



Pneumolysis and “Silent Hypoxemia” in COVID-19

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Abstract COVID-19 can evolve to a severe lung compromise with life-threatening hypoxemia. The mechanisms involved are not fully understood. Their understanding is crucial to improve the outcomes. Initially, past-experience lead to the implementation of standardized protocols assuming this disease would be the same as SARS-CoV. Impulsive use of ventilators in extreme cases ended up in up to 88% fatality. We compare medical and physiological high altitude acute and chronic hypoxia experience with COVID-19 hypoxemia. A pathophysiological analysis is performed based on literature review and histopathological findings. Application of the Tolerance to Hypoxia formula = Hemoglobin/PaCO₂ + 3.01 to COVID-19, enlightens its critical hypoxemia. *Pneumolysis* is defined as progressive alveolar-capillary destruction resulting from the CoV-2 attack to pneumocytes. The adequate interpretation of the histopathological lung biopsy photomicrographs reveals these alterations. The three theoretical pathophysiological stages of progressive hypoxemia (silent hypoxemia, gasping, and death zone) are described. At high altitude, normal low oxygen saturation (SpO₂) levels (with intact lung tissue and adequate acid–base status) could be considered *silent hypoxemia*. At sea level, in COVID-19, the *silent hypoxemia* starting at SpO₂ ≤ 90% (comparable to a normal SPO₂ {88–92%} at 3500 m)

suddenly evolves to critical hypoxemia. This, as a consequence of progressive *pneumolysis* + inflammation + overexpressed immunity + HAPE-type edema resulting in pulmonary shunting. The proposed treatment is based on the improvement of the Tolerance to Hypoxia (Hemoglobin factor), oxygen therapy, inflammation reduction, antibiotics, antitussives, rehydration & anticoagulation if required. Understanding the pathophysiology of COVID-19 may assist in this disease’s management.

Keywords HAPE · Tolerance to hypoxia · SARS-cov-2 · Pneumolysis · EPO · Open circuit earth space suits

Introduction

COVID-19 has been referred to as the most significant public health crisis since World War II [1]. Fifty years of experience treating patients at high altitude are useful in explaining the critical hypoxia encountered in COVID-19, causing countless deaths. With current ineffective viral treatment along with a poor understanding of hypoxia, the devastation continues. COVID-19, a multifaceted disease, was initially considered a SARS (Severe Acute Respiratory Syndrome) “pneumonia” inducing ventilator use. However, up to 88.1% died on ventilators in New York [2]. An initial lower high altitude incidence may be due to extreme ultra-violet radiation [3] and other climatologic conditions. Additionally, high altitude physiological adaptation such as downregulated ACE2 receptor expression [4] and higher tolerance to hypoxia [5] may play a role.

In COVID-19, similarities to High-Altitude Pulmonary Edema (HAPE) were observed. Nevertheless, with adequate treatment, HAPE reverts within a few days, leaving no sequelae. Conversely, unlike pneumonia, CoV-2

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induces rapid lung inflammation and alveolar-capillary destruction [6, 7] as described in a recently submitted paper: “COVID-19 simulating extreme high-altitude exposure with altered oxygen transport physiology, multiple diseases, and scarce need of ventilators: Andean Condor’ s-eye-view”.

We propose that alveolar-capillary destruction should be named *pneumolysis* (pneumo = lung; lysis = destruction), resulting in progressive hypoxemia, subsequent hypercapnia, and pulmonary shunts [8]. These lead to critical hypoxia, and if the patient survives, he can develop pulmonary fibrosis and sequelae. Furthermore, as hypoxia progresses, simulating a fast Mt. Everest ascent, it could trigger pulmonary hypertension and, consequently, HAPE-type edema in the remaining intact lung tissue, further aggravating the hypoxemia.

Pneumolysis should not be confused with “pneumonolysis”. Pneumonolysis was a term mostly used in the middle of the XXth century. It referred to the surgical separation of the parietal pleura and fascia of the chest wall (*extrapleural pneumonolysis*), or the separation of the visceral and parietal layers of the pleura (*intrapleural pneumonolysis*), in pulmonary tuberculosis [9].

Histopathology

Lung biopsy histopathological findings of a patient suffering from severe COVID-19 are shown in the photomicrographs in Fig. 1. The patient was extubated before the biopsy. The microbial culture revealed *Acinetobacter*

Baumannii, a Gram-negative bacillus that is aerobic, pleomorphic, and non-motile (opportunistic pathogen frequent among immunocompromised individuals). Three days later, his condition deteriorated, so he was intubated once more and passed away 14 days later. The pathological findings were: intra-alveolar Masson Body, which is a histomorphologic hallmark of organizing pneumonia. However, it is also associated with other conditions, such as the proliferative phase of diffuse alveolar damage, which seems to be the case in COVID-19. Pneumocytes nuclear atypia also described, in our criteria, could be due to the alterations resulting from CoV-2 entrance into pneumocytes for self-replication. The presence of RBCs in the alveoli shows the hemorrhage, possibly resulting from capillary stress failure due to pulmonary hypertension secondary to intense hypoxemia. Likewise, it could be due to the Pneumolysis itself, compromising the capillaries, producing capillary fragility. The severe lung pneumocyte damage and secondary superinfection are shown in Fig. 1. These microabscesses could explain the effectiveness of the use of Azithromycin and other antibiotics.

