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ORIGINAL RESEARCH

Doppler study of middle cerebral artery blood flow velocity and cerebral autoregulation during a simulated ascent of Mount Everest

ARAM Ter MINASSIAN, MD; LAURENT BEYDON, MD; MAURO URSINO, PhD; BERNARD GARDETTE, PhD; CLAUDE GORTAN, PhD; JEAN PAUL RICHALET, MD, PhD

From the Département d'Anesthésie-Réanimation, CHU d'Angers, 49033 Angers-France (Drs Ter Minassian and Beydon), the Dipartimento di Elettronica, Informatica e Sistemistica, Universita degli studi di Bologna-Viale Risogimento No. 2, 40136 Bologna-Italy (Dr Ursino), COMEX, 36 Bd de l'Océan, 13009 Marseille-France (Drs Gardette and Gortan), and ARPE, laboratoire "Réponses cellulaires et fonctionnelles à l'hypoxie," Université Paris 13, 93017 Bobigny-France (Dr Richalet).

Objective.—To explore cerebral hemodynamics in 8 healthy volunteers in a hypobaric chamber up to the altitude of Mount Everest after a progressive stepwise decompression to 8848 m.

Methods.—Physiological, clinical, and transcranial Doppler data were collected after at least 3 days at 5000, 6000, and 7000 m and within 4 hours of reaching 8000 m and returning to sea level.

Results.—Three subjects were excluded at 8000 and 8848 m because of acute neurological deficits. Heart rate increased; mean arterial pressure remained stable; PaO_2 and $PaCO_2$ decreased with altitude; hemoglobin (Hb) and hematocrit (Ht) increased; arterial O_2 content decreased over 6000 m; middle cerebral artery blood flow velocity (MCAv) increased only during acute exposure to 8000 m; and the corresponding pulsatility (PI) and resistivity indices (RI) decreased over 5000 m. PI and RI correlated with heart rate. The transient hyperemic response (THR) of MCAv to common carotid compression was depressed at 8000 m.

Conclusions.—At 8000 m, the increase in MCAv seemed to reflect the normal hemodynamic response to acute hypoxia. The decrease of THR at this altitude could be an indication of impaired cerebral autoregulation. The role of impaired cerebral autoregulation in the genesis of acute neurologic deficits, observed at 8000 m and above in 3 subjects, remains speculative.

Key words: hypoxia, brain, hemodynamics, Doppler (transcranial)

Introduction

Few physiological studies have been performed at altitudes above 7000 m. Operation Everest II[1] included experiments on long-term acclimatization to high altitude but not on cerebral hemodynamics. Climbing at high altitude is associated with a significant risk of mortality and of morbidity with neurological consequences. Following prolonged exposure to high altitudes, climbers may show a neurobehavioral impairment on return to lower altitudes.[2] Furthermore, subjects climbing at extreme altitudes over 7500 m, and even those reaching 5500 to 6800 m, show an increased prevalence of magnetic resonance imaging (MRI) abnormalities, including cortical atrophy.[3] The role of a limitation of cerebral blood flow (CBF) and cerebral oxygen delivery to metabolic requirements is unknown.

The main purpose of this study was to use transcranial Doppler (TCD) for investigating the long-term changes of cerebral hemodynamics in volunteers during a simulated ascent to the altitude of Mount Everest and to investigate the effect of acute exposure at an altitude of 8000 m after a progressive stepwise acclimatization up to 7000 m (Operation Everest III, COMEX 97).

