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LETTER TO THE EDITOR
EDİTÖRE MEKTUP

An another cause of COVID-19 related pulmonary fibrosis: The high oxygen supplement

Nur Aleyna YETKİN(ID)
Nuri TUTAR(ID)

Department of Chest Diseases, Erciyes University Faculty of Medicine, Kayseri, Turkey
Erciyes Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Kayseri, Türkiye

To the Editor,

Hypoxemic respiratory failure has come to the fore during the pandemic. Non-invasive mechanical ventilation and high-flow oxygen devices have been used frequently in respiratory failure and acute respiratory distress syndrome (ARDS) caused by COVID-19. Especially in the progression to intubation, we continue this high oxygen support and even give some patients 90-100% high fractions of O_2 (FiO_2) support for days. The fibrotic mechanisms after viral infections can be triggered by age, direct cellular damage, increased cytokine levels, induction of profibrotic pathway by viral antigens, and trauma of mechanical ventilation (1). Also, it is known that pulmonary fibrosis may develop after ARDS and hyperoxia is a crucial issue that will come to the fore as a cause of pulmonary fibrosis developing after COVID-19.

Although potentially lifesaving in the short term, long-term hyperoxia is not without risks and is implicated in organ toxicity processes such as acute lung injury (2). In experiments on animals, it has been shown that FiO_2 levels, which have a toxic effect, vary between species (3). DAD was found in patients with $FiO_2 \geq 0.4$ (2). Another single-center study defined excessive oxygen exposure as $FiO_2 \geq 0.5$ (3). Prolonged exposure to hyperoxia leads to reactive oxygen species (ROS) production, capable of damaging alveolar epithelial cells, thus causing disturbances in the pulmonary system and gas exchange impairment (4). Although it is known that ROS causes cell damage and organ dysfunction, the biochemical mechanisms have not been clarified. It is also known that FiO_2 causes absorptive atelectasis through the displacement

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Address for Correspondence (Yazışma Adresi)
Dr. Nur Aleyna YETKİN
Department of Chest Diseases,
Erciyes University Faculty of Medicine,
KAYSERİ - TURKEY
e-mail: alleynakemik@gmail.com

of alveolar nitrogen and decreased mucociliary clearance.

ARDS is characterized by severe respiratory failure and results from pulmonary edema due to increased permeability of the alveolar-capillary barrier. The pathogenesis of membrane damage is complex. Inflammatory cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-8 are released. The histological feature of ARDS, called DAD, manifests itself as a time-dependent exudative followed by a fibroproliferative phase. The fibroproliferative phase ultimately results in fibrosis. However, it has been proven that fibroproliferation and collagen deposition are responsible for the main pathogenesis since the onset of ARDS. When the transbronchial biopsy samples taken on the 10 ± 3rd day of patients' admission to the ICU with ARDS diagnosis were examined, 64% reportedly developed fibrosis.

Post COVID-19 Fibrosis

Although the mechanism of post-viral lung fibrosis has been studied in other viral outbreaks such as influenza and SARS, the root cause has not yet been clarified. Middle east respiratory syndrome-CoV and post-SARS-CoV follow-up studies identified a prevalence of post-viral lung fibrosis of up to 62%. These patients had more extended ICU stays, were older, and had higher peak lactate dehydrogenase levels than patients without pulmonary fibrosis. However, there is no study containing pathological data from that time. As the COVID-19 pandemic has taught us, this topic is likely to be at the forefront. A study of individuals with severe pneumonia during the H1N1 epidemic demonstrated high levels of transforming growth factor-beta 1 (TGF-β1). High levels of TGFβ1 were also shown in the serum, bronchial epithelial cells, and alveolar epithelial cells in the previous SARS-CoV-1 outbreak (5). TGF-β1 is known to increase fibrosis by increasing the extracellular matrix protein and stimulating fibroblast migration. In a previous study among COVID-19 patients, TGF-β1 levels were significantly higher in severe cases. Thus, increased cytokine levels and more severe lung injury may be highly associated with fibrosis.

TGF-β is a cytokine that plays a role in many diseases and is expressed in various tissues in pathological processes, including hyperoxia. It is known from previous animal studies that the expression of TGF-β is increased in the hyperoxic lung (6,7). Three-day-old newborn rats were treated with hyperoxic conditions (80% O_2) for seven days, and TGF-β levels were found to be high in these rats (7).

