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

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摘要：自 2019 年 12 月爆发以来，2019 年新型冠状病毒已在全球造成 2596 人死亡，并且有超过 11，000 名患者仍处于严重状况。该病毒和由该病毒引起的医疗状况被命名为 SARS-CoV-2 和 COVID-19。虽然已经广泛应用了抗病毒、对症和功能支持性疗法，每天仍有 100 多名患者死于该病毒感染。COVID-19 最常见的致命并发症是急性呼吸窘迫综合征（ARDS）。SARS-CoV-2 在世界范围内的大流行可能仍然存在。其它病毒感染引起的肺炎亦可导致 ARDS，出现类似的危重情形，这些病毒包括如非典型的急性呼吸系统综合症（SARS）、中东呼吸综合征（MERS）和流感病毒引起的肺炎。因此，制定更有效的降低病毒所致的 ARDS 死亡率的策略，不但是当前抗新冠疫情的迫切需要，也是全球范围内降低病毒性肺炎死亡率的长期需要。ARDS 曾被称为湿肺，血管泄漏导致的肺水肿是其最重要的病理特征之一，重型 COVID-19 的临床表现和胸部计算机断层扫描图像特征（白肺）符合 ARDS。确定水肿液从何处及如何渗漏到肺部，是制定基于机制的预防和阻止水从肺毛细管向肺间质渗漏的策略，降低湿肺死亡率的关键。对于轻度和中度病例，非类固醇消炎药，如用于风湿性关节炎的药物，可能有助于防止和减少这种漏水。免疫抑制剂（如西罗莫司和巨蜥）可能使病毒感染、免疫反应和非免疫炎症造成的损伤高峰时间错开，从而降低肺漏水程度，防止危及生命情况出现。使用清火中草药可能也有抗炎用。对于严重病例，血液透析可能是消除大多数炎症介质和细胞毒性物质的有效策略。

主要论点：

- SARS-CoV-2 感染导致的肺毛细血管通透性增加需要得到特别重视
- 炎性风暴导致危及生命的肺水肿
- 血中的 SARS-CoV-2 可通过肺毛细血管上的 ACE2 进入肺内，加重肺感染
- 血中的 SARS-CoV-2 可通过与全身毛细血管上的 ACE2 结合，进入组织器官，并标记血管内皮细胞，进而使血管内皮细胞受到免疫攻击
- 病毒载量、免疫反应和炎症高峰相遇时，易发生炎症风暴
- 血液透析可以消除血液中的大多数炎症中介和细胞毒性物质
- 抗病毒药物、糖皮质激素、免疫抑制剂、非类固醇消炎药、青霍中草药、抗氧化剂、ACE-2 调节剂、干细胞、抗体之间的疗效权衡赞成炎性细胞因子和血液透析应考虑
- 现有疾病减少器官的功能储备，使患者难以因 SARS-CoV-2 感染而存活器

官水肿

Introduction

The 2019 novel coronavirus has killed 2596 globally since the outbreak began in December 2019 and more than 11,000 patients are still in severe conditions. The virus and medical conditions caused by the virus were named as SARS-CoV-2 and COVID-19. Although antiviral, symptomatic, and functionally supportive treatments have been applied, more than 100 patients die each day from infection with the virus. The most common deadly complication of COVID-19 is acute respiratory distress syndrome (ARDS)[1]. SARS-CoV-2 infection may become pandemic. ARDS is caused by various similar viruses, such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and influenza viruses[2-4]. Thus, strategies for decreasing the mortality of virus-initiated ARDS are needed at the urgent, long-term, and broad levels. ARDS was previously referred to as wet lungs with vascular leaking[5], which described the clinical manifestations and chest computed tomography images of COVID-19-ARDS[6-8]. Determining from where and how water is leaking into the lungs will lead to the development of mechanism-based management strategies for reducing mortality. These approaches can be used to prevent and stop water leakage from the pulmonary capillary into the lung interstitial space. For mild and moderate cases, nonsteroidal anti-inflammatory drugs, such as those used for rheumatoid arthritis, may be useful for preventing and deceasing this water leakage. Administration of immunosuppressants, such as sirolimus and tacrolimus, may stagger the peak times of injuries caused by viral infection, immune response, and non-immune inflammation to decrease the extent of water leakage and prevent life-threatening conditions. Using anti-flame (Qing-Huo) Chinese herbs may also be useful. For severe case, blood dialysis can be an effective strategy for eliminating most inflammatory mediators and cytotoxic substances.

