

# THE UNIVERSITY OF WARWICK

**Original citation:**

Gavlak, J. C., Stocks, J., Lavery, A., Fettes, E., Bucks, R., Sonnappa, S., Cooper, J., Grocott, M. P., Levett, D. Z., Martin, D. S., Imray, C. (Chris) and Kirkham, F. J.. (2013) The Young Everest Study : preliminary report of changes in sleep and cerebral blood flow velocity during slow ascent to altitude in unacclimatised children. Archives of Disease in Childhood, Vol.98 (No.5). pp. 356-362.

**Permanent WRAP url:**

<http://wrap.warwick.ac.uk/53933>

**Copyright and reuse:**

The Warwick Research Archive Portal (WRAP) makes the work of researchers of the University of Warwick available open access under the following conditions.

This article is made available under the Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported (CC BY-NC-ND 3.0) license and may be reused according to the conditions of the license. For more details see: <http://creativecommons.org/licenses/by-nc-nd/3.0/>

**A note on versions:**

The version presented in WRAP is the published version, or, version of record, and may be cited as it appears here.

For more information, please contact the WRAP Team at: [wrap@warwick.ac.uk](mailto:wrap@warwick.ac.uk)

warwick**publications**wrap

highlight your research

<http://go.warwick.ac.uk/lib-publications>



OPEN ACCESS

# The Young Everest Study: preliminary report of changes in sleep and cerebral blood flow velocity during slow ascent to altitude in unacclimatised children

Johanna C Gavlak,<sup>1,2</sup> Janet Stocks,<sup>2</sup> Aidan Laverty,<sup>1</sup> Emma Fettes,<sup>1</sup> Romola Bucks,<sup>3</sup> Samatha Sonnappa,<sup>1,2</sup> Janine Cooper,<sup>4</sup> Michael P Grocott,<sup>5,6,7</sup> Denny Z Levett,<sup>5</sup> Daniel S Martin,<sup>5</sup> Christopher H Imray,<sup>8</sup> Fenella J Kirkham<sup>7,9,10</sup>

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/archdischild-2012-302512>).

For numbered affiliations see end of article

## Correspondence to

Dr Johanna C D Gavlak, Department of Paediatric Respiratory Medicine, Great Ormond Street Hospital for Children NHS Trust, Walrus Ward Level 1, Morgan Stanley Clinical Building, Great Ormond Street, London WC1N 3JH, UK; Johanna.Dingle-Gavlak@gosh.nhs.uk

Received 22 June 2012

Revised 14 December 2012

Accepted 19 December 2012

## ABSTRACT

**Background** Cerebral blood flow velocity (CBFV) and sleep physiology in healthy children exposed to hypoxia and hypocarbia are under-researched.

**Aim** To investigate associations between sleep variables, daytime end-tidal carbon dioxide (EtCO<sub>2</sub>) and CBFV in children during high-altitude ascent.

**Methods** Vital signs, overnight cardiorespiratory sleep studies and transcranial Doppler were undertaken in nine children (aged 6–13 years) at low altitude (130 m), and then at moderate (1300 m) and high (3500 m) altitude during a 5-day ascent.

**Results** Daytime (130 m: 98%; 3500 m: 90%,  $p=0.004$ ) and mean (130 m: 97%, 1300 m: 94%, 3500 m: 87%,  $p=0.0005$ ) and minimum (130 m: 92%, 1300 m: 84%, 3500 m: 79%,  $p=0.0005$ ) overnight pulse oximetry oxyhaemoglobin saturation decreased, and the number of central apnoeas increased at altitude (130 m: 0.2/h, 1300 m: 1.2/h, 3500 m: 3.5/h,  $p=0.2$ ), correlating inversely with EtCO<sub>2</sub> ( $R^2$  130 m: 0.78; 3500 m: 0.45). Periodic breathing occurred for median (IQR) 0.0 (0; 0.3)% (130 m) and 0.2 (0; 1.2)% (3500 m) of total sleep time. At 3500 m compared with 130 m, there were increases in middle (MCA) (mean (SD) left 29.2 (42.3)%,  $p=0.053$ ; right 9.9 (12)%,  $p=0.037$ ) and anterior cerebral (ACA) (left 65.2 (69)%,  $p=0.024$ ; right 109 (179)%;  $p=0.025$ ) but not posterior or basilar CBFV. The right MCA CBFV increase at 3500 m was predicted by baseline CBFV and change in daytime SpO<sub>2</sub> and EtCO<sub>2</sub> at 3500 m ( $R^2$  0.92); these associations were not seen on the left.

**Conclusions** This preliminary report suggests that sleep physiology is disturbed in children even with slow ascent to altitude. The regional variations in CBFV and their association with hypoxia and hypocapnia require further investigation.

## INTRODUCTION

Sleep disordered breathing (SDB) is reported in acclimatised and non-acclimatised adults sleeping at altitude.<sup>1,2</sup> Despite frequent exposure and concerns over developmental effects,<sup>3</sup> there are limited data from children,<sup>2</sup> particularly during slow acclimatisation. Nocturnal breathing is influenced by the delicate chemoreceptor balance affected by sleep stage.<sup>4</sup> The central medullary chemoreceptors respond to hydrogen ion concentration [H<sup>+</sup>], altered by partial pressure of carbon dioxide (pCO<sub>2</sub>) via the cerebrospinal

## What is already known on this topic

- Children have less periodic breathing in sleep than adults, after rapid ascent to 3500 m, despite similar mean and minimum overnight oxygen saturations (SpO<sub>2</sub>) and pCO<sub>2</sub>.
- At sea level, cerebral blood flow velocity (CBFV) is directly dependent on pCO<sub>2</sub>, but in normocarbic adults, CBFV increases at SpO<sub>2</sub><90%.
- Increased CBFV is seen in young children with sleep-disordered breathing, and may reverse in association with improved overnight oxygen saturation after adenotonsillectomy.

