echocardiography. Echocardiography was performed at LA and on each day at HA. It has previously been shown, that echocardiographic and invasive measurements of pulmonary artery pressure closely correlated at high altitude (Allemann et al. 2000). The echocardiographic recordings were performed by an experienced investigator using a portable ultrasound system (Cypress, Accuson Inc, USA). The recordings were stored together with data from a peripheral electrocardiographic lead on a videotape and analyzed off line. Systolic pulmonary-artery pressure was evaluated from the pressure gradient between the right ventricle and atrium using continuous-wave Doppler echocardiography and the clinically determined mean jugular venous pressure. In tricuspid regurgitation, as indirect parameter of pulmonary artery pressure, the continuous-wave Doppler beam was superimposed on the regurgitant jet into the right atrium by means of color Doppler, to obtain the maximal velocity within the Doppler spectrum. The trans-tricuspid pressure gradient was then calculated from the maximal velocity within the tricuspid jet of at least three beats, by a modification of the Bernoulli equation (trans-tricuspid pressure gradient equals four times the square of the velocity in the tricuspid jet).

Aerobic exercise test. Each subject performed a graded exercise test on a cycle ergometer (Ergoline er800s, Pilger, Switzerland) to determine maximal oxygen uptake (VO_2), maximal aerobic capacity and submaximal $\dot{V}O_2$-HR relationship during exercise at LA and on day 1 and 3 of HA. A McMaster protocol was applied for the children (Bar-Or 1983). The initial load and the increments were based on the child's height. Load was increased after each 2 min stage until the child could no longer pedal at the prescribed cadence of 50 rpm, in spite of encouragement by the investigator. Maximal aerobic capacity ($\dot{V}O_2$-test) for men will be performed with an initial load of 70 W and an increase by 30 W every 2 minutes until volitional exhaustion of the subject. All subjects breathed through a face mask from which expired gas concentrations were continuously monitored (Quark b2, Cosmed, Rome, Italy). Minute ventilation, $\dot{V}O_2$, CO_2 production and respiratory exchange ratio were then calculated. Heart rate was measured by Polar Vantage XL 4000 Sporttester (Leuenberger, Switzerland) at an interval of 5 seconds. Oxygen saturation was monitored by pulse oximetry throughout the test by forehead oximetry (OxiMax N-595, Nellcor, Leuag AG, Stans, Switzerland).

Fluid balance. Fluid balance was assessed at HA only. The participants of the study continuously noted their fluid intake and output at all days of HA. All fluid was taken by a single bottle which was filled up by the investigators only. Urine was collected in a bottle which never left the subject. Daily weight measurements were taken in the evenings and mornings at HA. The meals were standardized to ensure an adequate intake for sodium (65 mmol/d) and to cover sodium sweat losses in individuals who

are moderately active (RDA standard). Subjects adhered to a standardized diet with known composition in which calorie and sodium intake was measured individually.

Hypoxic ventilatory response. Hypoxic ventilatory response was measured at LA and at days 1 and 2 of HA. For the ventilatory response tests, subjects sat comfortably in an armchair situated in a quite room with temperatures between 20 and 24°C. The subjects breathed through a face mask connected to a metabolic cart (Quark b2, Cosmed, Rome, Italy); V_E, $P_{ET}CO_2$ and $P_{ET}O_2$ were continuously measured breath-by-breath. Arterial oxygen saturation (SaO2) was monitored by an oximeter using a finger probe (OxiMax N-595, Nellcor, Leuag AG, Stans, Switzerland). An initial 10-min hyperoxic period (F_IO_2 =0.59) was used before all ventilatory response tests performed at HA to eliminate possible depression caused by ambient hypoxia at HA and to measure HVR over the same saturation range as that measured at LA (Sato et al. 1992). Each subject was familiarized with the testing prior to the first measurement at LA. The acute isocapnic hypoxic ventilatory response (HVR) was measured by a method previously described by Severinghaus et al (1976). Initially, resting minute ventilation was assessed until minute ventilation, end-tidal CO2 and heart rate were stable. End-tidal oxygen pressure was then randomly reduced to three different levels (60, 50, 40 Torr) within 90-180sec and kept for 3 min. End-tidal CO2 was maintained at a 2 Torr higher level than during room air breathing within 0-2 Torr.

