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Short Commentary

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Mechanisms of Oxygenation Response to Prone Positioning and Recruitment Maneuvers in COVID-19 Pneumonia

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Abstract

In COVID-19 pneumonia, uncertainty still exists on the "best" respiratory treatment, despite thousands of published papers. Most of them, unfortunately, deal with epidemiology instead of the underlying physiologic mechanisms. Three mechanisms may lead to hypoxemia: venous admixture (through atelectatic/consolidated lung regions), intra-cardiac shunts, and bronchial anastomosis. In early-stage COVID-19 patients, venous admixture cannot account for the observed hypoxemia due to the lack of sufficient atelectasis. For the same reason, recruitment maneuvers and prone positioning may also be ineffective. Impaired perfusion distribution due to the loss of pulmonary vascular regulation and flow through bronchial anastomoses may better explain the observed hypoxemia.

Keywords: *Prone positioning; Recruitment maneuvers; COVID-19; ARDS*

Abbreviations: *ARDS: Acute Respiratory Distress Syndrome; Va/Q: Ventilation-Perfusion; PEEP: Positive End-Expiratory Pressure*

Introduction

At the time of writing this manuscript (August 2022) a PubMed search performed using the strings "COVID-19 pneumonia" plus "recruitment" and "COVID-19 pneumonia" plus "prone positioning", revealed 6970 and 847 indexed papers, respectively. Therefore, it comes as a surprise that, despite the impressive amount of respiratory treatment data that were accumulated during the COVID-19 pandemic, considerable uncertainty remains regarding a rational approach to its ventilation. Even more striking, is the hot debate on the nature of its associated respiratory failure. Is it typical or atypical Acute Respiratory Distress Syndrome (ARDS)? This question is not simply academic but relates fundamentally to the therapeutic approach; if COVID-19 pneumonia were typical ARDS, we just should apply the treatments indicated by decades of clinical trials and observations. Conversely, if this condition were atypical, an atypical approach might be necessary.

In our opinion, the problem lies in the roots of the evidence applied in the intensive care setting, which is strongly determined by results from clinical trials, while physiological evidence is less influential. Knowing that the 78% of the patients "respond" to prone positioning [1] or to recruitment maneuvers is important, of course, but not as interesting or helpful as understanding the physiological mechanisms that determine them.

In this report we discuss which are in our opinion, the possible mechanisms of gas-exchange impairment in COVID-19 pneumonia: the comprehension of such mechanisms is decisive in tailoring a rational therapeutic approach for the use of prone positioning and recruitment maneuvers.

Possible mechanisms of hypoxemia:

Before discussing the specifics of COVID-19 pneumonia, a brief summary is required of the mechanisms of impaired gas-exchange in typical ARDS. For simplicity, we refer to the Riley model [2], which defines venous admixture as the aggregate of low ventilation-perfusion (Va/Q) ratios and true shunt, i.e., the fraction of cardiac output per fusing the hypo-ventilated and the gasless pulmonary units.

1. Venous admixture is the primary explanation for hypoxemia in ARDS. Severity of hypoxemia relates directly to the amount of collapsed and consolidated lung [3,4], where 'collapse' refers to those units that are "empty" and therefore potentially openable, while 'consolidated' lung refers to

those units that cannot be opened because they are full of inflammatory material, edema, blood, fibrin, etc. In ARDS, the fraction of venous admixture is lower than the fraction of non-aerated tissue (either collapsed or consolidated), indicating the presence of hypoxic vasoconstriction that diverts the blood flow to pulmonary units already open [5]. Indeed, a venous admixture fraction of 20% may be observed when non-aerated tissue occupies more than 50% of the lung parenchyma [5].

2. Extra-pulmonary right-to-left shunting may also occur through a direct communication within the heart. Patent foramen ovale, though not commonly observed, has been described in ARDS patients [6].
3. An alternative route for right-to-left shunt is through the bronchial circulation [7]. In normal conditions, the majority of bronchial venous blood ultimately flows into the superior vena cava. However, a fraction of such desaturated blood flows into the pulmonary venous system, thereby contributing to the 0.5 – 1 % shunt fraction usually observed in normal physiology [7]. Remarkably, the pulmonary artery system also connects to the venous bronchial network through vessels which normally are not patent. When this anastomosis opens, a fraction of pulmonary artery blood may enter the bronchial tree, enhancing the discharge of systemic venous blood into the pulmonary veins (Figure 1) [8].

