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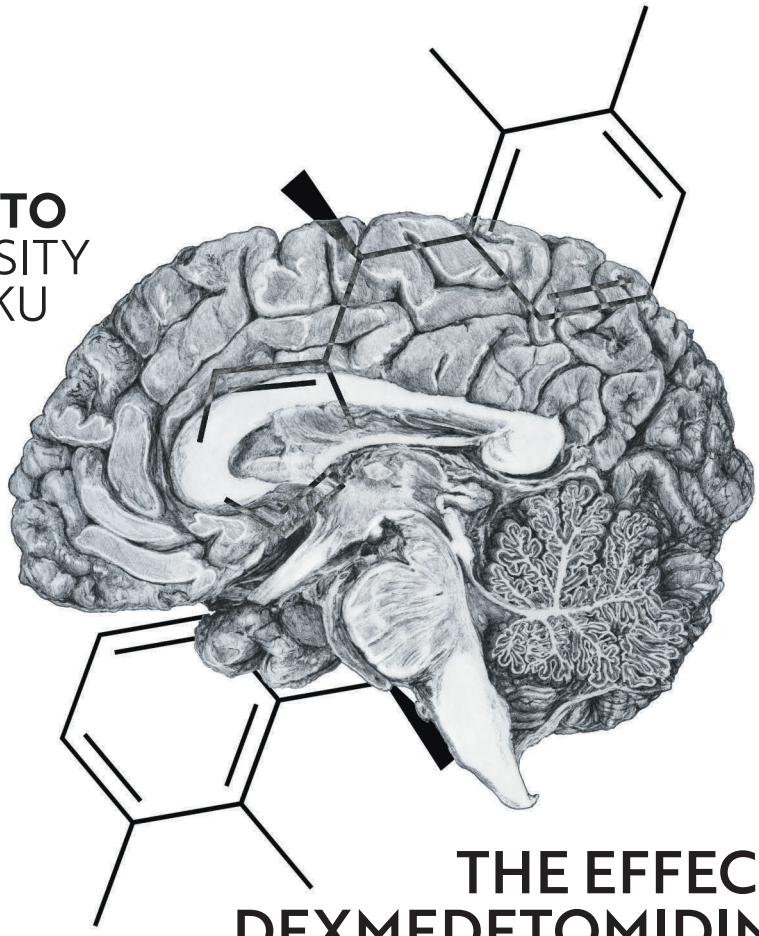

THE EFFECTS OF DEXMEDETOMIDINE ON CEREBRAL GLUCOSE METABOLISM, SYSTEMIC CYTOKINE RESPONSE AND CEREBRAL AUTOREGULATION

Studies on healthy volunteers and aneurysmal subarachnoid haemorrhage patients

Minna Kallioinen

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Trust yourself. Trusting yourself means living out what you already know to be true.

Cheryl Strayed

UNIVERSITY OF TURKU
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ABSTRACT

Dexmedetomidine is a very selective α_2-agonist that has become a popular sedative in the intensive care unit. It has characteristics that make it appealing especially for neurologically compromised patients. Aneurysmal subarachnoid haemorrhage (aSAH) is a complicated disease where cerebral physiology and the regulation of cerebral blood flow, i.e., autoregulation, are often disturbed. It is important that the used anaesthetic and sedative drugs do not cause further damage. The aim of this study was to explore how dexmedetomidine affects cerebral glucose metabolism, systemic cytokine response, and cerebral autoregulation. The first two studies included healthy male volunteers. The first study investigated the effects of dexmedetomidine on cerebral glucose metabolism along with three other anaesthetic drugs (propofol, sevoflurane, S-ketamine) and a placebo group. The second study investigated the effects of dexmedetomidine and propofol on the release of cytokines, chemokines, and growth factors. The third study included 10 aSAH patients. We examined the effects of dexmedetomidine on cerebral autoregulation with three increasing doses after the baseline sedation with propofol and/or midazolam was suspended. In the volunteer studies, we found that the cerebral glucose metabolism was lowest with dexmedetomidine. In addition, we found that dexmedetomidine induced an anti-inflammatory cytokine response, whereas propofol induced a partly pro-inflammatory and slightly anti-inflammatory cytokine response. In aSAH patients, dexmedetomidine did not alter the static cerebral autoregulation compared to baseline. However, after the dose of 1.0 μg/kg/h, we observed a minor but statistically significant decrease in dynamic cerebral autoregulation which may suggest that in aSAH patients sedated with dexmedetomidine, sudden decreases in mean arterial pressure should be avoided.

KEYWORDS: Dexmedetomidine, cerebral autoregulation, subarachnoid haemorrhage, immune system, cerebral glucose metabolism

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TIIVISTELMÄ

Deksmedetomidiini on erittäin selektiivinen α_2-agonisti, jonka monet ominaisuudet sopisivat erityisesti neurologisista sairauksista kärsiville potilaille. Aneurysmaattinen lukinkalvonalainen verenvuoto (aSAV) on monimutkainen sairauskokonaisuus, jossa aivojen metabolia ja aivoverenkierron itsesäätely ovat häiriintyneet merkittävästi. Onkin tärkeää, että näillä potilailla käytetyt anestesia-aineet ja sedatiivit eivät heikentäisi aivoverenkierron itsesäätelyä entisestään. Tämän väitöskirjan tavoitteena oli selvittää deksmedetomidiinin vaikutuksia aivojen glukoosimetaboliaan, sytokiinivasteeseen sekä aivoverenkierron itsesäätelyyn. Kaksi ensimmäistä osatyötä suoritettiin terveillä vapaaehtoisilla miespuolisilla koehenkilöillä. Ensimmäinen osatyö tarkasteli neljän yleisesti käytössä olevan sedatiivin (deksmedetomidiini, propofoli, sevofluraani ja S-ketamiini) sekä lumelääkkeen vaikutusta aivojen glukoosiaineenvaihduntaan. Toinen osatyö tutki deksmedetomidiinin ja propofolin vaikutusta immuunijärjestelmään mittaamalla eri sytokiinien, kemokiinien ja kasvutekijöiden pitoisuuksia ennen ja jälkeen lääkkeiden annostelun. Kolmas osatyö tehtiin 10:llä aSAV-potilaalla, joilla tutkimme, kuinka deksmedetomidiini vaikuttaa aivoverenkierron itsesäätelyyn kolmella eri annosnopeudella verrattuna sedaatioon propofolilla ja/tai midatsolaamilla. Kahden ensimmäisen osatyön tuloksena oli, että deksmedetomidiinilla aivojen glukoosimetabolia oli vähäisempää kuin muilla tutkituilla lääkeaineilla. Lisäksi havaitsimme, että deksmedetomidiini vähentää tulehdusta välittävien sytokiinien eritystä, kun taas propofolilla on kaksijakoinen vaikutus eli se toisaalta vähentää tulehdusmerkkiaineita ja toisaalta lisää niitä. aSAV-potilailla havaittiin, että deksmedetomidiinilla ei ollut vaikutusta aivoverenkierron staattiseen itsesäätelyyn, mutta dynaamisessa itsesäätelyssä havaitsimme heikkenemistä 1,0 µg/kg/h annoksen jälkeen. Tämä löydös saattaa viitata siihen, että kun deksmedetomidiinia käytetään aSAV-potilaiden sedaatiossa, tulee voimakkaita ja nopeita verenpainetason vaihteluita pyrkiä välttämään erityisen huolellisesti.

AVAINSANAT: Deksmedetomidiini, aivoverenkierron itsesäätely, lukinkalvonalainen verenvuoto, immuunijärjestelmä, aivojen aineenvaihdunta

Table of Contents

Abbreviations

ABP	Arterial Blood Pressure
ACA	Anterior Cerebral Artery
ADH	Antidiuretic Hormone
ANOVA	Analysis of Variance
ASA	American Society of Anesthesiologists Classification
aSAH.	Aneurysmal Subarachnoid Haemorrhage
β-NGF	β-nerve Growth Factor
BBB	Blood-Brain Barrier
bFGF	Basic Fibroblast Growth Factor
BP	Blood Pressure
CA	Cerebral Autoregulation
CBF	Cerebral Blood Flow
CBFV	Cerebral Blood Flow Velocity
cHb	Concentration of Deoxygenated Haemoglobin
$CMRO_{2.}$	Cerebral Metabolic Rate of Oxygen
CMR_{glu}	Cerebral Metabolic Rate of Glucose
CNS	Central Nervous System
cO_2Hb	Concentration of Oxygenated Haemoglobin
CPP	Cerebral Perfusion Pressure
CRP	C-reactive Protein
CT	Computer Tomography
CTACK	Cutaneus T-cell Attracting Chemokine
CVR	Cerebral Vascular Resistance
DAMP	Damage-Associated Molecular Pattern
DCI	Delayed Cerebral Ischaemia
EC	Effective Concentration
ECG	Electrocardiogram
EVD	External Ventricular Drain
[^{18}F]FDG	^{18}F-labelled Fluorodeoxyglucose
FFT	Fast Fourier Transform
FUR	Fractional Uptake Rate

FV	Flow Velocity
GI	Gastrointestinal
GMP.	Good Manufacturing Practice
GOM.	Global Oxygen Metabolism
GROα	Growth Regulated Oncogene α
GSK	Glycogen Synthase Kinase
Hb	Haemoglobin
HGF	Hepatocyte Growth Factor
HPLC	High-Performance Liquid Chromatography
HR	Heart Rate
HRRT	High-resolution Research Tomograph
IAV	Intra-assay Variation
ICP	Intracranial Pressure
ICU	Intensive Care Unit
ICU-CAM	Confusion Assessment Method for Intensive Care Unit
IFN	Interferon
IL	Interleukin
IP-10	IFN-y -Induced Protein 10
IV	Intravenous
LIF.	Leukemia Inhibitory Factor
LOC	Loss of Consciousness
LOR	Loss of Responsiveness
MAC	Mean Alveolar Concentration
MAP	Mean Arterial Pressure
MCA	Medial Cerebral Artery
MCP	Monocyte Chemotactic Protein
M-CSF	Macrophage Colony-Stimulating Factor
MIF	Macrophage Migration Inhibitory Factor
MIG	Monokine Induced by IFN-y
MIP	Macrophage Inflammatory Protein
MMSE	Mini-mental State Examination
MRI	Magnetic Resonance Imaging
NIRS	Near-Infrared Spectroscopy
NO	Nitric Oxide
NVC	Neurovascular Coupling
$PaCO_2$	Partial Pressure of Arterial Carbon dioxide
PaO_2	Partial Pressure of Arterial Oxygen
PAMP.	Pathogen-Associated Molecular Pattern
$P_{bt}O_2$	Brain Tissue Oxygen Pressure
PCA	Posterior Cerebral Artery

PCT	Procalcitonin
PDGF	Platelet-Derived Growth Factor
PET	Positron Emission Tomography
PI	Pulsatility Index
POCD	Post-Operative Cognitive Dysfunction
POD	Post-Operative Delirium
PPR	Pursuit Progression Analysis
PRR	Pattern Recognition Receptor
RANTES	Regulated On Activation Normal T-cell Expressed And Secreted
RCT	Randomized Controlled Trial
ROI	Region of Interest
SA	Static Autoregulation
SBP	Systolic Blood Pressure
SCF	Stem Cell Factor
SCGF	Stem Cell Growth Factor
SD	Standard Deviation
SDF-1α	Stromal Cell Derived Factor 1α
sROR	Static Rate of Autoregulation
TBI.	Traumatic Brain Injury
TCD	Transcranial Doppler
TCI	Target-Controlled Infusion
TFA	Transfer Function Analysis
Th1	Type 1 Helper
Th2	Type 2 Helper
THI	Total Haemoglobin Index
THRR	Transient Hyperaemic Response Ratio
THRT	Transient Hyperaemic Response Test
TLR	Toll-Like Receptor
TNF	Tumour Necrosis Factor
TOI	Tissue Oxygenation Index
TRAIL	TNF-Related Apoptosis Inducing Ligand
VEGF	Vascular Endothelial Growth Factor
VMCA	Medial Cerebral Artery Velocity
VMR	Vasomotor Reactivity

List of Original Publications

This thesis is based on the following original articles, which will be referred to in the text by the Roman numerals I–III

I Laaksonen L, Kallioinen M, Långsjö J, Laitio T, Scheinin A, Scheinin J, Kaisti K, Maksimow A, Kallionpää RE, Rajala V, Johansson J, Kantonen O, Nyman M, Siren S, Valli K, Revonsuo A, Solin O, Vahlberg T, Alkire M, Scheinin H. Comparative effects of dexmedetomidine, propofol, sevoflurane, and S-ketamine on regional cerebral glucose metabolism in humans: a positron emission tomography study. BJA, 121 (1): 281-290 (2018)

II Kallioinen M, Scheinin A, Maksimow M, Långsjö J, Kaisti K, Takala R, Vahlberg T, Valli K, Salmi M, Scheinin H, Maksimow A. The influence of dexmedetomidine and propofol on circulating cytokine levels in healthy subjects. BMC Anesthesiol (2019) 19:222

III Kallioinen M, Posti JP, Rahi M, Sharma D, Katila A, Grönlund J, Vahlberg T, Frantzen J, Olkkola KT, Saari TI, Takala R. Cerebral autoregulation after aneurysmal subarachnoid haemorrhage. A Preliminary study comparing dexmedetomidine to propofol and/or midazolam. Acta Anaesthesiol Scand 1 Jul 2020

1 Introduction

In treating patients with neurological or neurosurgical disorders, an ideal sedative or anaesthetic drug should have neuroprotective qualities and should maintain haemodynamic stability. It should not impair cerebral autoregulation, or increase intracranial pressure, and should preferably allow neurological evaluation without interrupting the sedation. Dexmedetomidine is a sedative drug that is increasingly used in intensive care units and in neurologically compromised patients. It seems to fulfil many ideal properties required in neurointensive care. It is a highly selective α_2-agonist that produces a sedation resembling natural sleep from which the patient is easily rousable even during the infusion (Huupponen et al., 2008). Another unique feature of dexmedetomidine is that it does not induce significant respiratory depression (Hsu et al., 2004; Venn, Hell, & Grounds, 2000; Venn, Karol, & Grounds, 2002), and it can therefore be a useful sedative also for patients without ventilatory support. In experimental models, dexmedetomidine has shown neuro- and cardioprotective effects (Dardalas et al., 2019), and it also seems to have anti-inflammatory properties, since it attenuates neuroinflammation and neuroapoptosis in vitro and in animal studies (Carr, Cios, Potter, & Swick, 2018). In humans, these anti-inflammatory effects are still unconfirmed. Clinical studies on the use of dexmedetomidine in brain-injured patients are seriously lacking.

Cerebral autoregulation refers to the brain's ability to maintain a steady blood flow despite changes in the systemic arterial pressure. It can be divided into static autoregulation and dynamic autoregulation, reflecting the capacity of cerebral vasculature to respond to fast (dynamic) and slow (static) changes in cerebral perfusion pressure. Other factors affecting cerebral blood flow include carbon dioxide reactivity and flow-metabolism coupling. Studies investigating dexmedetomidine's effects on cerebral autoregulation are scarce. In healthy volunteers, it weakens dynamic cerebral autoregulation (Ogawa et al., 2008) and decreases cerebral blood flow (Prielipp et al., 2002; Zornow, Maze, Dyck, & Shafer, 1993). Early canine studies (Karlsson, Forsman, Roald, Heier, & Steen, 1990; Zornow, Fleischer, Scheller, Nakakimura, & Drummond, 1990) elicited a concern that dexmedetomidine might not preserve the supply and demand balance between cerebral metabolic rate of oxygen and cerebral blood flow, thus predisposing to

cerebral ischemia. More recent studies have alleviated this concern to some degree (Akeju et al., 2014; John C Drummond et al., 2008). It remains unsolved how dexmedetomidine affects the compromised/weakened cerebral autoregulation during a neurological illness.

Aneurysmal subarachnoid haemorrhage (aSAH) is a highly injurious disease frequently affecting young, working age patients and causing great disability and high fatality. It is a disease involving all organ systems due to an intense systemic inflammatory response. aSAH patients are almost always treated in the intensive care unit, and the majority needs sedation and ventilatory support. A common neurological worsening after aSAH is caused by delayed cerebral ischemia (DCI). Neuroinflammation and impaired cerebral autoregulation are associated with DCI (Budohoski et al., 2012; Khey, Huard, & Mahmoud, 2020; Rätsep & Asser, 2001).

This thesis investigated the effects of dexmedetomidine on cerebral metabolic coupling of glucose and systemic expression of inflammatory cytokines in healthy volunteers. Additionally, we assessed dexmedetomidine in aSAH patients and its effects on cerebral autoregulation.

2 Review of the Literature

2.1 α-adrenergic receptors

The endogenous catecholamines, noradrenaline and adrenaline, bind to a class of membrane-bound proteins called the adrenergic receptors, or adrenoceptors. They belong to a wide family of receptors that operate through guanine nucleotide regulatory proteins (G-proteins) and are spread throughout the body to presynaptic, postsynaptic, and extra synaptic sites of activity (Nguyen, Tiemann, Park, & Salehi, 2017). Adrenoceptors are divided into α- and β-adrenergic receptors (Ahlqvist, 1948), which later have been pharmacologically divided to subtypes α_1 and α_2 and β_1 and β_2 (Lands, Arnold, McAuliff, Luduena, & Brown, 1967). These subtypes have been further classified into distinct subtypes; hence, the α_2-receptors have been subclassified into α_{2A}-, α_{2B}- and α_{2C} -subtypes (Calzada & Artiñano, 2001).

2.2 α-adrenoceptor agonists

There are two α-adrenoceptor agonists in clinical use, clonidine and dexmedetomidine. Clonidine is a non-selective α-adrenoceptor agonist that is mostly known and used for its antihypertensive properties. However, it also has sedative and analgesic effects which have made it a popular adjuvant to other anaesthetic agents (Nguyen et al., 2017). Dexmedetomidine is an imidazole molecule and the pharmacologically active dextro-enantiomer of medetomidine. Its molecular formula is C13H16N2. It is a highly selective α_2-agonist and has approximately 8 times greater selectivity to α_2-receptors than clonidine, α2:α1 ratio of 1620:1 vs 220:1 (Virtanen, Savola, Saano, & Nyman, 1988). Dexmedetomidine is also a more powerful sedative than clonidine, as the central α_1-adrenoceptor activation counters the sedative α_2-effects (Guo, Tinkienberg, & the, 1991).

2.3 Dexmedetomidine

2.3.1 The history of dexmedetomidine

The history of dexmedetomidine began in Finland, where it was developed by the Finnish pharmaceutical research and development company, Farmos Pharma. It was registered in the USA in 1999 and was originally approved only for intravenous sedation of mechanically ventilated patients in the ICU for up to 24 hours (FDA, 2021; Weerink et al., 2017). In 2008 in the USA, dexmedetomidine was indicated also for patients without ventilatory support during or prior to surgical and other procedures. In 2011, the European Medicines Agency approved the use of dexmedetomidine in adult ICU patients requiring light sedation (EMA, 2021). The approved indications for the use of dexmedetomidine differ on a global scale, and off-label use is commonly described in the literature.

2.3.2 Pharmacokinetics of dexmedetomidine

Dexmedetomidine is available as a water-soluble HCl salt. The recommended dose is 0.7 μg/kg/h and is thereafter titrated to the desired effect using a dose rage of 0.2-1.4 μg/kg/h. Dexmedetomidine is a lipophilic protein-bound molecule, and 94% of dexmedetomidine is bound to α1-glycoprotein and albumin (Weerink et al., 2017). The volume of distribution is large and dependent on bodyweight, and dexmedetomidine is rapidly redistributed to peripheral tissues. The distribution half-life is about 6 minutes in healthy volunteers. In preclinical animal studies, dexmedetomidine crosses the blood-brain and placenta barriers (Weerink et al., 2017). An increased volume of distribution has been observed in ICU patients with hypoalbuminemia (Iirola et al., 2011). Dexmedetomidine is metabolized in the liver via both direct glucuronidation and biotransformation by cytochrome P2A6 oxidation and is excreted mainly in urine with a small amount eliminated in the faeces. In healthy volunteers, an elimination half-life of 2.1-3.1 h is reported, and in ICU-patients the elimination half-lives ranged from 2.2-3.7 h (Weerink et al., 2017).

2.3.3 Pharmacodynamics of dexmedetomidine

2.3.3.1 Sedative effects of dexmedetomidine

Figure 1 summarises the pharmacodynamic effects of dexmedetomidine. The sedative effects of dexmedetomidine are caused by the stimulation of pre- and postsynaptic α_2-receptors in the locus coeruleus, which is the principal site of noradrenaline synthesis in the brain. (Correa-Sales, Rabin, American, & 1992, 1992;

Doze, Chen, Society, & 1989, 1989; Segal, Vickery, Walton, the, & 1988, 1988). The pons and medulla are the primary sites where the α_2-receptors in the central nervous system are located, and they are mainly responsible for the transmission of the alpha thetic activity to the peripheral nervous system. In locus coeruleus, dexmedetomidine decreases the noradrenaline release by activating the presynaptic α_2-receptors, whereas the activation of the postsynaptic α_2-receptors causes hyperpolarisation of neuronal membranes (Nguyen et al., 2017).