Respiratory plethysmography. These measurements were taken at LA and on both nights at HA. Nocturnal breathing pattern was recorded by computerized devices incorporating a respiratory inductive plethysmograph, a pulse oximeter, an ECG, and a position sensor (Somnostar, SensorMedics, Yorba Lainda, CA, USA). Displacement of inductance sensors was avoided by taping them directly to the skin and securing them with an elastic net (Somnostar). The Qualititative Diagnostic Calibration method was applied during natural breathing in supine position over 5 min. It provided relative gains of rib cage and abdominal inductive plethysmograph signals. Their sum was subsequently calibrated in absolute units (l) for 5-10 breaths with the nose clipped. Accuracy of calibration was verified in the mornings after the sleep studies, and regarded as acceptable if inductive plethysmographic tidal volumes were within 20% of the calibration bag volume. $P_{ET}CO_2$ was continuously measured throughout the night by a transcutaneous PCO_2 43°C electrode mounted on the volar forearm which was calibrated in vivo after 15 min of stabilization to equal $P_{ET}CO_2$. Rest/activity pattern during the nights was recorded by an accelerometer placed at the wrist as an indirect measure of sleep/wakefulness (Actiwatch, Cambridge Neurotechnology, Cambridge, UK).

Preliminary results and significance:

In Table 1 you find the characteristics of the study participants.

		Age	Height	Weight	BSA	FVC	FVC, %pred
Adults	Mean	44.0	179.0	73.9	1.92	5.33	105.8
	SD	4.2	6.8	7.5	0.13	0.60	10.6
	Min	36.6	169.0	61.0	1.72	4.24	89.4
	Max	57.1	190.0	91.3	2.20	6.25	136.0
Children	Mean	10.7	142.3	33.0	1.14	2.45	100.3
	SD	1.1	7.7	6.1	0.13	0.44	9.8
	min	9.2	129.5	24.3	0.95	1.54	77.5
	max	12.4	158.0	49.5	1.42	3.21	118.3

* n=20 fathers and 20 children (4 girls, 16 boys)
BSA=body surface area, FVC=forced vital capacity

All children and adults showed a normal FVC compared to reference values. One child and two adults were slightly overweight. Children and adults were also well matched in respect to fitness.

The cumulative incidence of acute mountain sickness (AMS) was similar when measured with the Lake Louise score, but was higher in children when measured with the AMS-C-Score. All children and their fathers were sick within 30 hours of altitude exposure, on day 3 of HA all participants were healthy again. These results have to be interpreted with caution, since 1. adult questionnaires were used in a population of children who might have problems to read and interpret the questionnaires as well as give appropriate responses. Nevertheless, it makes sense to be very cautious when taking children to HA, and make sure to adhere to recommendations regarding ascent rate and prompt descent in case of symptoms.

Maximal aerobic exercise performance at LA was similar in children and adults, respectively, when corrected per bodyweight. Both reduced there VO2max similarly by about 20% on day 1 and 3 of HA. But the heart rate behaved differently. While it stayed at equal levels throughout the altitude exposure in children, it decreased significantly from LA to HA in adults on both days at HA. It seems, therefore, that the cardiovascular response to HA is different in children and adults, but mechanism behind have to be determined. Possible differences could be a different cardiac output or a different arterio-venous oxygen content in the peripheral vascular system.

