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.

those with low levels of CRF,[8] so clearly efforts are needed to increase physical activity and CRF in obesity.[9,10]

Certainly, the small study from Kerrigan et al[1] suggests that CRF is more important than obesity regarding COVID -19 hospitalizations. Larger studies are needed to assess the impact of CRF in COVID-19 and other pandemics for "harder" end-points, including intensive care unit admissions, intubation and mechanical ventilation, and mortality.

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Does Hypoxia Itself Beget Worsening Hypoxemia in COVID-19?

To The Editor: Somers et al[1] discussed the possibility that in coronavirus disease 2019 (COVID-19) hypoxia itself may perpetuate further inflammation, pulmonary vasoconstriction, and thrombogenesis as well as possibly induce severe acute respiratory syndrome coronavirus 2 replication, resulting in a complex vicious cycle of more hypoxia. We have several comments which we hope will lead to greater discussions.

First, it is important to distinguish "hypoxia" (low oxygen [O_2] at the tissue level and not practical to measure) from "hypoxemia" (low O_2 level in the blood). This distinction is important because one may have tissue hypoxia without hypoxemia; for example, coronary artery occlusion causes hypoxia in the myocardium without necessarily hypoxemia. In this regard, they provided no guidance on how to determine hypoxia in the absence of hypoxemia; for example, should supplemental O_2 be given if there is elevated lactate or low mixed venous/low central venous O_2 saturation? Based on their hypothesis that tissue hypoxia may induce conditions that beget more hypoxia, are we to infer that they advocate supraphysiologic levels of O_2 (eg, targeting supraphysiologic partial pressure of 0_2 or oxygen saturation [SpO_2] closer to 100%)? In pre−COVID-19 acute respiratory distress syndrome, a meta-analysis of 25 randomized controlled trials of more than 16,000 patients showed that a liberal O_2 treatment strategy (median SpO_2 of 96%) was associated with increased mortality during hospitalization, at 30 days, and at "longest follow-up."[2] Although a multicenter study comparing liberal O_2 therapy (target $SpO_2 \geq 96\%$) with a conservative strategy (target SpO_2 88% to 92%) showed a clinically significant greater mortality at 90 days in the conservative O_2 therapy group,[3] the lower limit of 88% in the conservative O_2 group has been criticized to be too low. Indeed, a recent comprehensive analysis indicated that a target SpO_2 in the "Goldilocks" range of 94% to 98% is a safe compromise.[4] Somers et al[1] also suggested — consistent with their aforementioned line of reasoning — that hyperbaric O_2 therapy be considered for "advanced cases" of COVID-19 pneumonia. We believe hyperbaric O_2 treatment is likely to be highly impractical, fraught with infection control issues, and potentially harmful.[5-7]

Second, they cited studies showing that a hypoxic environment enhances replication of the hepatitis C virus and herpes viruses and posited that this may be occurring with severe acute respiratory syndrome coronavirus 2.[1] Contrary to their examples, hypoxia has been shown to suppress replication of influenza virus and adenovirus.[8,9] In this regard, expansion of COVID-19 has been observed to be limited

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.

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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