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.

(27%), and chest pain (22%); none had fever or features indicating acute illness.[10] Patients with milder initial infections may also have prolonged symptoms.

Systematic evaluation of the long-term sequelae of COVID-19 indicates that 70% of patients have impairment in one or more organs 4 months after initial infection, even amongst relatively healthy patients before infection.[2] The most commonly reported ongoing symptoms, regardless of hospitalisation status, were fatigue (98%), myalgia (88%), shortness of breath (87%), and headache (83%). Mild organ impairment was evidenced in the heart (32% of patients), lungs (33%), kidneys (12%), liver (10%), pancreas (17%), and spleen (6%), with 25% of individuals displaying evidence of multi-organ impairment. The risk of multi-organ impairment was significantly associated with hospitalisation.[2] Patients who were critically ill with COVID-19 may also be at risk for post-intensive care syndrome (persistent impairment in cognition, mental health, or physical function after survival of critical illness), although the incidence after COVID-19 is at present unknown. Medium- and long-term follow-up of 'long COVID' patients is warranted and requires multidisciplinary management.[2]

As we move gradually past this pandemic, clinicians and health policymakers may need to consider multiple strategies to tackle the upcoming challenges faced. Supplies of PPE will need to be adequate to cater to further waves of infection, particularly as variants resistant to vaccination emerge. They will also need to work with hospital administration to increase critical care bed capacity, which will be an investment in managing the increasing burden of high-morbidity patients undergoing surgery or becoming critically ill. Adaptive trials are encouraged to provide Level 1 evidence for therapeutic strategies, not only in COVID-19, but also in viral pneumonia inducing acute respiratory distress syndrome/acute lung injury.

Declarations of interest

DJB and JGH are editorial board members, and JGH is associate editor-in-chief of the *British Journal of Anaesthesia*. JGH accepts fees for the provision of advisory reports to the crown prosecution service, the police, solicitors, and coroners.

References

1. World Health Organization. *WHO coronavirus disease (COVID-19) dashboard* 2021. Available from: https://covid19.who.int. [Accessed 4 February 2021]
2. Hamilton W. Cancer diagnostic delay in the COVID-19 era: what happens next? *Lancet Oncol* 2020; **21**: 1000–2
3. Dennis A, Wamil M, Kapur S, et al. Multi-organ impairment in low-risk individuals with long COVID. *medRxiv* October 16 2020. https://doi.org/10.1101/2020.10.14.20212555
4. WHO United Nations Interagency Task Force on NCDs. *COVID-19 and NCD risk factors* 2020. Available from: https://www.who.int/docs/default-source/ncds/un-interagency-task-force-on-ncds/uniatf-policy-brief-ncds-and-covid-030920-poster.pdf?ua=1. [Accessed 15 January 2021]
5. Centers for Disease Control and Prevention. *COVID-19 hospitalization and death by age* 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html. [Accessed 15 January 2021]
6. Centers for Disease Control and Prevention. *COVID-19 hospitalization and death by race/ethnicity* 2021. Available from: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html. [Accessed 15 January 2021]
7. COVIDSurg Collaborative. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. *Lancet* 2020; **396**: 27–38
8. Gray M, Bird W. *Covid-19 will be followed by a deconditioning pandemic* 2020. Available from: https://blogs.bmj.com/bmj/2020/06/15/covid-19-will-be-followed-by-a-decondition-ing-pandemic/. [Accessed 15 June 2020]
9. Tenforde MW, Billig Rose E, Lindsell CJ, et al. Characteristics of adult outpatients and inpatients with COVID-19—11 academic medical centers, United States, March–May 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 841–6
10. Carfì A, Bernabei R, Landi F. Gemelli against COVID-19 post-acute care study group. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020; **324**: 603–5

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Putative antiviral effects of propofol in COVID-19

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Keywords: angiotensin-converting enzyme 2; COVID-19; propofol; severe acute respiratory syndrome coronavirus-2; severity

