REVIEW ARTICLE

Blood pressure at high altitude: physiology and clinical implications

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ABSTRACT

High altitude is a fascinating model of hypoxia effects on the human body, but it is also an extreme environment that directly influences millions of people who either travel to high altitude locations or live there permanently. A significant progress has been made over the past decades in the understanding of physiological background of responses to altitude, and recently, a number of studies regarding clinical aspects of high-altitude exposure have been published. In particular, more is known about the changes in systemic blood pressure (BP) in individuals exposed to high altitude as well as on the effects of antihypertensive drugs in this setting. The present article provides an overview of principal physiological and clinical aspects related to systemic BP control and its changes at high altitude, mainly during the acute exposure. The evidence on BP changes at rest and during exercise is discussed, as well as the underlying mechanisms and possible clinical implications.

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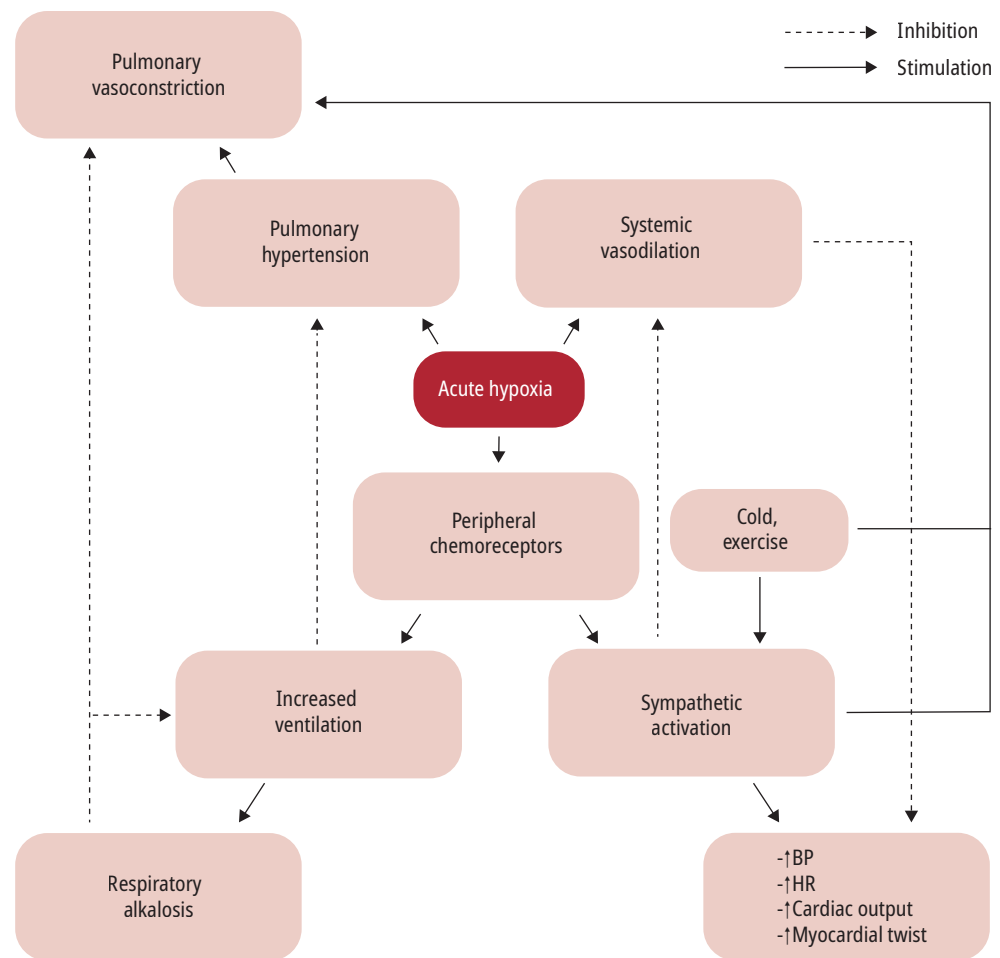Italy, phone: +39 02 619112903,
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Introduction   High altitude (HA) is an extreme environment, challenging for the human body. Cold, low air humidity, and high ultraviolet radiation levels may all make the adaptation to this condition difficult. However, the foremost factor underlying physiological responses to HA is the low atmospheric pressure and the consequent proportional reduction of oxygen partial pressure in the inspired air (hypobaric hypoxia; FIGURE 1).[1,2] This occurs even though the relative air composition remains the same as at sea level, with oxygen content being about 21%. The ensuing hypoxemia and tissue hypoxia trigger numerous regulatory mechanisms, which in most cases favor adaptation but may sometimes evolve into pathological conditions such as acute mountain sickness (AMS) or chronic mountain sickness (Monge disease).

