Acute respiratory distress syndrome: focusing on secondary injury

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Abstract

Acute respiratory distress syndrome (ARDS) is one of the most common severe diseases seen in the clinical setting. With the continuous exploration of ARDS in recent decades, the understanding of ARDS has improved. ARDS is not a simple lung disease but a clinical syndrome with various etiologies and pathophysiological changes. However, in the intensive care unit, ARDS often occurs a few days after primary lung injury or after a few days of treatment for other severe extrapulmonary diseases. Under such conditions, ARDS often progresses rapidly to severe ARDS and is difficult to treat. The occurrence and development of ARDS in these circumstances are thus not related to primary lung injury; the real cause of ARDS may be the "second hit" caused by inappropriate treatment. In view of the limited effective treatments for ARDS, the strategic focus has shifted to identifying potential or high-risk ARDS patients during the early stages of the disease and implementing treatment strategies aimed at reducing ARDS and related organ failure. Future research should focus on the prevention of ARDS.

Keywords: Acute respiratory distress syndrome; Secondary lung injury; Spontaneous breathing; Pulmonary circulation; Sedation

Introduction

Acute respiratory distress syndrome (ARDS) has been known for more than 50 years and is one of the most common severe diseases seen in the clinical setting.[1] With the continuous exploration of ARDS in recent decades, our understanding of ARDS has improved, and the definition of and treatment strategies for ARDS have evolved. ARDS describes diffuse lung injury caused by various conditions that trigger systematic inflammatory responses, and treatment strategies range from mechanical ventilation to lung protection and maintaining pulmonary blood flow to protect the pulmonary circulation. ARDS is currently understood as not a simple lung disease but a clinical syndrome with common pathophysiological properties, clinical characteristics, and treatment strategies and is an important part of multiorgan dysfunction syndrome caused by many precursor diseases.[2]

The causes of ARDS are divided into mainly intrapulmonary causes and extrapulmonary causes. The main intrapulmonary cause is pulmonary infection, while the extrapulmonary factors are sepsis, shock, acute kidney injury (AKI),[3] etc. The main difference between pulmonary-derived or extrapulmonary-derived ARDS is whether the damage starts in the alveolar epithelial cells or vascular endothelial cells and then develops into damage to the lung interstitium, which is the gas/blood exchange barrier.[4]

We have found that primary lung injury caused by aspiration (stomach contents, strong acids, strong bases, and irritating gases), severe pulmonary infections, respiratory burns, lung contusion, etc, usually has a rapid progression and that if the patient has no immune disease, antibiotics and other drugs can correct the inflammatory response and prevent the progression to ARDS. However, in the intensive care unit (ICU), ARDS often occurs a few days after primary lung injury or after a few days of treatment for severe extrapulmonary diseases. It can then progress rapidly to severe ARDS and is often difficult to treat. Under such circumstances, the occurrence and development of ARDS are not only related to the primary lung injury; a more common cause of ARDS development may be the "second hit" caused by inappropriate interventions based on inappropriate understanding.[5] Despite significant progress in our understanding of ARDS, its morbidity and mortality remain high.[1] In view of the limited effective treatments for ARDS, the strategic focus of ARDS has shifted to identifying potential or high-risk ARDS patients at early stages of the disease

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and implementing treatment strategies aimed at reducing ARDS and related organ failure. In this review, we summarize the rationale of, current evidence for, and future directions of therapeutic strategies to prevent ARDS or avoid ARDS exacerbation.

Avoiding Overhigh Cardiac Output (CO) Due to Increased Vascular Permeability

As early as 30 years ago, studies suggested that the pulmonary edema of patients who died of ARDS was significantly worse than that of survivors.[6] When the lung is directly or indirectly injured, the lung first enters the exudative phase: inflammatory cells accumulate, alveolar epithelial cells and the surrounding capillary endothelial cells are damaged, protein-rich fluid enters the alveoli and interstitium, the osmotic pressure disappears, and pulmonary edema forms and continues to increase as the disease progresses. In the clinical setting, lung edema always reflects damage. The typical pathophysiological change of ARDS is non-cardiogenic edema. However, in clinical practice, researchers have found that elevated pulmonary capillary wedge pressure (PCWP) is very common in ARDS patients.[7] Approximately 1/3 to 1/2 of ARDS patients have a PCWP greater than 18 mmHg.[8] As the inflammatory response during ARDS increases vascular permeability, ARDS patients are more sensitive to elevated PCWP than patients with cardiogenic edema. In this case, due to improper fluid overload during resuscitation, the use of positive-pressure ventilation, the renin angiotensin system disorder, glycocalyx injury, and so on, secondary lung injury will occur and aggravate pulmonary edema.

