

**THE PATHOPHYSIOLOGY OF COVID-19 AND THE TREATMENT STRATEGY
FOR CRITICALLY ILL PATIENTS BASED ON ORGAN PROTECTION
– AVOIDING HYPOXIA AND REDUCING DAMAGE
CAUSED BY NON-VIRAL ATTACKS**

Since December 2019, several cases of COVID-19 patients caused by SARS-Cov-2 infection have been detected in Wuhan, Hubei. With the epidemic outbreak, cases in other parts of China and other countries have been found, and more than 10% of patients need to be hospitalized, and some patients who progress to critically ill still have a high mortality rate even after advanced life support treatment in ICU. Previous single-center studies have found that if the required fraction of inspired oxygen (FiO₂) is higher than 60%, the 28-day mortality rate is 61.5%, and the mortality rate of patients receiving invasive mechanical ventilation for respiratory support is as high as 81%, among which the average age of patients who died Larger and more likely to have underlying disease.

I. Pathophysiology of COVID-19 and General Treatment

Because SARS-Cov-2 virus invades alveolar epithelial cells and causes damage, early pathological manifestations of COVID-19 in the lungs are edema, exudation, and inflammatory cell infiltration, which can cause secondary capillary endothelial cell damage and lead to increasing capillary permeability. With the expansion of lesions, respiratory distress symptoms appear due to hypoxia caused by oxygen diffusion disorders, which is more prominent in patients with cardiopulmonary diseases and during activities. Deep and rapid breathing can increase the negative pressure in the thorax, leading to increased transpulmonary pressure and transpulmonary capillary pressure, which not only exacerbates the damage to the alveolar epithelial cells and capillary endothelial cells in the original lesion but may also cause secondary damage to the unaffected lung tissue due to respiratory compensation and developed a typical ARDS with the help of gravity. Factors such as hypoxia, pulmonary capillary microthrombus, elevated PaCO₂, pulmonary edema, and lung capacity deviation from the functional residual capacity (FRC) can cause pulmonary hypertension and acute cor pulmonale (ACP). For patients that can maintain oxygen saturation at resting state may experience shock or sudden death due to the sudden decrease in cardiac output caused by the sudden increase in pulmonary circulation resistance and

myocardial hypoxia when the patient is temporarily deprived of oxygen or during daily activities. There is currently no clinically effective antiviral drug to block virus damage to the lungs. Monitoring vital signs and SpO₂, use oxygen therapy to prevent hypoxia, rest and limit physical activity, reduce stress and proper sedation for early severe patients may avoid or reduce the possibility of patients suffering from secondary respiratory cycle damage caused by increased respiratory drive due to compensatory hypoxia and sudden death or the need for advanced life support.

II. Effects and Risks of Non-Invasive Mechanical Ventilation (NIV) and High-Flow Nasal Cannula (HFNC)

Patients, who still have severe hypoxia, with or without respiratory distress symptoms, during routine oxygen therapy in medical centers, should be noted and transferred to ICU for upgraded respiratory support. Because non-invasive mechanical ventilation (NIV) and high-flow nasal cannula (HFNC) can provide patients with higher FiO₂ and certain positive end-expiratory pressure (PEEP), some patients with COVID-19 combined with mild to moderate ARDS can be significantly relieved after receiving NIV or HFNC and reduced respiratory drive to avoid tracheal intubation and mechanical ventilation. However, for patients receiving high concentrations of FiO₂ (above 60-70%) NIV or HFNC and yet cannot immediately relieve in a short period of time, or have strong respiratory drive ($V_t > 9\text{ml / kg}$ in NIV), patients will face the risk of secondary lung injury and elevated pulmonary artery pressure caused by hypoxia leading to multiple organ dysfunction and low intrathoracic negative pressure. Therefore, critically ill patients for a long period of time with strong respiratory drive will cause further damage to the patient's respiratory circulatory system, and severe respiratory distress may cause excessive excitement of the sympathetic nervous system and cause stress cardiomyopathy. Once stress cardiomyopathy occurs, the stroke volume of the right ventricle will exceed that of the left ventricle very quickly. The right cardiogenic pulmonary edema and gravity will accelerate type I respiratory failure caused by COVID-19 to ARDS. Therefore, the use of appropriate sedative drugs to inhibit patients with excessively respiratory drive may block or delay the progression of ARDS, and if necessary, establish an artificial airway early for invasive mechanical ventilation for respiratory support.

