Pathophysiological Mechanisms and Preventive and Therapeutic Strategies for Fatal Pulmonary Leakage Caused by 2019 Novel Coronavirus

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Abstract

Since its outbreak in December 2019, the 2019 novel coronavirus has caused 2,596 deaths globally, with over 11,000 patients remaining in severe condition. The virus and the medical condition it causes have been designated SARS-CoV-2 and COVID-19. Despite the widespread application of antiviral, symptomatic, and functional supportive therapies, more than 100 patients continue to die daily from this viral infection. The most common fatal complication of COVID-19 is acute respiratory distress syndrome (ARDS). The SARS-CoV-2 pandemic may persist globally. Pneumonia induced by other viral infections can also lead to ARDS, presenting similar critical conditions; these viruses include atypical severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and influenza virus-induced pneumonia. Therefore, developing more effective strategies to reduce the mortality of virus-induced ARDS is not only an urgent need for the current anti-COVID-19 efforts but also a long-term global requirement for reducing mortality from viral pneumonia. ARDS was once termed wet lung, and pulmonary edema resulting from vascular leakage constitutes one of its most important pathological features. The clinical manifestations and chest computed tomography imaging characteristics (white lung) of severe COVID-19 are consistent with ARDS. Identifying the source and mechanism of edema fluid leakage into the lungs is crucial for developing mechanism-based strategies to prevent and block water leakage from pulmonary capillaries to the pulmonary interstitium, thereby reducing mortality from wet lung. For mild and moderate cases, non-steroidal anti-inflammatory drugs, such as those used for rheumatoid arthritis, may help prevent and reduce this leakage. Immunosuppressants (such as sirolimus and monitor lizard) may stagger the peak timing of damage caused by viral infection, immune response, and non-immune inflammation, thereby reducing the degree of pulmonary leakage and preventing life-threatening situations. The use of heat-clearing Chinese herbal medicine may

also have anti-inflammatory effects. For severe cases, hemodialysis may represent an effective strategy for eliminating most inflammatory mediators and cytotoxic substances.

Full Text

Preamble

Pathophysiology-based mechanism and management strategies for deadly leaking lungs caused by 2019 novel coronavirus

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Abstract

Since the outbreak in December 2019, the 2019 novel coronavirus has caused 2,596 deaths globally, with more than 11,000 patients still in critical condition. The virus and the disease it causes have been named SARS-CoV-2 and COVID-19. Although antiviral, symptomatic, and functionally supportive therapies have been widely applied, more than 100 patients still die daily from infection. The most common fatal complication of COVID-19 is acute respiratory distress syndrome (ARDS). The SARS-CoV-2 pandemic may continue worldwide. Pneumonia caused by other viruses can also lead to ARDS, creating similar critical situations; these viruses include atypical severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and influenza viruses. Therefore, developing more effective strategies to reduce ARDS mortality caused by viruses is not only an urgent need for the current anti-COVID-19 efforts but also a long-term global need to reduce mortality from viral pneumonia. ARDS was previously known as wet lung, and lung edema caused by vascular leakage is one of its most important pathological features. The clinical manifestations and chest CT image characteristics (white lung) of severe COVID-19 are consistent with ARDS. Identifying where and how edema fluid leaks into the lungs is key to developing mechanism-based strategies to prevent and stop water leakage from pulmonary capillaries to the interstitial space, thereby reducing wet lung mortality. For mild and moderate cases, non-steroidal anti-inflammatory drugs, such as those used for rheumatoid arthritis, may help prevent and reduce this leakage. Immunosuppressants (such as sirolimus and tacrolimus) may stagger the peak times of damage caused by viral infection, immune response, and non-immune inflammation, thereby reducing the degree of lung leakage and preventing life-threatening situations. Using heat-clearing Chinese herbs may also have anti-inflammatory effects. For severe cases, hemodialysis may be an effective strategy to eliminate most inflammatory mediators and

cytotoxic substances.

