Cerebral Autoregulation in Subjects Adapted and Not Adapted to High Altitude

Gerard F.A. Jansen, MD; Anne Krins, BSc; Buddha Basnyat, MD; Andries Bosch, PhD; Joseph A. Odoom, PhD

Background and Purpose—Impaired cerebral autoregulation (CA) from high-altitude hypoxia may cause high-altitude cerebral edema in newcomers to a higher altitude. Furthermore, it is assumed that high-altitude natives have preserved CA. However, cerebral autoregulation has not been studied at altitude.

Methods—We studied CA in 10 subjects at sea level and in 9 Sherpas and 10 newcomers at an altitude of 4243 m by evaluating the effect of an increase of mean arterial blood pressure (MABP) with phenylephrine infusion on the blood flow velocity in the middle cerebral artery (Vmca), using transcranial Doppler. Theoretically, no change of Vmca in response to an increase in MABP would imply perfect autoregulation. Complete loss of autoregulation is present if Vmca changes proportionally with changes of MABP.

Results—In the sea-level group, at a relative MABP increase of 23±4%, during phenylephrine infusion, relative Vmca did not change essentially from baseline Vmca (2±7%, P=0.36), which indicated intact autoregulation. In the Sherpa group, at a relative MABP increase of 29±7%, there was a uniform and significant increase of Vmca of 24±9% (P<0.0001) from baseline Vmca, which indicated loss of autoregulation. The newcomers showed large variations of Vmca in response to a relative MABP increase of 21±6%. Five subjects showed increases of Vmca of 22% to 35%, and 2 subjects showed decreases of Vmca of 21% and 23%.

Conclusions—All Sherpas and the majority of the newcomers showed impaired CA. It indicates that an intact autoregulatory response to changes in blood pressure is probably not a hallmark of the normal human cerebral vasculature at altitude and that impaired CA does not play a major role in the occurrence of cerebral edema in newcomers to the altitude. (Stroke. 2000;31:2314-2318.)

Key Words: altitude ‣ autoregulation ‣ phenylephrine ‣ ultrasonography
Subjects and Methods
The study was approved by the medical ethics committee of the Academic Medical Center. It was carried out in July and August 1997 at Pheriche (4243 m), one of the highest permanent settlements in the Nepalese Himalayas. The control group was measured at sea level in Amsterdam. A history or signs of cerebrovascular or cardiac disease, the use of drugs for the prevention of AMS and psychoactive drugs, and a systolic blood pressure of >150 mm Hg were exclusion criteria for the study. The newcomers to higher altitude who participated in this study were trekkers from different backgrounds and were healthy. They spent 5 to 7 days at high altitude, of which 3 nights were spent at or above 3440 m. They had no AMS, as assessed with the AMS Lake Louise self-reporting questionnaire. Thus, they can be considered acclimatized to the high altitude for nearly 1 week. Trekkers with AMS were excluded from the study, because the use of phenylephrine to pharmacologically increase the systemic blood pressure might possibly aggravate preexisting high-altitude cerebral or pulmonary edema. The Sherpas who were studied were born and lived in the vicinity and were healthy. The sea-level control group consisted of healthy hospital workers.

During the study, the subjects were lying in a supine position with a pillow under the head. An intravenous needle, introduced in a forearm vein, was connected to a slow-running infusion with normal saline. A blood-pressure cuff (Propaq 104 EL, Protocol Systems Inc) was applied on the opposite upper arm to automatically measure MABP. Pulse oxygen saturation (SaO\textsubscript{2}, expressed as percent) and transcutaneous carbon dioxide pressure (P\textsubscript{CO\textsubscript{2}}, expressed as in millimeters of mercury) were measured with the Fastrac respiratory status monitor (model 765500–101, Sensormedics). SaO\textsubscript{2} was measured at the fingertip. The transcutaneous P\textsubscript{CO\textsubscript{2}} sensor was heated to 42\degree C and then attached to the skin below the clavicle with a double-sided adhesive ring.

