Differences in cerebrovascular regulation and ventilatory responses during ramp incremental cycling in children, adolescents and adults

Max E. Weston,[1,2] Alan R. Barker,[1] Owen W. Tomlinson,[1] Jeff S. Coombes,[2] Tom G. Bailey,[2] Bert Bond[1*]

[1] Children's Health and Exercise Research Centre, Sport and Health Sciences, College of Life and Environmental Sciences, University of Exeter, Exeter, United Kingdom

[2] Physiology and Ultrasound Laboratory in Science and Exercise, School of Human Movement and Nutrition Sciences, University of Queensland, Brisbane, Australia

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***Corresponding Author:**

Dr Bert Bond,
Children's Health and Exercise Research Centre, St Luke's Campus, University of Exeter, EX1 2LU, United Kingdom
Email: B.Bond@exeter.ac.uk
Telephone: +441392 724983

Abstract

Regulation of cerebral blood flow during exercise in youth is poorly understood. This study investigated the cerebrovascular and ventilatory responses to a ramp incremental cycle test to exhaustion in 14 children (mean ± SD age: 9.4±0.9 y), 14 adolescents (12.4±0.4 y) and 19 adults (23.4±2.5 y). Middle cerebral artery blood velocity (MCAv), partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) and ventilatory parameters were analysed at baseline, gas exchange threshold (GET), respiratory compensation point (RCP) and exhaustion. The increase in minute ventilation relative to CO_2 production during exercise was also calculated (V_E/VCO_2 slope). Relative change from baseline (Δ%) in MCAv was lower in children, compared to adolescents and adults at GET (15±10% vs 26±14% and 24±10%, respectively, $P \leq 0.03$, effect size (*d)*=0.9) and RCP (13±11% vs 24±16% and 27±15%, respectively, $P \leq 0.05$, $d \geq 0.8$). Δ%MCAv was similar in adults and adolescents at all intensities, and similar in all groups at exhaustion. The magnitude of the $\dot{V}_E$/ $\dot{V}CO_2$ slope was negatively associated with Δ%MCAv at GET and RCP across all participants ($P \leq 0.01$, r=-0.37 to -0.48). Δ%$P_{ET}CO_2$ was smaller in children and adolescents compared to adults at GET and RCP ($P \leq 0.05$, $d \geq 0.6$). In children, Δ%$P_{ET}CO_2$ and Δ%MCAv were not associated from baseline-GET ($\bar{r}$=0.14) and were moderately associated from RCP-exhaustion ($\bar{r}$=0.49). These relationships strengthened with increasing age, and were stronger in adolescents (baseline-GET: $\bar{r}$=0.47, RCP-exhaustion: $\bar{r}$=0.62) and adults (baseline-GET: $\bar{r}$=0.66, RCP-exhaustion: $\bar{r}$=0.78). These findings provide the first evidence on the development of the regulatory role of $P_{ET}CO_2$ on MCAv during exercise in children, adolescents and adults.

Key words: cerebral blood flow, end-tidal carbon dioxide, exercise, age, middle cerebral artery

New & Noteworthy: This is the first study to observe similar increases in cerebral blood flow during incremental exercise in adolescents and adults. Increases in cerebral blood flow during exercise were smaller in children compared to adolescents and adults, and were associated with a greater $\dot{V}_E$/ $\dot{V}CO_2$ slope. This study also provides the first evidence on the progressive development of the regulatory role of end-tidal CO_2 on cerebral blood flow during exercise during the transition from childhood to adulthood.

Introduction

The human brain has exquisite sensitivity to fluctuations in the partial pressure of arterial carbon dioxide ($PaCO_2$), and this is considered the primary regulator of cerebral blood flow (CBF) at rest in adults (1, 20). However, regulation of CBF during childhood and adolescence is poorly understood, and emerging evidence suggests that the regulatory role of $PaCO_2$ at rest is diminished in childhood (42). CBF is regulated through complex interactions between partial pressures of arterial blood gases (particularly $PaCO_2$), blood pressure, cerebral metabolism, sympathetic nerve activity and cardiac output (1, 47). Available data on CBF regulation in adolescents, which represent a group transitioning into adulthood, is also limited, though some evidence indicates that cerebrovascular reactivity (CVR) to CO_2 peaks around mid-teens (26). Collectively, the limited available data suggest that the mechanisms of CBF regulation, particularly the relationships between CBF and $PaCO_2$, are influenced by growth and development, and the need for investigation into mechanisms of CBF regulation in youth has been highlighted in order to advance understanding of cerebrovascular development (3). A greater insight into the influence of age on the regulatory role of $PaCO_2$ on CBF can be developed by studying the responses to exercise, where intensity-dependent alterations in $PaCO_2$ may reveal important control processes that are not detectable at rest.

During incremental exercise to exhaustion, CBF velocity, assessed by middle cerebral artery blood velocity (MCAv), follows an inverse parabolic relationship. In adults, MCAv increases by ~15-25% from rest to moderate intensity exercise (up to ~60% maximal workload) (41) and is positively related to increases in end-tidal CO_2 concentrations ($P_{ET}CO_2$), used as a surrogate of $PaCO_2$ (14, 27). MCAv then declines with increasing exercise intensity, to values near or below baseline at exhaustion (41), despite substantially elevated cerebral oxygen demand during maximal exercise (38). This paradoxical decrease in MCAv during high intensity exercise is associated with the decline in $P_{ET}CO_2$ in adults, as a result of cerebral vasoconstriction from hyperventilation-induced hypocapnia (14, 29).

The only available study investigating the MCAv response to exercise in children and adults observed a smaller relative increase in MCAv during step incremental exercise in prepubertal children (~10%), compared to adults (~25%) (14). This has led to the suggestion that children may have a limited capacity to further increase CBF in response to external stimuli, possibly due to elevated resting CBF (14, 26). In addition, during exercise in children, changes in MCAv, both before and after the gas exchange threshold (GET), were not related to changes in $P_{ET}CO_2$ (14). This suggests that there are marked child-adult differences in the mechanisms regulating CBF during incremental exercise, which are particularly interesting given that changes in $PaCO_2$ is considered the primary regulator of CBF during exercise in adults (41). This appears to not be the case in children, and no data are available on adolescents. Alongside increases in CVR (26) and declines in resting CBF during adolescence (7, 37), adolescents also have greater elevations in mean arterial pressure during exercise, compared to children (35). Therefore, the CBF response to incremental exercise, and its mechanisms of regulation, in adolescents may differ to that of both children and adults.

Since arterial carbon dioxide is regulated by an interaction between the respiratory and cerebrovascular systems (28), the study of CBF regulation during exercise in children and adolescents may be influenced by differences in the ventilatory responses to exercise. During exercise, children show a smaller increase in $P_{ET}CO_2$ compared to adults (14, 31, 33), alongside an exaggerated ventilatory response to increases in $PaCO_2$ (19, 32). Children also have a greater increase in minute ventilation ($\dot{V}_E$) relative to CO_2 production ($\dot{V}CO_2$) during exercise (i.e. a greater $\dot{V}_E/\dot{V}CO_2$ slope) (12, 19). Whether this is related to the CBF response to exercise has not been explored. Whilst ventilation, $P_{ET}CO_2$ and CBF are known to be closely linked in adults both at rest and during exercise (28), these relationships remain poorly understood in children and adolescents.

The purpose of the present study was to investigate the MCAv, $P_{ET}CO_2$ and ventilatory responses to ramp incremental exercise in children, adolescents and adults. A secondary aim was to explore if the ventilatory and cerebrovascular responses to exercise are related by investigating the relationship between the $\dot{V}_E/\dot{V}CO_2$ slope and changes in MCAv during exercise. Finally, this study aimed to determine the within-subject relationships between changes in MCAv and $P_{ET}CO_2$ during exercise, to explore whether such relationships are altered with age and exercise intensity. It was hypothesised that: 1) children would have a smaller relative change in MCAv and $P_{ET}CO_2$ during incremental exercise than adolescents and adults, 2) children and adolescents would have a higher relative $\dot{V}_E$ and breathing frequency during exercise compared to adults, 3) a greater $\dot{V}_E/\dot{V}CO_2$ slope would be associated with a blunted MCAv response to exercise, and 4) the relationships between exercise-induced changes in MCAv and $P_{ET}CO_2$ would strengthen with increasing age.

Methods

Participants

Twenty-one children (aged 8-10 years, 10 male, 11 female), 17 adolescents (aged 12-14 years, 10 male, 7 female) and 20 young adults (aged >19 years, 10 male, 10 female) were recruited for this study using convenience sampling (mean ± SD age: 9.3 ± 0.8, 12.3 ± 0.4 and 23.6 ± 2.4 years, respectively). Child and adolescent participants were recruited from a local school in Devon, United Kingdom. Following approval from the Sport and Health Sciences Ethics Committee, University of Exeter (190327/B/01), written informed consent was obtained for all adult participants. For the children and adolescents, written participant assent was obtained alongside written informed parental/guardian consent. Participants were initially screened for the study exclusion criteria, which included contraindications to maximal exercise, current use of any supplement or medication known to influence blood vessel function, and current or previous metabolic, cardiovascular, or cerebrovascular disease.