The use of Bipap or CPAP + PSV during NIV treatment may increase the risk of transpulmonary pressure and transpulmonary capillary pressure and lead to further lung

damage. Therefore, NIV in CPAP mode may have less secondary lung damage in patients with obvious symptoms of respiratory distress. During NIV treatment, the basic condition of COVID-19 patients needs to be evaluated, and the patient's response to respiratory support needs to be closely monitored. The following conditions can be used as an indication for replacing NIV with invasive mechanical ventilation: 1. Severity of the disease, simplified acute physiological score (SAPS) > 34 points and hypoxemia ($\text{PaO}_2 / \text{FiO}_2 \leq 175\text{mmHg}$); 2. Hypoxemia did not improve after 1 hour of NIV treatment; 3. Strong voluntary breathing caused a large tidal volume (tidal volume > 9ml / kg).

During the treatment of HFNC in COVID-19 patients, the vital signs and oxygenation need to be closely observed. The assessment of ROXI can help guide the administration of HFNC. Patients with $\text{ROXI} \geq 3.85$ or $\text{SpO}_2 \geq 93\%$ and respiratory rate < 25 times / min after HFNC treatment indicate a high success rate, that HFNC treatment can continue; those with $\text{ROXI} < 2.85$ or $\text{SpO}_2 < 93\%$ with respiratory rate > 30 times / min predict low success rate of using HFNC; $2.85 \leq \text{ROXI} < 3.85$ or $\text{SpO}_2 > 93\%$ but respiratory frequency > 25 times / min can continue HFNC treatment, with closely monitor the condition and vital signs; if $\text{ROXI} < 2.85$ or $\text{SpO}_2 < 93\%$ but respiratory frequency > 25 times/min need to switch to invasive mechanical ventilation immediately. Previous research and experience in COVID-19 treatment found that if HFNC failed and switch to NIV often results in failure of NIV treatment and delays intubation. Therefore, we suggest if HFNC treatment fails, it should be directly switched to tracheal intubation for invasive ventilation.

III. Protective Ventilation Strategies for Cardiopulmonary Oxygen Delivery Organs and Protective Alveolar Salvage Therapy

Because mechanical ventilation can cause barotrauma to the lungs, ARDS's lung-protective ventilation strategy, including small tidal volume (4-8ml / kg), restricted platform pressure, appropriate PEEP, and other measures are still applicable for invasive ventilation in COVID-19. Due to the higher correlation between ventilator-related lung injury and driving pressure / transpulmonary pressure caused by mechanical ventilation, limiting the driving pressure below 15cmH₂O or using transesophageal pressure monitoring of transpulmonary pressure may help better avoid ventilator-related Lung injury (VILI). More stringent lung-protective ventilation strategies need to be implemented to avoid or reduce the occurrence of VILI,

especially with more significant lesion caused by the viral invasion and the more severe ARDS.

