The Role of Alveolar Edema in COVID-19

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Abstract

The coronavirus disease 2019 (COVID-19) has spread over the world for more than one year. COVID-19 often develops life-threatening hypoxemia. Endothelial injury caused by the viral infection leads to intravascular coagulation and ventilation-perfusion mismatch. However, besides above pathogenic mechanisms, the role of alveolar edema in the disease progression has not been discussed comprehensively. Since the exudation of pulmonary edema fluid was extremely serious in COVID-19 patients, we bring out a hypothesis that severity of alveolar edema may determine the size of poorly-ventilated area and the blood oxygen content. Treatments to pulmonary edema (alcohol-oxygen vapor therapy and fluid management) may be great helpful for reducing occurrence of severe cases. Given that late mechanical ventilation may cause mucus (edema fluid) to be blown to the deep of the small airways, oxygen therapy should be given at the early stages. The optimal time and SpO_2 threshold for oxygen therapy are also discussed.

Keywords: SARS-CoV-2; ventilation-perfusion mismatch; alveolar edema; alcohol-oxygen vapor therapy; fluid management

Since the outbreak of novel SARS-like coronavirus (SARS-CoV-2), over 100,000,000 cases have been reported globally with an overall mortality rate of around 2%–5% (1). Acute respiratory distress syndrome (ARDS) and the serious complications (mainly multiple organ failure) are the most frequent causes of death (1).

The lung's initial response to acute viral infections has been characterized by innate immunity mediated damages of the alveolar endothelial and epithelial barriers and accumulation of protein-rich edema fluid within the interstitium and alveolus, and then a great decline in oxygen diffusion over the alveolar-capillary membrane (2). Blood flow through severely-damaged units, hereby, constitutes an intrapulmonary shunt and the hypoxia (2). Hypoxia inhibits K^+ channels but activates voltage gated Ca^{2+} channels, which raises cytosolic Ca^{2+} levels in muscular pulmonary artery smooth muscle cells and causes vasoconstriction (2). Thus at the tissue level, patients of acute lung injury often develop the hypoxic pulmonary vasoconstriction (HPV) (3), which is an essential protection mechanism of the lung that directs blood perfusion from badly-ventilated to well-ventilated alveoli to optimize gas exchange. However, dysregulated HPV may cause mismatched blood flow and alveolar ventilation, and may result in life-threatening hypoxemia (Figure 1) (4).

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Endothelial injury also induces intravascular coagulation, which leads to platelet aggregation and microthrombi formation (5, 6). While intravascular coagulation at well-ventilated alveoli may result in ventilation-perfusion mismatch. Recently, Herrmann et al. (7) modeled lung perfusion abnormalities and suggested that early COVID-19 hypoxemia may be mainly attributed to severe ventilation-perfusion mismatch.

Nevertheless, neither intravascular coagulation nor ventilation-perfusion mismatch could be easily corrected. Increasing inspired oxygen results in enhanced oxygenation, but however does not improve the ratio of arterial oxygen tension to fractional inspired oxygen (P_aO_2:F_iO_2) (7). Inhaled nitric oxide decreases total pulmonary vascular resistance, but however may increase blood flow to these low ventilation/perfusion regions, which causes further arterial desaturation (4). Initial anticoagulant treatments with low molecular weight heparin or aspirin have been shown to reduce mortality and achieve a significant improvement in P_aO_2:F_iO_2 in some patients, but however could not completely prevent occurrence of severe cases (6, 8, 9).

THE ROLE OF ALVEOLAR EDEMA IN COVID-19

Besides above pathogenic mechanisms, alveolar edema also plays a key role in the disease progression. Endothelial barrier disruption induces interstitial flooding via activation of the actin–myosin contractile apparatus (2). Then alveolar edema leads to hypoxia at the poorly ventilated units (2). Hypoxia in turn inhibits oedema fluid clearance, due in part to the disassembly of the keratin intermediate filament network, a fundamental element of the cellular cytoskeleton, therefore destructing the epithelial barrier (10). Therefore, a long-term hypoxia aggravates the disease by inducing more alveolar edema, which forms a vicious circle. Therefore treatments to alveolar edema may help to both reduce the size of poorly ventilated area and increase the blood oxygen content (Figure 1).

