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Treatment of COVID-19 by Inhaled NO to Reduce Shunt?

To the Editor:

We read with interest the letter by Gattinoni and coauthors on their computed tomography findings in patients with coronavirus disease (COVID-19) (1). They found a dramatic increase in the ratio between the shunt fraction and the fraction of gasless tissue, the ratio being almost three times higher than what they have seen in "typical" acute respiratory distress syndrome. They suggested this to be a "remarkable hyperperfusion of gasless tissue." Patients with COVID-19 do present with very low oxygenation ratio (Pa_{O_2}/FI_{O_2}), as for example in a study from Wuhan, China, with a median of 77 mm Hg and a mortality rate of more than 60% (2). Interestingly, the Pa_{O_2}/FI_{O_2} ratio was also very low in a previous coronavirus infection, the severe acute respiratory syndrome (SARS) 2002–2003, with a Pa_{O_2}/FI_{O_2} of 110 mm Hg in one study (3). This may possibly be related to the binding of SARS coronavirus to the ACE-2 (angiotensin-converting enzyme-2) protein that is present in endothelial cells (4), impeding hypoxic pulmonary vasoconstriction. This should increase perfusion of gasless tissue, even to the extent of calling it "hyperperfusion." It may be speculated that a similar mechanism also exists in COVID-19.

Gattinoni and coauthors concluded that continuous positive airway pressure or high positive end-expiratory pressure may worsen the condition and that prone position may be less successful in these patients (1). What, however, was not discussed is whether blood flow can be reduced in the gasless (atelectatic, fluid-filled, consolidated) tissue, thereby reducing shunt. One of the authors of this letter treated patients with SARS in Beijing in 2003 with inhaled nitric oxide (5). The inhaled nitric oxide is distributed to ventilated lung regions, dilating vessels and redistributing perfusion to these regions away from gasless, nonventilated lung regions. The Beijing results were rather dramatic, with a Pa_{O_2}/FI_{O_2} ratio increasing from 97 to 260 mm Hg, much more than seen when inhaled nitric oxide has been provided in "typical" acute respiratory distress syndrome. This suggests marked decrease of perfusion in gasless lung regions (5). In addition, large lung infiltrates seen on chest X-ray decreased within a few days. Neither the Pa_{O_2}/FI_{O_2} ratio nor chest X-ray findings improved in a control group without inhaled nitric oxide. Moreover, an antiviral effect was seen in cell culture tests when a nitric oxide donor, *S*-nitroso-*N*-acetylpenicillamine, was added to the cell culture (6).

These findings may make inhaled nitric oxide of interest also in the treatment of COVID-19. It may be that treatment should start as early as possible after the patient has been connected to a ventilator, realizing that when a "septic storm" has begun and multiorgan failure is developing, any treatment is likely to falter. ■

Originally Published in Press as DOI: 10.1164/rccm.202004-0940LE on June 24, 2020

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Heterogeneity of Acute Respiratory Distress Syndrome in COVID-19: "Typical" or Not?

To the Editor:

We read "COVID-19 Does Not Lead to a 'Typical' Acute Respiratory Distress Syndrome" by Gattinoni and colleagues with great interest

Author Contributions: All authors contributed equally to the conception, drafting, and final editing of this manuscript.

Originally Published in Press as DOI: 10.1164/rccm.202004-1106LE on June 24, 2020