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COVID-19 CORRESPONDENCE

Potential therapeutic value of dexmedetomidine in COVID-19 patients admitted to ICU

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Editor—The coronavirus 2019 disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an ongoing global health concern[1] that has so far caused >29 million infections and resulted in more than 900 000 deaths worldwide. The clinical manifestations of COVID-19 range from asymptomatic infection to severe acute respiratory failure and multi-organ dysfunction (MOD) requiring organ supportive therapy, such as mechanical ventilation in the ICU. Once established, multi-organ dysfunction is associated with reduced patient survival and quality of life after ICU discharge.[2] There is a pressing need to understand the disease mechanisms underlying COVID-19 in order to develop novel therapeutic strategies to improve patient survival.

Overwhelming immune activation resulting in a 'cytokine storm' and systemic hypoxaemia caused by pulmonary dysfunction may lead to cell death within vital organs, including brain, lung, kidney, liver, and gut, and are thought to contribute to multiple organ dysfunction and poor outcomes in COVID-19.[2] Although a number of therapeutic approaches have been proposed or trialled to modulate the dysregulated immune response in COVID-19, thus far only dexamethasone, a potent glucocorticoid steroid with broad effects on innate and adaptive immunity, has been shown to improve patient survival. Accumulating data show that cell necrosis and necroptosis (programmed cell death) are key cell death mechanisms implicated in both acute organ injury and chronic inflammatory disease.[3] When lung alveolar cells, lung macrophages, or both become infected with SARS-CoV-2, resultant cell death may lead to widespread immune cell activation through activation of pattern recognition receptors on innate immune cells. The therapeutic efficacy of antiviral therapies such as remdesivir,[4] a nucleotide analogue that inhibits viral RNA polymerase, or lopinavir/ritonavir, a combination viral protease inhibitor combination used for human immunodeficiency virus 1 (HIV-1) treatment, remains to be verified. Targeting angiotensin-converting enzyme 2 (ACE2),[5] the cell surface receptor whereby SARS-CoV-2 enters into cells for replication, or suppressing systemic inflammation with anti-tumour necrosis factor antibodies have also been suggested.

It might be advantageous to take a different perspective by targeting the cell death pathways involved in the development of multi-organ dysfunction during the infection. Strategies that inhibit upstream cell death pathways may prevent downstream immune activation implicated in COVID-19 associated multi-organ dysfunction. In addition, direct inhibition of alveolar cell death may preserve lung architecture and prevent some of the long-term sequelae such as the breathlessness experienced by patients who have recovered from COVID-19. Furthermore, preserving the alveolar capillary interface, which provides an anatomical barrier, may prevent secondary bacterial infection associated with SARS-CoV-2.

The potent and selective α_2-adrenoceptor agonist dexmedetomidine exerts sedative and analgesic effects and has been widely used as an adjunct for anaesthesia, analgesia, and sedation in the ICU.[6] In addition, dexmedetomidine has both cytoprotective and anti-inflammatory properties.[7] In fact, its organoprotective effects against acute organ injury, such as brain,[8] lung and kidney,[9] have been well established in preclinical settings. Mice treated with dexmedetomidine exhibited reduced inflammation-induced cell death (pyroptosis) in astrocytes and in turn protected neurones in sepsis-induced brain injury.[8] The underlying protective mechanisms of dexmedetomidine include increasing parasympathetic tone,

