COVID-19 Lung Injury and High-Altitude Pulmonary Edema

A False Equation with Dangerous Implications

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Abstract

Amid efforts to care for the large number of patients with coronavirus disease (COVID-19), there has been considerable speculation about whether the lung injury seen in these patients is different than acute respiratory distress syndrome from other causes. One idea that has garnered considerable attention, particularly on social media and in free open-access medicine, is the notion that lung injury due to COVID-19 is more similar to high-altitude pulmonary edema (HAPE). Drawing on this concept, it has also been proposed that treatments typically employed in the management of HAPE and other forms of acute altitude illness—pulmonary vasodilators and acetazolamide—should be considered for COVID-19. Despite some similarities in clinical features between the two entities, such as hypoxemia, radiographic opacities, and altered lung compliance, the pathophysiological mechanisms of HAPE and lung injury due to COVID-19 are fundamentally different, and the entities cannot be viewed as equivalent. Although of high utility in the management of HAPE and acute mountain sickness, systemically delivered pulmonary vasodilators and acetazolamide should not be used in the treatment of COVID-19, as they carry the risk of multiple adverse consequences, including worsened ventilation–perfusion matching, impaired carbon dioxide transport, systemic hypotension, and increased work of breathing.

Keywords: high-altitude pulmonary edema; coronavirus disease; nifedipine; acetazolamide; acute respiratory distress syndrome

(Received in original form April 12, 2020; accepted in final form April 24, 2020)

The views in this manuscript represent the views of the authors and do not represent an official position of the U.S. government.

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CME will be available for this article at www.atsjournals.org.

Ann Am Thorac Soc Vol 17, No 8, pp 918–921, Aug 2020

DOI: 10.1513/AnnalsATS.202004-327CME
Internet address: www.atsjournals.org

Given the rapid pace and overwhelming magnitude of the coronavirus disease (COVID-19) pandemic, clinicians have struggled to determine the appropriate therapy for these critically ill patients. In the absence of high-quality, peer-reviewed information, many have reached out to colleagues around the world for input or sought information from the World Health Organization or professional societies, such as the American Thoracic Society and European Society of Intensive Care Medicine. Another major source of communications has been free open-access medicine and social medial platforms. Although these tools can be an excellent way to rapidly disseminate information to a broad audience (1), they also carry the risk of spreading erroneous information (2).

One question that has garnered significant attention is whether lung injury in COVID-19 differs from that in acute respiratory distress syndrome (ARDS) from other causes. Emerging from early descriptions of patients with respiratory failure due to COVID-19 have been observations that some patients have hypoxemia out of proportion to reported dyspnea or the extent of radiographic opacities, higher than typical respiratory system compliance and lesser work of breathing. In the face of these anomalies, some have speculated that COVID-19 lung injury is not a typical form of ARDS and, instead, is more closely related to high-altitude pulmonary edema (HAPE) (3). This conclusion, which has been amplified on social media, has led to further speculation that therapies commonly used in the prevention and treatment of HAPE and other acute altitude illnesses might be of benefit in patients with lung injury due to COVID-19.

A review of the pathophysiology of HAPE and ARDS, and a close examination of the mechanisms of action of the medications used in the management of HAPE, should make it clear, however, that COVID-19

lung injury is not, in fact, akin to HAPE, and that treatments used for HAPE will be of no benefit or, worse, lead to patient harm.

Pathophysiological Mechanisms of HAPE and Lung Injury in COVID-19

HAPE and ARDS fall in a category of what is referred to as noncardiogenic edema—pulmonary edema that develops in the absence of left heart dysfunction and elevated left atrial pressure. Other entities in this category include immersion pulmonary edema, negative-pressure pulmonary edema, neurogenic pulmonary edema, and re-expansion pulmonary edema. These forms of noncardiogenic edema have several features in common, including varying degrees of hypoxemia, alterations in lung compliance, and diffuse bilateral opacities on chest imaging. Although they all develop due to imbalances in Starling forces, the mechanism by which those imbalances develop varies between entities. Here, we consider the differing pathophysiological mechanisms of HAPE and ARDS in greater detail.

