REVIEW ARTICLE

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High Altitude Hypertension

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Abstract

***Background:** High altitude (HA) presents unique physiological challenges, primarily due to hypobaric hypoxia, which affects multiple organ systems, including the cardiovascular system. Blood pressure (BP) responses at HA vary widely, with some individuals experiencing transient or sustained hypertension. Understanding these responses is essential for optimizing medical management in individuals traveling to or residing at HA.*

***Objective:** This review examines the effects of HA on BP regulation, the physiological mechanisms underlying BP changes, the impact on normotensive and hypertensive individuals, and the role of antihypertensive medications in HA environments.*

***Findings:** Acute exposure to HA generally leads to an initial increase in BP, driven by sympathetic activation and vascular changes. While some individuals experience normalisation with acclimatisation, others develop persistent hypertension, which may indicate maladaptive responses. The prevalence of acute HA illnesses does not appear to be significantly different between normotensive and hypertensive individuals, though long-term cardiovascular risks remain uncertain. Medication selection for BP control at HA requires careful consideration, as some antihypertensive agents, such as ACE-inhibitors and beta-blockers, may have unintended effects on oxygenation and acclimatisation.*

***Conclusion:** BP regulation at HA is highly variable and influenced by individual adaptation. While most cases of HA hypertension are transient, persistent elevations warrant medical attention. Future research should explore the long-term cardiovascular consequences of HA exposure and refine treatment strategies for individuals with pre-existing hypertension. A proactive approach, including pre-travel assessment, continuous BP monitoring, and tailored medication adjustments, is essential for ensuring cardiovascular health at HA.*

Introduction

Enjoyment, work, and athletic competition draw a large number of people to high altitude. The key changes at high altitude (HA) include decreases in temperature and ambient humidity, but the defining environmental feature is a drop in barometric pressure, causing a decrease in the partial pressure of oxygen in the tissues. A series of physiological responses are triggered by this hypobaric hypoxia which, in most cases, help the individual tolerate and adapt to the low oxygen conditions. However, in other cases, maladaptive responses occur, leading to one of three forms of acute altitude illness: acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE).

Apart from these, hypertension is the most common cardiovascular disease observed in people sojourning at high altitudes[1,2]. The effect of chronic hypobaric hypoxia, induced by living at high altitude (HA), on blood pressure (BP) is uncertain and may vary across different populations. Research on this relationship and other cardiopulmonary changes at HA has been ongoing for more than 50 years[3], yet it remains uncertain whether the relationship between BP and HA is causal or a result of coincident lifestyle factors.

An inverse association between altitude and BP has been observed, which may be due to various factors. These include structural changes in the vasculature, as well as a number of socio-cultural, biological, chemical, and physical factors acting separately or in combination[4,5]. However, the possible benefit of altitude-related hypoxia on systemic BP may diminish when genetic and lifestyle-related risk factors become dominant, as seen in populations of Tibetan origin, where they start showing a hypertensive response[6,7].

Physiological Response to High Altitude

Acute exposure to high altitude (HA) leads to a decrease in blood pressure (BP) due to a reduction in systemic vascular resistance. Functional sympatholysis has been proposed as the probable explanation for this phenomenon. The indirect effect of hypobaric hypoxia at HA, acting via increased sympathetic activation, leads to vasoconstriction, whereas the direct effect of hypoxia on blood vessels causes vasodilation. This creates a conflict between two opposite effects on the blood vessels.

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Studies have shown that during acute exposure to HA, the direct effect of hypoxia dominates, causing vasodilation, a phenomenon known as functional sympatholysis. Over time, as acclimatisation occurs and the oxygen content of the blood increases, causing a reduction in cardiac output and stroke volume, functional sympatholysis diminishes. Hence, the indirect effect of hypoxia via sympathetic vasoconstriction leads to increased BP during chronic exposure[8].

Thus, acute hypoxia initially causes a decrease in BP, followed by an increase, which continues until the acclimatisation process mitigates hypoxia, leading to a subsequent BP reduction or near-normalisation. However, in the Indian population, this initial BP decrease has not been observed; rather, acute exposure raises BP, followed by a decline with long-term exposure. A similar initial BP increase has been noted in white lowlanders during the early days of acute HA exposure[9-11].

Several explanations for this BP response have been proposed, including adrenergic system activation, increased arterial stiffness, endothelin (ET) release, and reduced vasodilatory responses[12,13]. This BP increase generally lasts for about 6 days (the acclimatisation period) but can persist for up to 9 weeks.[14] Conversely, long-term exposure to HA (more than 2 years) in white lowlanders has been associated with a reduction in both systolic and diastolic BP[15]. This is supported by evidence showing that HA natives exhibit a lower prevalence of hypertension[16].

