Early Oxygen Inhalation to Prevent SARS-CoV-2-induced Acute Respiratory Distress Syndrome

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Abstract: Acute respiratory distress syndrome (ARDS) and the serious complications are the most frequent causes of death of SARS-CoV-2 infection. We bring out a hypothesis that early low-flow oxygen inhalation would maintain the hypoxic pulmonary vasoconstriction (an essential protection mechanism of the lung that optimize gas exchange) and accelerate the re-absorption of pulmonary edema fluid. The optimal time for oxygen therapy was analyzed and four comments are proposed: (1) Finger SpO₂ should be measured at each time of nucleic acid test sampling and daily after admission. (2) If the patient’s SpO₂ was lower than the reference value by 3% or more, it is suggested to be immediately for standard low-flow oxygen inhalation. (3) If it was not possible to be admitted to hospital immediately, the patient is recommended to take oxygen in the home. (4) The Patients with low SpO₂ are advised to use prone position as much as possible.

Keywords: SARS-CoV-2; acute respiratory distress syndrome; hypoxic pulmonary vasoconstriction; alveolar edema; early low-flow oxygen
Introduction
Since the outbreak of novel SARS-like coronavirus (SARS-CoV-2), more than 2,200,000 cases have been reported globally with an overall mortality rate of around 2%–3%.\textsuperscript{1–3} Acute respiratory distress syndrome (ARDS) and the serious complications (mainly multiple organ failure) are the most frequent causes of death.\textsuperscript{1–3} Accordingly, 56% of the patients admitted to intensive care unit (ICU) were given non-invasive ventilation, 76% of whom required further orotracheal intubation and invasive mechanical ventilation.\textsuperscript{4} Nevertheless, in some underdeveloped countries, ventilators and supplyextracorporeal membrane oxygenation (ECMO) are in extraordinarily short, which may lead to much higher mortality rates. Non-hospital (home-based) therapies to improve patients’ breathing need to be developed urgently.

Oxygen maintains hypoxic pulmonary vasoconstriction
The lung’s initial response to injury induced by acute virus 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.\textsuperscript{5} Blood flow through this damaged unit, hereby, constitutes an intrapulmonary shunt and the hypoxia.\textsuperscript{5} Hypoxia inhibits K\textsuperscript{+} channels but activates voltage gated Ca\textsuperscript{2+} channels, which raises cytosolic Ca\textsuperscript{2+} levels in muscular pulmonary artery smooth muscle cells and causes vasoconstriction.\textsuperscript{6} Endothelin-1 and thromboxane A\textsubscript{2} may amplify, whereas prostacyclin and nitric oxide may moderate this process.\textsuperscript{7} Thus at the tissue level, patients of acute virus infections often develop the hypoxic pulmonary vasoconstriction (HPV),\textsuperscript{8} which is an essential protection mechanism of the lung that directs blood perfusion from badly-ventilated to well-ventilated alveoli to optimize gas exchange (figure). However, the efficiency of HPV decreases as the disease develops. When the percentage of lung that is hypoxic is high (over 70%), HPV would be eliminated because that the alveolar oxygen tension in the normoxic compartment would fall below the threshold for maintaining HPV.\textsuperscript{9} At this time, the HPV happens in both normoxic lung competes and hypoxic lung competes, which results in a general pulmonary vasoconstriction, leading to pulmonary hypertension (PH) and a risk of right-heart failure subsequently (figure).\textsuperscript{7,8}

Hypoxia inhibits oedema fluid clearance, due in part to the down-regulation of plasma membrane Na,K-ATPase.\textsuperscript{10} Hypoxia has also been shown to degrade and disassemble the keratin intermediate filament network, a fundamental element of the cellular cytoskeleton, therefore destructing the epithelial barrier.\textsuperscript{10} Therefore, a long-term hypoxia aggravates the disease by inducing more alveolar edema. If the patients were not treated in time, a systemic alveolar edema will develop (figure). Autopsy showed that pulmonary fibrosis was not serious in dead patients with SARS-CoV-2 infections.\textsuperscript{11} Intact alveoli could still be seen, but exudation was serious.\textsuperscript{11} coronavirus disease 2019 (COVID-19) has a prominent feature, that is, a large amount of mucus could be found in the small airway, and it may eventually block the airway,\textsuperscript{11} which may be an important reason for the high mortality after later mechanical ventilation and high-flow oxygen inhalation (The ICU mortality rate among those who required non-invasive ventilation was 79% and among those who required invasive mechanical ventilation was 86%).\textsuperscript{4}

