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Authors
Rieger, MG
Tallon, CM
Perkins, DR
et al.

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CARDIOPULMONARY AND CEREBROVASCULAR ACCLIMATIZATION IN CHILDREN AND ADULTS AT 3800 METERS

MG Rieger[1], CM Tallon[1], DR Perkins[2,3], K.J. Smith[4], M Stembridge[2,3], S Piombo[5], S Radom-Aizik[5], DM Cooper[5], PN Ainslie[1], AM McManus[1].

[1]*Centre for Heart, Lung & Vascular Health, University of British Columbia, Kelowna, BC, Canada*

[2]*Cardiff School of Sport & Health Sciences, Cardiff Metropolitan University, Cardiff, UK*

[3]*Youth Physical Development Centre, Cardiff School of Sport & Health Sciences, Cardiff Metropolitan University, Cardiff, UK.*

[4]*Cerebrovascular Health, Exercise, and Environmental Research Sciences, University of Victoria, Victoria, BC, Canada*

[5]*Pediatric Exercise and Genomics Research Center, University of California Irvine School of Medicine, Irvine, California*

Corresponding Author: Matt Rieger

Contact: mrieger@ualberta.ca

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Key Points:

- Children have different ventilatory and metabolic requirements than adults, which may present differently in the pulmonary and cerebral vasculature upon ascent to high altitude.
- We brought children (ages 7-14) and adults (ages 23-44) from sea level to high altitude (3000-3800 m) and assessed changes in ventilation, pulmonary artery systolic pressure (PASP), and cerebral blood flow over one week.
- Significant increases in ventilation were and decreases in left ventricle stroke volume were observed at a lower altitude in children than adults.
- PASP and CBF increased by a similar relative amount between children and adults at 3800 m.
- These results help us better understand age-related differences in compensatory responses to prolonged hypoxia in children, despite similar changes in pulmonary artery pressure and CBF between children and adults.

Matt Rieger is a PhD candidate in Kinesiology at the University of British Columbia Okanagan, studying under Professor Ali McManus at the Pediatric Exercise Research Laboratory. His research focuses on the interactions between exercise and environment among children, working towards a better understanding of vascular health across the maturational span. Away from the lab, Matt spends his time skiing and mountain biking.

ABSTRACT

Maturational differences exist in cardiopulmonary and cerebrovascular function at sea-level, but the impact of maturation on acclimatization responses to high-altitude is unknown. 10 children (9.8±2.5 y) and 10 adults (34.7±7.1 y) were assessed at sea-level (BL), 3000 m, and twice over 4 days at 3800 m (B1, B4). Measurements included minute ventilation ($\dot{V}_E$), end-tidal partial pressures of oxygen ($P_{ET}O_2$) and carbon dioxide, echocardiographic assessment of pulmonary artery systolic pressure (PASP) and stroke volume (SV), and ultrasound assessment of blood flow through the internal carotid and vertebral arteries was performed to calculate global cerebral blood flow (gCBF).

At 3000 m, $\dot{V}_E$ increased from BL by 19.6±19.1% (P=0.031) in children, but not in adults (P=0.835); SV was reduced in children (-11±13%, P=0.020) but not adults (P=0.827), which was compensated for by a larger increase in heart rate in children (+26 beats·min^{-1} vs. +13 beats·min^{-1}, P=0.019). Between B1 and B4, adults increased $\dot{V}_E$ by 38.5±34.7% (P=0.006), while $\dot{V}_E$ did not increase further in children. The rise in PASP was not different between groups; however, ΔPASP from BL was related to $\Delta P_{ET}O_2$ in adults (R^2=0.288, P=0.022), but not children. At BL, gCBF was 43% higher in children than adults (P=0.017), and this difference was maintained at high altitude, with a similar pattern and magnitude of change in gCBF between groups (P=0.845). Despite $\dot{V}_E$ increasing in children but not adults at a lower altitude, the pulmonary vascular and cerebrovascular responses to prolonged hypoxia are similar between children and adults.

INTRODUCTION

When travelling to high altitude, humans acclimatize to the reduced oxygen availability through integration of the ventilatory, metabolic, cardiovascular, and cerebrovascular systems (Bärtsch & Gibbs, 2007; Hoiland *et al.*, 2018; Palubiski *et al.*, 2020). These responses facilitate the effective transfer of oxygen from the alveoli to the pulmonary vasculature and the delivery of oxygen to peripheral tissue beds, which helps to normalise oxygen transport and gas exchange towards sea-level values. Acute and chronic adjustments to high altitude

exposure in healthy adults are well-described and reviewed elsewhere [see: (Luks *et al.*, 2021)]; however, evidence of these physiological adjustments in children have received far less attention (Kohler *et al.*, 2008; Kriemler *et al.*, 2008, 2016; Allemann *et al.*, 2012; Gavlak *et al.*, 2013).

The most important change occurring during hypoxic exposure is hyperventilation and related ventilatory acclimatization (West, 2006), caused by changes in the balance of O_2 and CO_2 chemoreception. This hyperventilaton gradually optimizes ventilation ($\dot{V}_E$) and increases arterial partial pressure of oxygen (P_aO_2). These ventilatory changes have not been described in hypoxic exposures lasting >40 hours in children, despite observations of the hypoxic ventilatory response (HVR) increasing linearly over several days at high altitude in adults (White *et al.*, 1987; Sato *et al.*, 1992). While 9 to 12-year-old children have previously demonstrated a higher isocapnic HVR at sea-level relative to adults, subsequent increases in the HVR following 6-8 hours and after two days at 3450 m were similar between groups (Kriemler *et al.*, 2016). Further child-adult comparisons have shown increases in $\dot{V}_E$ and ventilatory drive were similar following either one-hour of normobaric hypoxia (Morris *et al.*, 2017) or 40-hours of hypobaric hypoxia at 3450 m (Kohler *et al.*, 2008). In the latter instance, the arterial oxygen saturation (S_pO_2), and end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$) declined to the same extent in children and adults; however, no study has reported ventilatory changes to more prolonged periods of hypoxia and the impact this might have on other key physiological responses to high altitude.

Developmental differences in the cardiovascular responses to high altitude are apparent and most prominent in the pulmonary vasculature. For example, at 3450 m, the acute rise in pulmonary artery systolic pressure (PASP) is greater in young children (6-9 y; +24 mmHg) compared to adolescents (10-16 y; +13-15 mmHg) and adults (+6 mmHg) (Kriemler *et al.*, 2008; Allemann *et al.*, 2012). Given the importance of the alveolar partial pressure of oxygen (P_AO_2) on determining the extent of hypoxic pulmonary vasoconstriction (Swenson, 2013), reports of a similar (Honda *et al.*, 1986) or greater (Marcus *et al.*, 1994; Kriemler *et al.*, 2016) HVR in children compared to adults appear to be in contradiction with observations of an increased PASP in children at high altitude. For example, if a higher HVR is reflected in elevations in P_AO_2, this should reduce, not augment PASP.

In adults, alterations in arterial blood gases via ventilatory acclimatization to high altitude, along with changes to arterial oxygen content (C_aO_2), have an important influence on

determining the extent of cerebrovascular vasodilation (Hoiland *et al.*, 2016; Willie *et al.*, 2016). In children, resting cerebral blood flow (CBF) relative to cardiac output (Q) is highest at birth, with absolute flow eventually declining by 40-60% between the ages of ~6-20 years (Wu *et al.*, 2016), as anatomical somatic growth begins to outpace the neuronal pruning and cognitive development that is prioritized prior to puberty. Importantly, with these substantial elevations in cerebral blood flow during growth and development, the capacity for adaptation to changes in arterial blood gasses is not well-understood in children. At least over one-hour of poikilocapnic normobaric hypoxia (12.6% O_2), it was found that only vertebral artery flow (Q_{VA}) increased in adults, while increases in both ICA flow (Q_{ICA}) and Q_{VA} were apparent in the children (Morris et al., 2017). The influence of ventilatory acclimatization on cerebrovascular responses to more prolonged hypobaric hypoxia in both children and adults, however, are currently unknown.

