Pneumolysis in COVID-19: A Novel Concept Derived from High Altitude Physiology

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Abstract: The COVID-19 pandemic surprised everyone with a severe lung compromise giving rise to gasping and death from respiratory insufficiency. The understanding of lung compromise is essential to advances in the field of pneumology. It is well known that the SARS-CoV-2 adheres through its spikes to the ACE-2 receptors of type II pneumocytes and introduces its RNAm material in search of its reproduction. Pneumolysis, defined as "lung destruction", is the mechanism whereby the virus utilizes the alveolar cells to reproduce itself and destroys them in the process. The viral "attack" leads to dysfunction of the alveolar type II cells that work in conjunction with the type I alveolar cells, and a specialized thin oxygen and carbon dioxide permeable membrane. Once the virus is inside the cell, the organism's immune system attempts to attack the virus, causing significant inflammatory reactions with remarkable ineffectiveness. The following destruction of the alveoli gives rise to a shunt, uneven ventilation-perfusion, and alteration of diffusion, generating a rapidly progressive hypoxemia that is often lethal.

Keywords: Polycythemia, High altitude, EPO, Hematocrit and Hemoglobin, Excessive erythrocytosis, Chronic mountain sickness.

INTRODUCTION

Severe lung compromise in COVID-19 patients often evolves into life-threatening hypoxemia. A precise understanding of this viral pathology is crucial to improving the outcomes of this pandemic, and other future lung-compromising viral diseases. The lung compromise in COVID-19 was alarming (Figure **1**). Based on prior experience, standardized protocols were implemented worldwide, assuming this disease would be the same as SARS-CoV-1. Whether the lung compromise in SARS-CoV-1 was well understood back then remains a mystery. Since the current pandemic breakout, severe hypoxemia in the patients affected induced the impulsive use of ventilators resulting in over 88% fatality outcomes in extreme cases. Time has shown that the use of a high PEEP (Positive end-expiratory pressure) gave rise to fatal outcomes. Know-how on high altitude physiology and managing acute and chronic hypoxia-related medical conditions granted with us a different insight regarding COVID-19 hypoxemia. The interpretation of the COVID-19 critical hypoxemia can be enlightened by applying our Tolerance to Hypoxia formula = Hemoglobin/$PaCO_2$ + 3.01. The more hemoglobin available, the more significant the tolerance to hypoxia. Conversely, the lower the arterial Partial Pressure of Carbon Dioxide ($PaCO_2$), the greater the tolerance to hypoxia [1].

Pneumolysis

Pneumolysis (pneumo = lung, lysis = destruction), as initially described by our team, is the acute infectious disease derived from the inoculation of the Coronavirus-2 RNA or other viruses within the pneumocytes and intra-cellular viral replication, resulting in pneumocyte destruction (generally not compromising the bronchioles), accompanied by inflammation, edema, capillary vasodilatation, the formation of hyaline membranes, micro-abscesses, nuclear atypia; characterized by non-productive cough, initial silent hypoxemia, sudden onset of difficulty in breathing, fatigue, tachycardia, rapid progression to a reduced lung gas exchange area, and subsequent fibrosis. The term was first used on Jun 13, 2020 [2]. The pathophysiology of pneumolysis is precisely described [3].

DISCUSSION

The adequate interpretation of the histopathological lung biopsy photomicrographs (submitted to another journal) reveals the above-mentioned alterations. Due to the progressive *pneumolysis* + inflammation + overexpressed immunity + HAPE-type edema, the global pulmonary function is altered, resulting in pulmonary shunting, uneven ventilation-perfusion, and alteration of diffusion. The three theoretical pathophysiological stages of progressive hypoxemia