## What this study adds

- Low oxygen saturation (SpO<sub>2</sub>) is confirmed in sleeping children at altitude, and periodic breathing is related to pCO<sub>2</sub>.
- SpO<sub>2</sub> and pCO<sub>2</sub> reduction and cerebral blood flow velocity (CBFV) increase at altitude are lower if sea level right middle cerebral artery CBFV is higher, suggesting interaction with hypoxic hyperventilatory response.
- In acute hypoxia, cerebral oxygen delivery is maintained by an increase in CBFV anteriorly, but may fall posteriorly.

fluid (CSF) bicarbonate buffering system, and by changing cerebral blood flow (CBF).<sup>5,6</sup> The carotid body peripheral chemoreceptors respond to pO<sub>2</sub> as well as pCO<sub>2</sub> and pH.<sup>6</sup> There is a hypoxic ventilatory response (HVR) at pO<sub>2</sub> <60 mm Hg, but in place of the normoxic hypercapnic drive, the hyperventilation leads to hypocapnia, reducing the change in pCO<sub>2</sub> required to reach the apnoea threshold,<sup>7</sup> around which oscillations of pulse oximetry oxyhaemoglobin saturation (SpO<sub>2</sub>) and pCO<sub>2</sub> are associated with periodic breathing.<sup>1,8</sup>

Transcranial Doppler (TCD) measurement of change in CBF velocities (CBFV) can assess regional perfusion change.<sup>9</sup> At sea level, with

**To cite:** Gavlak JC, Stocks J, Laverty A, et al. *Arch Dis Child* Published Online First: [please include Day Month Year] doi:10.1136/archdischild-2012-302512

SpO<sub>2</sub>>97%, there is a linear relationship between middle cerebral (MCA) and basilar (BA) CBFV and pCO<sub>2</sub> between 20 and 60 mm Hg,<sup>6 9 10</sup> also mediated via local [H<sup>+</sup>]. However, although CBFV typically increases when SpO<sub>2</sub> is <90%,<sup>11</sup> the response to hypoxia is variable between subjects<sup>12 13</sup> and within subjects, both regionally<sup>12 14 15</sup> and diurnally.<sup>16</sup> Technical advances now allow informative portable physiological recording at altitude, overcoming many prior difficulties in studying healthy children.

The purpose of this Smiths Medical Young Everest Study<sup>17</sup> was to document natural sleep and daytime CBFV after gradual ascent to 3500 m in comparison with data collected at 130 m, to explore the effects of change in daytime end-tidal (Et) pCO<sub>2</sub> and SpO<sub>2</sub> and overnight SpO<sub>2</sub> on sleep physiology and daytime regional cerebral circulation, and to determine if altitude-induced sleep difficulties would impact on episodic memory recall.<sup>18</sup>

## METHODS

Children were recruited from families undertaking a trekking holiday in Nepal<sup>17</sup>; none had recently travelled to altitudes >1000 m. The study was approved by the UCL research ethics committee (ID:0894/001), and informed written assent/consent obtained from children and their parents. Baseline measurements were undertaken by five specialists in paediatric respiratory and sleep physiology/medicine at ≤130 m in England, and during slow graded ascent (5 days from sea level to 3500 m), planned to maximise safety and minimise acute mountain sickness risk.<sup>17 19</sup> Intermediate altitude studies were performed at Kathmandu (1300 m). After flying to Lukla (2670 m), the children trekked for 2 days, sleeping one night at 2650 m and the next at 2835 m, before ascending to Namche Bazaar (3500 m) on the third trek day (day 5 from sea level) where the high-altitude studies were undertaken. With the exception of the sleep studies, recordings were made in a research laboratory setting between 10:00 and 14:00 the day after arrival.<sup>17</sup>

## Sleep studies

Cardiorespiratory sleep studies (LS-100 LifeShirts, Vivometrics, USA) recorded overnight SpO<sub>2</sub>, ECG, body position, and

abdominal and thoracic respiratory effort via inductance plethysmography, but not nasal airflow. Overnight studies were recorded over the first two nights following arrival. Data from the first 6 h of sleep were analysed using paediatric industry standards (eg, 3% oxygen desaturations).

## Daytime recordings of vital signs

Daytime SpO<sub>2</sub>, EtCO<sub>2</sub>, heart rate (HR), Respiratory Rate (RR) (Tidal Wave 710 Monitor, Respironics, Pennsylvania, USA) and blood pressure were recorded.<sup>17</sup>

## Cerebral blood flow velocity

CBFV was measured by JCG and/or FJK, using TCD (EZ-Dop, DWL, Germany) in the BA and right and left MCA and anterior (ACA) and posterior (PCA) cerebral arteries, each located according to a previously described protocol for which the coefficient of variation was 7%.<sup>20</sup> Highest time-averaged maximum mean CBFV (cm/s) was reported over at least six cardiac cycles, analysed blind to subject and altitude. Assuming stable haemoglobin and vessel diameter, proportional change in cerebral oxygen delivery (COD) from baseline at altitude (Alt) compared with sea level (Sea) was calculated using the formula<sup>21</sup>:

$$\text{ChangeCOD} = \frac{[(\text{AltSpO}_2 \times \text{AltCBFV}) - (\text{SeaSpO}_2 \times \text{SeaCBFV})]}{(\text{SeaSpO}_2 \times \text{SeaCBFV})}$$

## Memory

Rivermead Memory Test story recall was used at all three altitudes to determine the ability to recall a short story immediately, and after a delay.<sup>22</sup>

## Statistical analysis

Descriptive statistics are reported at all three altitudes. Variables were examined for normality and non-parametric descriptives and statistical tests selected. Between altitude (130 m, 1300 m, 3500 m) and hemisphere (left, right) comparisons were conducted using paired samples t tests, or Wilcoxon's for two measures, and repeated measures analysis of variance (ANOVA), or