Experimental Protocol

Data are presented from a single experimental visit, which was set-up in the school for child and adolescent participants, and at the University of Exeter for adult participants. Participants visited the laboratory following an overnight fast (~08:00am). Stature and body mass were measured following standard procedures. Before being fitted with the experimental equipment, participants were provided with an opportunity to familiarise themselves by practicing pedalling on the electromagnetically braked cycle ergometer (Lode Paediatric Corival for children, Lode Excalibur for adolescents and adults, Lode, Groningen, The Netherlands).

Ramp Incremental Exercise

Participants completed three minutes of seated rest on the cycle ergometer to establish baseline measurements, before completing a ramp incremental test to exhaustion. The ramp rate was 7-10 $W \cdot min^{-1}$ for children, 10-20 $W \cdot min^{-1}$ for adolescents and 20-30 $W \cdot min^{-1}$ for adults, and was estimated to elicit exhaustion in 8-12 minutes (9, 49). Participants were asked to maintain a cadence of 70-90 revolutions per minute (rpm) throughout the test. Exhaustion was deemed to have been reached when cadence fell below 70 rpm for 5 consecutive seconds, despite strong verbal encouragement from the researchers.

Experimental Measures

MCAv was measured bilaterally throughout the exercise protocol using transcranial Doppler (TCD) ultrasonography (DWL, Compumedics, Germany). Insonation of the left and right MCA was performed from an initial depth of 45-50 mm using two 2 MHz probes, secured in place with an adjustable headset (DiaMon, DWL, Germany) (coefficient of variation for baseline MCAv: 7.0%). MCAv data were collected at 200 Hz using an analogue-to-digital converter (Powerlab; model – 8/30, ADInstruments, USA) interfaced with a laptop computer, and stored for off-line analysis (LabChart 8, ADInstruments, USA).

Participants were fitted with a leak-free facemask (Hans-Rudolph, Kansas, USA) and breath-by-breath pulmonary oxygen uptake ($\dot{V}O_2$), $\dot{V}CO_2$, $\dot{V}_E$, breathing frequency (f_R), tidal volume ($\dot{V}_T$) and $P_{ET}CO_2$ were collected through a preVent® Flow Sensor connected to a metabolic cart (Medgraphics Cardiorespiratory Diagnostics, UK). Prior to each data collection, the gas analyser was calibrated with gases of known concentration, and the flow was manually calibrated using a 3-L syringe across a range of flow rates.

Data Analyses

Beat-by-beat mean, maximum, and minimum MCAv data were exported using 10 s stationary averages. Left and right MCAv data were averaged when both signals were maintained throughout the protocol. MCA pulsatility index (PI) was calculated using the Gosling flow pulsatility index, as the difference between systolic and diastolic MCAv divided by MCAv mean (18). Breath-by-breath cardiopulmonary data were linearly interpolated to 1 s and averaged into 10 s bins for analysis, and time-aligned with MCAv data from exercise onset. $\dot{V}O_{2peak}$ was determined as the highest 10-s average in $\dot{V}O_2$ achieved during the test. To allow comparison between age groups, $\dot{V}_E$, $\dot{V}_T$ and $\dot{V}O_{2peak}$ data were scaled allometrically to control for body size (46). Allometric scaling was performed using log-linear regression models (46), with body mass entered as a predictor variable. Age group (children, adolescent, or adult) was also added as a categorical predictor variable to produce a scaling exponent (b) that was suitable for all age groups, for $\dot{V}_E$ (b=0.51), $\dot{V}_T$ (b=0.69) and $\dot{V}O_{2peak}$ (b=0.58). Data were then scaled using a power function ratio (Y/X^b).

Data were analysed at baseline, gas exchange threshold (GET), respiratory compensation point (RCP) and exhaustion. At these metabolic landmarks, changes in ventilation and $P_{ET}CO_2$ occur, and given their influence on CBF during exercise, these data points were chosen to facilitate comparison between age groups, in line with previous work (14, 34). Baseline was taken as the average of the last 60 s of seated, stationary rest on the ergometer prior to commencing the incremental ramp test. The

GET was determined as the disproportionate increase in $\dot{V}CO_2$ relative to $\dot{V}O_2$ (6) and verified by an increase in the ventilatory equivalent of oxygen ($\dot{V}_E/\dot{V}O_2$) without an increase in the ventilatory equivalent of carbon dioxide ($\dot{V}_E/\dot{V}CO_2$). The RCP was identified as the inflection in the $\dot{V}_E/\dot{V}CO_2$ slope and an increase in both $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ (6). Both the GET and RCP were independently verified by two researchers. The $\dot{V}_E/\dot{V}CO_2$ slope was calculated from the start of the test up to the RCP using linear regression.

Statistical Analyses

All data are presented as mean ± standard deviation (SD). Statistical analyses were performed using SPSS version 26 (IBM, USA), with statistical significance set *a priori* at $P \leq 0.05$. Differences in descriptive and ramp test variables between age groups were explored using a one-way analysis of variance (ANOVA) with age group (children, adolescents, adults) as the independent variable. Changes in MCAv and $P_{ET}CO_2$ during exercise are presented as both absolute and relative change from baseline (Δ%). The response of the main outcome variables (MCAv, $P_{ET}CO_2$, $\dot{V}_E$, $\dot{V}_T$, f_R) to incremental exercise were analysed using a two-way mixed model ANOVA, with exercise intensity (baseline, GET, RCP, exhaustion) as the within-subject factor, and age group as the between-subject factor. To investigate if there was an effect of sex on MCAv during exercise, a three-way mixed model ANOVA was performed, with exercise intensity as the within-subject factor, and sex and age group as the between subject factors. Effect sizes have been calculated and reported to support the use of the *P*-value. For the ANOVA main and interaction effects, these were displayed as partial eta squared (η_p^2) and interpreted as <0.06 = small, 0.06-0.14 = moderate and ≥0.14 = large (11). Significant differences from ANOVAs were located using pairwise comparisons and interpreted using the *P*-value and standardised effect sizes (*d*). An effect size (*d*) was interpreted as small if <0.5, moderate if 0.5-0.8 and large if ≥0.8 (11).

The relationships between the $\dot{V}_E/\dot{V}CO_2$ slope and Δ%MCAv at the GET and RCP were analysed using Pearson's correlation across the whole sample. The within-subject relationship between $\Delta\%P_{ET}CO_2$ and Δ%MCAv was explored using linear regression to derive the regression slope and the correlation coefficient (*r*) for each participant. Correlations were performed across three different portions of the ramp test: from the start of the ramp test up to the GET, from the GET up to the RCP, and from the RCP to the end of the test. This generated three *r* values and three *P* values for each participant. Individual *r* values were then corrected using Fisher's *Z* transformation (Z_F), which normalises the sampling distribution of obtained Pearson *r* values (17). Mean slope and Z_F statistics were analysed between age groups (children, adolescents, and adults) and exercise intensity (baseline-GET, GET-RCP, RCP-exhaustion) using a two-way mixed model ANOVA. To calculate an average correlation coefficient for each exercise intensity for each age group, group mean Z_F values were back-transformed to an r value ($\bar{r}$) for ease of interpretation. This approach yields a smaller bias than simply averaging *r* values (13, 39).

Results

Data are presented for a final sample size of 47, with 14 children (six male), 14 adolescents (nine male) and 19 adults (nine male) included in the final analyses. The reasons for data loss were the absence of an identifiable RCP (n=6, four children, two adolescents) or an inadequate MCAv signal throughout the test for data analysis (n=5, three children, one adolescent, one adult). Both MCAv signals were maintained in 35 participants (10 children, 9 adolescents, 16 adults), with only left MCAv in six participants (2 children, 3 adolescents, 1 adult) and only right MCAv in six participants (2 children, 2 adolescents, 2 adults). Participant characteristics and ramp test responses for the final sample are shown in Table 1, and baseline cardiorespiratory and cerebrovascular data are shown in Table 2.

MCAv There were no main or interaction effects for sex (all $P>0.43$, $\eta_p^2<0.003$) meaning male and female data from each age group have been pooled throughout. Baseline MCAv was lower in adults compared to children ($P<0.01$, $d=1.8$) and adolescents ($P<0.01$, $d=1.5$, Table 2). There was a main effect of age ($P<0.01$, $\eta_p^2 = 0.34$) and exercise intensity ($P<0.01$, $\eta_p^2 = 0.57$) for changes in MCAv during the ramp test, but no intensity*age interaction ($P=0.19$, $\eta_p^2= 0.06$) (Figure 1A). Absolute MCAv was higher in children and adolescents at all exercise intensities, compared to adults ($P<0.01$, $d=0.9$-1.6).