Subjects and methods

This experiment was performed during Operation Everest III (COMEX) in Marseille (France). The selection of subjects, location and schedule of operations, and a general description of the study and time course of the

Corresponding author: A. Ter Minassian. Département d'Anesthésie, CHU Larrey 49033 ANGERS Cedex-France (e-mail: lbeydon.angers@invivo.edu).

main physiological parameters have been published elsewhere.[4] Briefly, after approval by the local ethics committee and the receipt of written informed consent, 8 healthy subjects (mean age 27, range 23 to 37) were selected. Before inclusion in the study, all subjects had undergone bilateral cervical sonography (Acuson, 128XP, 7.5-MHz linear probe) to confirm that none had carotid or vertebral artery stenoses. TCD measurement was also performed to verify the existence of adequate transcranial acoustic windows and the permeability of the anterior and posterior communicating arteries (Angiodyne, 2-MHz probe, Doppler Measurement System, Montpellier, France). Subjects were first studied at sea level (SL); they then underwent a 6-day acclimatization at 4350 m in the Vallot Observatory on Mont Blanc. Within 24 hours of completing this acclimatization period, they were taken to a hypobaric chamber (COMEX, Marseille, France), where they remained for 31 days. Here, measurements were performed at the simulated altitudes of 5000, 6000, 7000, and 8000 m, and also immediately after return to sea level (RSL). All measurements were performed after at least 3 days of acclimatization at the relevant altitude. The only exceptions were those at 8000 m and at RSL, both of which were performed within 4 hours of ''arrival.''[4]

Measurements of TCD were performed by the same experienced investigator. He entered the chamber after breathing pure O_2 for 30 minutes. During his stay, he wore a kind of space suit, with an airtight hood, allowing him to breathe O_2-enriched air without contaminating the chamber.

Sequential TCD measurements of both middle cerebral arteries were obtained at rest, in a supine position, and with the head tilted up to 30° for each condition. Doppler recordings were performed as described below and were stored for off-line analysis using an analog-to-digital converter (Windograph, Gould Electronics).

We first collected the spectral outline of the blood velocity in the middle cerebral artery (MCAv) using a 2-MHz hand-held probe. Reproducibility (previously measured range: ±5%) of these measurements was optimized by marking the skin above the correct acoustic window of the temporal bone, as assessed at SL, with a waterproof colored dot. Depth of insonation was identical at all altitudes for each volunteer, and the angle of insonation of the MCA was kept as close as possible to 0°C by searching for the Doppler shift of the highest frequency.

Resistivity (RI) and pulsatility (PI) indices[5] of both MCAs were calculated over 3 different periods of 15 seconds on each side. These indices were derived from systolic (Vsyst), diastolic (Vdiast), and mean (Vmean) velocities according to the following equations:

$$PI = (Vsyst - Vdiast)/V\ mean$$

$$RI = (Vsyst - Vdiast)/V\ syst$$

For each variable, we averaged the 6 values obtained before carrying out statistical analyses and comparisons. We next used a 2-MHz probe secured to a special helmet over the left temporal acoustic window to perform an ipsilateral common carotid artery compression test. This compression test was designed to make an indirect assessment of cerebral autoregulation in the form of a transient hyperemic response (THR) of the left MCA. It was performed after a 10-minute period of rest and consisted of a 3- to 5-second compression of the left common carotid artery, which was released during diastole. This test was conducted at least 3 times on each subject, at all levels. The ethics committee had requested, for safety reasons, that carotid compression be as short as possible. For the same reason, it also refused to allow carotid compression at 8848 m. Accordingly, we chose to compress the carotid artery for 3 to 5 seconds, which corresponds to the shortest duration that has been validated as representing the time needed for vasodilation to occur after a sudden blood pressure drop.[6]

Successive tests were separated by a period of at least 30 seconds. The THR was calculated as the ratio of the MCAv, averaged over the first 3 cardiac cycles immediately following compression release, to the MCAv averaged over the last 3 cycles preceding compression. Although subjects were requested to breathe as regularly as possible, some showed a low-frequency respiratory oscillatory pattern of MCAv. In such cases, we performed compression tests during the zenith of an MCAv oscillation. In addition to Doppler recordings at all altitudes, we collected mean arterial pressures (MAPs) (Dynamap, Johnson and Johnson) and heart rate. The acute mountain sickness (AMS) score ranging from 0 to 3 (absence of symptoms to severe symptoms) was based on 4 items: 1) headache, 2) digestive symptoms, 3) dizziness, and 4) fatigue.[7] Arterial capillary blood gases (Chiron Diagnostics) were sampled from an ear lobe following the application of capsaicin cream to obtain a maximal local vasodilation. Venous hemoglobin concentrations (Hb) (CO-oximeter, model 270, Chiron) and hematocrit (Ht) scores were obtained at all altitudes except after RSL. From the blood samples, arterial O_2 content (CaO_2) was computed as follows: $CaO_2 = (SaO_2 \times Hb \times 1.34) + (0.003 \times PaO_2)$. Analysis was limited to data recorded up to 8000 m. Statistical analysis was based on a 2-way analysis of variance with pairwise multiple comparison procedures to separate for differences between subjects and altitudes (Student-Neuman-Keuls method). Within-subject variability of THR was calculated at each altitude as the ratio of the maximal minus

