Author/s:
Lankadeva, YR;Shehabi, Y;Deane, AM;Plummer, MP;Bellomo, R;May, CN

Title:
Emerging benefits and drawbacks of α2-adrenoceptor agonists in the management of sepsis and critical illness

Date:
2021-03-01

Citation:
Lankadeva, Y. R., Shehabi, Y., Deane, A. M., Plummer, M. P., Bellomo, R. & May, C. N. (2021). Emerging benefits and drawbacks of α2-adrenoceptor agonists in the management of sepsis and critical illness. British Journal of Pharmacology, 178 (6), pp.1407-1425. https://doi.org/10.1111/bph.15363.

Persistent Link:
https://hdl.handle.net/11343/298233

Lankadeva Yugeesh (Orcid ID: 0000-0002-3589-9111)

Emerging benefits and drawbacks of alpha$_2$-adrenoceptor agonists in the management of sepsis and critical illness

Yugeesh R Lankadeva PhD[1,4]; Yahya Shehabi MBBS, PhD[2]; Adam M Deane MBBS, PhD[3,4]; Mark P Plummer, MBBS, PhD[3,4]; Rinaldo Bellomo MD, PhD[4]; Clive N May PhD[1,4]

[1]*Preclinical Critical Care Unit, Florey Institute of Neuroscience and Mental Health, Melbourne, Victoria, Australia*

[2]*Department of Intensive Care Medicine, Monash Health, School of Clinical Sciences, Monash University, Melbourne, Prince of Wales Clinical School of Medicine, University of New South Wales; Sydney; Australia*

[3]*Department of Intensive Care Medicine, Royal Melbourne Hospital, Melbourne, Victoria, Australia*

[4]*Centre for Integrated Critical Care, School of Medicine, University of Melbourne, Melbourne, Victoria, Australia*

Conflicts of Interest: None

Address correspondence: Yugeesh. R Lankadeva (PhD),

Florey Institute of Neuroscience and Mental Health, University of Melbourne,
30 Royal Parade, Parkville, Victoria, 3052 Australia

E-mail: yugeesh.lankadeva@florey.edu.au; Phone: +61-3-8344-0417 Fax: +61-3-9035-3107

Running title (60 characters): alpha$_2$-adrenoceptor agonists in sepsis and critical illness

Word Count: 9,414 (excluding Abstract, Table, Figure Legends and References)

Abbreviations:

α: alpha

ACh: Acetylcholine (ACh)

α7 nAChR: nicotinic ACh receptor

AKI: Acute kidney injury

APACHE II: Acute Physiology and Chronic Evaluation II

ATP: Adenosine triphosphate

BBB: Blood brain barrier

CI: Confidence interval

CPB: Cardiopulmonary bypass

DAMPS: Damage-associated molecular patterns

DESIRE trial: Dexmedetomidine for Sepsis in Intensive Care Unit

FDA: Federal Drug Administration

ICU: Intensive care unit

IL: Interleukin

IFN: Interferon

JAK2: Janus kinase (JAK2)

K_{ATP} channels: ATP-sensitive potassium channels

MAP: Mean arterial pressure

MENDS trial: Maximising Efficacy of Targeted Sedation and Reducing Neurological Dysfunction

MIDEX and PRODEX trials: Dexmedetomidine Versus Midazolam or Propofol for Sedation during prolonged mechanical ventilation

NF-κβ: nuclear factor kappa-light-chain-enhancer of activated B cells

OR: Odds ratio

PAMPS: Pathogen-associated molecular patterns

RASS: Richmond Agitation Sedation Scale

RCT: Randomised clinical trial

RVLM: Rostral ventrolateral medulla

SEDCOM trial: Safety and Efficacy of Dexmedetomidine Compared with Midazolam

SNA: Sympathetic nerve activity

SOFA: Sequential organ failure assessment

SPICE: Sedation Practice in Intensive Care Evaluation

STAT3: Signal transducer and activator of transcription 3

Th1: CD4+ T-helper type 1 cells

Th2: CD4+ T-helper type 2 cells

TNF-α: Tumour necrosis factor alpha

Abstract

Alpha$_2$-adrenoceptor agonists are increasingly being used for the provision of comfort, sedation and the management of delirium in critically ill patients with and without sepsis. In this context, increased sympathetic and inflammatory activity are common pathophysiological features linked to multi-organ dysfunction, particularly in patients with sepsis or those undergoing cardiac surgery requiring cardiopulmonary bypass. Experimental and clinical studies support the notion that the alpha$_2$-adrenoceptor agonists, dexmedetomidine and clonidine, mitigate sympathetic and inflammatory overactivity in sepsis and cardiac surgery requiring cardiopulmonary bypass. These effects can protect vital organs, including the cardiovascular system, kidneys and brain. We review the pharmacodynamic mechanisms by which alpha$_2$-adrenoceptor agonists might mitigate multi-organ dysfunction arising from pathophysiological conditions associated with excessive inflammatory and adrenergic stress in experimental studies. We also outline recent clinical trials that have examined the use of dexmedetomidine in critically ill patients with and without sepsis and in patients undergoing cardiac surgery.

Key words: alpha$_2$-adrenoceptor agonists, dexmedetomidine, clonidine, critical illness, sepsis, cardiac surgery, cardiopulmonary bypass,

1. INTRODUCTION

Effective management of sedation, pain, agitation and delirium is a cornerstone of the management of critically ill patients in the intensive care unit (ICU) (Devlin et al., 2018).

Over the years, propofol and benzodiazepines (i.e. midazolam, lorazepam and diazepam) have been commonly used to manage sedation, agitation, and delirium in ICUs, with other adjunct agents such as ketamine recommended for patients that require mechanical ventilation (Devlin et al., 2018). Opioids such as fentanyl, morphine and remifentanil are currently also recommended for management of pain in patients in ICUs (Devlin et al., 2018). However, critically ill patients often demonstrate unpredictable pharmacokinetics and pharmacodynamics, due to underlying hemodynamic instability, drug interactions, altered protein binding, and multi-organ dysfunction, which can complicate achieving optimal levels of sedation and analgesia (Skrobik, Leger, Cossette, Michaud & Turgeon, 2013). Compared with lighter sedation levels, deep sedation and respiratory depression have often been associated with poor health outcomes, including, prolonged ventilation, delirium and mortality (Girard et al., 2008; Mehta et al., 2012; Shehabi et al., 2018; Stephens et al., 2018). Thus, ideal drugs for sedation and analgesia in critically ill patients should induce a safe hemodynamic profile, cause minimal respiratory depression, be eliminated independently of organ function, have a short biological half-life and no active metabolites.

Over recent years, the alpha (α)$_2$-adrenoceptor agonist, dexmedetomidine, has gained more popularity in the intensive care management of patients due to its sedative, analgesic and anxiolytic properties with a lesser undesirable side effect profile than clonidine (Fairbanks, Stone & Wilcox, 2009; Knaus et al., 2007). A distinctive feature in the pattern of sedation

achieved by dexmedetomidine is rousable and more interactive sedation, with minimal respiratory depression compared with traditional sedatives such as propofol and midazolam (Girard et al., 2008; Mehta et al., 2012; Shehabi et al., 2018; Stephens et al., 2018). Furthermore, the anxiolytic features of dexmedetomidine lower the prevalence of delirium and agitation amongst adult patients in ICU (Reade et al., 2016; Riker et al., 2009; Skrobik, Duprey, Hill & Devlin, 2018). Due to these potential benefits, the current sedation guidelines recommend dexmedetomidine use over benzodiazepines for light-to-moderate sedation in critically ill patients (Devlin et al., 2018).

There is emerging experimental evidence that dexmedetomidine may provide a degree of organ protection (blood vessels, kidney, heart and brain) during sepsis using different animal models. Accordingly, dexmedetomidine may have benefits for the treatment of patients with sepsis and those undergoing major cardiac surgery, where multi-organ dysfunction is a common phenotype that is associated with considerable morbidity and mortality (Bellomo et al., 2017; Evans et al., 2018; Kellum & Prowle, 2018; Sakr et al., 2012). In this review, we outline recent experimental research that delineates the pharmacodynamic mechanisms underlying the organ protective effects of α_2-adrenoceptor agonists, with emphasis on the pathophysiology of multi-organ dysfunction arising from sepsis and cardiac surgery requiring cardiopulmonary bypass (CPB). We also outline clinical perspectives on the benefits and drawbacks of using of dexmedetomidine for sedation in critically ill patients, both as standard-of-care treatment and for future ICU and peri-operative applications, where evidence for its safety and efficacy is mounting.

2. PHARMACOLOGY OF ALPHA$_2$- ADRENOCEPTOR AGONISTS

α_2-adrenoceptors belong to a family of membrane-bound guanine nucleotide binding protein coupled receptors, which consist of three main sub-types; α_{2A}-, α_{2B}- and α_{2C}- (Aantaa, Marjamäki & Scheinin, 1995). The actions of α_2-adrenoceptor sub-types are related to their guanine nucleotide-binding protein coupled effector mechanisms. The three α_2-adrenoceptor subtypes are widely distributed both pre- and post-synaptically throughout the central nervous system and periphery, where they mediate a broad spectrum of pharmacodynamic actions. First, we will review the mechanisms of action of α_2-adrenoceptor agonists on the central nervous system to describe the sedative, analgesic and anxiolytic properties that are drawn on for the management of comfort and safety of critically ill patients.

2.1 Sedative effects of α_2-agonists

α_{2A}-, α_{2B}- and α_{2C}- adrenoceptor subtypes are expressed in many brain nuclei including the locus coeruleus in the pons (Aantaa, Marjamäki & Scheinin, 1995; Tavares, Handy, Bogdanova, Rosene & Gavras, 1996). The sedative effects of α_2-agonists are achieved mainly through activation of the α_{2A}- and α_{2B}- adrenoceptor subtypes (Nelson, Lu, Guo, Saper, Franks & Maze, 2003) while the anxiolytic effects are postulated to be mediated by its actions on the α_{2C}-adrenoceptor subtype (Figure 1) (Aantaa, Marjamäki & Scheinin, 1995). Activation of α_2-adrenoceptors inhibits adenylyl cyclase, reduces the levels of 3,5-cyclic adenosine monophosphate-dependent protein kinase and attenuates the phosphorylation of target regulatory proteins (Hayashi & Maze, 1993). Simultaneously, there is an efflux of potassium through calcium-activated potassium channels and an inhibition of calcium entry within nerve

terminals. The resultant change in membrane ion conductance leads to hyperpolarisation of the excitable cell membrane, which suppresses neuronal firing (Hayashi & Maze, 1993). The inhibition of neuronal firing within the locus coeruleus reduces the activity of the ascending noradrenergic pathways leading to sedation and anxiolysis. The pattern of sedation induced by α_2-adrenoceptor agonists closely resembles physiological sleep with minimal respiratory depression, which differs from other sedative agents such as propofol and midazolam, which target the g-aminobutyric acid or opioid receptors and induce deep sedation (Wu et al., 2016).

2.2 Antinociceptive effects of α_2-agonists

The mechanisms underlying the analgesic effects of α_2-adrenoceptor agonists relate to both supra-spinal and spinal modes of action (Fairbanks, Stone & Wilcox, 2009). The locus coeruleus is the site of origin for the descending medullo-spinal noradrenergic pathway, an important modulator of nociceptive neurotransmission (Fairbanks, Stone & Wilcox, 2009), with the central antinociceptive effects of α_2-agonists being attributed to its stimulation of α_{2A}-adrenoceptors in the locus coeruleus (Figure 1). In addition to their supra-spinal effects, α_2-agonists have been demonstrated to directly stimulate pre-synaptic α_{2A}- and α_{2C}-adrenoceptors in the spinal cord, thereby inhibiting the firing of nociceptive neurons (Fairbanks, Stone & Wilcox, 2009) (Figure 1). Stimulation of the substantia gelatinosa of the dorsal horn and the post-synaptic membranes of the intermediate neurons by α_2-agonists can promote efflux of potassium and inhibition of calcium entry leading to the cell membrane's hyperpolarisation, which can suppress transmission of pain signals to the brain (Fairbanks, Stone & Wilcox,

2009). In addition, α_2-agonists inhibit the neuronal firing of peripheral Aδ and C pain fibres by inhibiting the release of pro-nociceptive neurotransmitters such as substance P and glutamate (Maze & Fujinaga, 2000).

2.3 Pharmacokinetics of α_2-adrenoceptor agonists

At a clinical level, there are two central α_2-adrenoceptor agonists available for the treatment of patients, clonidine and dexmedetomidine. Clonidine and dexmedetomidine are both imidazoline compounds. Clonidine can be administered orally, transdermally or intravenously. Dexmedetomidine is the pharmacologically active dextroisomer of the veterinary sedative medetomidine and is only currently approved for intravenous use. At clinically relevant doses, the distribution half-lives of dexmedetomidine and clonidine are 6 minutes and 20 minutes, respectively for adult patients (Dyck, Maze, Haack, Vuorilehto & Shafer, 1993). The elimination half-life of dexmedetomidine is approximately 2 hours, via hepatic glucuronidation and cytochrome 450 hydroxylation into inactive, non-toxic metabolites, followed by excretion in the urine (95%) and faeces (4%) (Weerink, Struys, Hannivoort, Barends, Absalom & Colin, 2017). The elimination half-life of clonidine is much longer, 12-16 hours, with 50% excreted renally in the form of active metabolites and the remaining undergoing hepatic glucuronidation and cytochrome 450 hydroxylation into inactive metabolites (Weerink, Struys, Hannivoort, Barends, Absalom & Colin, 2017). Clonidine is 20% bound to plasma proteins and displays a volume distribution of 1.7-2.5 L/kg, whereas dexmedetomidine is 90% protein bound to serum albumin and α_1-glyocprotein and has a volume distribution of 1.3-2.4 L/kg (approximately 90-194 L). Dexmedetomidine has a much greater selectivity towards α_2-adrenoceptors than

clonidine, with an α_2:α_1 selectivity ratio of 1620:1 vs. 220:1, respectively (Virtanen, Savola, Saano & Nyman, 1988; Weerink, Struys, Hannivoort, Barends, Absalom & Colin, 2017).

