

# Pulmonology phenotype acts strangely

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### ABSTRACT

When compared to other recognised respiratory illnesses, the SARS-CoV-2 pneumonia light phenotype acts strangely and is less understood. We think that early COVID-19's histological characteristics can be regarded as the disease's pathophysiological distinguishing feature. Alveoli in lung cryobiopsies are nearly unblemished, and there are dilated post capillary pulmonary venules in addition to enlarged/hyperplastic alveolar capillaries.

Therefore, blood overflow near well-ventilated alveoli could explain hypoxemia by causing a decrease in the typical V/Q ratio. This could shed light on type L COVID-19's usual symptoms, including joyful hypoxemia, prone positioning in response to wakefulness, CPAP and PEEP responsiveness, and platypnea orthodeoxia.

**Key Words:** *Respiratory failure; COVID-19; ARDS; Cryobiopsy, Ventilation perfusion ratio*

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### INTRODUCTION

The first cases of an unidentified pneumonia were discovered in Wuhan, the Chinese province of Hubei, at the beginning of December 2019. Due to its similarities to the SARS-CoV, the virus that caused the SARS epidemic in 2002–2003, and the Middle East Respiratory Syndrome virus, the pathogen that causes this new disease was identified as a novel member of the RNA betacoronavirus family and was given the name Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (MERS-CoV). Following this, the illness brought by SARS-CoV-2 infection was referred to as "coronavirus disease 2019." (COVID-19). The clinical severity of COVID-19 ranges widely. Severe and critical cases typically present with bilateral interstitial pneumonia, which appears to fit the Berlin definition of Acute Respiratory Distress Syndrome. Mild disease is typically seen in approximately 81% of patients, while severe or critical forms are found in 14 and 5% of patients, respectively (ARDS). The COVID-19 pandemic first affected a western nation, Italy. End of February 2020 saw the discovery of the first case, and shortly afterward, the Northern provinces' hospitals were overrun by thousands of patients. Patients frequently required hospital admission, and many of them required mechanical ventilation, supplemental oxygen, and intensive care unit (ICU) style respiratory support.

When SARS-CoV-2 started to spread throughout our nation, we thought we were going to see an increase in interstitial pneumonia cases that, from a pathophysiological standpoint, were comparable to those brought on by influenza viruses, cytomegalovirus, or *Pneumocystis jirovecii*, among other pathogens. Each of us imagined patients in respiratory distress with rapidly deteriorating clinical circumstances who would need to be referred to the intensive care unit (ICU) right away. In the ICU, protective invasive mechanical ventilation, pronation, as well as Extra Corporeal Membrane Oxygenation (ECMO) [1-3].

We were all shocked to encounter utterly unanticipated patients as soon as COVID-19 patients began to be admitted to our hospitals. Many of them didn't even mention their dyspnea symptoms. Despite horrifying CT scan results or alarmingly low PaO<sub>2</sub>/FiO<sub>2</sub> ratios, there is no feeling of being out of breath, no quick shallow breathing, and no demand for accessory breathing muscles. The way the lungs of these patients responded to artificial breathing was also unexpected. We saw an unanticipated respiratory response, as if the lungs were "soft" rather than "stiff," as they should be in ARDS, in the rare cases where we were forced to treat with Non Invasive Ventilation (NIV) as a bridge to intubation or for lack of alternative options. Our beliefs were challenged by the utterly unexpected clinical and pathologic behaviour this disease displayed. But it was only a matter of time until these merely subjective experiences were verified by science. In fact, Gattinoni et al. published a very intriguing report in *Critical Care* in April 2020 titled "COVID-19 pneumonia: ARDS or not? ". In this

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article, the authors propose that COVID-19 ARDS can be classified into two pathophysiological phenotypes: the so-called light phenotype (type L) and the heavy phenotype (type H). Low ventilation/perfusion ratio (V/Q ratio), low weight, and low reclinability are all characteristics of the light phenotype that sustain lung compliance (low elastance, i.e. high compliance). Gattinoni himself described a cohort of 16 critically ill patients, with relatively normal lung compliance (50,2 14,3 ml/cm H<sub>2</sub>O) despite a drastically increased shunt fraction (0.5 0,11). This phenotype is typical of the early stage of the disease, but it can also be seen in some severe instances. A difference this large is not typical of ARDS [4].