Table 1. Physiological parameters at various altitudes (means ± SD)†

Altitude	*Barometric pressure (mm Hg)*	*MCAv ($cm \cdot s^{-1}$)*	*PI*	*RI*	*Ht (%)*	*SaO_2 (%)*	*$PaCO_2$ (mm Hg)*	*PaO_2 (mm Hg)*	*CaO_2 ($ml \cdot dL^{-1}$)*	*AMS score*
SL	760	65	0.83	0.54	46	98	40.3	101.8	19.8	0.1
± SD		5	0.12	0.04	3	1	3.1	3.9	1.8	0.2
5000 m	422	66	0.82	0.53	52*	90*	27.5*	51.1*	19.8	0.3
± SD		7	0.13	0.05	3	2	1.4	3.4	1.4	0.5
6000 m	370	67	0.64*	0.44*	53*	89*	19.8*	49.3*	20.8	1.3*
± SD		8	0.13	0.06	3	3	2	3.3	1.5	0.8
7000 m	324	74	0.68*	0.46*	56*	79*	18*	40.2*	17.4*	2.6*
± SD		15	0.11	0.05	3	3	2.6	5	1.1	1.5
8000 m	284	93*	0.59*	0.43*	57*	74*	14.3*	37*	18.4*	2.3*
± SD		28	0.09	0.04	5	9	2.1	4.6	2.5	1.3
RSL	760	75	0.79	0.52		98	31.6*	102.3		0.3
± SD		11	0.07	0.03		1	2.1	6		0.7

† Below 8000 m, $n = 8$; at 8000 m, $n = 7$; SL indicates sea level; RSL, return to sea level.

* Statistically significant difference between means for each variable is at $P < .05$. Asterisk marks those significantly different from sea level.

minimal value of THR divided by the mean of the 3 values. Linear regression was used as needed, and multiple linear regression was performed to assess if SaO_2 or Doppler-derived parameters were correlated to AMS score (Sigma Stat, Jandel Scientific).

Results

Neurological symptoms prompted O_2 inhalation and emergency recompression from 8000 m to SL in 1 subject and from 8848 m in 2 others. The symptoms included aphasia, paralysis, and dizziness. They disappeared within 1 minute following pure oxygen inhalation, but 1 subject had persistent headaches. Neurological examination and MRI were performed 3 hours later in 2 subjects and were normal. The third one was judged fit enough to remain in the chamber under O_2. He came out 18 hours later for examination and MRI, both of which were normal.[4] Mean values of the physiological data at the different altitudes and the corresponding barometric pressures are shown in Table 1.

The AMS scores increased with altitude, reaching a maximum value at 7000 m. PaO_2 and SaO_2 decreased with altitude, with a minimum value at 8000 m of 37.0 ± 4.6 mm Hg and 74 ± 8.6%, respectively. At all altitudes, arterial pH was significantly higher than at SL. $PaCO_2$ was lower at all altitudes than at SL, and its lowest value, 14.3 ± 2.1 mm Hg, was recorded at 8000 m. Arterial oxygen content (CaO_2) decreased above 6000 m.