**Table 1** Vital signs and sleep variables

	Sea level (130 m)	Moderate altitude (1300 m)	High altitude (3500 m)	High altitude %Δ from sea	p Value
Mean daytime oxygen saturation (SpO <sub>2</sub> ; %)*	98 (98, 99)	NA	90 (87, 91)†	-9.17 (2.1)	0.004
Mean overnight oxygen saturation (SpO <sub>2</sub> ; %)* ‡	97 (96, 98)	94 (92, 97)†	87(85, 88)† ¶	-11.1 (2.9)	<0.0005
§					
Minimum oxygen saturation (SpO <sub>2</sub> ; %)* ‡	92 (89, 93)	84 (78, 94)*	79 (76, 80)† ¶	-14.4 (7.7)	<0.0005
Number of oxygen desaturations per hour* ‡	0.2 (0, 1.2)	4.9 (2, 12)*	10.0 (4, 22)† ¶		<0.0005
Number of central apnoeas per hour* **	0.2 (0, 1.2)	1.2 (0.7, 3.2)	3.5 (1.1, 5.7)†		0.2
Periodic breathing (% TST)* **	0.0 (0, 0.3)	0 (0, 1.2)	0.2 (0, 1.15)†		0.5
Daytime EtCO <sub>2</sub> (mmHg)	42.7 (40, 45)	NA	36.0 (34, 38)†	-16 (5.1)	0.004
Daytime respiratory rate (breaths per min)	21 (20, 24)	NA	23 (22, 26)†	8.2 (7.0)	0.01
Daytime heart rate (bpm)	78 (72, 85)	NA	97 (87, 109)†	26.7 (16.3)	0.004

\*For the sleep and respiratory variables, transformation did not redress distributional problems, so data are presented as median and IQR (25th and 75th centiles), and were compared using Wilcoxon signed-rank test where there were no data at mid-altitude, or Friedman's ANOVA where data were available at all three altitudes, with posthoc testing using the Wilcoxon signed-rank test. p Values refer to significant change across all three altitudes.

†Significantly different from 130 m.

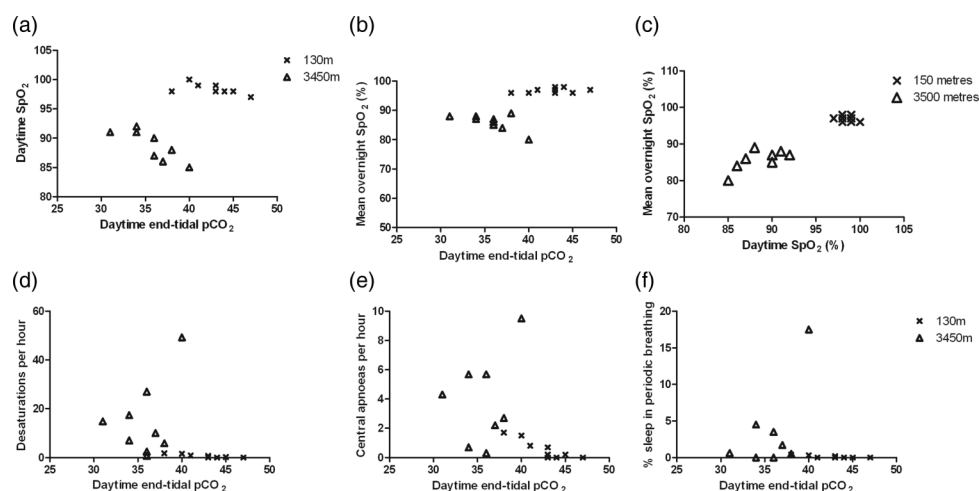
‡(n<sup>2</sup>) for mean overnight oxygen saturation=16.2, for minimum oxygen saturation=13.8 and for number of oxygen desaturations per hour=16.2.

§n=7 at moderate altitude.

¶Significantly different from 1300 m.

\*\*n=3 at moderate altitude, n=8 at high altitude.

EtCO<sub>2</sub>, end-tidal pCO<sub>2</sub>; TST, total sleep time; NA, equipment failure.



**Figure 1** Effect of daytime end-tidal carbon dioxide on other respiratory measurements. (a) Daytime haemoglobin oxygen saturation ( $\text{SpO}_2$ , %); (b) mean overnight  $\text{SpO}_2$ ; (d) number of desaturations per hour; (e) number of central apnoeas per hour; (f) percentage of total sleep time in periodic breathing each plotted against daytime end-tidal partial pressure of carbon dioxide ( $\text{pCO}_2$ ) for the nine children studied at 130 m (crosses) and 3500 m (open triangles); (c) relationship between mean overnight and daytime  $\text{SpO}_2$ . Mean overnight  $\text{SpO}_2$  was significantly correlated ( $R^2$  0.49,  $p=0.035$ ) with daytime values at 3500 m ( $\Delta$ ), whereas there was no correlation ( $R^2$  0.04,  $p=0.626$ ) at 130 m (x).

Friedman's ANOVA for three. Paired t tests or Wilcoxon signed-rank test and an appropriate Bonferroni correction were used for posthoc testing. Linear regression was used to examine the degree of association for continuous variables. Analysis was conducted using SPSS software for Windows (V17, SPSS Inc, Illinois, USA).

## RESULTS

### Participants

Nine children (5 boys) aged 6–13 years (mean age 8.8, SD 2.4), all right-handed and remaining well, were studied.<sup>17</sup> Lung function remained within 7% of sea level baseline in all but two.<sup>17</sup> All sleep studies at 130 m and 3500 m, but only seven at 1300 m, recorded at least 6 h of high-quality data (table 1).

