How to cite: Gardenghi G. Pathophysiology of worsening lung function in COVID-19. Rev Bras Fisiol Exerc 2020;19(2supl):S40-S46. DOI: https://doi.org/10.33233/rbfe.v19i2.4058

RBFEx
ISSN: 2675-1372

Brazilian Journal of Exercise Physiology

Review Article

Pathophysiology of worsening lung function in COVID-19

Fisiopatologia da piora da função pulmonar no COVID-19

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ABSTRACT

Introduction: The new coronavirus pneumonia (COVID-19) has emerged as the main threats to global health since December 2019. Addressing part of the pulmonary pathophysiology involved in the disease is important to help interested health professionals better understand the different aspects of this complex pathology. Aim: This article aims to present part of the pathophysiological process involved in pulmonary complications associated with Covid-19. Methods: An integrative literature review was carried out, with articles published between 2019 and 2020, in the Google and PubMed databases, using the following search terms: coronavirus, COVID-19, pulmonary complications, pneumonia. Results: 6 articles were included, addressing the proposed theme. Conclusion: The individual's infection with COVID-19 has the potential to cause significant changes in ventilatory capacity, leading to diffuse pulmonary impairment and worsening gas exchange. Further studies are needed to clarify the pathophysiology of this complex disease with a high potential for contagion, morbidity and mortality.

Key-words: Exercise; Intensive Care Units; Patient Safety.

RESUMO

Introdução: A nova pneumonia por coronavírus (COVID-19) surgiu como as principais ameaças à saúde global desde dezembro de 2019. Abordar parte da fisiopatologia pulmonar envolvida na doença é importante para ajudar os profissionais de saúde interessados a compreender melhor os diversos aspectos dessa complexa patologia. **Objetivo:** Esse artigo tem o intuito de apresentar parta do processo fisiopatológico envolvido nas complicações pulmonares associadas à Covid-19. **Métodos:** Foi realizada uma revisão integrativa da literatura, com artigos publicados entre 2019 e 2020, nas bases de dados Google e PubMed, utilizando os seguintes termos para pesquisa: coronavirus, COVID-19, complicações pulmonares, pneumonia. **Resultados:** Foram incluídos 6 artigos, abordando o tema proposto. **Conclusão:** A infecção do indivíduo pela Covid-19 tem potencial de causar alterações significativas na capacidade ventilatória, cursando com comprometimento pulmonar difuso e piora nas trocas gasosas. Mais estudos são necessários para esclarecer a fisiopatologia dessa doença complexa com alto potencial de contágio, morbidade e mortalidade.

Palavras-chave: Coronavirus infections; Communicable Diseases; Pneumonia.

Received: April 10, 2020. Accepted: April 17, 2020.

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Introduction

COVID-19, or the coronavirus, started in China in late 2019 as a set of cases of pneumonia with an unknown cause. The cause of pneumonia was found to be a new virus - severe acute respiratory syndrome coronavirus 2 or Sars-CoV-2. Now declared a pandemic by the World Health Organization (WHO), most people who contract COVID-19 suffer only mild symptoms. The WHO says that only one person in six becomes seriously ill "and will develop difficulty in breathing". Almost all of the serious consequences of COVID-19 have pneumonia. The WHO also says that elderly people and people with underlying problems, such as high blood pressure, heart and lung problems or diabetes, are more likely to develop serious illnesses [1].

Regularly, when people with COVID-19 develop cough and fever, this is a result of the infection that affects the bronchial tree. The lining of the bronchi is injured, causing inflammation. This, in turn, irritates the nerves in the lining of the airways, and in such situations, just a grain of dust can stimulate coughing. With the evolution of the condition, the virus reaches the gas exchange units (alveoli), igniting them and, consequently, promoting the filling of such alveoli by liquids, cellular debris and others, due to the alterations caused in the alveolar-capillary membrane. This condition will therefore be characterized as pneumonia, resulting in an inability of gas exchange with consequent hypoxemia and hypercapnia. Pneumonic conditions are associated with mortality, especially in the elderly [1].

