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Effect of exercise on cerebral perfusion in humans at high altitude

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Imray, C. H. E., S. D. Myers, K. T. S. Pattinson, A. R. Bradwell, C. W. Chan, S. Harris, P. Collins, A. D. Wright, and the Birmingham Medical Research Expeditionary Society. Effect of exercise on cerebral perfusion in humans at high altitude. *J Appl Physiol* 99: 699–706, 2005. First published May 26, 2005; doi:10.1152/japplphysiol.00973.2004.—The effects of submaximal and maximal exercise on cerebral perfusion were assessed using a portable, recumbent cycle ergometer in nine unacclimatized subjects ascending to 5,260 m. At 150 m, mean (SD) cerebral oxygenation (rSo_2%) increased during submaximal exercise from 68.4 (SD 2.1) to 70.9 (SD 3.8) ($P < 0.0001$) and at maximal oxygen uptake ($\dot{V}o_{2 max}$) to 69.8 (SD 3.1) ($P < 0.02$). In contrast, at each of the high altitudes studied, rSo_2 was reduced during submaximal exercise from 66.2 (SD 2.5) to 62.6 (SD 2.1) at 3,610 m ($P < 0.0001$), 63.0 (SD 2.1) to 58.9 (SD 2.1) at 4,750 m ($P < 0.0001$), and 62.4 (SD 3.6) to 61.2 (SD 3.9) at 5,260 m ($P < 0.01$), and at $\dot{V}o_{2 max}$ to 61.2 (SD 3.3) at 3,610 m ($P < 0.0001$), to 59.4 (SD 2.6) at 4,750 m ($P < 0.0001$), and to 58.0 (SD 3.0) at 5,260 m ($P < 0.0001$). Cerebrovascular resistance tended to fall during submaximal exercise ($P =$ not significant) and rise at $\dot{V}o_{2 max}$, following the changes in arterial oxygen saturation and end-tidal CO_2. Cerebral oxygen delivery was maintained during submaximal exercise at 150 m with a nonsignificant fall at $\dot{V}o_{2 max}$, but at high altitude peaked at 30% of $\dot{V}o_{2 max}$ and then fell progressively at higher levels of exercise. The fall in rSo_2 and oxygen delivery during exercise may limit exercise at altitude and is likely to contribute to the problems of acute mountain sickness and high-altitude cerebral edema.

maximal oxygen uptake; cerebral oxygenation; cerebral blood flow; cerebrovascular resistance; cerebral oxygen delivery

ALTERED CEREBRAL FUNCTION on ascent to altitude was part of the first description of mountain sickness in 1913 (40), and acute mountain sickness (AMS) and high-altitude cerebral edema (HACE) have been shown to be potentially serious clinical conditions that may occur on acute exposure to altitudes above 2,500–3,000 m. Exercise at altitude causes further decreases in arterial oxygenation and so may exacerbate cerebral hypoxia. However, the fall in arterial saturation that occurs during exercise at high altitude (14) might not affect cerebral oxygenation to the same extent as it does in peripheral tissues due to a compensatory increase in cerebral blood flow (24). Nevertheless, avoidance of strenuous exercise during ascent, and on arrival at altitude, is standard advice for reducing the risk of AMS and HACE. Evidence from clinical studies is conflicting. Higher AMS symptom scores were found in subjects exercising four times a day for 30 min at 50% of their altitude-specific maximal oxygen consumption ($\dot{V}o_{2 max}$), compared with no exercise, in a chamber study at simulated altitude of 4,800 m (41). Another study of mountaineers, however, showed that physical fitness and exercise intensity during ascent to 4,559 m were of minor importance for the development of AMS (3). It is also possible that other neurological conditions falling outside the usual definition of altitude sickness (2) could be related to exercise.

Near-infrared cerebral spectroscopy and transcranial Doppler measurement of middle cerebral artery (MCA) blood velocity offer continuous noninvasive assessments of cerebral perfusion. Cerebral spectroscopy has been shown to track changes in jugular venous bulb saturations in healthy volunteers under conditions of isocapnic hypoxia (12) and has also been validated by comparison with PET scanning, with ^{133}Xe washout methods and with internal carotid artery stump pressures (54). We have used this technique during dynamic studies of cerebral oxygenation at altitude and assessed the effects of hyperventilation, oxygen therapy, and CO_2 supplementation (19, 20) and during assessment of the effects of pressurization in a portable hyperbaric chamber (21). Assessments of cerebral blood flow and cerebral oxygenation during exercise and under field conditions have proven challenging. The standard, upright exercise cycle results in excessive head movement and use of arms, particularly as one approaches maximal exercise. To overcome these difficulties, we built a portable, recumbent exercise ergometer (Alticycle) for undertaking cerebral perfusion measurements in the field.

This study aimed to measure changes in cerebral perfusion at rest and during exercise up to $\dot{V}o_{2 max}$ at altitudes from 150 to 5,260 m to gain further insight into the factors that limit exercise and alter cerebral function on acute exposure to high altitude.

MATERIALS AND METHODS

Subjects. Eleven healthy white Europeans (1 woman; ages 32–65 yr) were studied. All were nonsmokers, normotensive, on no medication, physically fit, living at 50–150 m, with no recent exposure to high altitude, and were familiar with cycle ergometer-based exercise tests. Measurements were recorded at Birmingham, UK (150 m) and during an expedition to Bolivia. The first measurement at high altitude was made 24–36 h after arrival at 3,610 m (La Paz). Two subjects were subsequently excluded from the study because of excessive rises of blood pressure during exercise at this altitude. The group then

traveled by road, and repeat measurements were made on the remaining nine subjects 24–36 h after arrival at 4,750 m (Refugio Potosi) and 5,260 m, (ski station, Chacaltaya). All measurements at high altitude were therefore completed within 9 days of arrival in Bolivia. Barometric pressure was obtained from the mean of four portable barometers (Suunto Observer, Helsinki, Finland).

Alticycle. The Alticycle cycle ergometer has four novel features (Fig. 1). First, the cycling position is fully supine. The body of the subject is held by shoulder straps and a waist belt to the alticycle frame. The head, resting freely in a stable position, is isolated from the main body of the alticycle, and the arms are free. Second, the exercise load is provided by a friction brake applied to a 2-kg flywheel linked through a series of gears that allows it to rotate between 4,000 and 5,000 revolutions/min. This combination provides good inertia for cycling but with minimal weight. Third, power output and cadence are measured via a strain-gauged crank set assessing torque and cadence (Schoberer Rad Meβtechnik, Jülich, Germany). Power is measured directly in Watts on a second-by-second basis. Fourth, it folds into a self-contained compact backpack-style unit ($81 \times 37 \times 24$ cm, weight 25 kg), allowing it to be carried by a single person.