Dexmedetomidine produces a unique sedation that resembles natural sleep (Huupponen et al., 2008). Its sedative effects depend on the concentration, and plasma concentrations between 0.2 and 0.3 ng/ml result in a significant but rousable sedation. Plasma concentrations of above 1.9 ng/ml are thought to result in an unrousable, deep sedation (Ebert, Hall, Barney, Uhrich, & Colinco, 2000).

2.3.3.2 Analgesic effects of dexmedetomidine

The analgesic properties of dexmedetomidine are still mostly unclear, but they are thought to originate from binding to spinal cord and central α_2-receptors. The binding to α_2-receptors within the dorsal horn of the spinal column results in a decreased release of excitatory neurotransmitters, such as substance P and glutamate, and in hyperpolarization of interneurons (Ishii, Kohno, Yamakura, Ikoma, & Baba, 2008). Yet dexmedetomidine does not seem to have analgesic efficacy (Angst, Ramaswamy, Davies, & Maze, 2004; Kauppila, Kemppainen, Tanila, & Pertovaara, 1991). The analgesic effects may partly be a result of altered perception and awareness, as well as reduced anxiety, although an opioid-sparing effect has been observed in various trials (Blaudszun, Lysakowski, Elia, & Tramèr, 2012; Lundorf, Nedergaard, & Møller, 2016).

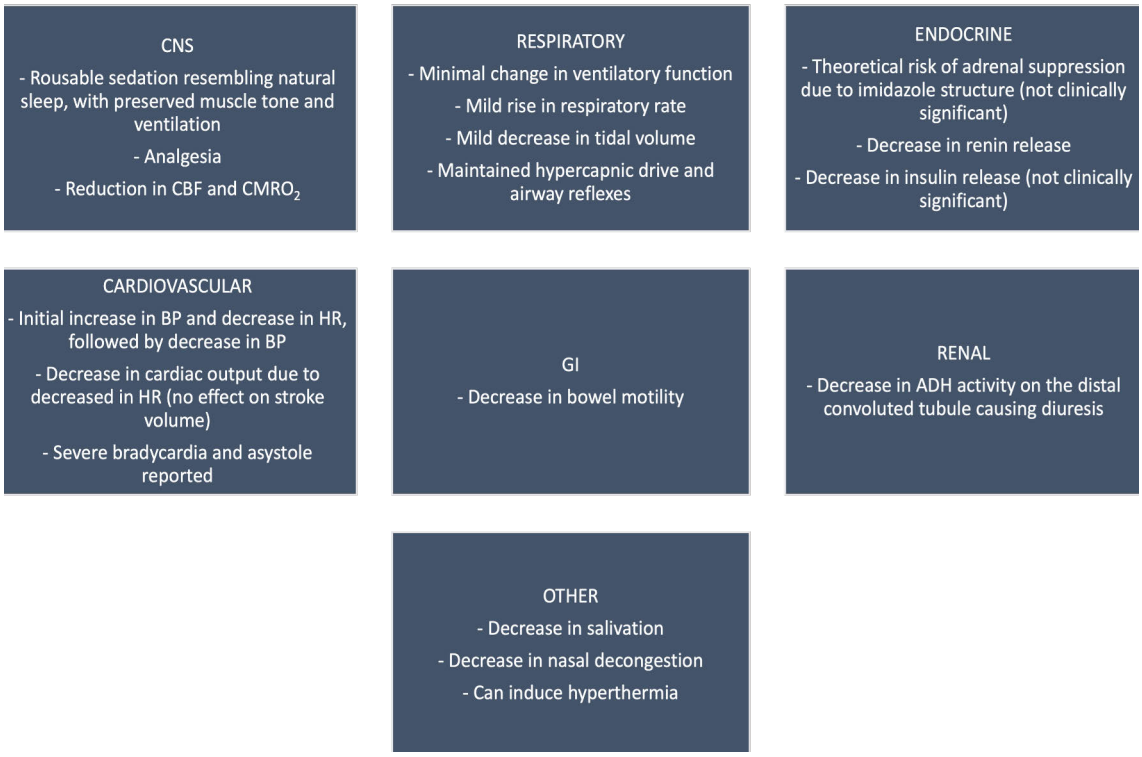


Figure 1 Summary of the pharmacodynamic effects of dexmedetomidine. Modified from Crowe et al. (Crowe, Gillian, & Moran, 2022). ADH: antidiuretic hormone, BP: blood pressure, CBF: cerebral blood flow, $CMRO_2$: cerebral metabolic rate of oxygen, CNS: central nervous system, HR: heart rate, GI: gastrointestinal

2.3.3.3 Common side-effects of dexmedetomidine

The most noticeable side-effects of dexmedetomidine are cardiovascular. The haemodynamic effects of dexmedetomidine are two-fold: it induces hypotension at lower plasma concentrations and, conversely, hypertension at higher plasma concentrations (Bloor, Ward, Belleville, & Maze, 1992; Ebert et al., 2000). An IV-bolus results in high peak plasma, which induces an increase in blood pressure and a significant decrease in heart rate. This response is a result of the activation of α_2-receptors in the vascular smooth muscle, which causes peripheral vasoconstriction. Conversely, bradycardia is thought to be caused by a consequent baroreceptor reflex (Ebert et al., 2000). After the IV-bolus, dexmedetomidine concentration decreases, resulting in vascular endothelial cell α_2-receptor activation and in vasodilatation (Talke, Lobo, & Brown, 2003). This, combined with the increased vagal activity and the suppression of the catecholamine release, results in a hypotensive phase. Higher maintenance doses normally trigger a progressive increase in MAP, and the hypertensive effects surmount the hypotensive ones at concentrations between 1.9

and 3.2 ng/ml (Ebert et al., 2000). At high plasma concentrations, dexmedetomidine also increases pulmonary vascular resistance, causing pulmonary hypertension (Ebert et al., 2000). Dexmedetomidine does not seem to impair systolic or diastolic cardiac function (Lee, Choi, Hong, & Oh, 2015). The decrease in cardiac output results from a lower heart rate, and no decrease in stroke volume has been observed until plasma concentrations rise above 5.1 ng/ml (Ebert et al., 2000).

2.3.4 Dexmedetomidine in ICU sedation

Sedation is used in critically ill patients to facilitate ventilator tolerance and to decrease the patient's discomfort. Guidelines consistently recommend minimal sedation, for it has been shown that excessive, unmonitored sedation may prolong the need for mechanical ventilation, increase the occurrence of delirium, and prolong the length of ICU stay (Page & McKenzie, 2021). In neurocritical setting, sedation is used particularly to decrease intracranial pressure and to generate haemodynamic stability. Sedation from which the patient is easily roused is especially desirable in neurologically compromised patients who need regular and frequent neurological assessment.

The most renowned large clinical trials investigating the efficacy of dexmedetomidine compared to standard care with midazolam or propofol are MIDEX (Jakob et al., 2012), PRODEX (Jakob et al., 2012), and SEDCOM (Riker et al., 2009). Their main finding was that dexmedetomidine was as suitable as midazolam and propofol considering time at target sedation without rescue medication. Time to extubation was also significantly shorter with dexmedetomidine compared to midazolam or propofol.

A Cochrane review including 7 studies with 1624 patients comparing the use of dexmedetomidine in long-term ICU sedation with conventional sedatives found a reduction in the duration of mechanical ventilation by 22%, as well as a reduction of 14% in the ICU length of stay with dexmedetomidine (K. Chen et al., 2015). No differences in mortality were observed. The recent SPICE III study with 3904 patients compared dexmedetomidine to standard care with propofol, midazolam, or other sedatives as the sole or primary sedative (Shehabi et al., 2019). The rate of death from any cause at 90 days was the primary outcome, and no difference between the groups was observed. However, more additional sedatives were needed to achieve the commended level of sedation in the dexmedetomidine group. Moreover, there were more adverse events, including a prolonged sinus arrest leading to cardiac massage, in the dexmedetomidine group. A later subgroup analysis of SPICE III trial showed, interestingly, a significant reduction in 90-day mortality with dexmedetomidine sedation in patients older than 65 years as well as operative patients who required mechanical ventilation for longer than 24 hours (Shehabi et

al., 2021). On the contrary, the risk of death was increased in medical patients under 65 years.

2.3.5 Dexmedetomidine in neurocritical patients

In neurocritical patients, dexmedetomidine appears to be a promising sedative. However, the neuroprotective properties that dexmedetomidine seems to possess have been mostly demonstrated in various preclinical studies with animal models of e.g., SAH and TBI, and in vitro. The effects in humans remain undetermined. According to a meta-analysis evaluating the use of dexmedetomidine in neurocritical care, dexmedetomidine seems to be efficient and safe, both as a sole sedative as well as an adjunct (Tsaousi, Lamperti, & Bilotta, 2016). The studies included in the meta-analysis comprised patients with TBI, SAH, ICH as well as patients who had undergone an elective neurosurgical procedure for tumours or unruptured cerebral aneurysms. Dexmedetomidine was associated with a better sedation score when compared to propofol but induced more bradycardia episodes and increased the need for vasopressors. The meta-analysis was not, however, able to show a clear haemodynamic impact of dexmedetomidine compared to propofol or midazolam. The evidence is unfortunately still limited in quantity and quality, and only 3 RCTs and 5 observational studies were included in the meta-analysis (Tsaousi et al., 2016). A more recent retrospective observational cohort study compared the use of dexmedetomidine with propofol in neurointensive care (Owusu et al., 2020). The study included 179 patients admitted to NeuroICU. The main finding was that the indications for the use of dexmedetomidine and propofol differed greatly. Propofol was mostly used to manage agitation associated with mechanical ventilation, while dexmedetomidine was used to facilitate extubation and alcohol withdrawal as well as to sedate patients in need of frequent neurological assessments (Owusu et al., 2020). The adverse effect profiles and clinical outcome were essentially comparable between the treatment groups.

2.4 Cerebral autoregulation

2.4.1 The concept of cerebral autoregulation

Cerebral autoregulation represents the homeostatic process in the brain that maintains stable cerebral blood flow (CBF) regardless of changes in the systemic blood pressure. The concept was first described by Forbes in 1928 (Forbes, 1928) and Fog in 1937 (Fog, 1937) when they observed cerebral surface vessels and noticed that a decrease in blood pressure led to vasodilation, while an increase in blood pressure caused vasoconstriction. This phenomenon was later described in

humans by Lassen in 1959 as the so-called 'autoregulation curve', which is a triphasic curve consisting of the lower limit, the plateau, and the upper limit (Lassen, 1959). The clinical studies conducted by Lassen calculated the CBF using the inert gas method, which measures the venous dilution of an intra-arterially injected indicator (Lassen, 1959). Positron emission tomography (PET) that measures cerebral oxygen and glucose metabolism is based on these principles (Beek, Claassen, Rikkert, & Jansen, 2008). In healthy adults, autoregulation works between 50 and 150 mmHg mean arterial pressure (MAP) (**Figure 2**). However, it is important to note that these limits are not fixed but are modified by various factors that decrease or increase CBF. Weakened or even destroyed cerebral autoregulation is commonly seen in various brain disorders (Paulson, Strandgaard, & Edvinsson, 1990).

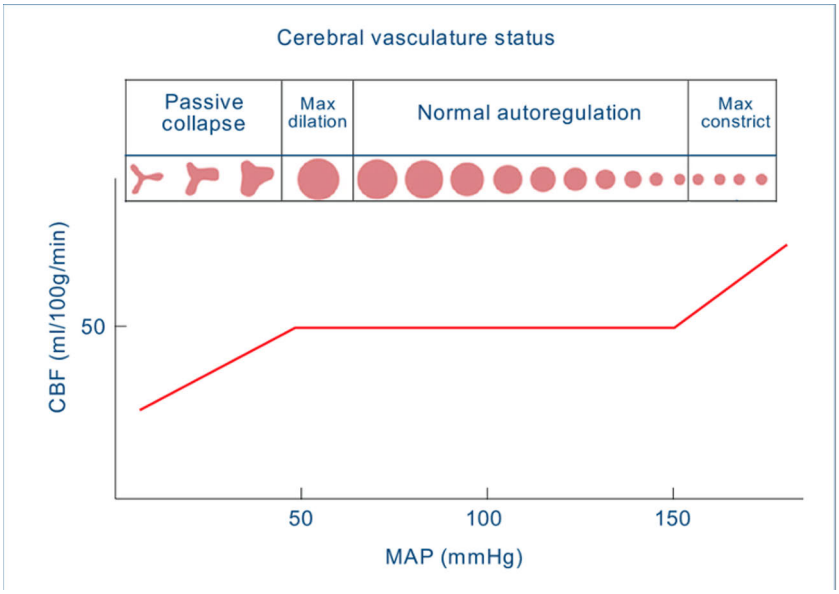


Figure 2 Autoregulation of cerebral blood flow (CBF) and mean arterial pressure (MAP), Max: maximum (H. Liu, Tariq, Liu, & Yu, 2017). Reprinted from the Journal of Anesthesia and Perioperative Medicine with permission from the authors.

2.4.2 The mechanisms of cerebral autoregulation

Cerebral autoregulation ensures that as MAP or CPP increases, the small cerebral arteries vasoconstrict and increase the vascular resistance. Similarly, when MAP or CPP decreases, the cerebral arteries vasodilate, leading to a decrease in the cerebrovascular resistance. As a result, CBF remains constant. To meet the cerebral metabolic demands in normal conditions, CBF must remain at around 50-60 ml/100 g/min, with women having somewhat higher rates (Rostrup et al., 2005;

Satterthwaite et al., 2014). Ischemic injury usually occurs when CBF drops below 22 ml/100g/min; however, this threshold may be altered by an underlying condition such as hypothermia or TBI (Velly & Bruder, 2018).

Cerebral autoregulation is separate from other systems that regulate CBF, such as CO_2 reactivity and flow-metabolism coupling, although these concepts significantly overlap (Baron et al., 1984; Lundar et al., 1985). CO_2 reactivity refers to a process called vasomotor reactivity (VMR), where the cerebral vascular tone is influenced by changes in the partial pressure of arterial CO_2 ($PaCO_2$) and, less significantly, of O_2 (PaO_2). Flow-metabolism coupling, or neurovascular coupling (NVC), portrays the regulation of CBF to answer to the metabolic demands of neural activity. Similar to VMR, NVC functions regardless of changes in CPP (Phillips, Chan, Zheng, Krassioukov, & Ainslie, 2016). The innate mechanisms of cerebral vasculature are complex and poorly understood. At least 4 mechanisms for cerebral autoregulation have been proposed: myogenic, neurogenic, metabolic, and endothelial (Armstead, 2016). Vascular smooth muscle, endothelium, and neighbouring neurons and astrocytes form a neurovascular unit (Lok et al., 2007) which fundamentally regulates cerebral myogenic tone (Thorup, Koch, Upton, Østergaard, & Rasmussen, 2019).

2.4.3 Assessment of cerebral autoregulation

Cerebral vasculature must have the ability to react to both fast and slow changes in CPP. Autoregulation is conceptually divided into static and dynamic components. Measurement of cerebral autoregulation is a complicated process. Direct and reliable non-invasive measurement of CBF is difficult, and therefore a surrogate is typically used (Beek et al., 2008). The most used surrogate for CBF is blood flow velocity in the medial cerebral artery (MCA) monitored by transcranial Doppler (TCD). The partial pressure of brain tissue oxygen (PbtO2) and the oxygen saturation of haemoglobin in the cerebral vasculature measured with near-infrared spectroscopy (NIRS) are also increasingly used. Assessing autoregulation requires also continuous measurement of blood pressure (Gianfranco Parati et al., 2003). The measurement of autoregulation essentially observes the change in CBF in response to the change in MAP or CPP. These methods offer metrics or indices to describe the relationship between pressure and flow, or its surrogate.

2.4.4 Transcranial Doppler

The Doppler principle was first described by Christian Andreas Doppler in 1842. It is a change that can be observed in the frequency of a sound wave produced by relative movement between the sound source and the observer (Rasulo, Peri, & Lavinio, 2008).

Principles and theories involving TCD are similarly based on the concept of Doppler to measure blood flow velocity in large vessels (Rasulo et al., 2008). Moving red blood cells reflect and change the frequency of the ultrasound wave produced by a piezoelectric crystal transducer (2 Hz). Doppler shift is the difference between the frequency of the original signal and the reflected signal. It is directly related to the blood flow velocity (Rasulo et al., 2008) and can be calculated as

$$F = (2FtV \cos \vartheta)/C$$

where F is the Doppler shift, Ft is the frequency of the wave emitted, V is the actual velocity, C is the velocity of sound in tissue, and $\cos \vartheta$ is the cosine of the angle between the insonated vessel and the direction of the ultrasound wave (Rasulo et al., 2008).

The Doppler frequency shift that is reflected consists of a distribution of frequencies and not of a single value. Meaningful velocity information can be obtained with different methods. The most common method is using Fast Fourier transform (FFT) algorithm to short segments (typically $\Delta t = 5$ ms) of the raw Doppler shifted signal in order to obtain the spectral distribution of power at each frequency. From this frequency, either the maximum frequency (maximum velocity) or its intensity-weighted mean are attained to denote the mean velocity for the time interval Δt (Panerai, 2009). In most TCD displays, these are presented as a colour coded sonogram (**Figure 3**).

Figure 3 Image of MCA velocity waveforms obtained with Transcranial Doppler.

There are four acoustic windows in the skull where the ultrasound beam is able to penetrate the skull. The most relevant to the cerebral autoregulation studies is the transtemporal window which is found above the zygomatic arch and enables the insonation of MCA, anterior (ACA) and posterior cerebral arteries (PCA) (Panerai, 2009). For clinical purposes, MCA is most used, as it receives 60-70% of ipsilateral carotid flow and represents hemispheric CBF. MCA is usually found at a depth of 50-55 mm and has a positive velocity pattern, meaning that the flow is towards the transducer. The autoregulation studies usually require stable and reliable continuous monitoring of CBFV signals, sometimes over several hours, requiring the use of a fixed head frame (Evans, 2001). In evaluating cerebrovascular status in for example SAH and acute ischaemic stroke, TCD has been shown to be a reliable and accurate tool (Pan, Wan, Xiang, & Guan, 2022). However, there are limitations for its use. First, it is highly operator dependent, requiring vast experience of the technique and deep knowledge of cerebrovascular anatomy. Second, the measurements are limited to large basal arteries and can therefore only provide an index of global not local CBF (Pan et al., 2022). Also, the velocity is affected by various factors, such as haematocrit value, age, gender, skull thickness, and CO_2 partial pressure in the blood. Finally, adequate acoustic windows are lacking in 10-15% of individuals (Purkayastha & Sorond, 2012).

2.4.5 Static autoregulation

Static autoregulation (SA) refers to steady-state changes in CBF in response to changes in MAP/CPP (Lassen & Christensen, 1976). Static autoregulation estimates the overall efficiency of autoregulation and the changes in CVR in response to changes in MAP/CPP without considering its latency (Tiecks, Lam, Aaslid, & Newell, 1995). Static autoregulation can be tested by monitoring CBF during pharmacologically induced changes in systemic blood pressure (Tiecks et al., 1995). Vasopressors, such as phenylephrine or noradrenaline, are used to manipulate MAP, while CBF can be measured by methods such as TCD or PET. The static rate of autoregulation (sROR) is analysed by measuring CBF at two constant blood pressure levels and calculating the ratio change between these two (Budohoski, Czosnyka, Kirkpatrick, et al., 2013).

An sROR of 100% or more is an indication of an intact cerebral autoregulation where CBF is independent of fluctuations in CPP. In contrast, an sROR of 0% indicates a complete loss of cerebral autoregulation where CBF linearly follows CPP. The measurement involves a pharmacological manipulation of MAP and sufficient time between the measurements to allow the flow and pressure to stabilise. The most reliable method of measuring static autoregulation is with direct perfusion methods, such as MRI, PET, and ^{133}Xe clearance, as they all allow the calculation of absolute CBF values (Budohoski, Czosnyka, Kirkpatrick, et al., 2013). These

methods measure CBF only intermittently. TCD, however, can be used for continuous bedside monitoring of CBF (Panerai, 2009).

2.4.6 Dynamic autoregulation

Dynamic autoregulation represents the changes in CBF in reaction to rapid changes in MAP/CPP over a timespan of seconds (Tiecks et al., 1995). The methods used for evaluating the dynamic autoregulation include TCD, laser Doppler flowmetry, PbtO2, thermal-diffusion regional CBF, and NIRS (Budohoski, Czosnyka, Kirkpatrick, et al., 2013). The heterogeneity of these various methods is considerable, and the interpretation of results is not simple. No regular and accepted standardised method for the evaluation of dynamic autoregulation exists, unlike for static autoregulation. The most used methods and algorithms can be classified into those that use a short manipulation of blood-pressure and those that depend on spontaneous fluctuations of blood pressure (Budohoski, Czosnyka, Kirkpatrick, et al., 2013).

