

Could reperfusion pulmonary oedema explain worsening progress in COVID-19 pneumonia?

Dear editor

The pathogen SARS-CoV-2 (also known as 2019-nCoV) is a novel coronavirus, primarily affecting the respiratory system.^{1,2} As it is the first time that it has caused infection in humans, information about the pathophysiology of the disease is limited. The most common cause of hospitalisation is pneumonia, and the most severe complication is acute respiratory distress syndrome (ARDS) for SARS-CoV-2 infected patients.¹⁻³

Clinical and radiological findings of COVID-19 pneumonia are diverse.¹⁻³ To date, in the literature, some patients have shown relatively good clinical progress and some have developed respiratory failure and ARDS. Interestingly, some patients who had severe clinical and radiological findings have been successfully treated with supportive therapy, including oxygen support, with or without treatment in the prone position.^{1,2,4}

The physiopathological process in ARDS with an atypical clinical course may differ from classic ARDS.¹⁻³ A few reports have tried to provide evidence on this issue but there are not enough studies in the literature. For example, Gattinoni *et al* identified two types of ARDS phenotypes, L and H types, in their study.³ They also suggested that perfusion might primarily be disrupted in the first type and ventilation in the second.

Bilateral diffuse infiltration and atelectasis have been frequently seen in COVID-19 pneumonia. Sticky mucus, epithelial damage and surfactant deficiency are the leading causes of hypoxaemic respiratory failure in SARS-CoV-2 infected patients. Also, some studies have reported the development of pulmonary hypoperfusion, often because of possible hypoxic pulmonary vasoconstriction and microthrombi. We believe that the reexpansion pulmonary oedema (RPE) mechanism that occurs during the treatment of SARS-CoV-2 infected patients could play a key role in the occurrence of the atypical course of ARDS, and may explain the subsequent radiological and clinical deterioration observed. To determine the relationship

between COVID-19 pneumonia and RPE, significant differences between classic ARDS and RPE need to be thoroughly understood first.

The factors that may be essential in the development of pulmonary oedema include: (i) an increase in vascular hydrostatic pressure, (ii) decreased oncotic pressure on the pulmonary capillary wall and/or (iii) increased capillary permeability as a result of a direct or indirect pathologic insult to the pulmonary tissue. The cause of pulmonary oedema could be cardiac or non-cardiac. The most recognised forms of non-cardiac pulmonary oedema are ARDS, RPE, high altitude pulmonary oedema, immersion pulmonary oedema, negative pressure pulmonary oedema, transfusion related acute lung injury and neurogenic pulmonary oedema. All of these clinical entities could cause hypoxaemia of varying degrees and diffuse bilateral opacities on chest imaging.

Pulmonary oedema might also develop when the collapsed lung is suddenly re-expanded. This condition is called RPE.⁵ The occurrence of RPE is induced by the possible mechanisms of hypoxia-reoxygenation or ischaemia-reperfusion injury.⁵ Blood flow is significantly reduced in the collapsed lung areas secondary to hypoxic pulmonary vasoconstriction and increased pulmonary vascular resistance. Also, considerable surfactant loss occurs in these areas and results in alveolar instability during ventilation. Variable degrees of hypoventilation and hypoperfusion is a common feature of both RPE and ARDS. While the collapsed lung areas are generally localised unilaterally in RPE, they are scattered heterogeneously in both lungs in ARDS. Both the quantity of the total affected lung area and the ratio of the affected lung to preserved lung areas are higher in ARDS than RPE.

During formation of RPE, hypoxic vasoconstriction disappears due to the sudden expansion of the alveoli. The affected lung areas are rapidly reventilated and reperfused. Oxygen radicals and cytokines reach the atelectatic lung regions and cause endothelial damage via increased blood flow. As a result, the permeability of the alveolocapillary membrane increases, and pulmonary oedema develops.⁵ Recovery of patients with lung collapse is expected with treatment methods that target hypoventilation and hypoperfusion. In

contrast, treatment outcomes, such as worsening of the clinical and radiological picture, could be achieved instead. These concepts seem to echo the clinical and radiological deterioration observed during the treatment of COVID-19 pneumonia, despite aggressive oxygen and mechanical ventilation support.

High flow oxygen therapy and positive pressure ventilation are frequently performed as life saving procedures in patients with COVID-19 pneumonia, especially in the first hours of hospitalisation or admission to the intensive care unit.^{1,2} These interventions are anticipated to result in a decrease in atelectasis and hypoxaemia and improvement in hypoperfusion. However, unexpectedly, these procedures could lead to reoxygenation and reperfusion injury, similar to that in RPE. Furthermore, cytokines released from affected lung tissues in RPE cause local and systemic adverse effects. To date, a cytokine storm has usually been observed in severe COVID-19 cases.² Cytokines released into the systemic circulation during reoxygenation and reperfusion injury could magnify this phenomenon and worsen clinical progress. In this respect, COVID-19 disease is similar to RPE. In the early period of severe COVID-19 pneumonia, in particular, the clinical benefit of the prone position has been demonstrated in many studies.^{2,4} The prone position allows the less affected lung to have a more prominent role in providing and maintaining oxygenation. This may also play a protective role against a rapid change in pulmonary dynamics in the affected lung area, among other positive effects.

'Primum non nocere' is one of the oldest and valid rules of medicine. We wanted to draw attention to the similarity of the pathophysiological mechanisms between COVID-19 related ARDS and RPE. In a condition characterised by diffuse atelectasis, such as pneumonia, it is challenging to assess whether worsening is the natural course of the primary disease or a treatment related condition. Treatment related secondary damage may play a role in some patients with an atypical course. We would like to caution clinicians that aggressive oxygen and positive pressure ventilation treatments could cause worsening of the clinical process by leading to sudden changes in pulmonary dynamics in the early phase of treatment for COVID-19

pneumonia. Further studies are required to clarify these issues.

Muhammet Sukru Paksu , ¹ **Mehtap Kilic**²

¹Paediatrics, VM Medical Park Samsun Hospital, Samsun, Turkey

²Paediatric Allergy and Immunology, VM Medical Park Samsun Hospital, Samsun, Turkey

Correspondence to Dr Muhammet Sukru Paksu, Paediatrics, VM Medical Park Samsun Hospital, Samsun 55200, Turkey; sukrupaksu@yahoo.com

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests MSP planned, revised and submitted the study. MK searched the literature and wrote the study. The submitted version of this manuscript has been seen and approved by the authors.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Handling editor Lara Nicole Goldstein



To cite Paksu MS, Kilic M. *Emerg Med J* 2020;**37**:705–706.

Accepted 6 September 2020
Published Online First 28 September 2020

Emerg Med J 2020;**37**:705–706. doi:10.1136/emered-2020-210085

ORCID iD

Muhammet Sukru Paksu <http://orcid.org/0000-0002-0246-5253>

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