Exercise tests. Subjects completed two tests at each altitude. A $\dot{V}O_{2\,max}$ test was undertaken first, followed by a submaximal test on the same day separated by a minimum interval of 4 h. Subjects rested for one-half hour before each test and then exercised gently for 5 min at 50 W to warm up. Subjects maintained a cadence rate of 55 pedal revolutions/min for each test. For the maximal test, starting loads for each subject were estimated to produce a test lasting ~10 min (53). The load was increased by 20-W increments per minute up to volitional exhaustion. In the submaximal test, subjects were required to complete 15 min of cycling comprising three 5-min, consecutive exercise periods at 30, 50, and 70% of the power of the altitude-specific $\dot{V}O_{2\,max}$, respectively.

Expired gas was analyzed breath by breath using a Cosmed K4b^2 portable gas-exchange unit (Cosmed, Rome, Italy) for oxygen uptake ($\dot{V}O_2$; photometric gas analyzer), end-tidal CO_2 (infrared absorption), and minute volume (turbine flowmeter). The Cosmed K4b^2 was chosen for its portability and performance at high altitude (6), which has been confirmed subsequently by the authors (36). Gases were collected via a tight-fitting Cosmed-modified Hans Rudolph facemask. Finger-pulse oximetry (arterial oxygen saturation) was measured using an Ohmeda Biox 3740 Pulse Oximeter (Ohmeda). Continuous beat-to-beat blood pressure was measured using the radial artery tonometry technique with a COLIN CBM-7000 monitor (ScanMed Medical Instruments, Moreton-in-the-Marsh, UK), and mean blood pressure was calculated from the formula mean blood pressure = diastolic blood pressure + 1/3(systolic blood pressure − diastolic blood pressure). Predicted heart rates at $\dot{V}O_{2\,max}$ were calculated using the formula 220 − age (yr).

Cerebral hemodynamics. MCA blood velocity was measured using a 2-MHz, pulsed-wave, range-gated Doppler ultrasound (DWL Multi-Dop T1, DWL Elektronische Systeme, Singen, Germany). The MCA time-averaged mean velocity (cm/s) was recorded electronically. A single, experienced operator performed the measurements by insonating the right MCA through the temporal bone window with the subject at rest. The insonation depth was initially set at 50 mm and then gradually increased to identify the optimal signal. Once found, the position was fixed using a locking headband, which allowed the subject to cycle freely. Occasionally, it was necessary to optimize the signal manually during a test by adjusting the direction but not the depth of the beam.

Cerebral regional oxygenation (rSO_2) was measured by continuous, noninvasive, near-infrared cerebral spectroscopy. The Critikon 2020 (Johnson and Johnson Medical, Newport, UK) spectroscope is based on a two-channel sensor and a coupling compensation system. Infrared light is emitted at four wavelengths (776.5, 819.0, 871.4, and 908.7 nm) from a light-emitting diode, and two silicon photodiode detectors are set 10 and 37 mm from the light-emitting diode. The absolute concentrations of oxyhemoglobin (in μM) and deoxyhemoglobin (in μM) are calculated from a modified version of the Beer-Lambert law. The dual detector sensor position was standardized over the right frontoparietal region of the head with sensor margins 3 cm from the midline and 3 cm above the supraorbital crest, taking care to avoid the sagittal and frontal sinus areas (18). The measurement of rSO_2 was calculated from the equation rSO_2 = (oxygenated hemoglobin/total hemoglobin) $\times$ 100.

Statistical analyses. Data was collected continuously by logging it to the DWL Multi-Dop T1. Offline analysis was subsequently undertaken. All data are reported as mean and standard deviation (SD) unless indicated otherwise. Resting measurements were taken immediately before the $\dot{V}O_{2\,max}$ test at each altitude. Heart rate, mean blood pressure, arterial saturation, end-tidal P_{CO_2}, minute volume, $\dot{V}O_2$, MCA blood velocity, cerebral deoxygenation, cerebral oxygenation, total hemoglobin, and rSO_2 were taken from a mean of the three last readings (−20, −10, and 0 s) at each level of exercise. Cerebrovascular resistance (CVR_{est}) was calculated using the formula CVR_{est} = mean arterial blood pressure/MCA blood velocity (26, 44), and cerebral oxygen delivery using the formula cerebral oxygen delivery = arterial oxygen saturation $\times$ MCV blood velocity (33).

The significance of changes occurring in resting measurements during ascent and changes in measurements during submaximal exercise were assessed by repeated-measures ANOVA (StatView for Windows, Abacus Concepts, Berkley, CA) with difference located using Tukey's honestly significant different post hoc test. Resting and $\dot{V}O_{2\,max}$ data were compared using paired *t*-tests. *P* values of <0.05 were considered significant.
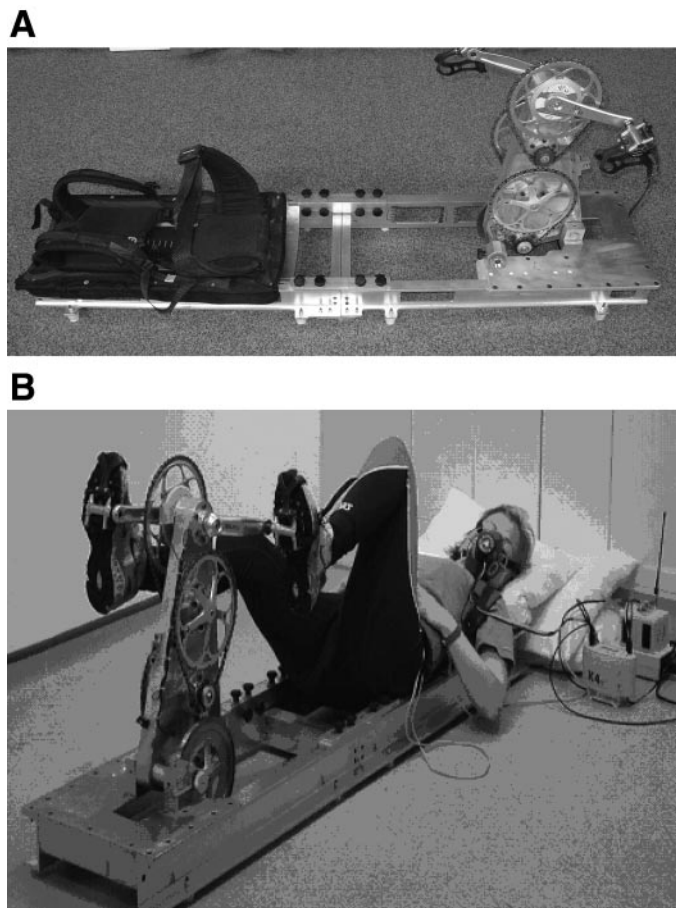

Fig. 1. *A*: Alticycle. *B*: Alticycle in use.