Pulmonary hypertension is one of the key features characterizing both AMS and chronic mountain sickness and is the key pathogenetic factor in one of the most severe forms of AMS, that is, high-altitude pulmonary edema. Because of that, pulmonary circulation in HA has been extensively investigated over the years both from a pathophysiological and clinical point

of view.[1] Conversely, the responses of peripheral circulation and, in particular, of systemic arterial blood pressure (BP) have received much less attention. Contrary to pulmonary hypertension, changes in BP have not been so far clearly associated with pathological responses to HA. From an epidemiological point of view, however, even minor BP changes induced by HA stay might after all be relevant. This is because in the general population, each mm Hg increase in systemic BP has a significant prognostic impact and also because the number of people exposed to elevated altitudes is nowadays considerable, including a relevant proportion of those with cardiovascular risk factors or diseases, such as arterial hypertension.[3,4] On one hand, brief HA exposures have become common due to the development of mass mountain tourism and high-altitude industries (eg, mining). On the other hand, millions of people permanently live at HA, mainly in Asia, South America, and Ethiopia. These highland populations were in the past characterized by healthy lifestyles from a cardiovascular point of view. However, the economic changes over the last decades have led to easier availability of poor quality food and to less active lifestyle,

not accompanied by adequate health education. As a consequence, these populations are now facing an unprecedented epidemic of obesity and spread of cardiovascular risk factors, including arterial hypertension.

Beside these epidemiological considerations, the study of cardiovascular responses to hypoxia in healthy people may represent a useful model for assessing complex hypoxia-related processes, which are common in pulmonary and cardiovascular diseases. The advantage of such a model is the possibility to investigate responses to hypoxia without the interference by major confounding factors commonly present in hypoxic patients, which may per se affect systemic BP levels (eg, obesity, sleep apnea, and heart failure).

On this background, the present article provides an overview of principal physiological and clinical aspects related to systemic BP control and changes at HA, focusing mainly on the acute exposure. In particular, the paper discusses the studies documenting BP changes at rest and during exercise, as well as addresses the underlying mechanisms and possible clinical implications.

Blood pressure and its regulation at high altitude Numerous laboratory studies addressed the impact of hypoxia on BP in animals and humans. Classic physiological studies showed that mean arterial pressure changes little during acute hypoxia (simulated altitude), despite important changes that occur in systemic hemodynamics. This is because a significant increase in cardiac output, mostly driven by a sympathetic-mediated increase in heart rate (stroke volume remains largely unchanged), is contrasted by a drop in peripheral vascular resistance, due to direct hypoxic vasodilation. The net effect on BP is thus near zero.[5]

While laboratory research provides a very detailed insight into physiological changes in BP and its regulatory mechanisms, this information cannot be readily extrapolated to real HA exposure of human beings. This is because: 1) the duration of simulated exposure is typically short (usually much less than 24 hours); therefore, it does not take into account changes that occur in regulatory mechanisms over longer time; 2) laboratory studies usually do not consider numerous other factors that may play a significant role in the extreme environment of high mountains, such as cold, physical exertion, emotional stress, changes in food and water intake. To address these limitations, a number of field studies were performed to assess the impact of HA on BP.

