Treating hypertension at high altitude: the quest for a magic bullet continues

Alejandro Velasco¹, Wanpen Vongpatanasin¹,², and Benjamin D. Levine²,³*

¹Hypertension Section, University of Texas Southwestern Medical Center, Dallas, TX, USA; ²Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA; and ³Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital, Dallas, TX, USA

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This editorial refers to ‘Changes in 24 h ambulatory blood pressure and effects of angiotensin II receptor blockade during acute and prolonged high-altitude exposure: a randomized clinical trial’, by G. Parati et al., on page 3113.

Exposure to a hypoxic hypobaric environment often induces a rise in blood pressure (BP), which poses a concern for the safety of hypertensive patients who travel to high altitudes. However, the mechanisms underlying the rise in BP are poorly understood, and there are no widely accepted guidelines or patient-centered strategies designed to manage patients either who develop hypertension at altitude, or who have deterioration of BP control during an altitude sojourn. Parati and colleagues have now demonstrated in a randomized double-blinded trial that treatment with the angiotensin receptor blocker telmisartan caused a minor reduction in the 24 h ambulatory BP at 3400 m altitude, but had no effect on BP at 5400 m altitude. This is a potentially important finding, which may affect the choice of anti-hypertensive treatment during travel to high altitude.

However, several features of the study may limit its clinical utility for patients with hypertension. First, and most importantly, like many reports in this field, the study was conducted in normotensive subjects without a history of hypertension; the response to drug treatment may differ between normotensive and hypertensive subjects. For example, telmisartan treatment at the highest dose of 80 mg daily induced a modest reduction in the 24 h ambulatory BP of 13–14/9–10 mmHg with the sea level, while previous studies in hypertensive patients showed 80 mg daily induced a modest reduction in the BP of 7/5 mmHg at sea level. 

Indeed, sympathetic nervous system activity increases immediately, and continues to rise throughout the period of exposure to high altitude. As oxygen content is restored by acclimatization, hypoxic vasodilation is abolished, leaving unopposed sympathetic vasoconstrictor tone and contributing to increasing BP. However, treatment with alpha- or beta-adrenergic receptor blockers by themselves failed to prevent completely the rise in BP in otherwise healthy subjects. Plasma renin activity (PRA), plasma volume, and serum aldosterone are reduced within several hours to weeks of high altitude exposure (Figure 1). A similar pattern of activation is observed with the endothelin system. Despite an immediate and sustained increase in endothelin-1 (ET-1) levels, treatment with the endothelin receptor blocker bosentan was largely ineffective in preventing high altitude-induced BP elevation. Circulating levels of cortisol and adrenocorticotropic hormone (ACTH) increase more slowly than those of endothelin, but previous studies have not addressed the role of glucocorticoids in BP regulation at high altitude.

Neurohormonal studies in native populations yield divergent results from studies of acute or subacute exposure in sojourners. While plasma volume and PRA return to levels similar to those of lowland populations, plasma norepinephrine (NE) of Andean
natives in a chronic hypoxic environment was significantly higher than NE levels obtained at sea level in the same subjects. The prevalence of hypertension in natives of high altitude was once thought to be low. However, a recent large population-based study showed overall prevalence of hypertension of 39% in a Tibetan population residing at 3658 m altitude, which is higher than the age-adjusted prevalence of hypertension of a Chinese population at lower altitude. The interaction of the high altitude environment with changes in lifestyle factors in recent years may be responsible for a higher prevalence of hypertension than previously appreciated. Future studies are needed to determine which populations are at risk for high altitude-induced hypertension and hypertensive target organ complications.

The study by Parati et al. is a welcome addition to the literature of blood pressure regulation at high altitude. It is clear though, that more studies are needed specifically in patients with hypertension, which address the mechanisms underlying the wide individual variability in the BP response to high altitude. Strategies of ambulatory BP monitoring, perhaps with simple, wrist watch style devices, along with therapeutic management approaches including (i) defining the threshold for supplemental treatment; and (ii) identifying the best patient-centered, complementary medications need to be tested directly based on the known pathophysiology of hypertension at altitude.

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**References**