Table 1. *Environmental measurements and subject characteristics for each altitude*

	Altitude, m			
	150	3,610	4,750	5,260
Atmospheric pressure, mmHg	743	496	435	410
Ambient temperature, °C	23.6	24.9	14.6	14.3
Body mass, kg	81.1 (9.7)	81.6 (9.7)	82.5 (10.3)	82.5 (10.9)
Height, cm	181.1 (5.1)			
Body mass index, kg/m^2	25.4 (2.9)			

Data are means (SD); $n = 9$. Body mass did not alter significantly during ascent.

The Research and Ethics Committee of the South Birmingham Health Authority granted approval for the studies, and subjects gave their written, informed consent.

RESULTS

No technical difficulties were experienced with the pulse oximeter or the Alticycle. The signal from the Colin blood pressure monitor occasionally required optimization by adjusting the sensor position over the radial artery, and this was a particular problem with the recordings at 5,260 m. The K4b^2 needed to be carefully cleared of condensation before each test. When using an early version of the Alticycle, background rumble interfered with the transcranial Doppler recordings when subjects exercised close to $\dot{V}O_{2\,max}$. Interference was eliminated initially using a 100-MHz filter. Although this was satisfactory, the Alticycle was adapted for all experimental data reported in this paper with a rubber interface placed between the joints of the Alticycle and the subject's head being supported independently of the ergometer by a firm pillow, removing the need for the 100-MHz filter. Good signals from the cerebral spectroscopy probe were maintained by careful cleaning of the forehead and probe with ethanol. Mean (SD) heart rate recorded at $\dot{V}O_{2\,max}$ was 90% (SD 7) of predicted of 150 m at 3,610 m, 81% (SD 5) of predicted at 4,750 m, and 74% (SD 4) at 5,260 m.

Environmental measures and subject characteristics for each altitude are listed in Table 1. Body mass did not change

significantly during the study. Resting and exercise cardiorespiratory data are shown in Table 2 and cerebral perfusion data in Table 3 and Figs. 2–5. With increasing altitude, resting heart rate, mean blood pressure, total hemoglobin, and oxyhemoglobin did not change (Table 2). Resting arterial oxygen saturation and end-tidal P_{CO_2} decreased at all altitudes compared with 150 m ($P < 0.0001$ for both) (Table 2). Resting $\dot{V}O_2$ increased at all altitudes compared with 150 m ($P < 0.05$). Resting ventilation also increased significantly at 4,750 m ($P < 0.05$) and 5,260 m ($P < 0.001$). Resting MCA blood velocity increased from 60.2 cm/s (SD 14.1) at 150 m to 73.4 cm/s (SD 20.4) at 5,260 m ($P < 0.05$), and resting rSO_2 decreased from 68.4% (SD 2.1) at 150 m to 62.4% (SD 3.6) at 5,260 m ($P < 0.0001$) (Table 3). There was no difference in resting CVR_{est} or cerebral oxygen delivery between the different altitudes (Fig. 2).

Exercise at 150 m (Tables 2 and 3). Mean arterial blood pressure did not change significantly during exercise. Oxygen saturation was unchanged during submaximal exercise but fell at $\dot{V}O_{2\,max}$ ($P < 0.0001$). End-tidal CO_2 was unchanged during submaximal exercise but was reduced from 36.3 Torr (SD 4.7) resting to 33.1 Torr (SD 5.3) at $\dot{V}O_{2\,max}$ ($P < 0.05$). Ventilation and $\dot{V}O_2$ rose progressively during both submaximal and $\dot{V}O_{2\,max}$ tests ($P < 0.0001$). MCA blood velocity rose initially but fell at the highest workloads with an increase from 60.2 cm/s (SD 4.1) at rest to 65.5 cm/s (SD 12.9) at 70% $\dot{V}O_{2\,max}$ ($P < 0.05$) and a reduction to 50.5 cm/s (SD 22.3) at $\dot{V}O_{2\,max}$