### Respiratory and sleep measures

Mean  $\text{SpO}_2$  was higher during daytime than overnight at 130 m and 3500 m (table 1). With increasing altitude, daytime and overnight mean  $\text{SpO}_2$  and  $\text{EtCO}_2$  decreased (table 1). Daytime RR and HR increased significantly (table 1). Compared with baseline, overnight  $\text{SpO}_2$  decreased significantly, both in terms of overall mean, and in the minimum reached overnight, while the number of oxygen desaturations increased (table 1). Despite no overall difference in the number of central apnoeas or

percentage of total sleep time spent in periodic breathing across the three altitudes, on posthoc testing, there were significant differences between 130 m and 3500 m (table 1). Daytime and mean overnight  $\text{SpO}_2$  were inversely correlated with daytime  $\text{EtCO}_2$  at 3500 m but not at 130 m (figure 1A,B; table 2), while minimum overnight  $\text{SpO}_2$  was weakly positively and inversely correlated with daytime  $\text{EtCO}_2$  at 150 m and 3500 m, respectively (figure 1C). The number of desaturations/hour and percentage of sleep spent in periodic breathing correlated with daytime  $\text{EtCO}_2$  at 130 m but not at 3500 m (figures 1D,F; table 2). The number of central apnoeas/hour was higher in those with lower daytime  $\text{EtCO}_2$  both at 130 and at 3500 m (figure 1E). Mean overnight  $\text{SpO}_2$  (range 80–89%) was significantly correlated ( $R^2$  0.51,  $p=0.03$ ) with daytime values (range 85–92%) at 3500 m, whereas, there was no correlation ( $R^2$  0.04,  $p=0.6$ ) at 130 m.

### Transcranial Doppler

There were significant increases in CBFV in the left MCA and both ACAs at 3500 m compared with 130 m (table 3, figure 2). Left MCA velocities were lower than right at sea level, and increased more at altitude (table 3).<sup>23</sup> There were no significant velocity changes in the PCA or BA. With the exception of the BA, calculated COD increased in all arteries. There was no

**Table 2** Relationship between daytime  $\text{EtCO}_2$ , daytime  $\text{SpO}_2$  and sleep variables at baseline (130 m) and altitude (3500 m)

	130 m				3500 m			
	$R^2$	p Value	$\beta$	Range	$R^2$	p Value	$\beta$	Range
Daytime $\text{SpO}_2$ (%)	0.32	0.1	−0.561	97–100	0.65	0.009	−0.806	85–92
Mean overnight $\text{SpO}_2$ (%)	0.12	0.4	0.353	96–98	0.40	0.066	−0.635	80–89
Minimum overnight $\text{SpO}_2$ (%)	0.46	0.046	0.675	84–94	0.38	0.078	−0.615	60–82
Number of desaturations/hour overnight	0.75	0.003	−0.865	0–1.7	0.16	0.3	0.398	0.7–49.3
Number of central apnoeas/hour overnight	0.78	0.002	−0.882	0–1.7	0.45	0.047	−0.673	0.3–9.5
% total sleep time spent in periodic breathing	0.76	0.017	−0.763	0–0.4	0.27	0.15	−0.159	0–17.5

$\text{EtCO}_2$ , end-tidal partial pressure of carbon dioxide;  $\text{SpO}_2$ , haemoglobin oxygen saturation from pulse oximeter.

**Table 3** Maximum cerebral blood flow velocities (CBFV) and cerebral oxygen delivery (COD) by hemisphere and altitude

		CBFV			COD	
		Sea level (130 m)	Moderate altitude (1300 m) (Kathmandu)	High altitude (3500 m) (Namche Bazaar)		Cerebral oxygen delivery
		Mean (SD) Velocity (cm/sec)	Mean (SD) % Change from low altitude	Mean (SD) % Change from low altitude	Mean (SD) % Change from moderate altitude	Mean (SD) % Change in from low to high altitude
MCA* (n=9)	Left	69.1 (12.5)	35.2 (33.4) <sup>1</sup>	29.2 (42.3) <sup>2</sup>	4.2 (19.3)	18.7 (44.0)
	Right	84.0 (8.4)	7.2 (11.4)	9.9 (12.0)	3.0 (10.9)	1.9 (7.5)
ACA* (n=7)	Left	45.3 (13.2)	43.4 (53.4)	65.2 (69.0) <sup>2</sup>	28.3 (42.7)	47.8 (60.4)
	Right	51.1 (22.4)	94.1 (159.7)	109.1 (179.2) <sup>2</sup>	13.5 (34.4)	41.6 (68.7)
PCA* <sup>5</sup> (n=7)	Left	37.4 (11.2)	40.5 (71.0)	49.9 (75.0)	15.1 (35.4)	34.9 (65.6)
	Right	38.7 (6.2)	21.1 (43.9)	17.5 (33.5)	6.4 (29.4)	12.6 (25.7)
BA* (n=9)		53.2 (12.6)	4.5 (16.4)	9.5 (21.8)	4.9 (14.0)	-1.3 (19.0)

Percentage change in COD was calculated using the following formula:  $((\text{AltSpO}_2 \times \text{AltCBFV}) - (\text{SeaSpO}_2 \times \text{SeaCBFV})) / (\text{SeaSpO}_2 \times \text{SeaCBFV})$  where: AltSpO<sub>2</sub> is the SpO<sub>2</sub> value at altitude; AltCBFV is the CBFV at altitude; SeaSpO<sub>2</sub> is the SpO<sub>2</sub> at sea level; and sea CBFV is the CBFV at sea level, and haemoglobin is assumed to be constant.

There were significant effects of hemisphere,  $F(1,8)=10.66$ ,  $p=0.011$ ,  $\eta^2=0.57$  and of altitude,  $F(2,7)=5.08$ ,  $p=0.043$ ,  $\eta^2=0.59$  on maximum MCA velocities, and a significant interaction,  $F(2,7)=5.33$ ,  $p=0.039$ ,  $\eta^2=0.60$ . Inspection of table 3 reveals that CBFV in the MCA significantly increased at moderate and high altitude, compared with sea level, to a greater degree in the left than in the right hemisphere.

Although inspection of table 3 shows that CBFV appeared to increase within the ACA, both left and right, this just failed to reach significance despite a large effect,  $F(2,5)=5.28$ ,  $p=0.059$ ,  $\eta^2=0.68$ , likely due to the small N, a finding confirmed by posthoc, pairwise comparisons which revealed significant increases in ACA CBFV in both hemispheres from low to high altitude. There were no significant effects of hemisphere or altitude on PCA, and no effect of altitude in the BA, all  $F<2.3$ .