Clonidine is approved for the treatment of hypertension, but its use outside of blood pressure control has been limited and, importantly, the subject of few controlled investigations. There have been small case series and small comparative studies of its use for sedation. However, such studies have shown significant hypotension and bradycardia, with no evidence of the benefits reported with dexmedetomidine. There is an ongoing randomised clinical trial (RCT) that is evaluating the efficacy of dexmedetomidine versus clonidine in regard to time to extubation, length of ICU stays, incidence and duration of delirium and sedation quality in 1,737 critically ill patients (NCT03653832).

Currently, dexmedetomidine is considered to be a more suitable agent for intensive care management of patients because its hypotensive and bradycardic effects are less prominent for any given level of sedation compared with clonidine (Weerink, Struys, Hannivoort, Barends, Absalom & Colin, 2017). The linear pharmacokinetic profile, shorter elimination half-life, rapid onset of sedative effect with a high neurospecificity, predictable hemodynamic response and minimal respiratory effects have made dexmedetomidine an attractive agent for operative and post-operative management of sedation and analgesia (Belleville, Ward, Bloor & Maze, 1992; Chorney, Gooch, Oberdier, Keating & Stahl, 2013). Thus, the clinical use of dexmedetomidine follows from these favourable pharmacokinetics and the approval of dexmedetomidine, but not clonidine, by the United States Federal Drug Administration (FDA) and the Australian Therapeutic Goods Administration for ICU sedation for up to 24 hours at a maximal dose range of 0.7-1.0 μg/kg/h for procedural sedation (Devlin et al., 2018).

2.4 Clinical trials using dexmedetomidine in critically ill patients

Despite FDA approval of dexmedetomidine being limited to 24 hours, the European Medicines Agency has recommended no such time-limit for its use in ICUs. Accordingly, dexmedetomidine has been used for longer periods in ICUs. In critically ill patients, a 7 day infusion of dexmedetomidine had sedative and analgesic effects, with predictable cardiovascular effects (Shehabi, Ruettimann, Adamson, Innes & Ickeringill, 2004). This paved the way for subsequent pivotal RCTs in mechanically ventilated critically ill patients. Dexmedetomidine was compared with lorazepam in the Maximising Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) trial in 2007 (Pandharipande et al., 2007) and with midazolam in the Safety and Efficacy of Dexmedetomidine Compared with Midazolam (SEDCOM) trial in 2009 (Riker et al., 2009). Furthermore, two multicentre, double blind-placebo controlled RCTs compared dexmedetomidine with midazolam and propofol in the Dexmedetomidine Versus Midazolam or Propofol for Sedation trials during prolonged mechanical ventilation (MIDEX and PRODEX trials), and demonstrated the safety and non-inferiority of dexmedetomidine as a first-line sedative in ventilated critically ill patients with reduced extubation time when compared with midazolam (estimated ratio of 1.07 confidence interval (CI): 0.97 to 1.18) and with propofol (1.00 CI 0.92-1.08) (Jakob et al., 2012). The putative advantage of dexmedetomidine over other sedatives (e.g. propofol or midazolam) is its ability to induce "rousable sedation", a state where the patient appears calm and asleep but is easily awakened by light touch or voice. This state is associated with minimal effect on the respiratory centre and thus preservation of respiratory drive and near normal ventilation. However, in the ICU this state cannot be achieved in all patients and, even at large doses,

dexmedetomidine may be unable to achieve sedation that is "safe" and the use of additional agents such as low dose propofol or midazolam and opioids may be required (Reade & Finfer, 2014; Shehabi, Bellomo, Mehta, Riker & Takala, 2013).

Clinical trials have also demonstrated that dexmedetomidine-based sedation provides some advantages over usual care with, typically, propofol, lorazepam or midazolam. These advantages include a reduction in the duration of sedation and ICU stay and a possible effect on reducing the duration of delirium (Jakob et al., 2012; Kawazoe et al., 2017; Pandharipande et al., 2007; Riker et al., 2009). However, undesirable cardiovascular effects (i.e. bradycardia and hypotension) were also noted. These findings and the desire to improve the quality of sedation towards a lighter level, led to the design and conduct of the Sedation Practice in Intensive Care Evaluation (SPICE III) trial (Shehabi et al., 2019). The SPICE III trial randomized 4,000 patients to receive dexmedetomidine as the primary sedative agent or usual care, which consisted of sedation using conventional agents (e.g. propofol or midazolam) to achieve the clinically desired level of sedation (Shehabi et al., 2019). The trial was open-label and randomization and treatment were initiated within a few hours of mechanical ventilation and continued based on clinical need for sedation or a maximum of 28 days. Clinicians were asked to aim for a target sedation score of -2 to 1 on the Richmond Agitation and Sedation Scale (RASS) whenever possible. The primary outcome was mortality at 90 days. First, this pivotal trial showed that such sedation did not affect overall mortality. It also did not affect mortality in key clinical pre-defined subgroups (Figure 2). However, it showed statistically significant heterogeneity of treatment effect according to age such that dexmedetomidine-

based sedation appeared to increase 90-day mortality in patients below the median age of 63.7 years with relative risk increase of 23.7% (Shehabi et al., 2019).

In contrast, in patients older than the median trial age, dexmedetomidine-based sedation appeared to decrease mortality with a relative risk reduction of 11%. Patients randomized to dexmedetomidine experienced a significant 9.2% increase in the percentage of RASS scores in the target light sedation range and a 12.2% decrease in the percentage of RASS score in the deep sedation range. These effects were associated with a small but significant decrease in the use of propofol and a marked decrease in the use of midazolam (from 11.9% to 2.9%). Finally, the use of opioids was slightly decreased in the dexmedetomidine group consistent with its known analgesic effect. Dexmedetomidine-based sedation increased the number of coma and delirium free days compared with usual care, consistent with previous RCTs (Shehabi et al., 2019). Importantly, the SPICE III trial suggested for the first time, an age-dependent and potentially dose-dependent effect of sedative agents on important patient-centred outcome such as mortality. Due to the secondary nature of the current sub-group analysis, it is imperative that such observations be confirmed in a subsequent clinical trial (SPICE IV). The SPICE IV, in contrast to SPICE III is planned to be a double-blind placebo controlled RCT of 3,500 mechanically ventilated patients who are older than 65 years of age. This trial, funded by the National Health and Medical Research Council of Australia, will provide a definitive evaluation of the age- and dose-dependent effects of dexmedetomidine as the primary sedative agent (ACTRN12620001088932).

In addition to dexmedetomidine continuing to be of interest for providing sedation to critically ill patients, there are emerging experimental and clinical studies evaluating whether

α_2- agonists offer a degree of organ protection, particularly in patients with sepsis and also those undergoing cardiac surgery requiring CPB.

3 ORGAN DYSNFUNCTION ARISING FROM SEPSIS

Despite recent advances in medical diagnostics and therapeutics, sepsis remains the most common cause of ICU admissions and the leading cause of mortality in ICUs worldwide. Sepsis is defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection" (Singer et al., 2016). From 1990-2017, the global annual incidence of sepsis was reported to be ~49 million, with an associated ~22% mortality (i.e. ~11 million cases) (Rudd et al., 2020). Sepsis-associated morbidity and mortality is highly proportional to the extent and degree of multi-organ dysfunction. The pathophysiological mechanisms driving sepsis-induced multi-organ dysfunction syndrome remain to be fully elucidated. However, common pathophysiological features include inflammatory and sympathetic overactivity, vascular dysfunction and microcirculatory abnormalities leading to regional organ-specific tissue hypoxia and mitochondrial dysfunction (Andreis & Singer, 2016; Lankadeva, Okazaki, Evans, Bellomo & May, 2019; Lankadeva et al., 2020c; Ma et al., 2019; Spapen, Jacobs & Honoré, 2017). Herein, we will review the recent experimental research that illustrates how α_2-agonists can mitigate some of these pathological processes that mediate organ dysfunction in sepsis.

3.1 Immunological pharmacodynamics of α_2-agonists in sepsis

3.11 Immune activation in sepsis

Sepsis is associated with an overwhelming immune response to an infection (Singer et al., 2016). The initial pro-inflammatory response in sepsis arises from an interplay between

pathogen-associated molecular patterns (PAMPS) from the invading pathogen and the release of intracellular damage-associated molecular patterns (DAMPS) from the injured host tissue (Beutler, Hoebe, Du & Ulevitch, 2003). Following the initial recognition of PAMPS and DAMPS by Toll-like receptors expressed on endothelial cells, translocation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κβ) drives the expression of multiple activator genes, including those for cytokines associated with inflammation such as tumour necrosis factor alpha (TNF-α), interleukin (IL)-1, IL-12, IL-18 and type I interferon (IFN). These initiating cytokines drive a cascade of secondary inflammatory cytokines (IL-6, IL-8, IFNδ) and chemokines (chemokine ligand 2 & 3 etc.). Production of inflammatory cytokines is an essential part of the initiation and escalation of the innate immune system, which is required to mount an immune response against the underlying infection in sepsis (Hotchkiss, Moldawer, Opal, Reinhart, Turnbull & Vincent, 2016). However, when inflammation becomes excessive and protracted, it can drive multiple deleterious processes including myocardial dysfunction, marked peripheral vasodilation, capillary leakage, endothelial dysfunction and microcirculatory abnormalities that can culminate in hypovolemia, tissue oedema, tissue hypoperfusion and hypoxia (Andreis & Singer, 2016; Suzuki et al., 2017). Furthermore, high levels of inflammatory cytokines can co-exist with significant innate immune suppression, which can culminate in nosocomial infections, immune paralysis and mortality (Hall et al., 2013). Accordingly, therapeutic approaches that mitigate the hyper-inflammatory phase of early sepsis may yield a degree of protection to multiple organs.

3.12 Anti-inflammatory effects of α_2-agonists

There is an accumulating body of pre-clinical evidence that α_2- agonists can modulate inflammation by stimulating the cholinergic anti-inflammatory pathway (Figure 1). A high density of α_{2A}- adrenoceptors are found in the dorsal motor nucleus of the vagus (Tavares, Handy, Bogdanova, Rosene & Gavras, 1996; Unnerstall, Kopajtic & Kuhar, 1984). Thus, α_2-agonists can stimulate efferent vagal activity and have a significant influence on vagal tone-regulated inflammation by activating the cholinergic anti-inflammatory pathway (Figure 1). Acetylcholine (ACh) is the major vagal nerve-derived neurotransmitter, which acts on the nicotinic ACh receptor (α7 nAChR) to inhibit release of TNF-α, IL-1, IL-6 and IL-8 (Tracey, 2007). Moreover, macrophages and other cytokine-producing cells also express ACh receptors, which can transduce intracellular signals to inhibit cytokine synthesis (Tracey, 2007). Thus, stimulation of the vagal nerve by α_2-agonists can inhibit production of pro-inflammatory cytokines by decreasing the nuclear translocation of NF-κβ, as well as, by activating the transcription factor signal transducer and activator of transcription 3 (STAT3) via phosphorylation of janus kinase 2 (JAK2), which is recruited by α7 nAChR (Chatterjee, Al-Abed, Sherry & Metz, 2009; de Jonge et al., 2005).

In keeping with the above notions, dexmedetomidine and clonidine have consistently been shown to significantly reduce plasma levels of pro-inflammatory cytokines in sheep subjected to gram-negative sepsis (Calzavacca et al., 2018; Lankadeva et al., 2015; Lankadeva et al., 2019b) and in rats subjected to endotoxin-induced septic shock (Hofer et al., 2009; Taniguchi, Kurita, Kobayashi, Yamamoto & Inaba, 2008). In agreement with such animal studies, significant reductions in TNF-α, IL-1β, IL-6 and C-reactive protein have been reported in critically ill patients with and without sepsis following treatment with dexmedetomidine

(Kawazoe et al., 2017; Memiş, Hekimoğlu, Vatan, Yandım, Yüksel & Süt, 2007; Ohta, Miyamoto, Kawazoe, Yamamura & Morimoto, 2020). There is ample evidence from rodent models of sepsis to support the notion that reducing inflammation with α_2-agonists might improve survival rates (Hofer et al., 2009; Taniguchi, Kurita, Kobayashi, Yamamoto & Inaba, 2008). However, future clinical studies are required to determine the optimal timing of drug administration and to prospectively identify patients with sepsis who are most likely to benefit from such therapeutic modulation of inflammatory immune pathways (Hotchkiss, Moldawer, Opal, Reinhart, Turnbull & Vincent, 2016).

3.2 Neural pharmacodynamics of α_2-agonists in sepsis

3.21 Sympathetic activation in sepsis

Critical illness with and without sepsis is frequently associated with a prolonged, excessive activation of the sympathetic nervous system (Dünser & Hasibeder, 2009). In septic patients, this is indicated by the high levels of plasma noradrenaline (Groves, Griffiths, Leung & Meek, 1973) that are positively correlated with mortality (Benedict & Rose, 1992). In experimental studies, differential increases in sympathetic outflow to the heart and kidneys occur in ovine sepsis (Lankadeva et al., 2015; Ramchandra, Wan, Hood, Frithiof, Bellomo & May, 2009) and renal sympathetic nerve activity (SNA) is increased in rats during intravenous infusion of live *Escherichia coli* or endotoxin (Julien, Oréa, Quintin, Piriou & Barrès, 2017; Pålsson, Ricksten, Delle & Lundin, 1988). In sepsis, there is evidence that the combination of hypotension and inflammation results in excessive activation of the sympathetic nervous system, which helps support arterial blood pressure. In early sepsis, before arterial pressure decreased, cardiac SNA progressively increased and this increase is inhibited by indomethacin, indicating a stimulatory

effect of prostaglandins (Booth, Ramchandra, Calzavacca & May, 2014). At the later stages of sepsis, the high level of cardiac SNA is partly mediated by the arterial baroreflex in response to the decrease in arterial pressure (Ramchandra, Wan, Hood, Frithiof, Bellomo & May, 2009). In contrast, following the onset of gram-negative sepsis, renal SNA is initially transiently inhibited, followed by a prolonged stimulation as hypotension developed (Ramchandra, Wan, Hood, Frithiof, Bellomo & May, 2009). The important contribution of the cardiac sympathetic activation to the increases in heart rate and cardiac output in sepsis is indicated by the effects of the β_1-adrenoceptor blocker, atenolol, to reduce these effects (Calzavacca, Lankadeva, Bailey, Bailey, Bellomo & May, 2014).