Heart rate increased with altitude (57 ± 4 min^{-1} at SL to 89 ± 12 min^{-1} at 8000 m), whereas MAP was unchanged (84 ± 4 mm Hg at SL to 90 ± 10 mm Hg at 8000 m). Hb concentration increased (14.8 ± 1 $g \cdot dL^{-1}$ at SL to 18.4 ± 1.5 $g \cdot dL^{-1}$ at 8000 m). MCAv and Doppler indices, PI and RI, remained unchanged up to 5000 m. Above 5000 m, PI and RI decreased, whereas MCAv was significantly increased only at 8000 m. An oscillatory pattern of MCAv in the low-frequency range (0.01–0.02 Hz) was observed in 4 subjects over 5000 m (Figure 1). PI and RI were significantly and linearly correlated to HR ($PI = -0.006\ HR + 1.15$, $n = 47$, $r = .61$, $P < .001$; $RI = -0.0025 + 0.67$, $n = 47$, $r = .59$, $P < .001$).

THR was lower than at SL only at 8000 m; within-subject variability of THR increased with altitude (Table 2, Figure 2). Measurements of THR carried out at SL before and after the experiment were similar (Table 2). SaO_2 was negatively correlated with the AMS score when all altitude values were pooled ($n = 47$, $r = .71$, $P < .001$). Multiple linear regression showed that among Doppler parameters (PI, RI, MCAv, and THR) and SaO_2, only SaO_2 correlated to AMS score.

We failed to discern any clinical (AMS), hemodynamic (HR, MAP, MCAv, and THR), or biological (Ht or blood gases) peculiarity in the 3 subjects who showed acute neurological impairment.

Discussion

Our study is the first to use TCD to explore the modification of cerebral hemodynamics during long-term ac-