A relatively high partial pressure of O_2 in the alveolar gas (PAO_2) facilitates alveolar fluid resorption by activating Na^+ transport across the alveolar epithelium, which makes an osmotic gradient responsible for the lung edema clearance (10). Hereby, appropriate oxygen inhalation would accelerate the resorption of pulmonary edema fluid. However, simple oxygen therapy would not achieve adequate effects on alveolar edema clearance. Alcohol-oxygen vapor therapy (oxygen inhalation with 20% alcohol as humidifying agent) decreases the surface tension of the foam inside the pulmonary alveoli and shows good therapeutic effects to pulmonary edema (11). Moreover, conservative fluid therapy also prevents lung edema formation and promotes lung edema resorption (12, 13). Unfortunately, these common therapies to pulmonary edema have not attracted enough attention in COVID-19 clinical practice.

Autopsy showed that pulmonary fibrosis was not serious in dead patients with SARS-CoV-2 infections. Intact alveoli could still be seen, but exudation was serious (14), suggesting the severe alveolar edema. COVID-19 has a prominent feature, that is, a large amount of mucus (edema fluid) could be found in the small airway (14), which is distinct from other acute pulmonary injuries.

When the disease develops into late stages, systemic alveolar edema and severe ventilation-perfusion mismatch occur, and the blood oxygen will decline sharply. Then the high flow oxygen therapy and mechanical ventilation will be required (Figure 1). However, high flow oxygen may also cause pulmonary-specific toxic effects, such as denitrogenation phenomena, inhibition of surfactant production and atelectasis (15). On the other hand, mechanical ventilation may cause mucus to be blown to the deep of the small airways, which then aggravates intrapulmonary shunt and alveolar hypoxia. These deleterious effects may be an important reason for the high mortality after high-flow oxygen inhalation and mechanical ventilation (The ICU mortality rate among those who required non-invasive ventilation was 79%

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and among those who required invasive mechanical ventilation was 86%) (16). Therefore, nebulized heparin treatments, alcohol-oxygen vapor therapy or other inhalation therapies should be given at the early stages of COVID-19.