Behaviour of Normotensives and Hypertensives at High Altitude

The effect of HA on BP in normotensive individuals has shown varied responses. Normotensive individuals may experience an increase, decrease, or no change in BP during acute exposure to HA[17-19]. On the other hand, hypertensive individuals have shown either a BP increase of up to 15 mm Hg or no significant change upon acute exposure[20,21].

In hypertensive individuals at rest, an initial BP increase is observed, followed by a gradual decline over days to weeks[20-22]. During exercise, a slightly greater BP increase has been noted in hypertensives compared to normotensives[21]. Thus, while both groups exhibit variable BP responses at HA, hypertensives tend to experience a more pronounced BP rise than normotensives.

Origin of Hypertension at High Altitude in Normotensives

A study found that after residing at HA for 12 months, more than 60% of initially normotensive individuals had systolic blood pressure (SBP) higher than optimal levels, while others maintained SBP within the normal range. Among them, 40% were actually hypertensive [diastolic blood pressure (DBP) >90 mmHg][23]. This indicates that, regardless of the duration of hypoxia exposure and the normalisation of oxygen content, some healthy individuals develop elevated systemic arterial pressure[24].

Normotensive individuals at sea level who ascend to HA frequently experience hypertension, as evidenced by abnormal 24-hour ambulatory systolic and diastolic BP values, along with increased daytime and nighttime BP readings[25]. Several factors have been proposed for hypertension at HA, including persistent sympathetic stimulation[26], an enhanced chemoreceptor reflex (noted in individuals prone to hypertension)[27], and the presence of "hyper-responders", who are predisposed to developing high-altitude pulmonary hypertension, along with a general lack of tolerance[28]. BP in individuals ascending to HA often remains elevated even after acclimatisation, primarily due to two key factors: they may be delayed acclimatisers, or they were borderline hypertensive at sea level, with their condition becoming apparent under the physiological stress of HA.

Our Research

A total of 600 patients with raised BP were analysed at a hospital located at HA to establish the relationship between hypertension and the duration of stay at HA. Hypertension was seen in the majority of individuals in the early days of arrival at HA, while the rest developed it over a period of two years at different times. Upon further investigation, it was discovered that most hypertensive patients at HA were affected within the first 3 months of their stay. Further analysis revealed that, among these cases, the majority developed hypertension within the first week of arrival. Hence, it was hypothesised that impaired acclimatisation might be contributing to hypertension.

To explore this further, we conducted a detailed study examining BP trends in individuals traveling to HA during the first 6 days of the acclimatisation period. A total of 398 normotensive sojourners from sea level ascending to HA (3,500 m) were studied, and their BP responses were recorded for six consecutive days at HA. Based on their BP response on the 6th day, they were divided into two groups: HBP (high BP group) and NBP (normal BP group).

Upon analysing the results, it was found that on the 6th day at HA, 347 out of 398 individuals normalised their BP (BP 140/90 mmHg. A detailed analysis of BP trends showed that the NBP group initially exhibited raised BP, which returned to normal levels within the 6-day acclimatisation period. However, in the HBP group, BP continued to rise from the 4th day onward.

Hence, it can be concluded that individuals whose BP does not return to normal by the 6th day at HA require regular follow-up, as they may experience delayed acclimatization leading to later BP normalisation or may develop persistent hypertension[29].

Consequences of High BP at High Altitude

The first question to address was whether the prevalence of acute HA illnesses is higher in hypertensive individuals than in normotensive individuals. According to the literature, one study found that the prevalence of acute mountain sickness (AMS) is not different between normotensive and hypertensive travelers[3].

Regarding high-altitude pulmonary oedema (HAPE), increased susceptibility in hypertensive individuals has never been formally investigated. Furthermore, there is no existing data linking hypertension to an increased risk of high-altitude cerebral oedema (HACE).

Additionally, we examined whether the complications of hypertension are more prevalent in hypertensive individuals compared to normotensive individuals at high altitude. Observations revealed that, in resting conditions, complications such as hypertensive retinopathy, intracranial bleeding, or myocardial infarction were not reported, even when systolic blood pressure (SBP) exceeded 190 mmHg or diastolic blood pressure (DBP) surpassed 125 mmHg for up to 28 to 42 days at high altitude[20]. Similarly, no complications were reported during exercise in individuals with hypertension at HA[31].

Many cases of sudden cardiac death (SCD) have been documented at high altitude[32], but a higher incidence of SCD in individuals with a prior history of hypertension has been associated with physical activity at HA. However, confounding variables such as fasting, hydration, physical fitness, and mountain activities were not accounted for[33]. Although hypertension has been observed in cases of SCD at HA, no study has established a direct causal link[34].

In conclusion, the majority of studies have dismissed the risk of complications arising in hypertensive individuals at high altitude. However, further research is needed.

