

# Going High with Preexisting Neurological Conditions

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## ABSTRACT

Baumgartner, Ralf W., Adrian M. Siegel, and Peter H. Hackett. Going high with preexisting neurological conditions. *High Alt. Med. Biol.* 8:108–116, 2007.—This review presents the potential impact of high altitude exposure on preexisting neurological conditions in patients usually living at low altitude. The neurological conditions include permanent and transient ischemia of the brain, occlusive cerebral artery disease, cerebral venous thrombosis, intracranial hemorrhage and vascular malformations, multiple sclerosis, intracranial space-occupying lesions, dementia, extrapyramidal disorders, migraine and other headaches, and epileptic seizures. New developments in diagnostic work-up and treatment of preexisting neurological conditions are also mentioned where applicable. For each neurological disorder, the authors developed absolute and relative contraindications for a trip to high altitude. These recommendations are not based on the results of controlled randomized trials, but mainly on case reports, pathophysiological considerations, and extrapolations from the low altitude situation.

**Key Words:** altitude illness; epilepsy; headache; hypoxia; migraine; stroke

## INTRODUCTION

**P**REEXISTING NEUROLOGICAL CONDITIONS are either stable or unstable. Patients with unstable neurological conditions show progressive (e.g., a patient with inoperable malignant glioma) or improving neurological deficits (e.g., a patient recovering from acute stroke). These patients should not travel to high altitude, because even minimal neurological deficits may worsen, and hypoxia might impair recovery. Patients with stable neurological deficits (e.g., a patient who suffered a stroke 5 yr ago) might become more easily fatigued with active ascent to altitude (e.g., by foot), and their neurological deficit may deteriorate be-

cause of exertion combined with altitude. Conversely, a trip to high altitude using a vehicle (passive ascent) eliminates the factor of exercise and may be more benign. Suggested absolute and relative contraindications for active and passive ascent to high altitude are proposed in Table 1.

Patients with preexisting neurological conditions may also suffer from comorbidities. For instance, patients with cerebrovascular disease may have other medical conditions, such as coronary and peripheral artery disease, cardiac arrhythmia, chronic obstructive pulmonary disease, arterial hypertension, obesity, and diabetes mellitus. Comorbid diseases may further impair neurological deficits at high alti-

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TABLE 1. ABSOLUTE AND RELATIVE CONTRAINDICATIONS FOR ASCENT TO HIGH ALTITUDE

Absolute contraindications for active and passive ascent
Patients with unstable preexisting neurological conditions (progressive, recovering, or fluctuating neurological deficits)
Patients with a high risk of stroke recurrence (e.g., lobar hemorrhage due to cerebral amyloid angiopathy)
Patients who suffered a transient ischemic attack within the last 90 days
Patients with preexisting neurological conditions leading to residual deficits of the central or peripheral nervous system should not ascend actively, but may perform a passive ascent using a transport vehicle.
Relative contraindications for active and passive ascent
Severe stenosis or occlusion of a cerebral artery
Space-occupying lesion
Poorly controlled seizure disorder
Known cerebral aneurysm

tude or represent a contraindication to such trips.

In this article, we discuss the potential impact of high altitude exposure on neurological disease in patients usually living at low altitude. New developments in diagnostic work-up and treatment of preexisting neurological conditions are also mentioned where applicable. It is important to note that the following recommendations are not based on the results of controlled randomized trials, but mainly on case reports, pathophysiological considerations, and extrapolations from the low altitude situation.

### PERMANENT AND TRANSIENT ISCHEMIA OF THE BRAIN

Stroke and transient ischemic attack (TIA) are emergency medical conditions at low altitude. The NINDS study and a meta-analysis have shown that intravenous thrombolysis with recombinant tissue plasminogen activator is beneficial for patients with ischemic stroke defined as focal neurological deficit lasting at least 24 hr (The National Institute of Neurological Disorders and Stroke

rt-PA Study Group, 1995; The ATLANTIS ECASS and NINDS rt-PA Study Group Investigators, 2004). Furthermore, treatment in a stroke unit reduced morbidity and mortality (Stroke Unit Trialists' Collaboration, 1997). Consequently, altitude visitors with suspicion of ischemic stroke must be brought as fast as possible to the nearest appropriate medical center, which is in the ideal case a stroke unit.