2.4.6.1 Transient hyperaemic test

The transient hyperaemic response test (THRT) is a simple, safe, and useful method for measuring the dynamic cerebral autoregulation (Giller, 1991; Smielewski, Czosnyka, Kirkpatrick, & Pickard, 1997). The test involves a short compression of the common carotid artery which then induces the compensatory vasodilatation of the arterioles. During the test, the flow velocity in the MCA is measured continuously. The common carotid artery is compressed on one side for 8-10 seconds, which induces a decrease in ipsilateral MCA flow velocity and hence in CPP. The cerebral arterioles should respond to the reduction in CPP through vasodilatation if the autoregulation functions properly. Once the compression is released, a temporary increase in MCA flow is observed (Giller, 1991; Smielewski et al., 1997). The integrity of autoregulation can be demonstrated by calculating the transient hyperaemic response ratio (THRR). This is the ratio between the velocity of systolic flow during the hyperaemic phase (two cycles after the compression release excluding the very first cycle) and the velocity of the baseline systolic flow:

$$THRR = (systolic\ FV\ hyperaemia)/(systolic\ FV\ baseline)$$

The normal THRR range is between 1.105 and 1.29 (Giller, 1991; Smielewski et al., 1997). Smielewski et al. observed cortical microcirculation using laser Doppler flowmetry during THRT and were able to show that the test reflects blood flow responses occurring at the level of tiny resistance cerebral arterioles (Smielewski et al., 1997). Two variables that affect the reliability of the THRR measurement are the strength and duration of the carotid compression. The strength of the compression

should cause a reduction of at least 40% in flow velocity (Mahajan, Cavill, & Simpson, 1998). There is some disagreement about the adequate duration of the compression, with some authors suggesting 5 seconds (Giller, 1991) and others recommending a longer, 10-second compression (Mahajan et al., 1998).

2.4.7 Cerebral blood flow, metabolism, and autoregulation with anaesthetic and sedative agents

2.4.7.1 Dexmedetomidine

Dexmedetomidine reduces CBF in healthy volunteers (Prielipp et al., 2002; Zornow et al., 1993). This reduction is believed to result either from direct cerebral smooth muscle vasoconstriction or, indirectly, from a decreased cerebral metabolism (Prielipp et al., 2002). According to early animal studies, dexmedetomidine did not reduce cerebral metabolic rate (CMR) together with CBF (Karlsson et al., 1990; Zornow et al., 1990). These observations raised concern that a reduction in CBF/CMR ratio could lead to compromised cerebral oxygen delivery and consequently ischaemia, which would be especially detrimental for patients with neurological insults. In healthy volunteers, with methods using TCD and jugular venous oxygen saturation, dexmedetomidine did not decrease $CBF/CMRO_2$ ratio, indicating that cerebral metabolic rate coupling was conserved during dexmedetomidine (John C Drummond et al., 2008). This coupling was preserved during both normo- and hypercapnia. Another study found that the CBF/CMR_{gluc} coupling was preserved during dexmedetomidine administration (Akeju et al., 2014).

Dexmedetomidine's effects on cerebral autoregulation have not been extensively studied. One study by Ogawa et al. suggested that dexmedetomidine weakened the dynamic cerebral autoregulation by delaying the restoration of CBF velocity (Ogawa et al., 2008). In patients with intracranial glial neoplasms, a loading dose of dexmedetomidine weakened dynamic autoregulation in the healthy hemisphere but not in the tumour affected hemisphere (Arulvelan, Manikandan, Easwer, & Krishnakumar, 2015). Studies investigating dexmedetomidine's effects on static cerebral autoregulation are lacking.

2.4.7.2 Propofol and midazolam

Propofol has been shown to maintain an intact flow-metabolism coupling in healthy volunteers and to cause a substantial reduction of CBF and a similar decrease in $CMRO_2$ compared to volatile anaesthetics when administered at equi-sedative doses (Alkire et al., 1995; Kaisti et al., 2003; Schlünzen, Juul, Hansen, & Cold, 2012). Cerebral autoregulation remains intact up to doses of 200 μg/kg/min (Stephan

Strebel et al., 1995). In one TCD study, propofol was observed to dampen vasomotor reactivity during hypercapnia, but it still had less effect on CBF than sevoflurane (Yuji Kadoi, Kawauchi, Saito, & Takahashi, 2009).

Midazolam reduces CBF and increases CVR in healthy volunteers (Forster, Juge, & Morel, 1982). The decrease in CBF was speculated to result from a decreased cerebral metabolism. Later, Ogawa et al. found that in healthy volunteers, midazolam might improve dynamic cerebral autoregulation (Ogawa et al., 2010).

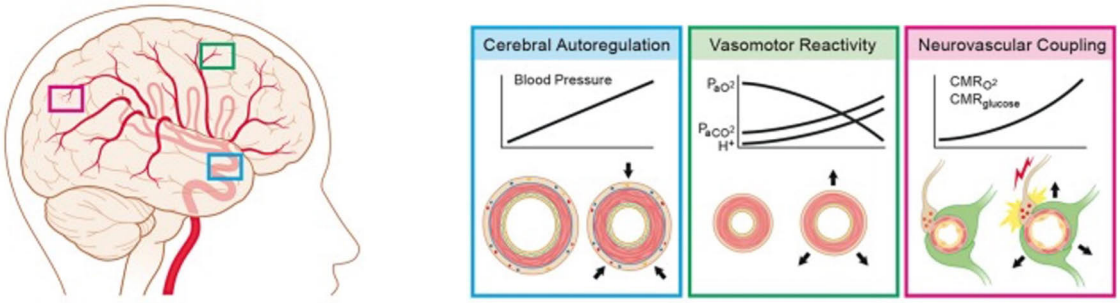
2.4.7.3 S-ketamine

The S-enantiomer of ketamine has been shown to increase whole brain CBF and blood volume in healthy male volunteers with no significant corresponding changes in $CMRO_2$ or CMR_{glu} (Långsjö et al., 2005a). In combination with propofol, S-ketamine did not impair dynamic cerebral autoregulation in ASA I-II patients undergoing elective abdominal surgery (Engelhard, Werner, Möllenberg, & Kochs, 2001). In TBI and aSAH patients sedated with metohexital, pain management with S-ketamine did not increase ICP compared to fentanyl but offered better haemodynamic stability (Schmittner et al., 2007). Therefore, a single-drug S-ketamine anaesthesia in neurosurgical patients is probably not optimal, but it might be suitable as an adjunct anaesthetic.

2.4.7.4 Sevoflurane

Contemporary halogenated volatile anaesthetics, such as isoflurane, sevoflurane, and desflurane, have direct vasodilatory effects (Matta, Heath, Tipping, & Summors, 1999; Matta, Mayberg, & Lam, 1995). Studies using TCD-based methods report generally dose-dependent increases in CBF with volatile anaesthetics (Jung, Sung, Kang, Kim, & Kim, 2014; Y. Kadoi, Kawauchi, Ide, Saito, & Mizutani, 2009; Oshima, Karasawa, Okazaki, Wada, & Satoh, 2003; Villa et al., 2012). However, results from PET studies suggest that volatile anaesthetics only slightly affect global CBF (Schlünzen, Cold, Rasmussen, & Vafaee, 2006; Schlünzen et al., 2004). Data from studies on sevoflurane in healthy volunteers is especially conflicting with reports of no change, increases, and decreases in CBF (Kaisti et al., 2002; Kolbitsch et al., 2000; Lorenz et al., 2001; Mielck, Stephan, Weyland, & Sonntag, 1999; Molnár et al., 2007). At 1.0 MAC, sevoflurane appears to narrow the plateau section of the autoregulatory curve (Goettel et al., 2016), impair dynamic autoregulation even at smaller doses (Ogawa et al., 2006), and blunt the cerebrovascular carbon dioxide reactivity (Nishiyama, Matsukawa, Yokoyama, & Hanaoka, 1999).

Figure 4 summarises the effects of several anaesthetics and sedatives on cerebral physiology and autoregulation in healthy humans.



GOM	CBF		CA	VMR	NVC
CMRO2 reduced	Increased	*Volatile Anesthetics*	> 1.5 MAC (Isoflurane, Desfluare) > 1 MAC sevoflurane	> 1.5 MAC (Isoflurane, Desfluare) > 1 MAC sevoflurane	Unknown
	Increased	*Nitrous Oxide*			Unknown
CMRO2 reduced	Region specific reduction	*Xenon*			Unknown
CMRO2 reduced	Reduced	*Propofol*	> 200 mcg/kg/min	Mixed Results	Unknown
CMRO2 increased	Increased	*Ketamine*			Unknown
CMRO2 reduced	Reduced	*Etomidate*			Unknown
CMRO2 reduced	Reduced	*Dexmedetomidine*			Unknown
	Dose and agent specific biphasic responses	*Opioids*			Unknown
CMRO2 reduced	Reduced	*Benzodiazepines*			Unknown
CMRO2 reduced	Reduced	*Barbiturates*			Unknown
	Dose and agent specific biphasic responses	*Lidocaine*			Unknown
		Regional Anesthesia	Stellate Ganglion Block		Unknown

Figure 4 The effects that different anaesthetic and sedative agents have on global oxidative metabolism (GOM), cerebral blood flow (CBF), cerebral autoregulation (CA), vasomotor reactivity (VMR) and neurovascular coupling (NVC) in healthy humans. Slupe, Kirsch 2018. Reprinted from the Journal of Cerebral Blood Flow & Metabolism with permission from SAGE Publications.

2.5 Dexmedetomidine and inflammation

2.5.1 Anaesthesia and inflammation

The purpose for the innate as well as adaptive immune system is to protect the host against pathogens. Different non-infectious stimuli, such as invasive procedures, surgery, and anaesthesia, may also produce a systemic inflammatory response and affect the immune system by several factors. Anaesthetics and sedatives can influence the immune system either directly by affecting the circulating immune cells or indirectly by influencing the neuroendocrine pathway (Schneemilch, Schilling, & Bank, 2004; Welden, Gates, Mallari, & Garrett, 2009).

However, the real impact of anaesthetics on systemic inflammation remains unclear because the research is mainly done on patients who are receiving surgery or whose immunological status is already compromised by an illness such as cancer

or sepsis. In addition, periprocedural interventions, such as mechanical ventilation, administration of blood products, or extra-corporeal circulatory support systems for example during cardiac surgery, will undoubtedly affect the immune system (Rossaint & Zarbock, 2019).

2.5.2 Immune response

The activation of the host immune response begins with a tissue injury. This is followed by the release of certain intracellular molecules and signalling mediators called alarmins, also termed 'damage-associated molecular pattern' (DAMPs) molecules (Lord et al., 2014). In the case of infection, the immune system is exposed to various foreign (non-self) molecules, known as Pathogen Associated Molecular Patterns (PAMPs) (Lord et al., 2014). These DAMPS and PAMPs then bind to pattern recognition receptors (PRR), such as Toll-like receptors (TLRs), which are found on the cell surface of various cell types, including leukocytes (Chan et al., 2012; Oppenheim & Yang, 2005). Alarmins bind to PRRs, which causes the activation of different signalling molecules within the cell, followed by the activation of transcription factors, which leads to the transcription of various genes, such as chemokines, cytokines, and other inflammatory mediators (Rossaint & Zarbock, 2019). These are then released into the extracellular space or are presented by the cell to activate sentinel cells of both the innate and adaptive immune system, including neutrophils, dendritic cells, monocytes, and macrophages (Bianchi & Manfredi, 2007).

2.5.3 Propofol and the immune system

Propofol (2,6-diisopropylphenol) is a very common anaesthetic agent used widely in perioperative and ICU settings. It is administered intravenously and acts via the GABAergic transmitter system. In previous studies, propofol has shown properties that support the immune system particularly in cancer patients (R. Li, Liu, Dilger, & Lin, 2018; Wigmore, Mohammed, & Jhanji, 2016). Propofol increases the tissue infiltration of natural killer (NK) T cells and T-helper cells. However, it does not affect T-cell counts or leukocyte cell apoptosis (Lim et al., 2018; Matsota et al., 2018). Propofol also seems to increase NK cell cytotoxicity (Cho et al., 2017) and the expression of tumour-killing effector molecules (D. Liu, Sun, Du, & Kong, 2018). Furthermore, it releases sympathetic catecholamines which lessen the stress-induced inhibition of NK cell activity (Shakhar & Ben-Eliyahu, 1998). In a recent retrospective study conducted in healthy volunteers, propofol appeared to be associated with increased pro-inflammatory cytokine release but also the activation of NK cells (Bosch et al., 2020).

2.5.4 Dexmedetomidine and the immune system

When used perioperatively, dexmedetomidine seems to attenuate perioperative inflammation, to have anti-inflammatory effects, and to preserve the immune function of surgical patients (K. Wang et al., 2019). Surgery activates the sympathetic nervous system, which may be manifested by an increased secretion of pituitary hormones. Adding dexmedetomidine to the anaesthesia regimen has resulted in an reduced stress response demonstrated by lower concentrations of norepinephrine, epinephrine, cortisol, and blood glucose (K. Wang et al., 2019). These findings represent dexmedetomidine's sympatholytic properties (Xian-wang Wang et al., 2015).

Dexmedetomidine can attenuate unnecessarily strong inflammatory responses by activating the cholinergic anti-inflammatory pathway (Ma et al., 2020). These inflammatory responses are thought to be the source of multiple complications, such as fatigue, atrial fibrillation, postoperative pain, and cognitive dysfunction (K. Wang et al., 2019). The collective data in a meta-analysis shows that perioperatively used dexmedetomidine has anti-inflammatory properties and reduces the pro-inflammatory cytokine production (K. Wang et al., 2019). After administration of dexmedetomidine to surgical patients, the concentrations of IL-6, TNF-α, CRP, IL-1β, and IL-8 decreased, while the concentration of IL-10 increased (K. Wang et al., 2019). In healthy volunteers, dexmedetomidine has decreased the concentrations of IL-18, L-selectin, E-selectin, and Granzyme B (Bosch et al., 2020). L- and E-selectin are adhesion molecules, and their low concentration can potentially reduce the recruitment of NK cells (Bosch et al., 2020). In other studies, dexmedetomidine has significantly increased the expression of NK cells, B cells, and CD4+ T cells and the ratios of CD4+:CD8+ and Th1:Th2 (K. Wang et al., 2019). Accordingly, during the perioperative period, dexmedetomidine appears to protect NK cells and the ratios of CD4+:CD8+ and Th1:Th2 of patients (Dong et al., 2017; Kim et al., 2014; Yang et al., 2017). However, the evidence on the effect of dexmedetomidine on the Th1:Th2 balance is not consistent (K. Wang et al., 2019).

2.5.5 The anti-inflammatory properties of dexmedetomidine

2.5.5.1 Animal and experimental studies

Studies on different animal models of sepsis support the anti-inflammatory properties of dexmedetomidine. The evidence of its effects on pro-inflammatory cytokines has been exceedingly consistent across studies, regardless of the used biological or pathological markers (Flanders, Rocke, Edwardson, Baillie, & Walsh, 2019). In addition, dexmedetomidine appears to have neuro- and cardioprotective

properties as well as beneficial effects for liver, spleen, lungs, and kidneys (Dardalas et al., 2019).

2.5.5.2 Human studies

The applicability of animal studies to humans is unclear, especially since the doses used in animal studies have mostly been considerably higher than in humans. A few studies have investigated the use of dexmedetomidine in septic patients. A review with 6 studies including altogether 242 patients found that dexmedetomidine decreased short-term mortality compared to other sedatives but did not affect the ICU length of stay (Zamani et al., 2016). Another study with 40 ICU patients noticed that compared to midazolam, dexmedetomidine decreased cytokine production after a 24-hour infusion, in particular the concentrations of TNF-α, IL-1β, and IL-6 (Memiş et al., 2007). In the MENDS study, a subgroup analysis of septic patients who received dexmedetomidine instead of lorazepam, had lower mortality and more days free from mechanical ventilation and neurological disorders (Pandharipande et al., 2010). In the DESIRE trial (Kawazoe et al., 2017), dexmedetomidine did not improve mortality or ventilator-free days. In the sub-analysis of the DESIRE trial, dexmedetomidine was correlated to lower levels of CRP and PCT during the first 14 days in the ICU (Ohta, Miyamoto, Kawazoe, Yamamura, & Morimoto, 2020). In the MENDS2 trial, dexmedetomidine did not impact the outcome of septic patients compared to propofol (Hughes et al., 2021). In a subgroup analysis of the large SPICE III trial, they randomized 83 septic patients to receive either usual care or dexmedetomidine as their sole or primary sedative (Cioccari et al., 2020). In the first 48 hours, the patients in the dexmedetomidine group received vasopressor doses similar to the usual care group. However, on multivariable adjusted analysis, patients receiving dexmedetomidine seemed to require lower vasopressor doses to maintain target MAP (Cioccari et al., 2020). Also, in another relatively recent study conducted in ICU patients with septic shock, changing propofol-sedation to dexmedetomidine reduced the vasopressor requirements in patients (Morelli et al., 2019).

2.5.5.3 Potential mechanisms of action

Dexmedetomidine induces anti-inflammatory and immune regulatory effects through various mechanisms. Several have been suggested, such as direct and indirect central sympatholytic effects as well as reduction in anxiety and stress; the direct modulation of macrophage and monocyte function through α_2-receptor mediated inhibition of apoptosis and cytokine production; effects mediated via central and peripheral α_2-receptor agonism; and stimulation of cholinergic anti-

inflammatory pathways (Flanders et al., 2019). The use of an α_2-receptor antagonist in experimental studies has generally shown reduction in α_2-receptor agonist-mediated anti-inflammatory effects, which implies that the effects are greatly receptor-mediated (Flanders et al., 2019).

2.5.6 Neuroinflammation and dexmedetomidine

2.5.6.1 Neuroinflammation

Tissue trauma triggers a systemic inflammatory response, whose intensity depends on the scale and site of the trauma as well as on the patient's co-morbidities and immunological status. A part of this systemic inflammatory response is neuroinflammation, which is critical in the pathophysiological processes behind neurological disorders (Alam, Hana, Jin, Suen, & Ma, 2018). The main reason for cognitive dysfunction and neuroinflammation following surgical trauma is believed to be the breakage in the blood brain barrier (BBB). This is caused by the inflammatory cascade starting with the DAMPs and PAMPs that activate the production of TNFα and other pro-inflammatory mediators via nuclear factor κβ (NK-κβ)-dependent transcription sequence (Alam et al., 2018). Consequently, an endothelial disruption occurs, increasing the permeability of the BBB, which allows the circulating leucocytes to migrate into the neuronal tissue and activate the microglia and astrocytes. The microglia and astrocytes are stimulated by the cytokine storm, which leads to increased synthesis and release of nitric oxide (NO) and an increase in intracellular Ca^{2+}-concentration (Alam et al., 2018). The process is illustrated in **Figure 5**. Resembling the illustrated iatrogenic tissue trauma, a widespread systemic inflammatory reaction is seen both in aSAH and TBI.

It is believed that neuroinflammation may lead to neurodegenerative conditions, including postoperative cognitive dysfunction (POCD) and increased risk of Alzheimer's disease (Alam et al., 2018; Xu et al., 2017). Also, neuroinflammation most likely affects the development of the early brain injury and DCI after aSAH (Geraghty, Davis, & Testai, 2019; Weiland et al., 2021).

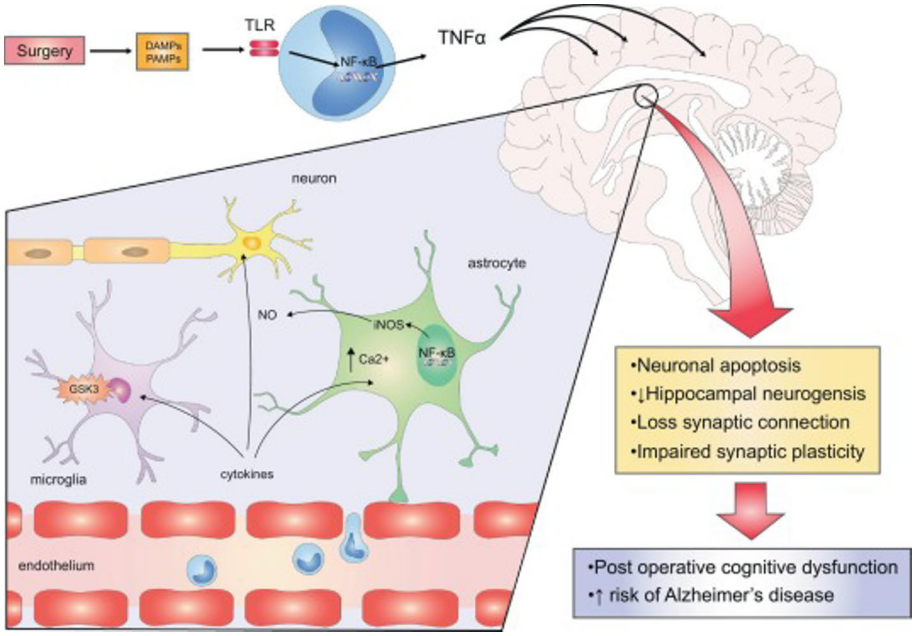


Figure 5 Illustration of the mechanism of postoperative neuroinflammation. The production of TNFα is triggered by DAMPs and PAMPs and other pro-inflammatory mediators via NF-κB. This leads to increased permeability of the blood-brain barrier (BBB). As a result, circulating lymphocytes travel into brain and activate microglia and astrocytes. The release of nitric oxide (NO) and intracellular Ca^{2+} is increased and GSK-3 dysfunction occurs. Ultimately the cascade leads to the development of neurological disorders such as Alzheimer's and POCD (Alam et al., 2018). Reprinted with permission from Elsevier

2.5.6.2 Neuroprotective effects of dexmedetomidine

Dexmedetomidine has been shown to attenuate neuroinflammation and neuroapoptosis in various in vitro and animal studies (Carr et al., 2018). The mechanisms behind these effects are complex and intricate. A very probable mechanism is the cholinergic anti-inflammatory pathway, which depends on functional vagal tone. When investigators used dexmedetomidine in an animal model after vagotomy, dexmedetomidine failed to exert its anti-inflammatory properties in the central nervous system (Zhu, Peng, Meng, & Ji, 2016). Another likely mechanism is by affecting microglia (Qiu et al., 2020; Yamanaka et al., 2017). In septic mice, dexmedetomidine reverses neurodegenerative changes and neuroapoptosis possibly by affecting the proteins that are key components in the regulation of apoptosis, Bcl-2 and Bcl-2-associated protein X (Ning et al., 2017). In another cerebral ischemia/reperfusion animal model, dexmedetomidine showed neuroprotective effects by reducing the oxidative stress and regulating a signalling pathway consisting of nuclear factor of activated T-cells 5 (NFAT5), Sirtuin 1 (SIRT1), and NF-E2-related factor 2 (Nrf2) (L. Chen et al., 2019). Finally, post-synaptic α_{2A}-adrenoceptors have

been shown to enhance the activity and connectivity of prefrontal cortex, which is an area intrinsic to regulation of attention and behaviour and believed to be essential in the pathogenesis of delirium (Arnsten & Pliszka, 2011; Choi et al., 2012).