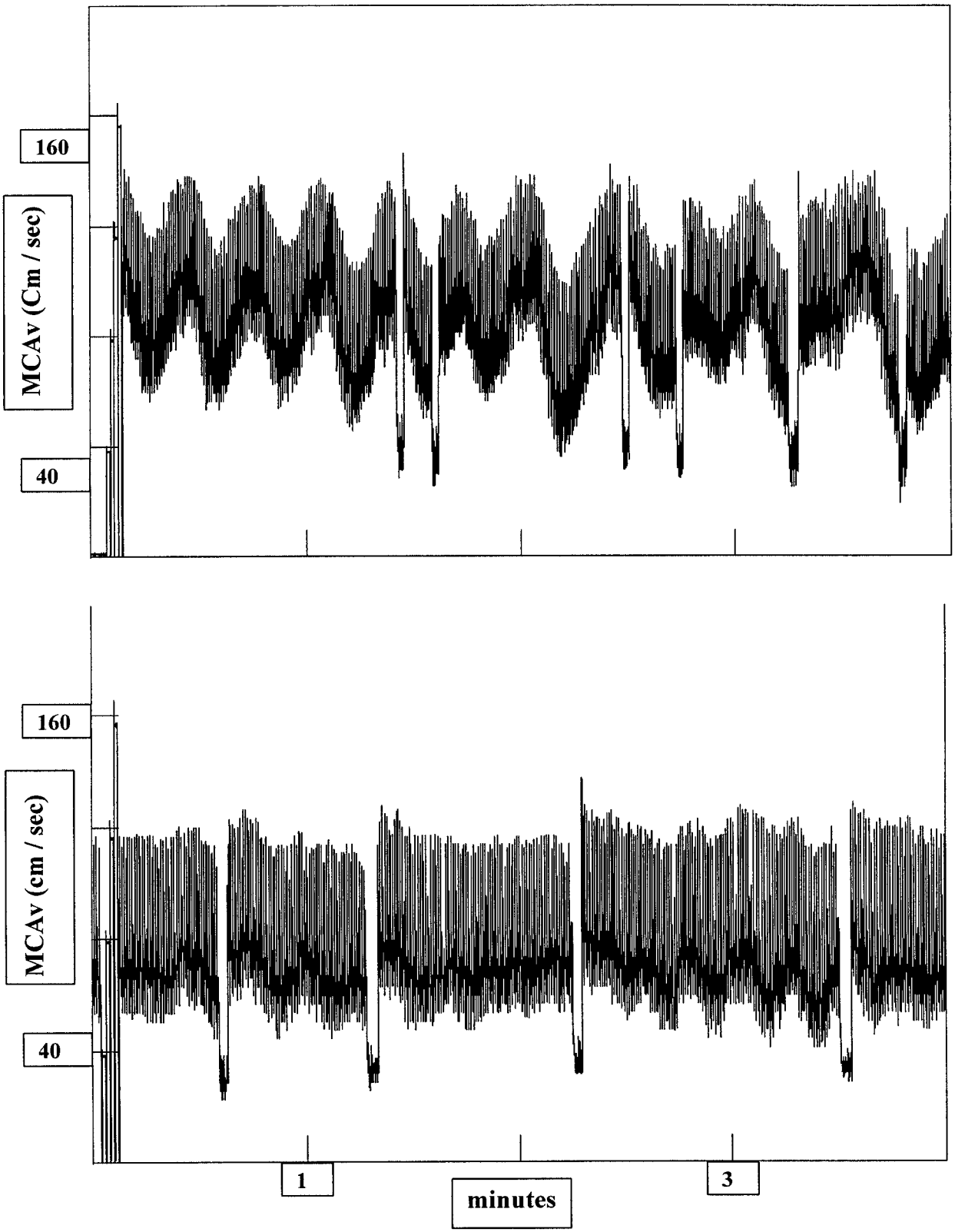

Figure 1. Spectral outline of continuous transcranial Doppler for middle cerebral artery blood flow velocity (MCAv): examples of 2 typical patterns recorded at 8000 m. Upper panel: continuous MCAv oscillations with a periodicity of 20 to 30 seconds. Lower panel: absence of MCAv oscillations. The sharp decreases in MCAv correspond to transient common carotid compression. Note that during MCAv oscillations, transient hyperemic responses were calculated only for the compression test, which was performed at the zenith of an MCAv wave.

Table 2. Transient hyperemic response (THR) of middle cerebral artery blood flow velocity (MCAv) to a 3- to 5-second common carotid compression at various altitudes and corresponding within-subject variabilities (WSV) (means ± SD)†

Altitude	*THR*	*WSV*
SL	1.24	0.06
± SD	0.07	0.03
5000 m	1.22	0.12
± SD	0.07	0.08
6000 m	1.26	0.10
± SD	0.07	0.06
7000 m	1.22	0.15*
± SD	0.05	0.10
8000 m	1.10*	0.15*
± SD	0.05	0.10
RSL	1.22	0.06
± SD	0.06	0.04

† Below 8000 m, $n = 8$; at 8000 m, $n = 7$; SL indicates sea level; RSL, return to sea level.

* Statistically significant difference between means for each variable is at $P < .05$. Asterisk marks those significantly different from sea level.

climatization to simulated extreme altitudes. Our TCD measurements showed that MCAv remained remarkably stable until 8000 m, whereas PI and RI began decreasing at 5000 m. Acclimatization to altitude is a process whereby cerebral hemodynamics and the control of breathing are linked. Hypoxia first induces a short-term change in cerebral circulation. The decrease in PaO_2 below about 50 mm Hg results in the dilatation of pial and cortical arterioles downstream from the circle of Willis.[8] In response to this effect and to the resulting decrease in cerebrovascular resistance (CVR), CBF increases. Such a decrease maintains a constant flow of oxygen to the brain. However, hypoxia acts on chemoreceptors to cause acute hyperventilation, hypocapnic alkalization of the CSF, and cerebral arteriolar vasoconstriction. Hypocapnic vasoconstriction tends to counteract hypoxic vasodilatation.