Chen and colleagues [2] retrospectively studied 99 patients with pneumonia caused by COVID-19. The average age of the patients was 55.5 years, including 67 men and 32 women. 51% of patients had chronic diseases. The patients presented clinical manifestations of fever (83%), cough (82%), shortness of breath (31%), muscle pain (11%), mental confusion (9%), headache (8%), headache throat (5%), rhinorrhea (4%), chest pain (2%), diarrhea (2%) and nausea and vomiting (1%). According to the imaging exam, 75% of patients had bilateral pneumonia, 14% of patients had multiple spots and ground-glass opacity, and 1% of patients had pneumothorax. 17% of patients developed acute respiratory distress syndrome (ARDS) and, among them, 11% of patients worsened in a short period and died from multiple organ failure.

Methods

An integrative literature review was carried out, with articles published between 2019 and 2020, in the Google and PubMed databases, using the following search terms: coronavirus, COVID-19, pulmonary complications, pneumonia, and 06 articles were selected for writing the present manuscript.

Histopathological findings

Luo *et al*. [3] describe, in data not yet published, histopathological findings related to a 66-year-old male patient who had symptoms of high fever and cough when he returned to Shenzhen City, coming from Wuhan on January 4, 2020 This individual had only hypertension as a comorbidity. On macroscopic examination (Figure 1), the surface of the entire lung showed a diffuse con-

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gestive appearance. There was punctual hemorrhage and partially hemorrhagic necrosis. Hemorrhagic necrosis was present mainly on the outer edge of the lower right lobe, middle lobe and upper lung lobe. The bronchi were swollen and the mucous surfaces were covered with hemorrhagic exudation. The cut surfaces of the lung showed severe congestive and hemorrhagic changes.

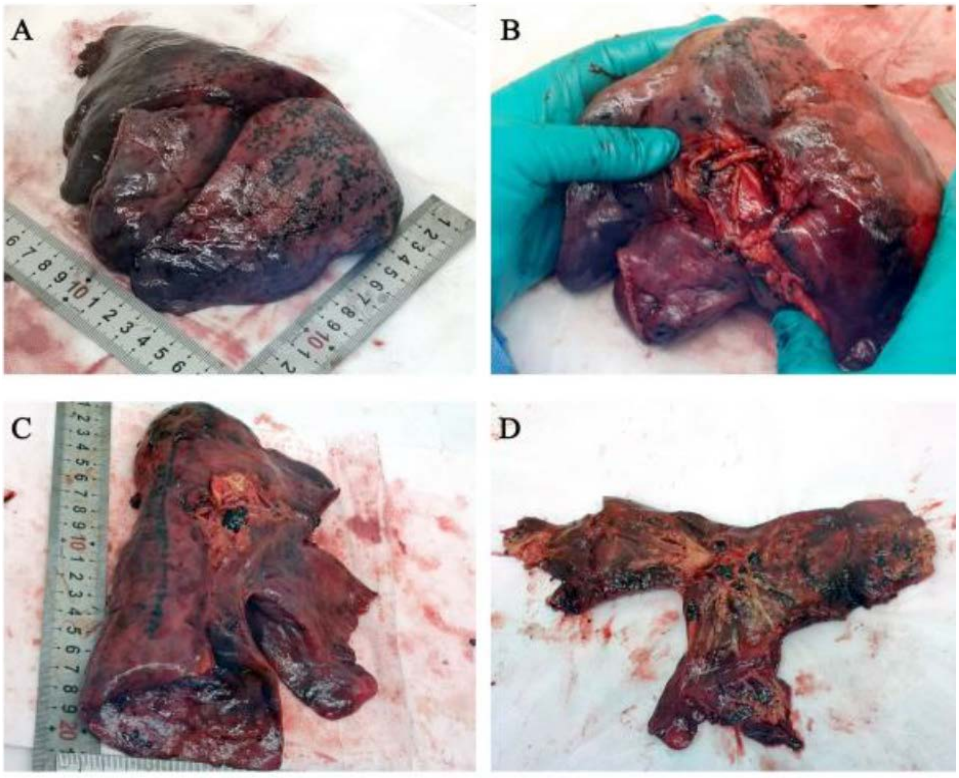

Figure 1. Macroscopic lung examination at COVID-19.
Morphology of the right lung (Panel A and B) and the left lung (Panel C and D). Hemorrhagic necrosis is obvious at the outer edge of the right pulmonary lobe. Image reproduced from the data of Luo and collaborators [3].

