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COVID-19 Lung Injury is Not High Altitude Pulmonary Edema

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As medical providers around the world struggle to care for patients with acute respiratory failure secondary to corona virus disease 2019 (COVID-19), extensive efforts have been made to compare this entity to other forms of acute respiratory failure observed prior to the current pandemic. Among the variety of theories put forth, one argument that has been made and amplified via social media is that COVID-19 lung injury is not like typical acute respiratory distress syndrome (ARDS) and instead is similar to high altitude pulmonary edema (HAPE) (Solaimanzadeh, 2020). As a group of physicians who have in some cases cared for patients with COVID-19 and in all cases cared for patients with HAPE and studied its pathophysiology and management, we feel it is important to correct this misconception, as continued amplification of this message could have adverse effects on management of these patients.

HAPE is a noncardiogenic form of pulmonary edema, as are ARDS due to bacterial or viral pneumonia, re-expansion pulmonary edema, immersion pulmonary edema, negative pressure pulmonary edema, and neurogenic pulmonary edema. All of these entities cause hypoxemia of varying degrees, and all cause diffuse bilateral opacities on chest imaging. Importantly, in all of these cases, edema accumulates in the interstitial and alveolar spaces of the lung as a result of an imbalance in Starling forces. What separates these entities, however, is the mechanism by which that imbalance develops. It is well established that HAPE occurs as a result of excessive and uneven hypoxic pulmonary vasoconstriction. This leads to a marked rise in pulmonary artery pressure with subsequent overperfusion of certain regions of the lung, increased pulmonary capillary hydrostatic pressure and leakage of fluid out of the vascular space into the alveolar space. (Swenson and Bärtsch, 2012)

This is a fundamentally different phenomenon than that seen in ARDS due to COVID-19, in which viral-mediated inflammatory responses are the primary pathophysiological mechanism; alveolar epithelial inflammation and dysfunction impair surfactant function and alveolar fluid clearance, leading to alveolar collapse and/or filling and, as a result, significant ventilation-perfusion mismatch. (Thompson et al., 2017) The resulting hypoxemia may not be accompanied by reduced compliance in the acute phase of presentation but such problems often develop as ARDS progresses. Observed increases in pulmonary artery pressure are a consequence of, rather than a cause of alveolar edema. Systemic viremia can also cause non-pulmonary organ dysfunction, a phenomenon not seen in HAPE.

Understanding the distinction between the pathophysiological mechanisms of these entities is critical for patient management. In most patients, HAPE can be treated with supplemental oxygen alone or descent to lower elevation when supplemental oxygen is not available. Raising the alveolar PO_2 decreases pulmonary artery pressure, leading to resolution of the alveolar and interstitial edema and complete recovery within hours to a few days. In contrast, supplemental oxygen may improve hypoxemia in COVID-19 but will not resolve the underlying inflammation or lung injury. Only good supportive care including mechanical ventilation, quite often for long periods of time, allows some patients to survive until their disease resolves.

HAPE can also be prevented or treated with pulmonary vasodilators such as nifedipine or sildenafil which decrease pulmonary artery pressure and, as a result, lower pulmonary capillary hydrostatic pressure. While use of such medications might decrease pulmonary artery pressure and improve right ventricular function, by releasing hypoxic pulmonary vasoconstriction and increasing perfusion to poorly and

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nonventilated regions of the lung, they have the potential to worsen ventilation–perfusion mismatch and, as a result, worsen hypoxemia. These agents might also cause or worsen hypotension. Vasodilators such as epoprostenol and nitric oxide do have a role in some patients with severe ARDS due to COVID-19 but only when given via the *inhalational* route which improves rather than impairs ventilation–perfusion matching.

COVID-19 mediated lung injury has proven to be a heterogeneous disease in which patients present with varying degrees of hypoxemia, alterations in lung compliance and other physiologic derangements. In this challenging time, we must identify the best means to care for these critically ill patients. That approach should be grounded in sound pulmonary physiology, clinical experience and, when available, evidence from clinical studies. We must avoid propagation of erroneous theories and treatments with potentially deleterious consequences for patient care.

Author Disclosure Statement

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