Many studies have been focused on patients who have already developed ARDS. However, more attention should be given to pre-emptively managing severely ill patients at risk of ARDS to avoid the emergence of secondary ARDS caused by improper treatment or second hits. One group reviewed the occurrence of ARDS in mechanically ventilated patients following their admission to the ICU and found that a positive fluid balance was the main factor associated with the occurrence of ARDS.[9] Even though the tidal volume was reduced and the plateau pressure (Pplat) was limited during mechanical ventilation, it was not possible to avoid ARDS caused by a positive fluid balance.[10] Furthermore, an observational study of patients with elective lung resection found that a positive fluid balance was an independent risk factor for ARDS.[11] However, some clinicians believe that inadequate fluid resuscitation can aggravate the inflammatory response of patients in shock, which then aggravates the damage to alveolar barrier function.[12]

However, full resuscitation does not mean excessive resuscitation, nor does it mean ignoring fluid management after resuscitation. Many studies have shown that conservative fluid management after resuscitation can prevent the occurrence and development of ARDS and improve survival. Clinicians are concerned that conservative fluid management for ARDS patients may be beneficial to the lungs but damage other organs, such as the kidney and brain. To explore this possibility, researchers divided ARDS patients into a conservative fluid management group (PCWP less than 8 mmHg or central venous pressure [CVP] less than 4 mmHg) and a liberal fluid management group (PCWP 14–18 mmHg or CVP 10–14 mmHg).[13] The duration of mechanical ventilation and ICU stay in patients with conservative fluid management were significantly shorter than that of the liberal fluid management group. Furthermore, they found that although bedside renal replacement therapy was not significantly different between the two groups, the incidence of AKI in the conservative group was lower than that in the liberal group after adjustment. Other studies have suggested that fluid management of ARDS patients does not affect their long-term survival. However, regarding patients' quality of life, studies have found that the mental and cognitive status of patients with ARDS is significantly better after conservative fluid management than after liberal fluid management. This difference might arise because conservative fluid management can avoid the occurrence of cerebral edema. Furthermore, as pulmonary edema is significantly alleviated, the dose of sedative drugs used for mechanical ventilation can be significantly reduced, which can also improve patient consciousness and cognition.[8]

In ARDS, pulmonary vascular permeability increases significantly, and the increase in pulmonary blood flow can cause a further increase in pulmonary edema. Physiologically, the lung is the only organ that receives 100% CO, and the pulmonary circulation is a low-resistance circulation. Previous studies have suggested that the incidence of ARDS in patients after cardiac surgery is very low. Our team has found that the minimum CO that guarantees tissue perfusion can reduce the production of extravascular lung edema during ARDS without causing other organ damage.[14] Therefore, we believe that excessive CO is not only unnecessary for ARDS patients but also likely to be harmful. The authors of a previous study have recommended that once shock is resolved, all ARDS patients undergo conservative fluid management to ensure tissue perfusion. CVP, PCWP, or extravascular lung water can be used as a monitoring indicator for fluid management. Personal fluid management should include a careful daily assessment of volume status, fluid balance, and diuretic potential. The Beijing Hemodynamics Consensus proposed that in ensuring tissue perfusion, the lower CVP is, the better the outcome.[15] Therefore, it is very important to monitor hemodynamics in patients with ARDS or at high risk of ARDS. Monitoring can avoid liberal infusion and insufficient tissue perfusion due to conservative infusion. Blood flow indicators can be used to achieve individual optimization of fluid management. As a result, it is possible to avoid secondary lung injury in critically ill patients with high-risk factors for ARDS, to minimize pulmonary edema during ARDS, and to ensure adequate blood flow in the pulmonary circulation while treating pulmonary edema.