Studies on conventionally measured BP indicated a possible pressor effect of HA exposure, although the data were not always consistent.[1,5,6] However, in a clinical setting, spot
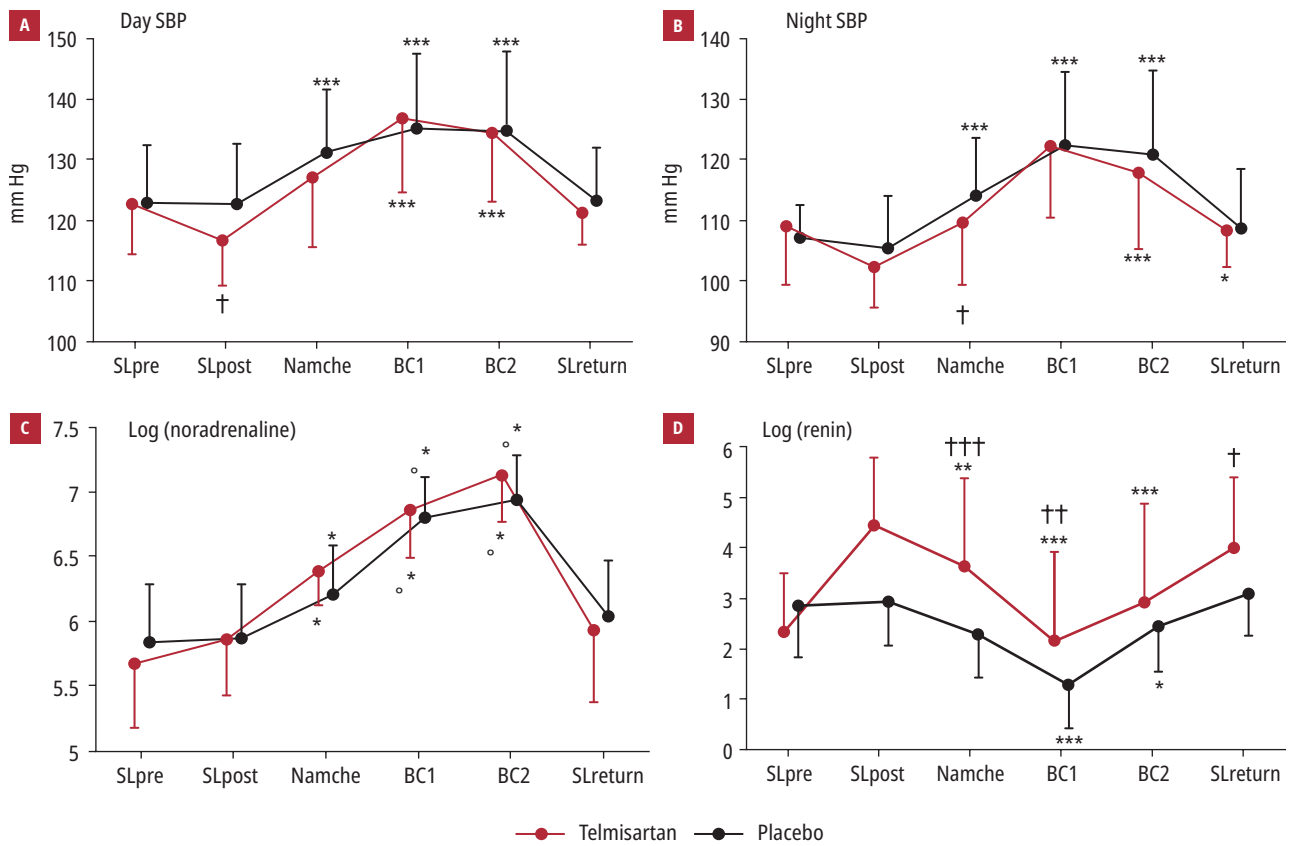
FIGURE 2 Changes in systolic blood pressure (SBP) during the day (**A**) and night (**B**) in healthy participants of the HIGHCARE-HIMALAYA study randomized to placebo (blue lines) or telmisartan, 80 mg once daily (red lines). Lower panels show parallel changes occurring in the levels of noradrenaline (**C**) and renin (**D**). Data obtained at sea level pretreatment (SLpre), at sea level posttreatment (SLpost), at 3400 m (Namche), at Mount Everest base camp, 5400 m, during the first 3 days (BC1) and after 11 to 12 days (BC2), and immediately after return to sea level (SLreturn). Different symbols indicate significance of differences between groups (cross symbols) and of differences between altitudes considering the SLpost as reference (circles and asterisks). Modified from Parati et al.[9]