Data are presented as mean or geometric mean (SD), velocities are reported as cm/s; <sup>1</sup>=significant between groups difference between low and moderate altitude; <sup>2</sup>=between low and high altitude.

<sup>3</sup>PCA values were transformed for the analysis using the natural logarithm; however, the mean (SD) values are provided for ease of interpretation.

\*Middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery (PCA), basilar artery (BA).

correlation between change in BA velocity and change in central apnoeas or percentage periodic breathing between 130 and 3500 m.

### Daytime SpO<sub>2</sub> and MCA velocities

An exploratory multiple regression analysis was built to predict right MCA CBFV at 3500 m, entering baseline right MCA CBFV at 130 m (step 1), daytime SpO<sub>2</sub> at 3500 m as a percentage of daytime SpO<sub>2</sub> at 130 m (step 2) and EtCO<sub>2</sub> at 3500 m as a percentage of EtCO<sub>2</sub> at 130 m (step 3). Right MCA CBFV at 130 m was not a significant predictor of right MCA CBFV at 3500 m ( $R^2$  0.2,  $p=0.225$ ). However, a model with right MCA CBFV at 130 m and daytime SpO<sub>2</sub> at 3500 m as a percentage of SpO<sub>2</sub> at 130 m was significant, with both right MCA CBFV at 130 m ( $\beta$  0.91 (95% CI 0.46 to 1.59),  $p=0.004$ ), and change in daytime SpO<sub>2</sub> ( $\beta$  -0.91 B -4 (95% CI -6.7 to -1.9),  $p=0.007$ ), as significant predictors ( $R^2$  change 0.60;  $p=0.006$ ,  $F[2,8]=1.79$ ;  $p=0.008$ ). EtCO<sub>2</sub> at 3500 m as a percentage of EtCO<sub>2</sub> at 130 m also contributed significant variance to right MCA CBFV at 3500 m ( $R^2$  change=0.13;  $p=0.034$ ;  $F[3,8]=20.21$ ;  $p=0.003$ ). Together, these three variables explained 92% of the variance in right MCA CBFV at 3500 m. Change in HR was not a significant predictor. Inspection of the  $\beta$  weights revealed that increase in right MCA CBFV and greater reduction in SpO<sub>2</sub> and EtCO<sub>2</sub> between 130 m and 3500 m significantly predicted right MCA CBFV at 3500 m. Sea level right MCA CBFV was not predictive until SpO<sub>2</sub> changes were entered into the model, consistent with an interaction between individual differences in right MCA CBFV and the degree to which SpO<sub>2</sub> and EtCO<sub>2</sub> were compromised at altitude. The residuals were normally distributed, consistent with good model fit to the data. For left MCA and BA velocities, none of the models were significant.

### Memory

There were no differences between Rivermead scores at the three altitudes.

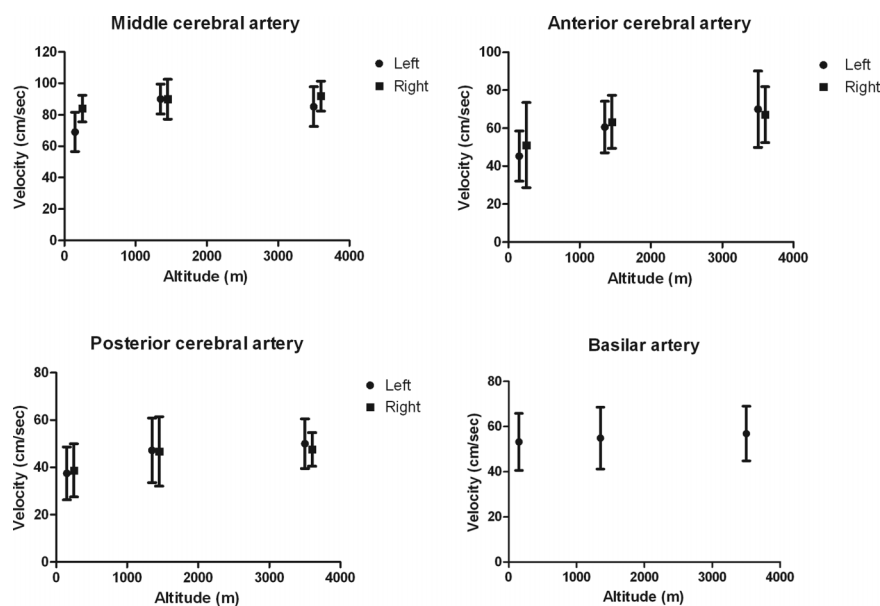
## DISCUSSION

### Respiratory and sleep physiology

Prior to this expedition, data on the effects of altitude on daytime and/or sleep physiology in children sojourning at altitude were lacking. This study appears to show that children have similar physiological responses to altitude as those recorded previously in adults,<sup>1 2</sup> but have less central apnoeas<sup>24</sup> and periodic breathing.<sup>2</sup> The number of central apnoeas, and percentage of periodic breathing in sleep, increased at high altitude, with concurrent increases in the number and severity of oxygen desaturations. EtCO<sub>2</sub> was associated with the number of central apnoeas at 130 m, suggesting that at normoxia in children, the baseline degree of hypocapnia may determine whether the apnoea threshold is reached. At 3500 m, as in adults,<sup>24</sup> the relationship was still significant, but without overnight EtCO<sub>2</sub> measurement, we could not determine the EtCO<sub>2</sub> at which apnoeas were triggered.<sup>2</sup> Daytime HR increased significantly (table 1), consistent with a 24% increase in cardiac output assuming no change in stroke volume.