Preventing High Pulmonary Vascular Resistance (PVR) and Acute Cor Pulmonale (ACP)

The lung is an aerating organ, and it is also a special blood-passing organ that can accept 100% CO. The pathophysiological process of ARDS caused by secondary injury mainly starts in the vascular endothelial cells. When

pulmonary vascular endothelial cells are damaged, they directly affect pulmonary blood vessels and pulmonary blood flow, that is, pulmonary circulation, which moves gases into and out of the lungs. However, when the pulmonary circulation is impaired, ventilation/perfusion is destroyed. Many clinical treatments can have large effects on blood flow and the occurrence and development of ARDS.

As early as 1977, researchers found that PVR in patients with acute lung injury was significantly increased and that even where hypoxia was corrected, PVR remained high.[16] The autopsy of patients who died from ARDS revealed that fibrin thrombosis may occur during ARDS and reduce pulmonary vascular perfusion.[17] In pathological examinations of deceased coronavirus disease 2019 (COVID-19) patients, clear structural disorders and the destruction of pulmonary blood vessels were found.[18] A large amount of epidemiological data suggest that 73% to 92% of ARDS patients have pulmonary hypertension (PH), and this incidence is related to the severity of ARDS and mechanical ventilation strategies.[19,20] Retrospective research conducted by our research team revealed that elevated CVP (mean CVP >10 mmHg) was independently associated with the occurrence of PH.[21] When the degree of PH is ameliorated, the prognosis of ARDS patients is improved significantly. A study found that the PCWP of ARDS-surviving patients was 29 mmHg and significantly lower than that (33 mmHg) of non-surviving patients.[19] Therefore, with the progression of ARDS or the emergence of secondary lung injury due to improper mechanical ventilation and other treatment measures, clinicians should be alert not only to the deterioration of ventilation but also subsequent pulmonary vascular damage and PH. When pulmonary vascular endothelial cells are injured, pulmonary blood vessel microthrombosis forms, pulmonary blood flow is blocked, and barrier function is impaired, which will aggravate pulmonary edema and trigger further deterioration of ARDS. From the perspective of the pulmonary circulation, ARDS can be considered a pulmonary manifestation of systemic hemodynamic changes.

Hypoxia, inflammation, microthrombosis, interstitial edema, structural changes, blood vessel remodeling, and improper mechanical ventilation can all cause increased pulmonary circulatory resistance and PH. However, regardless of the cause, the resulting PH can lead to right heart function impairment and the occurrence of ACP. The incidence of ACP caused by ARDS can reach 60%[22]; although the necessity of a low tidal-volume lung-protection ventilation strategy has been recognized and widely implemented, the incidence of ACP can still reach 20% to 25%.[23] As not all patients can have a Swan-Ganz catheter placed to evaluate PCWP in clinical practice, the presence of ACP is the main diagnostic criterion for evaluating PH, so it is important to evaluate the right heart function of patients by dynamic bedside ultrasound.

A right ventricular end-diastolic volume (RVEDV)/left ventricular end-diastolic volume (LVEDV) >0.6 can be used as the main criterion for evaluating the presence of ACP at the bedside. Researchers have found that RVEDV/LVEDV and systolic pulmonary arterial pressure can be used as independent predictors of death among ARDS patients.[24] Whether vasodilators should be used as treatment for PH during ARDS is controversial. From the authors' point of view, PH caused by hypoxia, inflammation or other pulmonary-derived causes can be treated effectively with vasodilators. However, if PH or ACP is caused by secondary lung injury, it is better to prevent it than to treat it.

