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What happens to people's lungs when they get coronavirus disease 2019?

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Summary. The novel coronavirus SARS-CoV-2 was first identified in Wuhan in December 2019 as cause of the consequent novel coronavirus disease 2019 (COVID-19). The virus has since spread worldwide. The clinical presentation following human infection ranges from a mild upper respiratory tract infection to severe acute respiratory distress syndrome and sepsis. We reviewed literature using *Pubmed* to identify relevant English-language articles published until April 15, 2020. Search terms include *novel coronavirus pneumonia, severe acute respiratory syndrome coronavirus 2, coronavirus and ventilation.* We summarized what SARS-CoV-2 infection means for the lungs. (www.actabiomedica.it)

Key words: SARS-CoV-2, Pneumonia, Respiratory failure, ARDS

The SARS-CoV-2 entry into the body

SARS-CoV-2 belongs to the *Sabercovirus* subgenus of the *Coronaviridae* family, *Nidovirales* order, and is the seventh coronavirus known to infect humans (1). The transmission of the virus is human to human through droplets emitted by coughing and sneezing (2). The consequences of the coronavirus disease 2019 (COVID-19) can be lethal, particularly in the elderly or those with comorbidities, such as hypertension, cardiac failure and diabetes (3).

SARS-CoV-2 uses the angiotensin converting enzyme II (ACE-2), as the cellular entry receptor (4). ACE-2 is a type I transmembrane metallocarboxypeptidase with homology to angiotensin converting enzyme (ACE). In contrast to ACE, which converts angiotensin I to the active vasoconstrictor, angiotensin II, ACE-2 breaks down angiotensin II to its metabolites including angiotensin- (1-9) and angiotensin- (1-7), which are potent vasodilators, and thus may be a negative regulator of the renin-angiotensin system. ACE-2 is expressed in different tissues such as upper and lower respiratory tract, myocardium and the gastrointestinal mucosa (5). In humans, it appears to have a role in blood pressure control and cardiac function. The physiologic role of ACE-2 in the airways is unknown. However, in mice, ACE-2 seems to protect animals from severe lung injury related to aspiration and sepsis (6).

During SARS-CoV-2 infection, three stages can occur: stage I, an asymptomatic incubation period with or without detectable virus; stage II, non-severe symptomatic period with the presence of virus; stage III, severe respiratory symptomatic stage with high viral load (7).

During the first stage a specific adaptive immune response is crucial to eliminate the virus and avoid disease progression to severe stages. When a protective immune response is impaired, virus will propagate and a massive destruction of the infected tissues will occur, such as intestine and kidney. The damage cells induce innate inflammation in the lungs mediated by pro-inflammatory macrophages and granulocytes. Lung inflammation is the main cause of life-threating respiratory disorders at the severe stage (8).

Inflammatory markers are increased with SARS-CoV-2 infection, ranging from CRP, IL-6, IFN-

gamma, to TNF-α (3)(9). This inflammatory response may lead to multi-organ failure and disseminated intravascular coagulation (DIC) (10). Furthermore, the hypoxia seen in patients with severe pneumonia may also lead to further end-organ dysfunction/damage and death in critically-ill patients (11).

Recent autopsy studies showed that the lungs are filled with clear liquid jelly, much resembling the lungs of wet drowning (8). Although the nature of the clear jelly has yet to be determined, hyaluronan (HA) may play a role. Interestingly, HA is associated with Acute Respiratory Distress Syndrome (ARDS) (12). The levels of inflammatory cytokines (IL-1, TNF-α) are high in the lungs of COVID-19 patients and these cytokines are strong inducers of HA-synthase-2 (HAS2) in CD31+ endothelium, EpCAM+ lung alveolar epithelial cells, and fibroblasts (13). HA has the ability to absorb water up to 1000 times its molecular weight. Therefore, reducing the presence or inhibiting the production of HA holds a great promise in helping COVID-19 patients breathe (14).

Clinical manifestations of COVID-19

Approximately 80% of patient present with mild illness, 14% present with severe illness, and 5% present with critical illness (15). The most common symptoms are: fever, cough, dyspnea, myalgia, fatigue. Less common symptoms include anorexia, sputum production, sore throat, confusion, dizziness, headache, rhinorrhea, chest pain, hemoptysis, diarrhea, nausea/vomiting, abdominal pain, conjunctival congestion (16).

