

# COVID-19 Pneumonia Subphenotyping: How does it Impact the Respiratory Care of Patients and how should we Act

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## ABSTRACT

Gattinoni et cols released an editorial describing two phenotypes of COVID-19 pneumonia: Type L, which was described as an “*atypical pneumonia*”, and Type H, that had characteristics of a typical acute respiratory distress syndrome (ARDS). This paper had big repercussion amongst academical community. According to Gattinoni, it is admissible to ventilate Type L patients with tidal volumes up to 9ml/kg. What should clinicians do at bedside?

**Keywords:** COVID-19 pneumonia, Atypical pneumonia, Baby lung, Transitioning type, Type L, Type H.

## Abbreviations

ARDS: Acute Respiratory Distress Syndrome; COVID-19: Coronavirus Disease 2019; CPAP: Continuous Positive Airway Pressure; FiO<sub>2</sub>: Inspired Fraction of Oxygen; HFNC: High Flow Nasal Canulla; NIV: Non-Invasive Ventilation; PaO<sub>2</sub>: Partial Pressure of Oxygen; P-SILI: Preeure Self-Inflicted Lung Injury; RCT: Randomized Clinical Trial.

## INTRODUCTION

The year of 2020 will be forever in the memories of humanity, specially healthcare workers. The fight against COVID-19 has been ruthless, and many did not survive the disease. Since the beginning of the SARS-CoV-2 pandemic, social distancing measures had tremendous economic impact in many countries. The Bureau of Economic Analysis announced a decrease of 32.9% in the real gross domestic product (GDP) of the United States of America<sup>1</sup> during second quarter of 2020, pointing the catastrophic effect of the virus in economy, not to talk in the loss of human lives. The world already has more than 20 million COVID-19 cases, with over 700.000 deaths,<sup>2</sup> that motivated changes in the way of living globally. The occurrence of coronaviruses as an emerging and reemerging infection throughout the world has already been described more than 13 years ago,<sup>3</sup> and, as predicted, we have been facing outbreaks with shorter intervals. Very likely, we will be battling other

pandemics in the coming years.

COVID-19 is a systemic entity, that can manifest itself with mild symptoms, such as fever, cough,<sup>4</sup> and even gastrointestinal features,<sup>5</sup> but can develop into a severe viral pneumonia, with grave hypoxemia, septic shock, and acute kidney injury. In April 2020, Gattinoni et cols published an editorial,<sup>6</sup> describing different phenotypes for the COVID-19 pneumonia, based on observation and discussions with colleagues. They proposed a categorization, with two basic types of viral pneumonia: types L and H.

## GATTINONI'S PHENOTYPES

Type L presents with (1) low elastance, (2) low ventilation-to-perfusion ratio, (3) low lung weight and (4) low lung recruitability. The amount of gas in the lung is nearly normal, and the hypoxemia could be explained by the loss of regulation and perfusion, and by the loss of hypoxic vaso-

constriction. CT scan would reveal only ground-glass densities, mainly located subpleurally and along the lung fissures, and consequently, lung weight would only moderately be increased. As the non-aerated tissue is very low, recruitability is very low.

Type *H* is a phenotype with ARDS characteristics: (1) high elastance, (2) high ventilation-to-perfusion, (3) high lung weight and (4) high lung recruitability. Increased lung edema reduces the gas volume in the lungs, increasing elastance. The superimposed pressure of the non-aerated areas promotes high ventilation-to-perfusion *ratio*, with high right-to-left shunt. Remarkably, CT scans show an increase of more than 1.5 kg, and the increased amount of non-aerated tissue is associated with increased recruitability.