Panel: Major viewpoints

- **Particular attention should be paid to the increased permeability of the pulmonary capillaries in SARS-CoV-2 infection**
- **Virus in the blood can infect the lungs through pulmonary capillary endothelial cells and exaggerate lung infection.**
- **Inflammatory storm causes life-threatening lung edema**
- **Binding of the virus and ACE2 at endothelial cells labels these cells with pathogens, making the endothelium a target of the host immune system**
- **Inflammatory storm occurs when the peaks of viral infection, immune response, and inflammation meet**
- **Blood dialysis may eliminate most inflammatory mediators and cytotoxic substances in the blood**
- **The tradeoffs between the therapeutic benefit and side effects of antiviral drugs, glucocorticoid, immunosuppressants, nonsteroidal anti-inflammatory drugs, Qing-Huo Chinese herbs,**

Dialysis can eliminate unwanted substances with molecular weights smaller than 15 kD as well as some medium-sized molecules with molecular weight of 15–35 kD from blood, represented by the partial clearance of α1-microglobin[9,10]. Therefore, this method eliminates most inflammatory mediators and cytotoxic substances. The question is whether high permeability of capillary side of the respiratory membrane is a major mechanism of wet lungs.

From where is water leaking?

ARDS was initially known as shock lung, wet lunghyaline membrane lung, and Da Nang lung, among other names. 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. A barrier between the lungs and air is formed by a monolayer of type 1 and 2 alveolar epithelial cells in the alveoli. Alveoli 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 the blood, specifically by 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, which is the space between the alveolus and pulmonary capillary, increases the distance that oxygen has to travel to reach the circulatory blood. Damage to the alveolar barrier results in water leakage from the interstitial space into the alveoli. A highly permeable or broken pulmonary endothelial barrier results in the 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 applicable to COVID-19; however, which factors are most important, preventable, and treatable requires further analysis.

SARS-CoV-2 is thought to infect cells through angiotensin converting enzyme-2 (ACE-2)[11,12]. ACE-2 is expressed at the luminal membrane of type 2 alveolar epithelial cells[11], vascular endothelial cells[13,14], and small intestine enterocytes[15]. SARS-CoV-2 can be transmitted through droplet, aerosol, and direct contact. Because most aerosol particles are less than 5 μm in size, virus in aerosol can easily reach the alveoli and infect the lungs using ACE-2 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 virus 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 staff in the alveoli of patients with severe infection indicate that increased permeability of the alveolar barrier is not major mechanism, or 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.

Mechanisms of water leakage

ACE2 on endothelial cells[13,14] 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 exaggerate lung infection. In addition to increasing the viral load in the lungs, binding of the virus and ACE2 at endothelial cells labels these cells with pathogens, making the endothelium a target of the host immune system. This may explain why organ edema caused 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 respiratory tract is killed by innate immune patrollers, eliminating the infection. During the incubation period, the virus replicates in the body. If the host immune response is rapid and strong, patients may not exhibit symptoms or only have mild illness. If the immune response is delayed and weak, the patient may become a viral carrier without symptoms. The worst scenario is a patient with a delayed but strong immune response to the virus. When the strong immune response meets with a high viral load, an inflammatory storm can occur.