Editor—Propofol, a short-acting i.v. anaesthetic drug, is commonly used as a first-line agent to sedate intubated coronavirus disease 2019 (COVID-19) patients with acute respiratory distress syndrome (ARDS) in the ICU. The COVID-19 global pandemic has led to a shortage of propofol in many countries.[1] Recently, it has been highlighted that patients receiving propofol sedation are at a risk of exacerbated infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that subsequently affects the severity of COVID-19.[2] Studies *in vitro* have indicated that propofol treatment can upregulate angiotensin-converting enzyme 2 (ACE2) expression, an essential receptor involved in the internalisation of SARS-CoV-2.[3,4] The suggestion that propofol contributes to the aggravation of the condition of intubated patients with COVID-19 by promoting SARS-CoV-2 cell entry has led to the use of alternative sedative drugs.[5]

This hypothesis has led to increasing uncertainty and concern surrounding the use of propofol in patients with COVID-19; however, it remains unclear whether there is a direct association between drugs that increase ACE2

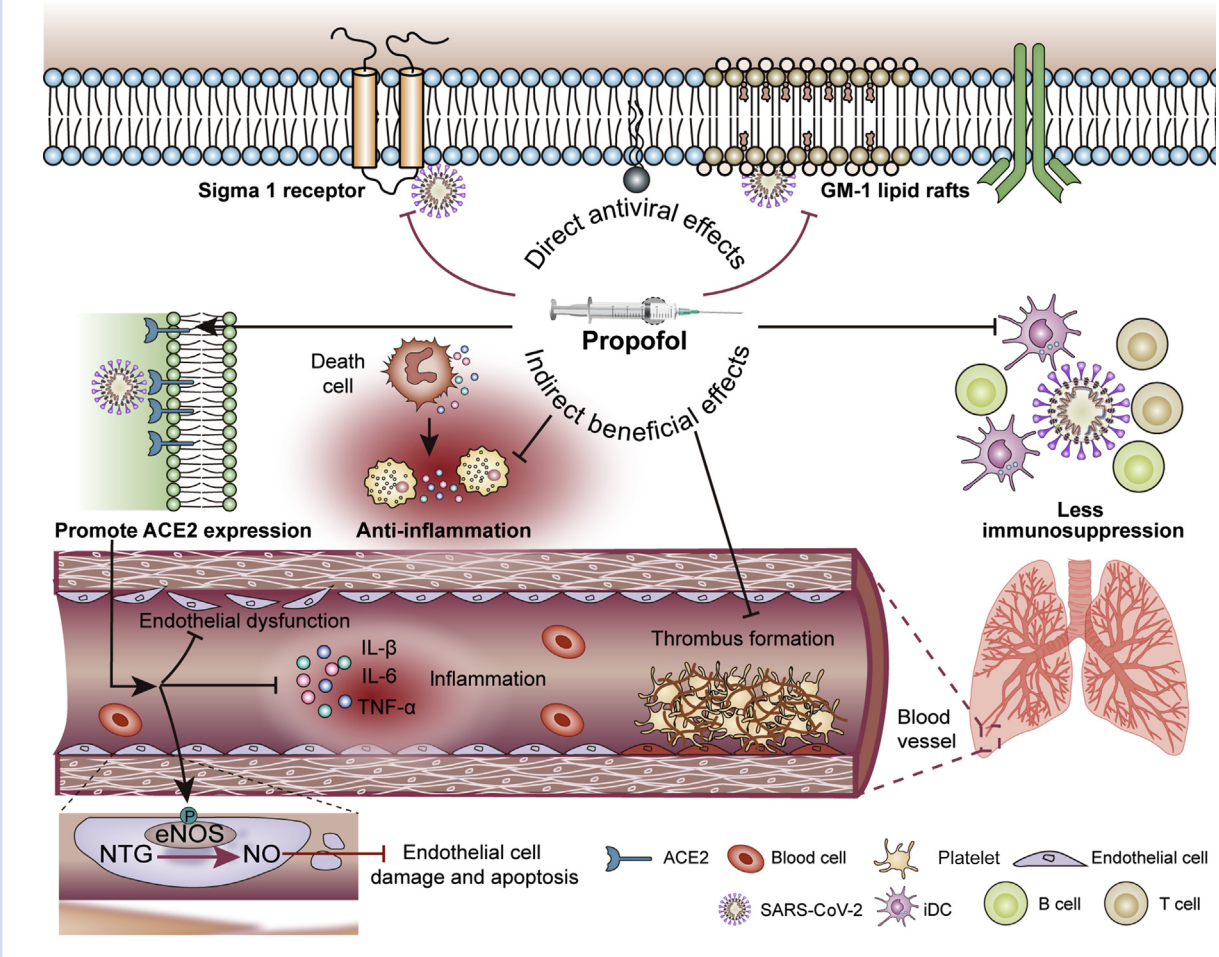

Fig 1. Putative mechanisms of the protective effects mediated by propofol in patients with COVID-19. Propofol may exert direct antiviral effects by disturbing GM1 lipid rafts and inhibiting sigma-1 receptors, and by indirect effects, including anti-inflammation, anti-thrombosis, and reduced immunosuppression. Additionally, elevated ACE2 expression induced by propofol treatment may protect pulmonary artery endothelial cells, inhibit apoptosis in vascular endothelial cells, and suppress SARS-CoV-2-induced systemic inflammatory cascade. ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; eNOS, endothelial nitric oxide synthase; GM-1, monosialotetrahexosylganglioside-1; iDC, immature Dendritic Cell; IL-1β, interleukin-1β; IL-6, interleukin-6; NO, nitric oxide; NTG, nitroglycerine; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; TNF-α, tumour necrosis factor-α.