The transitioning between the phenotypes would be related to self-inflicted lung injury (P-SILI), that is linked to an increased tidal volume and depth of negative intrathoracic pressure. As the patient progressively makes more effort breathing, P-SILI worsens, and so does the lung edema, due to inflammation and elevated lung permeability. The suggested treatment for Type *L* is, initially, the reverse of hypoxemia, offering increased FiO<sub>2</sub>, and high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV) for those with dyspnea. It is recommended that the work of breathing is measured, either through esophageal manometry or swings of central venous pressure. An esophageal pressure swing above 15 cmH<sub>2</sub>O is considered to increase the risk of lung injury, and should be a threshold not to postpone intubation. According to Gattinoni et cols, once intubated and deeply sedated, one could ventilate a Type *L* patient with tidal volumes up to 8-9 ml/kg, since lung compliance is high, and the strain is tolerable, even with volumes greater than 6ml/kg. There would be no indication for high PEEP, since the recruitability is low. Type *H* should be treated as severe ARDS, with high PEEP, prone positioning and extracorporeal support, if necessary.

## CRITICISM TO GATTINONI

Fan *et cols* criticized Gattinoni's paper, questioning the existence of the phenotypes and different approaches to both types. In this viewpoint paper,<sup>7</sup> they argue that COVID-19 is, at the end of the day, ARDS. Since Gattinoni had nearly one third of patients with type *H* pneumonia, it would not be expected that reports from New York City,<sup>8,9</sup> Seattle<sup>10</sup> and Boston<sup>11</sup> had found median lung compliance values between 26 and 35 ml/cm H<sub>2</sub>O, that are totally usual for ARDS patients. This values do not corroborate the existence of the Type *L* phenotype, specially if the proportion of cases is around 1/3 for Type *H* and 2/3 for Type *L*.

Martin J. Tobin wrote an editorial for *Chest*,<sup>12</sup> criticizing the very necessity of diagnosing ARDS in COVID-19 patients. Tobin argues that ARDS has been a questionable entity throughout the years, with its constituents, such as radiologic criteria, having lack of agreement amongst researchers.<sup>13</sup> Hypoxemia indices may fluctuate in patients with ARDS. Patients with all the criteria were no longer categorized as ARDS after receiving 100% oxygen for 30 minutes, causing the PaO<sub>2</sub>/FiO<sub>2</sub> *ratio* to increase.<sup>14</sup> On Tobin's opinion, all the discussion is a distraction, and does not substitute the bedside care, testing changes in the mechanical ventilator and observing its consequences on plateau pressure, pressure waveform, blood pressure and other parameters. The only consequence on making ARDS diagnosis would be avoiding volumes as high as 12ml/kg, since we have strong evidence on ventilating with volumes with no more than 6ml/kg.<sup>15</sup> There is a grey zone between 6 and 11ml/kg, and

we don't have enough evidence that ventilating patients with 6ml/kg or between 6 and 11ml/kg makes any difference on the outcomes.

Bos *et al* contested the subphenotyping of the disease, stating that the retrospective analysis of 70 patients in their ICU<sup>15</sup> showed no correlation between lung weight and compliance in patients with COVID-19 related ARDS. Most patients showed mixed features between the phenotypes, and their lung compliance was similar to the non-COVID-19 ARDS.

## GATTINONI'S REPLY

Gattinoni replied to his critics in an editor letter,<sup>16</sup> remarking that the phenotypes are extremes of a broad spectrum of manifestations in COVID-19 pneumonia. The *L* phenotype would be the early one, representing the "atypical" ARDS, characterized by lower elastance, lower V/Q *ratio*, lower recruitability and lower weight. The *H* phenotype would be the late one, characterized by higher lung elastance, higher right-to-left shunt, higher recruitability and higher lung weight. The transition between both would be related to the natural course of the disease and to Patient-Self Induced Lung Injury (P-SILI). He hypothesizes that the disparity between his cohort and the ones in the american ICU's is related to the fact that many patients are coming to the hospitals in late phases of the disease, with type *H* phenotype. He also remarks that the *L* type has a hypoxemia with far more lung gas volume than what is found in ARDS "baby lung", which would be related to the viral assault on the endothelium, accounting for pulmonary vascular dysregulation and hypercoagulable state. Finally, he remembers three large RCT's that found no differences between patients treated with tidal volumes around 7 versus 10ml/kg.<sup>17-19</sup>