2.5.6.3 Dexmedetomidine and postoperative cognitive dysfunction and delirium (POCD/POD)

Considering dexmedetomidine's presumed neuroprotective and anti-inflammatory properties, there has been interest in investigating its ability to prevent postoperative cognitive dysfunction (POCD) and postoperative delirium (POD). In clinical trials, the evidence is conflicting (Carr et al., 2018). The challenges in evaluating the clinical studies rise from the various methods used in diagnosing POCD and POD (MMSE and/or ICU-CAM) and different neurocognitive endpoints, or from different timing of the medication. A meta-analysis including 13 studies with over 1300 patients in total, the use of dexmedetomidine showed a reduction of 40% in the risk of POCD (C. Zhou, Zhu, Liu, & Ruan, 2016). In another meta-analysis including 18 studies with data from over 3300 patients, dexmedetomidine decreased the risk of POD in both younger and elderly patients and in both cardiac and non-cardiac patients (Duan et al., 2018). In the most comprehensive investigation of dexmedetomidine for the treatment of delirium and POCD in 404 non-cardiac surgery patients, there was no benefit to the use of dexmedetomidine in any of the endpoints (Deiner et al., 2017). In a non-cardiac surgery cohort of older patients, a low-dose infusion of dexmedetomidine from day 1 of surgery through postoperative day 1, did significantly reduce the incidence of POD up to 7 days after surgery (Su et al., 2016). On the other hand, another prospective RCT explored the efficacy of dexmedetomidine in the prevention of delirium in elderly cardiac surgery patients but found no significant advantage compared to placebo (X. Li et al., 2017).

2.6 Aneurysmal subarachnoid haemorrhage

2.6.1 Epidemiology of aneurysmal subarachnoid haemorrhage

Subarachnoid haemorrhage is a complicated disease often involving relatively young patients and causing high fatality and great disability. Intracranial aneurysms are seen in 3.2% of the general population (Vlak, Algra, Brandenburg, & Rinkel, 2011), and aneurysmal subarachnoid haemorrhages (aSAH) account for approximately 5% of all strokes (Sharma, 2020). The estimated global incidence of aSAH is around 9/100 000 persons/year with extensive regional variation. It tends to affect considerably younger patients than other types of strokes, and women have 1.24

greater risk of aSAH compared to men (Rooij, Linn, Plas, Algra, & Rinkel, 2007). Mortality rates vary from 32% to 67% despite considerable advances in the care of aSAH patients. The risk for permanent disability is high with a dependency rate of 50% among the survivors (Roux & Wallace, 2010).

2.6.2 Pathophysiology of aSAH

Nontraumatic subarachnoid haemorrhages are usually caused by ruptured saccular aneurysms, which account for 90% of intracranial aneurysms. Fusiform aneurysms, which are more common in posterior cerebral circulation, account for the remaining 10% (Drake & Peerless, 1997). Most common sites for intracranial saccular aneurysms are illustrated in **Figure 6**. Most aneurysms occur in the anterior circulation of Circle of Willis. 12% of intracranial aneurysms are located in the posterior circulation (Wiebers et al., 2003). Previously saccular aneurysms were thought to be congenital, but now they are recognised as acquired lesions (Sharma, 2020). Risk factors for the aneurysm rupture include female sex, size and location of aneurysms, hypertension, smoking, older age, Japanese or Finnish descent, and cocaine abuse (D'Souza, 2015).

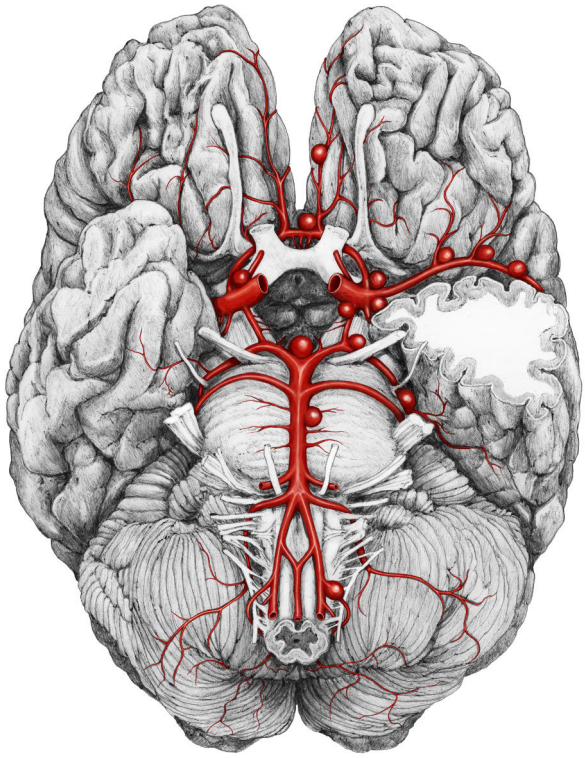


Figure 6 Most common sites of intracranial saccular aneurysms. Illustration by Inari Raaterova.

2.6.3 Classification of aSAH

The severity of aSAH is categorised using Hunt and Hess Score (Hess & Hess, 1968) and the World Federation of Neurosurgeons Scale (WFNS) (Drake, 1988). **Table 1** summarises the different grading systems of SAH. The Hunt and Hess score is more widely used and was originally designed as an indicator of surgical risk increasing from grades 1 to 5. The Fisher scale takes into account the distribution and the amount of blood on the first computed tomography (CT) scan (Fisher, Kistler, Neurosurgery, & 1980, n.d.). It does not correlate with clinical outcome, but it is suitable for evaluating the vasospasm and DCI risk after aSAH.

Table 1 Grading of subarachnoid haemorrhage. (Singer, Ogilvy, & Rordorf, 2021)

GRADE	FISHER	HUNT & HESS	WFNS
I	• no SAH or IVH detected • incidence of symptomatic vasospasm: 21%	• asymptomatic or minimal headache and slight neck stiffness • 70% survival	• GCS 15 • no motor deficit
II	• diffuse thin (< 1 mm) SAH • no clots • incidence of symptomatic vasospasm: 25%	• moderate to severe headache; neck stiffness; no neurologic deficit except cranial nerve palsy • 60% survival	• GCS 13-14 • no neurological deficit
III	• localized clots and/or layers of blood > 1 mm in thickness • no IVH • incidence of symptomatic vasospasm: 37%	• drowsy; minimal neurologic deficit • 50% survival	• GCS 13-14 • focal neurological deficit
IV	• diffuse or no SAH • ICH or IVH present • incidence of symptomatic vasospasm: 31%	• stuporous; moderate to severe hemiparesis; possibly early decerebrate rigidity and vegetative disturbances • 20% survival	• GCS 7-12 • with or without neurological deficit
V		• deep coma; decerebrate rigidity; moribund • 10% survival	• GCS < 7 • with or without neurological deficit

2.6.4 Management of aSAH

The immediate management of aSAH is targeted at stabilising life-threatening states and optimising physiology, minimizing neurologic injury, initiating nimodipine, and planning early definitive treatment. The primary goals are securing the airway, normalising cardiovascular function, and preventing rebleeding and seizures (Sharma, 2020). It is also vital to ensure cerebral perfusion. This often requires an early placement of an external ventricular drain (EVD) (Gigante et al., 2010), which also enables monitoring intracranial pressure (ICP) and cerebral perfusion pressure (CPP), calculated as MAP-ICP = CPP.

The management of blood pressure is crucial in the treatment of aSAH. Elevated blood pressure after aSAH is associated with higher mortality and can predispose to rebleeding before treating the aneurysm (Connolly et al., 2012). On the other hand, aggressive treatment of hypertension is problematic since a higher blood pressure is

required to maintain an adequate CPP due to elevated ICP. In general, there is no consistent data supporting specific blood-pressure targets for these patients. Myocardial dysfunction, hyperglycaemia, and neurogenic pulmonary oedema are typical complications after aSAH and are associated with an increased risk of poor outcomes (D'Souza, 2015). Sedation is one of the key methods for stabilising the patient and permitting the mechanical ventilation.

The ruptured aneurysm is treated by surgical clipping, endovascular coiling, or stenting, and this definitive treatment is recommended to be performed at the earliest possible time (Connolly et al., 2012). The treatment protocol is illustrated in **Figure 7.**

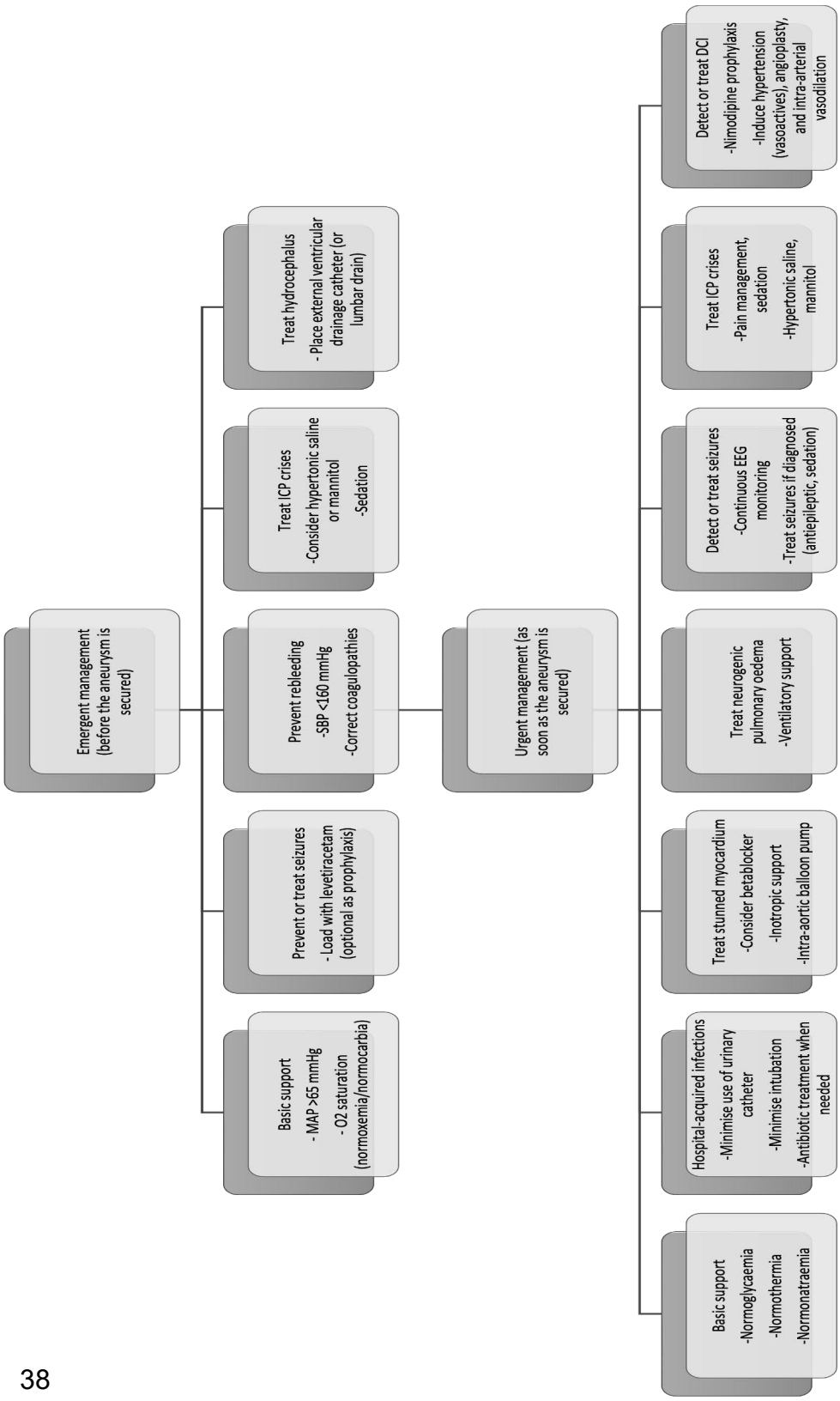


Figure 7 The management of aneurysmal subarachnoid haemorrhage. Modified from Claassen and Park 2022 (Claassen & Park, 2022). MAP=mean arterial pressure; SBP=systolic blood pressure; ICP=intracranial pressure; EEG=electroencephalogram; DCI=delayed cerebral ischaemia

2.6.5 Cerebral vasospasm and delayed cerebral ischemia

Cerebral vasospasm and delayed cerebral ischaemia (DCI) are feared complications of aSAH. Vasospasm refers to the narrowing of cerebral artery leading to decreased supply of blood flow. It is typically seen between 3 and 14 days after haemorrhage but can sometimes persist even up to 21 days (Sharma, 2020). Angiographic spasm may be seen in up to 70 to 90% of the patients, although symptomatic vasospasm occurs in only about a third of the patients (Kassell, Sasaki, Colohan, & Nazar, 1985). Vasospasm may lead to DCI and thereafter to cerebral infarction; however, DCI can also occur without vasospasm (Rabinstein et al., 2004). Systemic inflammatory response, neuroinflammation as well as impaired cerebral autoregulation and the following increase in ICP can all contribute to the development of DCI (Budohoski et al., 2012; Khey et al., 2020; Rätsep & Asser, 2001). DCI is difficult to recognise in sedated or comatose patients, but it can be suspected from different indirect signs, such as a spontaneously elevated blood pressure level or low $P_{br}O2$. Transcranial doppler ultrasonography (TCD) is widely used as a non-invasive bedside method to detect and follow-up vasospasm after aSAH (Soehle, Czosnyka, Pickard, & Kirkpatrick, 2004a). Perfusion computer tomography (CT) is used to detect regions of possible brain ischemia in patients who present with a new neurological deficit.

2.6.6 Nimodipine

The only pharmaceutical agent that has been shown to reduce the risk of DCI and to improve neurological outcome is nimodipine, a calcium-channel blocker that is usually administered for 21 days. It reduces the risk of poor outcomes in SAH patients by one third (Mees et al., 2007). Despite this, nimodipine has not been shown to decrease the incidence or severity of vasospasm (Macdonald, Pluta, & Zhang, 2007; Rowland, Hadjipavlou, Kelly, Westbrook, & Pattinson, 2012). It is obvious that vasospasm may not be the only cause for poor outcome and DCI, and investigations of other possible targets of therapy are being conducted (Khey et al., 2020; McConnell et al., 2016; Rowland et al., 2012).

2.6.7 Cerebral autoregulation in aSAH

According to studies evaluating static autoregulation with direct perfusion methods, static autoregulation often seems to be impaired after aSAH (Cossu et al., 1999; Dernbach, Little, Jones, & Ebrahim, 1988; Manno, Gress, Schwamm, Diringer, & Ogilvy, 1998; Muench et al., 2005; Tenjin et al., 1988) and the scale of the autoregulatory dysfunction is related to the severity of the injury (Tenjin et al., 1988). Dynamic autoregulation is also compromised after aSAH (Budohoski, Czosnyka, &

Kirkpatrick, 2015). (H. G. Cho, Shin, Shin, Lee, & Hong, 2003). Cerebral autoregulatory dysfunction has been shown to correlate with the incidence of DCI. This was first shown by Pickard et al. who observed that a failure in autoregulation preceding delayed ischemic complications was predictive of DCI (J. D. Pickard et al., 1992; John D Pickard, Matheson, Patterson, & Wyper, 1980). Harper's dual-insult theory suggests that two haemodynamic insults are needed to cause ischaemia and accordingly both vasospasm and weakened autoregulation or hypotension predispose to DCI (Harper, Deshmukh, Sengupta, Rowan, & Jennett, 1972; Harper & Glass, 1965) . Consistent with the dual-insult theory, Voldby et al. showed that solely detecting cerebral vasospasm did not predict DCI, but a combination of constricted arteries and dysregulation were perceived before delayed ischaemic complications in a large number of patients (Voldby, Enevoldsen, & Jensen, 1985). Later studies have reported similar findings (J. M. K. Lam, Smielewski, Czosnyka, Pickard, & Kirkpatrick, 2000; Rätsep & Asser, 2001). Vasospasm itself can also cause weakening of autoregulation (Soehle, Czosnyka, Pickard, & Kirkpatrick, 2004b).

It remains unclear if autoregulation monitoring can offer therapeutic benefits. Retrospective studies have shown that optimal CPP is increased after aSAH and before DCI, and, furthermore, the amount of time spent below or above the optimal CPP can predict worse outcome (Silverman et al., 2019; Weiss et al., 2022). The concept of individual CPP and MAP targets after aSAH seems to be a reasonable option to guide therapy and needs further evaluation. Two randomised controlled studies in aSAH patients included the status of autoregulation as an end point to examine the effect of pravastatin (Tseng, Czosnyka, Richards, Pickard, & Kirkpatrick, 2005, 2006) and erythropoietin (Tseng et al., 2009). Both statins and erythropoietin reduced the duration of autoregulation malfunction. Unfortunately, statins have no clinical benefit in patients with aSAH (Kirkpatrick et al., 2014), and no other clinical studies with erythropoietin have been published. Nevertheless, an important conclusion is that cerebral autoregulation during the acute phase of aSAH is a process that may be pharmacologically influenced.

2.6.8 Sedation in aSAH patients

Sedatives decrease the cerebral metabolic demand and reduce $CMRO_2$, which is beneficial in conditions where cerebral autoregulation is impaired, limiting the mismatch between metabolic supply and demand (Oddo et al., 2016). During the ICU stay in aSAH patients, therapeutic targets for analgesia and sedation should be adjusted to regulate elevated ICP and maintain adequate brain tissue oxygen pressure ($P_{bt}O_2$) in order to preserve or increase cerebral oxygen delivery.

(Oddo et al., 2016). It is recommended to formulate local protocols that include clinical sedation targets to avoid excessive sedation with emphasis on pain management and controlling agitation as well as improving ventilator synchrony (Oddo et al., 2016).

2.6.9 aSAH and inflammation

aSAH is a distinctly systemic disease that is characterised by an extensive inflammatory reaction which affects all organ systems, especially the cardiopulmonary system as well as the brain. There is a growing amount of evidence that neuroinflammation plays a key role in the acute and chronic stages of neuronal injury in aSAH (Lucke-Wold et al., 2016). In aSAH, the blood enters the subarachnoid space, and the subsequent red blood cell breakdown and degradation over time leads to deposits of haemoglobin, triggering a vigorous immune response and cytokine release. This is followed by an invasion of peripheral immune cells, macrophages, and neutrophils into the brain and the activation of innate immune cells, such as the microglia, within the brain (Lucke-Wold et al., 2016). There may also be an associated disruption of the blood-brain barrier which facilitates this migration (Lublinsky et al., 2019). The inflammatory reaction and the accompanying cytokine storm manifest themselves clinically as neutrophilia, pyrexia, and general cerebral oedema (Lucke-Wold et al., 2016). The inflammation is particularly evident in causing cerebral vasospasm, and thereafter DCI, as well as hydrocephalus (Sriram et al., 2022). Many pre-clinical (animal) models of SAH and aSAH have been studied, and novel treatments targeting neuroinflammatory pathways have proved to be effective in pre-clinical settings (Lucke-Wold et al., 2016; Sriram et al., 2022). The applicability of these treatments to clinical practice needs further exploration. Furthermore, certain serum cytokine patterns have been associated with poor functional outcomes and DCI (Ahn et al., 2019).

3 Aims of the Study

The aim of this study was to investigate the effects of dexmedetomidine on cerebral glucose metabolism and the inflammatory cytokine response in healthy volunteers, as well as cerebral autoregulation in aSAH patients. The specific objectives of each sub-study were as follows:

1. To compare the effects of dexmedetomidine and three commonly used anaesthetic drugs on regional cerebral metabolic rate of glucose (propofol, sevoflurane, S-ketamine) at equi-sedative doses in healthy volunteers using positron emission tomography.

