is altered in inflamed tissues of patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2016;22:315–326.

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.

Göran Hedenstierna, M.D.*
Uppsala University
Uppsala, Sweden

Luni Chen, M.D.
Karolinska Institute
Solna, Sweden

Magnus Hedenstierna, M.D.
Danderyd Hospital
Danderyd, Sweden

Gaetano Scaramuzzo, M.D.
University of Ferrara
Ferrara, Italy

ORCID IDs: 0000-0002-2923-6012 (G.H.); 0000-0001-9739-4082 (G.S.).

*Corresponding author (e-mail: goran.hedenstierna@medsci.uu.se).

References

1. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 does not lead to a "typical" acute respiratory distress syndrome [letter]. *Am J Respir Crit Care Med* 2020;201:1299–1300.
2. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;8:475–481.
3. Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, *et al*.; HKU/UCH SARS Study Group. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003;361:1767–1772.
4. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus: a first step in understanding SARS pathogenesis. *J Pathol* 2004;203:631–637.
5. Chen L, Liu P, Gao H, Sun B, Chao D, Wang F, *et al*. Inhalation of nitric oxide in the treatment of severe acute respiratory syndrome: a rescue trial in Beijing. *Clin Infect Dis* 2004;39:1531–1535.
6. Keyaerts E, Vijgen L, Chen L, Maes P, Hedenstierna G, Van Ranst M. Inhibition of SARS-coronavirus infection *in vitro* by S-nitroso-N-acetylpenicillamine, a nitric oxide donor compound. *Int J Infect Dis* 2004;8:223–226.

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

(1). In this letter, the authors describe 16 patients with coronavirus disease (COVID-19) who have a mean respiratory system compliance of 50.2 ± 14.3 ml/cm H_2O and marked shunt physiology. The authors suggest that these patients are representative of the primary pattern of physiologic derangements among their patients and those of colleagues with whom they've conferred. They discourage the use of prone positioning when compliance is "relatively high," similar to their recommendations in a recent article in which they additionally support ventilation with V_T up to 9 ml/kg in select patients with COVID-19 and relatively preserved compliance (2). We appreciate the authors' clinical observations and their expertise; however, we have several concerns with these two recommendations, which diverge from the best established evidence for acute respiratory distress syndrome (ARDS).

First, the authors' reported cohort is small and heterogeneous, in keeping with the well-established heterogeneity of ARDS. Many of their patients have similar compliance to those enrolled in clinical trials for ARDS therapies (3). For reference, patients enrolled in the PROSEVA (Prone Positioning in Severe ARDS) trial had a mean respiratory system compliance of 35 ml/cm H_2O (SD, 15) at the time of enrollment (3). Interestingly, a recent report of patients with COVID-19 from Seattle, Washington, described median respiratory system compliance of 29 ml/cm H_2O (interquartile range, 25–36) (4). That is to say, 75% of the patients in the Seattle cohort had lung compliance of 36 ml/cm H_2O or less. The discrepancy between the compliance measurements in the cohorts from Gattinoni and colleagues and Seattle highlights the difficulty in interpreting observations of small cohorts in a disease with well-established marked heterogeneity such as ARDS (5).

Second, respiratory system compliance was not used to determine eligibility for prone positioning in past trials. The PROSEVA trial enrolled severely hypoxemic patients, meeting the Berlin criteria for ARDS, who failed to stabilize early in the course of management (3). Though the authors may not support prone ventilation in patients with "relatively high compliance," exclusion of patients by these criteria would be inconsistent with existing evidence. Also, the effects of prone position on gas exchange are not limited to the shunt in fully atelectatic regions but instead include changes in edematous regions. Discouraging prone position based on a perception of limited recruitability risks foregoing a therapy with mortality benefit (3).

Finally, progression to a classic ARDS with dense posterior consolidation and elevated critical opening pressures (recruitability) is well described after mechanical ventilation, even in patients with initially preserved mechanics and without established lung injury (6). Patients with COVID-19–associated respiratory failure have multifocal pneumonia even in milder stages, and these regions are expected to have different elastic properties than unaffected tissue, causing regional stress and strain concentrations with potential to progress to severe ARDS (2, 4). Lung-protective strategies, including low V_T and prone positioning, exist to prevent this progression of lung injury.

We fully agree with the authors' final sentiment that patience and gentle ventilation are the best therapies for COVID-19 with associated ARDS. Furthermore, the rapid search for new insights into COVID-19 is appropriate and commendable. However, adopting the paradigm that COVID-19 is inconsistent with ARDS, with resulting specific treatment recommendations, risks discouraging compliance with our best evidence-based standards of care. Evidence from randomized controlled trials suggests that prone positioning and low V_T ventilation are the precise strategies for gentle ventilation that patients with ARDS, "typical" or not, should receive. ■

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

Jason H. Maley, M.D.*
Tilo Winkler, Ph.D.
C. Corey Hardin, M.D., Ph.D.
Massachusetts General Hospital
Boston, Massachusetts

ORCID ID: 0000-0002-7276-5550 (T.W.).

*Corresponding author (e-mail: jmaley@partners.org).

References

1. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 does not lead to a "typical" acute respiratory distress syndrome [letter]. *Am J Respir Crit Care Med* 2020;201: 1299–1300.
2. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, *et al*. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med* 2020;46:1099–1102.
3. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, *et al*.; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159–2168.
4. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, *et al*. Covid-19 in critically ill patients in the Seattle region - case series. *N Engl J Med* 2020;382:2012–2022.
5. Thille AW, Esteban A, Fernández-Segoviano P, Rodriguez JM, Aramburu JA, Peñuelas O, *et al*. Comparison of the Berlin definition for acute respiratory distress syndrome with autopsy. *Am J Respir Crit Care Med* 2013;187:761–767.
6. Gajic O, Dara SI, Mendez JL, Adesanya AO, Festic E, Caples SM, *et al*. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med* 2004;32:1817–1824.

COVID-19 Phenotypes and Potential Harm of Conventional Treatments: How to Prove the Hypothesis

To the Editor:

On the basis of recent correspondence (1) and an expert editorial (2), two phenotypes of severe coronavirus disease (COVID-19) pneumonia have been proposed: *"Type L, characterized by Low elastance (i.e., high compliance), Low ventilation to perfusion ratio, Low lung weight and Low recruitability and Type H, characterized by High elastance, High right-to-left shunt, High lung weight and High recruitability"* (2).

Originally Published in Press as DOI: 10.1164/rccm.202004-1293LE on June 24, 2020