High lung elastance (low compliance), high right-to-left shunt, high weight, and high reclinability are all characteristics of the type H phenotype. The final stages of the disease frequently exhibit this characteristic. Patients that exhibit this phenotype typically have more severe symptoms and have a state that is strikingly similar to conventional ARDS. The H phenotype has the same histological characteristics as ARDS, including diffuse alveolar damage (DAD), interstitial and alveolar proteinaceous edema, hyaline membranes, alveolar type II cells hyperplasia, and eventually, myofibroblastic proliferation and collagen deposition. Pneumony embolism was the primary cause of death in almost one-third of cases in one research, but considerable numbers of macro- and microthrombi have been recorded in several autopsy datasets [5]. These data point to an essential involvement of hypercoagulability in COVID-19, especially in the more severe condition, despite the fact that the considerable increase of thrombotic events in DAD attributable to COVID-19 compared to other causes of DAD has been contested. There is little information available on the L phenotype, which appears to have a distinct behavioural pattern distinct from other known respiratory disorders. We think that the histopathological characteristics of early COVID-19, which are mirrored in HRTC scan findings<sup>15</sup>, could explain the pathophysiological hallmark of the L Type of SARS-CoV-2 pneumonia. While many scientific papers proposed intriguing pathophysiological hypotheses and brilliant inferences, only a few studies actually documented what is happening in the lung [6]

We looked at 12 Covid-19 patients' histopathologic and immunological molecular characteristics when their sickness was still in its early stages (around 20 days after the onset of symptoms). They were all subjected to transbronchial cryobiopsy. These samples' intriguing properties, which differed significantly from those of the normal DAD, were revealed by morphological analysis.<sup>16</sup> Interstitial capillaries exhibited hyperplasia in the lung tissue. Postcapillary venules exhibited thicker, edematous walls and were twisted and dilated without vasculitis symptoms. In addition to platelet aggregates, we also identified additional indicators of endothelial dysfunction, such as upregulation of PD-L1 and indoleamine 2,3 dioxygenase-1 (IDO-1), although microthrombi were only occasionally observed<sup>16</sup>. But all of our patients received at least a prophylactic dose of heparin, which may have lessened this effect. Infiltration of perivascular CD4 T lymphocytes, patchy alveolar type II cell hyperplasia, and intra-alveolar accumulation of macrophages with a hybrid phenotype were additional strange characteristics.<sup>16</sup> Angiotensin converting enzyme 2 (ACE 2) receptor research was also carried out in the work by Dogliani C et al.<sup>16</sup> in lung tissue (data not published). Type 2 alveolar cells and endothelial cells, on the other hand, showed normal expression of ACE 2. IDO-1 was overexpressed by endothelial cells that enclose venules and alveolar capillaries. This enzyme plays a role in controlling vascular remodelling and tone. When overexpressed, it can maintain the pulmonary venules relaxation and capillary hyperplasia reported in our series. Additionally, normal DAD signs were uncommon or nonexistent. Hyaline membranes were absent, and only sporadic spots of intra alveolar proteinaceous oedema were seen [7].

Can the mechanism and clinical manifestation of the L phenotype be explained by the early COVID-19 histological hallmarks? is the important question that this research seeks to address. We will pay special attention to clinical traits such the so-called "happy hypoxemia," the reaction to awake prone positioning, the response to positive end expiration pressure (PEEP) or continuous positive airways pressure (CPAP), and reports of patients with platypnea orthodeoxia. As was already established, the alveoli in our lung samples were not atelectatic and lacked hyaline membranes. The alveolar side of the alveolar capillary barrier is therefore virtually completely intact. Vascular structures, on the other hand, seem to have undergone a significant rearrangement. Blood can overflow around these nearly perfect alveoli as a result of pulmonary venodilatation, pulmonary capillary dilation, and capillary hyperplasia. As a result, the ventilation/perfusion ratio (V/Q) is decreased since perfusion is increased while ventilation is maintained. This may be the primary cause of hypoxia in the COVID-19 L phenotype. Alveoli did not appear to be collapsed or obliterated, hence it is doubtful that atelectasis played a substantial role in the respiratory failure of COVID-19 [8].

Given the nearly complete absence of microthrombi in our lung samples and the lack of pulmonary embolism of bigger veins on computed tomography pulmonary angiography (CTPA), which all patients received prior to the cryobiopsy, the "dead space" effect appears to play a little role. Lang et al findings, which used a dual energy CT scan to demonstrate hyper perfusion in the afflicted areas in the mild forms of SARS-CoV-2 interstitial pneumonia, support this theory. Unquestionably, this is among the most intriguing clinical characteristics of COVID-19 patients. Numerous patients exhibit severe arterial hypoxia without correlating respiratory distress symptoms. A perception of dyspnea is not often expressed verbally. "Happy dyspnea" is the term used to describe this phenomenon. Without enhanced alveolar ventilation, Tobin et al. showed 3 cases of extreme "happy hypoxemia." Guan reported dyspnea in just 18,7% of 1099 hospitalised COVID-19 patients, despite low PaO<sub>2</sub>/FiO<sub>2</sub> ratios and abnormal CT scans. With a visual severity score of 16/20, the CT scan, which was performed 15 days following the onset of symptoms, reveals bilateral ground glass/crazy paving attenuation. In order to treat the patient's severe hypoxemic respiratory failure, CPAP therapy was initiated. according to the patient had severe respiratory failure while receiving CPAP, and they were tachypneic. A multipurpose nasogastric tube with a specialised pressure transducer allowed us to monitor the swing in esophageal pressure (Pes), even when tidal volume could not be measured (NutriVent Sidam Group).

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