Mechanical ventilation is the most common cause of increased PVR, and improper parameter settings have caused an increased incidence of ACP. High tidal volume is related to increases in PVR and the incidence of ACP. The setting of the Pplat is also related to the occurrence of ACP. When Pplat fluctuates between 18 and 26 cmH_2O, the incidence of ACP is 20%; when the Pplat is 27 to 35 cmH_2O, the incidence of ACP is 39%; and when the Pplat is above 35 cmH_2O, the incidence of ACP exceeds 42%.[25] The transpulmonary pressure gradient (TPG) is the difference between the mean pulmonary artery pressure (mPAP) and the pulmonary artery wedge pressure (PAWP), which can determine the PVR with CO, PVR = (mPAP–PAWP)/CO. A high positive end-expiratory pressure (PEEP) can significantly increase mPAP and TPG (as PEEP increases, mPAP increases from 25 to 28 mmHg, and TPG increases from 14.5 to 16.4 mmHg), and PVR has been found to also increase significantly, from 310 to 385 $dynes \cdot s^{-1} \cdot cm^{-5}$.[26] In addition, PaO_2/FiO_2 <100 mmHg and $PaCO_2$ >60 mmHg are risk factors for ACP during ARDS.[22] Therefore, the setting of the mechanical ventilation parameters must protect not only the lungs but also the circulation.

The ARDS hemodynamic management consensus proposed in 2016 put forward four management strategies for the purpose of circulation-protective ventilation: control lung infections actively, avoid PaO_2/FiO_2 <150 mmHg, maintain driving pressure <18 cmH_2O, and maintain $PaCO_2$ <48 mmHg. These strategies will help us to better manage ARDS.[27]

Regarding ARDS caused by COVID-19, the virus causes damage to vascular endothelial cells while it damages the alveolar epithelium.[28] Therefore, further aggravation of vascular damage should be avoided in the early stage. Regarding whether mechanically ventilated COVID-19 patients need special parameter settings, clinicians have suggested that although there are two types of patients with COVID-19, high compliance and low compliance, there is obvious heterogeneity in their respiratory mechanics, and there is no clear evidence to suggest a support strategy different from the traditional ARDS mechanical ventilation strategies. Until such evidence becomes available, clinicians should follow a circulation-protective ventilation management strategy for COVID-19 patients.

Avoiding Excessive Spontaneous Breathing and Driving Pressure

It has long been widely believed that it is beneficial for patients with mechanical ventilation to maintain sponta-

neous breathing.[29] In recent years, the concepts of lung-protection mechanical ventilation and circulation-protection mechanical ventilation have been proposed and confirmed. However, it remains controversial whether spontaneous breathing should be retained for mechanical ventilation patients. The retention of spontaneous breathing can ensure the use of the diaphragm and other respiratory muscles, avoiding muscle atrophy due to disuse, which is helpful for early weaning and extubation and can shorten the time of mechanical ventilation and ICU stay. Furthermore, the retention of spontaneous breathing reduces the necessary amounts of sedative and analgesic drugs and their associated side effects on patients. In addition, spontaneous breathing can increase dependent ventilation areas, which is a kind of recruitment; improve the ventilation/perfusion ratio; reduce intrapulmonary shunts and improve oxygenation. Besides, as mechanical ventilation is positive-pressure ventilation, it can reduce the preload and thus reduce CO, however, spontaneous respiration has the opposite effects.[30,31] As nearly 30% of ARDS patients have cardiac dysfunction, their retention of spontaneous breathing may be beneficial to improve their CO and cardiac perfusion.[32]

However, many studies suggest that maintaining spontaneous breathing can cause secondary lung injury. A new concept, patient self-inflicted lung injury (P-SILI), has recently been proposed.[33] P-SILI results from strong spontaneous breathing or respiratory driving during mechanical ventilation. During the inhalation process, airway pressure (Paw) increases (mechanical ventilation) or pleural pressure (Ppl) decreases (spontaneous breathing).[34] After the gas is inhaled, the lung tissue stress during tidal inhalation is the pressure distending the lung, that is, the transpulmonary pressure (P_L), and is the difference between Paw and Ppl. In positive-pressure ventilation under muscle paralysis, Paw constitutes the bulk of P_L.[35] When combined with spontaneous breathing, the Ppl is decreased, and P_L is increased. Thus, the probability of lung injury is greatly increased. In the healthy lung, changes in the local Ppl are evenly transmitted across the lung surface; this phenomenon is called "fluid-like" behavior.[36] This behavior can explain why we can replace Ppl with esophageal pressure. However, in ARDS, injured lungs exhibit "solid-like" behavior,[37] where a non-aerated lung region impedes the rapid generalization of a local change in P_L. In such cases, the lung expansion is heterogeneous. Therefore, there will be regional differences in P_L and different degrees of lung inflation. In this context, if spontaneous breathing is superimposed, it will cause more changes in Ppl and uneven conduction, resulting in uneven or excessive lung expansion.

