Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

in populations that reside at high altitudes.[10]

Third, we infer from their discussion that hypoxic vasoconstriction is a harmful process when in fact it is an adaptive mechanism in the lungs to try to improve the matching of the perfusion to the ventilation; for example, a teleological explanation is that it is more beneficial for the host if blood is diverted away from the more diseased (hypoxic) parts of the lungs to areas that are less so in an attempt to maximize oxygenation of venous blood. Because COVID-19 exhibits endothelialitis and microthrombosis,[11] these vascular pathologic processes are likely to prevent the occurrence of this salubrious mechanism of hypoxic vasoconstriction.

Edward D. Chan, MD
Rocky Mountain Regional Veterans Affairs Medical Center
Aurora, CO
National Jewish Health
Denver, CO
University of Colorado Anschutz Medical Campus
Aurora

Vibhu Sharma, MD
Rocky Mountain Regional Veterans Affairs Medical Center
Aurora, CO
University of Colorado Anschutz Medical Campus
Aurora

Potential Competing Interests: The authors report no potential competing interests.

ORCID
Edward D. Chan: https://orcid.org/JMCP3285_0000-0001-7612-7727; Vibhu Sharma: https://orcid.org/JMCP3285_0000-0003-3414-2675

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In Reply — Does Hypoxia Itself Beget Worsening Hypoxemia in COVID-19?

To the Editor: We appreciate the interest of Drs Chan and Sharma in our *Perspective* proposing the early use of oxygen in patients with coronavirus disease 2019 (COVID-19) pneumonia.

First, in the setting of a global pandemic with widespread fatalities and severely limited therapeutic options, it is important to consider all possible alternative therapies. Here it is relevant that four potential pharmacologic interventions tested on hospitalized patients with COVID-19 in the WHO Solidarity Trial showed no evidence of improvement in mortality, initiation of ventilation, or duration of hospitalization.[1] In this regard, other investigators have also proposed early oxygen therapy as a possible option for prevention of COVID-19 disease progression.[2]

Second, Drs Chan and Sharma place great emphasis on distinguishing between hypoxia and hypoxemia. In the context of tissue hypoxia possibly potentiating COVID-19 pathophysiology, this is a distinction without a difference. They belabor the point of how one should determine hypoxia — should we measure lactate or central venous oxygen saturation? This would certainly be an admirable exercise in more "normal" academic environments. However, in less elevated settings, such as in the midst of overwhelming patient need as was initially experienced in Wuhan, China,[3] and is more recently ongoing in the Czech Republic and elsewhere, we suggest a very simple approach — if the oxygen saturation is low or falling, then proceed as if the patient has tissue hypoxia. Regarding target oxygen levels, this awaits the conduct of pilot interventional proof-of-principle studies, but we believe a goal oxygen saturation of greater than or equal to 96% and even a range of 94% to 98% is very reasonable, especially in light of the comparative benefit of more aggressive oxygen supplementation in acute respiratory distress syndrome (ARDS) reported by Barrot et al.[4] Regarding hyperbaric therapy, Drs Chan and Sharma misrepresent our stance, which more correctly stated is that "If aggressive oxygen supplementation is beneficial in more comprehensive health care settings, hyperbaric oxygen as a further step may possibly alleviate advanced cases of COVID-19- pneumonia." They cite studies suggesting that hyperbaric oxygen may *reduce* lymphocyte proliferation, as an argument for its avoidance. Remarkably, they also cite work by Ackermann et al[5] which

reports widespread pulmonary lymphocytic inflammation with perivascular lymphocyte infiltration as a significant component of COVID-19 pulmonary pathophysiology. Drs Chan and Sharma make no mention of this seeming disconnect in their logic. We further submit that potential exacerbation of inflammation by hypoxia[6] is a strong rationale for trying to prevent tissue hypoxia in COVID-19. Similarly, risks of aerosol spread with hyperbaric therapy are real, but are also present in COVID-19 patients treated with continuous positive airway pressure and with high flow nasal oxygen. Intensive care unit therapy of COVID-19 pneumonia is also "fraught with infection control issues," but certainly not a reason to shrink from therapy. In the very ill patient with no other recourse, one should at least consider an empirical and/or individualized case-by-case approach to the risks and benefits of less-traditional therapeutic options.