The aim of this study was to investigate maturational differences in ventilatory, cerebrovascular, and cardiopulmonary adjustments to prolonged high-altitude travel in children and adults. We examined the hypotheses that after scaling for body size, a greater increase in $\dot{V}_E$ would be observed in children compared to adults (via its influence on increasing P_AO_2 and reducing P_ACO_2) and would attenuate both elevations in cerebral blood flow and PASP.

METHODS

Ethical Approval

This study was approved by the clinical research ethics board of the University of British Columbia (H18-02650), as well as the institutional research board at University of California. All experimental protocols and procedures conformed to the standards set by the Canadian government Tri-Council policy statement for integrity in research, as well as the declaration of Helsinki, except for registration in a database. A detailed verbal and written explanation of the procedures and measurements was provided to participants and parents/guardians before participation. All participants and parents/guardians provided written, informed consent and child participants provided written assent. No participants were taking any prescribed medications at the time of testing.

Participants

Ten children (ages 7-14 y, 7 female) and ten adults (ages 23-44 y, 7 female) were included in this study. All children had at least one biological parent in the adult group, however three of the adults were not biologically related to any of the participants. All participants lived below 600 m, and none had spent significant time (>1hr) above 2000 m in the four months prior.

Protocol

Baseline (BL) measures were taken at the Pediatric Exercise Research Laboratory (Kelowna, BC, Canada, 343 m above sea level) and the Pediatric Exercise and Genomics Research Center (Irvine, CA, 28 m above sea level). Participants were transported by van (~8 hours) to the Crooked Creek Station (CC; White Mountain Research Center, California) where they spent two nights, including one day of testing at 3000 m. The group was then driven to the Barcroft Field Station at 3800 m (B; White Mountain Research Center, California), where testing took place over the course of the next five days.

Ventilatory, cardiovascular, and cerebrovascular measures were taken at BL, after 1 night at 3000 m (CC), and twice at 3800 m (after 2-4 hours [B1], and after 3 nights [B4]). Balanced meals were provided at each station and participants fed ad libitum. Caffeine and alcohol were restricted 12 hours prior to testing, and participants were instructed to have light snacks only 4 hours prior to testing. Except for self-determined vigorous exercise, there were no restrictions on activities for children and adults. Children were actively engaged in a wide range of games and activities throughout the trip, and participants were free to go on short hikes through the area surrounding the facilities after testing was completed each day, mirroring an environment similar to other recreational family trips to high altitudes.

Measures

Body composition and maturation. At BL, height and sitting height (in the children) were measured with a portable stadiometer (Seca, Hamburg, Germany). Total body mass and fat mass were assessed using an electronic scale with foot-to-foot bioelectrical impedance (TBF-410, Tanita, Japan). Fat free mass (FFM) was calculated from total body mass and fat mass. The sex-specific predicted aPHV offset was calculated using height, sitting height, body mass, and age at BL in the children (Mirwald *et al.*, 2002).

Ventilation and gas exchange. $\dot{V}_E$, tidal volume (V_T), and breathing frequency (f_b) were assessed using a metabolic cart (TrueOne2400, ParvoMedics, Salt Lake City, UT, USA) with participants seated upright and breathing through a mouthpiece with a nose clip. The pneumotach (HR800L, Hans Rudolph, Shawnee, KS, USA) was calibrated prior to every test using a 3L syringe and the gas analyzers were calibrated using gases of known concentration. A second gas analyser (ML206, ADInstruments) connected to an analog-to-digital converter (Powerlab 16/30, ADInstruments, Colorado Springs, CO, USA), allowed for continuous breath-by-breath sampling of end-tidal carbon dioxide ($P_{ET}CO_2$), and the end-tidal oxygen ($P_{ET}O_2$). All ventilatory measurements were taken as minimum of a 60 s average after at least 10 min of quiet rest. A common allometric scaling exponent of 0.42 was identified through analysis of the loglinear relationship between FFM and $\dot{V}_E$ at baseline, and 0.86 through analysis of the loglinear relationship between FFM and V_T.

Oxygen saturation of capillary blood (S_PO_2) was estimated from pulse oximetry of the finger every 30 s and reported as the average of at least 3 consecutive readings (Rad 5, Masimo, Irvine, CA, USA).

Cerebral blood flow. Supine ultrasound assessments of the left internal carotid artery (ICA) and the left vertebral artery (VA) were performed following a 10 min period of supine rest, using a 15 MHz multifrequency linear array duplex ultrasound (Terason μSmart3300, Teratech, Burlington, MA, USA). In accordance with published technical recommendations (Thomas *et al.*, 2015) the diameter of the ICA (ICA_d) and VA (VA_d) were assessed using simultaneous B-Mode imaging and ICA (ICA_v) and VA velocity (VA_v) were assessed using pulse-wave mode. The ICA_d and ICA_v were measured at least 1.5 cm distal to the common carotid bifurcation to eliminate recordings of retrograde and turbulent flow. Ultrasound assessments were performed by two experienced sonographers, who have previously demonstrated an inter-observer coefficient of variation of 14 percent, and each sonographer performed assessments on the same set of participants at each stage. Images were recorded and stored as video for offline analysis, and data were anonymized and later analysed using specialised edge-detection software (Woodman *et al.*, 2001). Resting measurements were calculated as the average of at least 20 consecutive cardiac cycles.

Volumetric blood flow (Q) was calculated using the following equation:

ICA(Q_{ICA}) or VA flow (Q_{VA})

$$= \frac{peak\ envelope\ velocity}{2} * \left(\pi\left(\frac{diameter}{2}\right)^2\right) \#(1)$$

Global cerebral blood flow (gCBF) was estimated as twice the sum of unilateral Q_{ICA} and Q_{VA}.

Cardiovascular hemodynamics. Two-dimensional transthoracic echocardiography was performed using a commercially available ultrasound machine (Vivid Q, GE, USA) with a M5-S 1.5-4.6 MHz transducer. Subjects lay resting in the left lateral decubitus position with at least 10 minutes of rest before image acquisition. The modified Bernoulli equation was used to calculate PASP, where PASP = $4V^2$ + RAP, with V equal to the peak tricuspid regurgitation velocity and RAP equal to the estimated right atrial pressure (Rudski *et al.*, 2010). Measures of PASP are reported using the average of at least 3 cardiac cycles. Stroke volume (SV) was determined using velocity-time integral of the left ventricular outflow tract from the five-chamber view (Lang et al., 2015), and Q was subsequently calculated as the product of SV and heart rate (HR), which was collected using a 3-lead electrocardiogram. All data were digitally recorded and stored for offline analysis. A common allometric scaling exponent of 0.42 was identified for through analysis of the loglinear relationship between FFM and CO at baseline and 0.63 through analysis of the loglinear relationship between FFM and SV. Additionally, pulmonary vascular resistance (PVRi) was estimated by dividing PASP by CO.

Blood pressure (BP) of the brachial artery was obtained from a minimum of three automated measurements (Tango M2, Suntech, Morrisville, NC, USA), and mean arterial pressure was calculated from the average systolic blood pressure (SBP) and diastolic blood pressure (DBP) using the following formula:

$$MAP = \left(\left(\frac{1}{3}(SBP - DBP)\right)\right) + DBP$$

In addition, cerebrovascular conductance was calculated for gCBF, the ICA and VA as: CVC = gCBF or Q_{ICA} or Q_{VA} / MAP.

Statistics

All analyses were performed using SPSS (Version 25, SPSS; Chicago, IL). Descriptive statistics are presented as mean and standard deviation (SD). A Student's t-test was used to

identify differences in descriptive participant characteristics at baseline. Analyses of the primary outcome variables were performed using repeated measures analyses of variance (RM ANOVA) with time (BL, CC, B1 and B4) and age group (children and adults) as the within and between group factors respectively. Additionally, RM ANOVA analyses were performed on change scores from baseline where applicable with time (CC, B1, and B4) and age group (child, adult) as factors. When applicable, interactions and main effects were deconstructed using t-tests with Bonferroni correction. Linear regression analysis was used to quantify relationships between changes in PASP and changes in $\dot{V}_E$, $P_{ET}O_2$, and $P_{ET}CO_2$. Statistical significance was set *a priori* at $P<0.05$.