expression and the risk posed to patients with COVID-19. Fang and colleagues[6] analysed data from three clinical studies on COVID-19 during the early outbreak in Wuhan, China, and extrapolated that the severity of COVID-19 might increase in patients with diabetes and hypertension taking ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), which cause a significant increase in ACE2 expression, as observed in animal studies. However, a recent clinical study has shown that the use of ACEIs and ARBs was not closely associated with the diagnosis and severity of COVID-19 amongst patients with hypertension.[7] Although daily intake of ACEIs and ARBs significantly increases ACE2 mRNA expression and activity in rats,[8] this effect might not exist in humans. Evidence to support this came from a study investigating the expression and subcellular localisation of ACE2 in the upper and lower respiratory tracts of human donor tissues. That study provides strong evidence that the use of ACEIs and ARBs does not increase susceptibility to SARS-CoV-2 infection by enhancing ACE2 expression in either the initial or early essential cellular site of viral entry during respiratory transmission.[9]

In fact, propofol, *via* enhanced ACE2 expression, might have favourable effects on the vascular endothelium in patients with COVID-19. Propofol protects endothelial cells of human pulmonary artery by increasing transcription of ACE2 *via* a phosphatidylinositol 3-kinase-dependent mechanism, and its activity in cell membranes.[3] Propofol can also inhibit vascular endothelial cell apoptosis by activating the ACE2/angiotensin-(1–7)/Mas signalling pathway and increasing nitric oxide levels, the endothelium-derived relaxing factor, by upregulating the expression and phosphorylation of endothelial nitric oxide synthase.[4] Elevated ACE2 expression increases anti-inflammatory effects that suppress the systemic inflammatory cascade induced by SARS-CoV-2.[10] The multiple actions of propofol, including significant anti-inflammatory, anti-thrombotic, and fewer immunosuppressive effects, may facilitate recovery from lung injury in COVID-19.[11]