The results of recent hospital- (Johnston et al., 2000) and population-based (Lovett et al., 2003; Coull et al., 2004; Hill et al., 2004; Kleindorfer et al., 2005) studies and a post hoc analysis of the European Carotid Surgery Trial (Eliasziw et al., 2004) also indicate that patients who suffer a TIA defined as a focal neurological deficit lasting less than 24 hr must be treated as medical emergencies, since the stroke risk was 5.0%–5.3% within 48 hr, 8.0%–8.6% within 7 days, and 9.5%–20.13% within 90 days. Furthermore, a hospital-based study found that 25.1% of 1707 patients with TIA suffered a stroke (10.5%), recurrent TIA (12.7%), or cardiovascular event requiring hospitalization (2.6%) or died (2.6%) within 90 days after onset of symptoms of brain ischemia (Johnston et al., 2000). There is no clear evidence that the mechanism of TIA and the subsequent stroke risk differ at high compared to low altitude. Furthermore, it is tempting to speculate that hypoxia and elevated hematocrit might increase the area of infarction. It thus seems reasonable to suggest that mountaineers and others at altitude with suspicion of TIA also need an emergency diagnostic work-up, which will enable the rapid institution of an appropriate stroke-prevention therapy. A pragmatic alternative might be to start with aspirin, as the probability of an underlying intracranial hemorrhage is low (Warlow, et al., 2001). However, in a British study of 512 patients referred by their family doctor or a hospital doctor with the diagnosis of possible TIA, 317 (62%) were considered by the stroke neurologists not to have had a TIA, but other diseases such as migraine, isolated vertigo, syncope, and epilepsy (Dennis, et al., 1989). These findings suggest that the diagnosis of TIA should be clear before the administration of aspirin.

## STROKE RISK AT HIGH ALTITUDE

Cases of ischemic stroke have been reported in generally healthy lowlanders during short-term sojourns at high altitude (Clarke, 1983; Houston, 1987). However, no study has investigated whether short-term stays at high altitude change the incidence, prevalence, or mortality of stroke. Several case-control studies have investigated the stroke risk during long-term sojourn of lowlanders at high altitude. In a study conducted in young Pakistani adults, 10 of 4000 subjects living at a height of at least 4600 m and 1 of 4000 subjects living at Rawalpindi (height 600 m) suffered a stroke ( $p < 0.05$ ) (Niaz and Nayyar, 2003). Patient selection, incomplete diagnostic work-up (e.g., only the carotid arteries were investigated in some patients), and the fact that 8 of 10 stroke patients had high altitude cerebral edema (HACE), which is often associated with ischemic and hemorrhagic infarcts, limit the conclusions of the study (Niaz and Nayyar, 2003). In an Indian study, prospectively collected data of consecutive patients <45 yr of age hospitalized at Command Hospital, Chandimandir, Haryana, were reviewed to identify thrombotic complications, including stroke among patients living at high (>3000 m) and extremely high (>5000 m) altitude, as well as residents of low altitude (Anand et al., 2001). Stroke was the reason for hospital admission in 15 (0.89%) of 1692 patients at high altitude, and in 12 (0.06%) of 18,565 patients at low altitude (OR, 13.8; 95% CI, 6.1–31.5;  $p < 0.001$ ) (Anand et al., 2001). Another study of the Indian army found that strokes formed 13.7 per 1000 hospital admissions from high altitude areas, compared to 1.05 per 1000 in nonhigh altitude areas (Jha et al., 2002). In conclusion, the aforementioned studies suggest that the long-term sojourn of lowlanders at high altitude is associated with an increased risk of stroke. It is unclear whether these observations, obtained mainly in young male soldiers, are applicable to women and mountaineers who are not members of armed forces. One concern is that high altitude might have more impact on those with a history of stroke, but no data are yet available.

## STROKE RISK FACTORS AT HIGH ALTITUDE

A trip to high altitude will expose the mountaineer to several risk factors for stroke, including cerebral venous thrombosis (CVT), that are usually not present at low altitude. These factors include both a decrease in plasma volume and increased production of erythropoietin, causing higher hematocrit and hemoglobin and polycythemia, which is an independent risk factor for stroke (Kiyohara et al., 1989; Hart and Kanter 1990; Jaillard et al., 1995). An increased risk of thrombus formation may also result from (1) low ambient temperature, which reduces blood flow and may damage blood vessels; (2) bad weather conditions, which may entail forced inactivity; and (3) dehydration, which may facilitate stasis of blood in the extremities (Clarke, 1983; Houston, 1987). In addition, ischemic stroke and cerebral artery thrombosis are typical complications of high altitude cerebral edema (HACE) (Houston and Dickinson, 1975; Hackett, et al., 1976; Dickinson, 1981).