Many doctors believe that preserving spontaneous breathing can increase the patient's tidal volume and lead the patient to "recruit" lung tissues through their own efforts. However, excessive spontaneous breathing effort can result in "pendelluft."[38] In patients with ARDS, pendelluft results from the unevenness of Ppl transmission and the inconsistency of regional P_L. The force generated by diaphragm contraction is confined mainly to the area close to the diaphragm and creates a pressure gradient in the lungs, and gas transfers from the gravity-independent area to the dependent area. Even in the absence of high tidal volume, this process increases regional lung stress.[37] Therefore, due to gas transfer, the retention of spontaneous breathing does not increase the overall tidal volume but increases alveolar shear force, which aggravates lung injury. In addition, strong respiratory driving increases the endogenous PEEP and reduces the tidal volume.[39] As spontaneous breathing causes lung injury, lung compliance decreases, and tidal volume decreases. Under such conditions, doctors are forced to increase the setting parameters of the ventilator, triggering a vicious cycle.

In addition, the lack of synchronization between the patient's reserved spontaneous breathing and mechanical ventilation can cause lung damage. Such non-synchronization includes "double triggering" and "reverse triggering."[40,41] Double triggering is the process of two consecutive inhalations after one inhalation effort. The total tidal volume is the sum of the two inspiratory tidal volumes.[42] Reverse triggering means that the ventilator induces an inhalation effort of the patient; that is, the ventilator triggers the patient. Although the mechanism is currently unknown, reverse triggering can cause lung damage due to excessive P_L and tidal volume. Uneven changes in Ppl during spontaneous breathing, excessive P_L and tidal volume, the pendelluft effect, and patient-ventilator asynchrony can all cause secondary lung damage.

The injury caused by spontaneous breathing affects not only the alveoli but also pulmonary blood flow. Transvascular pressure is the difference between intravascular pressure and extravascular pressure. The negative Ppl generated during spontaneous breathing increases the transvascular pressure, expands the pulmonary blood vessels, increases the pulmonary blood flow, and increases lung perfusion.[43] In addition, a study found that if spontaneous breathing occurs during volume-controlled ventilation, it can cause a significant increase in transvascular pressure and aggravate pulmonary edema.[44] Decreased lung compliance caused by pulmonary edema and the abovementioned uneven lung ventilation during mechanical ventilation eventually led to lung secondary injury.

It is not easy to detect P_L in clinical practice. Therefore, driving pressure is often used to evaluate spontaneous breathing and respiratory driving.[45] Driving pressure represents the strain of the lung and the target for limiting the inspiratory volume. It may be used as a monitoring indicator during spontaneous mechanical ventilation.[46] Driving pressure is calculated as Pplat minus PEEP. It is currently recommended that the driving pressure be controlled within 15 cmH_2O.[47] Spontaneous breathing should be controlled from the perspective of respiratory mechanics. However, many studies have suggested that for mild ARDS, the advantages of retaining spontaneous breathing outweigh the disadvantages.[29,48] For severe ARDS, spontaneous breathing should be avoided in the early stage. However, a retrospective analysis suggests that even for patients with PaO_2/FiO_2 <150 mmHg, spontaneous breathing is unrelated to patient outcome.[49]

However, the strength of spontaneous breathing is not given by P_L in that article, which may be one of the reasons for the negative result. Many studies have suggested that for ARDS caused by COVID-19, spontaneous breathing should be avoided during the implementation of lung protection ventilation to reduce respiratory driving.[50,51] In addition, our research has revealed that controlling driving pressure is a part of circulation-protective ventilation. Our colleagues reported that fluctuating driving pressure and CVP were associated with worse outcome in patients with hypoxia who received mechanical ventilation during the first 72 h after ICU admission.[52] Thus, circulation-protective ventilation should be considered to remedy the deleterious effects associated with the lung-protective ventilation strategy and thereby decrease the incidence of hemodynamic disorders.