RESULTS

Participants

Both age groups included 7 females and 3 males, with a mean age of 9.8±2.5 y in the children and 34.7±7.1 y in the adults (Table 1, P<0.0001). Adults were heavier (P<0.0001), taller (P<0.0001), and had a higher body fat % than the children (23±9 % vs. 16±6 %, P<0.001).

Ventilation and gas exchange

Absolute $\dot{V}_E$ was higher in adults than children at all time points (P<0.001; Table 2); however, when scaled to FFM there were no differences between children and adults at BL, CC, or B1 (P>0.05 for all), with a slightly lower scaled V_E in children at B4 (P=0.005) relative to adults. Delta change in scaled $\dot{V}_E$ ($\Delta\dot{V}_E$) is illustrated in Figure 1. In children an increase of +20±19% was apparent at CC, (P=0.032), but not in adults (-1±19%, P=0.835, Figure 1). Upon arrival to Barcroft, $\Delta\dot{V}_E$ was maintained at CC levels in both groups, followed by progressive increase in $\dot{V}_E$ between B1 and B4 that was observed in adults (38.5±34.7%, P=0.006), but not in children (P=0.760).

At BL, f_B and scaled V_T (Table 2) were not significantly different between groups. The $\Delta\dot{V}_E$ increases in children at CC and B1 were driven by increased f_B (+2.8 and +7.2 breaths.min^{-1}, Table 2), with no increases observed in scaled V_T at any time (Table 2). In contrast, adults demonstrated no significant increase in f_b at any time, with a significant increase in V_T at B4 (P=0.020).

No differences were observed in $P_{ET}O_2$ and $P_{ET}CO_2$ (Table 2) between groups at BL (P=0.383, P=0.886, respectively). At CC, $P_{ET}O_2$ was higher (P=0.026) and $P_{ET}CO_2$ was lower in children compared to adults (P=0.005); however, these differences subsided by B1. At B4, $P_{ET}CO_2$ was 3mmHg lower in adults compared to children (P=0.007).

Cardiovascular hemodynamics

Once scaled for FFM there were no differences in Q between children and adults at any time (P=0.151). Scaled Q increased with altitude, with no time by age group interaction (P=0.912). Simple effects revealed non-significant increases in scaled Q in the adults at CC (P=0.062), B1 (P=0.091) and B4 (P=0.071), with significant increases in children at CC (P=0.014) and B1 (P=0.003), returning to BL values at B4 (P=0.238).

Children demonstrated a larger increase in HR at CC than adults (+26±13 beats·min^{-1} vs. +13±8 beats·min^{-1}, P=0.019, Figure 3). At CC, children demonstrated a 11±10% reduction in SV relative to BL (P=0.020), while SV was maintained in adults (-1±15%, P=0.827). While allometric scaling eliminated the main effect for group in SV, simple effects revealed a reduction scaled SV in children at CC, B1 and B4, and a maintenance of scaled SV in adults until B4 (Figure 2).

At BL PASP was similar between children and adults (Figure 3). While the rise in PASP was lesser in children compared to adults (+8 mmHg vs. +12 mmHg, P=0.034) at CC, it was similar between groups at B1. By B4, PASP was no longer elevated from BL in children, but remained elevated in adults. PVRi increased in both children and adults with initial ascent to altitude. Although the mean rise in PVRi was greater in adults at CC, this was not significantly different from children (31% vs 11%, P=0.072, Figure 3 Panel B).

Cerebral blood flow

There were no child-adult differences in diameter for either the ICA or VA at any time point, and no increase in ICA_d or VA_d with altitude was apparent (Table 4). Although ICA_v was 37% greater in children compared to adults at BL (Table 4, P=0.009), this increased to the same extent in both children and adults with altitude. Subsequently, Q_{ICA} was consistently elevated in children compared to adults (P=0.009), while no between-group differences were

found for Q_{VA} (P=0.317). Accordingly, CVC_{ICA} was consistently greater in children, while CVC_{VA} was not different between groups (Table 4). Flow through the ICA and VA followed similar temporal patterns with equal relative magnitudes of change between the children and adults (Figure 4). At B1, Q_{ICA} peaked in both groups (Children, +26±15% vs. Adults +31±21%; P=0.533), as well as Q_{VA} (Table 3, Children, +19±20% vs. Adults, 14±19%, P=0.611). No interaction was found for CVC through the ICA or VA (Table 4).

At BL, gCBF (Table 3) was 43% higher in children than adults (P=0.005), and this difference was maintained at high altitude. A comparable pattern of change in gCBF (Figure 4, Panel C) was observed between children and adults (P=0.845), with gCBF peaking at B1 (Children, 26.8±16.4% vs. Adults, 25.7±38.0%, P=0.937) preceding a slight decline at B4.

The fraction of Q perfusing the ICA and VA (gCBF/Q) at BL was significantly higher in children (29±12%) than adults (14±6%, P=0.005), and this difference was maintained throughout the duration of high-altitude exposure.

Integrative Responses

Regression analyses of relationships between PASP and ventilatory responses to increases in altitude (Δ from BL to CC and to B1) and during acclimatization (Δ from B1 to B4) are presented in Figure 5. In adults, a moderate positive association between $\Delta P_{ET}O_2$ and ΔPASP was found with an increase in altitude (Figure 6, Panel A, β=0.495, R^2=0.288, P=0.022), and during acclimatization (Figure 6, Panel B, β=1.113, R^2=0.487, P=0.037). In contrast, no significant relationships between $\Delta P_{ET}O_2$ and ΔPASP were found in children with increases in altitude or during acclimatization (P>0.05). The ΔPASP was also related to $\Delta P_{ET}CO_2$ (β=1.61, R^2=0.35, P=0.011) and ΔQ (β=3.54, R^2=0.26, P=0.032) in adults during increases in altitude, but not in children (P=0.688 and P=0.062 respectively). No relationships were found between $\Delta \dot{V}_E$ and ΔPASP in either group.

DISCUSSION

Our main findings revealed an important hyperventilatory response with altitude exposure that was elevated to a greater extent in children than adults (and correspondingly higher

$P_{ET}O_2$ in children) at 3000 m, and in support of our hypothesis, reflected in a lower PASP at this elevation. Associations were evident between the change in PASP and $P_{ET}O_2$ in adults both with initial altitude and with acclimatization to 3800 m in adults, but not in children. While we hypothesized that the rise in CBF at high altitude would be lesser in children, global cerebral perfusion peaked similarly at +26% in both children and +31% in adults upon arrival at 3800 m and declined comparably at day 4.

Ventilation

It is generally accepted that peripheral carotid body-mediated stimulation of the hypoxic ventilatory response occurs when $P_aO_2 \approx$ 55-70 mmHg (Dripps & Comroe, 1947; Weil *et al.*, 1970), depending on the level of hypocapnia (Cormack *et al.*, 1957; Duffin, 2007). At 3000 m, $P_{ET}O_2$ was 67 ± 5 mmHg in the children which was accompanied by a significant elevation in $\dot{V}_E$ and subsequent reduction in $P_{ET}CO_2$ relative to baseline; in adults, however, the $P_{ET}O_2$ of 62 ± 3 mmHg did not elicit an increase in $\dot{V}_E$. These observations suggest that the P_aO_2 threshold for hyperventilation is higher in children at 3000 m when compared to adults. While these findings of increases in resting $\dot{V}_E$ occurring at a lower altitude support the hypothesis of increased peripheral chemoreceptor sensitivity in young children (Springer *et al.*, 1988), these changes were normalized over time at 3800 m. Children tend to breathe with a higher f_b and lower V_T compared to adults even when scaled for body size (Mercier *et al.*, 1991; Rowland & Cunningham, 1997), and we found that initial increases in $\dot{V}_E$ at 3000 m included a minor increase in f_b (+1.8 breaths/min), with a larger increase (+7.4 breaths/min) upon arrival at 3800 m; however, f_b regressed back towards baseline levels after four days at 3800 m. While speculative, this may be a result of a shift towards improving gas exchange efficiency through reducing dead space/V_T ratio, or through improved ventilation-perfusion matching, which would increase oxygenation for a given V_T. It is important to note that the changes in breathing pattern observed in children did not increase $P_{ET}O_2$ or further reduce $P_{ET}CO_2$ over the four days at 3800 m, and accordingly, the improvement in S_PO_2 during this time was marginally less in the children than the adults (~1% vs. ~2%). Additional interactions in both the slope and sensitivity of peripheral and central chemoreceptors to both O_2 and CO_2 during acclimatization may explain these responses at 3800 m, but further work is needed to confirm this inference.