The early phase of acclimatization is observed as a progressive fall of $PaCO_2$ over hours to days, which is permitted by a reduction of CSF (and presumably extra cerebral fluid) HCO_3^- ion. Later, during acclimatization, the sensitivity of the carotid bodies to hypoxia increases.[9] This increased ventilatory drive also forces $PaCO_2$ down and pH up in both blood and CSF. The increased ventilation raises PaO_2 and SaO_2. Both permit CBF to fall toward normal. This was demonstrated by Severinghaus et al[10] and confirmed by several authors.[11,12] Polycythemia is involved in long-term acclimatization. It increases arterial O_2 content and blood viscosity. The latter is involved in the regulation of CBF.[13–16] The increase in viscosity would have induced dilation of pial vessels in a manner similar to the autoregulatory process observed following a decrease in cerebral perfusion pressure (CPP).

The MCAv after 3 days at each of the altitudes below 8000 m was not found to be significantly higher than at SL. A first explanation is that hypoxia might be having a direct vasodilatory effect on the large basal arteries of the circle of Willis. Such a vasodilatory effect of hypoxia on MCA cross-section would lead to an underestimate of flow variation by MCAv measurements and could explain the steady MCAv we observed up to 7000 m. This frequently evoked hypothesis is ruled out by previously published work. Indeed, the vasodilatory effect of hypoxia, like variations in $PaCO_2$ and CPP, has been shown to act mainly on small pial and cortical arteries downstream from the circle of Willis.[8] Furthermore, during comparable acute hypobaric hypoxia, the increase in MCAv[17–20] is of the same order of magnitude as the increase in CBF measured by nitrous oxide inhalation[10,12] or by the 133 Xenon technique.[21,22] Thus, it seems unlikely that hypoxia could have induced a sizeable vasodilatory effect on major arteries of the circle of Willis. A contradictory experiment by Giller at al[23] supports the opposite during exercise. These authors studied, using TCD, cerebral hemodynamics response to rhythmic handgrip in volunteers at SL. They speculated that the observed velocity increase was due to a sympathetically mediated vasoconstriction of the MCA. Thus, according to Giller et al, the increase in velocity we observed at 8000 m may be due to a vasoconstriction of the MCA. If these findings under exercise at SL were transposable to the resting condition at high altitudes, our findings of a rise in velocity at 8000 m could be related to an increase in sympathetic activity at the level of the MCA. The studies under hypobaric hypoxia mentioned above, by showing a parallel between the rise in Doppler velocity and true CBF (xenon and nitrous oxide measurements), tend to support that the differences in experimental condition may lead to different mechanisms.

Accordingly, in our experimental conditions, variations in velocity are likely to be proportional to variations in flow. In our study, MCAv increased only at 8000 m when SaO_2 fell below 79%, contrary to observations made in a study performed in acute hypoxic conditions, where MCAv increased once SpO_2 fell below 90%.[24] The difference in threshold for the rise in MCAv is likely to reflect the acclimatization elicited during the previously described process, which restored CaO_2. Thus, despite the fact that we did not study subjects at their