Whether a prothrombotic state develops from hypobaric hypoxia per se is much debated. During acute exposure to hypobaric hypoxia, several studies have shown coagulation abnormalities, such as a decrease of mean partial thromboplastin time, fibrinogen, and factor VII (Maher et al., 1976; Le Roux, et al., 1992; Hudson et al., 1999); other studies have shown no significant effect, especially with slower ascent to moderate altitude (Grover and Bärtsch, 2001). Data concerning the bleeding time are conflicting as it has been reported to increase (Doughty and Beardmore, 1994) or remain unchanged (Maher et al., 1976). Other factors influencing thrombosis, such as thrombocytosis (Maher et al., 1976), increased capillary fragility (Doughty and Beardmore, 1994) and endothelial cell damage (Le Roux et al., 1992), have also been observed. Overall, however, it is not clear that altitude per se induces a prothrombotic state (Grover and Bärtsch, 2001).

Although erythropoietin may induce polycythemia, recent studies have shown that cerebral neuronal, glia, and endothelial cells also have erythropoietin receptors and express this cytokine agent (Hudson et al., 1999; Gassmann

et al., 2003; Brines and Cerami, 2005; Grimm et al., 2005). Erythropoietin mediates an evolutionarily conserved, ancient immune response that limits damage to human tissues, including the brain, following an injury. This brain injury is nonspecific and includes stroke and hypoxia. The neuroprotective action of the administration of erythropoietin has been demonstrated in vitro and in animal models, and preliminary human data suggest that this agent may also be beneficial in patients with acute ischemic stroke (Ehrenreich et al., 2002). Thus, one might speculate that increased production of erythropoietin might be neuroprotective in patients with stroke occurring at high altitude.

### RECOMMENDATIONS

Patients who have suffered a stroke have an increased risk to suffer a second stroke. This risk is higher in the first year and depends on the etiology of stroke. Patients with stroke secondary to atrial fibrillation have a 10% annual stroke risk when treated with aspirin (European Atrial Fibrillation Trial Study Group, 1993), whereas this risk is much lower in patients who underwent carotid surgery for symptomatic severe carotid stenosis (Barnett et al., 1998; European Carotid Surgery Trialists' Collaborative Group, 1998). As shown in the previous section, high altitude might further increase the risk of stroke by mechanisms that are not well defined. Thus, every mountaineer who has suffered a stroke should define with his treating physician or a stroke neurologist his individual risk for stroke recurrence and whether antithrombotic therapy (antiplatelet agent, anticoagulation) is necessary. Furthermore, it might be useful to determine the time needed to reach the next hospital providing an acute diagnostic work-up and therapy of stroke. Based on these findings, the patient and his treating physician can make an individual decision as to whether a trip to high altitude is appropriate.

As already mentioned, patients who have suffered a TIA have a 25% risk to suffer a stroke, TIA, cardiac disease, or vascular death within the next 90 days (Johnston et al., 2000),

suggesting that they should not go to high altitude during the aforementioned period of time. For later trips, the decision to travel to high altitude should be based on the same evaluation as described for stroke patients.

### OCCLUSIVE CEREBRAL ARTERY DISEASE

It is unknown whether hypoxia may lead to hemodynamic insufficiency resulting in TIA or even stroke in patients with asymptomatic severe stenosis or occlusion of a cerebral artery. Since the increase in cerebral blood flow is an important adjustment to high altitude and since it seems likely that persons with occlusive disease will have an impaired ability to increase CBF, these patients may be at increased risk for cerebral hypoxia and altitude illness; we consider the presence of severe occlusive cerebrovascular disease as a relative contraindication for travel to high altitude.

### CEREBRAL VENOUS THROMBOSIS

The aforementioned hematological, rheological, and vascular changes occurring at high altitude suggest that altitude visitors, and especially mountaineers, might have an increased risk for developing venous thrombosis. Supporting this, young male soldiers were reported to have an increased risk for thrombosis of extracerebral veins during long-term sojourns at high altitude (Anand et al., 2001). Patients with CVT occurring at high altitude have been reported in case reports and small-scale studies (Fujimaki et al., 1986; Hackett, 1987; Jha et al., 2002; Saito and Tanaka, 2003). The main cause was assumed to be high altitude polycythemia, but some patients also had preexisting thrombophilia, mainly heterozygous protein S or C deficiency (Boulos et al., 1999; Basnyat et al., 2001; Jha et al., 2002). No study has investigated whether CVT occurs more often at high compared to low altitude, and the proportion of patients with CVT at high altitude who have familial thrombophilia is unclear. Thus, there is no evidence suggesting that

subjects who plan a trip to high altitude should undergo a check for familial thrombophilia. It is also uncertain whether women should stop oral contraceptives and hormone replacement therapy, which are well-known independent risk factors for deep and cerebral venous thrombosis. Clearly, their risk is already high if they also smoke cigarettes, and the added factor of high altitude would be of concern. The present authors recommend that mountaineers should stay well hydrated, avoid immobility to prevent deep venous thrombosis, and perhaps take oral aspirin.