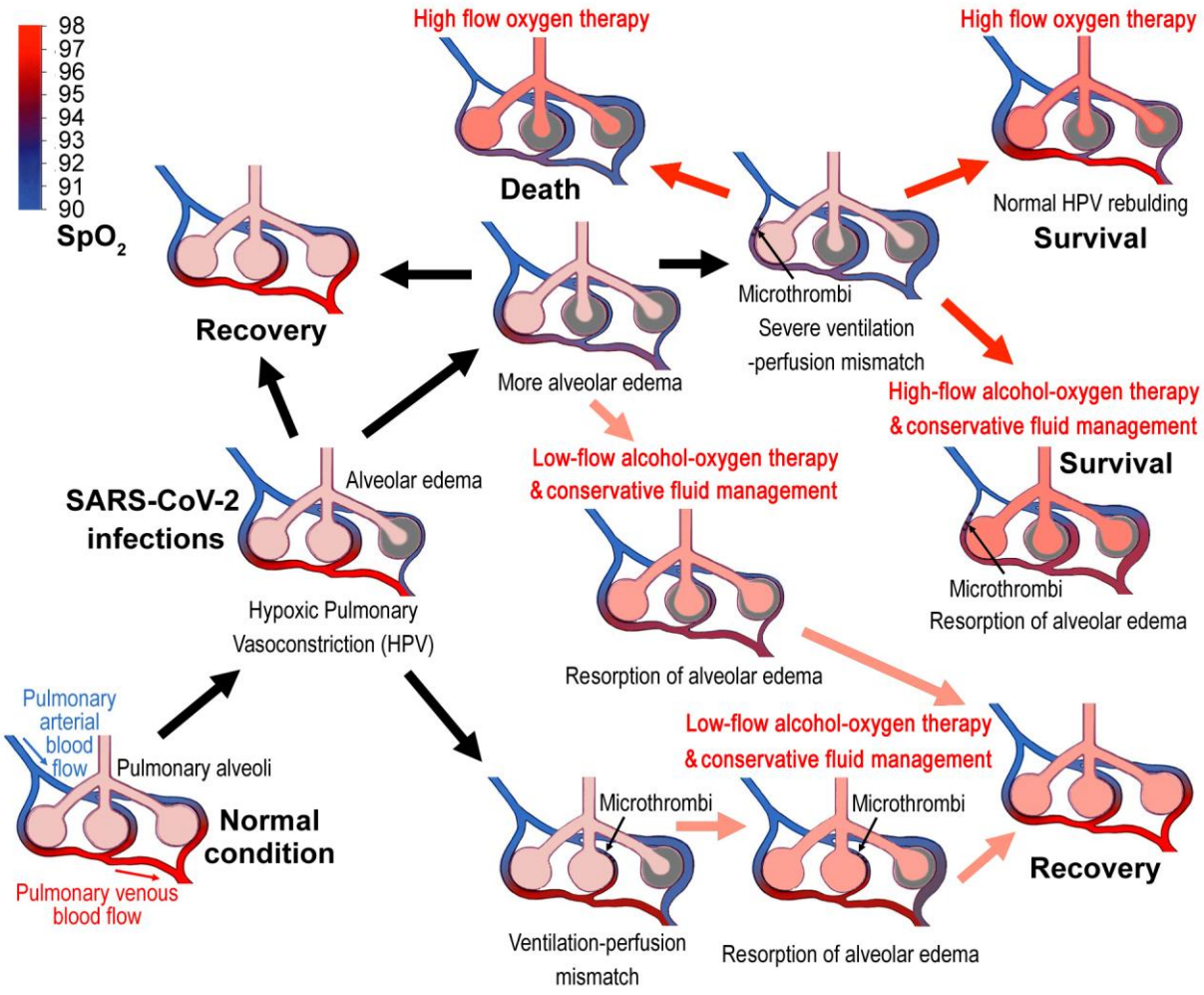

FIGURE 1 | Hypothetically pathogenic mechanisms of COVID-19 and the corresponding therapies
Virus infections cause alveolar edema and the hypoxic pulmonary vasoconstriction (HPV), which is an essential protection mechanism of the lung that directs blood perfusion from badly-ventilated to well-ventilated alveoli to optimize gas exchange. However, endothelial-injury-induced microthrombi formation may cause mismatched blood flow and alveolar ventilation, and may result in life-threatening hypoxemia. Both alcohol-oxygen vapor therapy and conservative fluid management promote lung edema resorption and show good therapeutic effects to pulmonary edema, and therefore are recommended. When the disease develops into late stages, systemic alveolar edema and severe ventilation-perfusion mismatch occur, and the blood oxygen will decline sharply. Then the high-flow oxygen therapy will be required. However, high-flow oxygen inhalation may cause several adverse effects and increase the mortality. In this case, humidification with 20% alcohol is also recommended. The blue to red gradient bar shows blood oxygen saturation (SpO_2).

THE OPTIMAL TIME AND SPO_2 THRESHOLD FOR OXYGEN THERAPY

In a retrospective case report that included 69 adults in Wuhan, China, 29% of patients showed dyspnea and 20% of cases (14 patients) showed oxygen saturation SpO_2 <90% [oxygen index (OI) <110 mmHg]

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during admission (17). In their report, as of February 4, 2020, 18 (26.9%) of 67 patients had been discharged, and five patients had died, with a mortality rate of 7.5%. Noticeably, all five deaths occurred in the SpO_2<90% group (17). The median time from onset of symptoms to admission was six days (inter quartile range 4-9 days) (17). However in the SpO_2 <90% group, the median occurrence time of lowest SpO_2 was only one day (inter quartile range 0-2 days) after admission (17). In other words, SpO_2 of some patients at admission were already very low, which may develop severe ARDS subsequently. Therefore, it may be too late for them to take oxygen therapy after admission. The best window period of oxygen therapy may be the six days from onset of symptoms to admission.

Dai et al. (18) classified COVID-19 patients into four stages according to the CT performances. Stage I: one or more lesions, in irregularly patchy or round shapes, generally showing ground-glass opacity with vascular enlargements. Stage II: more area lesions, found in bilateral lobes mainly at the sub-pleural areas, in irregularly patchy, round or reverse-butterfly shapes, diffused or scattered patches occasionally fusing into a large patch with a high density, vascular enlargements, reticular signs and bronchial wall thickening, sometimes with little fibrosis and atelectasis in sub-segments. Stage III: some lesions diminished or absorbed, the focus could be entirely absorbed, showing residual fibers. Stage IV: bilateral diffuse inhibitions, over half of the lung areas involved, occasionally extended to the entire lung and defined as the white lung, implying the systemic alveolar edema. However the patients in the stage IV group showed only slightly-declined SpO_2 (94.70±0.20%). While the stage II patients with only a small proportion of lung injury and HPV showed relatively high SpO_2 (97.2±0.91%) (18). SpO_2 < 95% may indicate late infection stages (18).

Moreover, a recent study demonstrated a high correlation between decreased SpO_2 and severe cases that 78.0% (32/41) of the patients with SpO_2 ≤95% would develop into severe diseases (19). The risk threshold of SpO_2 was 95%.

