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COVID-19 is different than High Altitude Pulmonary Edema. A position paper.

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COVID-19 is different than High Altitude Pulmonary Edema. A position paper.

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Dear Editor,

Recently, critical care specialists (URL, 2020) and researchers (Solaimanzadeh, 2020) have suggested that there are pathophysiological similarities between COVID-19 pneumonia and High Altitude Pulmonary Edema (HAPE). They have suggested that drugs known to be effective in patients suffering from acute mountain sickness or HAPE, such as acetazolamide, nifedipine and phosphodiesterase inhibitors might be useful to treat COVID-19. In this journal, a group of high altitude researchers has debunked this myth and expressed concerns that this misconception may adversely affect the management of COVID-19 patients (Luks et al., 2020). We support these concerns and echo their warning.

In contrast to HAPE (Bärtsch et al., 2005), the pathophysiology of COVID-19 is still unclear (Mason RJ, 2020). Both can present with severe hypoxemia. There are other similarities between COVID-19 and HAPE, but the differences far outweigh the similarities (Table 1).

- Hypobaric hypoxia is the sole cause of HAPE. There is abnormal hypoxic pulmonary vasoconstriction with high pulmonary artery and capillary pressure in response to alveolar hypoxia (Maggiorni et al., 2001). Hypoxia is not the cause of COVID-19.
- HAPE is not associated with any infectious agent. Alveolar epithelial inflammation is a secondary response to hypoxia and pulmonary hypertension, triggered by pro-inflammatory cytokines (Kubo et al., 1998). In COVID-19, respiratory failure is primarily caused by alveolar inflammation and destruction of cells.
- In HAPE patients, the excessive rise in pulmonary artery pressure is a direct response to hypobaric hypoxia in susceptible individuals that precedes endothelial dysfunction and pulmonary edema. In COVID-19 patients, the increase in pulmonary arterial pressure is

multifactorial and is associated with interstitial edema, hypoxemia and intravascular thrombosis (Tang et al., 2020).

- Although HAPE is a life-threatening condition, it can be reversed effectively by descent to lower altitude, administration of supplemental oxygen or placing the patient in a hyperbaric chamber. Critical care in an intensive care unit (ICU) is almost never necessary. Patients with COVID-19 typically present with a benign upper respiratory infection that progresses to severe acute respiratory distress syndrome (ARDS) (Gattinoni et al., 2020a) (Gattinoni et al., 2020b). Patients with ARDS due to COVID-19 require ventilator support for several days to weeks and may suffer from permanent residual lung fibrosis.
- HAPE is limited to the lungs and does not primarily involve other organs. COVID-19 can affect all tissues that have angiotensin converting enzyme 2 (ACE-2) receptors, which are utilized as entering receptors by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Tissues with ACE-2 receptors include the lungs, kidneys, heart, and possibly the central nervous system. The outcome of patients with COVID-19 disease is dependent not only on lung function but also on the involvement of the kidneys and the heart. In many patients, multi-organ system failure is the cause of death.
- Pre-existing diseases usually do not worsen the outcome of HAPE. Individuals can be genetically susceptible to high altitude illnesses, but there are only a few pre-existing conditions that worsen outcome, primarily pulmonary hypertension (Stream et al., 2009). COVID-19 is associated with a higher mortality in patients with pre-existing diseases including cardiovascular (hypertension, heart failure), pulmonary (chronic obstructive pulmonary disease) or metabolic (diabetes mellitus) conditions.

- HAPE mainly depends on the rate of decrease of the partial pressure of oxygen, that is the rate of ascent to high altitude. Age is not an independent risk factor for HAPE.

COVID-19 affects individuals of all ages, but patients older than 65 are at higher risk of severe ARDS, with high mortality.

For these reasons, we strongly caution against managing COVID-19 with treatments that are used for HAPE. COVID-19 and HAPE are fundamentally different in pathogenesis, pathophysiology, prognosis and treatment.

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Table 1. Differences between High Altitude Pulmonary Edema (HAPE) and COVID-19

HAPE	COVID-19
Hypoxia causative	Hypoxemia secondary to respiratory failure
No infectious agent	Transmitted viral disease
Hypoxia-induced pulmonary hypertension	Pulmonary hypertension due to multiple causes
Inflammatory factors secondary	Primary alveolar-interstitial inflammation
Reversible with supplemental oxygen	Not reversible with oxygen alone
Affects only the lung	Affects lung, kidney heart and nervous system
No multi-organ system failure	Deaths from multi-organ system failure
Rarely pre-existing conditions worsen outcome	Common pre-existing conditions worsen outcome
Genetic susceptibility	Possible genetic susceptibility
Age-independent	Increased mortality with increased age