Immobility is not a risk factor for cerebral but for deep venous thrombosis (Baumgartner et al., 2003). The reason is that cerebral veins and sinuses have a continuous blood flow and no valves, whereas venous flow in the limbs is not continuous, but requires the presence of valves and the activity of muscles.

#### **INTRACRANIAL HEMORRHAGE AND VASCULAR MALFORMATIONS**

No study has evaluated the influence of high altitude on the frequency of intracranial hemorrhage. Thus, the subsequent recommendations are based on theoretical considerations.

Patients with lobar hemorrhage, which mainly results from cerebral amyloid angiopathy, have a high risk of recurrence (Passero et al., 1995; O'Donnell et al., 2000; Izumihara et al., 2005), which was 21% in the first 2 yr in a prospective observational study (O'Donnell et al., 2000). These patients should not ascend to high altitude because of the difficulties of managing a recurrence in a remote setting. Conversely, the recurrence risk is much lower in primary intracranial hemorrhage due to hypertension (Hirohata et al., 1991; Chen et al., 1995; Maruishi et al., 1995; Passero et al., 1995). The influence of high altitude on the bleeding risk of cerebral aneurysms (Dickinson et al., 1983; Litch et al., 1997), arteriovenous malformations (AVM), and cavernous hemangiomas (cavernomas) is unclear. High altitude-related blood pressure changes (Puri et al., 1986; Sun, 1986; Hackett, 2001) could increase intraluminal pressure and rupture risk of aneurysms and AVMs. In addition, high altitude increases cap-

illary fragility (Doughty and Beardmore, 1994) and may damage endothelial cells (Le Roux et al., 1992), which could increase the bleeding risk. Furthermore, the increase in CBF on ascent could also increase risk of bleeding from aneurysms and malformations (Hackett, 2001). Without pertinent data, what to advise these patients is problematic and must be individualized according to the patient's assessment and acceptance of unquantifiable risk.

#### **MULTIPLE SCLEROSIS**

Patients with multiple sclerosis (MS) may develop new neurological signs and symptoms within a few hours or days due to an exacerbation of the disease, an increase of body temperature resulting from the physical effort, or an infection. There is no evidence that altitude per se causes problems for persons with MS. In fact, a camp for MS patients is operated in Vail, Colorado (2500 m), and they report no issues related to the altitude. However, patients with multiple sclerosis should be careful not to overexert and raise body temperature.

#### **INTRACRANIAL SPACE-OCCUPYING LESION**

Patients with symptomatic intracranial space-occupying lesions are neurologically unstable and should thus not travel to high altitude. Space-occupying lesions can be unmasked upon ascent to high altitude (Shlim and Heleen, 1990). MRI studies indicate that increases in brain volume are an unlikely cause (Mórocz et al., 2001; Bärtsch et al., 2004; Fischer et al., 2004). One possible mechanism, however, is an increase in peritumoral edema due to hypoxia. Shlim and others (1991) reported four such cases, two with meningioma and two with brain metastases. The frequency of people with asymptomatic intracranial space-occupying lesions who will unmask at high altitude is unknown, but is probably very small. In patients with known asymptomatic intracranial tumor or other space-occupying lesions, caution is warranted. In contrast, an arachnoidal cyst is a frequent finding at brain imaging and is as-

sumed to be a benign condition at low altitude. It is unclear, however, whether these cysts may increase in size and become symptomatic at high altitude and caution might be warranted (Hackett, 2000).

### DEMENTIA AND EXTRAPYRAMIDAL DISORDERS

The effect of high altitude on the symptoms and signs of patients with cognitive impairment or extrapyramidal disorders has not been investigated to our knowledge. However, in vitro and animal studies have shown that mild and moderate levels of hypoxia affect the synthesis, reuptake, and release of acetylcholine, dopamine, and amino acids (Gibson and Blass, 1976; Gibson et al., 1981a; Gibson et al., 1981b; Aikayama et al., 1992). Thus, high altitude might further impair the neurological dysfunctions of these patients. Furthermore, the use of dexamethasone for therapy of acute mountain sickness must be controlled, because it may reduce the effect of anticholinergic drugs and cholinesterase inhibitors (Table 2). Usui and others (2004) reported a patient who developed subcortical dementia after HACE. These findings suggest that patients with cognitive impairment or extrapyramidal disorders should ascend passively and under the surveillance of healthy persons to high altitude.