While implementing lung protection ventilation strategies, attention should be paid to the occurrence of ACP caused by ARDS and mechanical ventilation. Lung infection, $\text{PaO}_2 / \text{FiO}_2 < 150 \text{ mmHg}$, $\text{PaCO}_2 \geq 48 \text{ mmHg}$, and driving pressure $\geq 18 \text{ mmHg}$ will increase the risk of ACP in patients with ARDS. Therefore, when setting the tidal volume, the plateau pressure should be limited to $< 27 \text{ mmHg}$, and the driving pressure should be $< 18 \text{ mmHg}$. Although the ARDS guidelines recommend the use of low tidal volume ventilation and high PEEP strategies to re-engage expandable alveoli and maintain alveolar openness, it is hoped to reach a balance between lung openness and hyperventilation that is beneficial to lung openness, and does not increase pulmonary vascular resistance and endanger RV. However, in patients with severe ARDS caused by COVID-19, it is often difficult to re-expand the lung tissue that was completely collapsed and exudate. Moreover, this will increase the expansion of normal alveoli, leading to healthy alveolar damage and induced ACP. Even after assessing re-expandable lung re-expansion can temporarily improve oxygenation, the re-expanded alveoli are the risk of barotrauma after re-participation in the ventilated part, which still harms RV for the entire pulmonary circulation. This is like trying to sacrifice a part of the normal combat force (normal lung tissue) in the war to summon some wounded soldiers (re-expanded lung tissue) to join the battle that hurts the ally (right ventricle). At the same time, it has been clinically observed that many patients with severe ARDS caused by COVID-19 will have reduced lung compliance when using a high PEEP strategy. Therefore, lung compliance titration PEEP should be used during mechanical ventilation to select the appropriate PEEP to Lung damage caused by excessive swelling is minimized.

Similar to other causes of ARDS, early use of muscle relaxants in patients with moderate to severe ARDS caused by COVID-19 can reduce the likelihood of VILI. For patients with ARDS caused by gravity-dependent COVID-19, the prone position is safer for alveolar rescue treatment. Because the prone position can reduce pulmonary vascular resistance and increase central circulating blood volume to unload the right ventricle, patients with moderate to severe ARDS who require mechanical ventilation should be routinely placed in the prone position.

IV. Organ Protection and ECMO Treatment

Due to the effects of cardiopulmonary interaction and ventricular interrelationship caused by mechanical ventilation, the pulmonary artery pressure increased sharply, and the right ventricle was extremely dilated to compress the left heart. Severe hypoxemia caused myocardial hypoxia and decreased myocardial contractility. Along with the foregoing, plus the influence of upper intubation anesthesia-inducing drugs on peripheral vascular resistance, some patients with severe ARDS caused by COVID-19 suffered severe circulatory failure and brain, kidney, digestive and other oxygen depletion organ dysfunction at the beginning of mechanical ventilation, and even some patients will experience cardiac arrest after tracheal intubation.

Positive pressure ventilation may aggravate the occurrence or exacerbation of ACP induced by pulmonary hypertension. If patients with mechanical ventilation, muscle relaxants, prone position, and lung re-expansion treatment still cannot improve fatal hypoxemia or ACP-induced should be given ECMO support as soon as possible. Patients with clear ECMO indications in COVID-19 patients had significantly worse prognosis for delayed ECMO support. Because of systemic hypoxia caused by lung injury, which is the cause of critical illness in patients with COVID-19, hypoxia and elevated PaCO₂ are important factors for the occurrence of ACP. VV-ECMO mode should be preferred for patients with clear indications. VV-EMCO can correct hypoxia and restore PaCO₂ to normal. After successful establishment, VV-EMCO can quickly reduce the support condition of the ventilator, thereby protecting the cardiopulmonary and multiple organs throughout the body. If severe ACP or left ventricular dysfunction causes shock after fine hemodynamic treatment, you can consider switching to VAV-ECMO mode to increase systemic vital organ perfusion. The determination and any adjustment on the ECMO treatment mode should be made by an experienced ECMO team after careful evaluation of the cardiopulmonary ultrasound.

In summary, combined with the clinical manifestations of patients with severe COVID-19 and changes in the course of treatment, their clinical characteristics are often due to the continued increase in lung damage after virus invasion, which leads to respiratory failure, secondary circulation system changes and multiple organs impairment. Severe patients who have progressed to respiratory failure or ARDS should correct hypoxia as soon as possible, reduce respiratory drive, and adopt organ protective support strategies for treatment. Timely

block the cardiopulmonary injury caused by compensation and the damage caused by ventilation treatment is of great importance to save patients with COVID-19.