measurements in resting conditions are known to provide a very limited view of the individual's BP status, being confined to a single moment during the day and affected by both random and systematic errors, including white coat effect. Conventional BP measurements are thus ill suited to accurately explore the effects of environmental factors, such as barometric pressure, air temperature, and pollution, on BP levels. A more reproducible and extensive evaluation of BP can be achieved by means of 24-hour ambulatory BP monitoring, which has the additional advantage of assessing BP under daily life conditions, including daytime challenges and nighttime sleep.

On this background, several research groups applied this technique to evaluate BP changes at HA. Wolfel et al[7] and Veglio et al[8] provided initial evidence of BP increase during HA exposure. Following these studies, our group performed a study in Nepal (HIGHCARE [HIGH altitude Cardiovascular Research]-HIMALAYA) in 47 healthy volunteers evaluated at sea level, after a short (2–3 days) exposure to an altitude of 3400 m, then immediately after reaching 5400 m (Mount Everest base camp), and after 12-day stay at this altitude. A clear increase of 24-hour,

daytime, and nighttime BP was seen already at 3400 m, with a further BP increment after arrival at 5400 m. Blood pressure values remained stably elevated also after a prolonged stay at HA (FIGURE 2).[9] The increase in BP with altitude seems thus to be continuous and proportional to the altitude reached. In fact, in a more recent study in healthy volunteers, we observed that even the exposure to about 2000 m (eg, moderate altitude) may induce a modest but significant 24-hour BP increase (unpublished data). Furthermore, an increase in 24-hour BP was also found by our group in patients with hypertension acutely exposed to an altitude of 3200 m (see below).[10]

A more detailed analysis of HIGHCARE-HIMALAYA data revealed that at very high altitudes (5400 m), BP increase was particularly evident during the night, leading to a reduced nocturnal fall in BP (dipping). This phenomenon was not observed during acute exposure to 3400 m in the same study or in individuals exposed to an altitude of 2000 m.[9]

Physiological mechanisms involved in BP control are complex and their contribution in mediating a BP increase at altitude was the object of several studies. From a hemodynamic point of view, increased peripheral resistance seems to

be of key importance. Persistent chemoreceptor-mediated sympathetic activation was in fact demonstrated during hypobaric hypoxia exposure (an increase in plasmatic noradrenalin, but not adrenalin, levels was reported, as well as an increase in peroneal nerve sympathetic fiber firing in a microneurography study was observed),[9,11] while after the initial hours of exposure, the direct vasodilatory effect of hypoxia seemed to lose importance. The importance of chemoreflex activation is supported by the finding that an increase in blood oxygenation induced by slow, deep breathing was associated with an immediate decrease of BP values.[12] On the other hand, chemoreflex activation is accompanied by an alteration in arterial baroreflex (resetting to higher operating BP and reduced baroreflex sensitivity were reported in different studies).[11,13] However, cardiac output remains substantially unchanged despite a persistent increase in heart rate, because of reduced plasma volume (increase in urine output normally occurs over the first days of HA exposure) and the ensuing reduction in stroke volume. Contractility of the left ventricle is globally unaffected, although changes in contraction mechanics (particularly in left ventricular torsion) were shown, possibly due to impaired contraction of subendocardial layers of the myocardium.[14,15]