Our results support previous findings of low nocturnal SpO<sub>2</sub> at altitude in both native<sup>25 26</sup> and non-acclimatised children,<sup>2 27</sup> and illuminate the associated SDB patterns. The severity of hypoxia, hypoventilation and periodic breathing experienced at high altitude exacerbates sleep fragmentation, with recent evidence that hypoxia is the most important factor,<sup>28</sup> but our study is in line with previous literature showing no effect on episodic memory.<sup>29</sup> Mean daytime and overnight SpO<sub>2</sub> decreased at high altitude, despite increases in RR and decreases in EtCO<sub>2</sub> compatible with an intact HVR.

**Figure 2** Velocities in the left and right middle, anterior, posterior and basilar arteries at 130 m, 1350 m and 3500 m in nine children resident at sea level.



### Change in CBFV and COD in anterior and posterior circulations

To our knowledge, this study is the first to examine regional TCD velocities in children unaccustomed to high altitudes in relation to daytime respiratory variables and sleep. Exposure to hypoxia and hypocapnia has conflicting effects on cerebral perfusion. In adults residing at altitude, the cerebral circulation appears less sensitive to hypoxia than to hypocapnia,<sup>30</sup> but CBFV increases with decreasing  $pO_2$  at altitude in adults resident at sea level and in hypoxic adults at sea level, with no evidence for an effect of  $EtCO_2$ .<sup>31–32</sup> In our data, right MCA CBFV was generally higher than left, consistent with increased CBF to a larger hemisphere.<sup>33</sup> Although there was considerable variability,<sup>12</sup> left MCA and both ACA velocities increased, with increased calculated COD even assuming no increase in haemoglobin. However, BA and PCA velocities did not increase significantly.<sup>14</sup> In elite climbers, basilar CBFV reduces at altitude,<sup>13</sup> perhaps allowing build up of  $CO_2$  and, therefore, unstable breathing.<sup>6–34</sup> Although in our data the change in basilar velocity was not associated with change in central apnoeas or periodic breathing, this could be further explored in overnight studies. Calculated COD appears to fall in the basilar distribution on exposure to high altitude,<sup>35</sup> which may be related to reduced metabolic rate, but might increase the risk of compromise to the parieto-occipital cerebellar brain tissues associated with the common complaints of nausea, dizziness, ataxia and visual symptoms.<sup>36</sup>

### Asymmetry in haemodynamic response

In humans native to high altitude, CBFV changes in response to isocapnic hypoxia may show regional brain differences,<sup>12–37–38</sup> but there are few data in children resident at sea level exposed to hypoxic hypoxia. Although we lacked direct measurements of blood gases, the increase in RR and decrease in  $pCO_2$  suggests a response to hypoxia in this study, and there appears to be an interaction between baseline right MCA CBFV and change in day (and night-time)  $SpO_2$  and daytime  $EtCO_2$  in predicting 92% of the variance in high-altitude right MCA CBFV. This is consistent with the interaction between right MCA CBFV and the hypercapnic ventilatory response previously documented at sea level in healthy adults.<sup>5</sup> In turn, this means

that the degree of desaturation and hypocapnia at altitude is less and, therefore, the change in right MCA CBFV is less if right MCA CBFV is higher at sea level. Most adult studies have only reported right MCA CBFV, but Feddersen, who examined the left MCA, also found asymmetry.<sup>39</sup> There is evidence that the right hemisphere controls neural sympathetic outflow, with a possible interaction with  $pCO_2$ ,<sup>40</sup> but the direction and lateralisation of the association we have demonstrated requires further investigation, including direct measurement of blood gases.

### Control of change in CBFV on exposure to hypocapnic hypoxia at altitude

In line with previous data in adults, our data suggest the importance of oxygen content in the regulation of the ACA circulation, so that at altitude, in children resident at sea level, CBF, for which CBFV is a proxy, increases in response to hypoxaemia,<sup>32</sup> even when there is hypocapnia.<sup>30</sup>

### Limitations

MCA diameter may increase on acute exposure to 12% hypoxia or at extreme altitude (>5300),<sup>41</sup> In our study, the children made a slow ascent to 3500 m, and cerebral artery diameters were assumed to be unchanged, as is also the case with  $SpO_2$  as low as 70% at sea level.<sup>38</sup> A change of <10% in arterial diameter was recorded with  $EtCO_2$  as low as 20 mm Hg in adults.<sup>38</sup> Future studies should check the assumption that vascular diameter does not change over these ranges, and should look at regional cerebral perfusion variations and diurnal variation of CBF in relation to  $EtCO_2$  and breathing instability in various sleep stages, determined using EEG, to determine whether clinically relevant differences occur. In addition, recording pH, for instance, in urine, would be important, provided validation compared with blood measurements, which are difficult to justify on ethical grounds, is achieved. In combination with serial CBFV measurements, this would allow exploration of the metabolic compensation to hypocapnia, which occurs in the first 2–3 days after arrival at altitude, involving renal loss of serum bicarbonate, as well as reduction in CSF bicarbonate production, thereby minimising the deviation of arterial and CSF pH.

In summary, our preliminary data confirm that healthy children resident at sea level, and exposed to high altitudes during a slow ascent to 3500 m, experience periodic breathing and further haemoglobin oxygen desaturation during sleep. SpO<sub>2</sub> and EtCO<sub>2</sub> appear to be important determinants of the increase in right-sided MCA CBFV that occurs on exposure to altitude. Despite hypocapnia, this study demonstrates for the first time in children that there is an increase in CBFV at altitude, adequate to preserve COD in the distribution of all vessels but the BA.