Panel: Major Viewpoints

- **Increased pulmonary capillary permeability** caused by SARS-CoV-2 infection requires particular attention
- **SARS-CoV-2 in the bloodstream** can enter the lungs via ACE2 on pulmonary capillaries, aggravating lung infection
- **Inflammatory storm** leads to life-threatening pulmonary edema
- **Viral binding to ACE2** on endothelial cells labels these cells with pathogens, making the endothelium a target of the host immune system
- **Convergence of peaks** in viral load, immune response, and inflammation triggers inflammatory storm
- **Hemodialysis** can eliminate most inflammatory mediators and cytotoxic substances from the blood
- **Therapeutic trade-offs** among antiviral drugs, glucocorticoids, immunosuppressants, NSAIDs, heat-clearing herbs, antioxidants, ACE2 modulators, stem cells, and antibodies should be considered, favoring inflammatory cytokine control and hemodialysis
- **Pre-existing disease** reduces organ functional reserve, making it difficult for patients to survive organ edema caused by SARS-CoV-2 infection

Introduction

The COVID-19 pandemic has highlighted the critical need to understand the pathophysiology of virus-induced acute respiratory distress syndrome. While current therapies provide some benefit, the persistently high mortality rate demands mechanism-based strategies that target the fundamental processes of lung injury. This paper examines the mechanisms of vascular leakage in SARS-CoV-2 infection and proposes therapeutic approaches to prevent and treat deadly lung edema.

From Where Is Water Leaking?

ARDS was initially known by various names including shock lung, wet lung, hyaline membrane lung, and Da Nang lung. Regardless of the initiating factor, the clinical course is persistent and progresses to respiratory failure and death. It can be triggered by variable conditions in the respiratory tract, pulmonary blood circulation, or both. The barrier between lungs and air is formed by a monolayer of type 1 and 2 alveolar epithelial cells lining the alveoli, which are tiny air sacs in the lungs. Between the lungs and blood circulation, a barrier is formed by an endothelial cell monolayer of pulmonary capillaries. Oxygen must diffuse from the alveoli to the pulmonary capillary before being transported throughout the body via red blood cells. If the alveoli are filled with water or collapse (atelectasis), less oxygen can be taken up by the lungs. Water present in the pulmonary interstitial space—the space between the alveolus and pulmonary capillary—increases the distance that oxygen must travel to reach the circulatory blood. Damage to the alveolar barrier results in water leakage from the interstitial space into the alveoli, while a highly permeable or broken pulmonary endothelial barrier results in leakage of water into the interstitial space. Factors triggering ARDS can be present in the respiratory tract, interstitial space, and blood circulation. All three mechanisms may be applicable to COVID-19; however, which factors are most important, preventable, and treatable requires further analysis.

Mechanisms of Water Leakage

SARS-CoV-2 is thought to infect cells through angiotensin-converting enzyme 2 (ACE2)11,12. ACE2 is expressed at the luminal membrane of type 2 alveolar epithelial cells11, vascular endothelial cells13,14, and small intestine enterocytes15.

SARS-CoV-2 can be transmitted through droplets, aerosols, and direct contact. Because most aerosol particles are less than 5 µm in size, virus in aerosols can easily reach the alveoli and infect the lungs using ACE2 as a gate. The chance of transmission through enterocytes is low but cannot be completely excluded. The virus has been detected in the feces of some patients, indicating that it is discharged from the body rather than taken up by the intestine. Thus, type 2 alveolar epithelial cells are the first cells injured by SARS-CoV-2. Because the initial viral load is low and the virus may pass through the cells without killing them, the contribution of damaged type 2 alveolar epithelial cells to lung edema (wet lung) should not be overstated. The symptoms and signs of dry cough, lack of frothy sputum, and hyaline jelly substance in the alveoli of patients with severe infection indicate that increased permeability of the alveolar barrier is not a major mechanism, or at least not the only major mechanism, of deadly lung edema induced by SARS-CoV-2. Particular attention should be paid to disruptions in the endothelial barrier.