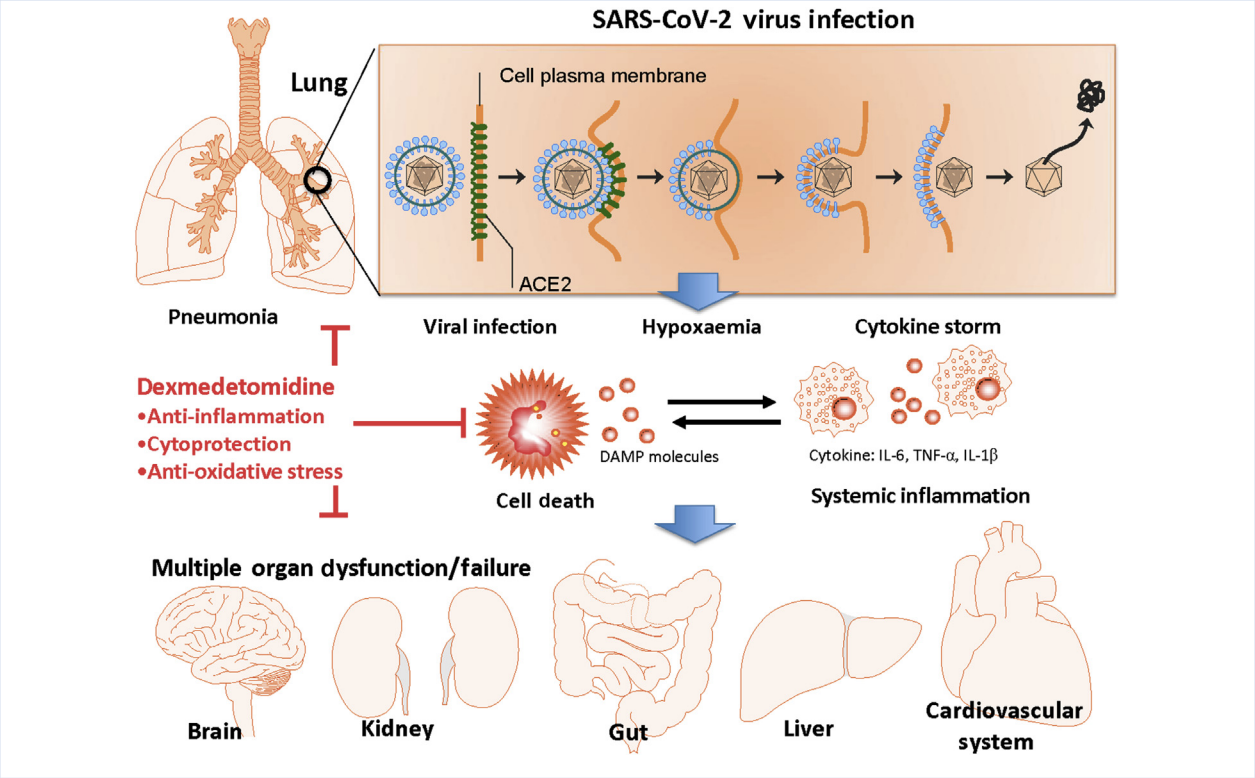

Fig 1. Putative mechanisms of SARS-CoV-2 infection induced dysfunction or failure of multiple organs (MOD/MOF) and the protection afforded by dexmedetomidine (DEX) in COVD-19 patients. SARS-CoV-2 can bind with angiotensin-converting enzyme 2 (ACE2) to enter human cells for replication and cause a viral pneumonia. The subsequent cell death, cytokine storm and systemic hypoxaemia caused by pulmonary dysfunction/failure are considered to be the pathogenesis of MOD/MOF which includes neurological dysfunction, acute kidney and liver injury, myocardial dysfunction. DEX has potent protective effects through up-regulating protective proteins and attenuating cell death and systemic inflammation, and, thereby may protect vital organs from MOD/MOF in COVID-19 patients who require sedation and mechanical ventilation in the ICU. In addition, its cholinergic anti-inflammatory mechanisms can suppress excessive inflammatory responses and its anti-oxidative effects preserve cells from oxidative stress conferring additional benefits to COVID-19 patients irrespective of other supportive treatments currently available. IL, interleukin; TNF- α, tumour necrosis factor-alpha. DAMP: Damage-associated molecular pattern.

dampening of the inflammatory response, prevention of cell death, and inhibition of oxidative stress.[10] By increasing parasympathetic tone and decreasing sympathetic tone, dexmedetomidine appears to confer protective effects on immune function by effects on T cells and natural killer cells. Furthermore, its cholinergic anti-inflammatory mechanisms might suppress excessive inflammatory responses.[10] A trial in the critical care setting has shown that dexmedetomidine was effective in attenuating the incidence of delirium in older patients.[6,11]

Based on these properties, we propose that dexmedetomidine may serve as a novel therapeutic strategy to attenuate the vital organ injuries in COVID-19 (Fig. 1), whilst simultaneously providing beneficial sedative effects to enable oxygen therapy *via* either noninvasive or invasive mechanical ventilation. ICU sedation with dexmedetomidine is associated with impaired ventilatory responses to hypoxia and hypercapnia to a similar extent as that associated with propofol sedation, indicating that ventilatory suppression by dexmedetomidine is likely caused by effects on both peripheral and central regulation of breathing.[12] This attenuation of respiratory drive could be beneficial for patients with COVID-19 requiring ventilatory support in which hypoxaemia-associated hyperventilation and respiratory distress are significant problems.

We propose that dexmedetomidine should be considered when sedation is required, during the early disease course to help prevent the onset or progression of multi-organ dysfunction in COVID-19. When deep sedation is required, dexmedetomidine may be used as a sedative adjunct together with other sedatives, such as propofol or midazolam. Its use as a single agent may also be considered to facilitate noninvasive ventilation or during liberation from invasive mechanical ventilation, although at high doses the risk of bradycardia and hypotension should be taken into consideration. In summary, there is a strong rationale for further clinical studies investigating the effects of dexmedetomidine on outcomes in ICU patients with COVID-19.

Declarations of interest

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Dexmedetomidine: another arrow in the quiver to fight COVID-19 in intensive care units

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Editor—Finnerty and Buggy[1] propose a role for lidocaine in coronavirus disease 2019 (COVID-19) patients involving neutrophil extracellular trap (NET)osis inhibition as a mechanism. We hypothesise that, given the anti-inflammatory effects of dexmedetomidine, it too may inhibit NETosis and so be beneficial in COVID-19 patients.

Dexmedetomidine, a selective α_2-adrenergic receptor agonist, has been studied extensively for long-term ICU use.[2–6] Based on studies investigating its effects in reducing sepsis-related lung injury and ischaemia–reperfusion injury of heart, kidney, brain, and intestine (organs commonly affected in COVID-19),[7] and based on the mechanistic models of COVID-19 pathogenesis,[8–11] we suggest that dexmedetomidine may have therapeutic potential in COVID-19. Our hypothesis is supported by a case report of improved oxygenation with dexmedetomidine in a COVID-19 patient[12] and by another encouraging report.[13]

Although dexmedetomidine-mediated improvements in hypoxic pulmonary vasoconstriction and ventilation–perfusion ratios were proposed explanations for improved oxygenation after dexmedetomidine administration in COVID-19 patients,[12] the anti-inflammatory properties of dexmedetomidine may also be instrumental in reducing disease severity. Such properties include favourable alterations of inflammation and immune function either directly via cell surface receptors or indirectly by altering sympathetic/parasympathetic imbalance.[7] There are several putative mechanisms by which dexmedetomidine might be advantageous in COVID-19 patients (Fig. 1). These involve inhibition of Toll-like receptor, high-