Propofol might also act as an antiviral agent in infected cells. It could inhibit SARS-CoV-2 entry and transmission by increasing the apparent size and number of lipid rafts and by dissociating cholesterol-sensitive proteins from monosialotetrahexosylganglioside-1 (GM-1) lipid rafts *in vitro*.[12] Propofol might have an antiviral effect by inhibiting the sigma-1 receptor,[2,13] a potential antiviral target against COVID-19.[14] Based on these properties, we summarise the potential mechanisms by which propofol might be advantageous in patients with COVID-19 (Fig. 1). Although physiological models of SARS-CoV-2 infection present a theoretical risk of propofol, these findings cannot be extrapolated to a clinical setting, where propofol exacerbates COVID-19. As the benefits outweigh the risks, we conclude that propofol should not be avoided because of concerns regarding ACE2 and diagnosis or aggravation of COVID-19.

However, prolonged sedation with propofol infusions for intubated and mechanically ventilated patients with COVID-19 and ARDS may have adverse side-effects, such as propofol infusion syndrome,[15] neuroleptic malignant syndrome,[16] and critical illness myopathy.[1] Therefore, prolonged propofol infusions might not be the ideal choice for patients with COVID-19 in the ICU.[1] Other sedatives, including midazolam and dexmedetomidine, provide suitable alternatives to propofol in such patients.

Declarations of interest

The authors declare that they have no conflicts of interest.

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References

1. Lonnqvist PA, Bell M, Karlsson T, Wiklund L, Hoglund AS, Larsson L. Does prolonged propofol sedation of mechanically ventilated COVID-19 patients contribute to critical illness myopathy? *Br J Anaesth* 2020; **125**: e334–6
2. Hirota K, Lambert DG. Propofol and SARS-CoV-2 infection. *Br J Anaesth* 2020; **125**: e475–6
3. Cao L, Xu L, Huang B, Wu L. Propofol increases angiotensin-converting enzyme 2 expression in human pulmonary artery endothelial cells. *Pharmacology* 2012; **90**: 342–7
4. Zhang L, Wang J, Liang J, et al. Propofol prevents human umbilical vein endothelial cell injury from Ang II-induced apoptosis by activating the ACE2-(1-7)-Mas axis and eNOS phosphorylation. *PLoS One* 2018; **13**, e0199373
5. Sohn JT. Propofol and sedation in patients with coronavirus disease. *Am J Emerg Med* 2020. https://doi.org/10.1016/j.ajem.2020.06.023. Advance Access published on June 18
6. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 2020; **8**: e21
7. Fosbol EL, Butt JH, Ostergaard L, et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. *JAMA* 2020; **324**: 168–77
8. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation* 2005; **111**: 2605–10
9. Lee IT, Nakayama T, Wu CT, et al. ACE2 localizes to the respiratory cilia and is not increased by ACE inhibitors or ARBs. *Nat Commun* 2020; **11**: 5453
10. Zheng C, Lei C, Chen Z, et al. Topical administration of diminazene aceturate decreases inflammation in endotoxin-induced uveitis. *Mol Vis* 2015; **21**: 403–11
11. Senthilkumaran S, Koushik M, Sanjay P, Thirumalaikolundusubramanian P. Propofol in COVID 19—from basic science to clinical impact. *Am J Emerg Med* 2020. https://doi.org/10.1016/j.ajem.2020.07.011. Advance Access published on July 9
12. Yuan Z, Pavel MA, Wang H, Hansen SB. Hydroxychloroquine: mechanism of action inhibiting SARS-CoV2 entry. *bioRxiv* 2020. https://doi.org/10.1101/2020.08.13.250217. Preprint published on August 14
13. Yamada M, Nakao S, Sakamoto S, et al. Propofol acts at the sigma-1 receptor and inhibits pentazocine-induced c-Fos expression in the mouse posterior cingulate and retrosplenial cortices. *Acta Anaesthesiol Scand* 2006; **50**: 875–81

14. Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* 2020; **583**: 459–68
15. Lucchetta V, Bonvicini D, Ballin A, Tiberio I. Propofol infusion syndrome in severe COVID-19. *Br J Anaesth* 2020; **125**: e441–2
16. Soh M, Hifumi T, Isokawa S, Shimizu M, Otani N, Ishimatsu S. Neuroleptic malignant syndrome in patients with COVID-19. *Am J Emerg Med* 2020; **38**: 2243. e1–3

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Characterising the pulmonary response to prone positioning. Comment on *Br J Anaesth* 2021; 126: 48-55

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Keywords: acute respiratory failure; ARDS; COVID-19; prone positioning; ventilatory ratio

Editor—Weiss and colleagues[1] recently published a detailed report on prone positioning during the coronavirus disease 2019 (COVID-19) pandemic. Prone positioning has been widely adopted both in intubated and non-intubated patients with respiratory failure. The response falls into four broad categories of *P/F* ratio change: no (or worse) change, improvement that is sustained on returning supine, improvement that is slightly diminished on return to supine, or improvement that is greatly diminished on return to supine.[2]

The main outcome reported was that prone positioning improved *P/F* ratio from 17.9 to 28.2 kPa after 81 (range: 61–119) min (immediate) across 36 subjects, of which 26 had a response of ≥20%. Results from 32 subjects indicate that the response persisted on return to supine (sustained). The immediate response to this first manoeuvre did not predict those who would survive. As the authors mentioned, van Meenen and colleagues[3] also reported lack of prognostic capacity of changes in *P/F* ratio to prone positioning in acute respiratory distress syndrome (ARDS) not attributable to COVID-19. However, this group compared *P/F* ratio values before prone positioning to those on return to supine (sustained), whereas Weiss and colleagues compared P/F ratio values before prone positioning to values whilst prone (immediate). It would be interesting to report if a sustained response was related to favourable outcome in the Weiss and colleagues COVID-19 cohort.

Measurement of immediate response to prone positioning is common in the published literature, with response usually defined as an increase in P/F ratio of ≥20% or by 20 mm Hg (2.7 kPa).[2] These are arbitrary criteria and cannot be utilised at the bedside. Although relatively easy to calculate, the *P/F* ratio encompasses a complex interaction between haemoglobin concentration, oxygen extraction, and pulmonary shunt fraction, making it sensitive to relatively small changes in FiO_2 whilst not accounting for PEEP or mean airway pressures.

The lack of association between immediate response to prone positioning and favourable outcome reported by Weiss and colleagues[1] is consistent with some pre-COVID-19 data. For example, in a reanalysis of the landmark Proning Severe ARDS Patients study,[4] no markers of gas exchange predicted those who would survive or not after initial prone positioning.[5] Here, 91% of subjects who were in the worst quintile for initial *P/F* ratio change (which ranged from −81 to −1 mm Hg or 10.8 to −0.1 kPa) survived. Other data illustrated no difference in *P/F* ratio between survivors and non-survivors after the first prone manoeuvre in 225 patients.[6] This presents a challenge to those caring for patients with COVID-19, as promising initial improvements in gas exchange might not translate into favourable clinical outcomes.

In the current report, death or progression to extracorporeal membrane oxygenation was more frequent in those displaying a diminished response to further prone manoeuvres. There are limited data on other factors that might have prognostic value based on response to prone positioning. Reduction in $Paco_2$ after a single episode of prone positioning was associated with improved 28-day survival (relative risk: 1.48; 95% confidence interval: 1.07–2.05; P=0.02), despite a trend for increasing $Paco_2$ in all patients over subsequent prone manoeuvres.[6] Decreases in $Paco_2$ of ≥1 mm Hg have previously been used to describe responders.[2] The ventilatory ratio can approximate dead-space ventilation and has shown predictive utility in ARDS patients, where initial measurement was higher in non-survivors than survivors (2.02 [0.8] *vs* 1.75 [0.5]; P<0.001).[7] Ventilatory ratio might be physiologically relevant

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