When expressed relative to baseline (Δ%MCAv), there was a main effect of both intensity ($P<0.01$, $\eta_p^2 =0.58$) and age ($P=0.04$, $\eta_p^2=0.14$), but no intensity*age interaction ($P=0.07$, $\eta_p^2=0.09$) (Figure 1B). At the GET, Δ%MCAv was lower in children compared to adults ($P=0.03$, $d=0.9$) and adolescents ($P=0.01$, $d=0.9$). At the

RCP, Δ%MCAv was lower in children compared to adults (*P*<0.01, *d*=1.1) and adolescents (*P*=0.05, *d*=0.8). At exhaustion, Δ%MCAv was not significantly different between age groups (*P*>0.14, *d*<0.6).

MCA Pulsatility Index No differences were observed in baseline PI between age groups (P=0.14-0.91, d=0.0-0.6, Table 2). There was an intensity*age interaction (*P*=0.03, η_p^2 = 0.07), with a greater PI in adults compared to both children and adolescents at the GET (P≤0.01, *d*≥0.9), RCP (P≤0.03, *d*≥0.7) and exhaustion (P≤0.06, *d*=0.7, Table 2).

$P_{ET}CO_2$ There was an intensity*age interaction (*P*<0.01, η_p^2 = 0.22, Figure 1C), with $P_{ET}CO_2$ lower in children compared to adults (*P*<0.01, *d*=1.6) and adolescents at the GET (*P*=0.05, *d*=0.8). Although not statistically significant, $P_{ET}CO_2$ was lower at the GET in adolescents compared to adults (*P*=0.06, *d*=0.6). At the RCP, $P_{ET}CO_2$ was lower in children compared to adults (*P*<0.01, *d*=1.6), and in adolescents compared to adults (*P*=0.02, *d*=0.8). $P_{ET}CO_2$ was not significantly different between children and adolescents at the RCP, although the effect size was large (*P*=0.09, *d*=0.9).

When expressed relative to baseline (Δ%$P_{ET}CO_2$), there was an intensity*age interaction (*P*<0.01, η_p^2 = 0.19) (Figure 1D), with Δ%$P_{ET}CO_2$ lower in children and adolescents, compared to adults, at both the GET (*P*<0.05, *d*>0.6) and RCP (*P*<0.05, *d*>0.7).

$\dot{V}_E$, $\dot{V}_T$ *and* f_R $\dot{V}_E$ increased during exercise, with an intensity*age interaction (*P*<0.01, η_p^2 = 0.48) (Figure 2A). $\dot{V}_E$ was higher in adolescents than children at baseline (*P*=0.06, *d*=0.8) and GET (*P*=0.06, *d*=0.7), although not statistically significant. At the RCP, $\dot{V}_E$ was greater in adults compared to adolescents (*P*=0.04, *d*=0.7) and children (*P*<0.01, *d*=1.8), and greater in adolescents compared to children (*P*=0.05, *d*=0.8). At exhaustion,

$\dot{V}_E$ was greater in adults compared to both adolescents (*P*=0.01, *d*=0.8) and children (*P*<0.01, *d*=2.6), and greater in adolescents compared to children (*P*<0.01, *d*=1.6).

$\dot{V}_T$ changed with a significant intensity*age interaction (*P*<0.01, η_p^2 = 0.29) (Figure 2B). At the GET and RCP, adults had a higher $\dot{V}_T$ compared to children (*P*<0.01, *d*≥1.2) and adolescents (*P*<0.01, *d*≥1.0). At exhaustion, $\dot{V}_T$ was higher in adults compared to both adolescents (*P*=0.04, *d*=0.7) and children (*P*<0.01, *d*=1.7) and was higher in adolescents than children (*P*=0.04, *d*=1.0).

f_R increased during the ramp test, with a significant intensity*age interaction (*P*<0.01, η_p^2 =0.16, Figure 2C). f_R was lower in adults compared to adolescents at baseline, GET and RCP (all *P*<0.01, *d*≥1.1), and was lower in adults than children at the GET and RCP (*P*<0.01, *d*>1.4). At exhaustion, f_R was similar in all age groups (*P*>0.3, *d*<0.5).

Heart Rate The heart rate response to exercise is shown in Table 2. There was a main effect of age (P<0.01, η_p^2=0.30), but no age*intensity interaction (P=0.19, η_p^2=0.06) on heart rate during exercise.

$\dot{V}_E/\dot{V}CO_2$ slope The magnitude of the $\dot{V}_E/\dot{V}CO_2$ slope was significantly greater in children compared to adults (*P*<0.01, *d*=2.4) and adolescents (P<0.01, *d*=1.4), and was significantly greater in adolescents compared to adults (P<0.01, *d*=1.0) (Table 1). To explore potential explanations for the blunted MCAv response in children, and in particular the relationship between the $\dot{V}_E/\dot{V}CO_2$ slope and Δ%MCAv across the sample, the relationship between the magnitude of the $\dot{V}E/\dot{V}CO2$ slope and Δ%MCAv was explored. The magnitude of the $\dot{V}_E/\dot{V}CO_2$ slope was significantly, negatively correlated with Δ%MCAv across the whole sample at the GET (Figure 3A) and RCP (Figure 3B).

Relationships between Δ%MCAv and Δ%$P_{ET}CO_2$

Figure 4 shows the individual regression slopes for Δ%$P_{ET}CO_2$ *vs* Δ%MCAv, separated by age group and exercise intensity. From baseline-GET, Δ%MCAv and Δ%$P_{ET}CO_2$ were significantly, positively correlated in 4 children (29% of sample), 8 adolescents (57%) and 17 adults (90%). Δ%MCAv and Δ%$P_{ET}CO_2$ were significantly, positively correlated in 3 children (21%), 5 adolescents (36%) and 5 adults (26%) from GET-RCP, and in 8 children (57%), 7 adolescents (50%) and 16 adults (84%) from RCP-exhaustion.

There was a significant main effect of exercise intensity on the group mean values of the Δ%$P_{ET}CO_2$ *vs* Δ%MCAv regression slope (P=0.02, η_p^2 = 0.09), but no significant main effect of age (P=0.13, η_p^2 = 0.09) or significant intensity*age interaction (P=0.06, η_p^2 = 0.10). The regression slope from baseline-GET was lower in children than adolescents (P=0.03, d=0.8) and adults (P<0.01, d=1.3), but was not different between adolescents and adults (P=0.28, d=0.4). From GET-RCP and RCP-exhaustion, the regression slope was similar between age groups (P>0.51, d≤0.2). In adults only, the regression slope was greater from baseline-GET than GET-RCP (P<0.01, d=0.9) and RCP-exhaustion (P=0.02, d=0.8). No other differences were present in the magnitude of the regression slope between exercise intensities within any age group (P>0.10, d≤0.5).

There was a significant intensity*age interaction for changes in Z_F during the ramp test (P=0.04, η_p^2 = 0.11). From baseline-GET, Z_F was lower in children compared to adolescents (P=0.02, d=0.8) and adults (P<0.01, d=1.8), and lower in adolescents, compared to adults (P=0.05, d=0.7). No differences between age groups were present in Z_F from GET-RCP (P>0.40, d≤0.4). From RCP-exhaustion, Z_F was lower in children compared to adults (P=0.02, d=0.9). Z_F was not significantly different from RCP-exhaustion between adolescents and children (P=0.41, d=0.3), nor between adolescents and adults (P=0.15, d=0.5). Z_F from RCP-exhaustion was greater than from GET-RCP in all age groups (P<0.03, d≥0.8), and compared to baseline-GET in children only (P=0.02, d=0.8). In adults, Z_F from baseline-GET was greater than from GET-RCP (P<0.01, d=1.4). No other differences in Z_F between exercise intensities were present within each age group (P>0.10, d≤0.5).

Discussion

The novel findings from this study suggest that the regulatory role of $PaCO_2$ on cerebrovascular responses during incremental exercise show inter-individual variability, which appears to be modified by age during the transition from childhood to adulthood. Specifically, in agreement with the hypotheses, relative changes in MCAv during ramp incremental exercise were smaller in children compared to both adolescents and adults, whilst changes in $P_{ET}CO_2$ during the ramp test were greater in adults, compared to adolescents and children. Adults had a greater $\dot{V}_E$ at RCP and exhaustion compared to children and adolescents, accompanied by a greater $\dot{V}_T$, whilst children and adolescents had an elevated f_R at GET and RCP. In addition, the present study found that the ventilatory and cerebrovascular responses to exercise were related, with the magnitude of the $\dot{V}_E/\dot{V}CO_2$ slope negatively associated with Δ%MCAv during exercise across the sample. Finally, the present study observed stronger relationships between $\Delta\%P_{ET}CO_2$ and Δ%MCAv during exercise with increasing age.