3.22 Detrimental effects of sympathetic activation in sepsis

There is increasing awareness that the high level of sympathetic activation in sepsis might have detrimental effects, including myocardial dysfunction (Kumar, Haery & Parrillo, 2001), hepatic inflammation and metabolic dysregulation (Aninat, Seguin, Descheemaeker, Morel, Malledant & Guillouzo, 2008). Catecholamines have also been shown to contribute to the formation of thromboses and microcirculatory abnormalities (De Backer et al., 2013) and to stimulate the growth of several gram-positive and negative bacteria *in vivo* (Evans, Miles & Niven, 1948). Furthermore, sympathetic overstimulation is accepted as a critical mediator of sepsis-induced immunosuppression (Lankadeva et al., 2020c; Martelli, Yao, McKinley & McAllen, 2014) These findings have led to the suggestion that sympatholytic therapies may offer a degree of organ protection during sepsis (Andreis & Singer, 2016).

3.23 Sympatholytic effects of α_2- agonists

It is established that α_2-agonists activate pre-synaptic α_{2A}-adrenoceptors on neurons in central autonomic nuclei and the spinal cord and also on peripheral sympathetic nerves to inhibit release of noradrenaline from both central and peripheral nerve terminals, thereby reducing global SNA (Figure 1) (Allen & Guyenet, 1993; Hong, Milne, Loomis & Jhamandas, 1992; Sun & Guyenet, 1986). Injection of clonidine into the rostral ventrolateral medulla (RVLM) decreased arterial pressure, heart rate, and renal SNA (Yamazato, Sakima, Nakazato, Sesoko, Muratani & Fukiyama, 2001) and intracerebroventricular administration of dexmedetomidine reduced arterial pressure, heart rate, and plasma noradrenaline levels (Shirasaka, Qiu, Kannan & Takasaki, 2007). There is also evidence that dexmedetomidine inhibits both parvocellular neurons in the paraventricular nucleus of the hypothalamus, which play a role in the control of sympathetic outflow, and magnocellular neurons, that influence vasopressin release (Shirasaka, Qiu, Kannan & Takasaki, 2007). The α_2-agonists, dexmedetomidine and clonidine, have also been demonstrated to reduce renal SNA towards pre-morbid levels in ovine gram-negative sepsis (Lankadeva et al., 2015; Lankadeva et al., 2019b) and in rats subjected to endotoxemia (Julien, Oréa, Quintin, Piriou & Barrès, 2017). Moreover, α_2-agonists also have a central action to increase vagal tone (Sharp, Wang & Mendelowitz, 2014). This effect contributes to their ability to cause bradycardia and to reduce inflammation, as shown by their action to decrease the circulating levels of cytokines in sepsis (Figure 1) (Calzavacca et al., 2018; Lankadeva et al., 2015; Lankadeva et al., 2019b).

3.3 Vascular pharmacodynamics of α_2-agonists in sepsis

3.31 Sepsis-induced vasoplegia

Sepsis is characterised by life threatening falls in blood pressure, due to peripheral vasodilatation, in part due to reduced pressor responsiveness to the high circulating levels of endogenous catecholamines (Andreis & Singer, 2016; Geloen et al., 2013; Lankadeva et al., 2015). Multiple mechanisms have been implicated in such sepsis-induced vasoplegia including excessive release of vasodilators such as nitric oxide and eicosanoids, excessive opening of adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channels, reduced calcium sensitivity, decreased density of vascular α_1-adrenoceptors, vasopressin deficiency and dysfunction of the hypothalamic-pituitary-adrenal axis and renin-angiotensin-aldosterone system (Buckley, Singer & Clapp, 2006; Kimmoun, Ducrocq & Levy, 2013). Noradrenaline is currently the recommended vasopressor for first-line therapy to restore mean arterial pressure (MAP) in patients with septic shock (Rhodes et al., 2017). However, a major unresolved problem encountered during treatment of septic shock is that 15-20% of patients do not respond to low or moderate doses of noradrenaline (from 0.05 to 0.2 mcg/kg/min), which can result in hypotension, organ hypoperfusion, multi-organ dysfunction and mortality (Annane et al., 1998). In some patients, even doses of noradrenaline >1.0 mcg/kg/min may be insufficient to achieve a target MAP of >65 mmHg (Annane et al., 2018).

In rodent sepsis, the sympathetic overstimulation and increases in nitric oxide and inflammatory cytokines contribute to the down-regulation of vascular smooth muscle α_1-adrenoceptors and angiotensin type 1 receptors, respectively (Bucher, Kees, Taeger & Kurtz, 2003; Schmidt, Höcherl, Kurt, Moritz, Kurtz & Bucher, 2010). The corresponding down-regulation of vascular α_1- adrenoceptors and angiotensin type 1 receptors can contribute to the sepsis-induced reduction in pressor responsiveness to adrenergic vasopressors (noradrenaline

and phenylephrine) and non-adrenergic vasopressors (angiotensin II) reported in human and ovine sepsis (Annane et al., 1998; Annane et al., 2018; Lankadeva et al., 2015; Lankadeva et al., 2019b).

3.32 Restoration of vascular sensitivity in sepsis by α_2-agonists

Development of therapies that reverse vasopressor hypo-responsiveness in septic shock would improve circulatory management of haemodynamics and may be of benefit to patients. Both clonidine (200 μg/kg) and dexmedetomidine (100 μg/kg) administered at supra-therapeutic doses restore vascular reactivity in endotoxic rats (Geloen et al., 2013), which has been proposed to be due the inhibition of SNA and up-regulation of vascular α_1-adrenoceptors, which were downregulated or desensitised in sepsis (Pichot, Geloen, Ghignone & Quintin, 2010) (Figure 1). Subsequently, these findings in rodents were validated in an ovine model of hyperdynamic sepsis, in which clinically relevant doses of clonidine (1 μg/kg/h) and dexmedetomidine (0.5 μg/kg/h) reduced the high levels of renal SNA and restored pressor responsiveness to phenylephrine and noradrenaline (Lankadeva et al., 2015; Lankadeva et al., 2019b). In accord, a prospective crossover clinical study, in 38 septic patients, demonstrated that switching from usual care propofol to dexmedetomidine (0.7 μg/kg/h) significantly reduced noradrenaline requirements to attain target MAP (Morelli et al., 2019). Whether this represents the effect of α_2-agonists or a reduction in hypotensive properties of propofol or both is currently not known. In this regard, a recent post-hoc subgroup analysis of patients with septic shock (N=83) included in the SPICE III trial reported similar vasopressor requirements in the first 48 hours in patients. However, on multivariable adjusted analysis (for admission diagnosis, baseline noradrenaline equivalents/MAP ratio, continuous renal replacement

therapy, age, hydrocortisone treatment, and liver cirrhosis), vasopressor requirements to maintain target MAP were significantly lower in the dexmedetomidine than in the usual care group (ratio of difference in geometric means 1.44 [1.07, 1.95]) (Cioccari et al., 2020).

3.33 Mechanisms by which α_2-agonists improve vascular responsiveness in sepsis

An important observation in ovine sepsis was that clonidine not only restored vasopressor responsiveness to the α_1-adrenoceptor agonist, phenylephrine, but also to a non-adrenoceptor agonist, angiotensin II (Lankadeva et al., 2015). These findings suggest that α_2-agonists may also modulate vasopressor responsiveness via direct vascular actions, independent of their central sympatholytic actions. For instance, α_2-agonists may have a direct vascular action by preventing excessive opening of vascular K_{ATP} channels. K_{ATP} channels cause hyperpolarisation and relaxation of vascular smooth muscle cells and have been proposed to play a critical role in the development of vascular hypo-responsiveness in septic shock (Buckley, Singer & Clapp, 2006). The two most common subunits of K_{ATP} channels are, the sulphonylurea receptor and a pore forming subunit belonging to the Kir6.0 family. There is evidence that, in sepsis, the K_{ATP} channel sulphonylurea receptor becomes dysfunctional or uncoupled from the pore forming subunit. (O'Brien, Thakur, Buckley, Singer & Clapp, 2005). Selective inhibition of the vascular K_{ATP} channel pore forming Kir6.0 subunit effectively restores pressor responses in isolated rat blood vessels incubated with lipopolysaccharide (O'Brien, Thakur, Buckley, Singer & Clapp, 2005). Importantly, dexmedetomidine and clonidine, at clinically relevant concentrations, have been shown to directly bind and inhibit vascular K_{ATP} channels, primarily through their effects on the pore forming subunit Kir6.0 in vascular smooth muscle cells (Kawahito et al., 2011; Kawano, Yamazaki, Chi, Kawahito &

Eguchi, 2012). Furthermore, α_2-agonists can increase phospholipase A activity (Cussac, Schaak, Denis & Paris, 2002), which can directly contribute to increased sensitivity of vascular α_1-adrenoceptors and angiotensin type 1 receptors to endogenous and exogenous noradrenaline and angiotensin II. However, delineation of the pharmacodynamics of α_2-agonists on the vasculature requires further detailed *in vitro* functional investigations in blood vessels isolated from clinically relevant animal models at the appropriate time frames of sepsis onset and treatment.

3.4 Renal pharmacodynamics of α_2-agonists in sepsis

3.41 Renal tissue hypoperfusion and hypoxia in septic acute kidney injury

Acute kidney injury (AKI) is a frequent complication in sepsis, which develops in up to 50% of patients, one-third of whom do not leave the hospital alive (Bagshaw, George, Bellomo & the, 2008; Bagshaw et al., 2009; Bagshaw et al., 2007). Sepsis-induced hypotension coupled with microcirculatory dysfunction can lead to impaired perfusion and oxygen delivery to the kidneys. Renal medullary tissue hypoperfusion and hypoxia are common pathophysiological features of sepsis- and cardiac surgery-associated AKI (Evans et al., 2018; Evans et al., 2020; Lankadeva, Okazaki, Evans, Bellomo & May, 2019; Ma et al., 2019). There is compelling experimental evidence that the renal micro-circulation uncouples from the macro-circulation during development of septic AKI. For instance, an early onset of renal medullary tissue ischemia and hypoxia occurs in ovine sepsis, several hours before the development of AKI, despite elevated or unchanged renal blood flow, renal oxygen delivery and renal cortical perfusion and oxygenation (Calzavacca, Evans, Bailey, Bellomo & May, 2015; Lankadeva, Kosaka, Evans, R. & May, 2018; Lankadeva, Kosaka, Evans, Bailey, Bellomo & May, 2016).

Renal medullary tissue hypoxia can decrease ATP generation leading to mitochondrial dysfunction (Nourbakhsh & Singh, 2014), thus initiating a vicious cycle of progressive loss in renal function (Lankadeva, Okazaki, Evans, Bellomo & May, 2019; Spapen, Jacobs & Honoré, 2017). Renal medullary hypoxia cannot be directly evaluated in patients. Importantly, recent experimental studies have validated that bladder urinary oxygenation has a positive and significant correlation with renal medullary tissue oxygenation during the development of septic AKI (Lankadeva, Kosaka, Evans, R. & May, 2018; Lankadeva, Kosaka, Evans, Bailey, Bellomo & May, 2016), as long as these measures are not confounded by the simultaneous presence of severe oliguria or arterial hyperoxemia (Ngo et al., 2019). In accord, the presence of renal medullary tissue hypoxia in patients with sepsis has recently been indirectly confirmed by demonstrating decreases in bladder urinary oxygenation, (Osawa et al., 2019). Thus, we propose that therapies for sepsis should be chosen with consideration of their effects on the renal microcirculation and they should not exacerbate the underlying pathophysiological and reparative processors of AKI.

3.42 Reno-protective effects of α_2-agonsits

In established ovine septic AKI, we have shown that resuscitation with noradrenaline worsens the underlying renal medullary ischemia and hypoxia, an effect not observed with non-adrenoceptor agonists such as angiotensin II or vasopressin (Lankadeva, Kosaka, Evans, R. & May, 2018; Lankadeva, Kosaka, Evans, Bailey, Bellomo & May, 2016 ; Lankadeva et al., 2020d; Okazaki et al., 2020). Importantly, co-administration with dexmedetomidine significantly reduced the noradrenaline requirements to attain target MAP, an effect associated with preservation of renal medullary perfusion, renal medullary oxygenation and kidney

function in septic sheep with AKI (Lankadeva et al., 2019b) (Figure 3). Similarly, in rodent models of sepsis dexmedetomidine protected against AKI, although treatment was given prior to sepsis, which is not a clinically relevant treatment time (Feng et al., 2019; Kang et al., 2018; Qiu et al., 2018; Tan, Chen, Yuan, Gong, Li & Zhou, 2015).

The reno-protective mechanism of dexmedetomidine in rodent models has been attributed to its anti-inflammatory properties, which can mitigate micro-circulatory dysfunction in sepsis (Miranda, Balarini & Bouskela, 2015) (Figure 1). Similarly, in septic sheep with AKI, both clonidine and dexmedetomidine reduced the levels of pro-inflammatory cytokines (TNF-α and IL-6) levels, while preserving the levels of an anti-inflammatory cytokine (IL-10) (Calzavacca et al., 2018; Lankadeva et al., 2019b). In addition, α_2-agonists can act directly on renal α_{1B}-adrenoceptors to stimulate sodium reabsorption in the renal proximal convoluted tubules and loop of Henle. However, these effects can be offset by the diuretic and natriuretic responses induced by central inhibition of anti-diuretic hormone and by the reduced renal sympathetic outflow suppressing renin release from the juxtaglomerular apparatus (Gellai & Edwards, 1988) (Figure 1). In agreement, significant increases in urinary output and sodium excretion have been observed in response to clonidine and dexmedetomidine treatment in ovine septic AKI, independent of changes in glomerular filtration rate, as estimated via creatinine clearance (Calzavacca et al., 2018; Lankadeva et al., 2019b). It is conceivable that a reduction in renal tubular sodium reabsorption induced by α_2-agonists will reduce the metabolic demand, oxygen utilization and further contribute to the preservation of renal medullary oxygenation in septic AKI (Figure 3).