Inflammatory storm is a catastrophic even that occurs in the late stage of SARS-CoV-2-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 designed for 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 starts with cytokines[16,17], which are small proteins released by immune cells. Cytokine storm is a part of inflammatory storm[18,19]. The first batch of inflammatory factors released are represented by cytokines, such as interleukins, tumor necrosis factor-α, and interferons. Interleukins and tumor necrosis factor-α regulate lymphocyte proliferation and apoptosis, inflammation, fever, chemokine

production, and many other functions. Interferons disturb virus replication. The second batch of inflammatory factors released are chemokines. Chemokines are chemotaxis cytokines released after the immune/inflammatory cells are stimulated by cytokines in the first batch of inflammatory factors. 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 then transmigrate 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. Leukocyte infiltration 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 granular leukocytes, in lesions and those still in the blood circulation release a third batch of inflammatory mediators and cytotoxic substances[19]. Inflammatory mediators mediate the positive feedback of inflammation until the pathogens are destroyed. Cytotoxic substances caused injury to all cell types. Additionally, endothelial cell contraction and injury increase capillary permeability. A high capillary permeability allows water and protein to leak from the capillaries into the interstitial space[20]. Inflammatory cytokines, chemokines, leukotrienes, prostaglandins, platelet-activating factor, complements, histamine, bradykinin, reactive oxygen species, and nitric oxide can increase vascular permeability[16,19-22].

Although systemic inflammation affects all capillaries in the body, lung edema is more severe than edema in other organs during COVID-19 infection for 4 reasons. First, the lung is the first organ infected with SARS-CoV-2. Second, the area of the total capillary bed is larger than that of any other organ. Third, all blood must pass through the lungs to become oxygenated. Fourth, all venous blood that drains 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 remaining compensative capacity of organ function.

Existing disease in an organ decreases an organ's functional reserves and make it more difficult for a patient to survive organ edema.

Currently, no single drug is sufficient for treating leaking lungs. Antiviral drugs[23-25] 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 virus already present in the body. Manipulating the balance between virus killing and tissue damage caused immune reactions and inflammation remains challenging.

Sustained and high doses of glucocorticoids should not be used unless the patient is under life-threatening conditions. The side effects of these agents may overcome their benefits, as glucocorticoids inhibit nearly all functions in the body. Immunosuppressant drugs with fewer side effects, such as sirolimus[25] and tacrolimus, are available for decreasing the immune response and inflammation. Administration of convalescent plasma[24] from patients who have recovered from SARS-CoV-2 infection may trigger immune killing of the virus. However, this serum may also target cells carrying the virus. Thus, incorrect treatment timing may exaggerate cell injury.

Nonsteroidal anti-inflammatory drugs, such as those used to treat rheumatic arthritis, decrease lipid mediators, including leukotrienes, prostaglandins, and platelet-activating factor. For example, chloroquine inhibits phospholipase A_2[26], 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 and lysophospholipid is a substrate for platelet-activating factor. Hydrolysis of glycerophospholipids and the production of lysophospholipid cause damage to the cell membrane. Prostaglandins are products of cyclooxygenase-1 (COX-1) and COX-2; these enzymes 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 drugs for treating life-threatening conditions, such as wet lungs.

Information from hospitals has indicated that anti-flame (Qing-Huo) Chinese herbs are effective for treating COVID-19, although this has not been tested in strictly double-blind clinical trials. However, many anti-flame Chinese herbs inhibit inflammation[27], 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 ACE-2 are difficult to predict because the level and location of ACE-2 determine how easily infection occurs, the cell distribution of the virus, and cell labeling by the virus. In addition, ACE-2 is an important regulator of blood pressure.

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

Antibodies against pro-inflammatory cytokines[28,29], such as interleukin-1β, tumor necrosis factor-α, and interleukin-6 are available. Although an antibody Although antibody or cytokine blocker[16,28] 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 meets[30]. The only strategy for treating all of these conditions is blood dialysis.

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-α, interleukin-1β, and interleukin-6, are smaller than 20 kD. Thus, blood dialysis may eliminate most inflammatory mediators and cytotoxic substances, and serve a life-saving strategy for COVID-19.

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