The smaller increase in Δ%MCAv during incremental exercise in children compared to adults is in agreement with the only existing study comparing cerebrovascular responses to incremental exercise in children and adults, which utilised a step incremental protocol to exhaustion (14). This study reports similar increases in Δ%MCAv to those of Ellis et al., (14) in children (~10-15%) and adults (~20-30%), but extends these findings showing the increase in Δ%MCAv was very similar in adolescents and adults, despite smaller increases in $\Delta\%P_{ET}CO_2$ in adolescents. This may provide indirect support for a greater cerebrovascular reactivity to CO_2 in adolescents, compared to adults, as they experience similar increases in Δ%MCAv from smaller changes in $P_{ET}CO_2$. Developmental changes in CVR remain unclear and are likely influenced by both the stimulus and measurement of CBF. Using magnetic resonance imaging techniques, Leung et al., (26) observed increases in CVR during adolescence until mid-teens, before declining into adulthood, whilst Tallon et al., (42) observed similar CVR to CO_2-breathing in children and adults using TCD. Nevertheless, the present study provides indirect support for a greater cerebrovascular response to changes in $P_{ET}CO_2$ during adolescence, compared to both childhood and adulthood. However, the present data are during exercise, with smaller elevations in $P_{ET}CO_2$ compared to a resting CO_2 challenge.

Another important consideration is the regulatory role of changes in blood pressure during exercise. Ellis et al., (14) observed no relationship between changes in MCAv and mean arterial pressure during incremental exercise in children nor adults, but this has not been explored in adolescents. Adolescents have greater increases in mean arterial pressure during exercise, compared to children (35), and altered cerebral autoregulation compared to adults (45), and these differences may further contribute to the MCAv response to exercise in adolescents, and forms an important area for further investigation.

Collectively, these age group differences suggest a potentially important role of hormonal changes occurring during puberty on CBF during exercise (15, 26). In addition, it has been suggested that these hormonal effects, in particular oestrogen and the metabolites of testosterone, could show a sex-dependence during puberty (15, 22, 37). Nevertheless, the present study found no effect of sex on the MCAv response to incremental exercise in any age group, in agreement with previous work in prepubertal children and young adults (14). An additional important consideration is the effect of cardiorespiratory fitness on the MCAv response to exercise. In particular, $\dot{V}O_{2peak}$

increases with maturation (5), in agreement with the present findings. In adults, Brugniaux et al., (8) observed a significantly greater increase in MCAv in active compared to sedentary individuals during incremental exercise. It is possible that the significantly lower $\dot{V}O_{2peak}$ in children, compared to adolescents and adults, may be contributing to the blunted MCAv response to exercise in the present study. Overall, however, future research is needed to explore the potential interactions between sex, maturation, cardiorespiratory fitness and CBF responses to exercise using larger sample sizes across maturity stages.

The MCA pulsatility index can provide an indirect measure of arterial stiffness in the brain (25) and could provide further insight into age-related differences in cerebrovascular function from childhood to adulthood. PI is known to increase with age during adulthood (4), and this is the first study to demonstrate similar resting MCA PI in children, adolescents and young adults. Lefferts and Smith (25) recently highlighted that dynamic conditions, such as exercise, may elucidate differences in MCA PI that are not detectable at rest. Indeed, in the present study, PI was significantly greater during exercise in adults, compared to children and adolescents. These data could indicate greater arterial stiffness in the brain during exercise in adults, and/or improved pulsatile damping in the paediatric brain (24). These novel data highlighting differences in both MCA velocity and pulsatility during exercise in children and adolescents, compared to adults, further strengthens the need for future research to better understand CBF regulation in the developing brain.

The smaller $\Delta\%P_{ET}CO_2$ observed during exercise in children and adolescents compared to adults in the present study is in agreement with previous research (14, 31, 33). The reasons for this are likely multi-factorial, and possibly related to smaller CO_2 storage and production, alongside a smaller $\dot{V}_T$ and body size in children (31). Furthermore, children have greater ventilatory sensitivity to CO_2 production during exercise (19), supported by an elevated $\dot{V}_E/\dot{V}CO_2$ slope in the present study, which could underpin the smaller changes in $P_{ET}CO_2$. Indeed, the elevated f_R at the GET and RCP in children and adolescents support this, possibly lowering $PaCO_2$ through hyperventilation to compensate for a lower $\dot{V}_T$ compared to adults.

In addition to an elevated f_R during exercise in children and adolescents, it is commonly reported that children have a greater $\dot{V}_E$ when expressed relative to body mass both at rest and during exercise, compared to adults (14, 19, 33). This is often considered to reflect a less “efficient” ventilatory response in youth, as a result of the neural control of ventilation not yet being fully developed (23). However, a limitation of previous work studying the ventilatory response to exercise in children compared to adults is the potentially inappropriate use of ratio scaling in an attempt to remove the influence of body mass. This approach may be ineffective, as ratio-scaled data often remains significantly, negatively correlated with body mass (46). This has led to the preferred use of allometric scaling to appropriately compare developmental differences in exercise data, which more appropriately removes the confounding influence of body size (46). Using this approach, the present study is the first to find a similar $\dot{V}_E$ at rest and GET between age groups, contrary to previous data using the ratio-scaled method (14, 19, 33). In this study, $\dot{V}_E$ was augmented to a greater extent at RCP and exhaustion with increasing age, and was highest in adults. This appears to be driven by a substantially elevated $\dot{V}_T$ in adults compared to children and adolescents across the duration of the ramp test.

In the present study, the $\dot{V}_E/\dot{V}CO_2$ slope was greater in children compared to adolescents and adults, and greater in adolescents compared to adults. This is often thought to be reflective of lower ventilatory efficiency in children and adolescents, but could also be a marker of age-related differences in CO_2 storage capacity or $PaCO_2$ set point (12). This supports previous studies comparing children and adults (19) and children and adolescents (12), but whether this is related to the blunted MCAv response observed during exercise in children has not been explored.

It has previously been suggested that the smaller increases in Δ%MCAv during incremental exercise in children is due to a reduced 'cerebrovascular reserve', in that there is a limited capacity to further increase MCAv above the already elevated levels of resting perfusion compared to adults (14, 26). The present data further supports this hypothesis in children, and provides additional insight into the blunted MCAv response observed. Given that that both the respiratory system and cerebrovascular reactivity act to defend reductions in pH in the brain tissue (28), one explanation for the blunted Δ%MCAv increase during exercise in children could be their different ventilatory response to exercise. In children, the greater $\dot{V}_E/\dot{V}CO_2$ slope may result in a relatively lower CO_2 accumulation, defending of arterial pH (lower $PaCO_2$) and therefore smaller increases in MCAv (less H^+ washout required in the brainstem). The significant, negative correlation between the magnitude of the $\dot{V}_E/\dot{V}CO_2$ slope and the MCAv amplitude at the GET and RCP in the present study provides the first evidence that the different ventilatory response to exercise in children is associated with smaller exercise-induced increases in MCAv. Alternatively, smaller increases in MCAv during exercise in children may potentially result in lower ventilatory efficiency (with the respiratory system having to defend arterial pH through removal of CO_2). However, the interactions between ventilation and cerebrovascular reactivity have recently been debated, with some evidence showing that $\dot{V}_E$ plays a direct role in determining CVR (30), whilst others suggest it has little effect on CBF or CVR (10, 21). Importantly, these previous data are at rest and in adults, and given the emerging evidence suggesting distinctly different mechanisms of CBF regulation in children (3), the present study extends these findings and suggests an association between the ventilatory and cerebrovascular responses to exercise in children.

In addition to exploring age-related differences in the MCAv and ventilatory responses to exercise, the present study provides novel insight regarding the potential role of $P_{ET}CO_2$ in regulating the MCAv response to incremental exercise in children, adolescents, and adults. In adults, changes in $P_{ET}CO_2$ and MCAv were strongly correlated up to the GET, and from the RCP to exhaustion. However, from the GET to RCP, where smaller changes in both $P_{ET}CO_2$ and MCAv are observed, a weak relationship was observed. This is in agreement with previous work during incremental exercise, showing that the increase and decrease observed in MCAv during incremental exercise is strongly, positively associated with intensity-dependent changes in $P_{ET}CO_2$ in adults (14, 27). However, in the present study, the relationship between increases in $P_{ET}CO_2$ and MCAv from baseline to GET was weaker in adolescents compared to adults, and weaker in children compared to both adolescents and adults. These data suggest that age (and possibly maturation) has a marked influence on the factors regulating the increases in MCAv during incremental exercise, with $P_{ET}CO_2$ having a dominant role in adulthood, but not in children. This supports the findings of Ellis et al., who also reported no relationship between changes in MAP and MCAv in children during incremental exercise (14). Consequently, the mechanisms underpinning exercise-induced increases in MCAv in children remain largely unresolved, with the present data suggesting a less dominant role of $P_{ET}CO_2$ in children, which seems to develop during adolescence and into adulthood.