Pathophysiology

The pneumolysis in incipient disease could give rise to *Silent hypoxemia*. Cov-2 incubation time takes longer (4–7 days) than other coronavirus or influenza virus. Initially, incipient hypoxia induces gradual pulmonary hypertension and alveolar recruitment. The oxygen dissociation curve fulfills the oxygen demand, with minimal

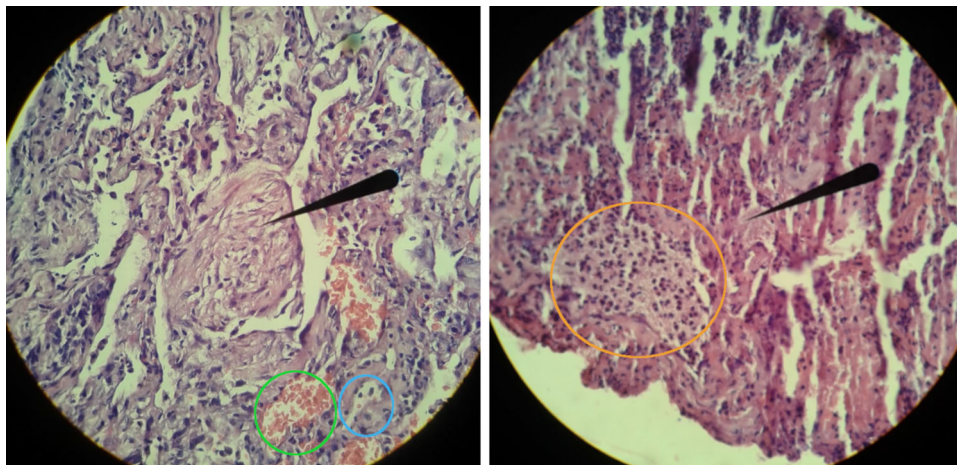


Fig. 1 *Left.* Photomicrograph of a lung biopsy from a patient suffering from severe lung compromise (pneumolysis) in COVID-19. The black arrow shows the presence of a Masson Body inside an alveolus. In the green circle, alveoli are filled with red blood cells, possibly resulting from intra-alveolar hemorrhage. In the blue circle, the thickened interstitium resulting from fibrosis is shown. *Right.* Photomicrograph of a COVID-19 lung biopsy showing pneumolysis.

The black arrow points to hyaline type membranes that can result from the fibrinous exudate and necrotic debris of cells. In the orange circle, a microabscess with pneumocystis can be appreciated. Nuclear atypia in the pneumocytes can also be observed. Photo and pathological analyses are courtesy of Dr. Felipe de Jesus Montelongo (Intensivist) and Dr. Manuel Gabriel Romo Sanchez (Pathologist) from the Hospital General de Ecatepec Las Americas, ISEM, México

increase in ventilation, adjusting PaCO₂ levels (which is 20 times more diffusible than oxygen), maintaining a normal acid–base status. COVID-19 extreme hypoxia is similar to acute exposure to the summit of Mt. Everest, where the PaO₂ = 24.6 mmHg [10]. As pneumolysis progresses, hyperventilation increases gradually, possibly reducing the PaCO₂; however, once the lung becomes more severely compromised, ventilatory insufficiency gives rise to an increase of the PaCO₂, acidosis, and along with a low hemoglobin count [7, 911], respiratory distress and “gasping” occurs. Possible ventilation, PaO₂, PaCO₂, and pH changes in pneumolysis can be divided into three theoretical pathophysiological stages: (1) *Silent hypoxemia*, (2) *Gasping and* (3) *Death zone* (Fig. 2). Superimposed edema, inflammatory, and immune reaction with pulmonary shunts in COVID-19 with a low hemoglobin count [9], can aggravate hypoxemia. Tolerance to hypoxia (depending on high hemoglobin and a low PaCO₂) rapidly decreases, thereby ending life (Fig. 3) [5].