During the studies at high altitude, the barometric pressure of the Fastrac monitor was set at 447 mm Hg, corresponding to the altitude of 4243 m in Pheriche. Data were obtained at 3 time periods: resting control period (T\textsubscript{1}), during induced hypertension with phenylephrine (T\textsubscript{2}), and after discontinuation of phenylephrine when MABP had returned to resting control period levels (T\textsubscript{3}). Ventilation and body temperature were kept constant between the 3 groups, autoregulation curves were constructed from these 4 consecutive registrations.

Transcranial Doppler Measurements
Blood flow velocity of the middle cerebral artery (Vmca) was determined by using a 2-MHz pulsed-wave transcranial Doppler probe with on-line spectrum analysis (T2–64B; EME). With a hand-held probe, Doppler signals from the left middle cerebral artery (MCA) were identified through the temporal window and obtained at a depth of 45 to 55 mm, corresponding to the proximal segment of the MCA. In each subject, a constant depth range and angle of insonation were kept throughout the study. When the Doppler signal was inadequate on the left side, the right MCA was insonated. The mean Vmca was calculated automatically by the standard algorithm of the instrument and is computed as the time-mean of the maximum velocity envelope, expressed in centimeters per second. The Vmca was registered as displayed on the TCD apparatus over 4 to 6 heart cycles.

Induced Hypertension
After measurements were obtained at T\textsubscript{1}, phenylephrine (0.2 mg/mL) was slowly administered through an infusion pump (Perfusor Secura FT, Braun), with the aim of elevating MABP approximately 20 mm Hg from the resting control value. This increase in blood pressure was normally reached within 10 to 15 minutes, and during a period of stable blood pressure the measurements were repeated (T\textsubscript{2}). The phenylephrine infusion rate at T\textsubscript{2} expressed in milligrams per kilogram per minute, was calculated for each subject. Then, the phenylephrine infusion was discontinued, allowing MABP to return to resting control period values (T\textsubscript{3}).

Assessment of CA
CA was derived from the MABP and Vmca values as obtained during the resting control period T\textsubscript{1} and during the period of induced hypertension T\textsubscript{2}. Theoretically, full autoregulatory capacity would be present if no change inVmca occurs in response to an increase of systemic arterial pressure, and it implies that Vmca is independent of changes of MABP. Absent autoregulation would theoretically occur if Vmca changes proportionally with alterations of MABP, rendering Vmca completely pressure passive. To compare autoregulation between the 3 groups, autoregulation curves were constructed from the resting control period values of MABP and Vmca, assumed as 100\%, and the MABP and Vmca values during phenylephrine infusion, calculated as percentage of their resting control period values.

Data Analysis
Blood gas data and hemodynamic variables are given as means and SD or SEM. Comparisons of means between groups and within groups were made with Student’s t test and ANOVA. A value of P<0.05 was considered statistically significant in all tests.

Results
The demographic data of the 3 groups are presented in Table 1. During the infusion of phenylephrine, the subjects did not report adverse effects on their well-being. Three additional subjects, a sea-level volunteer, a Sherpa, and a newcomer to the altitude, developed cardiac arrhythmias during the infusion of phenylephrine. TheirVmca and MABP registrations were unreliable and the data were rejected. The physiological variables of the 3 groups at measuring points T\textsubscript{1}, T\textsubscript{2}, and T\textsubscript{3} are presented in Table 2. The newcomers to the altitude showed significantly higher resting control MABP values than the Sherpas and the sea-level subjects. SaO\textsubscript{2} and P\textsubscript{CO\textsubscript{2}} values in the sea-level subjects were significantly higher than those in the Sherpas and the newcomers to the altitude.

During the induced increase of blood pressure at T\textsubscript{2}, the phenylephrine infusion dose in the sea-level subjects (3.0±0.4 \( \mu \)g \( \cdot \) kg\textsuperscript{-1} \( \cdot \) min\textsuperscript{-1}), the Sherpas (3.5±1.0 \( \mu \)g \( \cdot \) kg\textsuperscript{-1} \( \cdot \) min\textsuperscript{-1}), and the newcomers to the higher altitude (3.0±1.1 \( \mu \)g \( \cdot \) kg\textsuperscript{-1} \( \cdot \) min\textsuperscript{-1}) was not significantly different. There was a nonsignificant difference in increase of MABP between the Sherpas (24±6 mm Hg; 29±7\%) compared with the newcomers to the altitude (20±5 mm Hg; 21±6\%) and the sea-level subjects (19±2 mm Hg; 23±4\%). After extrapolation from the phenylephrine log dose-pressor response curve, as determined by Elliott and coworkers,\textsuperscript{11} we calculated that for a 20-mm-Hg increase in MABP, the Sherpa group should have a phenylephrine infusion dose of approximately 2.9 \( \mu \)g •