It has been suggested that increases in cardiac output may have a role in meeting increased cerebrovascular demands during hypercapnia in children, since the responses of MCAv, $P_{ET}CO_2$ and MAP in children were also poorly aligned during a CO_2 breathing challenge (42). Although changes in cardiac output during incremental exercise are similar in children and adults when appropriately scaled for body size (36), the ratio of CBF to ascending aortic flow is much greater in children compared to adults at rest, reflecting a greater percentage of cardiac output delivery to the brain during childhood (48). Therefore, it seems possible that increases in cardiac output and/or a greater proportion of cardiac output delivery to the brain in children could underpin the increase in MCAv from baseline to GET during incremental exercise. Children also have elevated cerebral oxygen consumption, compared to adults (44), with cerebral oxygen consumption increasing with exercise in adults (16). Given the blunted MCAv response to exercise in children, alongside elevated resting cerebral oxygen consumption (44), it is possible that exercise-induced increases in cerebral metabolism are smaller in children, which in turn could mean that smaller increases in CBF are required. Whilst the interactions between CBF and cerebral metabolism during exercise in adults is well documented (41), this remains poorly understood in children, with challenges in assessing cerebral metabolism during exercise. However, this remains speculative, since cardiac output and cerebral oxygen consumption were not measured in the present study.

In the present study, the relationship between the decrease in $P_{ET}CO_2$ and the fall in MCAv from the RCP to exhaustion was significantly stronger in adults, compared to children, in agreement with previous work (14). This could indicate that cerebral vasoconstriction from hyperventilation-induced hypocapnia occurs during higher intensity exercise in children, but to a smaller degree than seen in adults. The weaker relationship observed in children could be a result of the smaller degree of hyperventilation (lower $\dot{V}_E$) observed after the RCP in children, compared to adults. Furthermore, the decrease in MCAv may reflect cerebral vasoconstriction in response to elevated blood pressures during higher intensity/maximal exercise, to protect the developing brain from over-perfusion (14), but this requires further investigation.

The inclusion of adolescents in the present study provides further novelty on the potential maturation of these responses from childhood to adulthood, and observed a moderate relationship between changes in MCAv and $P_{ET}CO_2$ up to the GET, and from RCP to exhaustion. This suggests that $PaCO_2$ plays more of a regulatory role in adolescents than children, but to a lesser extent than in adulthood. This could represent developmental changes in the regulatory factors of MCAv during exercise, with the regulatory role of $PaCO_2$ becoming more dominant from childhood to adulthood. A key observation was the presence of wide inter-individual variability in the relationships between $\Delta\%P_{ET}CO_2$ and $\Delta\%$MCAv throughout the incremental test. This was true across all age groups studied, and could be due to inter-individual differences in cerebrovascular reactivity, cerebral autoregulation or exercise-induced changes of important regulatory factors of CBF, such as sympathetic nerve activity, cerebral metabolism or cardiac output, and requires further investigation.

Study considerations

This study has a number of methodological strengths, including the use of a ramp, rather than step-wise, incremental exercise protocol which was of similar duration between age groups, “anchoring” data analyses to ventilatory landmarks, and the removal of any confounding influences of body size through allometric scaling of volume data. These allow for appropriate between age-group comparisons. The present study is the first to explore the MCAv response, and its relationship with $P_{ET}CO_2$, during exercise in adolescents. It is important to note that, although sex differences were explored in the present study, the unequal sex-distribution between age groups and subsequently low sample size for some sub-groups may limit the generalisability of results; thus warranting corroboration of present findings in further, larger, studies. Furthermore, longitudinal research is needed in larger samples of boys and girls to enhance understanding on the effects of age, maturation and sex on CBF regulation during exercise, which have been shown to affect resting CBF (37).

The present study utilised TCD to measure cerebral blood velocity in the MCA. This approach allows continuous, non-invasive measurements during whole-body, upright cycling in adults and children (14, 27, 34, 43). However, TCD does not measure vessel diameter, and cerebral blood velocity is only an appropriate surrogate of CBF if vessel diameter remains unchanged. Changes in MCA diameter are known to occur during marked alterations in $P_{ET}CO_2$ in adults (+15 mmHg, -13 mmHg) (2), which is an important consideration when considering hypercapnia during exercise at the GET and RCP and hypocapnia at exhaustion. Importantly, the absolute changes in $P_{ET}CO_2$ in the present study were smaller than this, albeit during exercise as opposed to rest. Overall, TCD is considered an appropriate and practical measurement technique to measure CBF during exercise (29). Secondly, $P_{ET}CO_2$ was used as a surrogate of $PaCO_2$. $P_{ET}CO_2$

provides a better estimate of $PaCO_2$ during exercise in children than in adults, but nevertheless, it is considered an acceptable, non-invasive surrogate of $PaCO_2$ during exercise (31).

A limitation of the present study is the absence of blood pressure measurements during exercise, since alterations in MAP are an important consideration when investigating changes in CBF during exercise (29, 41). However, Ellis et al., (14) found no relationship between changes in MAP and MCAv during incremental exercise (both before and after the GET) in children nor adults. Though limited to a single study, this suggests that changes in MAP are unlikely to be confounding the main outcomes of the present study. Finally, only the response of the MCA, and not the posterior cerebral artery was measured. Whether regional differences in the cerebrovascular response to incremental exercise are present in children has not been explored. This forms an important question for future research, given the differential responses of the MCA and posterior cerebral artery to incremental exercise in adults (41). Furthermore, the influence of ventilation on cerebrovascular responses to exercise may be more pronounced in the posterior circulation (10), given the location of the central chemoreceptors in the brainstem, which is supplied by the posterior cerebral circulation (40).

Conclusions

The present study found marked differences in the cerebrovascular and ventilatory responses to ramp incremental exercise in children, adolescents, and adults. Children showed smaller increases in Δ%MCAv during exercise compared to adolescents and adults, which was associated with a greater $\dot{V}_E/\ \dot{V}CO_2$ slope during exercise. In adults, intensity-dependent changes in $P_{ET}CO_2$ and MCAv were strongly, positively related, whereas these relationships were weaker in children. The relationships between $\Delta\%P_{ET}CO_2$ and Δ%MCAv were stronger in adolescents than children, but were weaker compared to adults. These data suggest marked developmental differences in the regulation of cerebrovascular responses to incremental exercise, with the regulatory role of $PaCO_2$ becoming more influential from childhood, through adolescence, into adulthood.

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The authors declared no potential conflicts of interest, financial or otherwise.

Author contributions

MEW – study conceptualisation and design, data collection, data and statistical analysis, data interpretation, drafted and finalised the manuscript

ARB – study conceptualisation and design, data analysis, data interpretation, critical review of the manuscript

OWT – data analysis, data interpretation, critical review of the manuscript

JSC – study conceptualisation and design, data interpretation, critical review of the manuscript

TGB – study conceptualisation and design, data interpretation, critical review of the manuscript

BB - study conceptualisation and design, data analysis, data interpretation, critical review of the manuscript

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Figure Captions

Fig 1. Relative changes from baseline (Δ%) in MCAv (A) and $P_{ET}CO_2$ (B) to incremental ramp exercise in children, adolescents and adults. GET, gas exchange threshold. RCP, respiratory compensation point. *a, P*<0.05 children *vs* adults, *b, P*<0.05 children *vs* adolescents, *c, P*<0.05 adolescents *vs* adults.

Fig 2. Minute ventilation, ($\dot{V}_E$, A), tidal volume ($\dot{V}_T$, B) and breathing frequency (f_R, C) responses to ramp incremental exercise in children, adolescents and adults. GET, gas exchange threshold. RCP, respiratory compensation point. *a, P*<0.05 children *vs* adults, *b, P*<0.05 children *vs* adolescents, *c, P*<0.05 adolescents *vs* adults.

Fig 3. The relationship between the magnitude of the $\dot{V}_E/\dot{V}CO_2$ slope and Δ%MCAv at the gas exchange threshold (A) and respiratory compensation point (B).

Fig 4. Individual regression lines for Δ%$P_{ET}CO_2$ *vs* Δ%MCAv from baseline-GET, GET-RCP and RCP-exhaustion in children (A, B, C, respectively), adolescents (D, E, F, respectively) and adults (G, H, I, respectively). Solid lines indicate significant (*P*<0.05) positive correlation, dashed lines indicate P>0.05. $\bar{r}$, corrected mean correlation coefficient. GET, gas exchange threshold, RCP, respiratory compensation point. *a, P*<0.05 children *vs* adults, *b, P*<0.05 children *vs* adolescents.

Table 1. Participant characteristics and ramp test responses.