The Dexmedetomidine for Sepsis in Intensive Care Unit (DESIRE) trial was conducted in 201 patients with sepsis and reported that dexmedetomidine did not significantly effect renal outcomes or 28-day mortality (Kawazoe et al., 2017). However, a recent sub-group analysis focussed on 104 severe septic patients with Acute Physiology and Chronic Evaluation II (APACHE II) scores of ≥23 and reported reductions in serum creatinine, improvements in renal sequential organ failure assessment (SOFA) sub-scores, and a reduction in 28-day mortality rate (22% vs. 42%) (Nakashima et al., 2020). In agreement with such findings, a single-centre clinical trial in 200 septic patients also reported reductions in serum creatinine and urinary injury biomarkers in those receiving dexmedetomidine compared with propofol, an effect which was accompanied by decreases in plasma inflammatory cytokines (TNF-α and IL-1) (Liu et al., 2020). Despite a current lack of convincing clinical evidence to prove the renal benefits of dexmedetomidine in sepsis, it is plausible that therapeutic strategies which protect the kidneys from ischemic and hypoxic injury may not only mitigate AKI, but also its subsequent transition to chronic kidney disease and end-stage renal disease (Lankadeva, Okazaki, Evans, Bellomo & May, 2019).

3.5 Cardiac pharmacodynamics of α_2-agonists in sepsis

3.51 Myocardial dysfunction in sepsis

Myocardial dysfunction occurs in approximately 25% of patients with severe sepsis and is characterised by impaired cardiac contractility, diastolic dysfunction and reductions in cardiac index and left ventricular ejection fraction (Cioccari, Luethi, Weber, Hilton, Takala & Bellomo, 2016; Rudiger & Singer, 2007; Suzuki et al., 2017). Mechanisms contributing to sepsis-induced myocardial dysfunction include excessive and sustained sympathetic and

inflammatory activation, which can lead to impaired functionality of β_1-adrenoceptors, voltage-activated calcium channels and ryanodine receptors, resulting in reduced intracellular calcium and less actin-myosin cross-bridge formation (Rudiger & Singer, 2007; Suzuki et al., 2017).

In ovine sepsis, there is a high degree of correlation between the increases in cardiac SNA and heart rate, suggesting that increased sympathetic drive to the heart plays an important role in driving sepsis-induced tachycardia (Ramchandra, Wan, Hood, Frithiof, Bellomo & May, 2009). Catecholamines also modulate the balance between pro-inflammatory and anti-inflammatory cytokines in the heart via a β_2-adrenoceptor mediated pathway. For instance, CD4+ T-helper type 1 (Th1) activation can stimulate macrophages and natural killer T cells to induce pro-inflammatory cytokine production. Conversely, CD4+ T-helper type 2 (Th2) can inhibit macrophage activation, T cell proliferation and suppress cytokine production (de Montmollin, Aboab, Mansart & Annane, 2009). Selective blockade of β_1-adrenoceptors that are expressed only on Th1 cell surface membranes is proposed to promote the β_2-adrenoceptor pathway and facilitate Th2 cell responses, thus promoting the anti-inflammatory pathway in sepsis (de Montmollin, Aboab, Mansart & Annane, 2009). This is supported by the finding that selective β_1-adrenoceptor blockade in early ovine sepsis with atenolol significantly increased the plasma levels of the anti-inflammatory cytokine, IL-10, and substantially attenuated the degree of tachycardia (Calzavacca, Lankadeva, Bailey, Bailey, Bellomo & May, 2014). A single centre RCT in septic patients has also reported that β_1-adrenoceptor blockade with esmolol was associated with reductions in heart rate, norepinephrine requirements and 28-day mortality from 81% to 41% (Morelli, Ertmer, Westphal & et al., 2013). The excessively high mortality in the usual care arm of this trial, however, limits the internal validity of these results.

Nevertheless, these studies support the notion that mitigating the excessive sympathetic and inflammatory activity in sepsis may confer a degree of cardio-protection.

3.52 Effects of sympathetic activation on cardiac function in sepsis

Sepsis in humans and large mammalian animal models (pigs and sheep), at least in the first 48 hours, is characterised by a hyperdynamic circulation with peripheral vasodilation and an increase in cardiac output. (Chvojka et al., 2008; Corrêa, Jeger, Pereira, Takala, Djafarzadeh & Jakob, 2014; Langenberg, Wan, Egi, May & Bellomo, 2006; Sharma & Dellinger, 2003) At these early stages of sepsis, the central sympatholytic properties of α_2-agonists are likely to be beneficial due to suppression of cardiac SNA, which will reduce heart rate, contractility, cardiac output and myocardial oxygen consumption and myocardial lactic acid release (Figure 1). In accord, reductions in heart rate and cardiac output towards pre-morbid levels have consistently been reported in ovine hyperdynamic sepsis following administration of dexmedetomidine (0.5 μg/kg/h) and clonidine (1.0 μg/kg/h) in the first 48 hours of infection (Calzavacca et al., 2018; Lankadeva et al., 2015; Lankadeva et al., 2019b). Similarly, in an ovine model of endotoxemia, administration of clinically relevant doses of dexmedetomidine (0.5-1.0 μg/kg/h) was associated with a reduced degree of tachycardia, lower arterial and portal lactate levels and lesser impairments in exogenous lactate clearance (Hernández et al., 2016). As previously mentioned, α_2-agonists can also stimulate vagal efferent nerve activity to reduce heart rate and also to activate the cholinergic anti-inflammatory pathway, thereby mitigating the deleterious cardiac effects of excessive inflammatory cytokines (Vincent, Bakker, Marécaux, Schandene, Kahn & Dupont, 1992) (Figure 1).

3.53 Cardiac effects of α_2-agonists in sepsis

There is an extensive literature on dexmedetomidine being an efficacious cardioprotective drug in patients undergoing major surgical procedures. A meta-analysis of 18 clinical studies in patients undergoing cardiac surgical procedures demonstrated that dexmedetomidine improved post-operative systolic blood pressures and lowered the incidence of tachycardia and arrythmias (Gong, Ma, Zhong, Li, Lv & Xie, 2017). Meta-analysis of patients undergoing non-cardiac surgeries has also reported dexmedetomidine improving post-operative cardiac outcomes including reduced levels of myocardial ischemia and non-fatal myocardial infarction, even though this drug increased incidence of peri-operative hypotension and bradycardia (Biccard, Goga & de Beurs, 2008). However, there remains a paucity of information regarding the effects of α_2-agonists on cardiac health outcomes in patients with sepsis and this warrants further investigation, particularly at early stages of hyperdynamic sepsis.

3.6 Cognitive pharmacodynamics of α_2-agonists in sepsis

3.61 Neuroinflammation in sepsis

Sepsis-associated delirium is a common phenotype in ICUs, and its incidence can range from 8%-70% depending on the inclusion and exclusion criteria utilised (Bolton, Young & Zochodne, 1993; Sprung et al., 1990). The degree of sepsis-associated delirium can range from mild inattentiveness or disorientation, agitation and hypersomnolence to severe disturbances in consciousness such as coma, and is strongly correlated with increased mortality (Ely et al., 2004). The pathophysiology of sepsis-induced delirium is not fully understood but has been proposed to be associated with excessive systemic inflammation (van Gool, van de Beek & Eikelenboom, 2010). In sepsis, exaggerated peripheral inflammatory responses to an

underlying infection can either disrupt the blood brain barrier (BBB) or activate the innate immune responses within the circumventricular organs that lack a BBB (e.g. area postrema) (Hofer et al., 2008; van Gool, van de Beek & Eikelenboom, 2010). The infiltration and/or production of pro-inflammatory cytokines (TNF-α, IL-1β) and chemokines (monocyte chemoattractant protein 1) in the brain can induce the expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors and N-methyl-D-aspartate receptors on neurons, which has deleterious consequences on cognition and behaviour (Stellwagen & Malenka, 2006). Furthermore, inflammatory cytokines such as TNF-α and IL-1β can activate microglia, the resident macrophages in the brain (Stellwagen & Malenka, 2006; van Gool, van de Beek & Eikelenboom, 2010). In the setting of central inflammation and BBB disruption, microglia can differentiate into one of two activated phenotypes, Th1 and Th2. The Th1 phenotype has high phagocytic properties and is pro-inflammatory, whilst the Th2 phenotype is involved in tissue repair and remodelling and is anti-inflammatory (Stellwagen & Malenka, 2006; van Gool, van de Beek & Eikelenboom, 2010). Activation of microglia into the Th1 phenotype in sepsis can further amplify neuroinflammation via releasing nitric oxide, prostaglandin E_2, cytokines, reactive oxygen species and glutamate, leading to ischemia, hypoxia and apoptosis in susceptible brain regions, which can clinically manifest as delirium (Stellwagen & Malenka, 2006; van Gool, van de Beek & Eikelenboom, 2010). Supporting this notion, marked activation of microglia within the cerebral cortex has been reported in patients that have succumbed to sepsis (Lemstra et al., 2007). Therefore, therapeutic strategies that mitigate neuroinflammation in sepsis may yield favourable cognitive functional outcomes for patients.

3.62 Neuroprotective effects of α_2-agonists in sepsis

The vagus nerve is proposed to play a critical role in neuro-immune communications during inflammatory stimuli (Tracey, 2007). As outlined previously, α_2-agonists act centrally to activate vagal nerve efferent nerve activity and inhibit pro-inflammatory cytokine synthesis in damaged tissue via the cholinergic anti-inflammatory pathway, which may reduce the degree of neuroinflammation in sepsis (Figure 1). In *in vitro* investigations, dexmedetomidine dose-dependently suppressed lipopolysaccharide-induced inflammatory mediators (nitric oxide, prostaglandin E_2, TNF-α and IL-1β) within activated microglia, albeit at supra-therapeutic doses (Peng, Wang, Wang & Chen, 2013).

There is clinical evidence that dexmedetomidine mitigates the incidence of delirium in post-operative patients and in critically ill patients. Two clinical studies have shown an effect of prophylactic dexmedetomidine to prevent post-operative delirium. In elderly patients, undergoing non-cardiac surgery, that were randomised to receive either dexmedetomidine (N=309) or placebo (N=300) perioperatively, there was a significant reduction in the incidence of delirium by post-operative day 5 (5.5% vs 10.3%, respectively) (Li et al., 2020). In a double-blinded RCT of 700 patients over the age of 65 years undergoing non-cardiac surgical procedures, a substantial reduction in the incidence of delirium during the first 7 days after surgery was reported in those that received dexmedetomidine (Su et al., 2016). A more recent study compared nocturnal dexmedetomidine infusion to placebo in ICU patients at risk of delirium. In this setting, dexmedetomidine infusion was effective at preventing delirium (Skrobik, Duprey, Hill & Devlin, 2018). These consistent findings align with the findings of the SPICE trials and other trials of dexmedetomidine as a sedative. Importantly, in a multicentre RCT of agitation and delirium treatment in ventilated patients who could not be

extubated because of delirium, dexmedetomidine was superior to usual care in terms of achieving more ventilator free days, reduced time to extubation and faster resolution of delirium (Figure 4) (Reade et al., 2016). Similar reductions in the incidence of delirium have been reported in non-intubated patients with dexmedetomidine, which was superior to haloperidol and effective as rescue medication for failed haloperidol therapy (Carrasco et al., 2016). Collectively, these pre-clinical and clinical findings support the notion that the anti-inflammatory properties of dexmedetomidine offer a degree of protection from sepsis-induced neuroinflammation.

3.7 Clinical trials using dexmedetomidine in sepsis

There are limited observational data describing dexmedetomidine use in patients with sepsis. The largest analysis used a national database from patients admitted to 1200 hospitals in Japan (Aso, Matsui, Fushimi & Yasunaga, 2020). The investigators obtained data for 50,671 patients who were diagnosed with sepsis, mechanically ventilated for >2 days and received sedation with either dexmedetomidine, midazolam or propofol within one day of ICU admission. There were 13,759 patients who received dexmedetomidine and 36,912 who received either propofol or midazolam. Patients who received dexmedetomidine had lesser mortality than those who received midazolam or propofol (unadjusted 28-day mortality: 19.6% vs 24.1%, difference, -4.5%; 95% CI -5.3 to -3.7). Using multivariable logistic regression analysis, dexmedetomidine was associated with lower mortality (odds ratio [OR]: 0.78; 95% CI: 0.73 to 0.84). Finally, the authors also conducted 1:1 propensity score matching, with propensity scores generated using logistic regression with generalized estimating equations to cluster within hospitals. Again, mortality was less in those that received sedation with dexmedetomidine (OR: 0.85; 95% CI

0.80 to 0.91). Patients receiving dexmedetomidine sedation also had fewer days of mechanical ventilation than patients receiving propofol or midazolam sedation (Aso, Matsui, Fushimi & Yasunaga, 2020). This large dataset suggests a strong association between dexmedetomidine use and reduced mortality in patients with sepsis. However, the rationale to combine data from patients receiving a short-acting sedative (propofol) and a long-acting sedative (midazolam) is not immediately apparent. Furthermore, such an association does not establish causality.

Two studies have reported outcomes from a subgroup of patients with sepsis as part of a larger RCT trial (Table 1). The MENDS trial was a blinded parallel group RCT comparing dexmedetomidine to lorazepam in 106 mechanically ventilated patients admitted to two tertiary ICUs in the United States (Pandharipande et al., 2007). In a pre-specified subgroup analysis of 63 patients with sepsis, patients receiving dexmedetomidine had more days free of 'brain dysfunction' and mechanical ventilation and the risk of dying at 28 days was reduced by 70% [hazard ratio 0.3 (0.1, 0.9)] (Pandharipande et al., 2007). While this was a pre-specified subgroup analysis, limitations of this study are that a diagnosis of sepsis was not used to stratify randomization at baseline and the definition of sepsis differed between analyses. Importantly, in a pre-specified subgroup analysis of the SPICE III trial in 2,495 patients with suspected or proven infection there was no statistical difference in the primary outcome of death from any cause at 90 days, which occurred in 409 of 1,245 patients (32.9%) in the dexmedetomidine group and in 397 of 1250 patients (31.8%) in the usual care group (risk difference 1.1 percentage points (95% CI -2.6 to 4.8) (Shehabi et al., 2019). The proportion of patients with septic shock was not reported at baseline, however septic shock was a cause of death in 224 patients receiving dexmedetomidine and 201 patients receiving usual care (Shehabi et al.,

2019). The DESIRE trial was an open-label parallel group RCT conducted in 8 ICUs in Japan (Kawazoe et al., 2017). Two hundred and one mechanically ventilated patients with sepsis were randomised to sedation with or without dexmedetomidine. This study is the only RCT conducted solely in patients with sepsis in which the primary outcome is a clinical outcome rather than a pharmacodynamic effect. The co-primary outcomes were mortality and ventilator free days, both censored at 28 days. The sample size was based on mortality of 40% in the group without dexmedetomidine and 20% in the group with dexmedetomidine (relative risk reduction of 50%). Patients with urinary tract sepsis were included and 69% had septic shock at study entry. At 28 days after randomisation 19 patients assigned dexmedetomidine and 28 patients assigned no dexmedetomidine had died (hazard ratio 0.69, 95% CI 0.38 to 1.22) with similar number of ventilator free days (median [interquartile range], dexmedetomidine 20 [5-24] vs. no dexmedetomidine 18 [0.5-23]). Subsequent sub-group analyses of the DESIRE trial have reported no effect on lactate clearance (Miyamoto et al., 2018), but a reduction in the renal SOFA score by day 4 (Nakashima et al., 2020) and reductions in inflammatory markers such as C-reactive protein and procalcitonin levels (Ohta, Miyamoto, Kawazoe, Yamamura & Morimoto, 2020) were observed in those patients that received dexmedetomidine compared with usual care (Table 1).

