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.

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

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Keywords: COVID-19; dexmedetomidine; ICU; inflammation; NETosis; sedation

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-

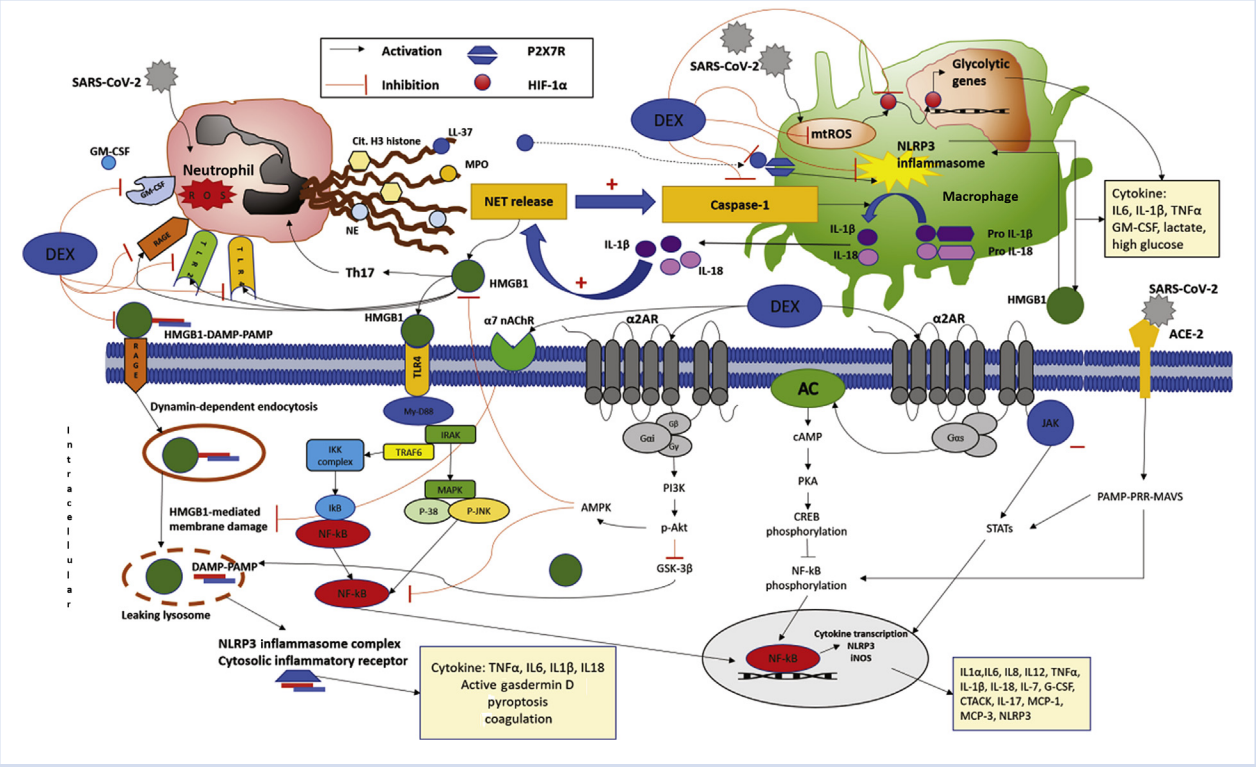

Fig. 1. Putative mechanisms of feedforward interactions between neutrophils, macrophages, and organ-specific cells potentiating NETosis during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and molecular mechanisms of organ protective and anti-inflammatory effects of dexmedetomidine. SARS-CoV-2 uses ACE-2 as its cell entry receptor and activates MAVS that stimulate viral-infected cells to secrete cytokines by activating NF-κB/STAT signalling pathways. SARS-CoV-2 infection results in NLRP3 inflammasome activation, and aggravates pyroptosis and production of DAMPs, such as HMGB1, that play potential key roles in establishing feedforward interactions between neutrophils, macrophages, and organ cells potentiating NETosis and pyroptosis during SARS-CoV-2 infection. Dexmedetomidine inhibits HMGB1/TLR and HMGB1/RAGE-mediated NETosis. Dexmedetomidine-mediated inhibition of NLPRP3 inflammasome, NF-κB, and JAK/STAT signalling pathways, and activation of cholinergic pathways confers anti-inflammatory and organ-protective effects and may reduce oxidative-stress-mediated pyroptosis and thrombotic complications of COVID-19 disease. Dexmedetomidine inhibits mt-ROS and may thereby prevent SARS-CoV-2-triggered mt-ROS production and stabilisation of HIF-1α and consequent sustained aerobic glycolysis mediating cytokine storm and inflammation. AC, adenylyl cyclase; ACE-2, angiotensin-converting enzyme 2; AMPK, adenosine monophosphate-activated protein kinase; cAMP, cyclic adenosine monophosphate; Cit. H3 histone, citrullinated H3 histone; COVID-19, coronavirus disease 2019; CREB, cyclic adenosine monophosphate response element-binding protein; CTACK, cutaneous T cell-attracting chemokine; DAMP, damage-associated molecular pattern; DEX, dexmedetomidine; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte–monocyte colony-stimulating factor; GSK-3β, glycogen synthase kinase 3 beta; HIF-1α, hypoxia-inducible factor-1α; HMGB1, high-mobility group box 1; IκB, inhibitor of nuclear factor-κB; IKK complex, inhibitor of nuclear factor-κB kinase; IL1α, interleukin 1α; IL-1β, interleukin 1β; IL6, interleukin 6; IL-7, interleukin 7; IL8, interleukin 8; IL12, interleukin 12; IL-17, interleukin 17; IL-18, interleukin 18; iNOS, inducible nitric oxide synthase; JAK/STAT, Janus kinase/signal transducers and activators of transcription; LL-37, cathelicidin antimicrobial peptide; MAPK, mitogen-activated