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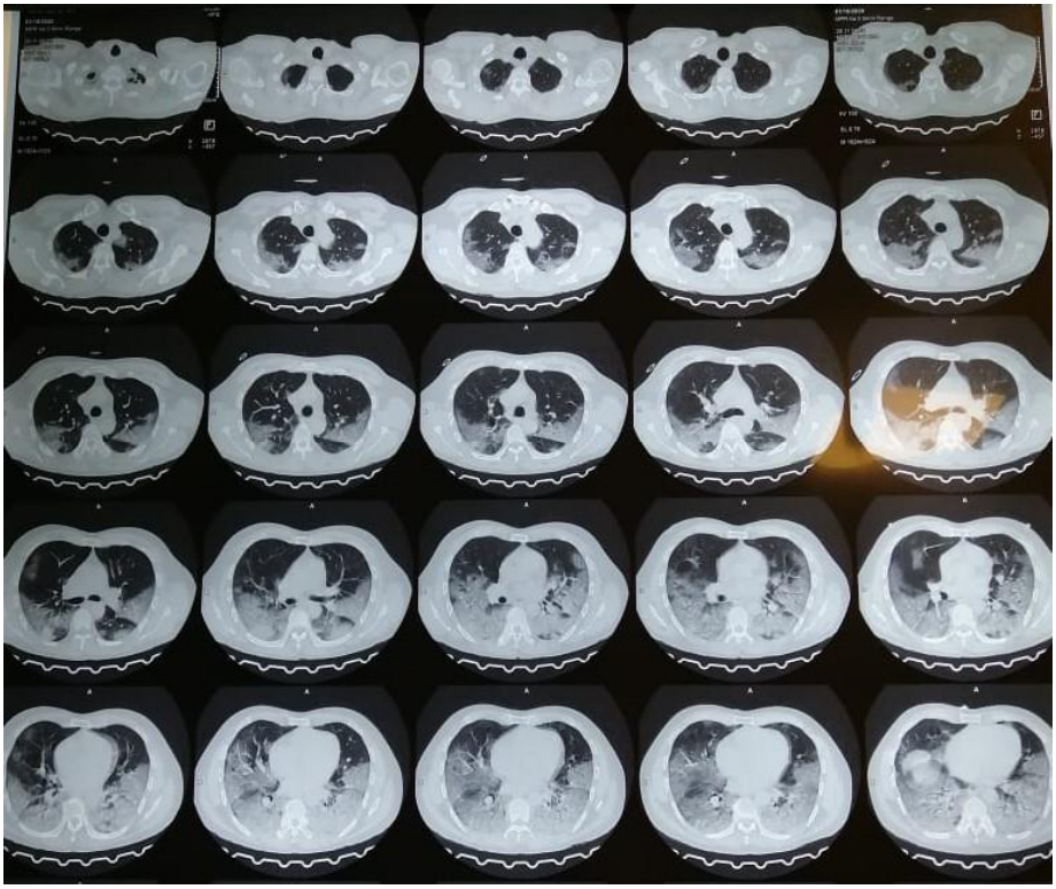

Figure 1: Lung CAT scan of a patient with COVID-19 with extensive multilobar compromise affecting the lung and its gas exchange surface area.

(**silent hypoxemia, gasping, and death zone**) help explain the pathology of COVID-19 [3]. As pneumolysis progresses, compromising more and more lung surface area, as evidenced in the CAT scans (Figure **1**), hypoxemia gradually increases. Normal lungs' surface area is around 70 square meters (about the size of half a tennis court). If this surface area is steadily reduced by progressive pneumolysis (Figure **2**), hypoxemia gradually aggravates.

The term "**silent hypoxemia**" is commonly used to describe apparently normal ventilation in COVID-19 patients despite their low oxygen saturation (SpO_2) below 90% at sea level and below 80% in the city of La Paz, Bolivia, located between 3,100 and 4,100 masl (La Paz normal SpO_2 = 88 - 92%, average barometric pressure = 495mmHg). Silent hypoxemia is the first stage of the theoretical pathophysiological stages of progressive hypoxemia. The decrease of PaO_2 is linear, as observed in some arterial blood gases performed during this pandemic [3]. However, initially, ventilation and fundamentally arterial carbon dioxide tension ($PaCO_2$) do not significantly change. Ventilation at rest only mildly increases at the beginning as a normal physiologic response [4].

Interestingly, the same phenomenon is observed upon arriving at high altitude where the Inspired oxygen tension (PIO_2) is reduced due to a decreased barometric pressure. Newcomers do not normally present shortness of breath at rest unless they perform physical activity and their oxygen requirements increase. Nevertheless, they present a low arterial partial pressure of oxygen (PaO_2) of 60mmHg and a SpO_2 of around 90% (at the altitude of La Paz). At sea level, the normal values are 95mmHg and 98%, respectively. The compensating hyperventilation due to an increased work of the pneumo-dynamic pump in travelers to high altitude [5] is mild and not clinically alarming, and this could be interpreted as a true "silent hypoxemia".

Similarly, in COVID-19's pneumolysis, there is mild hyperventilation, almost unnoticeable. The $PaCO_2$ is maintained regardless of the gradual lung surface area functional decrease. This is due to carbon dioxide (CO_2) being 20 times more diffusible than oxygen.