There have also been a series of smaller proof-of-concept clinical studies to evaluate the pharmacodynamic effects of dexmedetomidine during sepsis (Table 1). A single-centre parallel-group RCT was performed in 40 patients with sepsis comparing the effect of dexmedetomidine and midazolam on gastric tonometry and inflammatory markers. There was no statistical difference in gastric intramucosal pH with administration of dexmedetomidine

(mean (SD), dexmedetomidine 6.37 (0.3) vs. midazolam 6.4 (0.5)) (Memiş, Hekimoğlu, Vatan, Yandım, Yüksel & Süt, 2007). There were, however, statistically significant decreases in inflammatory markers (TNF-α, IL-1β and IL-6) at 24 hours post commencement of dexmedetomidine (Memiş, Hekimoğlu, Vatan, Yandım, Yüksel & Süt, 2007). As outlined above, the recognised anti-inflammatory properties of dexmedetomidine provide a mechanistic rationale for the therapeutic benefit of dexmedetomidine in sepsis reported in the aforementioned clinical trials. The same authors subsequently compared the effects of propofol and dexmedetomidine infusions on hepatic blood flow using indocyanine green plasma disappearance rate in 40 patients with septic shock and reported no statistical differences in the indocyanine green plasma disappearance rate, concluding that dexmedetomidine is unlikely to exacerbate sepsis-induced splanchnic hypoperfusion (Memiş, Kargi & Sut, 2009). Another single centre randomized clinical trial allocated 20 patients with septic shock to dexmedetomidine or propofol, and with transcranial Doppler ultrasonography measured cerebrovascular reactivity of the middle cerebral artery to manipulation of arterial carbon dioxide. Cerebrovascular reactivity was attenuated under dexmedetomidine sedation compared with propofol sedation (mean 2.0 (0.3) cm/s/mmHg vs. 2.6 (0.3) cm/s/mmHg) (Kadoi, Saito, Kawauchi, Hinohara & Kunimoto, 2008). However, the cerebrovascular reactivity under dexmedetomidine was only marginally lower than the normal range and the clinical relevance of these findings are uncertain.

There is an association between dexmedetomidine use and survival, from a large national dataset (Aso, Matsui, Fushimi & Yasunaga, 2020), and a striking mortality benefit from a single subgroup analysis of a small RCT in which sepsis was not stratified at baseline

(Pandharipande et al., 2010). However, no mortality benefit was demonstrated in the only RCT conducted solely in patients with sepsis (Kawazoe et al., 2017), albeit with point estimate that favoured benefit. In the largest cohort of patients within a RCT (SPICE III), patients were stratified on enrolment based on sepsis and the effect of dexmedetomidine on mortality in this cohort is somewhere between a reduction of 2.6% and an increase of 4.8% (Shehabi, Bellomo, Mehta, Riker & Takala, 2013). Several multi-centre RCTs comparing dexmedetomidine with propofol or midazolam sedation have enrolled patients with sepsis or infection but have not reported outcomes for these subgroups; 276/375 patients in the SEDCOM trial (Riker et al., 2009), 269/500 patients in the MIDEX trial (Jakob et al., 2012), and 263/437 in the PRODEX trial (Jakob et al., 2012). In the absence of these datasets and a comprehensive meta-analysis, there appears to be no substantial mortality benefit of dexmedetomidine in sepsis. Whether dexmedetomidine has similar or greater beneficial effects when used solely in patients with sepsis and septic shock currently remains unknown.

There is an apparent disconnect between clinical and experimental findings in sepsis. Possible explanations could be related to the dose of dexmedetomidine used, concomitant interventions, timing of administration, heterogenous patient populations with pre-existing comorbidities and the outcomes assessed in clinical trials.

4 ORGAN DYSNFUNCTION ARISING FROM CARDIAC SURGERY

Approximately 2 million coronary artery bypass graft procedures or valve replacement/repair procedures requiring CPB are performed annually worldwide (Hu, Chen, Liu, Yu, Zou & Ding, 2016). Major unresolved clinical complications arising from CPB include the development of post-operative cognitive dysfunction (Tan, Brewster, Horrigan & Sarode, 2018) and AKI (Evans et al., 2018; Kellum & Prowle, 2018). Short-term post-operative cognitive dysfunction occurs in 20-50% of patients after CPB, and 10-30% of these patients develop long-term cognitive disabilities (Tan, Brewster, Horrigan & Sarode, 2018). Similarly, the incidence of post-operative AKI is approximately 22% in patients undergoing CPB (Hu, Chen, Liu, Yu, Zou & Ding, 2016). The systemic immune response to cardiac surgery requiring CPB has often been compared to the response in sepsis. For instance, CPB can lead to a strong peripheral inflammatory response triggered by surgical site injury that is compounded by the contact between blood and artificial perfusion tubing and membranes in the heart-lung machine, which can lead to the release and recognition of DAMPS (Akira & Takeda, 2004). As mentioned previously, excessive peripheral inflammation can contribute to neuroinflammation via disruption of the BBB and/or direct activation of central inflammatory processes within the circumventricular organs. Therefore, it is conceivable that that intra-operative neuroinflammation (i.e. activated microglia) may be a contributing factor for post-operative cognitive dysfunction (Safavynia & Goldstein, 2019). There is also compelling experimental evidence that intraoperative overstimulation of renal SNA during CPB leads to tissue hypoperfusion and hypoxia, particularly within the renal medulla (Evans et al., 2020; Iguchi et al., 2019; Iguchi et al., 2020; Lankadeva et al., 2019a; Lankadeva et al., 2020a; Lankadeva et al., 2020b). In accord, renal medullary hypoxia, as indirectly assessed by the

progressive development of a greater degree of bladder urinary hypoxia during CPB, has been reported in the sub-group of patients that developed post-operative AKI (Zhu et al., 2018). In view of these observations, it is logical to propose that perioperative use of dexmedetomidine during CPB should mitigate excessive inflammatory and sympathetic overactivity and reduce the incidence of post-operative cognitive dysfunction and post-operative AKI.

4.1 Clinical trials using dexmedetomidine in cardiac surgery

The use of dexmedetomidine as an adjunct to anaesthesia for cardiac surgery and/or as sedative agent following cardiac surgery and/or as a preventive treatment for the development of delirium and AKI has been studied in several small to medium sized single centre studies. Although the findings have not been uniform, larger studies and recurrent observations in this population all suggest that dexmedetomidine compared with propofol use was associated with hemodynamic stability and decreased onset of delirium (2 interquartile range (1-4) vs 1 (1-4) days) and reduced duration of delirium (2 (1-4) vs 3 (1-6) days) (Shi, Jin, Qiao, Li, Ma & Ma, 2019). In addition, although the studies are limited in size and number, it appears that perioperative dexmedetomidine compared with usual care may reduce both the incidence of post-operative AKI (14% vs 32%) and the length of hospital stay (12 CI (10-17) vs 15 (11-21) days) following aortic surgery requiring CPB (Soh, Shim, Song, Bae & Kwak, 2020). However, no large multicentre double blinded multicentre RCTs have been performed to test the robustness of such initial findings and thus its use in cardiac surgery cannot be currently recommended. Although there are biomarker signals suggesting that peri-operative dexmedetomidine administration might be beneficial in patients having CPB (Shi, Jin, Qiao, Li, Ma & Ma, 2019; Soh, Shim, Song, Bae & Kwak, 2020), the mechanisms underlying its

putative beneficial effects on the brain and kidneys remain unclear. Furthermore, the optimal dosage of dexmedetomidine required to reduce post-operative brain and kidney injuries in CPB remains controversial and requires future experimental investigations to establish safety and efficacy using clinically relevant animal models of CPB.

CONCLUSIONS

The sedative, anxiolytic and analgesic properties of the α_2-agonist, dexmedetomidine, are appealing resulting in increasing off-label use for prolonged sedation in critically ill patients with and without sepsis, and as an adjunct to general anaesthesia for patients undergoing CPB. It is widely accepted that excessive and protracted inflammatory and sympathetic activation can drive organ dysfunction arising from sepsis and CPB. Although, there is controlled experimental evidence indicating that the anti-inflammatory and sympatholytic properties of α_2-agonists confer multi-organ protection in sepsis, these findings have not always translated in heterogenous populations of patients with sepsis or those undergoing CPB given a range of doses of dexmedetomidine administered at different times. Therefore, an in-depth understanding of the mechanisms, optimal dosages and timings for α_2-agonist administration in clinically relevant models of sepsis and CPB are essential to provide the detailed scientific rationale for the design of large double blinded multicentre RCTs. Such RCTs are essential to determine the safety, efficacy and cost-effectiveness of dexmedetomidine therapy in patients with sepsis and those undergoing cardiac surgery.

NOMENCLATURE OF TARGETS AND LIGANDS

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding *et al.*, 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019).

ACKNOWLEDGEMENTS

The studies referred to from the CNM and YRL laboratories have been funded by National Health and Medical Research Council of Australia grants (NHMRC, 454615, 1009280, 1050672, 1122455, 1185777). YRL was supported by a Future Leader Postdoctoral Fellowship by the National Heart Foundation of Australia (NHF, 101853). YS and his Institution received research grants from the NHMRC and In-kind support (study medication – dexmedetomidine; GNT1043938) from Pfizer and Orion Pharma in support of the SPICE III Trial.

CONFLICTS OF INTEREST

YS received travel support and speaker's honorarium for participation in educational symposia from Pfizer, Orion and Abbott Laboratories. The other authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

YRL developed the theoretical formalism, wrote the manuscript and created the table and figures. YS and RB provided clinical perspectives on using α_2-agonists in randomised clinical trials in critically ill patients. AMD and MPP provided clinical perspectives on using α_2-agonists in patients with sepsis. CNM provided intellectual input on the effects of sympathetic

activation in sepsis and critical illness and on the sympatholytic properties of α_2-agonists. All authors reviewed and approved the manuscript.

Figure legends

Figure 1: A schematic summarising the putative multi-organ benefits of alpha$_2$- adrenoceptor agonists in sepsis and cardiac surgery requiring cardiopulmonary bypass

Figure 2: Differential effect of dexmedetomidine vs. usual care (control) on mortality in patients from the SPICE III trial. Adapted from (Shehabi et al., 2019)

The Y-axis represents the percentage mortality and the X-axis specific subgroup of patient (High Acute Physiology and Chronic Health Evaluation (APACHE) II score above the median value for the trial; $PaO_2/FiO2$ ratio below the median for the trial; presence of sepsis at randomization; admission to ICU after surgery [Operative]). No difference in mortality was seen in each subgroup according to the use of dexmedetomidine (in yellow) for sedation compared with usual care (in black).

Figure 3: Adjunct treatment with dexmedetomidine reduces noradrenaline requirements to restore target blood pressure and preserves renal medullary tissue perfusion and oxygenation in ovine septic acute kidney injury. Adapted from (Lankadeva et al., 2019b)

Norepinephrine dose, mean arterial pressure, renal medullary perfusion and renal medullary oxygen tension (pO_2) during infusion of Escherichia coli (E. coli) from 0 to 30 hour and subsequent treatment with noradrenaline + dexmedetomidine (n=8, blue circles) or vehicle-saline (n=8, open circles) in conscious sheep. Noradrenaline (0.1-1.0 µg/Kg/min) and dexmedetomidine (0.5 µg/Kg/h) were infused from 24-30 h of sepsis. Time 0 is the mean of the 24th hour of the baseline period and times 24-30 h are means of 1 h periods. Data are within-

animal mean ± standard error of mean. P values represent treatment-time interactions from a two-way repeated-measures analysis of variance from 24-30 h of sepsis.

Figure 4: Differential effects of dexmedetomidine vs. placebo in mechanically ventilated patients with agitated delirium. Adapted from (Reade et al., 2016).

The Y-axis represents the time (in hours) to a particular outcome of interest. The X-axis identified specific outcomes of interest. Treatment with dexmedetomidine (in blue), when compared with placebo (in orange) decreased the time to a patient being ready for extubation, the actual time to extubation, the time spent in a state of delirium and the time to first becoming delirium free

REFERENCES

Aantaa R, Marjamäki A, & Scheinin M (1995). Molecular pharmacology of alpha 2-adrenoceptor subtypes. Ann Med 27**:** 439-449.

Akira S, & Takeda K (2004). Toll-like receptor signalling. Nat Rev Immunol 4**:** 499-511.

Alexander SPH, Christopoulos A, Davenport AP, Kelly E, Mathie A, Peters JA*, et al.* (2019). The consise guide to pharmacology 2019/20: G protein-coupled receptors. Br J Pharmacol 176**:** S21-S141.

Allen AM, & Guyenet PG (1993). Alpha 2-adrenoceptor-mediated inhibition of bulbospinal barosensitive cells of rat rostral medulla. Am J Physiol 265**:** R1065-1075.

Andreis DT, & Singer M (2016). Catecholamines for inflammatory shock: a Jekyll-and-Hyde conundrum. Intensive Care Med 42**:** 1387-1397.

Aninat C, Seguin P, Descheemaeker PN, Morel F, Malledant Y, & Guillouzo A (2008). Catecholamines induce an inflammatory response in human hepatocytes. Crit Care Med 36**:** 848-854.