#### Author affiliations

- <sup>1</sup>Department of Paediatric Respiratory Medicine, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK  
<sup>2</sup>Portex Respiratory Unit, UCL Institute of Child Health, London, UK  
<sup>3</sup>Department of Psychology, University of Western Australia, Perth, Australia  
<sup>4</sup>Developmental Neuroscience Unit, UCL Institute of Child Health, London, UK  
<sup>5</sup>Centre for Altitude Space and Extreme Environment Medicine, UCL Institute of Child Health, London, UK  
<sup>6</sup>Anaesthesia and Critical Care Research Unit, University Hospitals Southampton NHS Foundation Trust, Southampton, UK  
<sup>7</sup>Department of Clinical and Experimental Sciences, University of Southampton, Southampton, UK  
<sup>8</sup>Department of Vascular Surgery, University Hospitals Coventry and Warwickshire NHS Trust, Warwick Medical School, Coventry, UK  
<sup>9</sup>Neurosciences Units, UCL Institute of Child Health, London, UK  
<sup>10</sup>Department of Child Health, University Hospitals Southampton NHS Foundation Trust, Southampton, UK

**Contributors** JCG collected and analysed the data, and wrote the first draft of the paper. JS designed the study, collected and analysed the data, and edited the draft of the paper. AL collected and analysed the data, and edited the draft of the paper. EF collected and analysed the data, and edited the draft of the paper. RB undertook the final statistical analysis of the data, and edited the draft of the paper. SS collected and analysed the data, and edited the draft of the paper. JC analysed the memory data, and edited the draft of the paper. MPG designed the study, collected and analysed the data, and edited the draft of the paper. DZL designed the study, collected and analysed the data, and edited the draft of the paper. DSM designed the study, collected and analysed the data, and edited the draft of the paper. CHI designed the study, collected and analysed the data, and edited the draft of the paper. FJK designed the analysis and analysed the data, edited the draft of the paper, and acts as guarantor for the data.

**Funding** The Young Everest Study was funded by Smiths Medical.

**Competing interests** None.

**Ethics approval** UCL Research Ethics Committee.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/3.0/>

#### REFERENCES

- Berssenbrugge A, Dempsey J, Iber C, *et al*. Mechanisms of hypoxia-induced periodic breathing during sleep in humans. *J Physiol* 1983;343:507–26.
- Kohler M, Kriemler S, Wilhelm EM, *et al*. Children at high altitude have less nocturnal periodic breathing than adults. *Eur Respir J* 2008;32:189–97.
- Virues-Ortega J, Bucks R, Kirkham FJ, *et al*. Changing patterns of neuropsychological functioning in children living at high altitude above and below 4000 m: a report from the Bolivian Children Living at Altitude (BoCLA) study. *Dev Sci* 2011;14:1185–93.
- Dempsey JA, Veasey SC, Morgan BJ, *et al*. Pathophysiology of sleep apnea. *Physiol Rev* 2010;90:47–112.
- Xie A, Skatrud JB, Morgan B, *et al*. Influence of cerebrovascular function on the hypercapnic ventilatory response in healthy humans. *J Physiol* 2006; 577(Pt 1):319–29.
- Ainslie PN, Duffin J. Integration of cerebrovascular CO<sub>2</sub> reactivity and chemoreflex control of breathing: mechanisms of regulation, measurement, and interpretation. *Am J Physiol Regul Integr Comp Physiol* 2009;296:R1473–95.
- Dempsey JA, Smith CA, Przybylowski T, *et al*. The ventilatory responsiveness to CO<sub>2</sub> (2) below eupnoea as a determinant of ventilatory stability in sleep. *J Physiol* 2004;560(Pt 1):1–11.
- Dempsey JA. Crossing the apnoeic threshold: causes and consequences. *Exp Physiol* 2005;90:13–24.
- Kirkham FJ, Padayachee TS, Parsons S, *et al*. Transcranial measurement of blood velocities in the basal cerebral arteries using pulsed Doppler ultrasound: velocity as an index of flow. *Ultrasound Med Biol* 1986;12:15–21.
- Park CW, Sturzenegger M, Douville CM, *et al*. Autoregulatory response and CO<sub>2</sub> reactivity of the basilar artery. *Stroke* 2003;34:34–9.
- Gupta AK, Menon DK, Czosnyka M, *et al*. Thresholds for hypoxic cerebral vasodilation in volunteers. *Anesth Analg* 1997;85:817–20.
- Noth U, Kotajima F, Deichmann R, *et al*. Mapping of the cerebral vascular response to hypoxia and hypercapnia using quantitative perfusion MRI at 3 T. *NMR Biomed* 2008;21:464–72.
- Jansen GF, Kagenaar DA, Basnyat B, *et al*. Basilar artery blood flow velocity and the ventilatory response to acute hypoxia in mountaineers. *Respir Physiol Neurobiol* 2002;133:65–74.
- Garbin L, Habetswallner F, Clivati A. Vascular reactivity in middle cerebral artery and basilar artery by transcranial Doppler in normals subjects during hypoxia. *Ital J Neurol Sci* 1997;18:135–7.
- Smith KJ, Wong LE, Eves ND, *et al*. Regional cerebral blood flow distribution during exercise: Influence of oxygen. *Respir Physiol Neurobiol* 2012; 184:97–105.
- Meadows GE, O'Driscoll DM, Simonds AK, *et al*. Cerebral blood flow response to isocapnic hypoxia during slow-wave sleep and wakefulness. *J Appl Physiol* 2004;97:1343–8.
- Scruse E, Laverty A, Gavlak JC, *et al*. The Young Everest Study: effects of hypoxia at high altitude on cardiorespiratory function and general well-being in healthy children. *Arch Dis Child* 2009;94:621–6.
- Beebe DW. Neurobehavioral effects of obstructive sleep apnea: an overview and heuristic model. *Curr Opin Pulm Med* 2005;11:494–500.
- Levett DZ, Martin DS, Wilson MH, *et al*. Design and conduct of Caudwell Xtreme Everest: an observational cohort study of variation in human adaptation to progressive environmental hypoxia. *BMC Med Res Methodol* 2010;10:98.
- Padayachee TS, Kirkham FJ, Lewis RR, *et al*. Transcranial measurement of blood velocities in the basal cerebral arteries using pulsed Doppler ultrasound: a method of assessing the Circle of Willis. *Ultrasound Med Biol* 1986;12:5–14.
- Imray CH, Myers SD, Pattinson KT, *et al*. Effect of exercise on cerebral perfusion in humans at high altitude. *J Appl Physiol* 2005;99:699–706.
- Aldrich FK, Wilson B. Rivermead Behavioural Memory Test for Children (RBMT-C): a preliminary evaluation. *Br J Clin Psychol* 1991;30(Pt 2):161–8.
- Vavilala MS, Kincaid MS, Muangman SL, *et al*. Gender differences in cerebral blood flow velocity and autoregulation between the anterior and posterior circulations in healthy children. *Pediatr Res* 2005;58:574–8.
- Burgess KR, Johnson PL, Edwards N. Central and obstructive sleep apnoea during ascent to high altitude. *Respirology* 2004;9:222–9.
- Gamponia MJ, Babaali H, Yugar F, *et al*. Reference values for pulse oximetry at high altitude. *Arch Dis Child* 1998;78:461–5.
- Vazquez JC, Montes FM, Rivera CA, *et al*. Clinical predictors of sleep disordered breathing in children at moderate altitude. *Arch Med Res* 2004;35:525–31.
- Yaron M, Waldman N, Niermeyer S, *et al*. The diagnosis of acute mountain sickness in preverbal children. *Arch Pediatr Adolesc Med* 1998; 152:683–7.
- Nussbaumer-Ochsner Y, Ursprung J, Siebenmann C, *et al*. Effect of short-term acclimatization to high altitude on sleep and nocturnal breathing. *Sleep* 2012;35:419–23.
- Thomas RJ, Tamisier R, Boucher J, *et al*. Nocturnal hypoxia exposure with simulated altitude for 14 days does not significantly alter working memory or vigilance in humans. *Sleep* 2007;30:1195–203.
- Norcliffe LJ, Rivera-Ch M, Claydon VE, *et al*. Cerebrovascular responses to hypoxia and hypocapnia in high-altitude dwellers. *J Physiol* 2005;566 (Pt 1):287–94.
- Ainslie PN, Burgess K, Subedi P, *et al*. Alterations in cerebral dynamics at high altitude following partial acclimatization in humans: wakefulness and sleep. *J Appl Physiol* 2007;102:658–64.
- Baumgartner RW, Bartsch P, Maggiorini M, *et al*. Enhanced cerebral blood flow in acute mountain sickness. *Aviat Space Environ Med* 1994; 65:726–9.
- Carne RP, Vogrin S, Litewka L, *et al*. Cerebral cortex: an MRI-based study of volume and variance with age and sex. *J Clin Neurosci* 2006;13:60–72.
- Xie A, Skatrud JB, Barci SR, *et al*. Influence of cerebral blood flow on breathing stability. *J Appl Physiol* 2009;106:850–6.
- Brothers MD, Wilber RL, Byrnes WC. Physical fitness and hematological changes during acclimatization to moderate altitude: a retrospective study. *High Alt Med Biol* 2007;8:213–24.
- Wilson MH, Newman S, Imray CH. The cerebral effects of ascent to high altitudes. *Lancet Neurol* 2009;8:175–91.