Table 2. *Cardiorespiratory data during exercise at different altitudes*

	150 m					3,610 m					4,750 m					5,260 m				
	Rest	30%	50%	70%	$\dot{V}O_{2max}$	Rest	30%	50%	70%	$\dot{V}O_{2max}$	Rest	30%	50%	70%	$\dot{V}O_{2max}$	Rest	30%	50%	70%	$\dot{V}O_{2max}$
Heart rate, beats/min	68	98	119	133	164	78	124	132	148	142	78	108	121	134	135	72	92	107	118	130
	(14)	(9.3)[a]	(13.1)[a]	(13.4)[a]	(9)	(10)	(9)	(7)	(8)	(27)	(12)	(9)	(8)	(8)	(11)	(12)	(24)	(22)	(18)	(5)
Mean BP, mmHg	106	112	115	120	112	107	123	130	138	123	107	114	122	128	122	108	109	116	126	107
	(12)	(9)	(12)	(11)	(18)	(20)	(12)	(14)	(17)	(19)	(13)	(13)	(17)	(15)[b]	(15)[c]	(14)	(8)	(9)	(12)[c]	(14)
Oxygen, saturation %	99.0	98.6	98.1	97.1	94.9	89.5	83.7	81.9	80.6	83.1	82.3	73.76	71.2	71.6	74.1	81.8	68.9	69.9	72.1	74.6
	(0.8)[e]	(0.5)	(0.8)	(0.7)	(2.8)[e]	(4.7)[e]	(5.1)	(4.1)	(4.2)[e]	(11.5)[e]	(4.6)[e]	(8.5)	(8.5)	(6.1)	(9.3)	(4.7)[e]	(15.1)	(8.6)	(4.4)[e]	(5)[e]
End-tidal P_{CO_2}, Torr	36.2	38.6	38.4	37.3	33.1	25.0	29.7	23.4	21.1	19.3	24.1	24.1	22.3	20.9	19.0	21.5	23.7	21.4	19.4	14.9
	(4.7)	(3.7)	(3.8)	(4.6)	(5.3)[b]	(1.8)[d]	(12.2)	(2.2)	(2.4)[d]	(1.7)[e]	(1.8)[d]	(2.6)	(2.8)	(2.3)[e]	(2.7)[e]	(2.9)[d]	(2.1)	(1.8)	(1.9)[d]	(2)[e]
Ventilation, l/min	12.9	37.8	56.4	78.3	127	20.7[b]	44.8	80.1	111	138	24.0[b]	45.6	76.8	112.9	147	30.7[b]	45.3	79.1	106.5	145
	(2.2)	(4.9)	(8.1)	(9.9)	(25.4)	(6.1)	(9.9)	(21.5)	(18.5)	(24)	(5.3)	(9.6)	(18.5)	(22.4)	(35)	(5.6)	(13)	(13.1)	(16.6)	(26.8)
$\dot{V}O_2$, ml·min^{-1}·kg^{-1}	5.7	19.9	28.2	36.6	43	10.7	18.5	29.1	32.8	35.4	10.9	17.1	25.4	31.7	36.4	11.0	18.3	25.8	29.4	37.0
	(1.5)	(1.4)	(3.3)	(4.1)	(7.7)	(6.1)	(4.2)	(7.3)	(9.5)	(6.3)	(5.4)[b]	(3.5)	(6.5)	(6.1)	(8.5)	(1.0)[d]	(8.5)	(6.9)	(6.7)	(7.8)

Data are means (SD) for the 9 subjects completing the study; [a]$n = 7$. Differences are reported between altitudes for resting values and for exercise at each altitude; 70% maximal oxygen uptake ($\dot{V}O_{2max}$) and $\dot{V}O_{2max}$ are compared with rest. BP, blood pressure; $\dot{V}O_2$, oxygen uptake. Significant differences: [b]$P < 0.05$; [c]$P < 0.01$; [d]$P < 0.001$; [e]$P < 0.0001$.

Table 3. *Cerebral perfusion data during exercise at different altitudes*

	150 m					3,610 m					4,750 m					5,260 m				
	Rest	30%	50%	70%	$\dot{V}_{O_{2max}}$	Rest	30%	50%	70%	$\dot{V}_{O_{2max}}$	Rest	30%	50%	70%	$\dot{V}_{O_{2max}}$	Rest	30%	50%	70%	$\dot{V}_{O_{2max}}$
MCA blood velocity, cm/s	60.2 (14.1)	66.1 (12.5)	69.4 (14.9)	65.5 (12.9)§	50.5 (22.3)*	64.5 (14.1)	76.1 (13.8)	71.7 (13.8)	66 (17.3)§	50.6 (21.7)§	66.6 (20.5)	87.2 (25.7)	83.4 (20.9)	78.7 (20.7)§	58.6 (19.4)§	73.4 (20.4)*	81 (28.6)	83.3 (24.7)	81 (19.6)	67.1 (16.3)§
Cerebral HbDO₂, μM	33.6 (6.2)	35 (5.4)	34.8 (4.9)	34.6 (3.3)	33.9 (6.6)	34.7 (5.2)	39.3 (4.4)	41.7 (4.6)	44.4 (5.4)	44.0 (6.8)	40.6 (4.5)	48.6 (6.6)	50.7 (6.1)	54.9 (6.9)	47.6 (6.4)	41.2 (3.9)	42 (4.9)	45.5 (3.9)	49.2 (8.6)	47.7 (5.8)
Cerebral HbO₂, μM	77 (12.4)	76.4 (19.3)	80.3 (21.7)	83.2 (22.6)	77.3 (15.8)	70.2 (14.6)	75.5 (10.1)	77.8 (10.7)	79.7 (10.5)	76.6 (18.3)	72.1 (17.1)	77.9 (13.2)	80 (13.6)	81.7 (16.4)	77.4 (23.6)	68.3 (11.9)	64.5 (13.3)	68.9 (8.8)	71.8 (7.9)	65.7 (10.7)
Cerebral total Hb, μM	104.7 (22.6)	109.4 (21.5)	111.9 (21)	114.6 (21.3)	108.2 (24.9)	107.6 (21.5)	114.6 (14.1)	118.2 (14.8)	122 (15.7)	112 (27)	11.0 (15.4)	126 (18.5)	131.5 (18.9)	134.6 (21.9)	114.7 (16.6)	110 (15.4)	103 (26)	110 (22.1)	113 (19.5)	116 (20.8)
Cerebral oxygenation, %	68.4 (2.1)	68.6 (2.6)	69.9 (3.4)	70.9 (3.8)§	69.8 (3.1)*	66.2 (2.5)	64.6 (2.5)	63.7 (1.8)	62.6 (2.1)§	61.2 (3.3)§	63 (2.1)	61.4 (2.2)	60.6 (2.0)	58.9 (2.1)§	59.4 (2.6)	62.4 (3.6)	57.9 (10.1)	60.1 (4.4)	61.2 (3.9)‡	58 (3.0)

Data are means (SD) for the 9 subjects completing the study. MCA, middle cerebral artery; HbDO₂, deoxyhemoglobin; HbO₂, oxyhemoglobin. Differences are reported between altitudes for resting values and for exercise at each altitude; 70% $\dot{V}_{O_{2max}}$ and $\dot{V}_{O_{2max}}$ are compared with rest. Significant differences: *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$; §$P < 0.0001$.

($P < 0.01$) (Fig. 2). rS_{O_2} increased from 68.4% (SD 2.1) at rest to 70.9% (SD 3.8) during submaximal exercise ($P < 0.0001$) and to 69.8% (SD 3.1) at $\dot{V}_{O_2\,max}$ ($P < 0.05$) (Fig. 3). CVR_{est} and cerebral oxygen delivery were not significantly different between resting and $\dot{V}_{O_2\,max}$ (Figs. 4 and 5).