Cardiovascular

Increases in Q at high altitude are dependent on the level of hypoxemia, in attempt to maintain systemic oxygen delivery under a reduced C_aO_2 (Naeije *et al.*, 1982). In sufficient time Q is restored towards sea level values as C_aO_2 improves with acclimatization (Klausen, 1966; Vogel & Harris, 1967). While we found that changes in Q throughout acclimatization were similar between children and adults, the rise in HR at 3000 m was two-fold greater in children, compensating for an 11% reduction in SV. In contrast, in adults SV was only significantly reduced from BL by the fourth day at 3800 m. Most investigations of cardiac function at high altitude in adults implicate a maintenance, then gradual reduction of SV (Klausen, 1966; Alexander *et al.*, 1983; Stembridge *et al.*, 2014); however, when data from a prior study of children are extrapolated (Allemann *et al.*, 2012) an approximate 20% reduction in SV was apparent after only 40 h at 3450 m, similar to our findings. A more immediate reduction in SV in children could be attributable to more rapid loss of body water (Rieger *et al.*, 2022), and subsequently plasma volume in children; however, there is also evidence to suggest that the balance between sympathetic and vagal control of cardiac output may differ between children and adults (Galanter *et al.*, 1999; Harteveld *et al.*, 2021). In support of this, we found that MAP was increased at high altitude in children, but not in adults, and furthermore, during exercise at 3540 m, adults have previously demonstrated a 16% reduction in maximal HR, while no reduction in maximum HR in children ages 9-12 was observed (Kriemler *et al.*, 2016). Despite this report, it is unclear if maturational differences in the adrenergic and muscarinic regulation of cardiac output, or changes in ventricular function (such as a reduction in left ventricular filling pressure) can be implicated in the increased chronotropic response to early hypoxia in children.

Two separate investigations reported that PASP was higher in children compared to adults immediately after arrival to altitude (Kriemler *et al.*, 2008), and that an inverse relationship existed between age and PASP in children and adolescents ~40 hours after arrival (Allemann *et al.*, 2012). In contrast, we found that at 3000 m, children demonstrated a lower PASP than adults, with a tendency for a smaller increase in PVR; however, no significant group or interaction effect across all times was present. Direct comparisons between studies are difficult, as the Kriemler et al. study reported increased PASP in children after more rapid exposure (4-5 hours vs 18-24 hours) to a higher altitude (3450 m vs 3000 m) than ours, and differences are further confounded by our use of a staged ascent, which attenuates the rise in PASP compared to a direct ascent (Baggish *et al.*, 2010). Increases in PVR during hypoxia in adults appear to have multiple temporal components (Swenson, 2013), with a rapid increase

in PASP over the first few minutes (Teppema *et al.*, 2007), and a slower increase that is fully expressed ~2-8 hours after exposure (Dorrington *et al.*, 1997; Talbot *et al.*, 2005). If maturational differences in the duration of the separate components of this biphasic response are present, differences in the PASP response to early HA exposure in the present study could be attributable to a more rapid adjustment occurring in children at 3450 m.

We found no relationships between $\Delta P_{ET}O_2$ and ΔPASP in children in our investigation. It is unlikely that changes in PASP are completely independent of changes in local oxygenation of the lung; however, it is possible that sensing mechanisms alternative to alveolar PO_2 and PCO_2 may have a stronger role in regulating PASP during hypoxia in the immature lung. Alternatively, as hypoxic pulmonary vasoconstriction occurs primarily to redirect flow through vascular beds to better-ventilated portions of the lung; a weaker relationship between $P_{ET}O_2$ and PASP may be indicative of more efficient matching of $\dot{V}_E$ to perfusion in children, or it may also be a result of maturational differences in acid-base changes at high altitude. Importantly however, the peak PASP at 3800 m was similar between age groups, and reductions in PASP were still observed in children, despite no further increases in $\dot{V}_E$ or $P_{ET}O_2$ over 4 days of sojourn at 3800 m. Notwithstanding, potential differential mechanisms regulating PVR in children during hypoxia deserve further investigation, especially in view of the higher frequencies of high altitude pulmonary edema in children (Hultgren & Marticorena, 1978; Sophocles & Bachman, 1983).

Cerebrovascular

Although gCBF was 43% higher in children than adults at baseline, the relative (26-27%) increases in gCBF were identical between groups on the first day at 3800 m. At least in adults, a greater reactivity of the posterior circulation to hypoxia has been commonly described (Ogoh *et al.*, 2013; Subudhi *et al.*, 2014; Hoiland *et al.*, 2019), potentially as a mechanism to preferentially protect hypothalamic- and brainstem- related functions; however, these observations are not universal (Willie *et al.*, 2014; Hoiland *et al.*, 2017). While we tended to observe larger increases in Q_{ICA} than Q_{VA} in both groups, the relative contribution of the ICA to gCBF was consistent between groups and across time at BL, CC, and B1. We have previously reported that the incidence of acute mountain sickness is greater in children compared to adults upon ascent to 3800 m (Rieger et al., 2022); however, the current findings indicate that these age-related differences in are unlikely to related to differences in cerebrovascular reactivity to high altitude.

Methodological Considerations:

While ratio-scaling of cardiorespiratory measurements to body weight or FFM is commonly used, the relationship between FFM and metabolic rate is not linear. We used group-specific allometric scaling exponents for key outcome measurements, which more appropriately reflects the log-linear relationship between metabolism and body size, and respective changes in $\dot{V}_E$ and cardiac output that occur during hypoxia and high altitude. The group exponents were created using measurements taken at baseline, and possible changes in FFM with a high-altitude sojourn were not included in subsequent calculations.

It is possible that the gradient of arterial to end-tidal PO_2 and PCO_2 differ between children, and we did not use analysis of blood gasses to evaluate potential differences by age. $P_{ET}CO_2$ has been demonstrated to be a strong predictor of P_aCO_2 in children at rest and during exercise (Ohuchi *et al.*, 1999) and in adults during hypoxia (Tymko *et al.*, 2015), but end-tidal to arterial gradients of O_2 and CO_2 have not been validated in children during hypoxia.

Conclusions

These data highlight that the regulatory mechanisms governing $\dot{V}_E$ and PASP at high altitude are different between children and adults. During early acclimatization to 3000 m, $\dot{V}_E$ is greater and PASP is lower in children, with a stronger relationship between PASP and $P_{ET}O_2$ observed in adults. Despite different rates and magnitudes of ventilatory acclimatization between children and adults, and a much higher baseline CBF in children, the cerebrovascular response to high altitude is similar between age groups. Importantly, while subtle age differences in ventilatory and cardiopulmonary responses to high altitude are evident, the pulmonary vascular response after prolonged hypoxia (6 days) is similar between children and adults.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors have no competing interests to declare.

