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Opinion

High-Altitude Pulmonary Edema in the Context of COVID-19

Eduardo Garrido [1,*], Javier Botella de Maglia [2], Oriol Sibila [3], Gustavo Zubieta-Calleja [4]

1. Hypobaria and Biomedical Physiology Unit, University of Barcelona, Hospitalet de Llobregat, Spain; E-Mail: eduardogarrido@movistar.es
2. Intensive Care Unit, University and Polytechnic Hospital La Fe, Valencia, Spain; E-Mail: jbotellademaglia@gmail.com
3. Pneumology and Respiratory Allergy Department, Hospital Clinic, Barcelona, Spain; E-Mail: osibila@clinic.cat
4. High Altitude Pulmonary and Pathology Institute, La Paz, Bolivia; E-Mail: gzubietajr@gmail.com

* **Correspondence:** Eduardo Garrido; E-Mail: eduardogarrido@movistar.es

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Abstract

High-altitude pulmonary edema (HAPE) and COVID-19 pneumonia are different diseases, but HAPE-susceptible individuals (whose susceptibility often has a genetic basis) can also suffer from severe COVID-19. We hypothesized that certain pathogenic mechanisms might overlap if such a coincidence occurs, since these patients could react to alveolar hypoxia with a more intense and heterogeneously distributed pulmonary vasoconstriction than non-HAPE-susceptible patients. It is also not known how future altitude acclimatization might affect lowlanders with COVID-19 pulmonary sequelae, and how the loss of adaptation to chronic hypoxia might differ by genetic lineage among highland natives who have recovered from severe COVID-19 around the world. Although the incidence of CoV-2 in high-altitude locations seems to be lower, a correct differential diagnosis of both conditions is essential, especially in high-altitude areas where health resources are scarce, considering that there is sometimes a similarity between COVID-19 pneumonia and HAPE.

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Keywords
Altitude; genetics; hypoxia; pulmonary edema; COVID-19

The outbreak of CoV-2 disease (COVID-19) led to the publication of many scientific studies that investigated various aspects of this disease. Due to certain similarities between COVID-19 pneumonia and high-altitude pulmonary edema (HAPE), the therapeutic utility of nifedipine, sildenafil, tadalafil, and acetazolamide was initially considered [1]. However, due to differences in the pathophysiology of both conditions and the mechanisms of action of these drugs, these medications might be not only useless but even harmful to patients suffering from COVID-19 pneumonia, as stated by other researchers [2, 3].

HAPE is a life-threatening disease of non-cardiogenic etiology and is caused by exaggerated pulmonary hypertension in response to hypobaric hypoxia. The overall incidence rate is around 6% in those lowlanders who rapidly reach high altitudes but increases to 15% at the height of 5,500 m [4]; the incidence rate increases up to 60% if there is a history of HAPE [5]. The clinical symptoms might be confused with those of pneumonia, considering that even cyanosis and fever may be present [6]. However, it often differs from typical COVID-19 pneumonia, as it does not involve silent initial changes but rather acute alveolar edema, although both conditions may have radiological similarities (Figure 1).

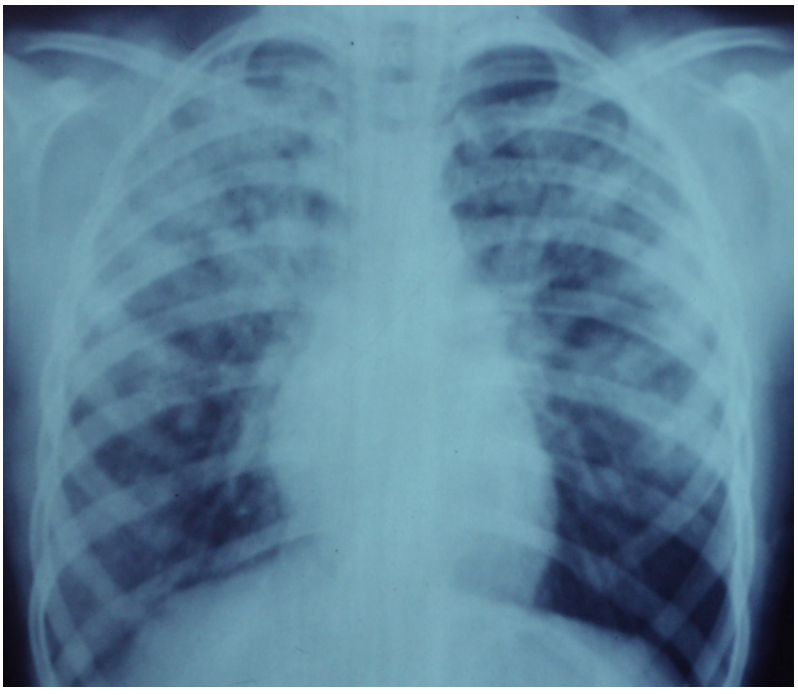

Figure 1 High-altitude pulmonary edema shows a typical radiological chest pattern (diffuse and asymmetric bilateral opacities, like cotton wool blotches), which resembles the chest pattern of many cases of COVID-19 pneumonia. (Image from Zubieta-Calleja et al. [17] reproduced with permission from Bentham Sci. Publ.].