As shown in Figure 2, histopathological findings showed extensive interstitial fibrosis with partially hyaline degeneration and pulmonary hemorrhagic infarction. The small vessels showed hyperplasia, thickening of the vessel wall and stenosis / occlusion. Interstitial infiltration of inflammatory cells, including lymphocytes and mononuclear cells. Pulmonary interstitial fibrosis was confirmed and no other bacterial and fungal infections were found by special staining.

There was alveolitis with atrophy, proliferation, desquamation and various changes in the squamous metaplasia of alveolar epithelial cells (mainly type II), as listed in Figure 3. The remaining pulmonary alveoli showed a thickened septum, necrosis and desquamation of alveolar epithelial cells. In addition, massive fibrous exudate, giant multinucleated cells and intracytoplasmic viral inclusion bodies. Necrotizing bronchiolitis and manifest necrosis of the bronchiolar wall, with epithelial cells present in the lumen.

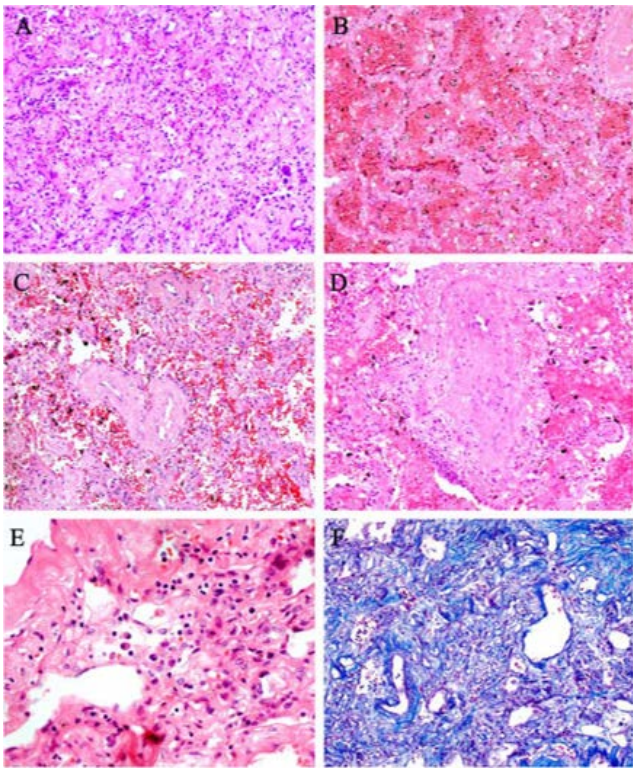

Figure 2. Pulmonary interstitial histopathology associated with a critical patient in COVID-19.
A: Massive pulmonary interstitial fibrosis. B: Pulmonary hemorrhagic infarction. C: Vascular wall thickening and stenosis of the lumen. D: Thromboangiitis Obliterans surrounded by inflammatory cells. E: Infiltrated interstitial plasma cells. F: Pulmonary interstitial fibrosis. Image reproduced from the data of Luo and collaborators [3].

