Editorial

Endothelin-1 and the Pulmonary Vascular Response to Altitude
A New Therapeutic Target?

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Ascent to high altitude is normally associated with a modest increase in pulmonary artery pressure. The increased right ventricular afterload, coupled with hypobaric hypoxia-induced reductions in blood oxygen content, may lead to diminished peripheral oxygen delivery and result in dyspnea, fatigue, and exercise intolerance. The predominant mechanism responsible for the increase in pulmonary artery pressure at altitude is hypoxic pulmonary vasoconstriction, which is mediated through an oxygen-sensitive pulmonary artery smooth muscle cell voltage-gated K⁺ channel. The primary site of hypoxic pulmonary vasoconstriction is the small (50 to 200 μm) muscular pulmonary arteries, although the pulmonary venous circuit may contribute up to 20% of the pressor response. A more clinically significant and potentially fatal cardiovascular consequence of exposure to altitude is the development of high-altitude pulmonary edema (HAPE). Risk factors for HAPE include gender, rate of altitude ascent, recent respiratory infection, and prior acclimatization; a genetic susceptibility also has been suggested. Although the mechanisms responsible for the development of HAPE remain unclear, it is associated with greater increases in pulmonary artery pressure and increased pulmonary capillary pressure, which results in hydrostatic pulmonary edema. The increased capillary pressure despite normal left ventricular function suggests that an exaggerated pulmonary venoconstrictor response may play a critical role. A variety of vasoactive substances are elaborated in the pressor response to altitude and in particular HAPE, including endothelin-1 (ET-1), a potent pulmonary arterial and venous constrictor. In this issue of Circulation, Modesti and colleagues provide further evidence of the contribution of ET-1 to the pulmonary vascular responses to altitude by demonstrating that the administration of bosentan, a dual ETₐ and ETᵦ receptor antagonist that is approved for the treatment of chronic pulmonary arterial hypertension, attenuated the pressor response in normal subjects at altitude.

1. The ACME-1 participants were experienced mountain hikers, and none developed HAPE. Accordingly, whether pretreatment with bosentan reduces the incidence or severity of HAPE is unknown.

2. The degree of elevation in PASP at altitude was modest, and estimated PASP remained in the normal range. Because bosentan had no effect on symptom severity, the significance of the reduction in PASP is questionable. Furthermore, whether Doppler estimates of PASP within this narrow range are sufficiently sensitive to accurately reflect changes in the true intravascular pressures, even in highly experienced hands, is unclear.

3. Although the improvement in arterial oxygen saturation observed with bosentan reached statistical significance, it is of questionable clinical relevance because it did not persist beyond day 1. Additionally, the difference was small. Because oxygen saturations in this range fall on the steep part of the oxyhemoglobin saturation curve, even minuscule changes in PO₂ (2 to 3 mm Hg) would result in these changes in oxygen saturation.

One of the more interesting findings of the ACME-1 study is the demonstration of an acute effect of bosentan on urinary volume and free water clearance. Ascent to high altitude normally results in an increase in urinary volume and free water clearance, an effect that may reduce the risk and severity of pulmonary edema in HAPE-susceptible individuals. Thus, the absence of this response in the bosentan-

In the Acute Mountain Illness and Endothelin-1 (ACME-1) Study, Modesti et al evaluated the effects of bosentan or placebo administered in a randomized, double-blind fashion on Doppler estimates of pulmonary artery systolic pressure (PASP) and a variety of parameters of renal salt and water handling in 20 healthy, nonacclimatized volunteers with prior mountain hiking experience. Compared with the placebo-treated group, the bosentan-treated group had lower PASP and higher arterial oxygen saturation after 1 day at altitude. However, bosentan administration also was associated with a lower urinary volume and free water clearance, whereas sodium clearance and tubular function were unaffected. Altitude-related symptoms, assessed with the Lake Louise scoring system, were unaffected by treatment. Thus, although ET receptor antagonism produced a potentially favorable pulmonary vascular effect in this setting, the renal consequences may be detrimental.

The ACME-1 investigators and participants deserve praise for performing a detailed study under less-than-ideal laboratory conditions. Their study also underscores the importance of global assessments of pharmacological effects, because beneficial effects of a drug on one hemodynamic circuit may be offset by adverse effects on others. There are, however, several limitations to the conclusions that can be derived from this study.
treated group in the ACME-1 study raises concern about a potentially deleterious effect on lung edema formation in the setting of full-blown HAPE. Pedal edema occurs in ≈20% of patients with pulmonary artery hypertension treated with bosentan\(^6\) and usually can be managed easily by adding a low-dose diuretic. Whether combining a diuretic with bosentan in HAPE-susceptible individuals would attenuate the effects on water clearance observed in this study is worth addressing. In addition, the development of ETA-selective antagonists for pulmonary artery hypertension may provide the opportunity to explore whether these compounds have divergent renal properties: eg, leaving the ET\(_B\) receptor unblocked may promote ET\(_B\)-mediated renal vasoconstriction,\(^14–16\) thereby facilitating the altitude-induced diuresis while still inhibiting the ET\(_A\)-mediated pulmonary vasomotor response.

Several other pulmonary vasodilators, including nifedipine and sildenafil, have been demonstrated to attenuate the altitude-induced pulmonary pressor response and the severity of HAPE.\(^7,8\) In the absence of studies demonstrating the superiority of any one treatment strategy, the availability and cost of nifedipine make it the preferred treatment at present. Nevertheless, bosentan is a welcome addition to the treatment arsenal for altitude sickness, and future studies comparing treatments, particularly in HAPE-susceptible individuals, are likely to provide further insight into the management of this complex disorder.

Disclosures

Dr Rubin has received honoraria from and served as a consultant or advisory board member for Actelion, Myogen, and Pfizer.

References

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