Third, Drs Chan and Sharma cite other viruses which may not proliferate in hypoxic conditions. It is certainly no surprise that biology is not uniform across organisms, and obvious that any effects of oxygen versus hypoxia on COVID-19 replication needs in vivo testing to more definitively answer this question. However, the concept of oxygen modulation in the treatment of viral infections is gaining increased attention and we refer Drs Chan and Sharma to an excellent analysis by Shen et al[2] regarding oxygen rich environments disrupting viral replication and improving the antiviral immune response.

Fourth, Drs Chan and Sharma infer that limited expansion of COVID-19 in populations residing at high altitude suggests hypoxia may be suppressing COVID-19 proliferation. Given their nuanced and critical analysis of our paper, we are bemused at their somewhat simplistic approach to understanding COVID-19 in conditions of altitude. We strongly encourage them to consult the website of their own institution, National Jewish Health, under the section "Coronavirus: Information and Resources," subsection "COVID-19 (Coronavirus) and Altitude."[7] Here it is clearly explained that individuals who are acclimated to high altitude may actually be protected from severe effects of COVID-19 because of lower levels of angiotensin-converting enzyme 2 (ACE2) expression. By contrast, those who travel from low to high altitude are "at higher risk of severe complications from COVID-19, as they have higher levels of ACE2." We would argue that this "hypoxic preconditioning" as possible protection against COVID-19 provides further support for the concept of hypoxia as a potential pathophysiologic mediator in COVID-19 disease. In fact, one of their colleagues indicates that COVID-19 patients at altitude need more aggressive oxygen therapy, and have been transferred to hospitals at lower elevation "to help the recovery process," presumably because of richer oxygen levels. The National Jewish Health website includes a link to a paper by Arias-Reyes et al[8] which provides further detail regarding COVID-19 and altitude, pointing out that other factors that may attenuate coronavirus proliferation at altitude include lower humidity, increased temperature fluctuations, and high levels of ultraviolet radiation. There is no mention of hypoxia inhibiting COVID-19 proliferation. In fact, Arias-Reyes et al[8] conclude by proposing that "higher tissue oxygenation…could be explored for potential therapy for acute respiratory distress associated with COVID-19."

Finally, Drs Chan and Sharma emphasize the adaptive benefits of hypoxic pulmonary vasoconstriction (HPV). In conditions of regional reductions in partial pressure of oxygen, HPV is an adaptive mechanism that diverts perfusion to better ventilated areas of the lung. However, in acute diffuse inflammatory lung injury where alveolar hypoxia is widespread, such as "in ARDS, both HPV and pulmonary vascular damage can lead to pulmonary hypertension and right ventricular dysfunction."[9] In COVID-19 pneumonia, pulmonary hypertension may represent an important target for disease amelioration.[10] HPV may contribute significantly to the increased pulmonary vascular resistance due to the rapid progression of lung injury and hypoxia. However, whether the HPV response is amplified or attenuated in COVID-19 remains to be resolved.[9] Drs Chan and Sharma further reference the interesting phenomenon of pulmonary vascular microthrombi in COVID-19,[5] but seem incurious as to the important and compelling potential role for hypoxia in promoting thrombosis.[11,12]

Virend K. Somers, MD, PhD
Mayo Clinic
Rochester, MN

Tomas Kara, MD, PhD
Mayo Clinic
Rochester, MN

Brno Municipal Hospital of Merciful Brothers
Brno and Faculty of Medicine and Dentistry
Palacky University
Olomouc, Czech Republic

Jiang Xie, MD, PhD
Beijing Anzhen Hospital
Capital Medical University
China

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ORCID

Jiang Xie: https://orcid.org/0000-0002-1737-9083

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