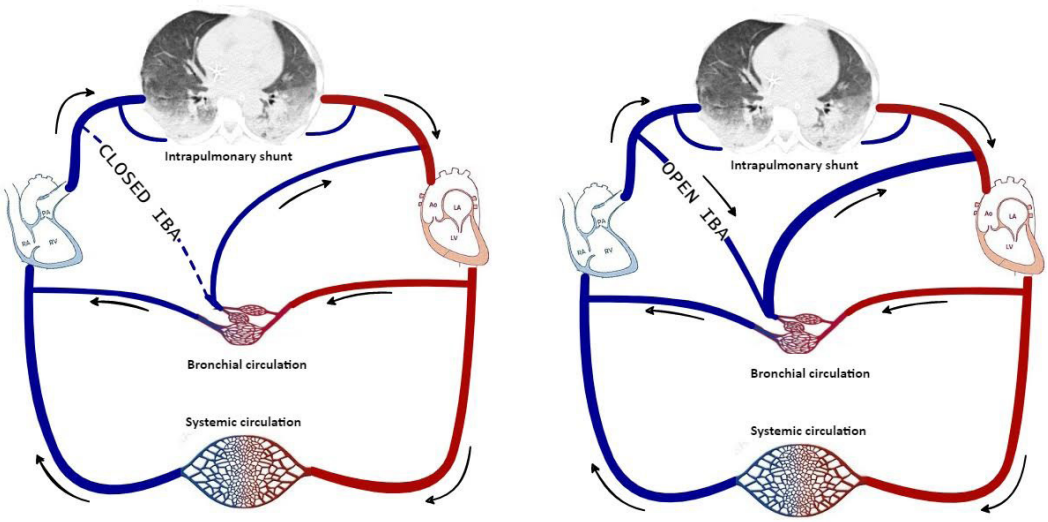

Figure 1: COVID-19 disease and potential mechanisms of shunt through the bronchial circulation. Normal subjects (left image): a small amount of venous blood from bronchial circulation flows directly to the left heart through the deep bronchiolar veins, contributing to the normally observed physiological venous admixture. COVID-19 patients (right image): the venous blood collected into the pulmonary artery is in part redirected to the bronchial circulation through open intra-bronchial anastomoses (IBAs), thus increasing the flow in the deep bronchiolar veins and subsequently the amount of venous admixture.

Understanding which of the abovementioned mechanisms are involved in a given patient leads to the appropriate treatment: opening the collapsed units (mechanism 1); closing the intra-cardiac communications (mechanism 2) or, possibly, decreasing the blood flow/pressure through the diseased lung regions (mechanism 3).

Possible mechanisms underlying recruitment and prone positioning:

Recruitment: The prerequisite for a recruitment maneuver to work is the significant presence of collapsed pulmonary units. The aim of such an intervention is to open collapsed alveolar units, while positive end-expiratory pressure (PEEP) only maintains patency of what previously has been opened by recruitment. The pressure required to open collapsed pulmonary units, defined as opening pressure, ranges around 20-30 cm H_2O, and relatively few pulmonary units (about 10%) open at pressures greater than 45 cm H_2O [9,10].

Prone Positioning: Prone positioning is often considered a recruitment maneuver that opens collapsed dorsal pulmonary units. Unfortunately, it is often forgotten that the opening of dorsal pulmonary units observed after pronation is associated with the collapse of other pulmonary units in ventral regions. Therefore, net recruitment is the difference between the number of opened and closed units after the change of position. Because the lung mass is greater in the dorsal than in the central regions, positive net recruitment usually occurs after pronation. As a consequence, improved oxygenation is usually observed, as the

perfusion distribution remains nearly unmodified after pronation [11]. When consolidated rather than collapsed tissue prevails in the dorsal regions, the consolidated units will not open during pronation. Instead, they "compress" the ventral pulmonary units, increasing the probability of their collapse. Apart from any improvement of gas-exchange, however, the benefit of prone positioning lies in the more homogeneous distribution of parenchymal stress and strain [12].

Mechanisms of hypoxemia in COVID-19 patients:

To discuss the mechanisms of hypoxemia in COVID-19 patients it is convenient to divide the time-course of COVID-19 disease into stages. The main differences between COVID-19 pneumonia and typical ARDS are best represented in early COVID-19 pneumonia, during which COVID-19 patients often present clinical characteristics quite different from typical ARDS. The separate assessment of the early and late stages of COVID-19 disease allows one to identify specific and distinct patterns that often were under-recognized during the first waves of the pandemic, when all patients were enrolled in clinical studies even if they were in different stages of COVID-19 disease. It is unquestionable that in the early phase, COVID-19 patients usually present severe hypoxemia (PaO_2/FiO_2 as low as 50 mmHg) associated with near-normal lung mechanics, with respiratory system compliances higher than 50 mL/cm H_2O [13]. High respiratory system compliance suggests that the lungs' gas-volume is well preserved. This association has been proved by quantitative CT scan analyses indicating that gas-volume and lung-weight are near-normal in the early phase of COVID-19 pneumonia, regardless of the severity of oxygenation, while non-aerated tissue is usually <10% of the lung parenchyma [13]. This anatomical finding excludes the possibility that the degree of hypoxemia and extent of venous admixture (sometimes greater than 50%) may be due to the true shunt flowing through non-aerated lung tissue. At the beginning of the pandemic, we hypothesized that the hypoxemia was primarily due to the loss of pulmonary vasoconstriction, with a dual effect: 1. decrease of Va/Q, and 2. increased perfusion of non-aerated tissue [14]. This mechanism is likely operating but cannot totally account for the observed hypoxemia, as the hypoxemia associated with Va/Q mismatch is easily corrected by increasing the inspired fraction of oxygen; therefore, the high venous admixture we observed must be due to true shunt. However, to explain the observed venous admixture, the modest quantity of non-aerated tissue should be hyper-perfused, which is unlikely. Therefore, other mechanisms, leading to true shunt, must help explain the severity of hypoxemia. An intra-cardiac shunt may be easily confirmed or excluded with echocardiography, and is unlikely to be present in such a high number of patients. Therefore, the third proposed mechanism should also be considered. Galambos C, (2021) and Ackermann M, et al. (2020), recently reported an increased flow through the bronchial anastomosis, which may convey up to 30% of the cardiac output [8,15]. Hence, to account for the observed hypoxemia in the early phase of COVID-19 pneumonia, it is likely that more than one mechanism operates at the same time.