A similar general pulmonary vasoconstriction has been observed in patients with acute altitude sickness.\textsuperscript{7,8} If they were not treated in time, a systemic alveolar edema will develop, when the effectiveness of high-flow oxygen therapy will be greatly compromised. On the contrary, an early low-flow oxygen inhalation shows a good therapeutic effect,\textsuperscript{12} no matter whether the general pulmonary vasoconstriction occurs or not (figure).
Figure: Hypothetical mechanism of early low-flow oxygen therapy to patients of acute virus infections or altitude sickness. 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, more alveolar edema results in a general pulmonary vasoconstriction, leading to pulmonary hypertension (PH) and a risk of right-heart failure. Early low-flow oxygen inhalation maintains the HPV and accelerates the re-absorption of pulmonary edema fluid. If the patients were not treated in time, a systemic alveolar edema will develop, and the small airway will be blocked with mucus, when the effectiveness of oxygen therapy will be greatly compromised. A similar general pulmonary vasoconstriction has been observed in patients with acute altitude sickness. An early low-flow oxygen inhalation shows a good therapeutic effect. The blue to red gradient bar shows blood oxygen saturation (SpO₂).

Therefore, we intend to extend the experience of altitude sickness therapy (early low-flow oxygen inhalation) to treat SARS-CoV-2 patients. When the area of lung injury is small at the early stages, low-flow oxygen inhalation would keep the capillary around the well-ventilated alveoli dilated and maintain the HPV (figure). On the other hand, a relatively high partial pressure of O₂ in the alveolar gas (P_{A}O_{2})
facilitates alveolar fluid re-absorption by activating Na⁺ transport across the alveolar epithelium, which makes an osmotic gradient responsible for the lung edema clearance. Hereby, appropriate oxygen inhalation could accelerate the re-absorption of pulmonary edema fluid and alleviate the disease (figure). For patients who have just developed general pulmonary vasoconstriction, oxygen inhalation may reverse the vasoconstriction and rebuild the HPV, so as to avoid the occurrence of ARDS and reduce the mortality (figure). But if they were treated later, the therapeutic effect of oxygen inhalation will be greatly compromised (figure).

It should be noted that high-flow oxygen inhalation should not be adopted in the early stages. High mixed venous oxygen tension (PvO₂) inhibits HPV because of the reversed diffusion of oxygen, that is, if enough oxygen could bind the receptor in the small alveolar-capillary-arteriole space, the vessels will not vasoconstrict. In addition, upon a high-flow and high-concentration oxygen inhalation, the reflex stimulation to respiration by hypoxia will disappear, resulting in a more serious retention of CO₂, which may lead to the CO₂ anesthesia or even a respiratory arrest.

The optimal time 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 SpO₂ <90% during admission. Patients with SpO₂ <90% had a significantly higher risk of death (5/14). However, the median time from onset of symptoms to admission was 6 days (inter quartile range 4-9 days). In the SpO₂ <90% group, the median occurrence time of lowest SpO₂ was 1 day (inter quartile range 0-2 days) after admission. In other words, SpO₂ of some patients at admission were very low [SpO₂ <90% and oxygen index (OI) <110 mmHg, which indicated a severe ARDS]. 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.

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 SpO₂ ≤93%, or OI ≤300 mmHg is defined as the severe condition, and then the oxygen therapy was given. The World Health Organization (WHO) suggested SpO₂ ≤90% as a diagnostic standard for the severe pulmonary infection. However a recent study demonstrated that patients in the stage IV group (classified by CT images with bilateral diffuse lesions in more than half of the lung field) showed only slightly-declined SpO₂ (94.70±0.20%). While the stage II patients with only a small proportion of lung injury and HPV showed relatively high SpO₂ (97.2±0.91%). Thus the diagnostic standard of SpO₂ 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 ARDS: (1) For the suspected cases with symptoms, finger SpO₂ (with finger oximeter ideally) should be measured at each time of nucleic acid test sampling and daily after admission. However, finger SpO₂ varies greatly with the altitude and the age, 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. (2) If the patient’s SpO₂ was lower than the reference value by 3% or more, it is suggested to be hospitalized immediately for standard low-flow oxygen inhalation (e.g. if the reference value was 98%, then ≤95% is the diagnostic standard). (3) If it was not possible to be admitted to hospital immediately, the patient is recommended to take oxygen in the home, such as with a portable oxygen respirator. During the in-home oxygen therapy, finger SpO₂ should be monitored continually to
assure that SpO2 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.\textsuperscript{17} This upper limit may also be applicable to the patients with chronic respiratory diseases. However, if SpO2 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. (4) 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.\textsuperscript{5,18} Therefore, patients with low SpO2 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 the acute pulmonary injury will be worsened by the mechanical stretch during the strained breathing.\textsuperscript{5,19}

**Contributors**

SY conducted the literature search and drafted the manuscript. SCJ contributed to the discussion of ideas and helped with the writing. ZLL contributed to the discussion of ideas and the writing.

**Declaration of interests**

We declare no competing interests.

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