HAPE

Pulmonary edema develops in HAPE due to exaggerated hypoxic pulmonary vasoconstriction (HPV) and marked elevations in mean pulmonary artery (PA) pressure as high as 45–60 mm Hg (4, 5). The key aspect of these changes is that HPV occurs unevenly throughout the lung. As a result, regions of the pulmonary vasculature with less vasoconstriction experience both increased pressure and increased blood flow, leading to increased pulmonary capillary hydrostatic pressure and subsequent leakage of fluid from the vascular space to the interstitial and alveolar spaces. Often termed over-perfusion edema, this leakage occurs first by dynamic, noninjurious, and quickly-reversible changes in alveolar capillary permeability. Ultimately, if pressures rise high enough, mechanical rupture with capillary stress failure occurs (6–9). This concept is supported by the patchy nature of the radiographic opacities in HAPE and magnetic resonance imaging studies in HAPE-susceptible individuals demonstrating heterogeneity of pulmonary blood flow in response to hypoxia (10, 11). It also explains why pulmonary edema is not seen in other forms of pulmonary arterial hypertension, where vascular pathology develops more evenly in the lung. Exercise exacerbates edema formation at altitude by increasing pulmonary blood flow and over-perfusion of the unprotected regions.

In addition to excessive HPV, alterations in alveolar fluid clearance contribute to the development of edema. Hypoxia decreases the activity and expression of the alveolar epithelial apical membrane epithelial sodium channel and basolateral membrane sodium–potassium ATPase, thereby decreasing active sodium transport across the alveolar wall and reducing alveolar fluid reabsorption (12–14). Importantly, although early studies in HAPE, mostly in patients many days after the onset of symptoms, suggested that HAPE has an inflammatory basis (15, 16), further studies combining echocardiography and bronchoalveolar lavage (BAL) demonstrated that inflammation is absent in the early phases of HAPE. Instead, mild alveolar hemorrhage occurs with leakage of plasma proteins proportional to the PA pressure without neutrophils or proinflammatory cytokines (17). HAPE is thus primarily a problem of abnormal hydrostatic pressure, whereas inflammatory responses more likely represent a healing response to the mechanical injury of the alveolar–capillary barrier.

ARDS and COVID-19

ARDS is a fundamentally different form of lung injury than HAPE. The various causes of ARDS range from noninfectious conditions, such as pancreatitis, aspiration of gastric contents, and severe trauma, to severe pulmonary and nonpulmonary sepsis. The common, but not exclusive, feature of all these causes is the generation of an intense host cytokine-mediated inflammatory response that recruits and activates neutrophils and other immune cells to the lung, increases capillary permeability, impairs surfactant production and function, inhibits active alveolar epithelial fluid reabsorption, and initiates cell death by various pathways. This leads to alveolar flooding, atelectasis, severely diminished lung compliance, ventilation–perfusion mismatch, and right-to-left shunt (18). The impairments in gas exchange are exacerbated by cytokine-mediated impairment of normal ventilation–perfusion matching mechanisms, such as HPV. With control of the initiating cause, recovery can occur with return of full lung function in some patients, but, in many patients, long-lasting abnormalities in pulmonary function and chest imaging persist (18). Increased PA pressure is seen in ARDS (19, 20), but the changes are generally lower (mean PA pressure = 25–30 mm Hg) than seen in HAPE, and result from a broader array of mechanisms beyond HPV, including microthrombotic occlusion, positive end-expiratory pressure, and high sympathetic nervous system activation. Importantly, increased PA pressure is a *consequence* of ARDS rather than the cause. BAL early in the course of ARDS demonstrates intense neutrophilia and high concentrations of proinflammatory cytokines (21) in contrast to the very noninflammatory milieu of early HAPE (17).

ARDS secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has the same hyperinflammatory characteristics as seen with usual ARDS. A recent study (22) involving BAL in mechanically ventilated patients with COVID-19 found high mRNA expression of proinflammatory cytokines, similar to that seen in earlier studies of ARDS. In select patients, hypoxemia may not be accompanied by severely reduced compliance in the acute phase of presentation (23). Whether this is truly a distinguishing feature of COVID-19 lung injury or simply reflects the fact that many patients were intubated early in their disease course has not been examined. By initiating mechanical ventilation sooner than typically done, we may simply be observing the earliest phase of ARDS in some patients. As is clear from other published reports, however, many patients with COVID-19 lung injury do have markedly reduced compliance (24), similar to that reported in other studies of ARDS (25, 26)

Therapeutics in HAPE Are Inappropriate for COVID-19

One of the implications of the argument that COVID-19 lung injury is akin to HAPE is that therapies used for prevention and

treatment of the latter may be efficacious in the former. The primary treatment of HAPE is provision of supplemental oxygen or, when not available, descent to lower elevation. This immediately raises the alveolar and arterial partial pressure of oxygen, both of which act to reduce HPV, lower PA pressure, and decrease the hydrostatic pressure gradient driving edema formation. Complete recovery can be seen within hours to days, depending on the severity of the presentation. Increasing the fractional concentration of oxygen mitigates the hypoxemia seen in COVID-19, but does not, in and of itself, promote resolution of lung injury. Instead, time and appropriate supportive care, often including long courses of invasive mechanical ventilation, are necessary to allow the lungs to heal.

