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Erythropoietin and HAPE

Dear Editor:

In their very interesting study, Basu et al. (2) reported that, in lowland residents travelling to high altitude, the development of high altitude pulmonary edema (HAPE) was associated with higher plasma erythropoietin (EPO) levels. The authors speculated that hypoxemia may have been more severe in affected individuals, and may therefore have resulted in greater stimulation of EPO secretion. The purpose of this letter is to clarify the physiology underlying stimulation of EPO secretion at high altitude, and to consider how this might inform the study's findings.

Basu et al. noted that the oxygen sensor responsible for hypoxic stimulation of renal EPO secretion remains unknown. This is no longer the case, and the hypoxia-inducible factor (HIF) family of transcription factors alluded to by the authors is now known to mediate oxygen-regulated EPO expression [reviewed by Schofield and Ratcliffe (4)]. HIF is the central regulator of cellular oxygen homeostasis throughout the body. It directly or indirectly regulates the expression of several hundred genes, of which the gene encoding EPO is the best known. HIF is primarily regulated through its own oxygen-dependent degradation. The crucial step that initiates HIF degradation is a hydroxylation reaction catalyzed by specific oxygen-sensitive prolyl hydroxylase-domain enzymes, which thereby constitute the definitive oxygen sensor underlying hypoxic stimulation of EPO secretion.

In a recent review of this field (6) we described emerging evidence that HIF also plays a key role in systemic cardiopulmonary physiology, including the pulmonary vascular response to hypoxia. HAPE is caused by an excessive hypoxic pulmonary vasoconstrictive response, characteristic of HAPE-susceptible individuals, in which HIF and its target genes have been implicated (1,3,5). Thus HIF, the transcriptional activator of EPO expression, may also be an important factor in the pathogenesis of HAPE, and the association between higher EPO levels and HAPE reported by Basu et al. may in part reflect common involvement of this cellular oxygen-sensing mechanism.

It is also relevant to note that there is wide inter-individual variation in both hypoxia-induced EPO secretion and hypoxic pulmonary vasoreactivity, which could arise in part from common genetic variation within the HIF transcriptional signaling system (6). It is therefore conceivable that specific polymorphic variants within the HIF system could confer both greater susceptibility to HAPE and an unusually vigorous EPO-secretive response to the hypoxia of high altitude. Thus, a further theoretical explanation for the reported association between HAPE and higher EPO levels is that these might be co-manifestations of a particular HIF-related physiological phenotype.

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