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Author contributions

M.G.R and A.M.M. contributed to the conception and design of the study. M.G.R, C.M.T., D.R.P., K.J.S., M.S, S.P. S.A., D.M.C., P.N.A, and A.M.M were involved in acquisition, analysis, or interpretation of the data. M.G.R. and A.M.M. drafted the manuscript, and all authors were involved in revising it critically for important intellectual content. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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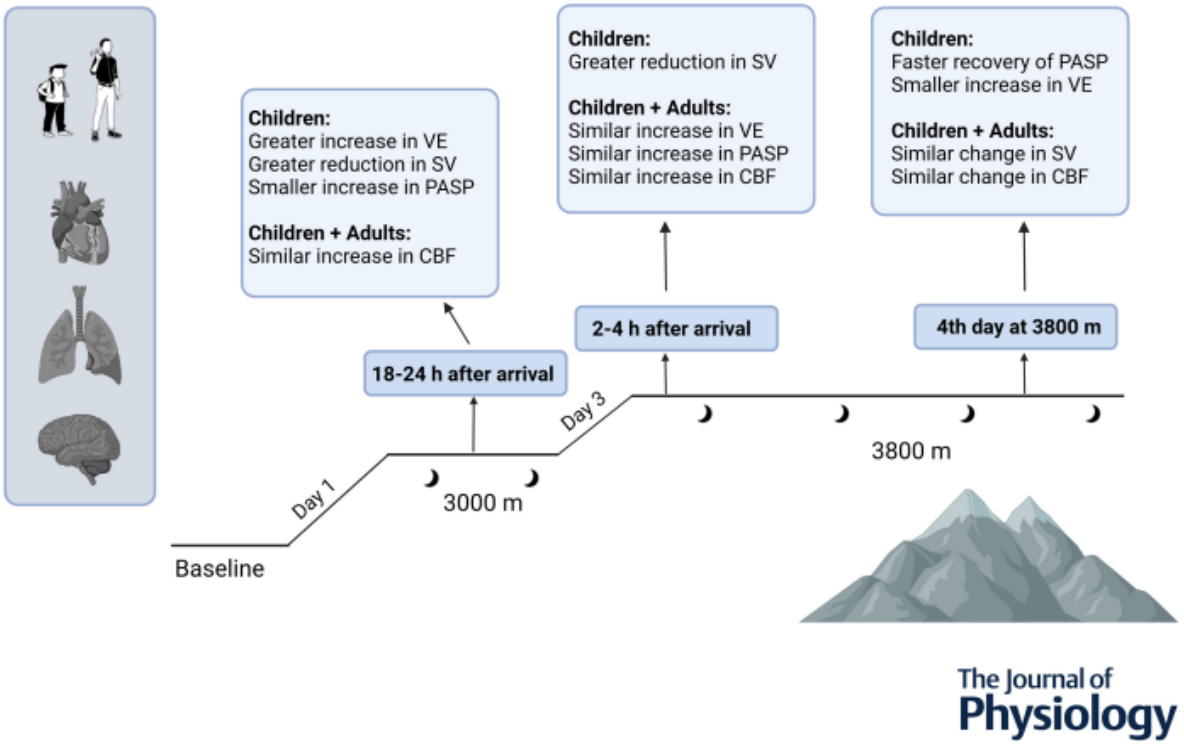

Abstract. Cardiopulmonary and cerebrovascular function continues to develop through childhood and adolescence, but the impact of maturation on acclimatization responses to high-altitude is unknown. 10 children (9.8±2.5 y) and 10 adults (34.7±7.1 y) were passively brought from sea level to high-altitude and measurements of minute ventilation (VE), stroke volume (SV), pulmonary artery systolic pressure (PASP), and cerebral blood flow (CBF) were obtained at 3000 m and twice at 3800 m. Children demonstrated a greater increase in VE, a smaller increase in PASP, and a greater reduction in SV, paired with larger chronotropic response at 3000 m compared to adults, but age-related differences in cardiopulmonary function and ventilatory changes diminished at 3800 m. Baseline CBF was consistently elevated in children compared to adults, but relative changes in CBF with altitude were similar between children and adults at all times.

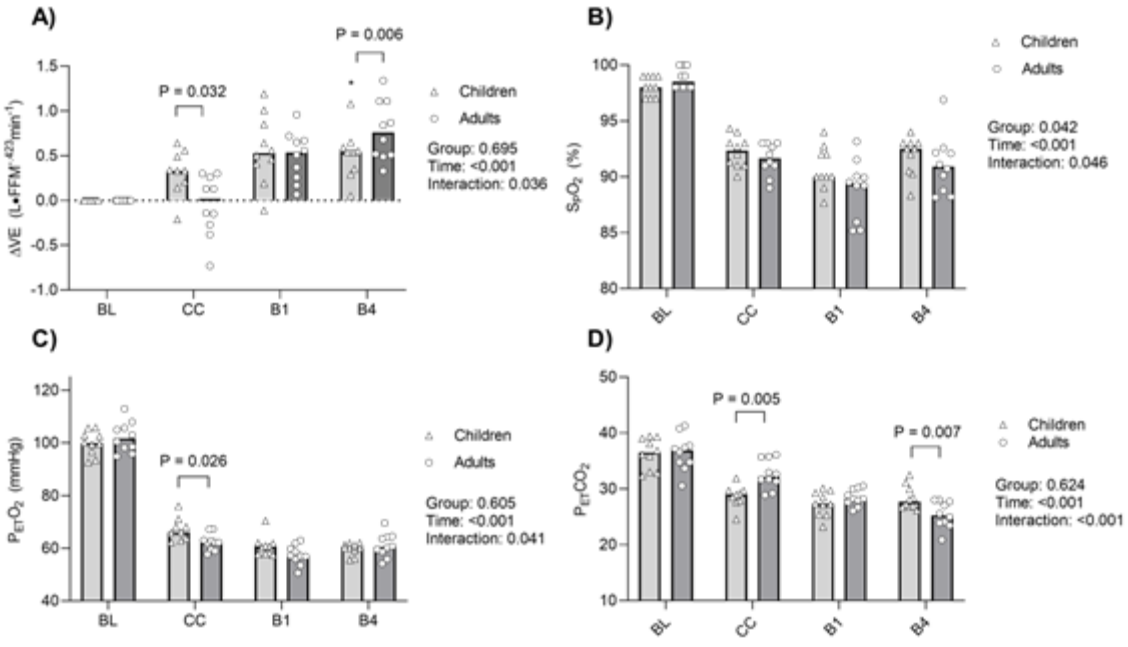

Figure 1. Changes in minute ventilation ($\dot{V}_E$) allometrically scaled to fat free mass (FFM, Panel A), peripheral oxygen saturation (S_PO_2, Panel B), and end-tidal partial pressures of oxygen ($P_{ET}O_2$, Panel C) and carbon dioxide ($P_{ET}CO_2$, Panel D) at sea level baseline (BL), at Crooked Creek Station at 300 m elevation (CC), on the first day at Barcroft Station (B1, 3800 m) and on the fourth day at Barcroft Station (B4, 3800 m) in children and adults. Statistical analyses were performed with two-way ANOVAs with time and group as fixed factors. Independent samples *t*-tests were used to identify group differences where interaction effects existed. Participants for $\Delta\dot{V}_E$, $P_{ET}O_2$ and $P_{ET}CO_2$ included 10 children and 10 adults at BL, B1 and B4, and 9 children and 10 adults at CC. Comparisons for S_PO_2 included 10 children and 10 adults at all stages.