- 37 Binks AP, Cunningham VJ, Adams L, *et al.* Gray matter blood flow change is unevenly distributed during moderate isocapnic hypoxia in humans. *J Appl Physiol* 2008;104:212–17.
- 38 Willie CK, Macleod DB, Shaw AD, *et al.* Regional brain blood flow in man during acute changes in arterial blood gases. *J Physiol* 2012;590(Pt 14):3261–75.
- 39 Feddersen B, Ausserer H, Neupane P, *et al.* Right temporal cerebral dysfunction heralds symptoms of acute mountain sickness. *J Neural* 2007;254:359–63.
- 40 Diedrich A, Porta A, Barbic F, *et al.* Lateralization of expression of neural sympathetic activity to the vessels and effects of carotid baroreceptor stimulation. *Am J Physiol Heart Circ Physiol* 2009;296:H1758–65.
- 41 Wilson MH, Edsell ME, Davagnanam I, *et al.* Cerebral artery dilatation maintains cerebral oxygenation at extreme altitude and in acute hypoxia—an ultrasound and MRI study. *J Cereb Blood Flow Metab* 2011;31:2019–29.





## The Young Everest Study: preliminary report of changes in sleep and cerebral blood flow velocity during slow ascent to altitude in unacclimatised children

Johanna C Gavlak, Janet Stocks, Aidan Laverty, et al.

*Arch Dis Child* published online March 7, 2013  
doi: 10.1136/archdischild-2012-302512

---

Updated information and services can be found at:  
<http://adc.bmj.com/content/early/2013/03/06/archdischild-2012-302512.full.html>

---

*These include:*

- |                               |   |
|-------------------------------|---|
| <b>References</b>             | This article cites 41 articles, 19 of which can be accessed free at:<br><a href="http://adc.bmj.com/content/early/2013/03/06/archdischild-2012-302512.full.html#ref-list-1">http://adc.bmj.com/content/early/2013/03/06/archdischild-2012-302512.full.html#ref-list-1</a>   |
| <b>Open Access</b>            | This is an open-access article distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. See:<br><a href="http://creativecommons.org/licenses/by-nc/3.0/">http://creativecommons.org/licenses/by-nc/3.0/</a> and<br><a href="http://creativecommons.org/licenses/by-nc/3.0/legalcode">http://creativecommons.org/licenses/by-nc/3.0/legalcode</a> |
| <b>P&lt;P</b>                 | Published online March 7, 2013 in advance of the print journal.   |
| <b>Email alerting service</b> | Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.  |
- 

---

Advance online articles have been peer reviewed, accepted for publication, edited and typeset, but have not yet appeared in the paper journal. Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include the digital object identifier (DOIs) and date of initial publication.

---

To request permissions go to:  
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:  
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:  
<http://group.bmj.com/subscribe/>

**Topic  
Collections**

Articles on similar topics can be found in the following collections

[Open access](#) (39 articles)  
[Airway biology](#) (146 articles)

---

**Notes**

---

Advance online articles have been peer reviewed, accepted for publication, edited and typeset, but have not yet appeared in the paper journal. Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include the digital object identifier (DOIs) and date of initial publication.

---

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>