Exercise at 3,610 m (Table 2 and 3). Mean arterial blood pressure did not change significantly during exercise. Arterial oxygen saturations were reduced at all levels of exercise compared with baseline ($P < 0.0001$). End-tidal CO_2 during submaximal exercise rose initially but was reduced from 24.9 Torr (SD 1.7) at rest to 21.1 Torr (SD 2.4) at 70% $\dot{V}_{O_2\,max}$ ($P < 0.001$) and to 19.3 Torr (SD 1.7) at $\dot{V}_{O_2\,max}$ ($P < 0.0001$). Ventilation and $\dot{V}_{O_2}$ rose progressively during the tests ($P < 0.0001$). MCA blood velocity rose initially and fell with maximal exercise, with an increase from 64.5 cm/s (SD 14.1) at rest to 66.0 cm/s (SD 17.3) at 70% $\dot{V}_{O_2\,max}$ ($P < 0.0001$) and a reduction to 50.6 cm/s (SD 21.7) at $\dot{V}_{O_2\,max}$ ($P < 0.0001$) (Fig. 2). rS_{O_2} was reduced from 66.2% (SD 2.5) at rest to

62.6% (SD 2.1) during submaximal exercise ($P < 0.0001$) and to 61.2% (SD 3.3) at $\dot{V}_{O_2\,max}$ ($P < 0.0001$) (Fig. 3). There was a rise in CVR_{est} from 1.7 (SD 0.41) at rest to 2.16 (SD 0.57) at $\dot{V}_{O_2\,max}$ ($P < 0.05$) (Fig. 4) and a fall in cerebral oxygen delivery from 5,811 (SD 1,419) at rest to 4,665.6 (SD 1,324) at $\dot{V}_{O_2\,max}$ ($P < 0.01$) (Fig. 5).

Exercise at 4,750 m (Tables 2 and 3). Mean arterial blood pressure increased from 107 mmHg (SD 13) to 128 mmHg (SD 15) during submaximal exercise ($P < 0.05$) and remained elevated at $\dot{V}_{O_2\,max}$ compared with resting ($P < 0.001$). End-tidal CO_2 rose initially but was reduced from 23.7 mmHg (SD 2.0) at rest to 20.9 mmHg (SD 2.3) at 70% $\dot{V}_{O_2\,max}$ ($P < 0.0001$) and to 19.0 mmHg (SD 2.7) at $\dot{V}_{O_2\,max}$ ($P < 0.0001$). Ventilation and $\dot{V}_{O_2}$ rose progressively during the tests ($P <$
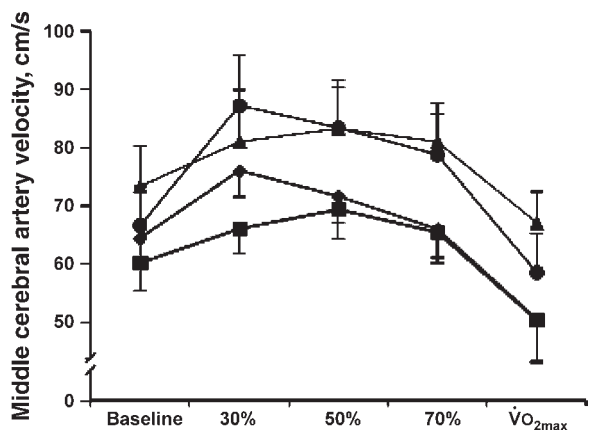

Fig. 2. Changes in middle cerebral artery blood velocity during exercise at different altitudes (■, 150 m; ◆, 3,610 m; ●, 4,750 m; ▲, 5,260 m). Values are means and SE. Velocity at rest increased with increasing altitude ($P < 0.05$). At all altitudes, velocity increased during submaximal exercise ($P < 0.05$–0.0001) but fell at maximal oxygen uptake ($\dot{V}_{O_2\,max}$; $P < 0.01$–0.0001).
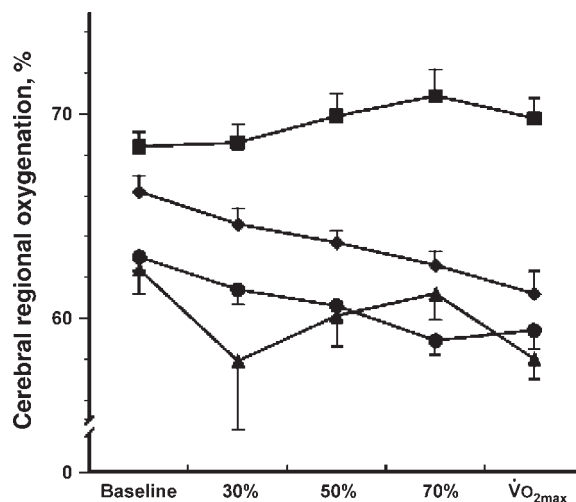

Fig. 3. Changes in cerebral oxygenation at different altitudes (■, 150 m; ◆, 3,610 m; ●, 4,750 m; ▲, 5,260 m). Values are means and SE. Resting oxygenation decreased with increasing altitude ($P < 0.0001$). At 150 m, oxygenation increased during submaximal exercise ($P < 0.0001$) and at $\dot{V}_{O_2\,max}$ ($P < 0.05$). At higher altitudes, oxygenation was reduced during submaximal exercise and at $\dot{V}_{O_2\,max}$ ($P < 0.01$–0.0001).
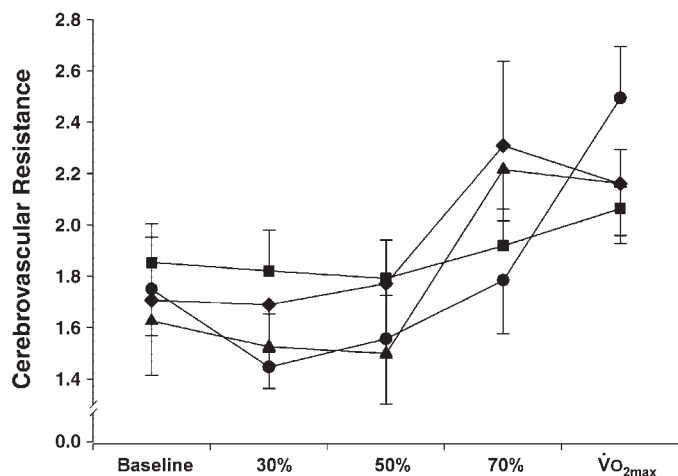
Fig. 4. Changes in cerebrovascular resistance at different altitudes (■, 150 m; ◆, 3,610 m; ●, 4,750 m; ▲, 5,260 m). Values are means and SE. Resting values did not change with increasing altitude. Resting and $\dot{V}_{O_2 max}$ values were not significantly different at 150 m but rose at 3,610 m ($P < 0.05$), 4,750 m (not significant), and 5,260 m ($P < 0.0001$).