2. To examine how single drug dexmedetomidine or propofol anaesthesia without any surgical or other nociceptive stimuli affects the inflammatory cytokine response in healthy subjects.

3. To investigate how dexmedetomidine affects the dynamic and static cerebral autoregulation compared to baseline sedation with propofol and/or midazolam in patients with aneurysmal SAH.

4 Materials and Methods

4.1 Overview

Both study I and II were conducted under the same research collaboration "The Neural Mechanisms of Anaesthesia and Human Consciousness (LOC-2013)" performed at the Turku University Hospital, Finland (Scheinin et al., 2021). Study I was conducted at the Turku PET centre, University of Turku, Finland, as an open label, randomised controlled, parallel group, phase IV clinical drug trial. It was Part 6 of the larger study collaboration. The laboratory samples for study II were collected during Part 2 of this collaboration (Scheinin, 2022). The protocols were approved by the Ethics Committee of the Hospital District of Southwest Finland and the Finnish Medicines Agency Fimea. Written informed consent was obtained from all subjects according to the Declaration of Helsinki.

Study III was conducted in the Intensive Care Unit in Turku University Hospital, Turku, Finland. The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland and the Finnish Medicines Agency Fimea. Written informed consent was obtained from the next of kin.

A summary of the studies is shown in **Table 2**.

Table 2 A summary of studies I, II and III.

Study	I	II	III
Name and place	The Neural Mechanisms of Anaesthesia and Human Consciousness Part 6 Turku PET Centre 2015	The Neural Mechanisms of Anaesthesia and Human Consciousness A substudy of Part 2 Turku University Hospital 2013	The effects of dexmedetomidine on cerebral autoregulation in aneurysmal subarachnoid patients compared to propofol and/or midazolam Intensive Care Unit, Turku University Hospital 2013-2016
Objective	To measure regional cerebral metabolic rate of glucose (CMR_{glu}) after administration of dexmedetomidine, propofol, S-ketamine, sevoflurane or placebo	To measure acute immunological biomarkers (cytokines, chemokines, growth factors) after administration of dexmedetomidine or propofol	To investigate the effects of dexmedetomidine on cerebral static and dynamic autoregulation compared to baseline sedation with propofol and/or midazolam
Method	Positron emission tomography [^{18}F]FDG was used as the tracer to quantify 15 brain regions of interest	Multi-parametric immunoassays for detecting 48 different biomarkers in blood samples taken at baseline and at highest drug concentration	A bedside transcranial Doppler ultrasound for assessing cerebral autoregulation with transient hyperaemic response test, strength of autoregulation and static rate of autoregulation at baseline and at three increasing doses of dexmedetomidine
Subjects	180 healthy male volunteers	35 heathy male volunteers	10 aneurysmal subarachnoid haemorrhage patients

4.2 Subjects

4.2.1 Study participants and patients

Two of the presented studies recruited healthy male volunteers (I, II), and one study (III) was conducted on aSAH patients. Studies I and II recruited altogether 215 healthy male volunteers, and study III recruited 10 aSAH patients. The demographics of the aSAH patients are shown in **Table 3**.

Table 3 Demographics of the aSAH patients that were included in the analysis of study III. Data is presented as mean +/- SD.

Age (yr.)	58.1 ± 11.1
Height (cm)	173.4 ± 8.2
Weight (kg)	74.8 ± 11.4
Sex (male/female*)	5 / 4
GCS at admission (grade)	(n)
15	1
13	1
12	2
9	1
6	1
5	1
3	2
Hunt & Hess (grade)	(n)
3	4
4	4
5	1
Fisher (grade)	(n)
3	2
4	7
Aneurysm	(n)
ICA (dx/sin)	3 (2/0)
MCA (dx/sin)	4 (2/2)
ACA	3
Treatment	(n)
Coiling	7
Coiling and stenting	0
Clipping	2
Study performed days after rupture	(n)
2	3
3	3
4	2
5	1
Smoking (yes/no/not known)	4/4/1
Hypertension (yes/no)	2/7
Diabetes (yes/no)	0/9
***The one excluded patient was female, 61 years old, had GCS 6 at admission, Fisher 4, Hunt&Hess 4, had ICA l.sin aneurysm that was treated with coils and stent three days after rupture,, she was a smoker and had diabetes and hypertension**	

4.2.2 Inclusion criteria

In studies I and II, the inclusion criteria were male sex, age 18-30 yrs., ASA physical status class I, normal hearing, right handedness, non-smoking, good sleep quality, fluency in Finnish language, and normal results through physical examination and laboratory tests including drug screening. Fasting from the previous midnight was required, and the use of any medication or alcohol was prohibited for 48 hours and caffeine products for 10-12 hours before the study session.

In study III, aSAH patients aged 18-80 years who required sedation and mechanical ventilation were included after securing the aneurysm (coiling or clipping).

4.2.3 Exclusion criteria

For studies I and II, the exclusion criteria included use of any medications, smoking, recent or current significant disease, and clinically significant abnormal findings in hearing test, physical examination, or laboratory screening.

For study III, the exclusion criteria were pregnancy, nursing women, carotid stenosis, sick sinus syndrome, mean arterial pressure < 55 mmHg, heart rate < 50 beats/min, baseline middle cerebral artery (MCA) flow velocity ≥ 120 cm/s suggesting vasospasm, and clinical signs of DCI. Patients who did not require sedation or mechanical ventilation were also excluded.

4.3 Study designs

4.3.1 Study I

The goal was to recruit 40 subjects to each drug group, except 20 each to S-ketamine and placebo groups. In total, 180 subjects were recruited due to 20 premature withdrawals and dropouts. With balanced permuted block sizes of 16, subjects were randomised to receive either dexmedetomidine (Dexdor 100 µg/ml; Orion Pharma, Espoo, Finland), propofol (Propolipid 10 mg/ml; Fresenius Kabi, Uppsala, Sweden), sevoflurane (Sevorane 100%; Abbvie, Espoo, Finland), S-ketamine (Ketanest-S 25 mg/ml; Pfizer, Helsinki, Finland), or saline placebo. To guarantee a truly random allocation of treatments, the person responsible for randomisation did not recruit the subjects.

4.3.1.1 Monitoring and anaesthetic protocol

Two cannulas were placed in two forearm veins to administrate anaesthetics and Ringer's acetateand ^{18}F-labelled fluorodeoxyglucose ([^{18}F]FDG), and a radial artery

cannula was placed for all blood sampling. The drug administration protocol (**Figure 8**) started with a 20-minute stabilisation phase, followed by a 40-minute pseudo steady-state phase. We used target-controlled infusion with Harvard 22 syringe pump to administer the anaesthetics (Harvard Apparatus, South Natick, MA, USA). The syringe pump was connected to a portable computer running Stanpump software ("Stanpump Software," 2021) employing previously reported pharmacokinetic parameters (Domino et al., 1984; Marsh, White, Morton, & Kenny, 1991; Talke et al., 2003). The aim for each of the drug groups was to achieve a sample where 50% of the subjects were unresponsive and 50% maintained responsiveness, defined as the 50% effective concentration for loss of responsiveness (LOR) to verbal command (i.e., $EC_{50\ for\ LOR}$) or minimum alveolar concentration (MAC) for LOR (i.e., MAC_{LOR}) for sevoflurane. The selected $EC_{50\ for\ LOR}$ values were drawn from previous studies: 1.5 ng/ml for dexmedetomidine, 1.7 µg/ml for propofol, and 0.75 µg/ml for ketamine (Kaskinoro et al., 2011; Langsjo et al., 2012; Långsjö et al., 2005b). The end-tidal target for the administration of sevoflurane was MAC_{LOR} 0.9% (Kaskinoro et al., 2011). Each drug was administered for 60 minutes, after which the subjects were transferred to the PET scanner room for a 30-minute PET scan.

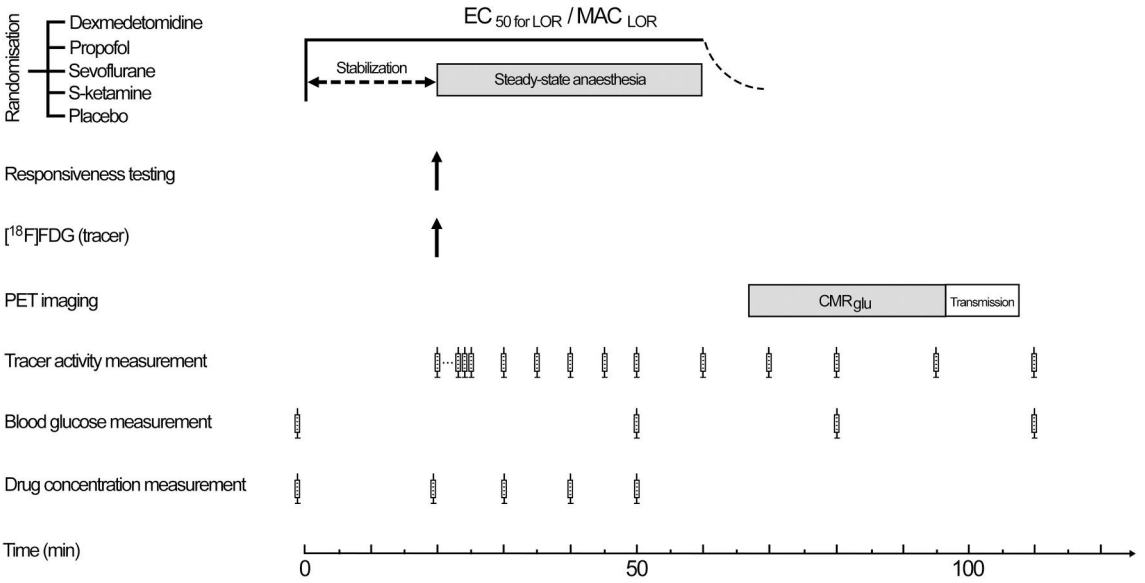


Figure 8 Study design of study I: CMRglu, cerebral metabolic rate of glucose; PET, positron emission tomography. Sequence of events and timing of measurements and blood samples. EC50 for LOR, Effective concentration 50 for loss of responsiveness; MACLOR, minimum alveolar concentration for LOR; [^{18}F]FDG, ^{18}F-labeled fluorodeoxyglucose.

Study sessions were performed in a dim and quiet room. The subjects were asked to press a customised handle secured on both wrists and were accordingly classified

as responsive or unresponsive. We performed this testing just before injection of [^{18}F]FDG. Concentrations of the i.v. anaesthetics in plasma were measured using validated methods at baseline and at 19, 30, 40, and 50 minutes after the start of the infusion. For dexmedetomidine and S-ketamine, we used high-performance liquid chromatography (HPLC) with tandem mass spectrometry; to measure propofol concentrations, we used HPLC and fluorescence detection. Interassay coefficients of variation in the relevant concentration ranges were 1.2-2.9%, 3.7-8.0%, and 0.7-2.2%, respectively.

4.3.1.2 PET data acquisition and assessment

The PET tracer [^{18}F]FDG was used to quantify CMR_{glu} in 15 brain regions of interest (ROIs). ^{18}F was produced by irradiating enriched [^{18}O]H_2O with protons (cyclotron CC 18/9, D.V. Efremov Institute, St. Petersburg, Russia). [^{18}F]FDG was synthesised according to GMP regulations using an automated synthesis device (Fastlab; GE Heathcare, Chicago, IL, USA). Radiochemical purity of the product exceeded 95%. Each subject underwent an MRI scan with a Philips Ingenuity PET-MR 3T scanner for anatomical reference (Philips Medical Systems, Best, Th Netherlands).

20 minutes after starting the administration of the anaesthetic, a 300 MBq dose of [^{18}F]FDG was introduced using a Rad Injector (Tema Sinergie, Faenza, Italy). After 40 minutes at pseudo-steady-state phase, retention of [^{18}F]FDG was considered to be stabilised and we ended the administration of anaesthetic. Then, a final 30-minute PET scan was performed, followed by a transmission scan using a High-Resolution Research Tomograph, a dual-layer crystal-detector scanner with an isotropic 2.5 intrinsic spatial resolution (HRRT; Siemens Medical Solutions, Knoxville, TN, USA) (Jong et al., 2007; Wienhard, 2002).

Approximately 45 to 50 minutes after tracer injection, the PET emission data acquisition in list-mode format was started. We used a high-precision, stereotactic tracking device (Polaris Vicra; Notrhern Digital, Waterloo, Ontario, Canada) attached to the subject's head to monitor head motion. An iterative OP-OSEM algorithm with resolution modelling (12 iterations, 16 subsets, including corrections for attenuation, scatter, random events) was used to run image formation (Comtat et al., n.d.). PET emission data were histogrammed into a single 30-minute frame reflecting the assumption of steady [^{18}F]FDG retention at this late time window. If a head movement > 2.5 mm was detected, scans were divided into subframes and then co-registered into a single 30-minute frame with the multiple acquisition frame image reconstruction procedure and the attenuation correction realignment algorithm (Johansson, Keller, Tuisku, & Teräs, 2016). This procedure was needed in four dexmedetomidine scans, two S-ketamine scans, and two sevoflurane scans.

For tracer kinetic modelling, we collected twenty-four arterial tracer activity blood samples from each study subject. Immediately after the injection of [^{18}F]FDG, the first 12 samples were obtained at intervals of 15 seconds, followed by additional samples at 4, 5, 10, 15, 20 ,25, 30, 35, 40, 50, 60, and 90 minutes after the injection of [^{18}F]FDG.

4.3.1.3 Data analysis

After tracer injection and plasma radioactivity data, we conducted calculation of voxel-wise maps of CMR_{glu} on the basis of average [^{18}F]FDG retention at 50-80 minutes. Next, the individual MRIs were co-registered with the parametric images of subjects utilising statistical parametric mapping software (version 8, SPM8; Wellcome Institute, London, UK). The voxel-wise maps of CMR_{glu} were calculated following the equation (Phelps et al., 1979)

$$CMRglu = (FUR\ x\ Cglu)/LC$$

where FUR is the fractional uptake rate of [^{18}F]FDG relative to the integral (0-90 min) of [^{18}F]FDG concentration in plasma, C_{glu} is plasma glucose concentration, and LC is the lumped constant (0.65) (H.-M. Wu et al., 2003). Using the average brain tissue density (1.04 g/ml), CMR_{glu} values were converted into units of μmol 100 g/min.

We identified 15 ROIs we wanted to analyse, including the prefrontal cortex, lateral occipital cortex, parietal cortex, lateral temporal cortex, lateral occipital cortex, precuneus, anterior cingulate cortex, posterior cingulate cortex, entorhinal cortex, striatum, cerebellum, insula, thalamus, amygdala, pallidum, and hippocampus. ROIs were generated automatically with the help of individual T1-weighted MRI data and FreeSurfer software (version 5.3) ("FreeSurfer Software," 2021). The voxel average, regional CMR_{glu} values were obtained within these 15 ROIs.

4.3.2 Study II

47 participants were enrolled in the original study, but only 35 samples could be analysed at the time due to technical and convenience issues. We administered dexmedetomidine (Dexdor 100 μg/ml, Orion Pharma, Espoo, Finland) or propofol (Propofol-Lipuro 10 mg/ml, B. Braun, Melsungen, Germany) intravenously using computer driven target-controlled infusions (TCI) with the aim of reaching pseudo steady-state plasma concentrations. To administer the drugs, we used a Harvard 22 syringe pump (Harvard Apparatus, South Natick, MA, USA) connected to a portable computer running Stanpump software (Shafer, Siegel, Cooke, & Scott, 1988).

We randomised the subjects using permuted blocks to receive either dexmedetomidine (n=17) or propofol (n=18) at increasing concentrations. In the dexmedetomidine group, we started the drug-infusion at target concentration of 1.0 ng/ml, followed first by 0.5 ng/ml target concentration increase and 0.25 ng/ml additions thereafter until loss of responsiveness (LOR) was achieved. The pharmacokinetic parameters by Talke et al. were employed (Talke et al., 2003). In the propofol group, we started the drug-infusion at target concentration of 1.0 µg/ml, followed first by 0.5 µg/ml target concentration increase and 0.25 µg/ml additions thereafter until LOR was achieved. The pharmacokinetic parameters by Marsh et al. were used (Marsh et al., 1991). After LOR, we increased the infusions by 50% to reach a state presumed to represent the loss of consciousness, after which we terminated the drug infusions. We used a verbal stimulus to test the subject's responsiveness at each concentration level. Ultimately, the subject's responsiveness was the guiding factor in the completion of the session, as the emphasis in the original study was on EEG changes during the infusions. Consequently, there was substantial variation in the total duration of the infusions and the highest target dose between subjects. All study sessions were conducted in the morning.

4.3.2.1 Blood sample collection and immunological assays

We placed two vein cannulas, one in each forearm, for the administration of the anaesthetic agents and for blood sampling. We collected blood samples for the immunological assays at baseline (without drug) and at highest anaesthetic concentration (150% of the LOR concentration) immediately before the drug infusion was ended. From each venous blood sample, a separate 100 µl aliquot of serum was frozen at –70°C until further analyses. We determined the plasma concentrations of dexmedetomidine and propofol by using high-performance liquid chromatography with tandem mass spectrometry and fluorescence detection.

For each subject, we quantified the changes in the immunological signalling molecules between the baseline and the highest concentration. A single assay run for all analyses was performed using the Bio-Plex Pro Human Cytokine 21- and 27-plex magnetic bead suspension array kits (Bio-Rad Laboratories, Hercules, CA, USA) as described previously (Nieminen et al., 2014). Results were analysed using the Bio-Plex 200 System and Bio-Plex Manager 6.0 Software (Bio-Rad Laboratories). The 21-plex panel contained interleukin 1α (IL-1α), IL-2 receptor α (IL-2Rα), IL-3, IL-12p40, IL-16, IL-18, macrophage migration inhibitory factor (MIF), monokine induced by IFN-γ (MIG), β-nerve growth factor (β-NGF), stem cell factor (SCF), stem cell growth factor-β (SCGF-β), stromal cell-derived factor 1α (SDF-1α), tumor necrosis factor β (TNF-β), cutaneous T cell-attracting chemokine (CTACK), growth-regulated oncogene α (GROα), hepatocyte growth factor (HGF), interferon α2 (IFN-α2),

leukemia inhibitory factor (LIF), monocyte chemotactic protein 3 (MCP-3), macrophage colony-stimulating factor (M-CSF), and TNF-related apoptosis inducing ligand (TRAIL) assays (**Table 4**). The 27-plex contained IL-1β, IL-1 receptor antagonist (IL-1ra), IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p70, IL-13, IL-15, IL-17, monocyte chemotactic protein 1 (MCP-1), macrophage inflammatory protein 1α (MIP-1α), MIP-1β, platelet-derived growth factor (PDGF), regulated on activation normal T cell expressed and secreted (RANTES), TNF-α, basic fibroblast growth factor (bFGF), eotaxin, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN-γ, IFN-γ-induced protein 10 (IP-10), and vascular endothelial growth factor (VEGF) assays (**Table 5**). The persons responsible for the cytokine measurements did not participate in the study protocol and were oblivious to subject's status and anaesthetic drug.

Table 4 The cytokines included in the Bio-Plex Pro Hyman Cytokine 21 array kit.

	Bio-Plex Pro Human Cytokine 21 array kit	
IL-1α	MIG	GROα
IL-2Rα	β-NGF	HGF
IL-3	SCF	IFN-α2
IL-12p40	SCGF-β	LIF
IL-16	SDF-1α	MCP-3
IL-18	TNF-β	M-CSF
MIF	CTACK	TRAIL

Table 5 The cytokines included in the Bio-Plex Pro Human Cytokine 27 array kit.

Bio-Plex Pro Human Cytokine 27 array kit			
IL-1β	IL-8	MCP-1	GM-CSF
IL-1ra	IL-9	MIP-1α	IFN-γ
IL-2	IL-10	MIP-1β	IP-10
IL-4	IL-12p70	PDGF	VEGF
IL-5	IL-13	RANTES	TNF-α
IL-6	IL-15	bFGF	Eotaxin
IL-7	IL-17	G-CSF	

4.3.3 Study III

The trial was performed in the Intensive Care Unit in Turku University Hospital, Turku, Finland. All patients aged 18-80 years who suffered from aSAH and required sedation and mechanical ventilation after securing the aneurysm (by coiling or clipping) were considered eligible.

4.3.3.1 Monitoring and study protocol

ICP was measured continuously using intraparenchymal catheters, either Neurovent-PTO (Raumedic AG, Helmbrechts, Germany) or Codman® ICP Monitor system (DePuy Synthes, Wokingham, UK). Neurovent-PTO was used in seven patients, whereas Codman was used in one patient. Four patients had both parenchymal ICP catheter and an external ventricular drainage (EVD) for the treatment of hydrocephalus. In two patients, ICP was measured intermittently as they only had EVD, and cerebrospinal fluid was continuously drained. We continuously monitored cerebral oxygenation with bilateral near-infrared spectroscopy (NIRS) using INVOS™ cerebral oximetry. In the seven patients with Neurovent-PTO, we could also monitor brain tissue oxygenation ($P_{bt}O_2$). We used transcranial doppler (TCD) to measure bilateral V_{MCA} with 2 MHz probes (Atys, Soucieu-en-Jarrest, France) secured with an adjustable head frame.