Annane D, Bellissant E, Sebille V, Lesieur O, Mathieu B, Raphael JC*, et al.* (1998). Impaired pressor sensitivity to noradrenaline in septic shock patients with and without impaired adrenal function reserve. Br J Clin Pharmacol 46**:** 589-597.

Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S*, et al.* (2018). Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med 378**:** 809-818.

Aso S, Matsui H, Fushimi K, & Yasunaga H (2020). Dexmedetomidine and mortality from sepsis requiring mechanical ventilation: A Japanese nationwide retrospective cohort study. J Intensive Care Med DOI: 10.1177/0885066620942154.

Bagshaw SM, George C, Bellomo R, & the ADMC (2008). Early acute kidney injury and sepsis: a multicentre evaluation. Crit Care 12**:** R47-R47.

Bagshaw SM, Lapinsky S, Dial S, Arabi Y, Dodek P, Wood G*, et al.* (2009). Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy. Intensive Care Med 35**:** 871-881.

Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M*, et al.* (2007). Septic acute kidney injury in critically ill patients: Clinical characteristics and outcomes. Clin J Am Soc Nephrol 2**:** 431-439.

Belleville JP, Ward DS, Bloor BC, & Maze M (1992). Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. Anesthesiology 77**:** 1125-1133.

Bellomo R, Kellum JA, Ronco C, Wald R, Martensson J, Maiden M*, et al.* (2017). Acute kidney injury in sepsis. Intensive Care Med 43**:** 816-828.

Benedict C, & Rose J (1992). Arterial norepinephrine changes in patients with septic shock. Circ Shock 38**:** 165-172.

Beutler B, Hoebe K, Du X, & Ulevitch RJ (2003). How we detect microbes and respond to them: the Toll-like receptors and their transducers. J Leukoc Biol 74**:** 479-485.

Biccard BM, Goga S, & de Beurs J (2008). Dexmedetomidine and cardiac protection for non-cardiac surgery: a meta-analysis of randomised controlled trials. Anaesthesia 63: 4-14.

Bolton CF, Young GB, & Zochodne DW (1993). The neurological complications of sepsis. Ann Neurol 33: 94-100.

Booth LC, Ramchandra R, Calzavacca P, & May CN (2014). Role of prostaglandins in determining the increased cardiac sympathetic nerve activity in ovine sepsis. Am J Physiol Regul Integr Comp Physiol 307: R75-R81.

Bucher M, Kees F, Taeger K, & Kurtz A (2003). Cytokines down-regulate α1-adrenergic receptor expression during endotoxemia. Crit Care Med 31: 566-571

Buckley JF, Singer M, & Clapp LH (2006). Role of KATP channels in sepsis. Cardiovasc Res 72: 220-230.

Calzavacca P, Booth L, Lankadeva Y, Bailey S, Burrell L, Bailey M, *et al.* (2018). Effects of clonidine on the cardiovascular, renal and inflammatory responses to experimental bacteremia. Shock 51: 348-355.

Calzavacca P, Evans RG, Bailey M, Bellomo R, & May CN (2015). Cortical and medullary tissue perfusion and oxygenation in experimental septic acute kidney injury. Crit Care Med 43: e431-439.

Calzavacca P, Lankadeva YR, Bailey S, Bailey M, Bellomo R, & May C (2014). Effects of selective beta1-adrenoceptor blockade on cardiovascular and renal function and circulating cytokines in ovine hyperdynamic sepsis. Crit Care 18**:** 610.

Carrasco G, Baeza N, Cabré L, Portillo E, Gimeno G, Manzanedo D*, et al.* (2016). Dexmedetomidine for the treatment of hyperactive delirium refractory to haloperidol in nonintubated ICU patients: A nonrandomized controlled trial. Crit Care Med 44**:** 1295-1306.

Chatterjee PK, Al-Abed Y, Sherry B, & Metz CN (2009). Cholinergic agonists regulate JAK2/STAT3 signaling to suppress endothelial cell activation. Am J Physiol Cell Physiol 297**:** C1294-C1306.

Chorney SR, Gooch ME, Oberdier MT, Keating D, & Stahl RF (2013). The safety and efficacy of dexmedetomidine for postoperative sedation in the cardiac surgery intensive care unit. HSR Proc Intensive Care Cardiovasc Anesth 5**:** 17-24.

Chvojka J, Sykora R, Krouzecky A, Radej J, Varnerova V, Karvunidis T*, et al.* (2008). Renal haemodynamic, microcirculatory, metabolic and histopathological responses to peritonitis-induced septic shock in pigs. Crit Care 12**:** R164-R164.

Cioccari L, Luethi N, Bailey M, Shehabi Y, Howe B, Messmer AS*, et al.* (2020). The effect of dexmedetomidine on vasopressor requirements in patients with septic shock: a subgroup analysis of the Sedation Practice in Intensive Care Evaluation [SPICE III] Trial. Crit Care 24**:** 441.

Cioccari L, Luethi N, Weber U, Hilton A, Takala J, & Bellomo R (2016). The native cardiac output in human sepsis: a systematic review. Crit Care Resusc 18**:** 148-156.

Corrêa TD, Jeger V, Pereira AJ, Takala J, Djafarzadeh S, & Jakob SM (2014). Angiotensin II in septic shock: effects on tissue perfusion, organ function, and mitochondrial respiration in a porcine model of fecal peritonitis. Crit Care Med 42**:** e550-559.

Cussac D, Schaak S, Denis C, & Paris H (2002). α2B-Adrenergic Receptor Activates MAPK via a Pathway Involving Arachidonic Acid Metabolism, Matrix Metalloproteinases, and Epidermal Growth Factor Receptor Transactivation. J Biol Chem 277**:** 19882-19888.

De Backer D, Donadello K, Sakr Y, Ospina-Tascon G, Salgado D, Scolletta S*, et al.* (2013). Microcirculatory alterations in patients with severe sepsis: Impact of time of assessment and relationship with outcome*. Crit Care Med 41**:** 791-799.

de Jonge WJ, van der Zanden EP, The FO, Bijlsma MF, van Westerloo DJ, Bennink RJ*, et al.* (2005). Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. Nat Immunol 6**:** 844-851.

de Montmollin E, Aboab J, Mansart A, & Annane D (2009). Bench-to-bedside review: Beta-adrenergic modulation in sepsis. Crit Care 13**:** 230-230.

Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP*, et al.* (2018). Clinical Practice Guidelines for the Prevention and Management of Pain,

Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med 46**:** e825-e873.

Dünser MW, & Hasibeder WR (2009). Sympathetic overstimulation during critical illness: Adverse effects of adrenergic stress. J Intensive Care Med 24**:** 293-316.

Dyck JB, Maze M, Haack C, Vuorilehto L, & Shafer SL (1993). The pharmacokinetics and hemodynamic effects of intravenous and intramuscular dexmedetomidine hydrochloride in adult human volunteers. Anesthesiology 78**:** 813-820.

Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE, Jr.*, et al.* (2004). Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 291**:** 1753-1762.

Evans DG, Miles AA, & Niven JS (1948). The enhancement of bacterial infections by adrenaline. Br J Exp Pathol 29**:** 20-39.

Evans RG, Lankadeva YR, Cochrane AD, Marino B, Iguchi N, Zhu MZL*, et al.* (2018). Renal haemodynamics and oxygenation during and after cardiac surgery and cardiopulmonary bypass. Acta Physiol 222**:** e12995.

Evans RG, Iguchi N, Cochrane AD, Marino B, Hood SG, Bellomo R*, et al.* (2020). Renal hemodynamics and oxygenataion during experimental cardiopulmonary bypass in sheep under total intravenous anesthesia. Am J Physiol Regul Integr Comp Physiol 318**:** R206-R213.

Fairbanks CA, Stone LS, & Wilcox GL (2009). Pharmacological profiles of alpha 2 adrenergic receptor agonists identified using genetically altered mice and isobolographic analysis. Pharmacol Ther 123**:** 224-238.

Feng X, Guan W, Zhao Y, Wang C, Song M, Yao Y*, et al.* (2019). Dexmedetomidine ameliorates lipopolysaccharide-induced acute kidney injury in rats by inhibiting inflammation and oxidative stress via the GSK-3β/Nrf2 signaling pathway. J Cell Physiol 234: 18994-19009.

Gellai M, & Edwards RM (1988). Mechanism of alpha 2-adrenoceptor agonist-induced diuresis. Am J Physiol Renal Physiol 255**:** F317-F323.

Geloen A, Chapelier K, Cividjian A, Dantony E, Rabilloud M, May CN*, et al.* (2013). Clonidine and dexmedetomidine increase the pressor response to norepinephrine in experimental sepsis: A pilot study*. Crit Care Med 41**:** e431-e438

Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT*, et al.* (2008). Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet 371**:** 126-134.

Gong Z, Ma L, Zhong Y-L, Li J, Lv J, & Xie Y-B (2017). Myocardial protective effects of dexmedetomidine in patients undergoing cardiac surgery: A meta-analysis and systematic review. Exp Ther Med 13**:** 2355-2361.

Groves AC, Griffiths J, Leung F, & Meek RN (1973). Plasma catecholamines in patients with serious postoperative infection. Ann Surg 178**:** 102-107.

Hall MW, Geyer SM, Guo C-Y, Panoskaltsis-Mortari A, Jouvet P, Ferdinands J, *et al.* (2013). Innate immune function and mortality in critically ill children with influenza: a multicenter study. Crit Care Med 41**:** 224-236.

Harding, S.D., Sharman, J.L., Faccenda, E., Southan, C., Pawson AJ, Ireland S, Gray AJG, Bruce L, Alexander SPH, Anderton S, Bryant C, Davenport AP, Doerig C, Fabbro D, Levi-Schaffer F, Spedding M, Davies JA, NC-IUPHAR (2018). The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. Nucleic Acids Res. 46, D1091-1106. doi:10.1093/nar/gkx1121.

Hayashi Y, & Maze M (1993). Alpha 2 adrenoceptor agonists and anaesthesia. Br J Anaesth 71**:** 108-118.

Hernández G, Tapia P, Alegría L, Soto D, Luengo C, Gomez J, *et al.* (2016). Effects of dexmedetomidine and esmolol on systemic hemodynamics and exogenous lactate clearance in early experimental septic shock. Crit Care 20**:** 234.

Hofer S, Bopp C, Hoerner C, Plaschke K, Faden RM, Martin E, *et al.* (2008). Injury of the blood brain barrier and up-regulation of icam-1 in polymicrobial sepsis. J Surg Res 146**:** 276-281.

Hofer S, Steppan J, Wagner T, Funke B, Lichtenstern C, Martin E, *et al.* (2009). Central sympatholytics prolong survival in experimental sepsis. Crit Care 13**:** R11.

Hong M, Milne B, Loomis C, & Jhamandas K (1992). Stereoselective effects of central alpha 2-adrenergic agonist medetomidine on in vivo catechol activity in the rat rostral ventrolateral medulla (RVLM). Brain Res 592**:** 163-169.

Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, & Vincent J-L (2016). Sepsis and septic shock. Nat Rev Dis Primers 2**:** 16045-16045.

Hu J, Chen R, Liu S, Yu X, Zou J, & Ding X (2016). Global incidence and outcomes of adult patients with acute kidney injury after cardiac surgery: A systematic review and meta-Analysis. J Cardiothorac Vasc Anesth 30**:** 82-89.

Iguchi N, Kosaka J, Booth LC, Iguchi Y, Evans RG, Bellomo R, *et al.* (2019). Renal perfusion, oxygenation, and sympathetic nerve activity during volatile or intravenous general anaesthesia in sheep. Br J Anaesth 122**:** 342-349.

Iguchi N, Kosaka J, Iguchi Y, Evans RG, Bellomo R, May CN, *et al.* (2020). Systemic haemodynamic, renal perfusion and renal oxygenation responses to changes in inspired oxygen fraction during total intravenous or volatile anaesthesia. Br J Anaesth 125**:** 192-200.

Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, *et al.* (2012). Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA 307**:** 1151-1160.

Julien C, Oréa V, Quintin L, Piriou V, & Barrès C (2017). Renal sympathetic nerve activity and vascular reactivity to phenylephrine after lipopolysaccharide administration in conscious rats. Physiol Rep 5**:** e13139.

Kadoi Y, Saito S, Kawauchi C, Hinohara H, & Kunimoto F (2008). Comparative effects of propofol vs dexmedetomidine on cerebrovascular carbon dioxide reactivity in patients with septic shock. Br J Anaesth 100**:** 224-229.

Kang K, Gao Y, Wang S-C, Liu H-T, Kong W-L, Zhang X*, et al.* (2018). Dexmedetomidine protects against lipopolysaccharide-induced sepsis-associated acute kidney injury via an α7 nAChR-dependent pathway. Biomed Pharmacother 106**:** 210-216.

Kawahito S, Kawano T, Kitahata H, Oto J, Takahashi A, Takaishi K*, et al.* (2011). Molecular mechanisms of the inhibitory effects of clonidine on vascular adenosine triphosphate–sensitive potassium channels. Anesth Analg 113**:** 1374-1380

Kawano T, Yamazaki F, Chi H, Kawahito S, & Eguchi S (2012). Dexmedetomidine directly inhibits vascular ATP-sensitive potassium channels. Life Sci 90**:** 272-277.

Kawazoe Y, Miyamoto K, Morimoto T, Yamamoto T, Fuke A, Hashimoto A*, et al.* (2017). Effect of dexmedetomidine on mortality and ventilator-free days in patients requiring mechanical ventilation with sepsis: A randomized clinical trial. JAMA 317**:** 1321-1328.

Kellum JA, & Prowle JR (2018). Paradigms of acute kidney injury in the intensive care setting. Nat Rev Nephrol 14**:** 217-230.

Kimmoun A, Ducrocq N, & Levy B (2013). Mechanisms of vascular hyporesponsiveness in septic shock. Curr Vasc Pharmacol 11**:** 139-149.

Knaus AE, Muthig V, Schickinger S, Moura E, Beetz N, Gilsbach R, *et al.* (2007). Alpha2-adrenoceptor subtypes--unexpected functions for receptors and ligands derived from gene-targeted mouse models. Neurochem Int 51**:** 277-281.