0.0001). MCA blood velocity rose initially and fell at maximal workloads, with an increase from 66.6 cm/s (SD 20.5) at rest to 78.7 cm/s (SD 20.7) at 70% $\dot{V}_{O_2 max}$ ($P < 0.0001$) and a reduction to 58.6 cm/s (SD 19.4) at $\dot{V}_{O_2 max}$ ($P < 0.0001$) (Fig. 2). rS_{O_2} was reduced from 63.0% (SD 2.1) at rest to 58.9% (SD 2.1) during the submaximal exercise test ($P < 0.0001$) and was reduced to 59.4% (SD 2.6) at $\dot{V}_{O_2 max}$ ($P < 0.0001$) (Fig. 3). The rise in CVR_{est} from 1.75 (SD 0.61) at rest to 2.49 (SD 1.25) at $\dot{V}_{O_2 max}$ was not significant ($P = 0.057$; Fig. 4), but there was a fall in cerebral oxygen delivery from 5,487 (SD 1,688) at rest to 4,270 (SD 1,295) at $\dot{V}_{O_2 max}$ ($P < 0.01$; Fig. 5).

Exercise at 5,260 m (Tables 2 and 3). Mean arterial blood pressure increased from 108 mmHg (SD 14) at rest to 126 mmHg (SD 12) during submaximal exercise ($P < 0.001$) but was reduced to 107 mmHg (SD 14) at $\dot{V}_{O_2 max}$ compared with resting. Arterial oxygen saturations were reduced compared with resting ($P < 0.0001$). End-tidal CO_2 rose initially but then was reduced from 21.3 Torr (SD 2.9) at rest to 19.4 Torr (SD 1.9) at 70% $\dot{V}_{O_2 max}$ ($P < 0.001$) and to 14.9 Torr (SD 2.0) at $\dot{V}_{O_2 max}$ ($P < 0.0001$). Ventilation and $\dot{V}_{O_2}$ rose progressively during the tests ($P < 0.0001$). MCA blood velocity rose initially and fell at maximal exercise, with an increase from 73.4 cm/s (SD 20.4) at rest to 81.0 cm/s (SD 19.6) at 70% $\dot{V}_{O_2 max}$ ($P < 0.001$) and a reduction to 67.1 cm/s (SD 16.3) at $\dot{V}_{O_2 max}$ ($P < 0.0001$) (Fig. 2). rS_{O_2} was reduced from 62.4% (SD 3.6) at rest to 61.2% (SD 3.9) during submaximal exercise ($P < 0.01$) and was reduced to 58.0% (SD 3.0) at $\dot{V}_{O_2 max}$ ($P < 0.0001$) (Fig. 3). There was a rise in CVR_{est} from 1.63 (SD 0.64) at rest to 2.16 (SD 0.7) at $\dot{V}_{O_2 max}$ ($P < 0.0001$) (Fig. 4) and a fall in cerebral oxygen delivery from 6,158 (SD 1,690) at rest to 5,049 (SD 1,264) at $\dot{V}_{O_2 max}$ ($P < 0.01$) (Fig. 5).

DISCUSSION

The cardiopulmonary effects of exercise at altitude have been studied extensively, but the effect of exercise on cerebral perfusion has received limited attention. No comparable studies of cerebral oxygenation at $\dot{V}_{O_2 max}$, or any combined measurements of cerebral oxygenation and MCA blood velocity

at $\dot{V}_{O_2 max}$, at high altitude have been reported. Our results showed reductions in cerebral oxygenation and oxygen delivery during submaximal and maximal exercise at altitude.

The major determinants of cerebral blood flow are arterial P_{O_2} (Pa_{O_2}), arterial P_{CO_2} (Pa_{CO_2}) (1), and blood pressure, and each of these is altered by both exercise and altitude. Reductions in both Pa_{O_2} and Pa_{CO_2} on acute exposure to altitude, and during exercise at altitude, will have opposing effects on cerebral blood flow. Furthermore, the effects of these stimuli will be modified and vary with acclimatization. An important part of the respiratory acclimatization to altitude is the change in the hypercapnic ventilatory response, resulting in increased ventilatory sensitivity to CO_2 (26). It has been shown that both cerebral blood flow and cerebral oxidative metabolism returns toward baseline by 3 wk at 5,260 m (31). In the present study, the responses observed at 4,750 and 5,260 m probably reflected partial acclimatization since they were performed 4–7 days after arrival at 3,610 m.

Our finding that acute exposure to the three altitudes had no effect on resting mean systemic arterial blood pressure is consistent with other reported studies (50). The rise in mean blood pressure in response to submaximal exercise at each high altitude was similar to that found at 150 m but was only significantly increased at the two highest altitudes. The fall in blood pressure at $\dot{V}_{O_2 max}$ is consistent with other reports (50, 51). The changes in blood pressure we observed with exercise at altitude are well above the range at which autoregulation has been shown to occur. Autoregulation maintains a constant cerebral blood flow of 50–60 ml·100 g^{-1}·min^{-1} over arterial pressures ranging from 60 to 140 mmHg (16). Experience during carotid endarterectomy under loco-regional anesthesia suggests that cerebral blood flow during the cross-clamp phase can be increased with a fairly modest rise in blood pressure, avoiding the need for shunting. A rise in systolic blood pressure of 35–45 mmHg can reverse neurological deficits (46) and is also associated with improved regional cerebral oxygenation (22). The rise in blood pressure may maintain cerebral perfusion during submaximal exercise at altitude, but the fall in blood pressure at $\dot{V}_{O_2 max}$ could be a critical factor limiting exercise.
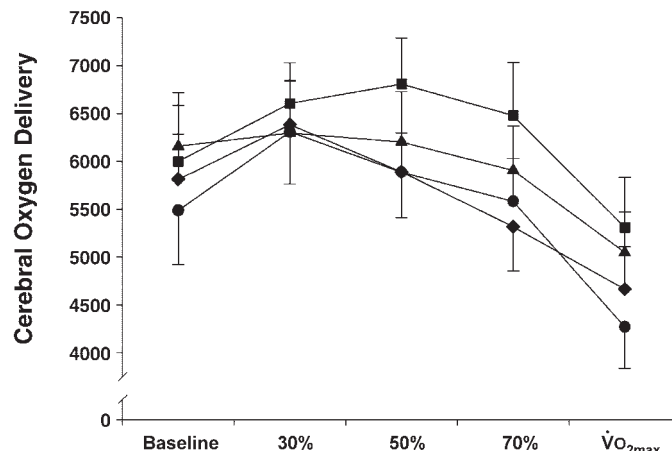