The most common laboratory abnormalities in patients hospitalized with pneumonia are lymphopenia and elevated liver transaminases. Other abnormalities include neutrophilia, thrombocytopenia, decreased hemoglobin, decreased albumin, and renal impairment (3)(7) (16). Pulse oximetry may reveal low oxygen saturation (SpO2 <95%), as a consequence of pneumonia.

Recent studies pointed out a significant relationship between troponin (TnI) levels and fatal outcome in patients with confirmed COVID-19 (17). The underlying mechanism of this association is not completely understood. One case report study demonstrated the presence of coronavirus and inflammatory markers in autopsy specimens of the myocardium (18), thereby suggesting that these patients may develop myocarditis. Another potential cause of myocardial injury is occlusive thrombus formation on ruptured coronary plaque, related to intense inflammatory stress on pre-existent coronary artery disease. The effect of inflammation on plaque disruption has been partially proved by CANTOS trial (19).

The chest imaging findings may vary with the patient's age, immunity status, disease stage, underlying diseases and drug interventions. Clinical data from Zhongnan Hospital of Wuhan University described such typical CT/X-ray imaging manifestations, multiple, patchy, sub-segmental or segmental ground-glass density shadows in both lungs. They were classified as "paving stone-like" changes by fine-grid or small honeycomb-like thickening of interlobular septa. Also multiple, patchy or large patches of consolidation in both lungs, with a little grid-like or honeycomb-shaped interlobular septal thickening, especially in the middle and lower lobes, more common in the elderly or severe condition patients, were considered typical radiological findings (20).

Respiratory failure as a consequence of COVID-19

Respiratory failure may occur in patients with COVID-19 pneumonia. In Italy, up to 12% of all patients with COVID-19 required ICU admission following respiratory failure (21). Furthermore, ARDS is the most common complication in patients with respiratory failure and may occur in 60–70% of patients with COVID-19 admitted to the ICU (22). Interestingly, patients with COVID-19 pneumonia may present an atypical form of ARDS characterized by a dissociation between their relatively preserved lung mechanics and the severity of hypoxemia (23). A possible explanation for such severe hypoxemia occurring in compliant lungs is the loss of lung perfusion regulation and hypoxic vasoconstriction.

Oxygen therapy should be considered immediately when patients affected by severe acute respiratory infection have the following conditions: hypoxemia (PaO_2 <60 mmHg or SpO_2 <93% when breathing air); respiratory distress (respiratory frequency> 24

times/min); hypotension (systolic blood pressure <100 mmHg) (24). It is reasonable setting the initial oxygen flow to 5 L/min, and then titrating the oxygen flow to maintain SpO_2 at 94%-98%. If the patient's initial SpO_2<85%, oxygen storage masks (oxygen flow> 12 L/min) should be preferred to correct hypoxemia. If there is no improvement or deterioration after 1 to 2 hours, other respiratory support methods should be replaced immediately. The patient should be instructed to wear a surgical mask or a simple open mask when inhaling the nasal catheter (25).

High flow nasal cannula (HFNC) is a new type of breathing support method, where the gas flow can be adjusted up to 60-70 L/min and FiO_2 from 0.21 to 1.0. Compared with oxygen therapy, HFNC can reduce the rate of tracheal intubation and mortality in patients with hypoxic respiratory failure. Therefore, HFNC treatment could be selected when oxygen therapy cannot correct hypoxemia. In a retrospective study, *Wang Ke at al*. screened 318 patients with COVID-19 pneumonia and showed that HFNC was the most common ventilation support for these patients, but patients with lower PaO_2/FiO_2 (<200 mHg) were more likely to fail (26).

After treatment with HFNC, the efficacy response should be monitored closely (1-2 hours). If critical conditions persist, HFNC should be replaced with non-invasive ventilation (NIV) in a timely manner (22). Recent data suggest that COVID-19 patients who are hypoxemic respond well to PEEP, indicating a crucial role for NIV, as a therapeutic measure to prevent intubation (27). For patients with PaO2/FiO2≤150mmHg, invasive ventilation should be implemented as soon as possible.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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