The World Health Organization (WHO) and BMJ Best Practice suggested SpO_2 ≤90% or signs of severe respiratory distress, central cyanosis, shock, coma and/or convulsions as diagnostic standards for the severe pulmonary infection (20, 21). And according to the novel coronavirus pneumonia diagnosis and treatment plan (trial version 7) published by the National Health Committee of China, either respiratory rate (RR) ≥30 times per minute, or resting state SpO_2 ≤93%, or OI ≤300 mmHg is defined as the severe condition, and then the oxygen therapy was given (22). However, the median SpO_2 / respiratory rate value was significantly higher in COVID-19 patients than in non-COVID-19 patients, which implies that a normal breathing rate could mask profound hypoxia and make severity assessment in COVID-19 patients more difficult in out-of-hospital settings (23). Besides, based on above analysis, the diagnostic standard of SpO_2 either ≤90% or ≤93% may be too low to take the oxygen therapy in time.

FOUR CLINICAL COMMENTS

Based on the above analysis, we propose four comments to prevent SARS-CoV-2 patients from developing into severe hypoxemia: (a) For the suspected cases with symptoms, finger SpO_2 (with finger oximeter ideally) should be measured at each time of nucleic acid test sampling and daily after symptom onset. However, finger SpO_2 varies greatly with the altitude and the age (4), and the finger oximeter itself may have a large deviation, so it is recommended that each oximeter should be calibrated with several healthy people of different ages to get the reference value. If the patient's SpO_2 was lower than the reference value by 3% or more (e.g. if the reference value was 98%, then ≤95% is the threshold for oxygen therapy), it is suggested to be hospitalized immediately for standard low-flow oxygen inhalation with 20% alcohol as humidifying. If it was not possible to be admitted to hospital immediately, the patient is recommended to

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take oxygen in the home, such as with a portable oxygen respirator. During the in-home oxygen therapy, finger SpO_2 should be monitored continually to assure that SpO_2 has been restored to 96%, but not higher than that. This is because saturation above this level likely causes an increased risk of death without plausible benefit (24). This upper limit may be lower for the patients with chronic respiratory diseases. For instance, the oxygen treatment goal should be 88%-92% for patients with chronic type II respiratory failure (22). Nevertheless, if SpO_2 cannot be enhanced afterwards, the patient should seek medical advice or go to the hospital in time. The in-home oxygen therapy may be of great significance for countries with a shortage of medical resources. (b) For the patients with very low SpO_2, high-flow oxygen inhalation should be applied. Nevertheless, humidification with 20% alcohol is also recommended on this occasion. (c) Fluid management should be considered for all COVID-19 patients and conservative fluid therapy should be applied to severe cases. Detailed guidance of fluid administration in patients with COVID-19 has been discussed elsewhere (25). For the in-home patients, appropriate reduction in water intake might be an expedient measure. (d) The prone position could reduce the risk of ventilation-associated lung injuries by the combined effects of more uniform distribution of breathing and less compression of the left lower pulmonary lobe by the heart (2, 26–28). Therefore, patients with low SpO_2 are advised to use prone position as much as possible. In addition, the patients should avoid any vigorous activity that may increase respiratory rate and tidal volume, because that pulmonary injury will be worsened by the mechanical stretch during the strained breathing (2, 26–28).

CLINICAL OUTLOOK

In summary, we suggest that in the beginning of the COVID-19 pulmonary involvement (decrease of SpO_2 of 3%) the patients should receive immediate alcohol-oxygen vapor therapy and fluid management. However this is merely a concept paper that needs to be tested in controlled randomized trials. It should be noted that not only SpO_2 is important but also the patient's associated tachypnea or hyperpnea and SpO_2 should be interpreted with caution as there is a left-sided shifting of the oxyhemoglobin dissociation curve due to tachypnea / hyperpnea induced by hypoxemia (29). Thus, SpO_2 monitoring with a finger oximeter is just a stop-gap measure, and the CT performance is still a "golden rule". Besides, COVID-19 ARDS is a very complex disease, with intrapulmonary shunting, impaired lung diffusion, inflammation, et al. (30–32). We cannot expect that early alcohol-oxygen vapor therapy and fluid management can prevent every COVID-19 patient from the development of ARDS. Antiviral drugs, anti-inflammatory agents and anticoagulant therapies (e.g. heparin as mentioned above) should be adopted accompanying with pulmonary edema treatments.

CONFLICT OF INTEREST

Si-Cong Jiang was employed by the Chengdu KangHong Pharmaceutical Group Comp. Ltd. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

SY conceptualized the analysis and wrote the original draft. SCJ and ZLL reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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