## CAN WE VENTILATE TYPE L PATIENTS WITH TIDAL VOLUMES UP TO 9ML/KG, AFTER ALL?

There is no doubt that COVID-19 can be the cause of typical ARDS. The hot topic resided on the existence of Type *L*, and the suggestion of ventilating those patients with volumes up to 8-9ml/kg. Is it acceptable after all?

To answer that question, we must think about what we have learned about ARDS in the last decades. Although Tobin's statement that the constituents of ARDS criteria could fluctuate in the real world, and the fact that these imperfect criteria are part of a categorization created by physicians in order to simplify a complex condition, there are some assumptions we could make. We already know that tidal volumes up to 6ml/kg are quite safe.<sup>20</sup> Much of the learning we did about ARDS was about what we shouldn't do, and using high tidal volumes is definitely in the list. Protective ventilation was a big innovation on the matter, reducing mortality of this dramatic syndrome.<sup>21</sup> Although Gattinoni's description of the Type *L* pneumonia seems veridical, it is not easy to determine if volumes higher than 6ml/kg could trigger the development of typical ARDS in COVID-19. In order to settle this association, RCT's are necessary. Gattinoni's editorial was actually about 3 phenotypes: Type *L*, Type *H* and the "transitioning type" between the first two. Despite the academical debate, there are important questions that the intensive care physician at the bedside would certainly like to have an answer: (1) What should be the criteria to start a full protective ventilation on Type *L*? (2) How could a doctor at bedside detect that the patient is already transitioning into Type *H*, before lung compliance is already downhill,

along with PaO<sub>2</sub>/FiO<sub>2</sub> ratio? (3) Is it not safer to stay within the limits of 6ml/kg, considering that the moment when the transitioning into typical ARDS starts is not completely elucidated?

The answer to the first two questions needs a RCT, analyzing two groups with Type *L* patients receiving mechanical ventilation. Control group would receive protective ventilation, and the intervention group would be on tidal volumes up to 8-9ml/kg. This configuration enables the comparison on outcomes, and the possibility of detecting the evolution of both groups into Type *H*. It would not be easy to enroll patients into the study, since Type *L* that needs mechanical ventilation is a very specific kind of patient. Most of them would be treated with non-invasive ventilation or HFNC, and the necessity of mechanical ventilation could be an indication that they are already transitioning into Type *H*. What would be the threshold on elastance, lung weight and PaO<sub>2</sub>/FiO<sub>2</sub> ratio to determine that the transitioning is on course? And how could we access lung weight on these patients, without exposing them to multiple CT scans? These questions are hard to answer, and could bring indecisions to clinicians. We must take under consideration that many patients already have lung diseases, such as chronic obstructive pulmonary disease, that could lead to misinterpretations on the compliance and elastance values, making the task even harder.

Answering the third question is not so hard. Acknowledging that we have many doubts on the pathophysiology of the disease, and that we are dealing with patients with multiple comorbidities and organ dysfunctions, it is advisable to take a more conservative strategy at this moment. As Tobin stated on his editorial, “the mindset for care at the bedside is antithetical to that needed for conducting a clinical trial”. This could not be more appropriated at this time, when we are in the midst of a pandemic, with high levels of uncertainty about the disease. Giving the lung a gentle ventilation, avoiding tidal volumes higher than 6ml/kg seems the most reasonable management at the moment, even though we know that this will not be possible in all cases. Sometimes, we might have to deal with special situations, like a persistent hypercapnia, with important respiratory acidosis. Keeping these patients well sedated, sometimes under neuromuscular blockade<sup>22</sup> and with protective ventilation is probably the best we can do at this point.

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