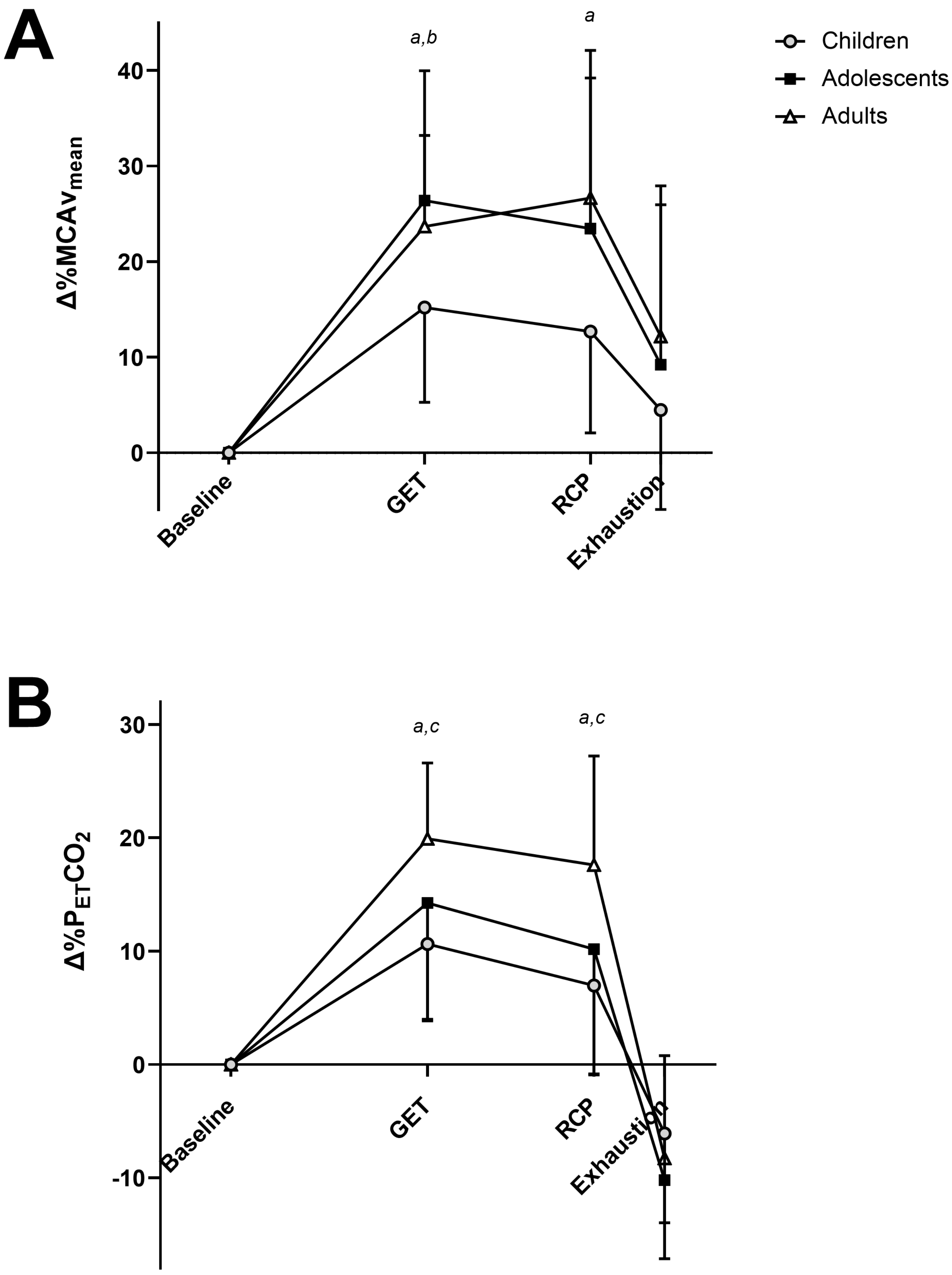
	Children (n=14)	**Adolescents (n=14)**	**Adults (n=19)**
Age (y)	$9.4 \pm 0.9^{a,b}$	$12.4 \pm 0.4^{b,c}$	$23.4 \pm 2.5^{a,c}$
Stature (cm)	$136 \pm 6^{a,b}$	$153 \pm 10^{b,c}$	$173 \pm 10^{a,c}$
Body mass (kg)	$31.2 \pm 5.3^{a,b}$	$45.3 \pm 10.2^{b,c}$	$70.5 \pm 12.8^{a,c}$
$\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	$0.96 \pm 0.14^{a,b}$	$1.71 \pm 0.48^{b,c}$	$2.67 \pm 0.64^{a,c}$
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-0.58} \cdot min^{-1}$)	$133 \pm 14^{a,b}$	$191 \pm 45^{b,c}$	$230 \pm 47^{a,c}$
Ramp test duration (s)	633 ± 79	592 ± 111	672 ± 100
Peak power (W)	$80 \pm 12^{a,b}$	$147 \pm 31^{b,c}$	$281 \pm 65^{a,c}$
GET ($L \cdot min^{-1}$)	$0.58 \pm 0.08^{a,b}$	$0.91 \pm 0.28^{b,c}$	$1.27 \pm 0.32^{a,c}$
GET (%$\dot{V}O_{2peak}$)	$61 \pm 6^{a,b}$	$53 \pm 7^{b,c}$	$48 \pm 6^{a,c}$
RCP ($L \cdot min^{-1}$)	$0.87 \pm 0.12^{a,b}$	$1.42 \pm 0.44^{b,c}$	$2.24 \pm 0.51^{a,c}$
RCP (%$\dot{V}O_{2peak}$)	$91 \pm 5^{a,b}$	83 ± 9^{b}	85 ± 5^{a}
$\dot{V}_E/\dot{V}CO_2$ slope	$29.2 \pm 2.2^{a,b}$	$25.6 \pm 2.9^{b,c}$	$22.4 \pm 3.3^{a,c}$

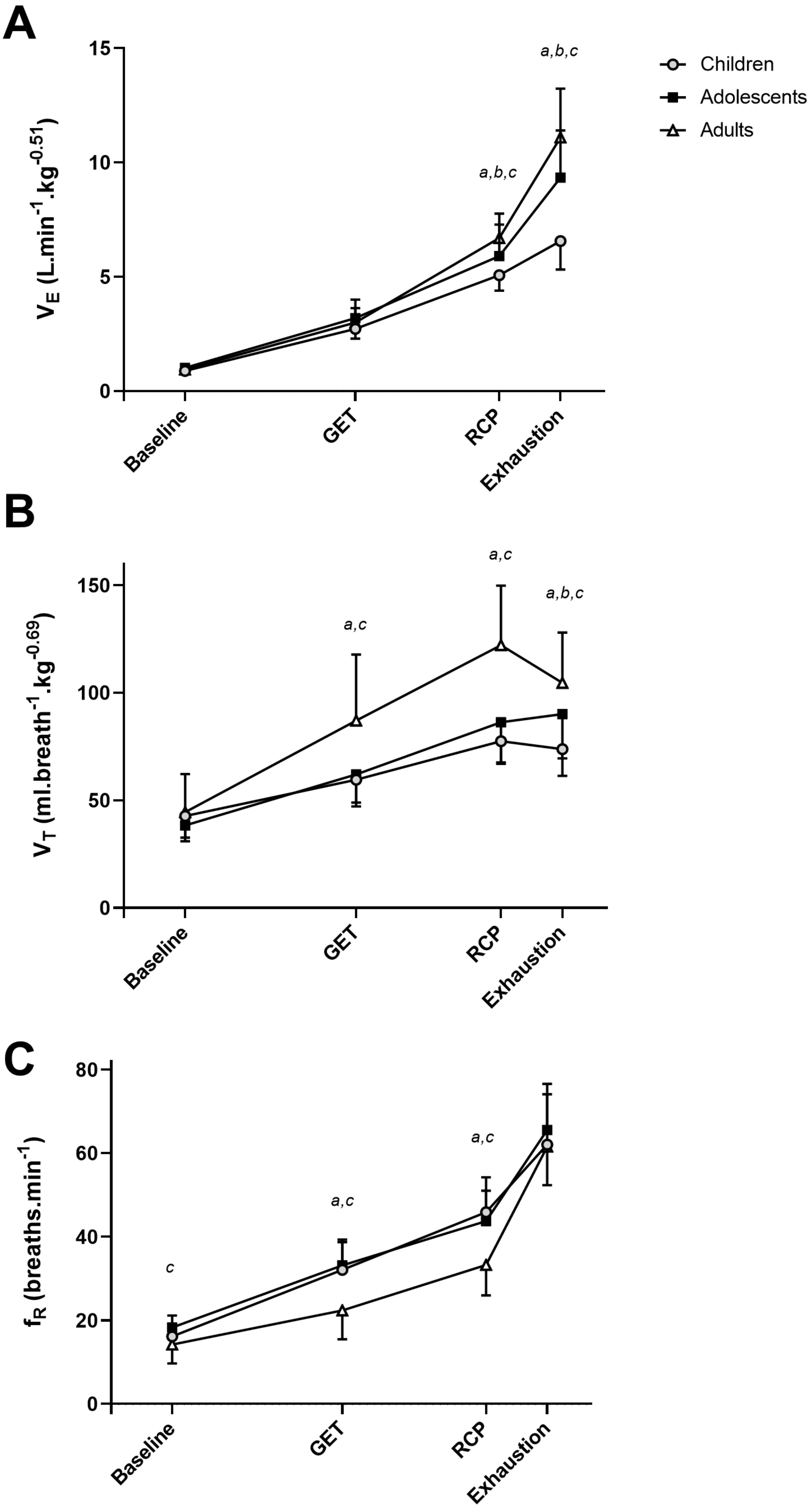
Data shown as mean ± standard deviation. $\dot{V}O_{2peak}$, peak pulmonary oxygen uptake. GET, gas exchange threshold. RCP, respiratory compensation point, $\dot{V}_E$, minute ventilation, $\dot{V}CO_2$, carbon dioxide production. *a, P*<0.05 children *vs* adults, *b, P*<0.05 children *vs* adolescents, *c, P*<0.05 adolescents *vs* adults