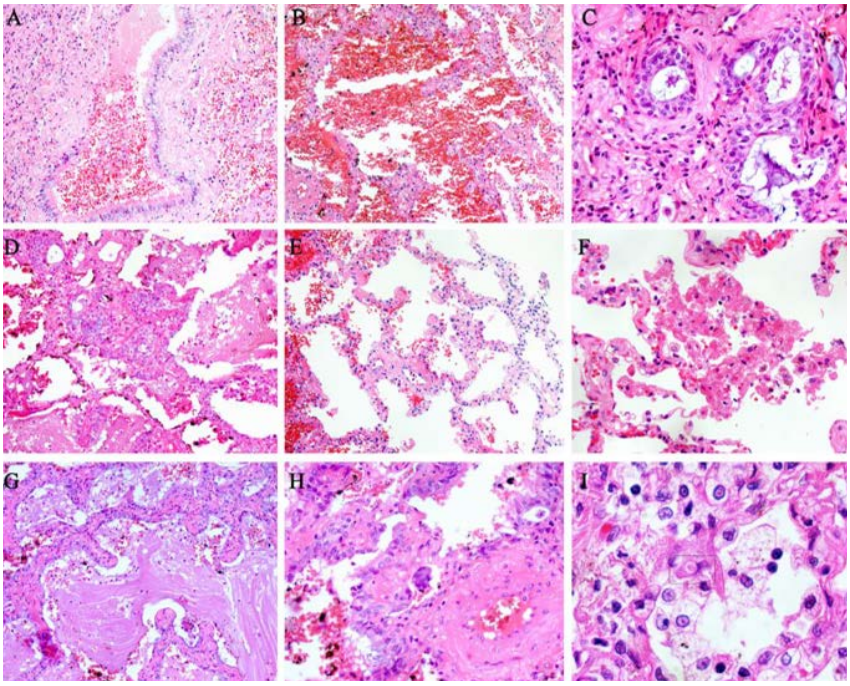

Figure 3. Changes in the pulmonary alveoli of COVID-19.
A: Necrotizing bronchiolitis, necrotic bronchial epithelial cells are present in the lumen. B: Atrophy of alveolar epithelial cells. C and D: Various changes in squamous metaplasia of alveolar cells. E: Thickened alveolar septum. F: Necrosis and desquamation of alveolar epithelial cells. G: massive fibrinous exudate in the lumen. H: Multinucleated giant cell. I: Intracytoplasmic viral inclusion body in an alveolar epithelial cell (indicated in the box). Image reproduced from the data of Luo and collaborators [3].

Chart 1. Summary of anatomical and pulmonary histopathological findings in COVID-19, based on the study by Luo et al. [3].	
• Lung tissue with diffuse congestive appearance or partially hemorrhagic necrosis on macroscopic examination	• Bronchiolitis and alveolitis with proliferation, atrophy, desquamation and squamous metaplasia of epithelial cells
• Massive interstitial pulmonary fibrosis and partially hyaline degeneration	• Varying degrees of hemorrhagic pulmonary infarction
• Small vessel hyperplasia, vessel wall thickening, stenosis or lumen occlusion	• Focal monocytes, lymphocytes and plasma cells infiltrating the pulmonary interstitium
• Prominent alveolar congestion containing edema fluid, peeling epithelial cells and inflammatory cells	• Atrophy, vacuolar degeneration, proliferation, desquamation and squamous metaplasia in alveolar epithelial cells
• Multinucleated giant cells and intracytoplasmic viral inclusion bodies	• Massive pulmonary interstitial fibrosis
• Positive immunohistochemical results for cells of the immune system, including CD3, CD20, CD79a, CD4, CD8, CD5, CD68 and CD38	

Abnormalities seen on chest tomography (CT)

COVID-19 pneumonia manifests with abnormalities in chest CT, even in asymptomatic patients, with rapid evolution of unilateral to diffuse bilateral ground-glass opacities that evolve or coexist with consolidations in 1-3 weeks. Combining the assessment of imaging resources with clinical and laboratory findings can facilitate the early diagnosis of COVID-19 pneumonia [4].

Abnormalities in chest CT before symptoms

Shi et al. [4] retrospectively reviewed the chest CT findings of 81 patients with confirmed COVID-19. Patients were subdivided into 4 groups based on the duration of clinical symptoms. Group 1 consisted of 15 patients who underwent a chest CT scan before any clinical symptoms; group 2 underwent a CT scan within 7 days after the onset of symptoms; group 3 patients were examined 7 to 14 days after the onset of symptoms. It is important to note that all 81 patients [including those without symptoms] had an abnormal chest CT consistent with viral pneumonia. In the asymptomatic group, the typical pattern was ground--glass, multifocal and peripheral opacities (Figure 4). Thickening of the interlobular septum, thickening of the adjacent pleura, nodules, round cystic changes, bronchiectasis, pleural effusion and lymphadenopathy were rarely observed in the asymptomatic group.

