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

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The letter has been written without any financial support

AJRCCM Articles in Press. Published June 24, 2020 as 10.1164/rccm.202004-0940LE

Dear Editor,

We read with interest the letter by Gattinoni and co-authors on their CT findings in COVID-19 patients. They found a dramatic increase in the ratio between the shunt fraction to the fraction of gasless tissue, the ratio being almost three times higher than what they have seen in "typical" ARDS (1). They suggested this to be a "remarkable hyperperfusion of gasless tissue". COVID-19 patients do present with very low oxygenation ratio (PaO_2/F_IO_2), as for example in a study from Wuhan, China, with a median of 77 mmHg and a mortality rate of more than 60% (2). Interestingly, the PaO_2/F_IO_2 ratio was also very low in a previous coronavirus infection, the SARS 2002-2003 with a PaO_2/F_IO_2 of 110 mmHg in one study (3). This may possibly be related to the binding of SARS Coronavirus to the ACE-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 exists also in COVID-19.

Gattinoni and co-authors 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 SARS patients in Beijing 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, non-ventilated lung regions. The Beijing results were rather dramatic with a PaO_2/F_IO_2 ratio increasing from 97 to 260 mmHg, much more than seen when inhaled nitric oxide has been provided in "typical" ARDS. 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 PaO_2/F_IO_2 ratio, nor chest x-ray findings improved in a control group without inhaled nitric oxide.

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Moreover, an antiviral effect was seen in cell culture tests when a nitric oxide donor, S-nitroso-N-acetylpenicillamine, SNAP, 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.

AJRCCM Articles in Press. Published June 24, 2020 as 10.1164/rccm.202004-0940LE

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