### PREEXISTING MIGRAINE AND OTHER HEADACHES

In a recent study, the presence of headache at low altitude was not a risk factor for the development of high altitude headache (Silber et al., 2003). Women reported headaches of greater severity (5 to 10 points on a scale of 0 to 10, where 0 was pain free and 10 the worst pain of one's life) and a greater frequency of headaches at high altitude (Silber et al., 2003). These differences between sexes are probably caused by a combination of differences in the reporting of pain between men and women and genuine physiologic differences between men and women (Headache Classification Committee of the International

TABLE 2. INTERACTIONS BETWEEN DRUGS USED FOR HIGH ALTITUDE ILLNESS AND FOR PREEXISTING NEUROLOGICAL CONDITIONS

Acetazolamide	Increases the effect of oral anticoagulants, barbiturates, phenytoin, and carbamazepine (Spina et al., 1996; Arzneimittelkompendium der Schweiz, 2005)
Aspirin	Increases the risk of bleeding in patients who are anticoagulated Increases the effect of barbiturates, phenytoin, and valproate and may cause adverse events (personality changes, pathological nystagmus, tremor, ataxia)
Dexamethasone	Increases the risk of gastrointestinal hemorrhage in patients with aspirin pretreatment Increases the effect of oral anticoagulation (Costedoat-Chalumeau et al., 2000) May reduce the effect of anticholinergic drugs and cholinesterase inhibitors
Nifedipine	Phenytoin reduces the bioavailability and possible efficacy of nifedipine Carbamazepine reduces plasma concentration and efficacy of nifedipine Valproate increases the plasma concentration and efficacy of nifedipine Nifedipine reduces the needed dose of tacrolimus, because both drugs are metabolized by cytochrome P4503A4
Benzodiazepines	Contraindicated in patients with myasthenia gravis May worsen the symptoms of sleep apnea syndrome

Headache Society (IHS) (2004). At low altitude, the incidence of most headache disorders is higher in women compared with men, suggesting that women may be more susceptible to headache at high altitude as well (Silber et al., 2003). Clinicians working at high altitude locations, however, have noted that altitude can be a trigger for migraine (Hackett, 2001), which is also acknowledged by the International Headache Society, or may change the character of migraine events (Murchoch, 1995). Overall, the presence of preex-

isting migraine or other headaches is not a contraindication for a trip to high altitude.

### EPILEPTIC SEIZURES

Acute, severe hypoxia may cause epileptic seizures, a fact more relevant and well known in aviation medicine. De novo seizures in sojourners at altitude, without an underlying seizure focus and with or without HACE, are anecdotal, but may be fatal (Basnyat 1998).

In persons with seizure disorders, however, exacerbation possibly due to altitude has been more commonly observed, at least in those not on medication. Shlim noted two persons with new onset seizure within hours after flying to Lhasa (3700 m) (Shlim, personal communication). On subsequent work-up, one was found to have epilepsy; the cause for the other was unexplained. On Mt. McKinley, a camp worker had a grand mal seizure within 12 hr of abrupt ascent to 4300 m. She had a childhood history of epilepsy, but had discontinued her medications years earlier since she had been without seizures. She remained at altitude, taking phenytoin, and had no further problems (Hackett, unpublished observation). In another case, an 11-year-old girl suffered from a first seizure on a chair lift at 3000 m, and subsequent evaluation revealed a previously unknown epileptic focus (Hackett, unpublished observation). Other case reports have been published (Basnyat et al., 2004). The mechanism of exacerbation might be related to the respiratory alkalosis of altitude or to the hypoxia. However, sleep deprivation at high altitude (e.g., due to headache or respiratory problems) may be another seizure-provoking factor. Other conditions may also present with seizure, such as cerebral venous thrombosis (Grotta, 1996).

In contrast to these apparently unusual events, syncope is common at high altitude (Nicholas and O'Meara, 1993). Since syncope of any cause may infrequently have attendant seizure activity (convulsive syncope), confusion of convulsive syncope with a true seizure is inevitable. Systematic studies of patients with seizure disorders are sorely needed to deter-

mine whether high altitude is truly a risk for these individuals. Anecdotally, those with seizure disorders have had no increase in frequency or severity of seizures when medications were continued at high altitude, although a breakthrough seizure could occur at any altitude (Basnyat, 2001).

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