Fig. 5. Changes in cerebral oxygen delivery at different altitudes (■, 150 m; ◆, 3,610 m; ●, 4,750 m; ▲, 5,260 m). Values are means and SE. Resting values did not change with increasing altitude. Resting and $\dot{V}_{O_2 max}$ values were not significantly different at 150 m but fell at 3,610 m ($P < 0.01$), 4,750 m ($P < 0.01$), and 5,260 m ($P < 0.01$).

Near infrared cerebral spectroscopy measures changes in cerebral tissue oxygenation, which is dependent on blood flow, arterial oxygenation, cerebral metabolism, and arterial/venous partitioning (the relative proportion in either the arterial or venous vascular beds). The fall in arterial oxygen saturation at rest with increasing altitude was the most likely cause of the decrease in resting cerebral oxygenation and the increase in resting MCA blood velocity. Similar rises in MCA blood velocity have previously been reported and appear to be most marked on acute ascent, gradually returning toward normal over the following days to weeks (14, 23, 31). The small rise in cerebral oxygenation during submaximal exercise at 150 m could have occurred as a result of an increase in oxygen delivery induced by a gradual fall of cerebral vascular resistance and a matching increase in MCA velocity; but an alternative explanation for the observed rise in cerebral oxygenation could be decreased cerebral oxygen consumption. Similar changes in MCA blood velocity and cerebral oxygenation during submaximal exercise have been reported (17, 18, 34). At $\dot{V}_{O_2 \, max}$ at 150 m, there was a rise in CVR_{est} and an associated fall in MCA velocity. Despite this, near infrared cerebral oxygenation remained higher than the resting levels. This may be attributable to decreased $\dot{V}_{O_2}$, which has been described previously during exhaustive exercise at sea level (9).

In contrast, at the high altitudes studied, cerebral oxygenation (rS_{O_2}) fell progressively during submaximal exercise, with a further fall at maximal exercise. There was an increase in cerebral deoxygenated hemoglobin with both altitude and exercise. Saito and colleagues (42) showed similar changes in cerebral oxygenation at sea level and a fall at 2,700 and 3,700 m during submaximal exercise, which was equivalent to our level of 50% of $\dot{V}_{O_2 \, max}$. However, we found that although cerebral oxygen delivery was sustained to 70% $\dot{V}_{O_2 \, max}$ at sea level, at the high altitudes studied, oxygen delivery peaked at 30% $\dot{V}_{O_2 \, max}$ and thereafter fell. With partial acclimatization, there appeared to be a trend toward improved cerebral oxygen delivery as seen at 5,260 m. The increase in MCA blood velocity during submaximal exercise may have been due to several factors, the most important of which would appear to be increases in mean blood pressure, because there were only small changes in end-tidal CO_2. Our finding of a gradual fall of cerebral oxygenation during submaximal exercise and $\dot{V}_{O_2 \, max}$ at altitude may be attributed in part to the gradual fall in oxygen delivery, but an alternative explanation could be a decrease in cerebral oxygen consumption. We believe the slight differences in cerebral oxygenation during submaximal exercise at the two highest altitudes were due to the relatively small change in altitude and to some acclimatization between the two tests.

It has been shown that, during maximal exercise on a rowing machine in elite athletes (33), arterial oxygen saturation and regional cerebral oxygenation decrease but are maintained at resting levels with moderate hyperoxia (inspired oxygen fraction of 0.3). Exercise performance was also elevated without a change in muscle oxygenation, indicating that the cerebral hypoxia rather than muscle hypoxia appears to be a contributing factor for the limitation of exercise capacity. There was an observed reduction in arterial CO_2 at maximal exercise. In a second sea level study by the same group, cerebral perfusion was shown to increase in excess of the increases in the global

cerebral metabolic activity during the brain activation associated with exercise and that lactate supplements glucose as energy fuel for the brain when the plasma lactate level is elevated. Furthermore, as evidenced by mean MCA velocity determined by transcranial Doppler, cerebral perfusion was enhanced and cerebral oxygenation determined by near-infrared spectroscopy suggested flow increased to a larger extent than the corresponding metabolic oxygen demand (17).

We found no difference in resting CVR_{est} between the different altitudes, although there was a nonsignificant reduction of resting CVR_{est} with increasing altitude. CVR_{est} appeared to change in two distinct phases with exercise. Up to 50% of $\dot{V}_{O_2 \, max}$, there was a tendency for a small reduction in CVR_{est}, which was associated with a fall in arterial oxygen saturation and a rise in end-tidal CO_2. These changes would tend to increase cerebral blood flow, and this was reflected in the rise in cerebral oxygen delivery observed at all altitudes at 30% submaximal exercise. There appeared to be a second phase between 70% $\dot{V}_{O_2 \, max}$ and $\dot{V}_{O_2 \, max}$. In this phase, there was a marked rise in CVR_{est} at all altitudes, and this is associated with falls in end-tidal CO_2 and small rises in arterial oxygen saturation. Both of these changes would tend to decrease cerebral perfusion, and again this was reflected in the reduction of cerebral oxygen delivery observed at all altitudes at $\dot{V}_{O_2 \, max}$. Somewhat surprisingly, we found no direct correlation between end-tidal CO_2 and CVR_{est}. However, CVR_{est} is a product of the complex dynamic interrelationship between all variables mentioned above as well as changes in hypoxic and hypercapnic ventilatory responses and cerebrovascular responsiveness to CO_2.