### Table 1. Demographic Data of Subjects Measured at Sea Level and 2 Groups Measured at 4243-m Altitude

<table>
<thead>
<tr>
<th></th>
<th>Sea-Level Subjects (n=10)</th>
<th>Sherpas (n=9)</th>
<th>Newcomers at Altitude (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>35±6</td>
<td>26±10*</td>
<td>27±10*</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76±6</td>
<td>51±6*</td>
<td>67±13†</td>
</tr>
<tr>
<td>Men/women</td>
<td>8/2</td>
<td>6/3</td>
<td>7/3</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*P<0.05 vs sea-level subjects; †P<0.05 vs Sherpas.
Thus, each group had a similar infusion dose of phenylephrine for a similar increase in MABP. These doses are within the range as calculated for healthy young adults at sea level.11 Characteristically, in the sea-level group the rise in MABP during phenylephrine infusion produced only a very small increase (1 ± 4 cm/s) in Vmca (Figure 1A). In the Sherpas, Vmca increased 14 ± 6 cm/s from the resting control Vmca value (Figure 1B). In 7 newcomers to the higher altitude, Vmca increased 6, 9, 11, 15, 19, 20, and 20 cm/s (7%, 8%, 22%, 24%, 34%, 23%, and 35%, respectively) in response to phenylephrine infusion. In 3 newcomers to the altitude, Vmca decreased 5, 11, and 14 cm/s (7%, 21%, and 23%, respectively) from the resting control Vmca value (Figure 1C). After discontinuation of phenylephrine, in each group MABP and Vmca returned to values at T3 that were similar to the resting control MABP and Vmca values at T1. In each subject, Vmca at T3 differed by ≥9 cm/s from the resting control Vmca value at T1. These differences are within the intraobserver variability for repeat measures during resting situations.12 In the sea-level group, relative Vmca (102 ± 7%) during phenylephrine infusion remained essentially unchanged from the resting control Vmca value (P = 0.36), indicating intact CA (Figure 2). In the Sherpa group, relative Vmca (124 ± 9%) was significantly increased (P < 0.0001) from the resting control Vmca value, signifying impaired CA (Figure 2). In the newcomers, relative Vmca was not significantly different (111 ± 21%, P = 0.15) from the resting control Vmca value (Figure 2).

In this study we found that the CA, measured at an altitude of 4243 m, is impaired in the Sherpas as well as in the majority of the newcomers to the altitude. The present findings did not support the hypothesis that high-altitude natives have a normal cerebral autoregulatory response to increases of blood pressure.

No studies have been performed on CA in healthy humans either at high altitude or during acute hypoxia. However, CA has been investigated in dogs during acute hypoxia, and loss of CA was found at arterial PO2 (PaO2) of 25 mm Hg and at arterial SO2, 60% during normocapnia, with a concomitant decrease in arterial pH (PaCO2) to 37 ± 3 mm Hg.