Interestingly, the renin–angiotensin–aldosterone system (RAAS) does not seem to be involved in a BP increase at HA; on the contrary, its activity is suppressed at very high altitude (above 3400 m).[9] The mechanisms underlying this response are not clear, but the activation of kidney baroreceptors secondary to a BP increase or a direct inhibitory effect of hypoxia on renin secretion might be involved.[16] Other mechanisms may also be called into question in modulating BP changes occurring at HA, including an increase in aortic stiffness (possibly sympathetically mediated), impaired endothelial function and increase in blood viscosity due to hemoconcentration.[17-20] The latter phenomenon manifests itself relatively early during the exposure, due to loss of plasma volume, and is accentuated with time due to increased erythropoiesis in response to hypoxia. In fact, also very high hematocrit levels seen with chronic HA exposure in highlanders appear to be associated with higher BP levels.[21]

Regarding BP changes with a more prolonged HA exposure, the data are rather limited. A study in young army recruits indicated that elevated BP may persist even after 12-month stay.[22] Studies in highlanders provided inconsistent results, although a recent meta-analysis has suggested that there may be a direct linear association between altitude and BP.[23] Unfortunately, the epidemiological data coming from different altitudes are difficult to compare owing to major confounders: different lifestyles between countries and between urban and rural areas, climatic effects, genetic adaptations, and epigenetic mechanisms.[24]

Nighttime BP merits a special mention in this regard. It is still not clear why an increase in BP may be more pronounced during the night, but there are several hypotheses. Firstly, at HA, blood oxygenation during sleep is known to further decrease compared with daytime values, which might lead to a more pronounced chemoreceptor stimulation and thereby to the maintenance of abnormally high sympathetic tone also during sleep. Secondly, sleep at HA is typically characterized by the occurrence of central apneas, frequently assuming a periodic breathing pattern. Although, in contrast to obstructive apneas, the association of central apneas with elevated BP has not been documented, it cannot be fully excluded.[25] Finally, sleep quality at HA is frequently impaired because of AMS symptoms, drier inspired air, and psychological stress, and this may further affect nocturnal BP levels.
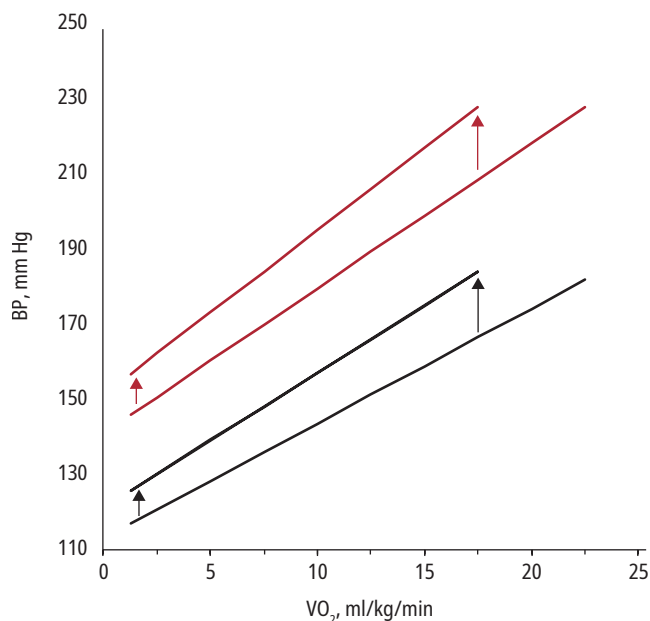
Blood pressure changes during exercise at high altitude