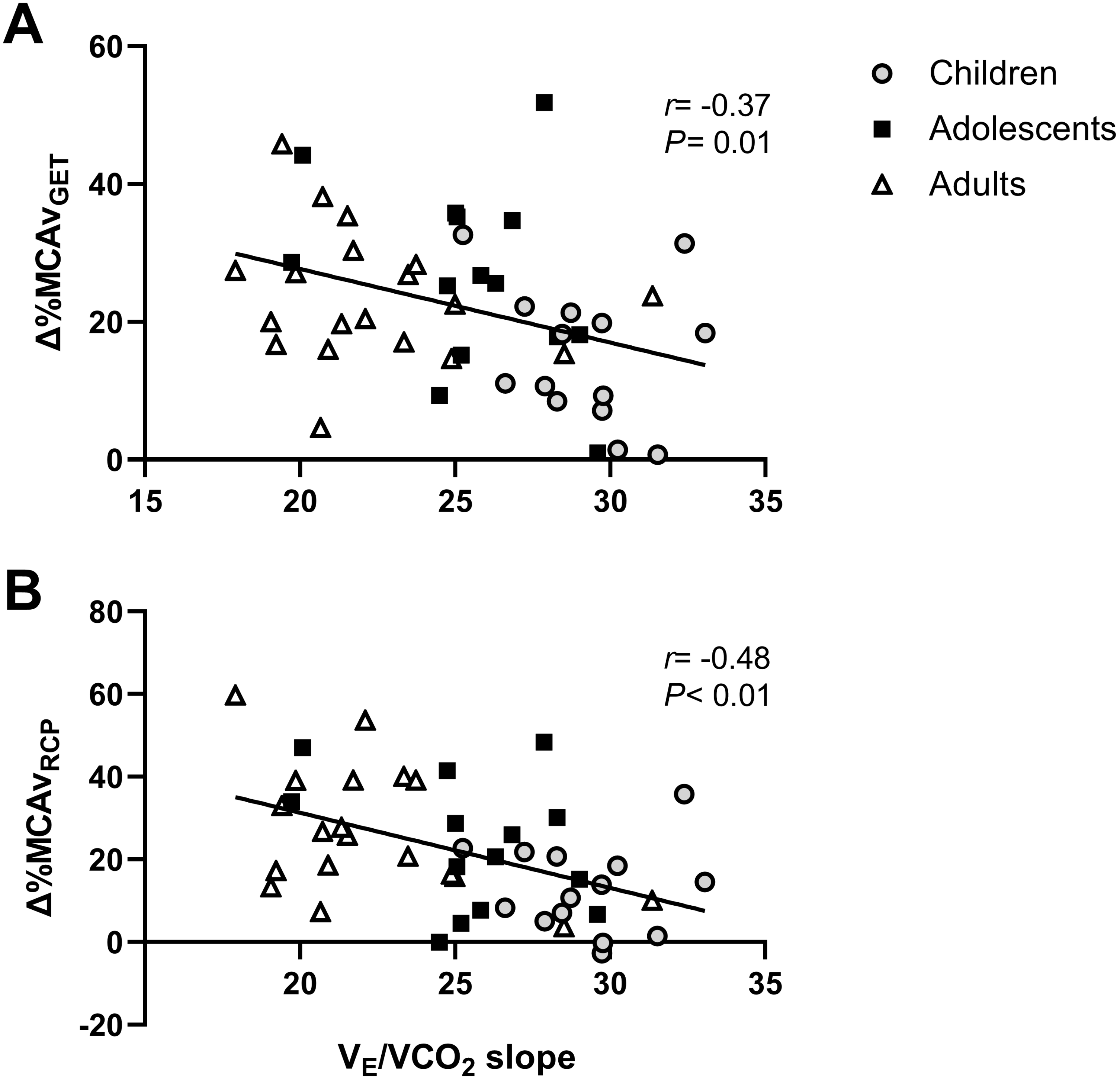
Table 2. Ramp test responses of MCAv, $P_{ET}CO_2$, heart rate and MCA pulsatility index in children, adolescents and adults.

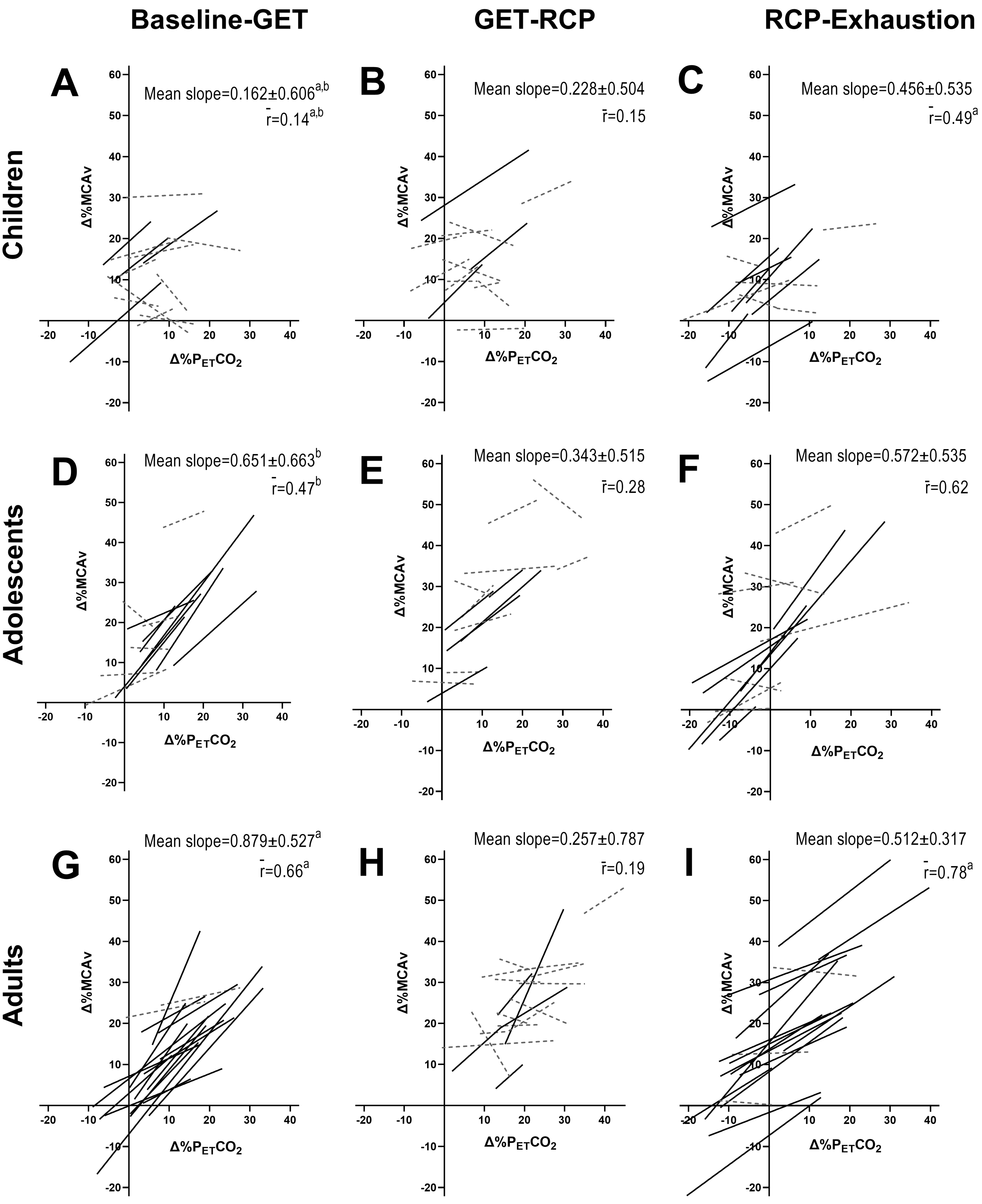
	Children (n=14)	Adolescents (n=14)	Adults (n=19)
MCAv ($cm.s^{-1}$)			
Baseline	93.8 ± 13.4^{a}	90.2 ± 12.8^{c}	72.6 ± 10.1^{a,c}
GET	107.7 ± 15.3^{a}	113.3 ± 14.5^{c}	89.7 ± 14.7^{a,c}
RCP	105.8 ± 18.8^{a}	110.5 ± 15.0^{c}	91.4 ± 13.6^{a,c}
Exhaustion	97.9 ± 16.2^{a}	97.4 ± 12.9^{c}	80.8 ± 12.7^{a,c}
$P_{ET}CO_2$ (mmHg)			
Baseline	33.8 ± 1.9	34.9 ± 2.4	35.0 ± 2.9
GET	37.3 ± 2.0^{a}	39.8 ± 3.5	41.9 ± 3.6^{a}
RCP	36.1 ± 1.5^{a}	38.3 ± 3.1^{c}	41.1 ± 4.3^{a,c}
Exhaustion	31.7 ± 2.7	31.3 ± 2.6	32.0 ± 3.1
Heart Rate (bpm)			
Baseline	86 ± 10^{a}	91 ± 9^{c}	77 ± 14^{a,c}
GET	130 ± 12^{b}	144 ± 16^{b,c}	126 ± 18^{c}
RCP	173 ± 11^{b}	184 ± 11^{b,c}	170 ± 12^{c}
Exhaustion	186 ± 9	190 ± 15	185 ± 8
MCA Pulsatility Index			
Baseline	0.74 ± 0.11	0.69 ± 0.09	0.74 ± 0.09
GET	0.79 ± 0.12^{a}	0.77 ± 0.11^{c}	0.90 ± 0.12^{a,c}
RCP	0.81 ± 0.16^{a}	0.80 ± 0.11^{c}	0.92 ± 0.15^{a,c}
Exhaustion	0.87 ± 0.17^{a}	0.89 ± 0.15	1.03 ± 0.25^{a}