The study protocol is outlined in **Figure 9**. To establish the baseline, we tested static and dynamic autoregulation during a constant rate of propofol (2-5 mg/kg/h) and/or midazolam infusion (0.03-0.3 mg/kg/h). Next, we terminated the baseline sedation (propofol and/or midazolam) and started dexmedetomidine (Dexdor® Orion Oyj, Helsinki, Finland) infusion at an initial dose of 0.7 µg/kg/h according to the total body weight. After two hours of constant rate dexmedetomidine infusion (in order to reach a steady state), static and dynamic autoregulation were tested again. After the autoregulation testing, we increased the dexmedetomidine dose to 1 µg/kg/h for two hours and then performed the autoregulation tests again. Finally, dexmedetomidine dose was increased to 1.4 µg/kg/h for another two hours, and the autoregulation tests were executed once more (**Figure 9**). After each two-hour period of dexmedetomidine infusion, arterial blood sample was drawn and stored. We later measured the plasma dexmedetomidine concentration by using high-performance liquid chromatography with tandem mass spectrometry and fluorescence detection. Temperature, haemoglobin (Hb), and ventilation were monitored and kept constant throughout the study to minimize their effect on TCD velocities.

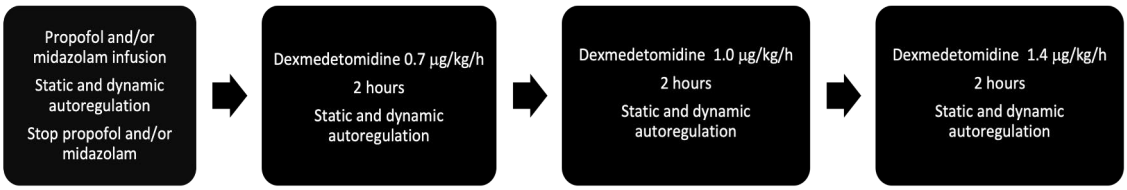


Figure 9 Study protocol in study III.

4.3.3.2 Dynamic autoregulation test

Dynamic cerebral autoregulation was evaluated with transient hyperaemic response test (THRT) (J. M. K. Lam et al., 2000; Smielewski et al., 1997). We compressed the common carotid artery for eight seconds and recorded the ipsilateral MCA flow velocity (FV) uninterruptedly before and after releasing compression. Two investigators were always present during the tests: the same investigator (author) performed the compression of carotid artery in all cases, while the FV readings were manually recorded by the other investigator. We visually evaluated the adequacy of the compression (a sudden decrease in V_{MCA} with no further decrease). The test was validated only if the haemodynamic parameters remained stable during the compression. We interrupted the test if there was sinus arrest or if ICP increased above 20 mmHg. When flow in carotid artery is blocked, a drop in CPP causes distal cerebrovascular dilatation as a compensatory mechanism, if autoregulation works appropriately. Consequently, when the compression is released, the V_{MCA} increases past the pre-compression value leading to hyperaemic response. However, in the case of autoregulation not functioning properly, no cerebrovascular dilatation or transient hyperaemia will follow.

Transient hyperaemic response ratio (THRR) was then calculated as described earlier (Giller, 1991; Smielewski et al., 1997).

$$THRR = (systolic\ FV hyperaemia)/(systolic\ FV baseline)$$

The baseline FV was systolic FV before compression. Due to overshoot phenomenon, we ignored the first cardiac cycle and calculated the average systolic $FV_{hyperaemia}$ from the systolic FV of the second and third cardiac cycles after the compression. We repeated THRR three times on both sides and maintained a 60-second interval between the measurements. We averaged the measurements from both hemispheres (Steiner, Coles, et al., 2003). Dynamic autoregulation was considered normal if THRR was ≥ 1.09 and impaired if THRR was < 1.09 (J. M. Lam, Smielewski, Czosnyka, Pickard, & Kirkpatrick, 2000).

Strength of dynamic autoregulation (SA) was calculated as

$$SA = (systolic\ FV hyperaemia\ x\ MAP\ of\ 60\ mmHG) \\ /(MAP\ x\ systolic\ FV baseline)$$

where systolic $FV_{hyperaemia}$ is the first flow velocity after releasing carotid compression and MAP of 60 mmHg represents the lower limit of autoregulation. MAP is the mean arterial pressure measured immediately before the THRT and, $FV_{baseline}$ is the flow velocity immediately before carotid compression (Harrison, Girling, & Mahajan, 1999). SA value < 1 suggests underregulation and > 1 hyperregulation (Mahajan et al., 1998).

4.3.3.3 Static autoregulation test

We tested static autoregulation by using noradrenaline infusion to increase the mean arterial pressure (MAP) by 20 mmHg while V_{MCA} was continuously monitored with TCD. When MAP reached the targeted level, the final V_{MCA} was considered to be the mean of the 20-minute V_{MCA} (Steiner, Johnston, et al., 2003).

We used patient's MAP and FV to calculate estimated cerebral vascular resistance (CVRe) (S Strebel et al., 1995):

$$CVRe = MAP/FV$$

There would be no change in FV if the percentage change of CVR is equal to the percentage change in MAP, which is an indication of intact autoregulation.

Static rate of autoregulation (sROR%) indicates the change in CVR calculated from the relation between CBFV and changing CPP.

$$sROR\% = 100\ x\ (\Delta CVR\%)/(\Delta CPP\%)$$

where CVR = CPP/FV (S Strebel et al., 1995).

In those patients who had only EVD and the ICP could not be continuously monitored, we used MAP in the formula. Hence, the sROR% was calculated as

$$sROR\% = 100\ x\ ((Initial\ Vmca)/(Final\ Vmca)) - ((Initial\ MAP) / (Final\ MAP))/(1 - (Initial\ MAP)\ /\ (Final\ MAP))$$

Static autoregulation is completely functional when sROR is 100% or more, meaning that CBFV is independent of CPP (S Strebel et al., 1995). sROR of 0% indicates that cerebral autoregulation is completely absent, and therefore CBFV is directly related to oscillations in CPP. sROR of 50% is considered as the cut-off value for failure of autoregulation. As a result, sROR quantitatively denotes the stability of changes in CBFV when ABP varies (Lang, 2002).

4.4 Statistical analysis

In study I, we performed the statistical analyses of regional CMR_{glu} data using analysis of variance (ANOVA). We first analysed all regions together using repeated ANOVA with region as a within factor and treatment as a between factor. If a

significant region by treatment interaction was observed, the analyses were continued for each region separately and for the whole brain CMR_{glu} (combination of all ROIs) using one-way ANOVA with treatment as a between factor, followed by paired comparisons of the different treatments using Tukey's *post hoc* tests for multiple correction. Pearson correlation coefficients were calculated for i.v. anaesthetics to assess the association between the mean measured drug concentration and whole brain CMR_{glu}, and χ^2 testing was used to compare responsiveness at the time of [^{18}F]FDG injection between treatments. We checked the normality of variables using the Kolmogorov-Smirnov test. A two-sided $p < 0.05$ was considered statistically significant.

In study II, we analysed the data with nonparametric methods due to outlying observations and skewed distributions. To test the difference in the change in concentrations between the groups, we used the Mann-Whitney U-test. Wilcoxon signed rank test was used to test the changes within drug groups. The mean intra-assay variation (IAV) in our study was 6.8%. In multiplex assays generally, IAV varies between assays and needs to be separately defined for each analyte. Therefore, the cut-off point was set to 10%, meaning that only concentration changes of at least 10% between the median baseline and the highest anaesthetic concentration were considered significant and are reported. In general, the 10% cut-off is much used in reporting multiplex assay results. Also, to adjust for multiple testing, Benjamini-Hochberg procedure was applied to control the false recovery rate at 0.05 (Benjamini & Hochberg, 1995). P-values lower than 0.05 were considered statistically significant.

In study III, we compared all physiological and TCD parameters including autoregulation indices at various dexmedetomidine doses to their corresponding baseline values recorded during propofol and/or midazolam. Power analysis was not performed, and our study sample size was founded on previous similar autoregulation studies using TCD measurements (Diringer et al., 2016; Jaeger, Soehle, Schuhmann, & Meixensberger, 2012; Otite et al., 2014). In the comparison, we used repeated measures analysis of variance with Dunnett's adjustment for multiple comparisons. P-values lower than 0.05 were considered statistically significant.

SAS System for Windows, version 9.4. (SAS Institute Inc., Cary, NC, USA) was used to perform all statistical analyses in all the studies in this series.

5 Results

5.1 Regional cerebral glucose metabolism with PET imaging (study I)

In study I, of the 180 subjects recruited, 160 were eventually evaluable for regional CMR_{glu}. Of these, 40 were dexmedetomidine, 40 propofol, 40 sevoflurane, 20 S-ketamine, and 20 placebos. Fifteen subjects withdrew from the study after randomisation and three sessions with S-ketamine, and one with sevoflurane had to be terminated due to excessive motor anxiety. Additionally, due to a programming error, one subject received only around 7% of the planned S-ketamine dose and was therefore excluded. We observed no clinically significant changes in vital parameters during the study period.

When administering the [^{18}F]FDG injection, 22 (55%) dexmedetomidine, 18 (45%) propofol, 34 (85%) sevoflurane, nine (45%) S-ketamine, and none of the placebo subjects were unresponsive to verbal command ($p < 0.001$). All drugs differed from placebo and sevoflurane differed from the other drugs in paired comparisons. The measured dexmedetomidine and S-ketamine concentrations were slightly higher than targeted.

Brain regions were analysed separately, as there was significant region by treatment interaction ($p < 0.001$) in the repeated measures ANOVA. There were statistically significant differences in all 15 ROIs and the whole brain CMR_{glu} ($p < 0.001$ for all) (**Figure 10**). The dexmedetomidine, propofol, and sevoflurane groups differed from the S-ketamine and placebo groups in paired comparisons (**Table 6**).

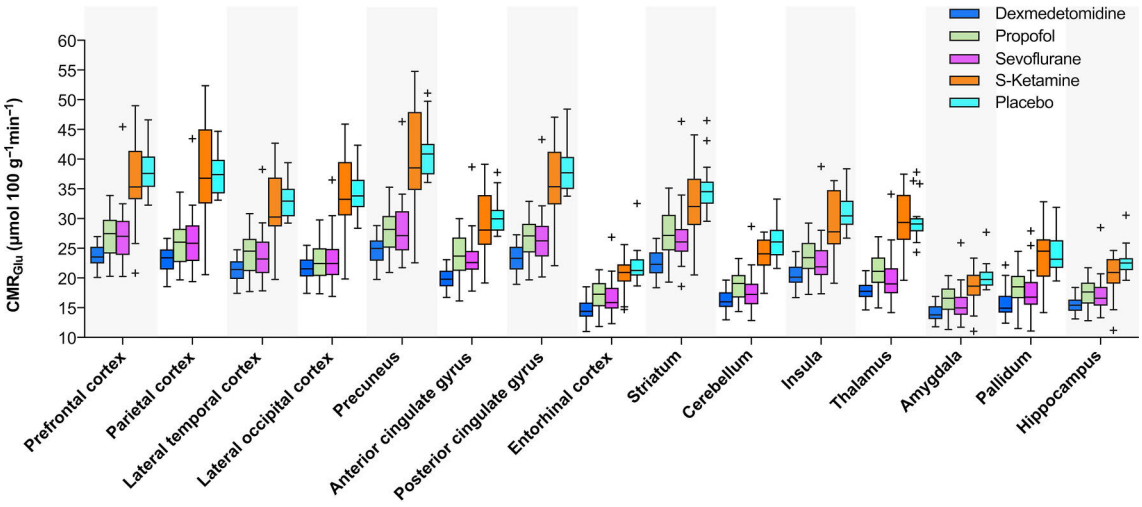


Figure 10 Boxplots of regional cerebral metabolic rate of glucose (CMRglu) in the 15 analysed regions of interest (ROIs) during dexmedetomidine, propofol, sevoflurane, S-ketamine, and placebo administration in 160 healthy subjects ($p < 0.001$ between the treatments in all ROIs). We observed lowest CMRglu values in the dexmedetomidine group. Boxes represent lower quartiles, medians and upper quartiles, whiskers represent 1.5×inter-quartile ranges below and above the lower and upper quartiles, respectively. Outlying values are marked with symbols.

Table 6 Cerebral metabolic rate of glucose (µmol 100/g/min) in the dexmedetomidine, propofol, sevoflurane, S-ketamine, and placebo groups. Tukey-corrected P-values for significant paired comparisons (*drug vs placebo) and between drugs († dexmedetomidine vs propofol, ‡ dexmedetomidine vs sevoflurane, ¶ drug vs S-ketamine). The number of symbols refer to level of significance (e.g. *p < 0.05, **p < 0.01 and ***p < 0.001). ºDegrees of freedom

Brain area	Dexmedetomidine				Propofol				Sevoflurane				S-Ketamine				Placebo		One-way ANOVA	
	Mean	SD	% of placebo		Mean	SD	% of placebo		Mean	SD	% of placebo		Mean	SD	% of placebo		Mean	SD	F (4,155)°	P-value
Prefrontal cortex	23.7	2.0	62.4	***, †††, ‡‡‡, ¶¶¶	27.1	3.5	71.2	***, ¶¶¶	27.2	4.3	71.5	***, ¶¶¶	36.3	7.1	95.5		38.0	3.9	72.47	<0.001
Parietal cortex	23.2	2.1	61.6	***, ††, ‡‡, ¶¶¶	25.9	3.8	68.7	***, ¶¶¶	26.2	4.4	69.6	***, ¶¶¶	37.9	8.0	100.4		37.7	3.4	88.49	<0.001
Lateral temporal cortex	21.4	2.0	64.9	***, †††, ‡‡, ¶¶¶	24.1	3.6	72.8	***, ¶¶¶	23.8	3.8	72.0	***, ¶¶¶	31.8	5.8	96.3		33.1	3.0	70.76	<0.001
Lateral occipital cortex	21.6	1.9	62.9	***, ¶¶¶	22.7	3.3	66.2	***, ¶¶¶	23.0	3.9	67.0	***, ¶¶¶	34.2	6.7	99.5		34.3	3.4	72.94	<0.001
Precuneus	24.8	2.3	60.6	***, †††, ‡‡‡, ¶¶¶	27.9	3.8	68.2	***, ¶¶¶	28.3	4.6	69.0	***, ¶¶¶	40.3	8.2	98.3		41.0	4.1	80.49	<0.001
Anterior cingulate gyrus	19.9	1.7	65.2	***, †††, ‡‡‡, ¶¶¶	24.0	3.3	78.6	***, ¶¶	23.4	3.5	76.6	***, ¶¶¶	29.1	5.5	95.3		30.5	3.1	67.21	<0.001
Posterior cingulate gyrus	23.3	2.4	60.7	***, †††, ‡‡‡, ¶¶¶	26.7	3.6	69.6	***, ¶¶¶	26.7	4.0	69.5	***, ¶¶¶	36.3	6.6	94.5		38.4	4.1	70.15	<0.001
Entorhinal cortex	14.6	1.6	66.3	***, †††, ‡‡‡, ¶¶¶	17.1	2.5	77.9	***, ¶¶¶	16.6	2.8	75.8	***, ¶¶¶	20.6	3.0	93.9		22.0	2.9	41.73	<0.001
Striatum	22.5	2.2	64.1	***, †††, ‡‡‡, ¶¶¶	27.7	3.7	78.8	***, ¶¶	26.8	4.4	76.4	***, ¶¶	32.6	6.1	93.0		35.1	4.1	57.13	<0.001
Cerebellum	16.3	1.6	62.6	***, †††, ¶¶¶	18.8	2.6	72.3	***, ¶¶¶	17.6	2.7	67.7	***, ¶¶¶	23.7	3.0	90.9		26.1	2.9	68.84	<0.001
Insula	20.4	1.9	65.7	***, †††, ‡‡, ¶¶¶	23.5	3.0	75.6	***, ¶¶¶	22.8	3.6	73.5	***, ¶¶¶	28.9	5.2	93.2		31.0	3.0	61.56	<0.001
Thalamus	17.8	1.6	60.4	***, †††, ‡‡, ¶¶¶	21.2	3.1	71.9	***, ¶¶¶	19.9	3.6	67.4	***, ¶¶¶	29.6	5.0	100.3		29.5	3.5	76.28	<0.001
Amygdala	14.1	1.3	69.9	***, †††, ‡‡, ¶¶¶	16.4	2.2	81.3	***	15.6	2.5	77.5	***, ¶¶	18.4	3.2	91.3		20.2	2.2	39.51	<0.001
Pallidum	15.6	2.3	64.7	***, †††, ‡, ¶¶¶	18.6	2.8	77.2	***, ¶¶¶	17.5	3.1	72.8	***, ¶¶¶	23.4	4.4	97.4		24.1	3.3	36.32	<0.001
Hippocampus	15.5	1.3	67.7	***, †††, ‡‡, ¶¶¶	17.6	2.3	77.0	***, ¶	17.1	2.5	74.9	***, ¶¶	20.4	3.5	89.2		22.9	2.4	48.46	<0.001
Whole brain	21.2	1.8	62.8	***, †††, ‡‡, ¶¶¶	24.1	3.2	71.4	***, ¶¶¶	23.8	3.7	70.5	***, ¶¶¶	32.3	5.6	95.9		33.7	3.1	81.42	<0.001

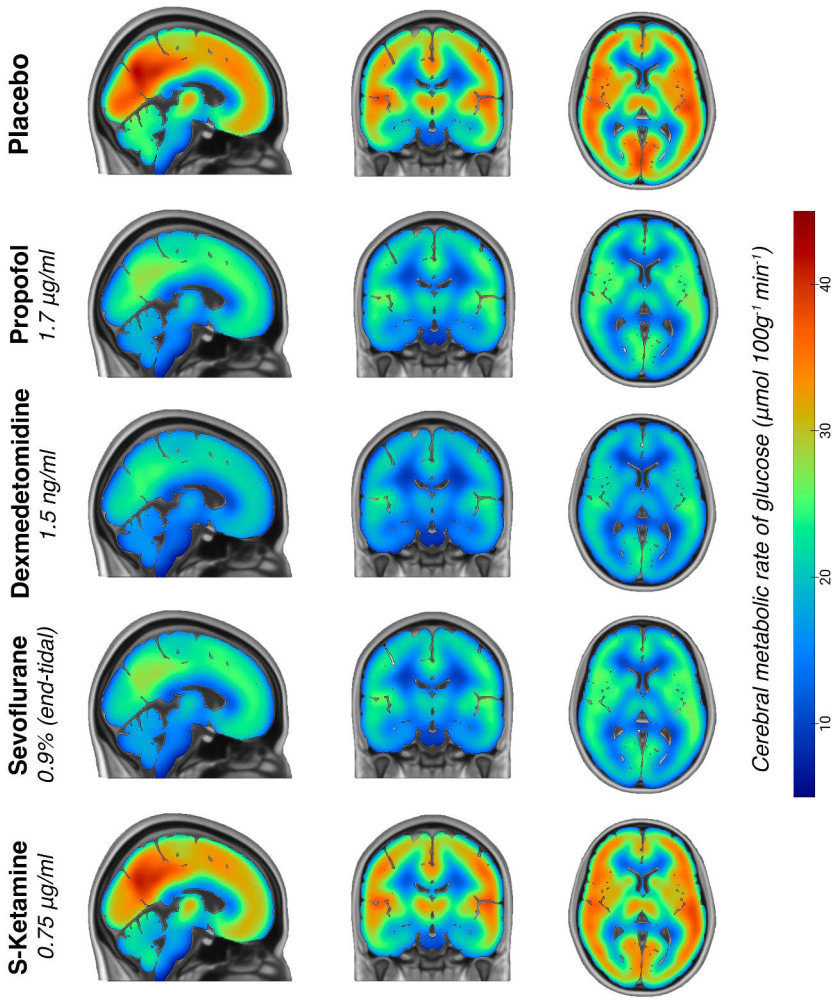


Figure 11 Group average cerebral metabolic rate of glucose in the different drug groups.

Dexmedetomidine induced the lowest CMR_{glu} in all brain regions and differed from all other drugs ($p < 0.05$), except that no significant difference was found in the lateral occipital cortex compared with propofol or sevoflurane, and in the cerebellum compared with sevoflurane (**Figures 10, 11** and **12**). The regional CMR_{glu} values were 30.1- 39.6% lower in the dexmedetomidine group compared with placebo. Propofol and sevoflurane did not differ from each other in any ROI. In the S-ketamine group, CMR_{glu} did not differ from placebo in any of the ROIs. In addition, we found weak but statistically significant associations between measured drug concentrations and CMR_{glu} in the dexmedetomidine and propofol groups.