Data on pulmonary fibrosis developing after COVID-19 are not yet clear.

The optimal time for follow-up imaging to assess for radiological clearance in COVID-19 is unknown. However, evaluating patients with abnormal radiological appearances in terms of fibrosis is recommended 12 weeks after discharge. In the first pathology study performed on 50 patients with appearances compatible with fibrosis in post-COVID radiology, 32% of them had organized pneumonia (at least focal Masson bodies), 18% had diffuse-mild or moderate to severe lymphoplasmacytic interstitial infiltration (interstitial giant cells), 26% had normal or minimal nonspecific findings, 8% had patchy collagenous interstitial scars in the absence of cellular infiltrate or fibroblastic foci, and 8% had airspace pigmented macrophages like DAD (8). The last 8%, the DAD-like portion, is like the histopathological data due to high oxygen damage. However, in this study, the level of FiO_2 patients received was not specified. The effect of oxygen levels in the group that did not respond to steroid treatment and the group with more prominent scar tissue and fibrosis is intriguing. The literature shows that the applied FiO_2 values are at doses that can cause lung damage. However, it has been stated in the studies that FiO_2= 21-100 support is given to keep SpO_2> 88 during pandemics (9). Studies have reported the mean duration of mechanical ventilation exceeded 16 days, so both the length of time the lungs are exposed to hyperoxia, and the risk of developing ventilator-associated lung injury (VALI) may be increased (10). However, the long-term multisystem morbidities associated with COVID-19 have not been fully documented, and concerns remain, especially regarding long-term pulmonary complications.

In light of all these reasons, hyperoxia in patients with respiratory failure due to COVID-19 may have exacerbated the severity of ARDS and increased fibrosis with both ARDS and direct toxic effects (Figure 1). However, it is unclear whether the lung injury is due to oxygen toxicity, ventilator-induced lung injury, cytokine storm, or other causes of ARDS. Detailed randomized controlled studies are needed to elucidate this issue.

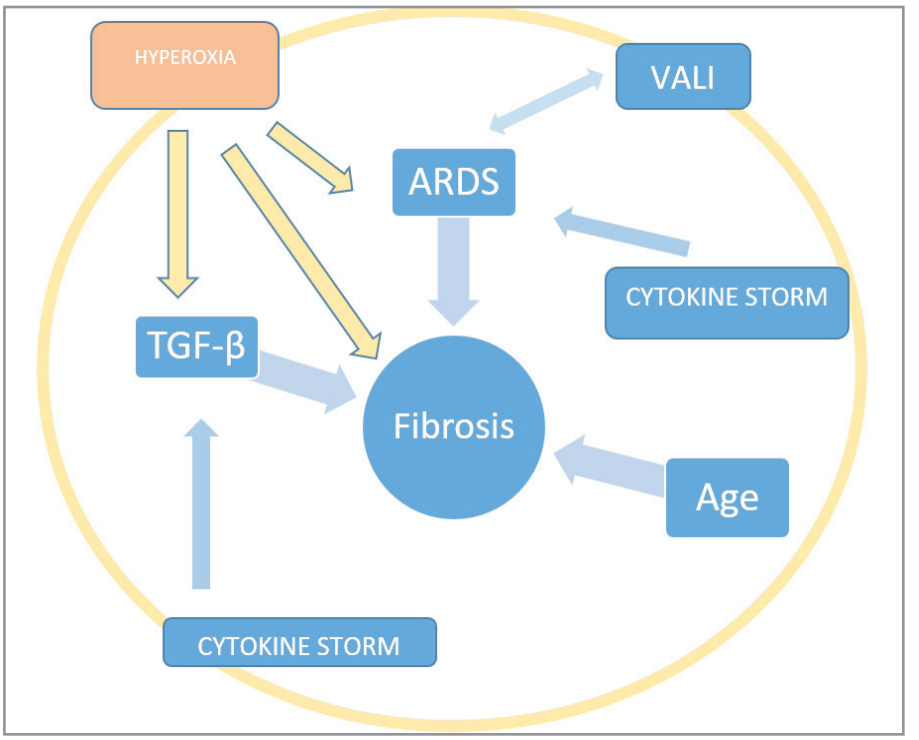

Figure 1. Conditions that play a role in the development of post-COVID-19 fibrosis.
(TGF-β: Transforming growth factor-beta, VALI: Ventilator-associated lung injury, ARDS: Acute respiratory distress syndrome).

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