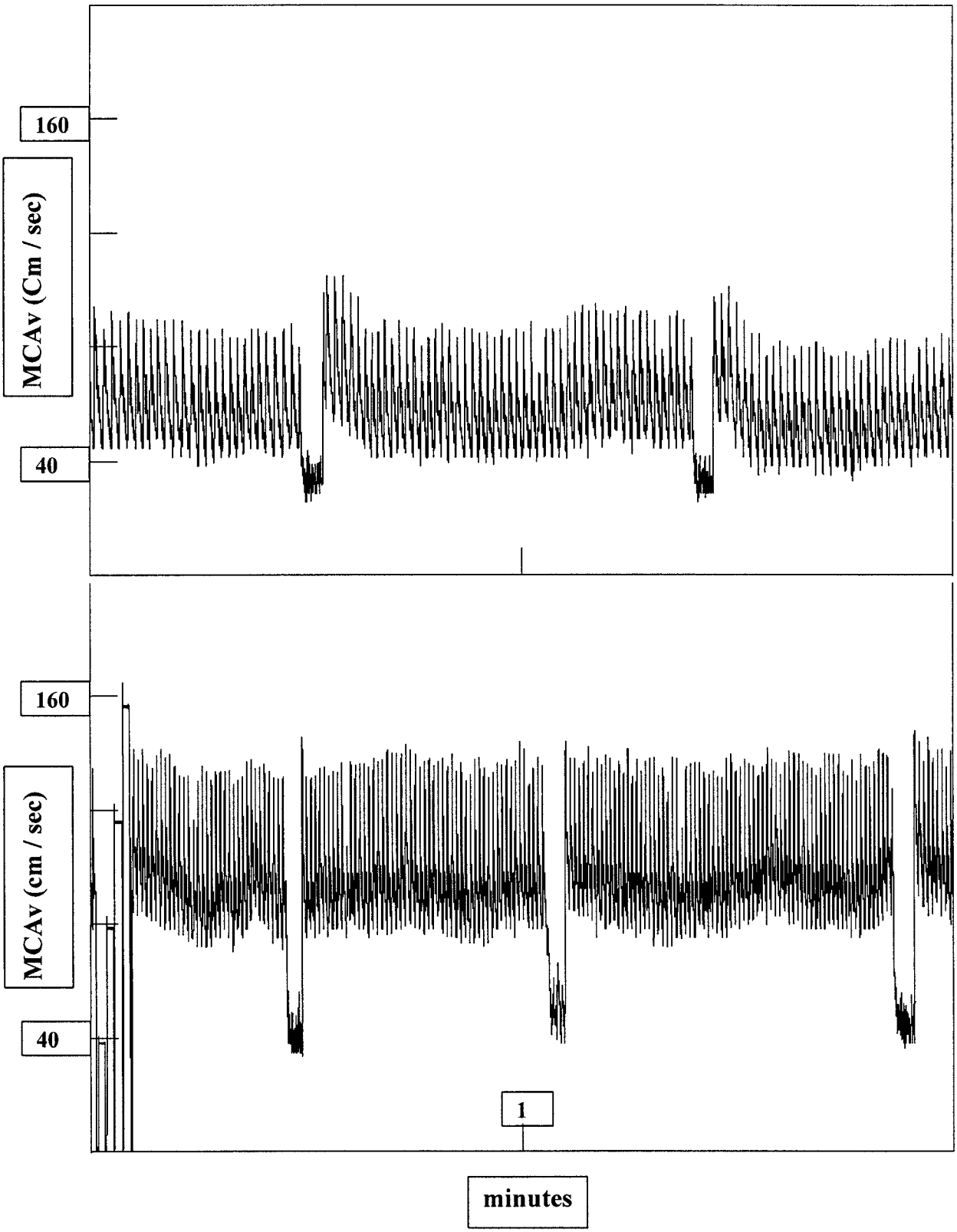

Figure 2. Transient hyperemic response (THR) of middle cerebral artery blood flow velocity (MCAv) at sea level after common carotid artery release (upper panel). Same subject at 8000 m. Note the absence of THR. Mean MCAv is increased and amplitude of undulation is decreased.

arrival to each altitude monitored, but after 3 days, the steadiness of MCAv values recorded at all steps below 8000 m seems to support the possibility of a secondary normalization of CBF after a possible initial rise[10–12] (we did not measure). Some authors have suggested that CBF does not return to normal within 3 days at moderate altitudes.[25,26] However, our subjects were studied after 6 days of acclimatization at 4350 m before entering the chamber. At higher altitudes, increased Ht could have modified the kinetics of normalization of MCAv. This process may not have occurred at 8000 m, as subjects only stayed a few hours at this altitude. Thus, at 8000 m, contrary to the lower levels studied, the effect was that of acute hypoxia and supports the fact that hypoxic cerebral vasodilation seems possible despite concurrent hypocapnia.

The fact that 3 of our 8 volunteers experienced transient neurological impairment over 7000 m[4] and the findings of Abraini et al, who reported a decrease in mental efficiency and psychomotor ability in the same experiment at these altitudes,[27] could suggest an inadequate O_2 delivery to the brain.