Kumar A, Haery C, & Parrillo JE (2001). Myocardial dysfunction in septic shock: Part I. Clinical manifestation of cardiovascular dysfunction. J Cardiothorac Vasc Anesth 15**:** 364-376.

Langenberg C, Wan L, Egi M, May CN, & Bellomo R (2006). Renal blood flow in experimental septic acute renal failure. Kidney Int 69**:** 1996-2002.

Lankadeva YR, Kosaka J, Evans RG, Bellomo R & May C (2018). Urinary oxygenation as a surrogate marker of medullary oxygenation during angiotensin II therapy in septic acute kidney injury. Crit Care Med 46**:** e41-48.

Lankadeva YR, Okazaki N, Evans RG, Bellomo R, & May CN (2019). Renal medullary hypoxia: A new therapeutic target for septic acute kidney injury?. Semin Nephrol 39**:** 543-553.

Lankadeva YR, Booth LC, Kosaka J, Evans RG, Quintin L, Bellomo R, *et al.* (2015). Clonidine restores pressor responsiveness to phenylephrine and angiotensin II in ovine sepsis. Crit Care Med 43**:** e221-229.

Lankadeva YR, Cochrane AD, Marino B, Iguchi N, Hood SG, Bellomo R, *et al.* (2019a). Strategies that improve renal medullary oxygenation during experimental cardiopulmonary bypass may mitigate postoperative acute kidney injury. Kidney Int 95**:** 1338-1346.

Lankadeva YR, Evans RG, Cochrane AD, Marino B, Hood SG, McCall PR, *et al.* (2020a). Reversal of renal tissue hypoxia during experimental cardiopulmonary bypass in sheep by increased pump flow and arterial pressure. Acta Physiol DOI: https://doi.org/10.1111/apha.13596**:** e13596.

Lankadeva YR, Kosaka J, Evans RG, Bailey M, Bellomo R, & May CN (2016). Intra-renal and urinary oxygenation during norepinephrine resuscitation in ovine septic acute kidney injury. Kidney Int 90**:** 100-108.

Lankadeva YR, Ma S, Iguchi N, Evans RG, Hood SG, Farmer DGS, *et al.* (2019b). Dexmedetomidine reduces norepinephrine requirements and preserves renal oxygenation and function in ovine septic acute kidney injury. Kidney Int 96**:** 1150-1161.

Lankadeva YR, May CN, Cochrane AD, Marino B, Hood SG, McCall PR, *et al.* (2020b). Influence of blood haemoglobin concentration on renal haemodynamics and oxygenation during experimental cardiopulmonary bypass in sheep. Acta Physiol DOI: https://doi.org/10.1111/apha.13583.**:** e13583.

Lankadeva YR, May CN, McKinley MJ, Neeland MR, Ma S, Hocking D, *et al.* (2020c). Sympathetic nerves control bacterial clearance. Sci Rep 10**:** 15009.

Lankadeva YR, Peiris RM, Okazaki N, Birchall IE, Trask-Marino A, Dornom A, *et al.* (2020d). Reversal of the pathophysiological responses to gram-negative sepsis by megadose vitamin C. Crit Care Med DOI: 10.1097/CCM.0000000000004770.

Lemstra AW, Groen in't Woud JCM, Hoozemans JJM, van Haastert ES, Rozemuller AJM, Eikelenboom P, *et al.* (2007). Microglia activation in sepsis: a case-control study. J Neuroinflammation 4**:** 4.

Li CJ, Wang BJ, Mu DL, Hu J, Guo C, Li XY, *et al.* (2020). Randomized clinical trial of intraoperative dexmedetomidine to prevent delirium in the elderly undergoing major non-cardiac surgery. Br J Surg 107**:** e123-e132.

Liu J, Shi K, Hong J, Gong F, Mo S, Chen M, *et al.* (2020). Dexmedetomidine protects against acute kidney injury in patients with septic shock. Ann Palliat Med 9**:** 224-230.

Ma S, Evans RG, Iguchi N, Tare M, Parkington HC, Bellomo R, *et al.* (2019). Sepsis-induced acute kidney injury: A disease of the microcirculation. Microcirculation 16**:** e12483.

Martelli D, Yao ST, McKinley MJ, & McAllen RM (2014). Reflex control of inflammation by sympathetic nerves, not the vagus. J Physiol 592**:** 1677-1686.

Maze M, & Fujinaga M (2000). Alpha2 adrenoceptors in pain modulation: which subtype should be targeted to produce analgesia? Anesthesiology 92**:** 934-936.

Mehta S, Burry L, Cook D, Fergusson D, Steinberg M, Granton J, *et al.* (2012). Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA 308**:** 1985-1992.

Memiş D, Hekimoğlu S, Vatan İ, Yandım T, Yüksel M, & Süt N (2007). Effects of midazolam and dexmedetomidine on inflammatory responses and gastric intramucosal pH to sepsis, in critically ill patients. Br J Anaesth 98**:** 550-552.

Memiş D, Kargi M, & Sut N (2009). Effects of propofol and dexmedetomidine on indocyanine green elimination assessed with LIMON to patients with early septic shock: a pilot study. J Crit Care 24**:** 603-608.

Miranda ML, Balarini MM, & Bouskela E (2015). Dexmedetomidine attenuates the microcirculatory derangements evoked by experimental sepsis. Anesthesiology 122**:** 619-630.

Miyamoto K, Nakashima T, Shima N, Kato S, Ueda K, Kawazoe Y*, et al.* (2018). Effect of dexmedetomidine on lactate clearance in patients with septic shock: A subanalysis of a multicenter randomized controlled trial. Shock 50**:** 162-166.

Morelli A, Ertmer C, Westphal M, & et al. (2013). Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: A randomized clinical trial. JAMA 310**:** 1683-1691.

Morelli A, Sanfilippo F, Arnemann P, Hessler M, Kampmeier TG, D'Egidio A*, et al.* (2019). The effect of propofol and dexmedetomidine sedation on norepinephrine requirements in septic shock patients: A crossover trial. Crit Care Med 47**:** e89-e95.

Nakashima T, Miyamoto K, Shima N, Kato S, Kawazoe Y, Ohta Y*, et al.* (2020). Dexmedetomidine improved renal function in patients with severe sepsis: an exploratory analysis of a randomized controlled trial. J Intensive Care 8**:** 1.

Nelson LE, Lu J, Guo T, Saper CB, Franks NP, & Maze M (2003). The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. Anesthesiology 98**:** 428-436.

Ngo JP, Lankadeva YR, Zhu MZL, Martin A, Kanki M, Cochrane AD*, et al.* (2019). Factors that confound the prediction of renal medullary oxygenation and risk of acute kidney injury from measurement of bladder urine oxygen tension. Acta Physiologica 227**:** e13294.

Nourbakhsh N, & Singh P (2014). Role of renal oxygenation and mitochondrial function in the pathophysiology of acute kidney injury. Nephron Clin Pract 127**:** 149-152.

O'Brien AJ, Thakur G, Buckley JF, Singer M, & Clapp LH (2005). The pore-forming subunit of the KATP channel is an important molecular target for LPS-induced vascular hyporeactivity in vitro. Br J Pharmacol 144**:** 367-375.

Ohta Y, Miyamoto K, Kawazoe Y, Yamamura H, & Morimoto T (2020). Effect of dexmedetomidine on inflammation in patients with sepsis requiring mechanical ventilation: a sub-analysis of a multicenter randomized clinical trial. Crit Care 24**:** 493.

Okazaki N, Iguchi N, Evans R, Hood S, Bellomo R, May C*, et al.* (2020). Beneficial effects of vasopressin compared with norepinephrine on renal perfusion, oxygenation and function in experimental septic acute kidney injury. Crit Care Med 48**:** e951-e958.

Osawa EA, Cutuli SL, Bitker L, Canet E, Cioccari L, Iguchi N*, et al.* (2019). Effect of furosemide on urinary oxygenation in patients with septic shock. Blood Purif 23**:** 1-10.

Pålsson J, Ricksten SE, Delle M, & Lundin S (1988). Changes in renal sympathetic nerve activity during experimental septic and endotoxin shock in conscious rats. Circ Shock 24**:** 133-141.

Pandharipande P, Pun B, Herr D, Maze M, Girard T, Miller R*, et al.* (2007). Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 298**:** 2644 - 2653.

Pandharipande P, Sanders R, Girard T, McGrane S, Thompson J, Shintani A*, et al.* (2010). Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an a priori-designed analysis of the MENDS randomized controlled trial. Crit Care 14**:** R38.

Peng M, Wang YL, Wang CY, & Chen C (2013). Dexmedetomidine attenuates lipopolysaccharide-induced proinflammatory response in primary microglia. J Surg Res 179**:** e219-225.

Pichot C, Geloen A, Ghignone M, & Quintin L (2010). Alpha-2 agonists to reduce vasopressor requirements in septic shock? Med Hypotheses 75**:** 652-656.

Qiu R, Yao W, Ji H, Yuan D, Gao X, Sha W*, et al.* (2018). Dexmedetomidine restores septic renal function via promoting inflammation resolution in a rat sepsis model. Life Sci 204**:** 1-8.

Ramchandra R, Wan L, Hood SG, Frithiof R, Bellomo R, & May CN (2009). Septic shock induces distinct changes in sympathetic nerve activity to the heart and kidney in conscious sheep. Am J Physiol Regul Integr Comp Physiol 297**:** R1247-R1253.

Reade MC, Eastwood GM, Bellomo R, Bailey M, Bersten A, Cheung B, *et al.* (2016). Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: A randomized clinical trial. JAMA 315**:** 1460-1468.

Reade MC, & Finfer S (2014). Sedation and delirium in the intensive care unit. N Engl J Med 370**:** 444-454.

Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, *et al.* (2017). Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 43**:** 304-377.

Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, *et al.* (2009). Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 301**:** 489-499.

Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, *et al.* (2020). Global, regional, and national sepsis incidence and mortality, 1990-2017: Analysis for the global burden of disease study. Lancet 395**:** 200-211.

Rudiger A, & Singer M (2007). Mechanisms of sepsis-induced cardiac dysfunction. Crit Care Med 35**:** 1599-1608.

Safavynia SA, & Goldstein PA (2019). The role of neuroinflammation in postoperative cognitive dysfunction: Moving from hypothesis to treatment. Front Psychiatry 9**:** 752-752.

Sakr Y, Lobo SM, Moreno RP, Gerlach H, Ranieri VM, Michalopoulos A, *et al.* (2012). Patterns and early evolution of organ failure in the intensive care unit and their relation to outcome. Critical care (London, England) 16**:** R222-R222.

Schmidt C, Höcherl K, Kurt B, Moritz S, Kurtz A, & Bucher M (2010). Blockade of multiple but not single cytokines abrogates downregulation of angiotensin II type-I receptors and anticipates septic shock. Cytokine 49**:** 30-38.

Sharma V, & Dellinger RP (2003). The International Sepsis Forum's frontiers in sepsis: high cardiac output should not be maintained in severe sepsis. Crit Care 7**:** 272-275.

Sharp DB, Wang X, & Mendelowitz D (2014). Dexmedetomidine decreases inhibitory but not excitatory neurotransmission to cardiac vagal neurons in the nucleus ambiguus. Brain Res 1574**:** 1-5.

Shehabi Y, Bellomo R, Kadiman S, Ti LK, Howe B, Reade MC, *et al.* (2018). Sedation intensity in the first 48 hours of mechanical ventilation and 180-day mortality: A multinational prospective longitudinal cohort study. Crit Care Med 46**:** 850-859.

Shehabi Y, Bellomo R, Mehta S, Riker R, & Takala J (2013). Intensive care sedation: the past, present and the future. Crit Care 17**:** 322.

Shehabi Y, Howe BD, Bellomo R, Arabi YM, Bailey M, Bass FE, *et al.* (2019). Early sedation with dexmedetomidine in critically ill patients. N Engl J Med 380**:** 2506-2517.

Shehabi Y, Ruettimann U, Adamson H, Innes R, & Ickeringill M (2004). Dexmedetomidine infusion for more than 24 hours in critically ill patients: sedative and cardiovascular effects. Intensive Care Med 30**:** 2188-2196.

Shi C, Jin J, Qiao L, Li T, Ma J, & Ma Z (2019). Effect of perioperative administration of dexmedetomidine on delirium after cardiac surgery in elderly patients: a double-blinded, multi-center, randomized study. Clin Interv Aging 14**:** 571-575.

Shirasaka T, Qiu DL, Kannan H, & Takasaki M (2007). The effects of centrally administered dexmedetomidine on cardiovascular and sympathetic function in conscious rats. Anesthesia and analgesia 105**:** 1722-1728, table of contents.

Singer M, Deutschman CS, Seymour C, Shankar-Hari M, Annane D, Bauer M*, et al.* (2016). The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 315**:** 801-810.

Skrobik Y, Duprey MS, Hill NS, & Devlin JW (2018). Low-dose nocturnal dexmedetomidine prevents ICU delirium. A randomized, placebo-controlled trial. Am J Respir Crit Care Med 197**:** 1147-1156.

Skrobik Y, Leger C, Cossette M, Michaud V, & Turgeon J (2013). Factors predisposing to coma and delirium: fentanyl and midazolam exposure; CYP3A5, ABCB1, and ABCG2 genetic polymorphisms; and inflammatory factors. Crit Care Med 41**:** 999-1008.

Soh S, Shim JK, Song JW, Bae JC, & Kwak YL (2020). Effect of dexmedetomidine on acute kidney injury after aortic surgery: a single-centre, placebo-controlled, randomised controlled trial. Br J Anaesth.

Spapen HD, Jacobs R, & Honoré PM (2017). Sepsis-induced multi-organ dysfunction syndrome—a mechanistic approach. J Emerg Crit Care Med 1.

Sprung CL, Peduzzi PN, Shatney CH, Schein RM, Wilson MF, Sheagren JN*, et al.* (1990). Impact of encephalopathy on mortality in the sepsis syndrome. The Veterans Administration Systemic Sepsis Cooperative Study Group. Crit Care Med 18**:** 801-806.

Stellwagen D, & Malenka RC (2006). Synaptic scaling mediated by glial TNF-alpha. Nature 440**:** 1054-1059.

Stephens RJ, Dettmer MR, Roberts BW, Ablordeppey E, Fowler SA, Kollef MH*, et al.* (2018). Practice patterns and outcomes associated with early sedation depth in mechanically ventilated patients: A systematic review and meta-analysis. Crit Care Med 46**:** 471-479.