protein kinase; MAVS, mitochondrial antiviral-signalling protein; MCP-1, monocyte chemoattractant protein-1; MCP-3, monocyte chemoattractant protein-3; MPO, myeloperoxidase; My-D88, myeloid differentiation primary response 88; NE, neutrophil elastase; NET, neutrophil extracellular t rap; NF-κB, nuclear factor kappa light chain enhancer of activated B cells; NLRP3, nod-like receptor family pyrin domain-containing protein 3; PAMP, pathogen-associated molecular pattern; p-Akt, phosphorylated protein kinase B; PI3K, phosphoinositide 3-kinases; P-JNK, phophorylated c-Jun N-terminal kinases; PKA, cyclic adenosine monophosphate-dependent protein kinase; PRR, pattern recognition receptor; P2X7R, P2X purinoceptor 7; RAGE, receptors for advanced glycation end-products; mt-ROS, mitochondrial reactive oxygen species; Th17, T-helper (Th) cell 17; TLR, toll-like receptor; TRAF6, tumor necrosis factor receptor associated factor 6; TNFα, tumor necrosis factor-alpha; α2AR, α_2-adrenenergic receptor; α7 nAChR, α_7-nicotinic acetylcholine receptor.

mobility group box 1, nod-like receptor family pyrin domain-containing protein 3 (NLPRP3) inflammasome, nuclear factor kappa light chain enhancer of activated B cells (NFκB), and Janus kinase/signal transducers and activators of transcription (JAK/STAT) signalling pathways,[14–18] which may be responsible for feedforward interactions between neutrophils and macrophages stimulating NETosis and aggravating organ damage during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[8–10] Dexmedetomidine-mediated activation of cholinergic pathways and decreased sympathetic tone confer additional cytoprotective and anti-inflammatory benefits.[13]

Use of dexmedetomidine for sedation in COVID-19 may have a theoretical advantage of skewing the immune response away from T-helper (Th) cell 17 (Th17),[19] which has been linked with immunopathogenesis of severe COVID-19 pneumonia.[20] Additionally, dexmedetomidine increases expression of natural killer cells, B-cells, $CD4^+$ T cells, and the ratios of $CD4^+$:$CD8^+$ and Th1:Th2 cells, while decreasing $CD8^+$ T cells.[21] By increasing interferon gamma:interleukin 4 (INFγ:IL4) ratio,[7] dexmedetomidine may possibly improve Th1 immune response against viral infections.[7,21] Hypoxia-inducible factor-1α (HIF-1α)-induced changes in monocyte metabolism by SARS-CoV-2 infection have been identified to inhibit T-cell response directly and reduce epithelial cell survival.[22] As dexmedetomidine can suppress mitochondrial reactive oxygen species formation and inhibit HIF-1α-dependent glycolysis in preclinical settings,[23] we believe that early use of dexmedetomidine for sedation in COVID-19 patients admitted to ICU may have therapeutic value as well.