In severe cases or when oxygen is not available, pulmonary vasodilators, such as the calcium channel blocker, nifedipine, or the phosphodiesterase-5 inhibitors, sildenafil and tadalafil, can be used to reduce HPV and lower PA pressure. Small clinical trials and extensive clinical experience have provided support for their role in both prevention (27, 28) and treatment (29) of HAPE. Although acetazolamide has been shown to block HPV in animal (30, 31) and human (32) studies, it is not currently part of treatment protocols for HAPE. However, by promoting acclimatization to hypobaric hypoxia, in general, it has some carryover effect in HAPE prevention. Even though HAPE and COVID-19 share some clinical features, none of these therapies are appropriate for managing COVID-19 lung injury.

Nifedipine and Phosphodiesterase-5 Inhibitors

Nifedipine inhibits L-type calcium channels on the surface of vascular smooth muscle cells, thereby limiting the increase in the intracellular calcium concentration necessary for smooth muscle contraction. The phosphodiesterase-5 inhibitors, sildenafil and tadalafil, block degradation of nitric oxide (NO)–mediated cyclic GMP in vascular smooth muscle, thereby promoting vasodilation. Administration of these medications to patients with COVID-19 lung injury may lower PA pressure and potentially improve right ventricular function, but have the potential to worsen oxygenation. Patients with lung injury rely on HPV to maintain adequate ventilation–perfusion matching. Systemic administration of medications with pulmonary vasodilatory properties, however, will release HPV in poorly ventilated and shunt regions of the lung, thereby increasing perfusion of those areas. This will further exacerbate the already abnormal ventilation–perfusion mismatching in injured regions of the lung and, as a result, worsen gas exchange and arterial oxygenation.

Other pulmonary vasodilators, such as epoprostenol and NO, may have a role in some patients with ARDS, although studies have not demonstrated a mortality benefit with use on a broad basis (33). The key difference is that these agents are given by inhalation, which allows preferential delivery to the ventilated regions of the lung. By selectively vasodilating in these areas and not affecting the unventilated regions, they can improve ventilation–perfusion matching and, as a result, oxygenation (34).

Acetazolamide and Other Respiratory Stimulants

Beyond the pulmonary vasodilators, some have advocated for use of respiratory stimulants in COVID-19 (3). The drug most commonly used to stimulate ventilation and prevent acute altitude illness, as well as being used for other diseases at low altitude associated with hypoventilation, is the carbonic anhydrase (CA) inhibitor, acetazolamide. The drug generates a mild metabolic acidosis by inhibition of renal tubular CA, which offsets the braking effect on ventilation of the respiratory alkalosis resulting from the hypoxic ventilatory response. The ensuing improvements in arterial oxygen pressure afforded by the drug prevent or reduce acute mountain sickness severity (35).

Acetazolamide works best and most safely in subjects with otherwise normal lung function, low work of breathing, and the ability to increase ventilation easily without significant dyspnea or threat of respiratory muscle fatigue. In healthy humans, acetazolamide causes the moderately stimulated diaphragm to fatigue sooner, even in normoxia (36). At high concentrations, it also inhibits HPV (35) and thus, like nifedipine and sildenafil, can worsen ventilation–perfusion matching. For patients already dyspneic and verging on respiratory muscle fatigue, acetazolamide can increase dyspnea and precipitate respiratory failure by several means. In addition, if the patient cannot increase ventilation sufficiently, any pre-existing metabolic acidosis will worsen. Higher doses and/or impaired renal function increase the risk of red cell CA inhibition, which can precipitate hypercapnic respiratory failure, as happens in patients with severe chronic obstructive pulmonary disease and limited respiratory reserve (37).

Another respiratory stimulant, almitrine, has been discussed on social media in relation to COVID-19. Almitrine increases ventilation at high altitude (38) by direct stimulation of the peripheral chemoreceptors. In contrast to acetazolamide, it potentiates HPV (39) and has been studied in ARDS along with concurrent inhaled NO. Almitrine is not available in all countries, and it can cause polyneuropathies, a side-effect that has limited its applications in chronic conditions and deterred approval in some countries. As with acetazolamide, any respiratory stimulation in patients with acute lung injury who already have increased respiratory drive and are hyperventilating may be unwanted.

Conclusions

Although HAPE and COVID-19 share several features in common, these are all nonspecific attributes of many acute respiratory disorders, and their presence in both COVID-19 and HAPE in no way implies that these entities are at all related to each other. The pathophysiological mechanisms underlying these disorders differ in significant ways, as do the treatment approaches. Attempts to treat COVID-19 with medications typically used for acute altitude illness are likely of no benefit, and may even cause harm. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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