Recruitment in early COVID-19 pneumonia: When the patient is admitted with severe hypoxemia and near-normal respiratory mechanics, recruiting maneuvers (and associated higher PEEP) are illogical; indeed, their benefit, i.e., opening the few percent of non-aerated tissue, are likely overshadowed by their associated risks, namely: 1) hemodynamic impairment requiring large amount of compensatory intravenous fluids, which may harm patients with inflamed lungs [16]; and 2) unnecessary lung hyperinflation with increased risk of barotrauma (to which these patients are particularly vulnerable) [17] and increased pulmonary vascular pressures and resistances. We may speculate that if bronchial anastomoses are patent, any increase in the pulmonary artery pressure, which may already be elevated by COVID-19 related micro-thromboses, would increase flow through the bronchial shunt, thereby off-setting the possible benefit on oxygenation of decreasing the modest lung atelectasis. Therefore, in early COVID-19 pneumonia, unless a significant amount of collapsed tissue is observed by quantitative lung CT scan analysis, anatomical, physiological and rational considerations should discourage the use of high PEEP (for example the values suggested in the FiO_2/PEEP tables [18] developed for the management of typical ARDS).

Prone positioning in COVID-19 pneumonia: The oxygenation response to prone positioning is variable and likely depends on the anatomical and functional characteristics of a specific patient. A single finding, shared across multiple physiological studies which assessed the response to prone position [19-21], is that improved oxygenation usually follows pronation, but, most importantly, the advantage is quickly lost after the return to supine. This, in our opinion, points to a rather relevant role of the perfusion redistribution, as also characterizes the sitting [22] and Rodin's positions [23]. The mechanisms of improved oxygenation in COVID-19 disease are likely different compared to typical ARDS. Indeed, in typical ARDS, the oxygenation improvement is due to the redistribution of ventilation with unmodified distribution of lung perfusion. In contrast, in COVID-19 disease, the oxygenation improvement is due to a redistribution of pulmonary blood flow with unmodified distribution of ventilation, as the potential for recruitment and de-recruitment of pulmonary units, is low in early COVID-19 pneumonia. What exactly happens to the perfusion distribution during pronation is still unknown. One may speculate that, due to the compromised vascular tone, the blood flow will be more gravity dependent, leading to lower Va/Q in ventral regions and higher Va/Q in dorsal ones. Therefore, the final matching between ventilation and perfusion will strictly depend

on what happens to the dorsal lung regions when compared to the ventral ones. The possible presence of direct anastomosis makes the picture even more complex, as we do not know their location and under which mechanical and biological conditions they become patent. While most patients are "responders" to prone positioning, as defined by an increased PaO_2/FiO_2 ratio, either during mechanical ventilation or in awake conditions [1], the effects of prone positioning on outcomes is less clear. It must be remembered, however, that improved oxygenation does not signify improve outcome. Indeed, the increased survival observed in prone position in typical ARDS was likely due to a better distribution of stress and strain, which required, to be effective, extensive atelectasis [24]. These conditions are not present in early stages of COVID-19 pneumonia.

Conclusion

It must be always kept in mind that the cure of ARDS, either typical or atypical, is not the cure of hypoxemia, and COVID-19 disease is a good example of this: a decreased PaO_2 is rarely a problem so long as hemodynamic stability is maintained. The inappropriate application in early stages of COVID-19 pneumonia of the ventilatory strategy used in typical ARDS (low tidal volume and high PEEP, with its associated side effects), may have contributed to the high mortality rate initially observed in some centers. The use of a physiological thinking when treating COVID-19 patients, and the direct assessment of specific variables (fraction of aerated and non-aerated tissue, quantification of collapsed/consolidated tissue, shunt calculation, etc.) are fundamental for an appropriate use of respiratory support in a specific patient even when more solid RCT evidence becomes available.

Conflicts of Interest

LG reports a consultancy for General Electrics and SIDAM. He also receives lecture fees from ESTOR and Mindray. The rest of authors declare no conflicts of interest.

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