The factors limiting exercise at altitude may be different from those that limit exercise at sea level and may include diffusion limitation of $\dot{V}_{O_2}$ in the alveolus, the work of ventilation, respiratory muscle fatigue, and the possible steal of blood from limb locomotor muscles to respiratory muscles (8, 10, 30). The perception of dyspnea is also increased during exercise at altitude (5), which may lead to the premature ending of exercise. At altitude, $\dot{V}_{O_2}$ in the lung is diffusion limited (52), and this is further exacerbated by exercise. Our results do not support a diffusion limit of CO_2 at $\dot{V}_{O_2 \, max}$ at altitudes up to 5,260 m, but further studies are required with measurements of Pa_{CO_2}. Assessment of other vascular beds, such as exercising muscle, using near-infrared techniques could be used to determine whether there were significant steals of blood either to or from the cerebral circulation at $\dot{V}_{O_2 \, max}$. These techniques have been successfully used by Nielsen and colleagues at sea level (33).

Our findings of reduced cerebral oxygen delivery and increased CVR_{est} during exercise above 50% of maximum exercise at altitude may relate to the pathogenesis of AMS and HACE. Exercise is likely to exacerbate AMS through increased hypoxia and sodium retention (55), and our results confirm that the brain is subjected to increasing hypoxia during exercise. Our results may explain the deterioration seen in the accuracy of marksmanship caused by acute exposure to altitude and independent of exercise (47) as well as transient and focal neurological deficits occurring at altitude (2, 32). The large rises in blood pressure observed on exercising close to or at $\dot{V}_{O_2 \, max}$ could explain some of the focal and global transient and permanent neurological events observed at high altitude. Clinical examination at a later time point might miss the period

of profound hypertension. It is also of interest that the standard formula of $220 -$ age (yr) used to predict maximal heart rate provided a good estimate at 150 m but increasingly underestimated maximal heart rate at each of the high altitudes. This finding has implications for studies using this formula for predicting energy expenditure or work rate during exercise at altitude.

The reduction in cerebral oxygenation we demonstrated at submaximal exercise is relevant for normal climbing at $\dot{V}O_2$ of $50-75\%$ $\dot{V}O_{2\ max}$ (39). The finding that mountaineers with a more vigorous ventilatory response to hypoxia have more residual neurobehavioral impairment may be a result of reduced cerebral oxygen delivery (13). The hypercapnic vasoconstriction and subsequent reduced cerebral oxygenation might be due to a hypocapnic-driven reduction in cerebral blood flow (13). Schoene and colleagues (44) showed that the fall in arterial saturation on exercise at altitude was actually greater in subjects with a low hypoxic ventilatory drive. The observed reduction of cerebral oxygen delivery during exercise may be more important than absolute altitude in determining the development of AMS. At any given altitude, arterial and cerebral oxygenations are a dynamic variable dependent on absolute altitude, oxygen delivery, and $\dot{V}O_2$. A resting individual at a higher altitude may have the same cerebral oxygenation as an exercising individual at a lower altitude. Both subjects are at the same "virtual" altitude. Assessing cumulative hypoxic insult (time at a virtual altitude) over a 24-h period might more accurately predict the hypoxic stress an individual has experienced.

The limitations of the near-infrared cerebral spectroscopy method have been reviewed (43, 37). The two-sensor technique eliminates the contribution from the scalp and skull, thereby giving a measurement of tissue oxygenation at a depth of 2.5–5.0 cm. Concerns over contamination of the intracerebral readings with scalp blood flow have been raised in the past. Providing the spacing between the scalp detectors is adequate, scalp flow makes no significant contribution. This was demonstrated using laser Doppler velocimetry and occlusion of scalp flow using a pneumatic tourniquet (35). Near-infrared spectroscopy provides a measure of the proportion of blood that is oxygenated. It does not distinguish how much is in the arterial or venous part of the vascular bed. The proportion of total blood in the brain has been estimated to be 28% arterial and 72% venous (29). In this study, we assumed that neither hypoxia nor exercise affects the arteriovenous partitioning. However, partitioning of the arterial and venous volumes in the brain under hypoxic conditions at rest has been modeled (56), and it is possible that further changes could occur with exercise.

The transcranial Doppler technique is operator dependent and requires careful focusing of the ultrasound probe on the MCA. We standardized this as far as possible by using one experienced operator (28). We cannot be certain whether arterial diameter remained constant during the exercise tests at altitude, but other studies at sea level found no changes with either decreases or increases in Pa_{CO_2} (45) or during hypocapnia alone (49). Jorgensen and colleagues (24) showed that the increase in regional cerebral perfusion during exercise at sea level occurred in the MCA territory, with increases in mean MCA blood velocities of 19–32%. However, it has been suggested that much of the increase in MCA blood velocity in response to exercise could arise as an artifact from the increase in amplitude and frequency of the arterial pressure waveform used in Doppler ultrasound studies (38). Nevertheless, cerebral blood flow measured by ^{133}Xe clearance increased by 31% during submaximal exercise at sea level (48). Our finding of a 15% increase in MCA blood velocity was similar to the 14% reported by Hellstroem and colleagues (11), who combined duplex ultrasonography and transcranial Doppler ultrasonography. Our results are also comparable to those reported by Huang and colleagues (15), who, on acute exposure to 4,300 m, recorded increases in internal carotid flow velocity of 15–33% on exercising at 45 and 72% $\dot{V}O_{2\ max}$. Hellstroem and colleagues (11) performed a study at sea level in which a reduction in MCA blood velocity was found at 80–90% of maximal exercise. This was associated with a reduction of Pa_{CO_2}, again similar to our findings at 150 m. When exercising at 96% $\dot{V}O_{2\ max}$ at high altitude, Huang and colleagues (15) noted a small fall in internal carotid flow velocity, but flow remained higher than resting levels in contrast to our study.

Our results are consistent with the hypothesis that cerebral blood flow provides an important signal to the central nervous system and may become a factor limiting exercise at altitude, rather than cardiorespiratory capacity and muscle fatigue (25). Our finding of considerable reductions in cerebral oxygen delivery and cerebral oxygenation during exercise at altitude suggest that these may provide the critical signals. The reduction of cerebral oxygenation during exercise, if it persists during altitude acclimatization, may explain why $\dot{V}O_{2\ max}$ is reduced despite normalization of arterial oxygen content (7). Reduction in cerebral oxygenation during exercise may exacerbate the neurological features of AMS and contribute to the development of HACE and other neurological deficits. Our results lend credence to the time-honored advice to avoid strenuous exercise on arrival at high altitude.

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