Finally, by upregulating silent information regulator/Forkhead box transcription factor family O 3a (SIRT/FOXO3a) signalling[24] and by inhibiting stathmin-1/Bcl-2/caspase-9/caspase-3-mediated lidocaine-induced neurotoxicity,[25] dexmedetomidine used in conjunction with lidocaine may provide additional anti-inflammatory benefits, while improving the safety profile of lidocaine.

Although the wealth of scientific evidence from preclinical and clinical studies supports the organoprotective and anti-inflammatory effects of dexmedetomidine,[6,7] the role of dexmedetomidine as a novel therapeutic strategy to attenuate multi-organ dysfunction in COVID-19 remains hypothetical and awaits the outcome of clinical trials. Two such trials are ongoing and will assess whether or not dexmedetomidine has therapeutic benefits for patients with COVID-19. One of these trials (Immunomodulatory Profile of Dexmedetomidine Sedation in Patients Recovering After ARDS Covid-19; NCT04413864) seeks to study how dexmedetomidine changes the clinical status and immunomodulatory profile of intubated/ventilated patients with COVID-19 in ICU by determining changes in the interrelationship between cytokine levels and ICU delirium. The second study (Use of Dexmedetomidine in Light to Moderate Sedation in the Patient in the Palliative Situation of a SARS-CoV-2/COVID-19 Infection; NCT04350086) will be an investigation on patients with COVID-19 and respiratory failure, who are undergoing palliative care. Pending the results of these and other clinical trials investigating the immunomodulatory and therapeutic benefits of dexmedetomidine in patients with COVID-19, we advocate dexmedetomidine for sedation in patients with COVID-19 in ICU.

Declarations of interest

The authors declare that they have no conflicts of interest.

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High fresh gas flow during non-inhalational anaesthesia during the COVID-19 pandemic. Comment on *Br J Anaesth* 2020; 125: 773-778

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Keywords: COVID-19; environmental impact; healthcare costs; oxygen; sustainability

Editor—We read with interest the recent article of Zhong and colleagues[1] that provided a useful estimation of the cost and environmental benefits of using a 'high-flow' anaesthetic technique without inhalational anaesthetics. However, given the current pandemic status of coronavirus disease 2019 (COVID-19) and surges in case numbers around the world, we wonder if oxygen may be of greater value than just its monetary cost, as attributed by the authors. We agree that medical oxygen and air are relatively inexpensive (estimated costs of AU$0.40 [~ £0.22; US$0.28] and AU$0.028 [~ £0.015; US$0.02] 1000 L^{-1}, respectively), and that clinicians must take responsibility to reduce the economic burden and environmental impact of medical care. Of note, this study was conducted in Australia before the COVID-19 pandemic; Australia has until recently been relatively spared from the huge numbers of COVID-19-positive patients seen in other countries and from the impact on healthcare systems related to those numbers.

At the time of writing (15 October 2020), Australia had reported 27 364 cases with 904 deaths.[2] Other countries have been inundated with cases and their healthcare systems have strained to find enough resources to cope: for example, 676 455 cases with 43 383 deaths in the UK, 7 972 886 cases with 217 721 deaths in the USA, and 7 307 097 cases with 111 266 deaths in India.[2] Many hospitals in these countries have reported nearly, or completely, running out of oxygen as a result of the burden of both ventilated and non-ventilated patients (e.g. in the UK,[3] South Africa,[4] and India[5]).

For a given 6 h case with a circle system, running an inhalational agent-free anaesthetic with fresh gas flows (FGF) of 1 L min^{-1}, 36 L and 126 L of oxygen would be consumed with a fraction of inspired oxygen (FiO_2) of 0.3 and 0.5 respectively. The recommendation of Zhong and colleagues[1] of an FGF of 6 L min^{-1} would increase the oxygen consumption, for the same length of case, to 252 L and 792 L with FiO_2 of 0.3 and 0.5 respectively. Higher flows may be used for induction and emergence with both modes of anaesthesia, thus allowing a fair comparison. Within the confines of safety, improving cost efficiency and reducing environmental burdens must be a priority.[6] Given the current shortage of the most precious of medical resources in many countries across the world, we feel that the high-flow anaesthesia suggested here would be best left until after this pandemic has abated.

Declarations of interest

The authors declare that they have no conflicts of interest.

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