### Table 2. Physiological Variables, by Time Period

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sea-Level Subjects (n = 10)</th>
<th>Sherpas (n = 9)</th>
<th>Newcomers (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SaO2, %</td>
<td>T1 98 ± 2</td>
<td>89 ± 2*</td>
<td>88 ± 3*</td>
</tr>
<tr>
<td></td>
<td>T2 98 ± 2</td>
<td>89 ± 1*</td>
<td>88 ± 2*</td>
</tr>
<tr>
<td></td>
<td>T3 97 ± 1</td>
<td>88 ± 2*</td>
<td>88 ± 2*</td>
</tr>
<tr>
<td>Pco2, mm Hg</td>
<td>T1 37 ± 3</td>
<td>31 ± 5*</td>
<td>29 ± 2*</td>
</tr>
<tr>
<td></td>
<td>T2 36 ± 3</td>
<td>31 ± 5*</td>
<td>29 ± 2*</td>
</tr>
<tr>
<td></td>
<td>T3 36 ± 3</td>
<td>31 ± 5*</td>
<td>29 ± 2*</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>T1 69 ± 8</td>
<td>70 ± 14</td>
<td>75 ± 11</td>
</tr>
<tr>
<td></td>
<td>T2 49 ± 8</td>
<td>49 ± 9</td>
<td>55 ± 10</td>
</tr>
<tr>
<td></td>
<td>T3 67 ± 8</td>
<td>65 ± 12</td>
<td>70 ± 11</td>
</tr>
<tr>
<td>MABP, mm Hg</td>
<td>T1 85 ± 7</td>
<td>83 ± 6</td>
<td>94 ± 77*</td>
</tr>
<tr>
<td></td>
<td>T2 105 ± 6</td>
<td>107 ± 8</td>
<td>114 ± 77*</td>
</tr>
<tr>
<td></td>
<td>T3 82 ± 5</td>
<td>85 ± 7</td>
<td>97 ± 67*</td>
</tr>
<tr>
<td>Vmca, cm/s</td>
<td>T1 55 ± 9</td>
<td>61 ± 11</td>
<td>63 ± 12</td>
</tr>
<tr>
<td></td>
<td>T2 56 ± 11</td>
<td>75 ± 14*</td>
<td>70 ± 20</td>
</tr>
<tr>
<td></td>
<td>T3 55 ± 9</td>
<td>61 ± 10</td>
<td>64 ± 12</td>
</tr>
</tbody>
</table>

All variables are mean ± SD. T1 indicates period of resting control measurement; T2, period of phenylephrine infusion; and T3, period after discontinuation of phenylephrine.

*P < 0.05 vs sea-level subjects; †P < 0.05 vs Sherpas.

### Figure 1. Relationship between MABP and Vmca at 2 different MABP levels (during a resting control period and during phenylephrine infusion to increase blood pressure) for each individual at sea level (A) and at an altitude of 4243 m (B, C). A, Sea-level subjects uniformly showed no change in Vmca in response to an increase in MABP. B, Sherpas showed a pressure-passive increase of Vmca in response to phenylephrine infusion and blood-pressure increase. C, Newcomers to the altitude showed a divergent pattern of Vmca changes in response to increases of MABP. In 2 subjects Vmca decreased 11 and 14 cm/s, respectively, in response to phenylephrine infusion.
increase of CBF in all animals.\textsuperscript{1,2} It is thus possible that the loss of CA in the Sherpas and in the majority of the newcomers to the altitude in our study resulted from some degree of tissue ischemia or acidosis. According to Strandgaard and Paulson,\textsuperscript{13} these factors dilate the cerebral resistance vessels in an attempt to increase blood flow, and in these dilated vessels the normal vasomotor regulatory function, including the autoregulation, will be impaired. It has also been shown\textsuperscript{1,4} that loss of CA can be restored when hypocapnia is induced, with a resultant decrease in CBF. However, our data do not support this scenario (ie, that hypoxia dilates cerebral vessels with a resulting increase in CBF, thereby impairing CA, while the application of hypocapnia diminishes CBF, thereby restoring CA). Specifically, resting control \( V_{\text{mca}} \) values in the Sherpas, who have poor CA, are not different from the resting control \( V_{\text{mca}} \) values in the sea-level subjects who show perfect CA. Moreover, mean resting control \( V_{\text{mca}} \) was 64 cm/s in the 6 newcomers with impaired CA and 63 cm/s in the 4 newcomers with intact CA, indicating that CBF is similar in subjects with and without impaired CA. Probably, other effects of high-altitude hypoxia on the cerebral vessels may be responsible for the impaired CA at altitude.

First, it has been reported\textsuperscript{15} that in ischemic brain areas distal to an arterial occlusion, focal loss of CA is provoked mainly by tissue acidosis. However, in subjects after 5 days at 4300 m\textsuperscript{16} as well as in Andean high-altitude natives,\textsuperscript{17} it has been shown that cerebrospinal fluid pH is more alkaline than at sea level. Thus, it is unlikely that a decrease in cerebrospinal fluid pH is responsible for the impaired CA, as found in our study.