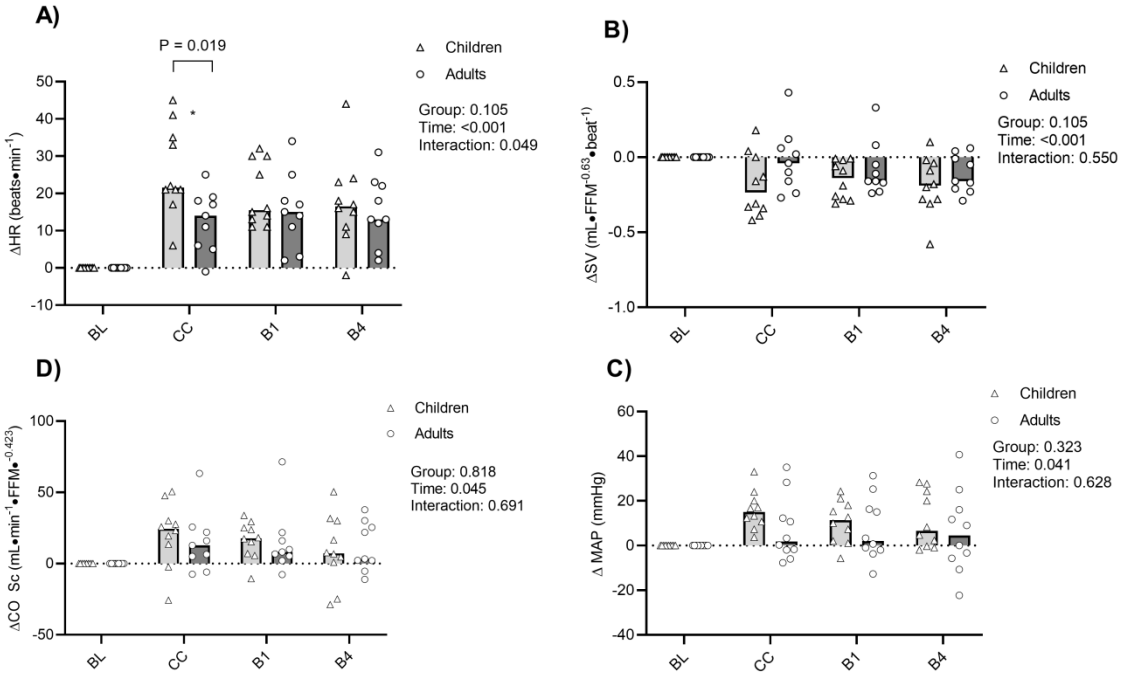

Figure 2. Changes in resting heart rate (ΔHR, Panel A), stroke volume allometrically scaled to fat free mass (ΔSV, Panel B), cardiac out put allometrically scaled to fat free mass (ΔQ, Panel C), and mean arterial pressure (ΔMAP, Panel D) at sea level baseline (BL), at Crooked Creek Station at 300 m elevation (CC), on the first day at Barcroft Station (B1, 3800 m) and on the fourth day at Barcroft Station (B4, 3800 m) in children and adults. All stages included comparisons between 10 children and 9 adults. Statistical analyses were performed with two-way ANOVAs with time and group as fixed factors. Independent samples T-tests were used to identify group differences where interaction effects existed, and pairerd T-tests were used to identify significant changes from BL when a main effect of time was present. ΔHR was significantly elevated from BL at all subsequent stages in children and adults (P<0.001 for all). SV was reduced from BL in children at CC (P=0.001), B1 (P=0.002) and B4 (P=0.003). In adults, SV was reduced from BL at B4 (P=0.013), but not CC (P=0.413) or B1 (P=0.102). CO increased from BL in children at CC (P=0.004) and B1 (P=0.001), but not B4 (P=0.100). In adults, CO was elevated at CC (P=0.030), B2 (0.042) and B4 (P=0.035). MAP was increased from BL in children at CC (P=0.0002), B1 (P=0.007), and B4 (P=0.019). No change in MAP occurred in adults at CC (P=0.146), B1 (P=0.137) or B4 (P=0.327).

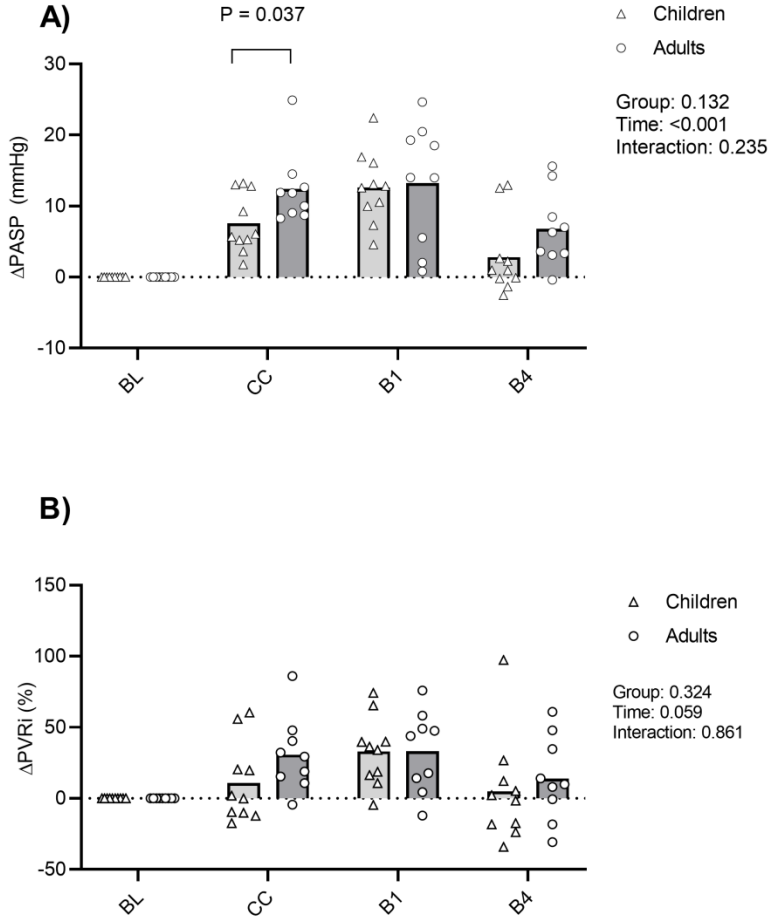

Figure 3. Changes in pulmonary artery systolic pressure (PASP) and changes in pulmonary vascular resistance index (PVR_i) from sea level baseline (BL), at Crooked Creek Station at 3000 m elevation (CC), on the first day at Barcroft Station (B1, 3800 m) and on the fourth day at Barcroft Station (B4, 3800 m) in children and adults. All stages included comparisons between 10 children and 9 adults. Statistical analyses were performed with two-way ANOVAs with time and group as fixed factors. Independent samples *t*-tests were used to identify group differences, and paired *t*-tests were used to identify significant changes from BL when a main effect of time was present. PASP was elevated from BL at CC (P<0.001) and B1 (P<0.001), but not B4 (P=0.136) in children. In adults, PASP was elevated from BL at all times (CC, P<0.001; B1, P=0.002; B4, P=0.005). PVR_i was elevated at B1 (P=0.002) in children, but not CC (P=0.249) or B4 (P=0.688). In adults, PVR_i was elevated at CC (P=0.004) and B1 (P=0.004), but not B4 (P=0.098).

