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In Response to ACE I/D Polymorphism and HAPE by Bhagi et al

To the Editor:

We read with profound interest the article titled “Positive Association of D Allele of ACE Gene With High Altitude Pulmonary Edema in Indian Population” by Bhagi et al.¹ In this study, a total of 154 unrelated Indian lowlanders were acutely introduced to high altitude (HA) at Leh (>3500 m) during a period of approximately 2 years. It is apparent that 79 of these 154 subjects experienced high altitude pulmonary edema (HAPE) within 48 to 72 hours after ascent to HA¹ while they were undergoing altitude-dependent acclimatization like the control group. Interestingly, subjects from both groups were staying in a controlled environment in terms of medical facilities during the period of acclimatization, but subjects who had HAPE were not started on medication or given oxygen supplementation until they were admitted to the hospital. It is likely that much discussion and deliberation must have taken place before this study protocol was approved by the institutional ethics committee of the Defence Institute of Physiology and Allied Sciences.

The authors also examined the possible association of gene polymorphisms of renin-angiotensin-aldosterone system pathways with arterial oxygen saturation (Sao₂) levels. However, the clinical significance of the use of Sao₂ for the diagnosis of HAPE remains obscure, predominantly because of the variability seen in its values in response to descent and supplemental oxygen. A significant amount of these variations in Sao₂ is likely to occur during evacuation from remote locations to medical facilities. Sao₂ is not part of the diagnostic criteria for HAPE as presented by the Lake Louise consensus.² HAPE is diagnosed by the presence of at least 2 of these symptoms—dyspnea at rest, cough, weakness or decreased exercise performance, and

chest tightness or congestion—and at least 2 of these signs—rales or wheezing in at least 1 lung field, central cyanosis, tachypnea, and tachycardia—in the setting of a recent gain of altitude.² It would have been interesting had the authors also studied the association between the alleles of the ACE gene and other physiological parameters (such as heart rate and respiratory rate) included in the Lake Louise criteria for HAPE. This would have probably given a more comprehensive association of gene polymorphisms of renin-angiotensin-aldosterone system pathways with HAPE.²

The authors concluded that the D/D genotype of the ACE gene appears to be associated with an increased risk of HAPE in an Indian population. The practical applications of these findings remain challenging, especially because HAPE is a disease with a very low incidence.³ Apte et al³ reported an incidence of HAPE of 0.31% in Indian male lowlanders after acute ascent (by air) to an altitude of 3400 m in the western Himalayas. Moreover, the incidence of HAPE and other HA-related illnesses can be reduced by following an altitude-dependent acclimatization schedule³; therefore, it would be more cost-effective to disseminate the information about the importance of acclimatization in the population rather than using the outcome of this study as a screening tool for early identification of HAPE-susceptible individuals in the community.

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altitude after a sojourn in the plains. *Med J Armed Forces India*. 2015;71:214–220.

In Reply to Dr Sikri et al

To the Editor:

Thanks to Sikri et al.¹ for showing interest in our research article.²

High altitude pulmonary edema (HAPE), a potentially fatal condition, is a rare form of altitude sickness that affects healthy lowlanders or nonacclimatized individuals who travel to high altitudes greater than 2500 m. The unrelated subjects selected for this study belong to different ethnic groups of an Indian population. All subjects with HAPE selected for the study were serving Army personnel who were acutely inducted to high altitude. A comparable number of control subjects selected for the study were also serving Army personnel who were acutely inducted and faced similar environmental challenges. Patients were admitted to Army Hospital of Leh, and after diagnostic confirmation of HAPE, blood samples were collected before the start of treatment. This procedure was well defined and uniformly followed throughout the study protocol. The present study purely aimed to seek the involvement of renin-angiotensin-aldosterone system pathway in genetic susceptibility to HAPE.³

Figure 1 of our article² shows arterial oxygen saturation (SaO₂) compared with genotypic profile of the angiotensin-converting enzyme gene (ACE) I/D polymorphism in HAPE and acclimatized control subjects groups. As Sikri et al. rightly pointed out in their letter, a significant amount of variation in SaO₂ is likely to occur during evacuation from remote locations to medical facilities; however, in this study, the setup of Army Hospital in Leh, in the Ladakh region of India, was in close proximity to that of the Army camp area, and no evacuation was required to provide medical help to the HAPE patients. When the volunteers complained about dyspnea at rest, cough, and breathlessness, they were immediately taken to the hospital. Also, both heart rate and SaO₂ levels were measured in seated volunteers via finger pulse oximeter. Hence, to the best of our understanding, the study of association between the alleles of the ACE gene and SaO₂ has given a fair idea about the involvement of renin-angiotensin-aldosterone system pathway genes in HAPE susceptibility. The idea of studying the association of HAPE with other physiological parameters (eg, heart rate and respiratory rate) included in the Lake Louise criteria for HAPE as suggested by Sikri et al in their letter is noted.

The present study indicated that the D/D genotype of the ACE gene appears to be associated with an increased

risk of HAPE in the Indian population. This finding could be an initial step toward the larger goal of designing screening criteria for early identification of HAPE-susceptible individuals in the community. This would not be a genetic discrimination, but a preventive step for the health of Army Jawans in the interest of the country. Since susceptibility to HAPE and other high altitude illnesses largely depends on the altitude attained, rate of ascent, and preacclimatization, a well-designed acclimatization schedule is always followed by Army personnel. Studies on different populations have suggested variability in individual susceptibility to altitude sickness depending on genetic makeup.⁴ Studies like the present one aim to understand the genetic basis of susceptibility to HAPE.

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Pitviper Envenomation Guidelines Should Address Choice Between FDA-approved Treatments for Cases at Risk of Late Coagulopathy

To the Editor:

We salute Dr. Kanaan and colleagues for their recent contribution, “The Wilderness Medical Society Practice Guidelines for the Treatment of Pitviper Envenomations in the United States and Canada,” an excellent paper encompassing many aspects of a complex disease.¹ Given the otherwise thorough treatment of the subject, it was a surprise to find that these guidelines contained such a minimal treatment of late coagulopathy, which we feel is among the most significant and challenging aspects of North American rattlesnake envenomation management