Stay at HA is frequently associated with physical effort (mountain climbing, work). When exercising at altitude, the stress of exercise adds to the stress caused by the reduced oxygen availability of this environment. Cardiovascular adaptation to exercise during acute HA exposure is characterized by higher heart rate, BP, and ventilatory equivalents at any given level of exercise compared with sea level, due to hypoxia-induced sympathetic activation.[26] However, exercise capacity is reduced at altitude as a consequence of low partial pressure of oxygen in the inspired air, limiting muscle oxygen delivery in a way that is directly proportional to the altitude at which effort is undertaken.[26] This may explain why absolute BP levels achieved at peak exercise might not be much different between HA and sea level, a finding which needs to be interpreted with caution, considering the reduced maximal oxygen consumption characterizing high altitude.[27]

Higher BP and heart rate, combined with a reduction in the subendocardial viability ratio (an index characterizing aortic pressure waveform, reflecting diastolic coronary perfusion and systolic energy requirements in the coronary circulation)[28] at any given level of exercise in hypoxia, may contribute to an imbalance between myocardial oxygen supply and demand in nonacclimatized exercising individuals.[29] This mechanism has been proposed to explain sporadic cases of myocardial ischemia reported in this specific setting.[30-32] Moreover, BP recovery after exercise might occur more slowly than at sea level, even after submaximal exercise.[33]

Patients with hypertension are likely more prone to develop high BP at exercise than normotensive individuals.[27,34-36] In particular, after

FIGURE 3 Schematic representation of changes in systolic blood pressure (BP) during exercise at high altitude. With increasing workload and oxygen consumption (VO_2, x axis) at altitude BP increases more steeply (dotted lines) than at sea level (continuous line). However, peak exercise BP is similar in both conditions because the achieved peak VO_2 is lower at altitude. In individuals under antihypertensive treatment (blue lines), the pattern is similar but BP is shifted towards lower values. Modified from Caravita et al.[27]

normalizing BP increase at altitude for the metabolic demands imposed by exercise, BP trajectories of hypertensive lowlanders exercising at altitude are shifted upwards and become steeper compared with those observed at sea level.[27] This means that if BP is not adequately controlled at sea level, it will be even more so during exercise at altitude (FIGURE 3).

Very few studies addressed the effect of pharmacological treatment on BP during exercise at altitude.[29] In this perspective, it should be acknowledged that some drugs (in particular, nonselective β-blockers) may have deleterious effects on exercise physiology at altitude, negatively affecting the ventilatory control and oxygen diffusion at the alveolar-capillary membrane level.[37] Conversely, a combination treatment with telmisartan and nifedipine GITS proved to have a good safety and efficacy profile, being able to produce a downward shift in the BP response to exercise and to improve muscle oxygen delivery.[33,36,38] Acetazolamide, which is frequently prescribed for the prevention of HA illnesses, has BP-lowering capabilities, both at rest and during exercise, which may come either from its diuretic properties or as a consequence of improved oxygenation at altitude.[38-40] However, especially at higher doses, it can promote metabolic acidosis, which can have a detrimental effect on exercise performance.

Clinical implications Several factors must be considered when assessing the clinical implications of the effects of HA exposure on BP.[1] First, there is a growing number of people reaching HA each year, which is related to the increase of leisure activities and travelling options. For instance, it is estimated that about 120 million people per year visit the Alps, with a sojourn that often implies a significant physical effort when undertaking sports and open-air activities. Second, many people at advanced age or affected by pathological conditions wish to go to HA. This raises several questions such as: 1) whether the effect of altitude exposure is the same as in healthy young people; 2) whether the extra burden imposed on the cardiovascular system to achieve acclimatization may be detrimental in these patients; and 3) whether treated hypertensive individuals should modify antihypertensive therapy to prevent excessive BP increase and, if yes, how.[2]