Second, it has been shown that Tibetans, who have lifelong adaptation to hypobaric hypoxia, have pulmonary arterioles that are devoid of any smooth muscle in the medial wall and exhibit minimal pulmonary vasoconstriction on hypoxia.\textsuperscript{18,19} An identical lack of medial wall in the cerebral vessels probably does not play a major role in explaining the impaired CA in the Sherpas. Thus, it appears that the underlying mechanism for the loss of CA in humans at higher altitude is still unknown.

It is of interest that nitric oxide, an extensively studied vasodilator produced by the endothelium, does not seem to be involved in the process of CA.\textsuperscript{20–22}

Various studies have used TCD sonography as a noninvasive measurement to evaluate CA in humans.\textsuperscript{23,24} During autoregulation testing, with use of TCD flow velocities as a measure of CBF, an excellent correlation has been found between the changes of CBF and TCD flow velocities.\textsuperscript{25} Use of \( V_{\text{mca}} \) to estimate changes in CBF during autoregulation testing requires that the diameter of the MCA remain unchanged. It is possible that the intravenous infusion of phenylephrine, an exogenous amine with \( \alpha_1 \)-agonist properties, may have produced a direct vasoconstriction of the MCA in our subjects at altitude. However, the sea-level subjects in our study, with supposedly intact CA, received doses of phenylephrine similar to those received by the Sherpas and the newcomers to the altitude. \( V_{\text{mca}} \) in the sea-level subjects did not increase, which suggests that there was no reduction in diameter of the insonated vessel. Other studies have been unable to show that \( \alpha_1 \)-adrenergic agonists produced vasoconstriction of the basilar arteries in in vitro studies,\textsuperscript{26,27} and of cerebral arteries in patients during anesthesia.\textsuperscript{28} It has also been demonstrated that during chronic high-altitude hypoxia, the cerebral arteries of adult sheep have decreased density of \( \alpha_1 \)-adrenergic receptors\textsuperscript{29} and decreased sensitivity to norepinephrine.\textsuperscript{30} Thus, it is likely that phenylephrine has no important direct or indirect effects on the diameter of the MCA, and the relative changes of \( V_{\text{mca}} \) in our subjects can be considered relative changes of CBF.

Two additional physiological factors could have influenced the TCD flow velocity values. Changes in \( \text{Sa}_2 \) and \( \text{PCO}_2 \) are associated with variations in TCD velocities. However, in our subjects the \( \text{Sa}_2 \) and \( \text{PCO}_2 \) values did not change during the study. Second, increases in peripheral vascular resistance and decreases of heart rate from the administration of phenylephrine may decrease cardiac output that could affect TCD values. However, it has been shown that at least in brain trauma patients,\textsuperscript{31} no correlation exists between the changes in cardiac output and changes in CBF, regardless of the status of cerebral blood pressure autoregulation.

In 2 newcomers to the altitude, decreases of \( V_{\text{mca}} \) of 14 and 11 cm/s (23% and 21%, respectively) in response to increases of systemic blood pressure were found. Although from our data it is not known whether these decreases represent the extremes of a normal autoregulatory response or a pattern of hyperactive autoregulation, these decreases may critically lower the oxygen supply to the brain in some subjects and may lead to cerebral ischemia and/or focal neurological deficits, as has been repeatedly reported in humans at altitude.\textsuperscript{32,33}

In conclusion, this study shows evidence for a poor CA in Sherpas at altitude. The majority of the newcomers to higher altitude also had an impaired autoregulation at that altitude, but in some newcomers the autoregulation was preserved. This finding indicates that an intact CA response to changes
in blood pressure is probably not a hallmark of the normal human cerebral vasculature at altitude. It also indicates that an impaired CA per se may not play a major role in the occurrence of HACE in newcomers at altitude, because Sherpas do not develop HACE at the altitude at which they live.

Acknowledgment
We are greatly indebted to the volunteers and the Sherpas from the Kumbu region who participated in the study, and we express our gratitude to the Himalayan Rescue Association in Kathmandu and Pheriche for their cooperation.

References
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