ACE2 on endothelial cells13,14 normally functions to convert angiotensin II into angiotensin 1-7 to regulate blood pressure. Additionally, SARS-CoV-2 is detectable in the blood. Thus, virus in the blood can infect the lungs through pulmonary capillary endothelial cells and exacerbate lung infection. In addition to increasing the viral load in the lungs, binding of the virus to ACE2 on endothelial cells labels these cells with pathogens, making the endothelium a target of the host immune system. This may explain why organ edema caused by SARS-CoV-2 is more severe than that caused by other viruses.

The details of SARS-CoV-2 infection remain unclear. Generally, most infected cells are not directly killed by the virus. The immune response and inflammation may injure both infected and bystander cells, with the extent of these processes depending on the viral load. In most cases, the virus in the respiratory tract is eliminated by innate immune patrols, clearing the infection. During the incubation period, the virus replicates in the body. If the host immune response is rapid and robust, patients may not exhibit symptoms or may only have mild illness. If the immune response is delayed and weak, the patient may become an asymptomatic viral carrier. The worst scenario is a patient with a delayed but strong immune response to the virus. When this strong immune response coincides with a high viral load, an inflammatory storm can occur.

Inflammatory storm is a catastrophic event that occurs in the late stage of SARS-CoV-2-induced ARDS. In response to a new virus, several days are required for an acquired immune response to become functional. This acquired immune response is mediated by lymphocytes specifically targeted against a pathogen/foreign antigen. The acquired immune response attacks the pathogen and cells carrying the pathogen until they are destroyed through an immune/inflammatory cascade.

The cascade begins with cytokines16,17, which are small proteins released by immune cells. Cytokine storm is a component of inflammatory storm18,19. The first wave of inflammatory factors released includes cytokines such as interleukins, tumor necrosis factor- , and interferons. Interleukins and tumor necrosis factor- regulate lymphocyte proliferation and apoptosis, inflammation, fever, chemokine production, and many other functions. Interferons inhibit virus replication. The second wave of inflammatory factors consists of chemokines. Chemokines are chemotactic cytokines released after immune/inflammatory cells are stimulated by the first wave of cytokines. They direct the migration of leukocytes to infected or damaged tissues, a process known as infiltration. Infiltration is precisely controlled by various cellular adhesion molecules on endothelial cells and leukocytes. When activated, endothelial cells express cellular adhesion molecules that facilitate leukocyte binding to endothelial cells and transmigration into inflamed/injured tissues. There, the leukocytes are further activated by inflammatory mediators and pathogenic factors. Adhesion molecules on endothelial cells determine the site of leukocyte infiltration, which plays a central role in inflammation. In many cases, injury resulting from inflammation is much more severe than that caused by etiological factors. Activated leukocytes, including lymphocytes, macrophages, and granulocytes, both in lesions and those still in the blood circulation, release a third wave of inflammatory mediators and cytotoxic substances19.

Inflammatory mediators mediate the positive feedback of inflammation until pathogens are destroyed. Cytotoxic substances cause injury to all cell types. Additionally, endothelial cell contraction and injury increase capillary permeability. High capillary permeability allows water and protein to leak from capillaries into the interstitial space20.

Inflammatory cytokines, chemokines, leukotrienes, prostaglandins, platelet-activating factor, complements, histamine, bradykinin, reactive oxygen species, and nitric oxide can increase vascular permeability16,19-22.

Although systemic inflammation affects all capillaries in the body, lung edema is more severe than edema in other organs during COVID-19 infection for four reasons. First, the lung is the first organ infected with SARS-CoV-2. Second, the total capillary bed area is larger than that of any other organ. Third, all blood must pass through the lungs to become oxygenated. Fourth, all venous blood draining metabolic waste, inflammatory cells, and mediators from the whole body enters the lungs.

How to Prevent and Stop Water Leakage in Organs

Significant edema causes organ dysfunction, which may result in death depending on the intensity of the edema and the remaining compensatory capacity of organ function. Existing disease in an organ decreases its functional reserves and makes it more difficult for a patient to survive organ edema.