Ensuring Adequate Sedation, Analgesia, and Necessary Neuromuscular Blocking Agents (NMBAs)

ARDS has always been one of the most challenging diseases with respect to the management of analgesia and sedation. In the clinical application of mechanical ventilation, the goals are to increase patient-ventilation synchronization, quickly wean from mechanical ventilation and achieve early rehabilitation. To achieve these goals, analgesia and sedation, preventing delirium, and improving patient communication are key components. However, as the understanding of analgesia and sedation treatment has improved, sedation, analgesia, and even NMBAs have been found to be effective treatments to avoid secondary lung injury during mechanical ventilation, which is an important part of both lung protection and circulation protection.[53] Analgesic and sedation therapy can improve lung compliance and reduce Pplat in ARDS patients.[54] This therapy can also inhibit spontaneous breathing in mechanical ventilation patients and avoid Ppl decreases and P_L increases caused by excessive spontaneous breathing.[55] In addition, sedation therapy can significantly reduce end-inspiratory P_L, increase end-expiratory P_L, and ensure safe alveolar expansion.[56] For circulation protection during mechanical ventilation, analgesia and sedation are basic treatments that can reduce pulmonary circulatory resistance, reduce the right heart afterload, and reduce the occurrence of ACP.[57]

There has always been much controversy over whether ARDS patients should be treated with NMBAs. Those who oppose the use of NMBAs believe that these drugs can aggravate patients' acquired weakness in the ICU, cause diaphragm damage or atrophy, and prolong patients' mechanical ventilation time.[58] A large-scale study published in the *New England Journal Medicine* (ROSE trial) in 2019 clearly revealed that the application of neuromuscular blockers did not improve the prognosis of patients with ARDS.[59] However, while NMBAs cannot improve the oxygenation of ARDS patients, they significantly reduce ventilator-induced lung injury, including barotrauma and pneumothorax. Although the use of NMBAs cannot improve the long-term prognosis, it can improve the short-term prognosis. In other words, NMBAs can avoid some acute events, such as strong spontaneous breathing and patient-ventilation asynchrony.[60]

The present guidelines published by the Society of Critical Care Medicine only weakly recommend the use of NMBAs in patients with ARDS.[61] Due to the risks of sedation drugs and NMBAs, we cannot recommend NMBA as a first-line treatment for all ARDS patients. Clinicians should evaluate patients individually when considering the application of NMBAs for preventing secondary lung injury. Future research on NMBAs should focus on circulation-protection mechanical ventilation in ARDS patients.

Protection Strategies

Many cases of ARDS are caused by "secondary hits" in the ICU. The basis for these events is increased pulmonary capillary permeability due to various causes. Inappropriate fluid resuscitation results in increased CO and increased pulmonary perfusion; insufficient sedation and analgesia result in strong spontaneous breathing, leading to increased transvascular pressure and pulmonary perfusion. Moreover, spontaneous breathing leads to an increase in P_L, severe alveoli injury, and an imbalance of ventilation and perfusion.

Therefore, the prevention of and treatment strategies for secondary ARDS must be based on the above causes of injury and considered from the aspects of circulation control, ventilation control, and position control, namely, the "CVP principle." Circulation control is applied mainly to control CO, select appropriate kinds of resuscitation fluid, protect the glycocalyx and prevent excessive leakage; the management of ventilation involves the reduction of fluctuation in ventilation, the strict implementation of lung-protection ventilation and active extracorporeal membrane oxygenation treatment when necessary. Position management seeks to avoid the deterioration of ventilation in dependent areas caused by long-term use of a single position and to actively implement a prone position [Figure 1].