Significantly, we observed an apparently challenging lag between the altitude at which PI and RI decrease (above 5000 m) and that at which MCAv rises (at 8000 m). It is known that PI and RI are influenced by several factors. Among them, CVR and also CPP—ie, the difference between MAP and intracranial pressure (ICP)—have a critical influence on the MCAv profile. Indeed, PI decreased with vasodilation and increased with decreasing CPP.[28] Furthermore, Bruder et al[29] showed that PI in anesthetized patients increases with hemodilution, suggesting that modification of blood viscosity could influence MCAv profile. Also, Michel and Zernikow[30] modeled the influence of heart rate on the flow velocity profile. They showed that PI and RI decrease with heart rate. Our finding of a correlation between PI and RI and with heart rate overall in this study is in accordance with the findings of these authors.

We did not find a correlation between MCAv and AMS scores; nor did PI, RI, or THR correlate with AMS during long-term acclimatization to progressive hypoxia. This agrees with the lack of correlation between absolute CBF or relative increase in CBF and AMS scores, which have been reported by Jensen et al[21] after 3 to 5 days at 3200 and 5430 m.

The THR was depressed by 50% at 8000 m. A THR to a sudden pressure drop is believed to reflect the vasodilatory capacity of pial and cortical arterioles downstream from the circle of Willis. First introduced into clinical practice and validated by Giller,[6] the relationship between THR and cerebral autoregulation has been modeled by Czosnyka et al.[31] A recent study has confirmed the high sensitivity of THR in detecting changes in autoregulation in healthy volunteers.[32] In this study, we used a 3- to 5-second compression of the common carotid artery, which is the shortest published duration for making estimations of THR. Mahajan et al[32] recommended the use of a 10-second compression to be sure that vasodilation is complete. The shortest time of compression we used did not seem to influence the THR, as in our volunteers at SL, we observed both a THR and a within-subject variability lower than that found by Mahajan et al[32] with a 10-second compression. This supports the view that autoregulation is a very fast mechanism initiated within a cardiac cycle, as has been shown by video angiometry.[33]

Our findings of an altered autoregulation during acute exposure to an altitude of 8000 m are in accordance to the results published by Levine et al,[34] who found an increased gain and coherence between MCAv and MAP in the low-frequency range during a chronic exposure to 5200 m. This increased gain and coherence reflects impaired cerebral autoregulation in response to slow oscillation of MAP. Nevertheless, Jansen et al[35] recently showed that autoregulatory response to changes in blood pressure is probably not a hallmark of the normal cerebral vasculature at altitude. These authors have shown that autoregulation was altered in newcomers to high altitudes as well as in sherpas who were born and live at 4243 m. They conclude that cerebral autoregulation does not seem to play a major role in the occurrence of cerebral edema. Accordingly, in our study, we did not find a correlation between THR and AMS score. Moreover, we did not observe THR values of the 3 subjects who disclosed neurological impairment to be different from those obtained from the rest of the group studied.

Interestingly, despite the reproducibility of our compression test, the within-subject variability increased with altitude. This phenomenon seemed to be due to an oscillatory pattern of MCAv in 4 subjects at each altitude step over 5000 m. The frequency range of MCAv corresponded to that of ''B'' waves according to the classification of Lundberg.[36] It is known that such an oscillatory pattern of MCAv is associated with periodic breathing and also with heart rate, MAP, and ICP fluctuations at the same frequency. The design of this study does not allow us to comment further on this issue. We conclude that there is a major dependency of Doppler parameters on heart rate up to 7000 m. However, at 8000 m, TCD was able to show modifications of cerebral hemodynamics consisting of a rise in MCAv and limitation of CVR change to a pressure drop as assessed by THR, which indicates impaired autoregulation. The increase in MCAv at 8000 m could reflect the normal cerebral hemodynamic response to acute hypoxia. The relationship

between altered cerebral autoregulation and neurological impairment we observed in 3 subjects at the same altitude remains speculative. One may hypothesize that, despite a progressive and stepwise exposure to hypobaric hypoxia up to 7000 m, a state of near-maximal cerebral vasodilation and the limitation on cerebral O_2 delivery could explain the high incidence of neurological impairment observed during further acute decompression at 8000 m and higher.

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