Currently, no single drug is sufficient for treating leaking lungs. Antiviral drugs23-25 inhibit virus growth but do not kill the virus. These agents should be administered as early as possible to reduce the viral load in patients. An immune response and inflammation are required to kill viruses already present in the body. Manipulating the balance between virus elimination and tissue damage caused by immune reactions and inflammation remains challenging.

Sustained and high doses of glucocorticoids should not be used unless the patient is under life-threatening conditions, as the side effects of these agents may outweigh their benefits.

Immunosuppressant drugs with fewer side effects, such as sirolimus25 and tacrolimus, may stagger the peak times of damage caused by viral infection, immune response, and non-immune inflammation, thereby reducing the degree of lung leakage and preventing life-threatening situations. Administration of convalescent plasma24 from patients who have recovered from SARS-CoV-2 infection may trigger immune-mediated killing of the virus. However, this plasma may also target cells carrying the virus, so incorrect treatment timing may exacerbate cell injury.

Nonsteroidal anti-inflammatory drugs, such as those used to treat rheumatoid arthritis, decrease lipid mediators including leukotrienes, prostaglandins, and platelet-activating factor. For example, chloroquine inhibits phospholipase A2, a class of enzymes that hydrolyze the sn-2 ester of glycerophospholipids to produce a fatty acid (typically arachidonic acid) and a lysophospholipid. Arachidonic acid is a substrate in the biosynthesis of leukotrienes and prostaglandins, while lysophospholipid is a substrate for platelet-activating factor. Hydrolysis of glycerophospholipids and production of lysophospholipid cause cell membrane damage. Prostaglandins are products of cyclooxygenase-1 (COX-1) and COX-2, enzymes that are blocked by aspirin and ibuprofen. Because most pro-inflammatory prostaglandins are products of COX-2, an inhibitor of cyclooxygenase-2 (celecoxib) is a more selective anti-edema drug. Although nonsteroidal anti-inflammatory drugs have some side effects, they are valuable for treating life-threatening conditions such as wet lungs.

Information from hospitals has indicated that heat-clearing (Qing Re) Chinese herbs are effective for treating COVID-19, although this has not been tested in strictly double-blind clinical trials. However, many heat-clearing Chinese herbs inhibit inflammation27, indicating their potential usefulness for treating COVID-19.

For anti-oxidants such as vitamin C, it is difficult to reach a dose with considerable therapeutic effects in vivo without causing intolerable side effects.

The effects of drugs on increasing or decreasing ACE2 are difficult to predict because the level and location of ACE2 determine how easily infection occurs, the cellular distribution of the virus, and viral labeling of cells. In addition, ACE2 is an important regulator of blood pressure.

Stem cells achieve therapeutic effects by differentiating into parenchymal cells or secreting endocrine/paracrine factors, and by promoting angiogenesis through differentiation into endothelial cells. These cells may be useful for treating COVID-19.

Antibodies against pro-inflammatory cytokines28,29, such as interleukin-1 , tumor necrosis factor- , and interleukin-6 are available. Although an antibody or cytokine blocker16,28 may be effective for inhibiting a specific cytokine, it may not be sufficient to treat wet lungs caused by an inflammatory storm given the large number of cytokines involved.

Many categories of inflammatory mediators and cytotoxic substances are involved in tissue edema caused by severe viral infection. Targeting one or several of these categories may not be effective for improving survival when the peaks of injuries caused by viral infection, the immune response, and non-immune inflammation meet30. The only strategy for treating all of these conditions is hemodialysis.

Chemokines, leukotrienes, prostaglandins, platelet-activating factor, complements, histamine, bradykinin, reactive oxygen species, and nitric oxide are smaller than 10 kD. Many pro-inflammatory cytokines, such as tumor necrosis factor- , interleukin-1 , and interleukin-6, are smaller than 20 kD. Thus, hemodialysis may eliminate most inflammatory mediators and cytotoxic substances, serving as a life-saving strategy for COVID-19.

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Declaration of Interests

The author declares no conflicts of interest.

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