Focusing on elderly individuals, it is widely accepted that BP increases with age because of the combined effect of atherosclerotic changes, large artery stiffening, renal function impairment, and arterial baroreflex dysfunction, with older people having on average higher systolic BP values than younger ones.[41,42] Few studies evaluated the effects of altitude exposure in the elderly, sometimes with conflicting results, and most of them focused on moderate altitude instead of HA. Levine et al[32] found that elderly individuals (mean age, 68 years) acclimatized well and fully after 5 days at 2500 m. In that study, acute hypoxia induced a decrease of BP, with BP values returning to baseline levels during a 5-day stay at HA. At the same time, heart rate slightly increased. A similar pattern of changes was maintained also during exercise in both conditions. In another study, conducted by Roach et al[43] in 97 elderly individuals (mean age, 70 years), during a multiday exposure to an altitude of 2500 m, BP increased on the first day of stay and decreased over the subsequent days. The values were much higher in hypertensive individuals. Finally, in a study by Veglio et al,[8] the BP response to moderate-altitude exposure (2950 m) was the same in older and younger adults (mean age, 65.2 years [range, 60–83 years] and mean age, 40.2 years [range, 32–45 years], respectively), both during daytime and nighttime, although the sample size of this study was too small to allow a robust comparison between groups.

The topic of patients with preexisting cardiovascular conditions who wish to reach HA locations has been extensively discussed in a recent consensus statement of experts and scientific societies.[2] In fact, even if the increase in BP observed during HA exposure, although important, should not, per se, represent a risk for a healthy person, this may not necessarily be true for diseased individuals. For example, hypertensive patients may be more susceptible to

TABLE 1 Main practical recommendations for patients with hypertension who are planning high-altitude stay and evidence on antihypertensive drugs use in this condition (adapted from Parati et al)[2]

Recommendations
Patients with moderate to severe hypertension and hypertensive patients with moderate to high cardiovascular risk should check BP values before and during HA stay.
Patients with well-controlled hypertension or with mild hypertension may reach very HA (>4000 m) with adequate medical therapy.
Patients with uncontrolled or severe hypertension should avoid HA exposure to prevent risk of organ damage.
When patients with moderate to severe hypertension and patients with hypertension at moderate to high cardiovascular risk are planning HA stay, adequate modification of their antihypertensive therapy should be considered in cooperation with their physician.

Evidence on the effects of antihypertensive drugs at HA		
Drugs	**Pros**	**Cons**
Angiotensin II receptor blockers (telmisartan, 80 mg)	Safely lowered BP in healthy individuals during short exposure to 3400 m	Ineffective during prolonged stay at very HA (5400 m)
Acetazolamide	May lower BP, prevent or improve mountain sickness symptoms, and increase oxygen saturation	Limited BP data, adverse effects with prolonged use
Other diuretics	No data	Not recommended (may worsen fluid depletion caused by HA stay)
Calcium antagonists (nifedipine)	Reduces pulmonary pressure, used in HAPE treatment. In combination with telmisartan (80 mg) and slow-release nifedipine (30 mg) in combination with telmisartan (80 mg) effectively lowered BP in hypertensive patients at an altitude of 3300 m.	Adverse effects typical for this group (headache, flushing, leg edema); no data on BP effects in monotherapy
β-Blockers (carvedilol, nebivolol)	Vasodilatory β-blockers maintained their BP lowering effects in healthy individuals during acute exposure to 4500 m.	Reduced exercise performance and blood oxygenation (less so with β$_1$-selective compound, nebivolol).
ACEIs	No data	Possibly the same as for angiotensin receptor blockers, due to RAAS suppression

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; HA, high altitude; HAPE, high--altitude pulmonary edema; RAAS, renin–angiotensin–aldosterone system; others, see FIGURE 1

HA due to an already elevated hypoxic peripheral and central chemoreflex sensitivity[44] and to alteration in calcium homeostasis.[45] This was confirmed by Wu et al,[46] who reported a greater increase in BP at HA in hypertensive Chinese railroad workers compared with healthy ones. As mentioned previously, in mildly hypertensive participants of the HIGHCARE-ANDES study, who were acutely exposed to HA (3259 m), an important pressor response to HA was shown, accompanied by increased BP reactivity to exercise in this condition.[10,27,33]