At high altitude, we live in permanent “*Silent hypoxemia*”. We ventilate slightly more than at sea level, but it is unnoticeable. Adequate acid–base balance is crucial [13]. La Paz (3100–4100 m), Bolivia, residents have perfectly healthy lives with tolerable hypobaric hypoxic levels: SpO₂ = 90% (> 98% standard at sea level). This value is remarkably similar to SpO₂ < 90% (even with FIO₂ 60%) in COVID-19 patients requiring ventilators at sea level. Likewise, when sea level travelers arrive at La Paz, their SpO₂ drops to around 88–92% and around 25% of them can present mild Acute Mountain Sickness (AMS).

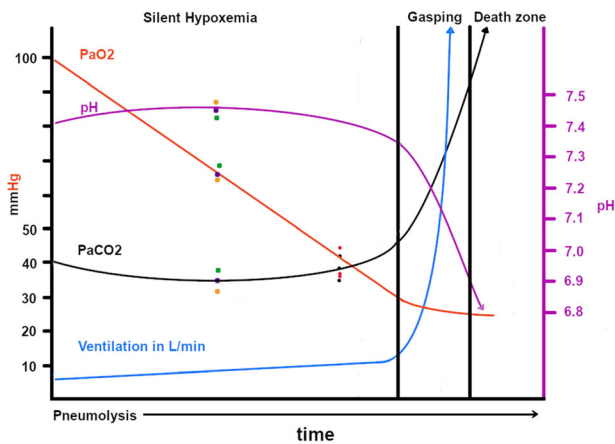


Fig. 2 Progressive COVID-19 lung compromise and expected schematic diagram showing the *three theoretical pathophysiological stages of pneumolysis*: Silent hypoxemia, Gasping and Death zone. Pneumolysis and Acid–Base alterations lead to severe hypoxemia, hypercapnia, acidosis, and the loss of life. The three set of points on the left (orange, purple and green) were obtained from data at https://www.youtube.com/watch?v=_KMLW8eO0q0 by Dr. Shiv Kumar Singh. The 3 (red and black) points on the right were obtained from [12]

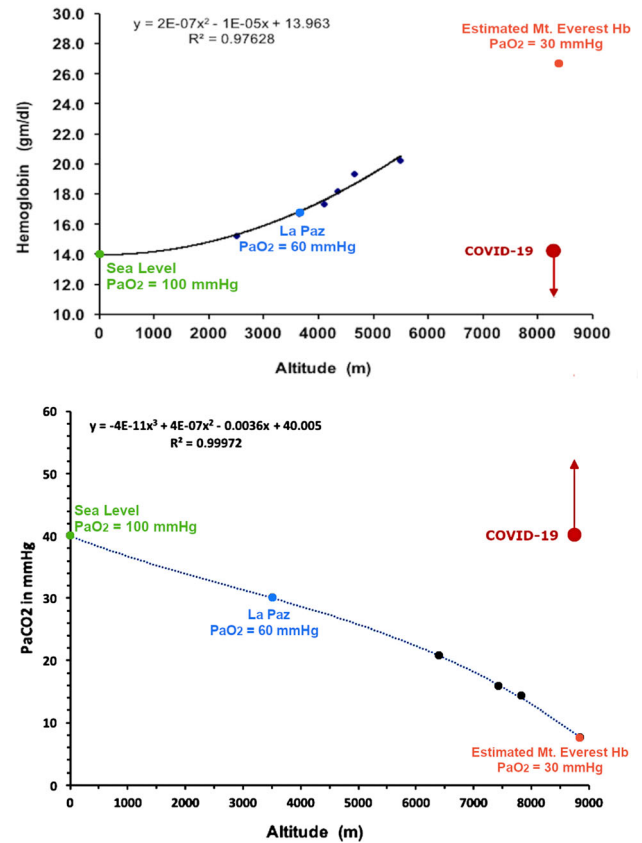


Fig. 3 Tolerance to Hypoxia = $(Hb/PaCO_2) \times 3.01$. Shown here are the two variables and the probable COVID-19 behavior. A) Hemoglobin–Altitude, B) PaCO₂–Altitude. Red arrows: acute hypoxia in COVID-19 pneumolysis, at sea level, simulating Mt. Everest extreme hypoxia, with hemoglobin and PaCO₂ values progressing oppositely to expected optimal life-sustaining physiology under chronic hypoxic conditions

Spontaneous resolution or adequate treatment resolves AMS in a couple of days. The other 75% are asymptomatic at rest with mild hyperventilation (almost unnoticeable) and some tachycardia, but can feel shortness of breath upon increasing physical activity or climbing stairs. This, until hemoglobin rises to the optimal level [14]. Patients living at high altitudes with SpO₂ > 85%, are generally asymptomatic. Chronic low SpO₂ at high altitude is compensated with a higher hematocrit as in Chronic Mountain Sickness (CMS), precisely referred to as *poly-erythrocythemia* (poly = many, erythrocyt = red blood cells, hemia = in the blood) [15]. Poly-erythrocythemic patients can sustain breath-holding far longer than normal hemoglobin count subjects [16]. They can even survive with a Mount Everest summit-like PaO₂ = 35 mmHg [15]. The RBCs increase in poly-erythrocythemia is an adaptation process of lung, heart, and other underlying diseases to a chronic hypobaric hypoxic environment [15]. Despite increased blood viscosity, circulation time in these patients is not altered [17].