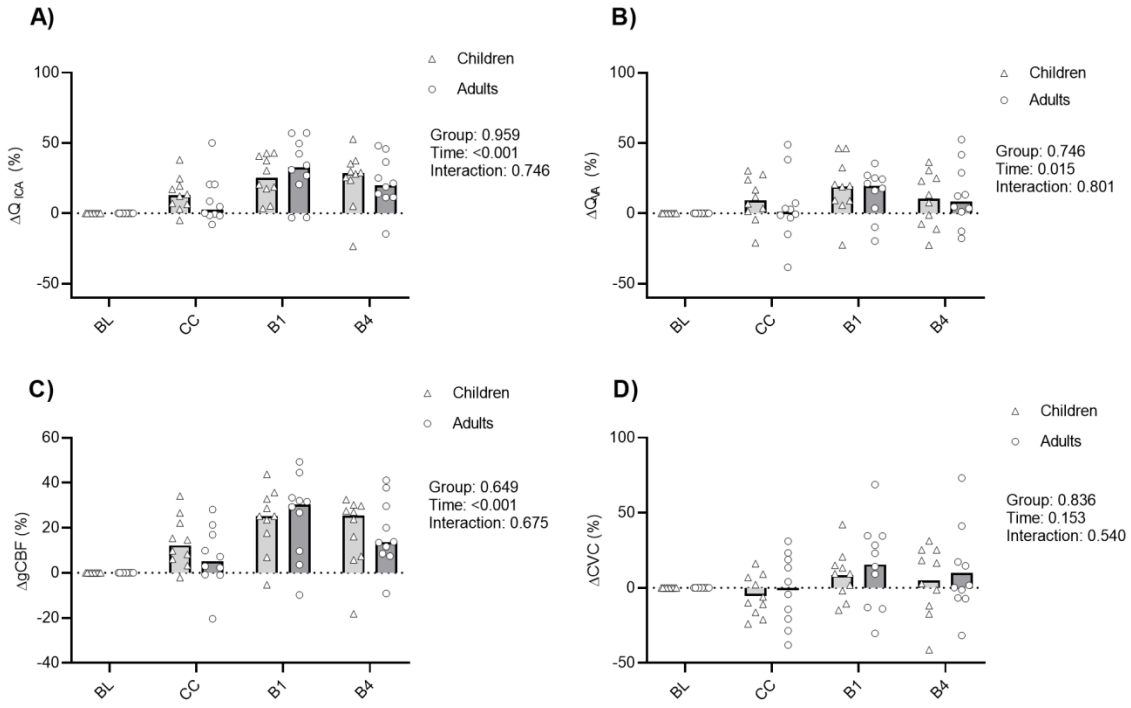

Figure 4. Change in flow through the internal carotid artery (Q_{ICA}, Panel A) vertebral artery (Q_{VA}, Pabel B), as well as change in global cerebral blood flow(gCBF, Panel C) and global cerebrovascular conductance (CVC, Panel D) from sea level baseline (BL) to Crooked Creek (CC, 3000 m), on the first day at Barcroft Station (B1, 3800 m), and on the fourth day at Barcroft Station (B4, 3800 m) in children and adults. All comparisons were made in 10 children and 10 adults across all stages. Statistical analyses were performed with two-way ANOVAs with time and group as fixed factors.

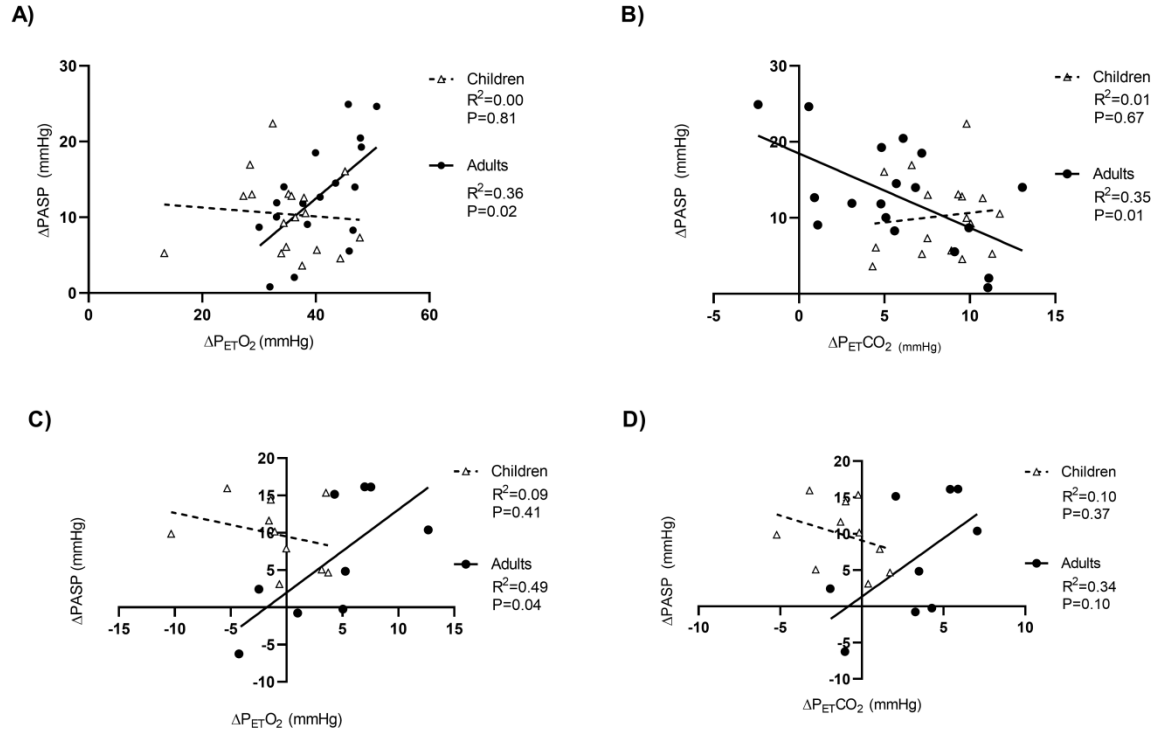

Figure 5. Relations between changes in end-tidal gas partial pressures of oxygen ($P_{ET}O_2$) and carbon dioxide ($P_{ET}CO_2$) and changes in pulmonary artery systolic pressure (PASP) during high altitude ascent (top panels) and during acclimatization (bottom panels). Panel A) Absolute reduction in $P_{ET}O_2$ vs. increase in PASP while ascending from BL to 3000 m, and from BL to 3800 m (children, n=9; adults, n=9). Panel B) Absolute reduction in $P_{ET}CO_2$ vs. increase in PASP while ascending from BL to 3000 m, and from BL to 3800 m (children, n=9; adults, n=9). Panel C) Change in $P_{ET}O_2$ vs. absolute reduction in PASP over 4 days at 3800 m (children, n=10; adults, n=9). Panel D) Reduction in $P_{ET}CO_2$ vs. reduction in PASP over 4 days at 3800 m (children, n=10; adults, n=9). Statistics were performed using linear regression analysis to indicate slope significance, with the R^2 to indicate relationship strength.

Table 1. Descriptive participant characteristics

	Children	Adults
n	10	10
F/M	7/3	7/3
Age (y)	9.8±2.5	34.7±7.1
Age range (y)	7-14	23-44
aPHV offset (y)	-2.0±2.5	—
Height (cm)	141±15	171±6
Weight (kg)	34.5±9.8	65.9±11.8

aPHV, age at peak height velocity.

Table 2. Gas Exchange

		Sea Level Baseline	3000 m Crooked Creek	3800 m Barcroft 1	3800 m Barcroft 4		P
V_E	Child (n=9)	6.11 ± 1.62	7.31 ± 1.71	7.91± 1.71	7.62 ± 0.86	Group	0.004
($L \cdot min^{-1}$)	Adult (n=10)	8.47 ± 1.52	8.25 ± 1.82	8.89 ± 2.62	12.46 ± 2.33	Time	<0.001
	P	0.005	0.295	0.367	<0.001	Interaction	<0.001
Scaled V_E	Child (n=9)	1.51 ± 0.37	1.81 ± 0.47	1.84 ± 0.01	1.88 ± 0.14	Group	0.635
($L \cdot min^{-1} \cdot FFM^{-0.423}$)	Adult (n=10)	1.62 ± 0.29	1.56 ± 0.26	1.74 ± 0.34	2.41 ± 0.51	Time	<0.001
	P	0.480	0.120	0.304	0.005	Interaction	0.002
T_V	Child (n=9)	370 ± 125	357 ± 36	321 ± 79	437 ± 102	Group	<0.001
($mL \cdot breath^{-1}$)	Adult (n=10)	654 ± 179	707 ± 258	770 ± 229	950 ± 313	Time	<0.001
	P	0.002	0.015	0.009	<0.001	Interaction	0.040
Scaled T_V	Child (n=9)	22.4±5.0	15.0±11.0	19.7±5.4	25.3±5.5	Group	0.052
($mL \cdot breath^{-1} \cdot FFM^{-0.86}$)	Adult (n=10)	22.9±7.1	24.3±8.4	26.4±5.5	33.4±12.7	Time	<0.001
	P	0.865	0.426	0.080	0.079	Interaction	0.044
f_B	Child (n=9)	17.1 ± 5.1	19.9 ± 3.1	25.5 ± 7.4	18.5 ± 3.8	Group	0.024
($breaths \cdot min^{-1}$)	Adult (n=10)	13.9 ± 3.8	12.3 ± 3.9	13.1 ± 4.9	14.6 ± 5.3	Time	<0.001
	P	0.042	0.001	0.001	0.080	Interaction	<0.001

Data expressed as mean + SD. Statistical comparisons were performed using two-way ANOVAs with group (children and adults) and time (BL, CC, B1, B4) as fixed factors. Independent samples t-tests were used to identify between group differences. V_E, minute ventilation; T_V, tidal volume; f_B, breathing frequency.