Whether BP changes induced by acute or chronic HA stay may be clinically relevant in terms of cardiovascular events is unclear. In theory, increased left ventricular afterload due to BP increase, combined with decreased coronary perfusion (due to shortening of diastolic period with higher heart rate typical for HA exposure) and with reduced blood oxygenation, might trigger cardiac ischemic events. This possibility is exemplified by a case of ischemic electrocardiographic alterations observed during an exercise test at HA but not present at sea level in the same individual.[29] On the other hand, Schmid et al[47] did not reveal significant risks in revascularized patients with coronary disease who performed exercise at HA, and the limited data in hypertensive individuals during altitude exposure do not indicate significant immediate risks.[10,48]

Regarding drug therapy, several studies tested the efficacy of different antihypertensive drugs in controlling BP during HA stay, and more generally, their effects on altitude pathophysiology. In fact, acclimatization mechanisms affect many biological pathways targeted by antihypertensive drugs. Among the classes of drugs frequently used for BP control, β-blockers must be mentioned. In healthy individuals exposed to HA, administration of carvedilol, a nonselective β-blocker, resulted in good BP control but at the cost of reduced arterial hemoglobin oxygen saturation and exercise tolerance. In the same study, nebivolol, a selective β$_1$-antagonist, also maintained its BP-lowering efficacy during HA exposure but was more effective in maintaining physiological nocturnal BP dipping and had a lower impact on exercise tolerance.[6,37]

In healthy lowlanders participating in the HIGHCARE-HIMALAYA study, telmisartan, a long-acting angiotensin receptor blocker, was able to maintain its sea-level BP-lowering efficacy at an altitude of 3400 m. However, during the exposure to an altitude of 5400 m, the drug became ineffective. This was likely caused by the suppression of RAAS (the traget system of telmisartan) at such altitude.[9] In hypertensive patients acutely exposed to HA (3200 m), the combination of telmisartan with a dihydropyridine calcium channel blocker (nifedipine GITS) maintained its sea-level effectiveness in lowering BP also at HA.[10]

A final mention must go to acetazolamide, a mild diuretic often used to prevent acute mountain sickness, which is also able to antagonize BP rise at HA as well as the parallel occurrence of central sleep apnea. Notably, this

drug may favor dehydration and electrolyte imbalance, so a special attention during its use is advisable.[39,49]

A summary of recently published practical recommendations for patients with hypertension who are planning an HA stay is presented in TABLE 1.[2]

Conclusions The cardiovascular system responds to the challenge of HA exposure in a complex manner, usually leading to adaptation, but in some cases contributing to acute and chronic altitude-related pathological conditions. The responses of BP and of its regulatory mechanisms to HA are significantly modified by the duration of the exposure. During the initial hours, direct vasodilation prevails with BP levels remaining stable or even reduced. Over the following days and weeks, increased sympathetic drive leads to a persistent increase in BP mostly mediated by vasoconstriction and elevated heart rate, despite the concomitant suppression of the RAAS (at very HA) and loss of plasma volume. This phase is characterized by a particularly pronounced BP increase at night, with a reduced nocturnal dipping, and by accentuated pressor response to exercise. Less is known about long-term adaptations of BP to altitude, but some studies imply that living at higher altitudes may favor the development of arterial hypertension with a possible role of polycythemia and increased blood viscosity.[23,50]

Finally, the prognostic impact of an altitude-related BP increase is unknown. Although initial evidence is available on the effects of BP-lowering drugs in this condition, it is unclear whether specific pharmacological interventions might be beneficial in hypertensive patients exposed to elevated altitudes. Reasonably, an individualized approach should be preferred, with some degree of caution being warranted in hypertensive patients at particularly high risk of cardiovascular events due to the presence of organ damage or comorbidities. Having said this, in most patients, the presence of cardiovascular conditions, including hypertension, is not a contraindication to HA exposure. Except for some very high-risk patient categories, practicing physicians must not discourage their patients from HA travel. Instead, they should provide informed advice on the few key safety rules to be followed in this challenging but also inspiring environment.

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