At sea level, post-COVID-19 patients with resulting lung fibrosis could also develop sea level poly-erythrocythemia (higher than normal hemoglobin values) [15] and reduced tolerance to exercise. At high-altitude, blood flow compensating mechanisms such as elevated erythropoietin production (potent vasodilator nitric-oxide stimulator) and perhaps angiogenesis [6], facilitate increased RBC transport. Endothelial compromise due to ACE2 binding by the virus could lead to platelet site aggregation resulting in thrombus formation. At 3500 m, normal hemoglobin count for men is 16 g/dl, and for women 14 g/dl. At sea-level, with progressive pneumolysis, normal hemoglobin count cannot supply sufficient oxygen to the tissues. Furthermore, mild anemia can be a significant disadvantage in a COVID-19 infection [11]. In these pandemic times, asymptomatic patients with low pulse oximetry values (< 90% at sea level and < 85% at 3,600 m) should be considered probable COVID-19. Pulse oximetry checks in public places should be mandatory.

Death rate tends to increase, following CoV-2 infection, in the presence of underlying conditions such as cancer, obesity, diabetes, old age, type-A blood, and others [18]. Antibiotic overuse with microbiome alterations could also be associated with a deficient immune system [19]. Chronic inflammation processes determine the permanent production of cytokines, interleukins, and other inflammatory molecules [20]. Likewise, “healthy” subjects suffering from asymptomatic underlying inflammation could have an over-reactive capacity to produce an abundance of inflammatory markers that add to the inflammation triggered by the virus. The so-called “cytokines storm” reaction could thus be explained (chronic inflammation + acute inflammation). Likewise, comorbidity in any disease implies worse outcomes. The inflammatory changes and immune dysregulation could give rise to irreversible damage [20]. Fast contagion of susceptible and immunosuppressed individuals could explain the epidemiological curve peak and subsequent fall, interpreted as nature’s cleansing.

COVID-19 lung CAT scans include a well delimited heterogeneous significant compromise simulating a “sheer curtain” image, rather than “ground glass”. This image suggests interstitial edema and localized inflammatory hemorrhagic processes [6] due to viral pneumolysis (Fig. 1). Many aspects of the evolution of these patients need to be further studied. A periodic follow-up of PaCO₂ levels and/or ETCO₂ could help give a clearer picture. It is also possible that once the PaCO₂ starts rising, the speed of the rise could be of prognostic value. The SpO₂ drop slope could also give a prognosis if followed carefully.

Treatment Proposal

We propose early administration of erythropoietin (EPO) 4000 IU, IV once or twice a week and/or blood transfusions depending on the severity. Hyperimmune plasma therapy should also be considered to be administered as whole blood, improving the hemoglobin levels and tolerance to hypoxia, provided there is a compatible blood typing. At high altitude, in the High Altitude Pulmonary and Pathology Institute (HAPPI-IPPA), for a couple of years, EPO has been used to improve the life quality of patients with pulmonary fibrosis or central ventilation alterations. Erythropoietin will not only stimulate RBC production but also help effective oxygen transport through nitric oxide stimulation, neuroprotection, and multiple-organ hypoxemia protective effects. These can be favorable in COVID-19 [21, 22]. Erythropoietin administration had positive results in one COVID-19 patient [23]. Thus raising the hemoglobin count strengthens the oxygen reservoir countering hypoxia.

At sea level, patients with a SpO₂ < 95% (at 3500 m SpO₂ < 85%), should immediately be placed on oxygen via nasal prongs, to avoid HAPE-type superimposed edema (superimposed pulmonary shunt), and rapid progression of hypoxemia. Waiting for diagnosis and treatment can lead to advanced pneumolysis. Adequate oral hydration is mandatory, as dehydration can result in additional clot formation. Prompt use of anti-inflammatory drugs such as acetylsalicylic-acid and corticosteroids, antibiotics due to superinfection, antitussive medication (promoting lung rest as bronchi are not compromised, nor is this a sputum productive pathology), and anticoagulants should also be considered.

Finally, we suggest a novel short-term strategy: “Earth open-circuit astronaut-resembling suits” with adequate outside air viral electric filtering re-breathing mechanisms to return to work and daily activities. This system could reduce contamination risk significantly. The increasing number of infections could be flattened without a quarantine. If built massively at lower prices, the economy could recover until immune supremacy takes over.

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Compliance with Ethical Standard

Conflicts of interest The authors declare that they have no Conflict of interest.

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