Su X, Meng ZT, Wu XH, Cui F, Li HL, Wang DX*, et al.* (2016). Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet 388**:** 1893-1902.

Sun MK, & Guyenet PG (1986). Effect of clonidine and gamma-aminobutyric acid on the discharges of medullo-spinal sympathoexcitatory neurons in the rat. Brain research 368**:** 1-17.

Suzuki T, Suzuki Y, Okuda J, Kurazumi T, Suhara T, Ueda T*, et al.* (2017). Sepsis-induced cardiac dysfunction and β-adrenergic blockade therapy for sepsis. J Intensive Care 5**:** 22-22.

Tan F, Chen Y, Yuan D, Gong C, Li X, & Zhou S (2015). Dexmedetomidine protects against acute kidney injury through downregulating inflammatory reactions in endotoxemia rats. Biomed Rep 3**:** 365-370.

Tan SI, Brewster DJ, Horrigan D, & Sarode V (2018). Pharmacological and non-surgical renal protective strategies for cardiac surgery patients undergoing cardiopulmonary bypass: a systematic review. ANZ J Surg 89: 296-302.

Taniguchi T, Kurita A, Kobayashi K, Yamamoto K, & Inaba H (2008). Dose- and time-related effects of dexmedetomidine on mortality and inflammatory responses to endotoxin-induced shock in rats. J Anesth 22**:** 221-228.

Tavares A, Handy DE, Bogdanova NN, Rosene DL, & Gavras H (1996). Localization of alpha 2A- and alpha 2B-adrenergic receptor subtypes in brain. Hypertension 27**:** 449-455.

Tracey KJ (2007). Physiology and immunology of the cholinergic antiinflammatory pathway. J Clin Invest 117**:** 289-296.

Unnerstall JR, Kopajtic TA, & Kuhar MJ (1984). Distribution of alpha 2 agonist binding sites in the rat and human central nervous system: analysis of some functional, anatomic correlates of the pharmacologic effects of clonidine and related adrenergic agents. Brain Res 319**:** 69-101.

van Gool WA, van de Beek D, & Eikelenboom P (2010). Systemic infection and delirium: when cytokines and acetylcholine collide. Lancet 375**:** 773-775.

Vincent JL, Bakker J, Marécaux G, Schandene L, Kahn RJ, & Dupont E (1992). Administration of anti-TNF antibody improves left ventricular function in septic shock patients. Results of a pilot study. Chest 101**:** 810-815.

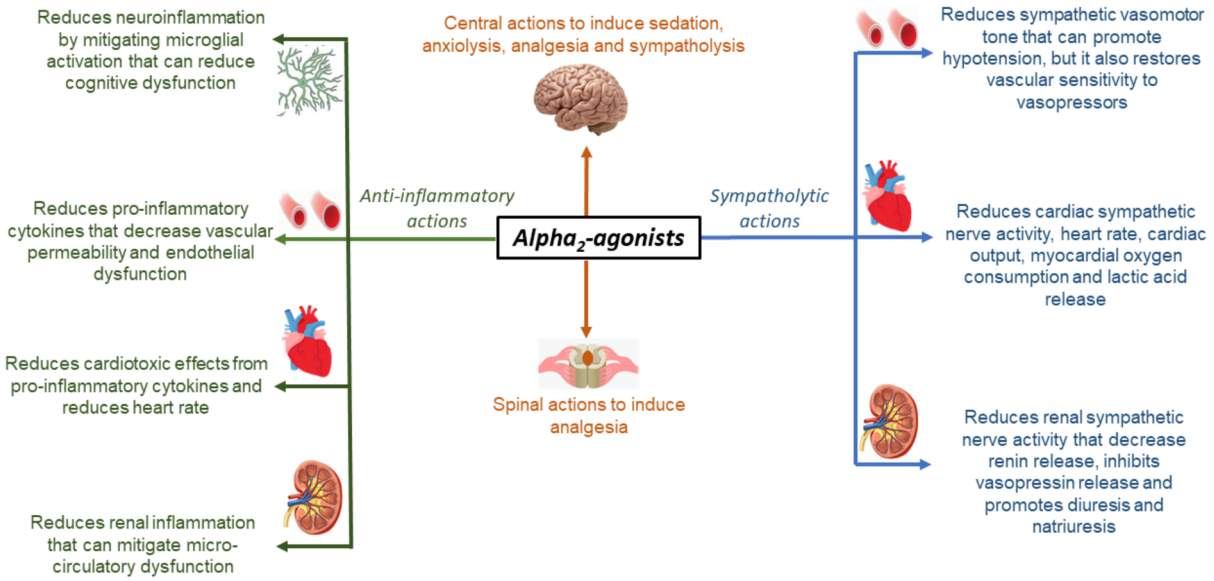
Virtanen R, Savola JM, Saano V, & Nyman L (1988). Characterization of the selectivity, specificity and potency of medetomidine as an alpha 2-adrenoceptor agonist. Eur J Pharmacol 150**:** 9-14.

Weerink MAS, Struys M, Hannivoort LN, Barends CRM, Absalom AR, & Colin P (2017). Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet 56**:** 893-913.

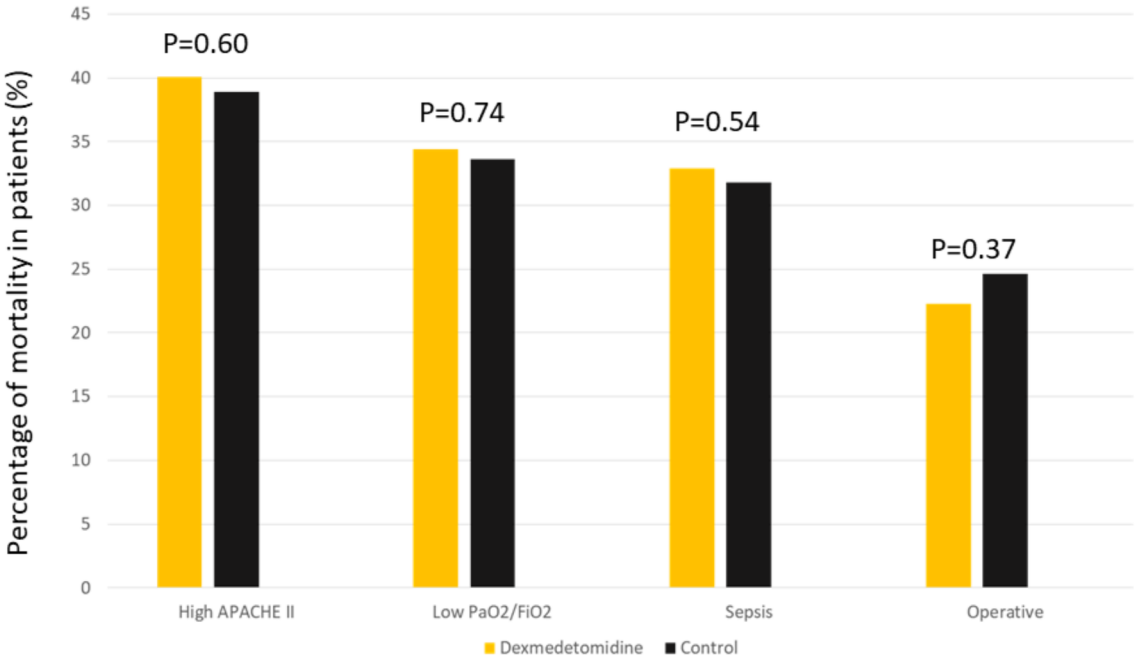
Wu XH, Cui F, Zhang C, Meng ZT, Wang DX, Ma J*, et al.* (2016). Low-dose dexmedetomidine improves sleep quality pattern in elderly patients after noncardiac surgery in the intensive care unit: A pilot randomized controlled trial. Anesthesiology 125**:** 979-991.

Yamazato M, Sakima A, Nakazato J, Sesoko S, Muratani H, & Fukiyama K (2001). Hypotensive and sedative effects of clonidine injected into the rostral ventrolateral medulla of conscious rats. American journal of physiology Regulatory, integrative and comparative physiology 281**:** R1868-1876.

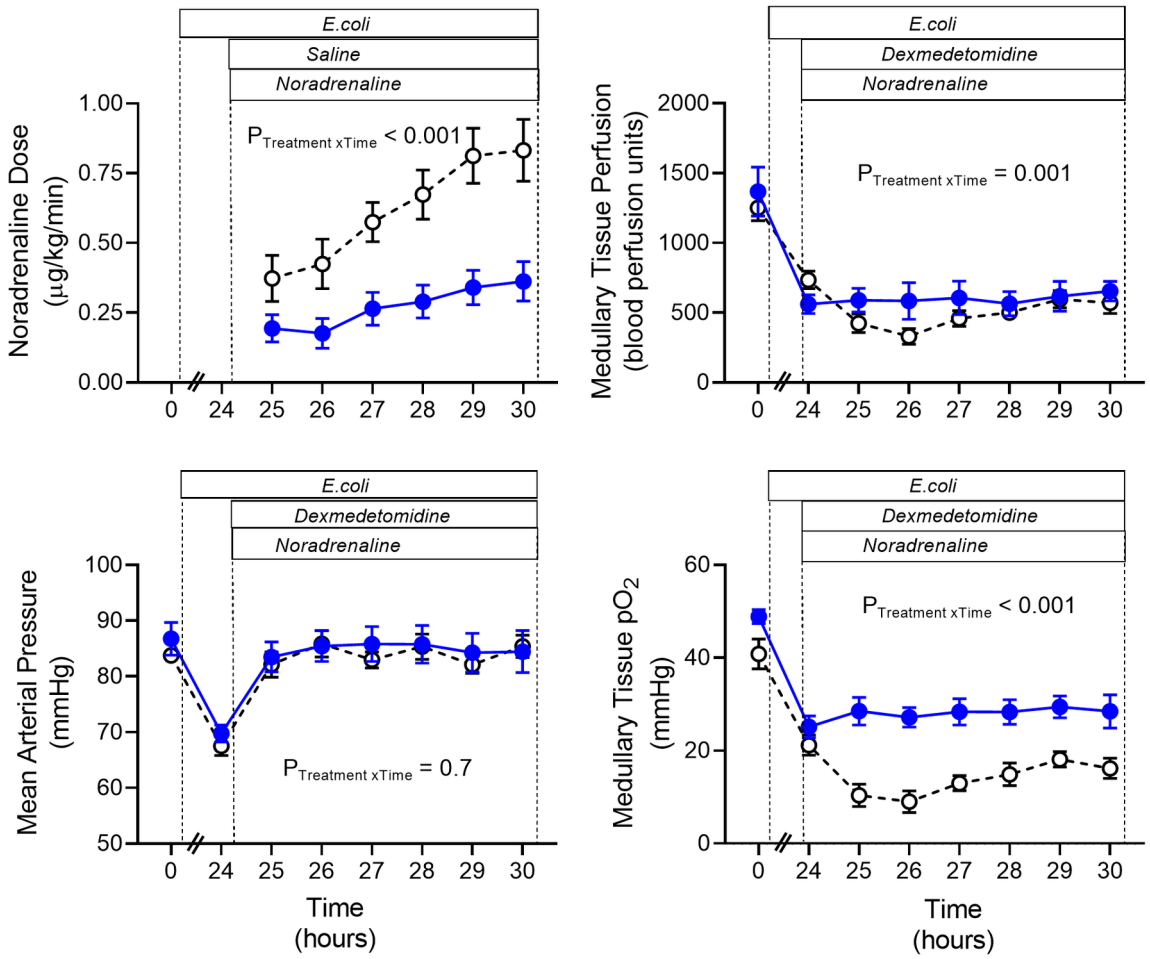
Zhu MZL, Martin A, Cochrane AD, Smith JA, Thrift AG, Harrop GK*, et al.* (2018). Urinary hypoxia: an intraoperative marker of risk of cardiac surgery-associated acute kidney injury. Nephrol Dial Transplant 33**:** 2191-2201.



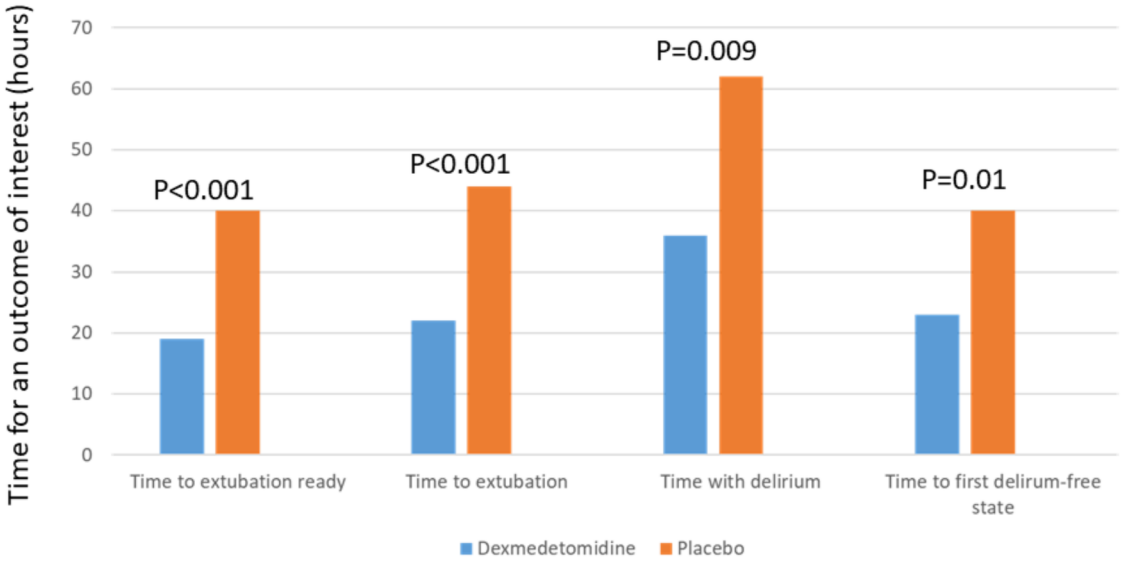
BPH_15363_Figure 1.tif



BPH_15363_Figure 2.tif



BPH_15363_Figure 3.tif



BPH_15363_Figure 4.tif