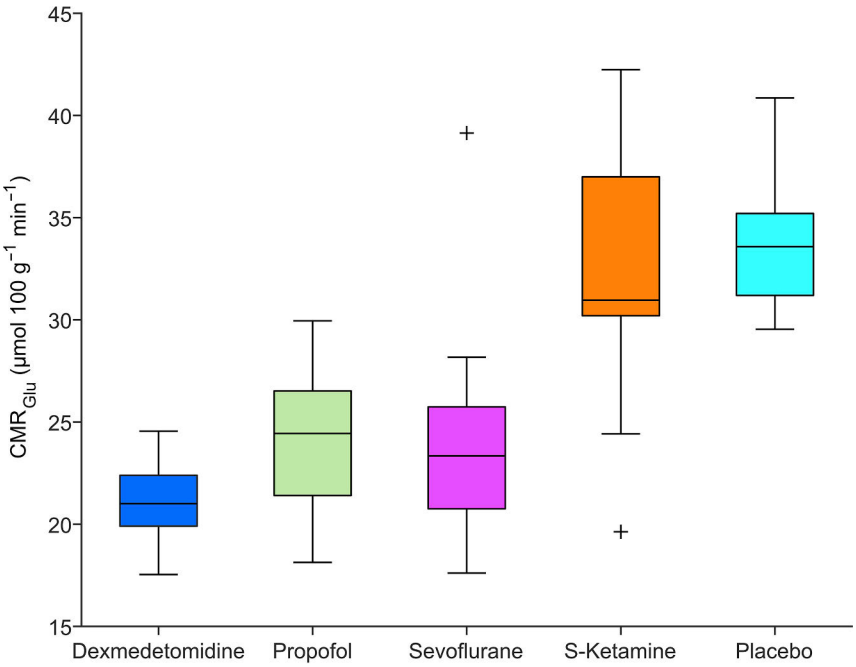


Figure 12 Boxplots of whole brain cerebral metabolic rate of glucose (CMRglu) in 160 healthy subjects. CMRglu was 63%, 71%, 71%, and 96% of placebo, in the dexmedetomidine, propofol, sevoflurane, and S-ketamine groups, respectively ($p < 0.001$ between the groups). Dexmedetomidine differed from all other groups. Boxes represent lower quartiles, medians, and upper quartiles, whiskers represent 1.5×inter-quartile ranges below and above the lower and upper quartiles, respectively. Outlying values are marked with symbols.

5.2 Immunological effects of dexmedetomidine and propofol (study II)

In study II, the administration of the anaesthetic was successful and uneventful in all 35 volunteers. We observed no clinically significant changes in the vital parameters of any of the study participants. The highest mean (standard deviation, SD) measured drug concentration was 3.19 ng/ml (0.89) for dexmedetomidine and 2.65 µg/ml (0.78) for propofol. The average infusion time was 125 (26) minutes for dexmedetomidine with a range of 79-166 minutes, and 100 (30) minutes for propofol with a range of 49-153 minutes. At baseline, no significant differences between the groups in the concentrations of the immunological analytes were detected. Ten of the analytes in the 21-plex panel were below the detection limit, and three of the analytes were below and one above the detection limit in the 27-plex panel.

Between the groups, we found that the changes in the concentration of eotaxin and PDGF differed significantly, specifically for eotaxin $p = 0.036$ and for PDGF $p = 0.022$ (Mann-Whitney U-test corrected for multiple testing). The concentration of

eotaxin decreased after the administration of dexmedetomidine, while PDGF increased after the administration of propofol (**Figure 13**).

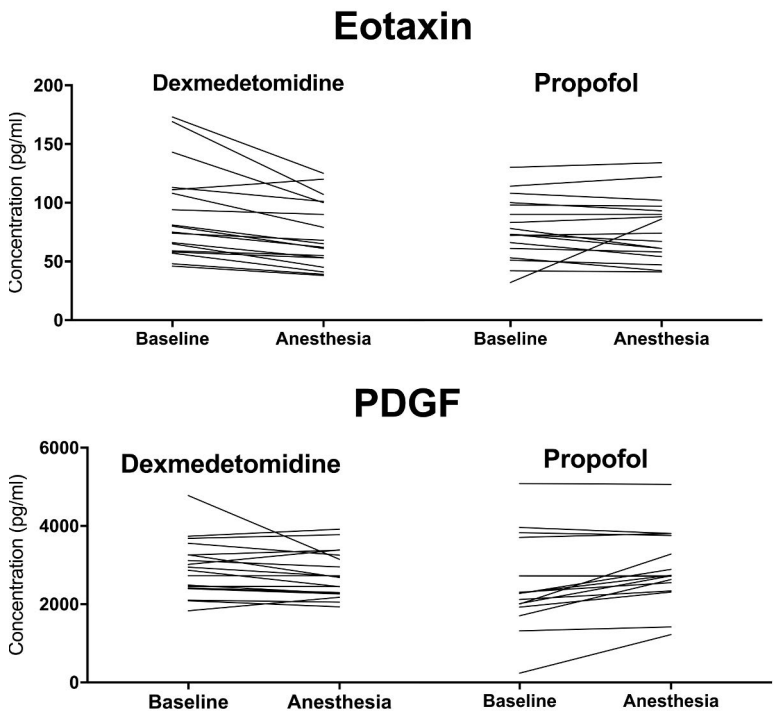


Figure 13 Eotaxin and PDGF concentrations shown individually at baseline and during dexmedetomidine and propofol anaesthesia. The changes were statistically significantly different between the groups ($p = 0.036$ and $p = 0.022$, respectively; Mann-Whitney U-test corrected for multiple comparison).

We observed statistically significant ≥ 10% changes in 9 analytes in the dexmedetomidine group and in 10 analytes in the propofol group (**Tables 7** and **8**). In the analysis within the groups, both dexmedetomidine and propofol significantly decreased the levels of MCP-1, CTACK, and MIF. Also, dexmedetomidine significantly decreased the concentrations of eotaxin, IL-18, IL-1rα, SCF, SCGF, and VEGF. Propofol significantly decreased the concentrations of HGF, MIG, and IP-10, and increased the concentrations of IL-5, IL-7, IL-17, and PDGF. We also analysed the effects of both drugs to the ratio of Th1 to Th2 cytokines, particularly IFN- γ to IL-4 and IL-5, but no statistically significant differences were found.

Table 7 Statistically significant ≥ 10% decreases of 9 cytokines in the dexmedetomidine group.

Cytokine	Baseline pg/ml [median (IQR)]	Anaesthesia pg/ml [(median (IQR)]	Unadjusted p-value	Adjusted p-value
MCP-1	40 (16)	30 (12)	<0.001	<0.001
CTACK	776 (171)	608 (227)	<0.001	0.002
MIF	180 (160)	123 (160)	<0.001	<0.001
Eotaxin	77 (52)	64 (48)	<0.001	<0.001
SCF	64 (15)	56 (16)	<0.001	<0.001
IL-18	44 (22)	36 (15)	0.012	0.038
IL-2rα	42 (17)	34 (12)	0.006	0.018
VEGF	54 (62)	47 (42)	0.016	0.04
SCGF	16305 (4218)	13006 (4003)	<0.001	<0.001

Table 8 Statistically significant ≥ 10% changes of 10 cytokines in the propofol group.

Cytokine	Baseline pg/ml [median (IQR)]	Anaesthesia pg/ml [median (IQR)]	Unadjusted p-value	Adjusted p-value
PDGF	2160 (460)	2625 (971)	0.002	0.02
IP-10	332 (188)	289 (112)	0.004	0.03
IL-5	6 (1)	8 (2)	0.006	0.03
IL-7	10 (4)	11 (3)	0.005	0.03
IL-17	158 (60)	175 (71)	0.008	0.03
MIG	245 (81)	201 (69)	<0.001	0.01
HGF	156 (24)	129 (33)	0.002	0.02
MCP-1	38 (16)	31 (14)	0.004	0.03
CTACK	598 (270)	534 (168)	0.005	0.03
MIF	227 (159)	113 (82)	<0.001	0.01

5.3 Cerebral autoregulation during the administration of dexmedetomidine (study III)

In study III, five male and five female patients were recruited. The mean age of the patients was 58.4 ± 10.5 years. However, only nine patients were analysed, because one patient did not have temporal acoustic window on either side for the TCD and was therefore excluded from the TCD-autoregulation testing.

Six patients had propofol infusion as the baseline sedation, while two patients had midazolam infusion, one patient had both midazolam and propofol infusions, and one patient had no sedation. The recruitment and the study protocol ensued during the first 24-48 hours after the surgical or endovascular treatment. Three

patients lacked temporal acoustic window on the left side and therefore had the doppler measurements obtained only from the right side. One patient was included only in the static testing, as he expressed profound bradycardia during the carotid compression required in the dynamic test.

Compared to baseline, we observed no significant differences between Hb, PaO_2, and $PaCO_2$ at each dose of dexmedetomidine (**Table 9**). Noradrenaline-infusion was used to control MAP and CPP.

Table 9 $PaCO_2$ PaO_2 and Haemoglobin (Mean ± SD) at baseline and at different doses of dexmedetomidine (Dex). There were no statistically significant changes at different dexmedetomidine doses compared to baseline.

	Baseline	Dex 0.7	p-value	Dex 1.0	p-value	Dex 1.4	p-value
PaCO2 mmHg	37.3±2.3	36.2±2.6	0.62	35.4±2.5	0.21	35.0±2.3	0.10
PaO2 mmHg	132.4±37.3	149.7±57.7	0.82	152.7±59.1	0.75	151.1±62.2	0.79
Hb g/l	124±16	127±15	0.92	128±14	0.88	129±14	0.79

Our main finding was that, compared to baseline, dynamic autoregulation was significantly lower after the 1.0 µg/kg/h dose of dexmedetomidine (0.75 ± 0.05, p = 0.02) (**Figure 14**, **Table 10**). No other statistically significant differences were observed in THRR or SA with dexmedetomidine compared with propofol and/or midazolam. In addition, we found no difference in the static parameters V_{MCA}, CVR, sROR%, and PI during dexmedetomidine infusion compared with propofol and/or midazolam (**Figure 15**, **Table 12**).

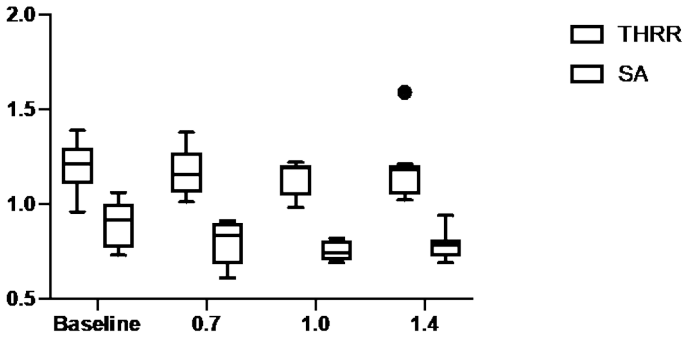


Figure 14 Dynamic autoregulation indices presented as boxplots, THRR and SA, at baseline (propofol/midazolam) and at each dose of dexmedetomidine. Boxes represent lower quartiles, whiskers represent 1.5 x inert quartile ranges below and above the lower and upper quartiles, respectively. Outlying values are marked with symbol. SA > 1 suggest underregulation and SA < 1 hyperregulation. THRR > 1.09 is considered normal autoregulation and < 1.09 impaired autoregulation.

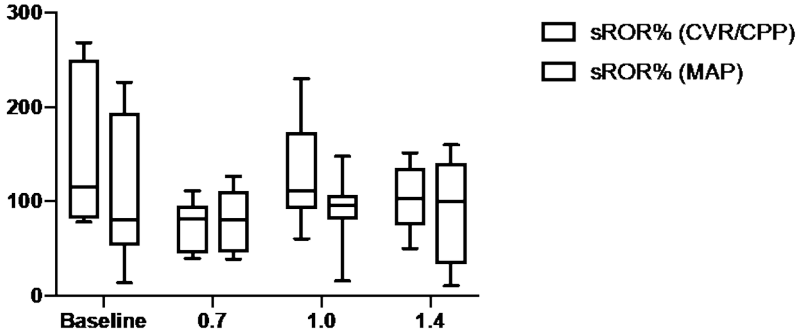


Figure 15 Static rate of autoregulation, sROR%, presented as boxplots. sROR% was calculated using MAP or CPP at baseline (propofol/midazolam) and at each dose of dexmedetomidine. Boxes represent lower quartiles, medians, and upper quartiles, whiskers represent 1.5 x inert-quartile ranges below and above the lower and upper quartiles, respectively.

Table 10 The indices for dynamic cerebral autoregulation at baseline (propofol and/or midazolam) and at different doses of dexmedetomidine (Dex). THRR = transient hyperemic response ratio, SA = strength of autoregulation.

	Baseline	Dex 0.7	p-value	Dex 1.0	p-value	Dex 1.4	p-value
THRR both	1.20 ±0.14	1.17±0.13	0.93	1.14±0.09	0.72	1.19±0.18	1.0
SA both	0.89±0.13	0.80±0.12	0.15	0.75±0.05	0.02	0.78±0.08	0.07

Table 11 The individual cerebral oxygenation indices, $PbtO_2$ and NIRS, and ICP values at baseline (propofol/midazolam) and at each dose of dexmedetomidine.

Patient	ICP baseline mmHg	ICP Dex 0.7	ICP Dex 1.0	ICP Dex 1.4	$P_{bt}O_2$ baseline mmHg	$P_{bt}O_2$ Dex 0.7	$P_{bt}O_2$ Dex 1.0	$P_{bt}O_2$ Dex 1.4	NIRS sin baseline %	NIRS sin Dex 0.7	NIRS sin Dex 1.0	NIRS sin Dex 1.4	NIRS dx baseline %	NIRS dx Dex 0.7	NIRS dx Dex 1.0	NIRS dx Dex 1.4
1	13	14	9	9	24.4	26	26.9	26	78	79	73	73	81	84	77	76
2	3	5	4	6	13.7	16.3	14	18.6	79	72	68	69	80	72	69	69
3	2	4	2	5	22	1	3.1	5	85	87	85	83	91	95	93	92
4									65	71	72	72	67	76	74	77
5	20	15	19	20	55	59	59	59	68	70	66	62	69	69	65	63
6	6	9	8	7	8.7	8.8	8.1	7.8	68	74	70	70	68	75	69	68
7									81	81	80	82	72	73	72	75
8	12	11	10	12					65	63	61	60	69	68	65	62
9	2	6	11	6	24	21	21	21	33	34	30	32	68	63	63	63
10	9	5	6	6	26.7	26.9	25.6	22.9	71	69	65	66	62	57	55	56

One patient had impaired dynamic autoregulation at baseline with impaired THRR values bilaterally, and we observed no change following the administration of dexmedetomidine. One patient had impaired dynamic autoregulation determined by THRT after the lowest, initial dose of dexmedetomidine, but not after higher doses. One patient showed an impaired THRR after the 0.7 µg/kg/h and the 1.0 µg/kg/h doses, but not after the highest dose of 1.4 µg/kg/h. Also, one patient had weakened dynamic autoregulation after the two highest doses. SA values were < 1 in all patients after every dose of dexmedetomidine, and we witnessed a statistically significant reduction in SA after the 1.0 µg/kg/h dose compared to baseline ($p = 0.02$).

The patient whose dynamic autoregulation was impaired at baseline also showed sROR% values < 50% throughout the study, suggesting a damaged static autoregulation as well. Three other patients had sROR% < 50% at some point during the study.

We observed no differences in cerebral oxygenation indices, $PbtO_2$ and NIRS, between baseline and the different doses of dexmedetomidine (**Table 11**). In a subgroup analysis of the data for the five patients in our group who had successful TCD measurements from both sides, we found no statistically significant differences in the autoregulation measurements at any dexmedetomidine dose compared to baseline.

Before starting the dexmedetomidine infusion, the cumulative dose of propofol was 6004 ± 4165 mg (N = 7) and that of midazolam was 125.7 ± 79 mg (N = 3). The measured mean dexmedetomidine concentrations were 0.7 ± 0.22 ng/ml (after 0.7 µg/kg/h for 2 hours), 1.19 ± 0.35 ng/ml (after 1.0 µg/kg/h for 2 hours), and 1.69 ± 0.39 ng/ml (after 1.4 µg/kg/h for 2 hours). We found no statistically significant differences in the dosages of noradrenaline during the study period.

Table 12 Vital parameters and results for static cerebral autoregulation at baseline (propofol and/or midazolam) and at different doses of dexmedetomidine (Dex); initial shows the baseline values before the augmentation of MAP, and final shows the values during increased MAP. The results during each dose of dexmedetomidine were compared to baseline. PI, sROR%, and V_{MCA} are reported as an averaged value for both sides. The table also displays the brain tissue oxygenation, $PtiO_2$, and near infrared spectroscopy (NIRS) values during baseline and each dose of dexmedetomidine. The NIRS values are mean values of both sides. No significant difference was seen between the doses. MAP = mean arterial pressure; CPP = cerebral perfusion pressure; ICP = intracranial pressure; CVR = cerebrovascular resistance; sROR = static rate of autoregulation; PI = pulsatility index; V_{MCA} = velocity of the blood flow the middle cerebral artery; $PtiO_2$ = brain tissue oxygenation; NIRS = near infrared spectroscopy.

	Baseline	Dex 0.7	p-value	Dex 1.0	p-value	Dex 1.4	p-value
MAP mmHg initial	80.70±10.51	87.50±9.0	0.22	88.90±7.99	0.11	89.10±7.72	0.10
MAP mmHg final	98.40±11.08	104.80±10.00	0.38	109.50±10.05	0.05	109.00±9.88	0.07
ΔMAP%	21.70±5.12	20.60±4.11	0.90	23.10±4.18	0.81	22.30±3.80	0.98
CPP mmHg initial	78.68±6.77	79.80±8.92	0.99	80.91±9.16	0.91	82.39±8.41	0.71
CPP mmHg final	91.15±6.79	97.23±9.11	0.34	100.53±7.38	0.08	101.15±9.37	0.06
ΔCPP mmHg	16.09±7.22	22.11±4.71	0.22	24.86±8.55	0.47	23.04±6.88	0.14
ICP mmHg initial	8.93±5.88	9.60±4.77	0.99	9.28±5.00	1.00	9.70±4.84	0.98
ICP mmHg final	9.55±6.18	9.56±4.85	1.00	8.84±4.90	0.99	9.88±5.50	1.00
ΔCVR%	22.66±14.26	15.02±7.18	0.41	22.26±11.52	0.99	19.09±13.39	0.86
sROR% (CPP)	150.89±84.37	75.22±27.75	0.08	128.25±58.35	0.84	104.82±36.92	0.42
sROR% (MAP)	110.01±77.97	80.45±33.63	0.55	91.78±35.23	0.82	89.79±54.82	0.77
PI	1.37±0.39	1.41±0.32	0.99	1.46±0.45	0.92	1.43±0.36	0.98
VMCA cm/s initial	67.50±24.50	64.67±21.38	0.98	60.28±18.57	0.81	60.33±19.40	0.82
VMCA cm/s final	66.63±22.17	68.33±22.72	1.00	61.00±17.94	0.90	62.67±22.43	0.96
$PtiO_2$ mmHg initial	24.9±14.8	22.7±18.5	0.99	22.5±18.3	0.99	22.9±17.7	0.99
$PtiO_2$ mmHg final	24.9±16	24.3±18.9	1.0	23.7±19.3	1.0	24.6±18.6	1.0
NIRS % initial mean	71.5±10.4	72±11	1.0	69.7±11.5	0.97	69.5±10.5	0.96
NIRS % final mean	72.3±9.7	72.6±10.8	1.0	71.3±11.2	0.99	70.8±10.7	0.98

6 Discussion

6.1 Results

The main findings of this study were that in healthy volunteers, dexmedetomidine induced the lowest CMR_{glu} compared to other investigated drugs, and it also induced an anti-inflammatory cytokine response according to immunological biomarkers sampled immediately after the administration of dexmedetomidine. In aSAH patients, no statistically significant differences were found in the indices of static autoregulation during the administration of dexmedetomidine compared to propofol and/or midazolam, but it was found to slightly, but statistically significantly, impair dynamic autoregulation after the dose of 1.0 µg/kg/h, but not after the highest or the lowest doses.

6.1.1 The effects of dexmedetomidine on CMR_{glu}

In human volunteer studies, it has been demonstrated that dexmedetomidine decreases CBF (John C Drummond et al., 2008; Prielipp et al., 2002; Zornow et al., 1993). Prielipp et al. indisputably presented this in an early human PET study where a 0.628 ng/ml average plasma concentration caused a 33% global reduction in CBF from baseline (Prielipp et al., 2002). In canine studies where dexmedetomidine was given during isoflurane (Zornow et al., 1990) or halothane (Karlsson et al., 1990) anaesthesia, a reduction in CBF was detected with the sagittal sinus outflow technique. The decrease in CBF would not be too concerning if it was coupled with or even a result from a decrease in metabolism. In neurological pathologies, it would in fact be most desirable. However, the troubling finding in the early canine studies was that the decrease in CBF seemed to not be associated with a simultaneous decrease in cerebral oxygen metabolism, which suggested that dexmedetomidine could cause ischaemia in the brain (Karlsson et al., 1990; Zornow et al., 1990). It is well established that in cerebral vessels, dexmedetomidine causes direct vasoconstriction (Coughlan et al., 1992) which could predispose the brain to ischemia if there were no concomitant decrease in cerebral metabolism. This metabolic uncoupling would be especially harmful in aSAH patients, who are already vulnerable to cerebral energy failure due to vasospasm and DCI.