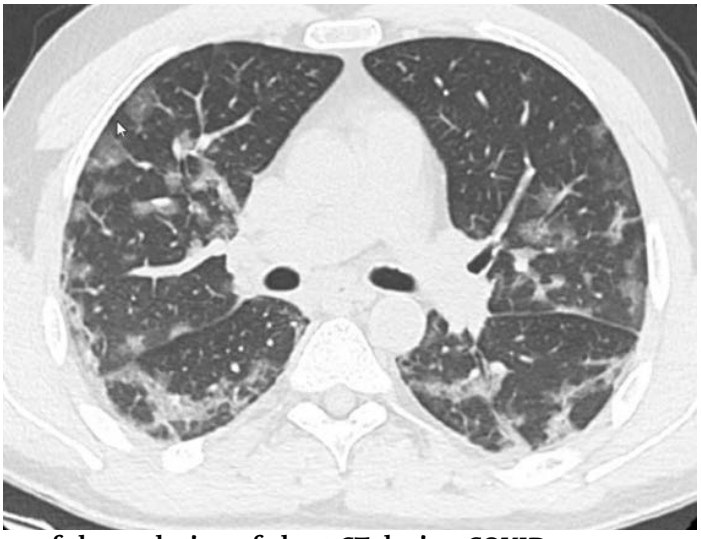

Figure 4. Illustration of the evolution of chest CT during COVID-19.
Hypothetical initial stage with bilateral, multifocal and predominantly peripheral ground-glass opacity. Source: author's archive image.

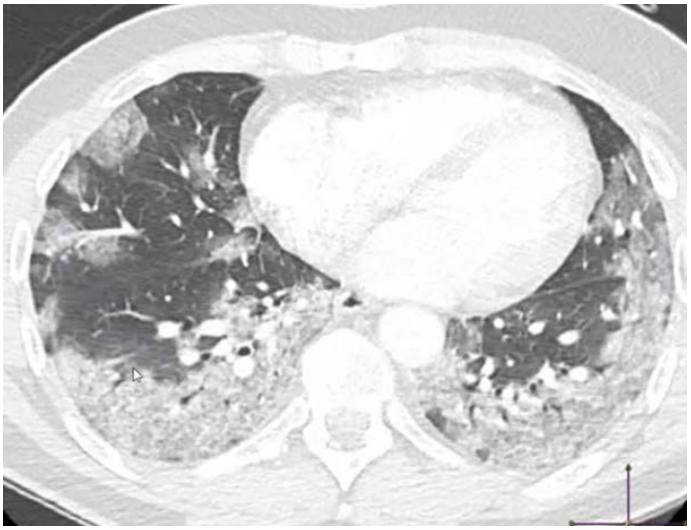

Figure 5. Illustration of the further evolution of ground-based opacities in ground glass in COVID-19. Lesions are now bilateral and multifocal. Source: author's archive image.

Still analyzing the study by Shi *et al*. [4], there was radiographic progression after the first symptoms. In group 2 (that is, in the first 7 days of symptoms), CT chest lesions became bilateral in 90% and diffuse in more than 50%, predominantly with ground-glass opacities (Figure 5). Pleural effusion and some cases of lymphadenopathy were also detected in group 2. In group 3 (ie, 7 to 14 days after symptoms), the ground-glass aspect was still the predominant finding on CT in more than 50% of cases, however, consolidation patterns were also seen in about a third of patients. Finally, in group 4 (that is, more than 14 days after symptoms), ground-glass opacities and reticular patterns were more common.

Association of COVID-19 with hemoglobin

Wenzhong & Hualan [5] released the results of their study, mentioning that in the viral replication phase after entering a person's organism, coronavirus RNA encodes the production of structural proteins (for the structure of the virus) and other non-structural proteins. One of these non-structural proteins invades hemoglobins, removes the iron atom and binds at the site, preventing oxygen from being carried. This would explain the rapidly evolving hypoxia picture. They postulate that the lung parenchyma lesions (ground glass) are a consequence of hypoxia and consequent necrosis and not a direct effect of the inflammatory process caused by the virus. This could explain people with comorbidities, especially diabetes, who decompensate quickly due to hypoxia, sometimes even with supplemental oxygen supply, as these individuals would have fewer binding sites in hemoglobins. Theoretically, in people without comorbidities, the initial viral load would be responsible for determining the severity of the condition since the higher the viral load, the more theoretically there are compromised hemoglobins. It is also suggested that the change in the structure of red blood cells would explain vessel damage and disseminated intravascular coagulation.

Conclusion

Infection of the individual by COVID-19 has the potential to cause significant changes in ventilatory capacity, leading to diffuse pulmonary impairment and worsening gas exchange. Further studies are needed to clarify the pathophysiology of this complex disease with high potential for spread, morbidity and mortality.

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