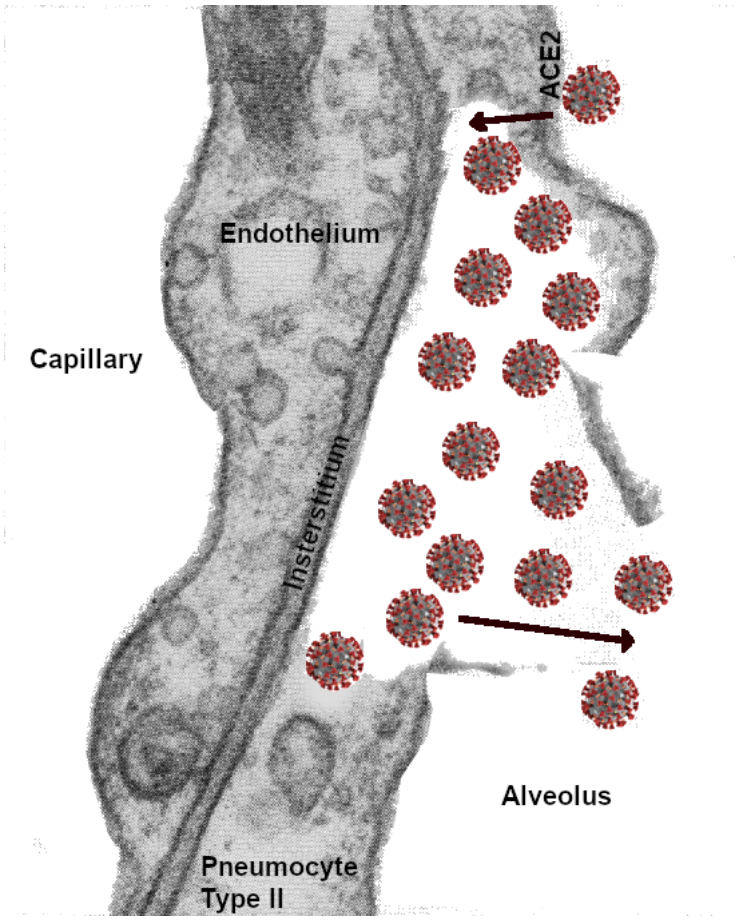

Figure 2: Diagram showing the pneumolysis induced by the invasion of pneumocytes by SARS-Covid-19, its reproduction, concomitant vasodilation, and end-result in the destruction of the alveoli.

Hence, oxygen is reduced, but CO_2 is not initially increased. However, as the functioning lung surface area reduction reaches a critical point, the lungs are unable to ventilate and eliminate carbon dioxide into the environment. This results in an increase of $PaCO_2$ and hence a more significant stimulus of the CO_2 sensors in the body, acidifying the blood (reducing the pH) and giving rise to the second stage: "**Gasping**". Here, extreme hyperventilation is evident and, unfortunately, useless since there is insufficient lung surface to reduce $PaCO_2$ levels and elevate PaO_2. This very dramatic stage corresponds to asphyxiation with full consciousness. Sustained useless hyperventilation of the pneumo-dynamic pump, accompanied by tachycardia of the hemo-dynamic pump (the heart), increases oxygen consumption of the respiratory and cardiac muscles. These responses represent a useless aggravating loop since more oxygen is required while maintaining significantly reduced lung O_2 and CO_2 exchange areas.

Respiratory muscles enter fatigue, hypoxemia is further aggravated, and the 3rd stage, termed the "Death Zone," ensues. This last stage is extremely difficult to reverse, except perhaps with the help of Extra-Corporeal Membrane Oxygenation. This equipment can remove the increased $PaCO_2$, thereby increasing and normalizing the pH and elevating the PaO_2. The problem is that the lung cannot rapidly recover until inflammation and the exaggerated immunity response are diminished. The ensuing fibrosis represents a pathological tissue reaction failing to recover the anatomical lung architecture and function. The implications of this process result in pulmonary insufficiency during exercise after recovery from this acute stage. According to the Oxygen Transport Triad, the only energy-efficient survival mechanism, in this case, is the increase in the number of red blood cells, hematocrit, and hemoglobin [5]. When going to high altitude, this life-saving response takes time (40 days for complete hematologic adaptation after traveling from sea level to 3500m). This is because increasing millions of red blood cells is a time-dependent logarithmic process resulting from increased erythropoietin and the organism's limited capacity to produce new cells. Unfortunately, the belief

that the rise in hematocrit is dangerous in all cases still prevails. Conversely, we consider it a normal physiological adaptation to a low inspired oxygen pressure at high altitudes, even during disease.

Understanding the genomics analysis of the virus can provide clues as to the treatment strategies [6]. From the pathophysiological view, we propose that treatment for COVID-19 should be based on improving the Tolerance to Hypoxia (Hemoglobin factor), decreasing inflammation and hyper-immune reaction, and the concomitant use of oxygen, antibiotics, rehydration, and anticoagulation drugs [7].

CONCLUSION

Knowing the pathophysiology of pneumolysis in COVID-19 and future alveolar-compromising viral diseases is fundamental to understanding the body's compensating mechanisms for coping with acute and chronic hypoxia-related diseases.

DECLARATION OF INTEREST

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