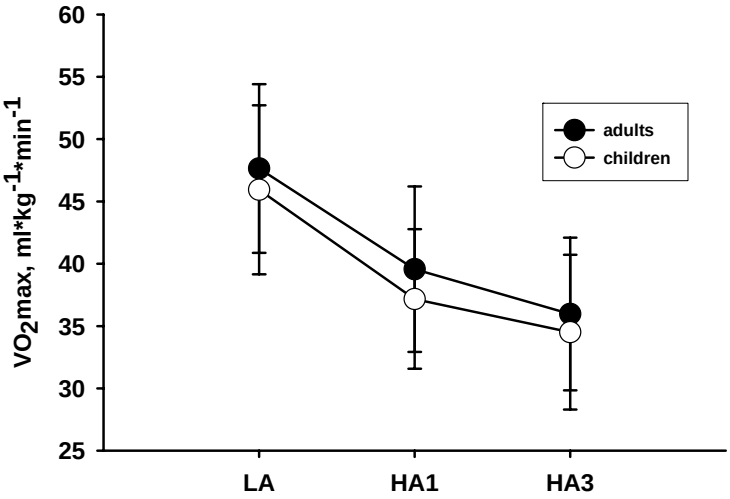

Fig 1: Maximal oxygen uptake corrected for body weight (VO2max) at low altitude (LA) and on day 1 and 3 at high altitude (HA1 and HA3)

During sleep, ascent to 3450m induced proportional increases of ventilation in children and fathers and similar reductions of SpO2. Breath rate increased more in children than adults. Periodic breathing was marked in fathers, but much less pronounced in children. It is still a matter of debate, whether periodic breathing plays a role in the occurrence of AMS. If so, it might explain part of the differences in AMS incidence we found between the two generations.

Resting ventilation was higher in children than in adults at LA and HA, and significantly rose at HA to the same extent. Children mainly increased ventilation by increasing respiratory frequency, adults increased ventilation by a parallel increase in respiratory frequency and tidal volume. The decrease in oxygen saturation between LA and HA was prominent and similar in both groups. Again, the extent of respiratory adaptations to HA seems to be similar between children and adults, but the mechanisms by which ventilation is increased are different, mainly due to the smaller lung volumes in children. Whether the inherited higher ventilation per kg bodyweight in children plays a role in the acclimatization process has to be determined.

Isocapnic hypoxic ventilatory response (HVR) is higher in children than in adults at LA and HA. Both groups increase their HVR with HA, but adults seem to increase their HVR more than children. HVR is a measure of hypoxia induced respiratory drive of a person. Whether the extent of the drive at LA, or the extent of increase at HA is important for the protection against AMS, is still controversial even among the adult population.

With HA, pulmonary artery pressure seems to increase more in children than in adults. This could be one important factor why children become more sick at HA than adults. The main postulated mechanism why a high pulmonary artery pressure leads to more AMS, is an inhomogeneous vasoconstriction in the pulmonary arteries leading to a diffusion limitation of oxygen into the blood.

Fluid balance is still in investigation. In an adult population, the literature postulates that those who become sick show more water retention and consequently increase bodyweight, due to renal and hormonal alterations, but whether this is true is also a matter of debate in the literature.

In 2006, we will finish data analysis and statistics, and several papers are prepared to be published in peer-reviewed international physiological or medical journals.

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Key words:

High altitude, children, high altitude illness

Collaborating partners/networks:

University Hospital of Zürich, Dept of Pneumology (Prof. K. Bloch)
University Hospital of Basle, Dept of Cardiology (PD Dr. HP Brunner)

Scientific publications and public outreach 2005:

Conference papers

Kohler, M., Kriemler, S., Handke E., Zehnder, M., Bloch, K.E. Adaptation of ventilation to acute altitude exposure in prepubertal children. International Conference of the American Thoracic Society, San Diego, 2006.

Kriemler, S., Zehnder, M., Kohler M., Brunner, H.P., Boutellier, U. Maximal aerobic performance of prepubertal children upon fast ascent to high altitude. 53rd Annual Meeting of American College of Sports Medicine, Denver, 2006.

Radio and television

MTW-Spezial vom Jungfraujoch: Forschung zwischen Himmel und Erde, Pioniere und Abenteuer, Bedrohung aus dem Kosmos, medizinisches Hoehen-Experiment, Geheimnisse im Weltraum, Hoechstgelegener Arbeitsort, Menschen Technik Wissenschaft, SF1, Januar 12, 2006.

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