Data shown as mean ± standard deviation. MCAv, middle cerebral artery blood velocity. $P_{ET}CO_2$, end-tidal carbon dioxide. GET, gas exchange threshold. RCP, respiratory compensation point. *a, P*<0.05 children *vs* adults, *b, P*<0.05 children *vs* adolescents, *c, P*<0.05 adolescents *vs* adults.


A
Children
Adolescents
Adults
a,b
a
40
30
20
10
0
Δ%MCAv_mean
Baseline
GET
RCP
Exhaustion
B
a,c
a,c
30
20
10
0
-10
Δ%P_ET CO2
Baseline
GET
RCP
Exhaustion


A
V_E (L.min-1.kg-0.51)
15
10
5
0
a,b,c
a,b,c
Baseline
GET
RCP
Exhaustion
Children
Adolescents
Adults
B
V_T (ml.breath-1.kg-0.69)
150
100
50
0
a,c
a,c
a,b,c
Baseline
GET
RCP
Exhaustion
C
f_R (breaths.min-1)
80
60
40
20
0
c
a,c
a,c
Baseline
GET
RCP
Exhaustion


A
B
Children
Adolescents
Adults
r= -0.37
P= 0.01
r= -0.48
P< 0.01
Δ%MCAv$_{GET}$
Δ%MCAv$_{RCP}$
60
40
20
0
80
60
40
20
0
-20
15
20
25
30
35
20
25
30
35
V$_E$/VCO$_2$ slope


Baseline-GET
GET-RCP
RCP-Exhaustion
Children
Adolescents
Adults
A
Mean slope=0.162±0.606^{a,b}
$\bar{r}$=0.14^{a,b}
B
Mean slope=0.228±0.504
$\bar{r}$=0.15
C
Mean slope=0.456±0.535
$\bar{r}$=0.49^{a}
D
Mean slope=0.651±0.663^{b}
$\bar{r}$=0.47^{b}
E
Mean slope=0.343±0.515
$\bar{r}$=0.28
F
Mean slope=0.572±0.535
$\bar{r}$=0.62
G
Mean slope=0.879±0.527^{a}
$\bar{r}$=0.66^{a}
H
Mean slope=0.257±0.787
$\bar{r}$=0.19
I
Mean slope=0.512±0.317
$\bar{r}$=0.78^{a}
Δ%MCAv
Δ%$P_{ET}CO_2$
60
50
40
30
20
10
-10
-20
-20
-10
10
20
30
40

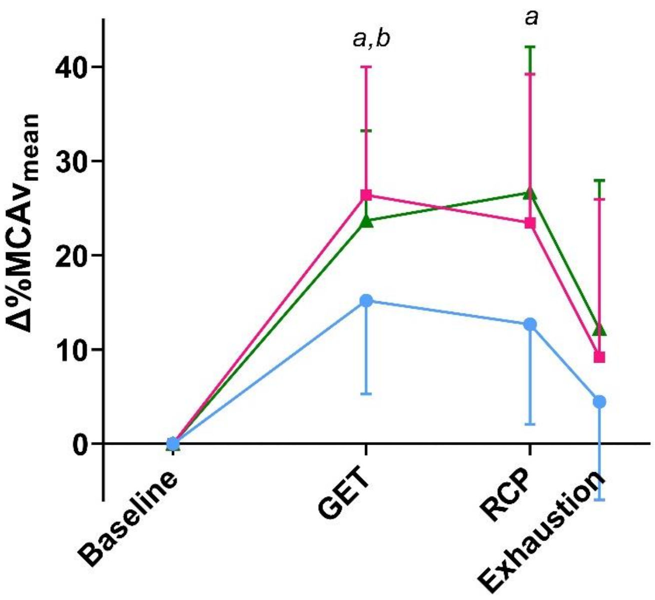
Differences in cerebrovascular regulation and ventilatory responses during ramp incremental cycling in children, adolescents and adults

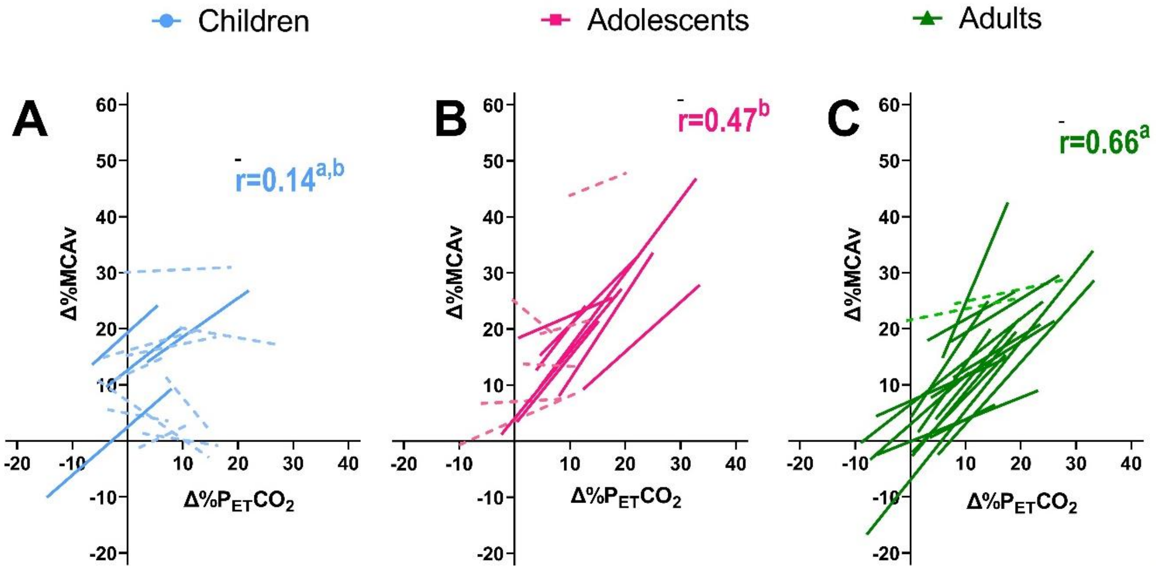
METHODS

14 children (9.4±0.9 y)
14 adolescents (12.4±0.4 y)
19 adults (23.4±2.5 y)

- Ramp incremental cycle test to exhaustion
- Measurements of middle cerebral artery blood velocity (MCAv) and end-tidal CO_2 ($P_{ET}CO_2$)

Results





CONCLUSIONS Increases in cerebral blood flow during exercise were smaller in children compared to adolescents and adults

The regulatory role of $P_{ET}CO_2$ on cerebral blood flow during exercise strengthens during the transition from childhood to adulthood