Medication Selection for Blood Pressure Control at High Altitude

Studies have shown that angiotensin-converting enzyme (ACE) inhibitors increase the hypoxic ventilatory response and improve high-altitude tolerance, making them a viable option for managing hypertension at HA[35]. However, ACE inhibitors have also been found to impair renal erythropoietin production, which could negatively impact haematologic responses at high altitude[36]. Therefore, their overall utility at altitude remains uncertain.

Angiotensin receptor blockers (ARBs), such as Telmisartan, have been shown to reduce both daytime and nighttime BP, but this effect has only been observed up to an altitude of 3,400 m. At 5,400 m, the drug was found to be ineffective due to the concomitant suppression of the renin–angiotensin system[25]. A combination of an ARB and a calcium channel blocker has been proven effective and safe in reducing BP in both untreated and previously treated hypertensive patients[3].

Beta-blockers have also been studied for hypertension at high altitude. Non-selective betablockers, such as Carvedilol, used in healthy individuals, have led to a significant reduction in BP at HA but were associated with decreased oxygen, saturation and reduced exercise tolerance. However, these side-effects have not been observed with highly selective beta-1 blockers like Nebivolol. Nebivolol effectively reduces BP at HA while preserving normal nocturnal BP dipping and causing less reduction in exercise tolerance[38].

Another highly useful drug is acetazolamide, which is commonly used to treat high-altitude illnesses. It has been found to help reduce BP elevation while also improving sleep apnea[39].

Important Observations from these Studies

The following key observations have been made across various studies on hypertension at high altitude:-

1. A large degree of interindividual variability in blood pressure responses at HA.
2. Inability to predict who will exhibit a brisk or blunted blood pressure response at high altitude.
3. Most studies have been conducted at elevations below 3,500 m, making it difficult to draw conclusions about blood pressure responses in hypertensive patients at elevations above 3,500 m.
4. Ethnic differences in blood pressure responses at HA have not been evaluated.
5. Studies primarily included individuals with mild-to-moderate hypertension, resulting in limited information about those with severe or highly variable (labile) hypertension.

Recommendations: Advice for Individuals Traveling to High Altitude

1. For individuals with uncontrolled hypertension planning to ascend to HA, the following is recommended:

Pre-exposure ambulatory BP monitoring should be conducted before induction to HA.

Ascent is absolutely contraindicated if:

a) Resting BP exceeds 160/100 mmHg, or

b) Systolic BP exceeds 220 mmHg during exertion

2. Medication adjustments for hypertensive individuals at HA should be made in two situations:

   a) If SBP >180 mmHg or DBP >120 mmHg, along with symptoms such as vision changes, shortness of breath, chest pain, or altered mental status.

   b) If SBP >220 mmHg or DBP >140 mmHg, even in the absence of symptoms.

   c) Transient BP elevations lasting only a few minutes should not prompt medication adjustments. Adequate rest should be ensured before measuring BP.

3. At HA, medication adjustments should be considered if hypertensive individuals show increased BP. However, since BP may decrease with acclimatisation, the following approach is recommended:

   a) Continuous BP monitoring to prevent excessive BP reduction or symptoms of hypotension.

   b) Upon descent to lower elevations, medications should be reverted to their original regimen.

4. For individuals with mild to moderate hypertension:

   a) If BP elevation is noted at HA, antihypertensive doses should not be increased immediately; instead, monitoring is recommended.

   b) For individuals with poorly controlled, labile hypertension or those with a history of marked BP increases at HA. BP should be closely monitored.

   c) If BP remains elevated, increase the dose of antihypertensive medication.

   d) If BP remains elevated despite dose adjustments, a second antihypertensive should be added.

   e) Throughout treatment, it is crucial to ensure that individuals do not experience symptoms of hypotension or syncope.

Conclusion

The initial increase in BP is a necessary adaptation to maintain oxygen supply to cells in a hypoxic environment. However, a sustained rise in BP indicates improper acclimatisation, where the body compensates by increasing BP instead of utilizing other physiological mechanisms.

BP responses at high altitude are highly unpredictable, affecting both normotensive and hypertensive individuals. A normotensive individual may develop persistent hypertension at HA, while a hypertensive may experience normalisation of BP.

There is no strong evidence in the literature suggesting increased mortality among hypertensive individuals at HA, except for a few anecdotal reports. Hypertension at HA differs from hypertension at sea level as it is initially a form of secondary hypertension, and target organ damage is difficult to assess since BP remains elevated throughout HA exposure.

The most effective drugs for managing hypertension at HA include ACE inhibitors, Angiotensin Receptor Blockers (ARBs), and Calcium Channel Blockers. However, caution is necessary – individuals taking antihypertensive medications must be informed to monitor their BP upon returning to lower altitudes and adjust their medication under medical supervision to prevent hypotension and syncope.

Ultimately, early recognition and management of HA hypertension are crucial to preventing long-term elevated BP at high altitude.

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