It is assumed that there is a genetic predisposition to HAPE, but few genetic polymorphisms (*JAK2, HRG,* and *CYP1B1*) possibly associated with HAPE-susceptible individuals have been identified [7]. Prolyl hydroxylase domain protein 2 (*EGLN1*) and HIF-1α inhibitory factor (*HIF1AN*) are also associated with the pathophysiology of HAPE [8], and abnormally elevated levels of HIF-1α are considered to be a HAPE susceptibility marker [9]. Additionally, angiotensin II type 1 receptor (*AT1R*) gene polymorphisms might be associated with HAPE susceptibility [10], and *A1166C AT1R* polymorphism is also associated with COVID-19 severity [11]. Interestingly, a slightly elevated plasma concentration of B-type natriuretic peptide might be related to an exaggerated pulmonary vascular response in hypoxia-susceptible individuals [12], as well as poor outcomes in COVID-19 patients [13].

As the two conditions are different and without known genetic analogies, we hypothesized that certain pathogenic mechanisms of both conditions might overlap in cases of COVID-19 pneumonia affecting HAPE-susceptible individuals, a scenario that has not been investigated yet. Such patients might respond to alveolar hypoxia with a pulmonary vasoconstriction stronger and more heterogeneously distributed than expected, causing alveolar edema in larger areas of the lungs. This might impair ventilation/perfusion mismatch and gas exchange, which might worsen hypoxemia and the course of the disease. A study proposed that severe cases of respiratory failure in COVID-19 might benefit from hyperbaric oxygen therapy [14]. Some individuals with endogenous susceptibility to HAPE might be found among these patients, however, we consider that in the setting of an intensive care unit, several complexities might challenge the management of a COVID-19 patient inside a hyperbaric chamber.

People with COVID-19 sequelae (residual fibrosis, pulmonary hypertension, bronchiectasis) might be prone to further difficulties when acclimatizing to high altitude, but such possibility has not been studied. With the probable exception of ethnic groups of Tibetan lineage, who have a singular genetic adaptation to hypoxia and develop an attenuated hypoxic pulmonary hypertension [15], it is unpredictable whether other high-altitude dwellers, especially Andean natives, will increase their risk of suffering from the *re-entry* HAPE when returning to their place of residence after recovering from COVID-19 pneumonia in a hospital at lower altitudes.

In a small group of highlanders, patients with COVID-19 pneumonia hospitalized at an altitude of 4,150 m, those with lower serum hematocrit and erythropoietin (EPO) levels had a higher mortality rate [16]. Interestingly, based on the oxygen transport triad concept, high-altitude residents suffering pneumolysis caused by SARS-CoV-2 recovered with higher hematocrit levels that before being affected by the COVID-19 disease [17]. The term *hypoxia paradox* was proposed due to the concomitance of profound hypoxemia and low plasma concentrations of EPO, having been observed that patients with severe COVID-19 and worse prognosis improved considerably after treatment with recombinant EPO analogs [18].

The combination of COVID-19 pneumonia and high-altitude hypoxia can be detrimental, but, overall, there appears to be a lower prevalence, severity, and mortality of COVID-19 in some populations living in high altitudes, an intriguing fact that needs to be confirmed [19]. Such a pattern might be associated with environmental factors, the downregulation of angiotensin-converting enzyme II, as well as a lower prevalence of certain comorbidities, such as diabetes mellitus, obesity, and hypertension which might protect individuals living at high altitudes against CoV-2 infection, especially those residing at more than 3,000 m above sea level [20, 21]. We argue that larger epidemiological studies are needed to confirm whether this benefit of highlanders is exclusively due

to their genetic and/or phenotypic adaptations to chronic hypoxia since other aspects related to health, social customs, or demographic distribution might also play a significant role.

Finally, considering that some HAPE patients might onset with non-specific insidious symptoms, and given that there might also be radiological features similar to COVID-19 pneumonia, a differential diagnosis should be carefully performed at high altitudes during the SARS-CoV-2 pandemic to implement the most appropriate therapeutic strategy under conditions of environmental hypoxia, especially in isolated mountainous areas where health resources are scarce.

Author Contributions

Dr. Garrido and Dr. Botella de Maglia have proposed the main ideas, have made the selection of the search for scientific documents and written the manuscript; Dr. Sibila and Dr. Zubieta-Calleja have elaborated the concepts and consequences of COVID-19 pneumonia in relation to altitude.

Competing Interests

The authors have declared that not competing conflict of interest exist.

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