Conclusion

The cause of the typical pathophysiological changes in ARDS is often considered to be a direct aggravation of the precursor disease. However, many cases of ARDS result from secondary lung injury caused by irregular clinical behavior or interventions. The lethality of sepsis lies in its attacks on various organs of the body, while the imbalance of immune responses and overreaction-triggered inflammation plays a crucial role in the sepsis process. At present, the efficacy of relevant immunomodulatory drugs and anti-inflammatory treatments is being verified and seems very promising. For the future management of ARDS, instead of discussing whether treatment measures are effective, focus should be given to avoiding secondary lung injury caused by the second hit. Efforts should be made to provide appropriate basic analgesia and sedation, avoid excessive spontaneous breathing, reduce respiratory driving, use conservative fluid management, and reduce PVR, which can protect the lungs and pulmonary circulation. If we avoid secondary hits, we can reduce the occurrence and development of ARDS and protect pulmonary microcirculation. Future research should focus on the prevention of ARDS.

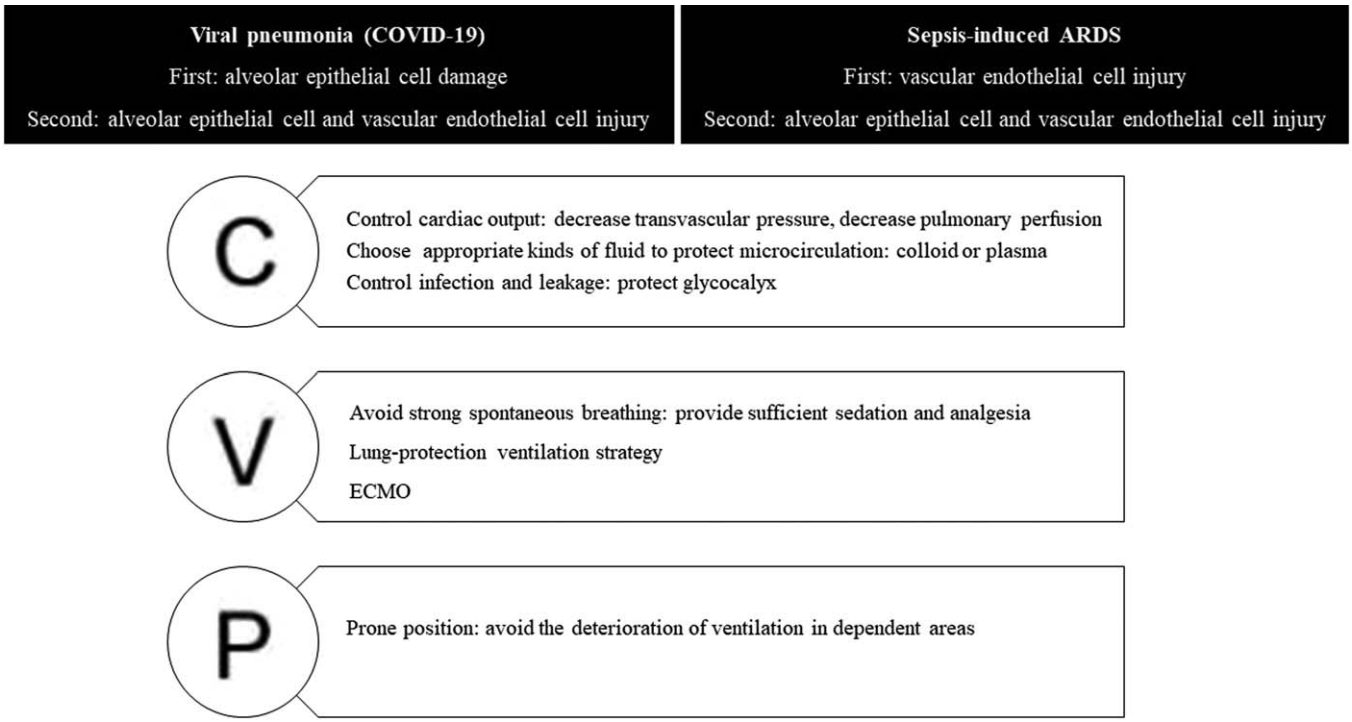

Figure 1: Protection strategies: the "CVP" principle. C means circulation, V means ventilation, and P means position. ARDS: Acute respiratory distress syndrome; COVID-19: Coronavirus disease 2019; ECMO: Extracorporeal membrane oxygenation.

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Conflicts of interest

None.

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