Table 3. Cardiovascular measurements

		Sea Level Baseline	3000 m Crooked Creek	3800 m Barcroft 1	3800 m Barcroft 4		P
SBP	Child (n=10)	102±6	116±11	111±10	123±8	Group	0.007
(mmHg)	Adult (n=10)	116±16	122±8	125±6	128±6	Time	<0.001
	P	0.021	0.190	0.005	0.184	Interaction	0.298
DBP	Child (n=10)	63±10	79±10	74±11	68±14	Group	0.025
(mmHg)	Adult (n=10)	72±18	80±5	78±±9	75±7	Time	0.005
	P	0.155	0.490	0.257	0.178	Interaction	0.018
MAP	Child (n=10)	76±8	91±10	86±7	86±10	Group	<0.001
(mmHg)	Adult (n=10)	87±17	93±5	94±7	93±4	Time	<0.001
	P	0.077	0.454	0.023	0.112	Interaction	0.185
HR	Child (n=9)	65±9	91±11	85±10	83±12	Group	0.003
($beats \cdot min^{-1}$)	Adult (n=9)	56±8	69±13	72±11	72±13	Time	<0.001
	P	0.006	0.009	0.001	0.122	Interaction	0.052
SV	Child (n=9)	42±12	36±10	37±11	36±11	Group	<0.001
($mL \cdot beat^{-1}$)	Adult (n=9)	68±19	67±17	64±19	63±18	Time	0.036
	P	0.002	<0.001	0.001	0.001	Interaction	0.672
Scaled SV	Child (n=9)	5.1±1.2	4.4±0.9	4.5±1.1	4.4±1.0	Group	0.57
($mL \cdot beat^{-1} \cdot FFM^{-0.63}$)	Adult (n=9)	5.8±1.0	5.7±1.2	5.4±1.3	4.9±1.3	Time	<0.001
	P	0.182	0.024	0.131	0.063	Interaction	0.117
CO	Child (n=9)	2.6±0.7	3.3±0.9	3.1±0.8	3.0±0.9	Group	0.03
($L \cdot min^{-1}$)	Adult (n=9)	3.7±0.8	4.5±1.1	4.5±1.2	4.4±0.9	Time	0.006
	P	0.004	0.016	0.007	0.004	Interaction	0.775
Scaled CO	Child (n=9)	650±140	800±184	762±173	722±181	Group	0.716
($mL \cdot min^{-1} \cdot kg^{-0.42)}$	Adult (n=9)	728±130	874±218	871±219	847±150	Time	0.016
	P	0.381	0.781	0.742	0.693	Interaction	0.411
PASP	Child (n=9)	23±3	31±5	36±7	26±6	Group	0.171
(mmHg)	Adult (n=9)	23±3	35±8	37±8	30±5	Time	<0.001
	P	0.913	0.034	0.822	0.113	Interaction	0.235
PVRi	Child (n=9)	9.2±2.6	10.2±3.4	12.4±4.3	9.4±3.4	Group	0.016
($mmHg \cdot L^{-1} \cdot min^{-1}$)	Adult (n=9)	6.4±1.3	8.1±1.3	8.5±2.6	7.1±1.5	Time	<0.001
	P	0.008	0.106	0.031	0.069	Interaction	0.467

Data expressed as mean + SD. Statistical comparisons were performed using two-way ANOVAs with group (children and adults) and time (BL, CC, B1, B4) as fixed factors. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, resting heart rate; SV, stroke volume; Q, cardiac output; PASP, pulmonary artery systolic pressure; PVRi, pulmonary vascular resistance index.

Table 4. Cerebral blood flow

		Sea Level	3000 m	3800 m			
		Baseline	Crooked Creek	Barcroft 1	Barcroft 4		P
ICAd	Child (n=10)	0.43±0.03	0.42±0.07	0.47±0.05	0.44±0.06	Group	0.149
(cm)	Adult (n=10)	0.42±0.07	0.42±0.05	0.43±0.06	0.42±0.07	Time	0.460
	P	0.390	0.127	0.103	0.119	Interaction	0.227
VAd	Child (n=10)	0.36±0.04	0.35±0.05	0.36±0.05	0.34±0.04	Group	0.430
(cm)	Adult (n=10)	0.37±0.06	0.37±0.06	0.37±0.07	0.37±0.06	Time	0.207
	P	0.602	0.394	0.700	0.143	Interaction	0.094
ICAv	Child (n=10)	53.7±12.1	57.6±9.4	61.9±11.0	59.0±8.9	Group	0.003
($cm \cdot s^{-1}$)	Adult (n=10)	39.2±9.9	43.8±11.4	45.8±11.2	48.2±14.8	Time	0.012
	P	0.009	0.008	0.005	0.063	Interaction	0.744
VAv	Child (n=10)	33.1±10.8	37.1±10.4	36.7±9.9	37.1±12.1	Group	0.019
($cm \cdot s^{-1}$)	Adult (n=10)	25.5±8.3	25.6±3.4	29.2±5	29.9±5.8	Time	0.071
	P	0.602	0.394	0.700	0.143	Interaction	0.521
Q_{ICA}	Child (n=10)	260±70	299±124	326±111	316±115	Group	0.009
($mL \cdot min^{-1}$)	Adult (n=10)	167±57	180±62	211±66	200±62	Time	<0.001
	P	0.008	0.014	0.007	0.010	Interaction	0.586
Q_{VA}	Child (n=10)	100±43	110±46	117±49	104±29	Group	0.317
($mL \cdot min^{-1}$)	Adult (n=10)	86±32	86±30	95±33	95±43	Time	0.069
	P	0.408	0.197	0.260	0.868	Interaction	0.448
CVC_{ICA}	Child (n=10)	3.4±1.0	3.3±1.3	4.1±1.5	3.8±1.6	Group	0.003
($mL \cdot min^{-1} \cdot mmHg^{-1}$)	Adult (n=10)	2.0±1.0	1.9±0.7	2.1±0.6	2.2±0.7	Time	<0.001
	P	0.008	0.009	0.001	0.010	Interaction	0.151
CVC_{VA}	Child (n=10)	1.3±0.7	1.2±0.6	1.5±0.7	1.1±0.4	Group	0.214
($mL \cdot min^{-1} \cdot mmHg^{-1}$)	Adult (n=10)	1.1±0.6	0.9±0.3	1.0±0.4	1.0±0.5	Time	0.076
	P	0.321	0.162	0.104	0.806	Interaction	0.181
$_{g}CBF$	Child (n=10)	720±174	818±223	886±235	841±220	Group	0.005
($mL \cdot min^{-1}$)	Adult (n=10)	505±223	534±162	614±160	591±199	Time	<0.001
	P	0.017	0.004	0.004	0.023	Interaction	0.375

Data expressed as mean + SD. Statistical comparisons were performed using two-way ANOVAs with group (children and adults) and time (BL, CC, B1, B4) as fixed factors. Independent samples *t*-tests were used to identify between group differences. ICA_d, internal carotid artery (ICA) diameter. VA_d, vertebral artery (VA) diameter; ICA_v; ICA velocity; VA_v, VA velocity; Q_{ICA}, ICA flow; Q_{VA}, VA Flow; CVC_{ICA}, cerebrovascular conductance ICA; CVC_{VA}; cerebrovascular conductance VA.