Previously, two small studies have focused on the relationship between brain oxygen metabolism and CBF during the administration of dexmedetomidine (John C Drummond et al., 2008; John Cornell Drummond & Sturaitis, 2010). One study included six healthy human volunteers and used TCD and jugular vein blood samples to calculate oxygen metabolism equivalent with the conclusion that dexmedetomidine might decrease oxygen metabolism along with CBF (John C Drummond et al., 2008). Another study included five neurosurgical patients and measured $PbtO_2$ during neurosurgical intervention and the administration of dexmedetomidine (John Cornell Drummond & Sturaitis, 2010). They observed no significant decreases in $PbtO_2$ during dexmedetomidine administration; however, the study contained many confounding elements that limit the applicability of the results. A more recent study on the subject used a sophisticated method of combined imaging of CBF with the arterial spin labelling functional MRI technique and [^{18}F]FDG-PET (Akeju et al., 2014). Dexmedetomidine suppressed CBF and CMR_{glu} in the thalamus, the default mode network structures and the frontoparietal regions bilaterally, but, because the study protocol did not include PET imaging with blood activity sampling, they could not determine the absolute regional CMR_{glu} effects of dexmedetomidine. Our study was able to demonstrate a significant reduction in absolute regional CMR_{glu}, and considering that similar reductions in CBF have regularly been reported before, our results suggest that dexmedetomidine preserves the coupling between brain metabolism and perfusion. Unfortunately, we did not measure CBF together with CMR_{glu}, and therefore the exact effects of dexmedetomidine on metabolic coupling remain unsolved.

Our results also show the potency for each anaesthetic in reducing CMR_{glu}. In humans, the potency for CMR_{glu} follows the order from most potent to least: dexmedetomidine > propofol > ketamine = placebo. Sevoflurane decreased metabolism as much as propofol, but the dose was not entirely equipotent. We observed greatest individual variability in CMR_{glu} with S-ketamine whose effects on CMR_{glu} were comparable to placebo.

6.1.2 Effects on immunological biomarkers

In study II, we collected samples for immunological analysis from healthy volunteers who were anaesthetised solely with either dexmedetomidine or propofol. The objective was to investigate single drug-induced changes in 48 immunological analytes and to obtain information about the actual immunological effects of these sedatives. Our study is exceptional in that the healthy subjects received only one anaesthetic without any surgical or other confounding stimuli. Also, we included a large, multi-parametric assay consisting of 48 analytes, in contrast to generally used 6-8 immunological analytes (Schneemilch, Ittenson, Ansorge, Hachenberg, & Bank,

2005; Sofra et al., 2013). We detected significant changes within the study groups in the concentrations of several inflammatory chemokines and cytokines. Between the groups, we observed a significant difference in the concentrations of PDGF and eotaxin.

According to our findings, dexmedetomidine induces primarily an immunosuppressive effect on the immune system, and propofol has both a minor anti-inflammatory but also a pro-inflammatory effect on the cytokine profile. These results stimulate the concept that choosing the anaesthetic or sedative drug individually, based on the current immunological state of the patient (e.g., aSAH, TBI, sepsis), could be beneficial. The postoperative levels of pro-inflammatory cytokines have been shown to decrease following the administration of dexmedetomidine (K. Chen et al., 2015; H. Zhou, Lu, Shen, Kang, & Zong, 2017). Also, compared to propofol, dexmedetomidine has demonstrated anti-inflammatory properties in ICU patients (Venn & Grounds, 2001). In animal studies and in experimental sepsis models, dexmedetomidine has attenuated the immune response and improved survival (Hofer et al., 2009; Y. Wu et al., 2013; Xiang, Hu, Li, & Li, 2014). In septic ICU patients, the administration of dexmedetomidine was found to be associated with lower levels of CRP and PCT compared to the control group (Ohta et al., 2020).

The results of our study are in accordance with previous discoveries, and in our study population, dexmedetomidine significantly decreased the concentrations of eotaxin, MCP-1, CTACK, MIF, IL-18, IL-2Rα, SCF, SCGF, and VEGF. Interestingly, a decrease in eotaxin was seen only with dexmedetomidine. Eotaxin is an eosinophil chemoattractant involved in leukocyte recruitment in allergic conditions (Rothenberg & Hogan, 2006), and in a murine model of sepsis, the levels of eotaxin were strongly upregulated (Cheng, Lukacs, & Kunkel, 2002). Eotaxin has also been linked to age-associated weakening in hippocampal neurogenesis (Villeda et al., 2011) as well as accelerated brain aging in neuro-psychiatric disorders (Ivanovska et al., 2020; Mohite et al., 2020). Considering that dexmedetomidine has shown some effect in lowering the risk of POCD (W. Chen et al., 2015; Duan et al., 2018; C. Zhou et al., 2016), the role of eotaxin in neuroinflammation could be an interesting target for future research.

In our subjects, propofol significantly increased the levels of IL-5, IL-7, IL-17, and PDGF. This could imply that propofol increases the reactivity of adaptive immune response. However, we also observed a decrease in the levels of pro-inflammatory chemokines MCP-1, CTACK, and MIF and in the anti-inflammatory HGF, IP-10, and MIG. These conflicting findings insinuate that propofol could have a pro-inflammatory effect on the immune system which is mediated through increasing the activation of lymphocytes and thus, adaptive immunity, but it also suppresses the innate immunity by decreasing the levels of several pro-inflammatory

chemokines. The anti-inflammatory HGF, IP-10, and MIG have all been linked to cancer and tumour growth and are being investigated in cancer research (Ding et al., 2016; Fajardo-Puerta, Prado, Frampton, & Jiao, 2016; Raemdonck, Steen, Liekens, Damme, & Struyf, 2015). This observation is particularly interesting, because evidence suggests that propofol might be superior to volatile anaesthetics in cancer patients (Enlund et al., 2014; Sekandarzad, Zundert, Lirk, Doornebal, & Hollmann, 2017; Wigmore et al., 2016; Yuki & Eckenhoff, 2016). The mixed pro- and anti-inflammatory effect that propofol seems to generate could be beneficial for cancer patients and would therefore validate choosing a certain anaesthetic individually. Conversely, dexmedetomidine appears to promote metastasis in rodents in breast, lung, and colon cancer (Lavon et al., 2018) and, in lung cancer patients, decrease overall survival after lung cancer surgery (Cata et al., 2017). This effect could originate from dexmedetomidine's anti-inflammatory properties that we observed in our study, or it could be a result of direct stimulation of cancer cells by dexmedetomidine.

Th1/Th2 balance can indicate the status of the immune system, and thus we aimed to investigate if dexmedetomidine and propofol affect the Th1/Th2 balance. For this, we measured the changes in the ratio of a Th1 cytokine (IFN-γ) to Th2 cytokines (IL-4 and IL-5). However, we did not find any significant changes in the Th1/Th2 ratio with either drug, not even with propofol which increased so many pro-inflammatory cytokine levels.

Considering our results, dexmedetomidine probably deserves further studies in patients with sepsis, which is typically associated with extensive release of cytokines. As stated earlier, aSAH is also a disease dominated by a vast cytokine storm and therefore aSAH patients might benefit from anti-inflammatory properties. Conversely, propofol could be advantageous in situations where the immune system benefits from a pro-inflammatory stimulation. However, the results from previous studies on dexmedetomidine in septic patients are highly conflicting (Hughes et al., 2021; Shehabi et al., 2019; Tasdogan, Memis, Sut, & Yuksel, 2009; Venn & Grounds, 2001; Zamani et al., 2016). It seems that the immune system and the circumstances affecting it are extremely complex and need further exploration.

6.1.3 The effects on cerebral autoregulation in aSAH patients

In study III, we investigated the effects of dexmedetomidine on static and dynamic cerebral autoregulation in aSAH patients compared to baseline sedation with propofol and/or midazolam. Each patient served as their own control. The main finding was that dexmedetomidine did not change static autoregulation indices compared to baseline. In dynamic autoregulation, we observed a decrease in SA after

the dose of 1.0 μg/kg/h, but there were no significant changes in other dynamic autoregulation indices even with higher doses.

Cerebral autoregulation is often impaired after aSAH, and this impairment is associated with poor outcome and the incidence of DCI (Budohoski et al., 2012; Jaeger, Schuhmann, Soehle, Nagel, & Meixensberger, 2007; Jaeger et al., 2012; J. D. Pickard et al., 1992; John D Pickard et al., 1980; Rynkowski et al., 2019). There are early studies on cerebral blood flow and autoregulation in aSAH patients demonstrating that static autoregulation is commonly impaired after the insult (Dernbach et al., 1988; Manno et al., 1998; Muench et al., 2005; Tenjin et al., 1988). However, in one relatively recent study, static autoregulation was not impaired after aSAH (Diringer et al., 2016). Most studies on cerebral autoregulation in aSAH patients have concentrated on its dynamic component and demonstrated that dynamic autoregulation is often compromised after aSAH (Budohoski et al., 2015). We decided to test both static and dynamic cerebral autoregulation, because the static and dynamic components of autoregulation can be differently affected in disease states; besides, some anaesthetic agents impair dynamic but not static autoregulation (Gupta, Heath, & Matta, 1997; Ogawa et al., 2006). To our knowledge, no other study has investigated both static and dynamic cerebral autoregulation in aSAH patients.

In healthy volunteers, dexmedetomidine has been shown to weaken dynamic autoregulation (Ogawa et al., 2008). In our study, we witnessed a small but significant decrease in SA after the dose of 1.0 μg/kg/h but not, however, after the first 0.7 μg/kg/h dose or the highest 1.4 μg/kg/h dose. It may be that the effect of dexmedetomidine on the dynamic component of autoregulation is dose dependent in aSAH patients. It is also possible that our patients were not overly susceptible to disturbances in the autoregulation indices since all patients had normal ICP levels. In addition, the blood pressure was kept constant with noradrenaline infusion during the whole duration of the study, and no hypotensive periods were allowed at any point. Elevated ICP is known to correlate with impaired cerebral autoregulation (de-Lima-Oliveira et al., 2018), and in volunteer studies, the decrease in MAP, CBF, and cardiac output that dexmedetomidine induces is not usually countered (Prielipp et al., 2002). In patients with traumatic brain injury, the reduction in CBF that dexmedetomidine induced was smaller if blood pressure was kept at the pre-sedation level (Xuemin Wang, Ji, Fen, & Wang, 2013). It is therefore possible that in our patients, cerebral autoregulation was functioning within the blood pressure levels we targeted but may have been disturbed outside of that range. In addition, we performed the studies during the early days of aSAH before the emergence of vasospasm and DCI. Therefore, we are unable to make any conclusion about how dexmedetomidine affects the cerebral autoregulation during vasospasm and DCI. Interestingly, even though we found no statistically significant differences between

the noradrenaline doses in our patients at different stages, we noticed a clear trend towards lower noradrenaline requirement as the dexmedetomidine dose increased. There was a similar observation in septic ICU patients, where switching from propofol sedation to dexmedetomidine significantly reduced the vasopressor requirements (Morelli et al., 2019). This implies that dexmedetomidine may be a valid option in sedating patients that are haemodynamically unstable or challenging and in situations where maintaining a certain blood pressure level is crucial.

Overall, our results suggest that if dexmedetomidine is used in aSAH patients, the maintenance of adequate blood pressure level is especially important and sudden decreases in blood pressure should be carefully avoided.

6.2 Methodological considerations

Studies I and II were conducted on healthy volunteers, and the cohort sizes were considered adequate for detecting possible differences between the groups. Only young male volunteers were included due to the exposure to radiation. A control group was included in study I but not in study II, because the samples for study II were collected during a separate study protocol.

The aim of study I was to compare the effects of commonly used anaesthetics and sedatives on regional cerebral glucose metabolism at equi-sedative doses. PET scanning is the most sophisticated and appropriate technique for investigating cerebral physiology and was therefore an obvious choice. The anaesthetic drugs chosen are very commonly used in clinical practice: dexmedetomidine, propofol, sevoflurane, and S-ketamine. There was special interest in investigating dexmedetomidine's effects on CMR_{glu}, as it has not been studied before. However, the measurement of CBF was not included in the methodology, which is a clear weakness in the study. The measurement of CBF would have required at least one additional separate PET imaging session for each subject. To avoid the added exposure to radiation, the measurement of CBF was abandoned and only CMR_{glu} was included in the study.

In study II, we evaluated the effects of dexmedetomidine and propofol on inflammatory biomarkers in healthy volunteers. The design of another investigation on the mechanisms of human consciousness provided the opportunity to collect samples from anaesthetised subjects without any confounding circumstances, such as surgery or other nociceptive stimuli. Therefore, we were able to study the actual immunological effects induced by a sole anaesthetic drug. However, we had to take the samples for the study immediately after the exposure, and we did not have a follow-up period. This means that the observed changes can only reflect the immediate immunological responses, and we might have seen different changes in the concentrations had we taken them 24-72 hours after the exposure. Also, the

results acquired from a study on healthy subjects cannot be directly applied to the treatment of critically ill patients, because the response these anaesthetics induce will most likely differ in acute illness or other stressful situations such as aSAH, TBI, or surgery.

Study III included aSAH patients treated in the ICU and needing ventilatory support and sedation. Power analysis was not performed, as the sample size was based on previously published autoregulation studies where TCD measurements were used. The original intention was to collect 15-20 patients, but the recruitment was unexpectedly slow (from year 2013 to 2016) and challenging mostly due to refusals of next of kin or suspicion of vasospasm in TCD. Therefore, the recruitment was terminated after 10 patients. Of our 10 patients, 8 had Fisher grade 4 aSAH and the rest had Fisher grade 3 aSAH (**Table 2**). The Fisher grade affects the CBF more profoundly than the Hunt&Hess grades (Engquist et al., 2018). It is therefore unlikely that the heterogeneity of Hunt & Hess grades in our patients influenced the results.

To reach a steady state of dexmedetomidine before the autoregulation tests, we used a two-hour infusion period after the commencement of dexmedetomidine and after each dose increment. This was to ensure that the concentration of dexmedetomidine reached the desired plasma level before the measurements, and to wash out the propofol which was stopped before starting the dexmedetomidine infusion. The carotid compression in all cases was performed by the same investigator (the author), who was also present in all tests and was responsible for collecting and preparing the samples for the measurement of dexmedetomidine plasma concentrations later.

There are several methods for investigating cerebral autoregulation, but there is no consensus on how it should be monitored (Czosnyka, Brady, Reinhard, Smielewski, & Steiner, 2009). PET scanning is a modern and the most reliable method for imaging CBF directly (Steiner, Coles, et al., 2003). The downside of PET scanning is that it is not possible to detect fast changes in CBF and therefore assessing dynamic cerebral autoregulation is impossible. We chose to use TCD due to its feasibility and versatility, and to avoid the need to transport sedated and intubated patients for imaging. Also, THRT for assessing dynamic autoregulation is considered safe in aSAH and allows a brief period of reduction in CBFV. In addition, we calculated SA which is not affected by haemodynamic factors (Mahajan et al., 1998). In healthy anaesthetised subjects, there is correlation between both dynamic autoregulation tests (thigh cuff, THRT and dynamic SA) and static rate of autoregulation (Tibble, Girling, & Mahajan, 2001; Tiecks et al., 1995). Nevertheless, the different methods are probably not equivalent or interchangeable (Budohoski, Czosnyka, Smielewski, et al., 2013).

6.3 Limitations of the study

In study I, the main limitation was that CBF was not measured together with CMR_{glu}. Therefore, we still lack knowledge of the precise metabolic coupling effects of dexmedetomidine. Another limitation is that only young male subjects were investigated and so the impact of age or gender on the results remains unknown. Also, the measurements were performed only for one target concentration of each of the four anaesthetics. In addition, the initial objective to compare equipotent doses of the anaesthetics was not quite achieved because 85% of the sevoflurane subjects were unresponsive at the time of [^{18}F]FDG injection compared to 45-55% in the other drug groups. Despite this limitation, CMR_{glu} was significantly lower in the dexmedetomidine group than in the sevoflurane group in the whole brain and in 13 of the 15 ROIs analysed.

In study II, one important limitation was that only male subjects were included as in study I. Also, we did not have a control or placebo group without anaesthesia and thus, the possible impact of circadian rhythm and other such factors remains unclear. Another limitation was that we did not have a follow-up period and, consequently, may not have detected responses requiring de novo -synthesis, which requires more time as it involves the primary synthesis of complex molecules. Instead, we might have only discovered the acute responses following the release of molecules from storage vesicles.

In study III, the most important limitation is that the sample size was very small and therefore our results can be considered merely preliminary, with larger studies needed to confirm our findings. A second limitation is that the baseline sedation differed among the patients. Whereas most patients had propofol sedation, two had only midazolam, one had both, and one had none. Also, the patients had already been continuously sedated for a few days before our study protocol, which can affect the autoregulation status. In a previous study, midazolam seemed to improve dynamic cerebral autoregulation, while propofol seemed to have no effect on it in healthy volunteers (Ogawa et al., 2010). In patients with traumatic brain injury, propofol has been shown to impair static autoregulation when used in large doses (more than 4 mg/kg/h) (Steiner, Coles, et al., 2003). After an over 12-hour infusion of propofol, it takes 3.5 hours to reduce the plasma concentration of propofol to 20% (Sahinovic, Struys, & Absalom, 2018). We suspended propofol 2 hours before the first and almost 6.5 hours before the last autoregulation tests, so it is unlikely that residual propofol had a significant effect on our results. However, midazolam may have influenced the dynamic autoregulation in our patients, although only three were administered midazolam. Considering TCD measurements, it is known that haematocrit, PaO_2 level, and temperature may affect the readings (Pan et al., 2022). In our patients, these were kept constant during the study period, and therefore it is not likely that they had much effect on our results. Also, the same investigator (the

author) performed all the TCD measurements to minimise the operator-related discrepancy.

Another limitation to consider is that TCD provides only an estimate of CBF and assumes that the MCA diameter varies only minimally during changes in MAP (Naqvi, Yap, Ahmad, & Ghosh, 2013; Verbree et al., 2017). Therefore, TCD measurements should be interpreted with caution for CBF. Finally, we performed our study protocol during the first days after aSAH, well before DCI usually develops; therefore, it is possible that the state of the cerebral autoregulation changes later.

6.4 Clinical implications and future studies

In study I, we demonstrated that dexmedetomidine induced the lowest cerebral glucose metabolism compared to other investigated drugs in healthy male volunteers. However, we did not measure the CBF concomitantly and therefore the effect of dexmedetomidine on CBF-metabolic coupling remains unresolved. A future study combining the measurement of CBF with a parallel measurement of CMR_{glu} or CMR_{O2} would finally resolve this ambiguity.

The findings of study II implicate that the choice of anaesthetic and sedative agent may impact the immunological status of the individual. The immune system is a complicated entity which is affected by multiple factors that are not entirely controllable. In the future, well-designed randomised controlled studies in diverse patient groups with different immunological circumstances could reveal if the choice of anaesthetic and sedative agents can affect the patient's survival or outcome.

Study III attempted to uncover the effects of dexmedetomidine on cerebral autoregulation in aSAH patients. Our findings suggest that in aSAH patients, dexmedetomidine preserves static cerebral autoregulation, but it might impair dynamic cerebral autoregulation in a dose-dependent manner, and therefore it seems essential to try to maintain the patient haemodynamically stable and to avoid severe fluctuations in blood pressure. However, our sample size was very small and consequently, larger future trials in aSAH and other neurologically compromised patient groups are needed. Preferably randomised controlled prospective studies with dexmedetomidine in neurocritical patients would uncover the safety and possible benefits of this popular sedative drug.

7 Summary and Conclusions

This study revealed the following conclusions:

1. At equi-sedative doses, dexmedetomidine, propofol, and sevoflurane decrease global CMR_{glu} compared with placebo and S-ketamine. Dexmedetomidine induces the lowest CMR_{glu}, and the rank in potency for reducing CMR_{glu} is dexmedetomidine>propofol>ketamine=placebo. (I) This finding alleviates the concern for possible detrimental effects of dexmedetomidine on the coupling of cerebral blood flow and metabolism. (I)

2. In healthy volunteers, dexmedetomidine seems to have a distinctly immunosuppressive effect on the immune system, whereas propofol seems to have mainly pro-inflammatory but also some anti-inflammatory effect on the immune system. (II)

3. In aSAH patients, the static cerebral autoregulation was not affected by dexmedetomidine. However, the dynamic autoregulation was slightly weakened after a dexmedetomidine dose of 1.0 μg/kg/h when compared to baseline sedation with propofol and/or midazolam. This could imply that during dexmedetomidine sedation, sudden decreases in arterial blood pressure may be unfavourable and should be carefully avoided. (III)

To summarise, dexmedetomidine is likely to preserve the cerebral blood flow and metabolic coupling in healthy subjects. Dexmedetomidine appears to have an anti-inflammatory effect on the systemic inflammatory cytokine release in healthy human subjects. In aSAH patients, our preliminary results show that dexmedetomidine seems to preserve static cerebral autoregulation but may weaken dynamic cerebral autoregulation compared to propofol and/or midazolam. Further studies are needed to confirm these preliminary findings.

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List of References

Ahlqvist, R. P. (1948). A study of the adrenotropic receptors. *The American Journal of Physiology*, *153*(3), 586–600. doi: 10.1152/ajplegacy.1948.153.3.586

Ahn, S.-H., Savarraj, J. P. J., Parsha, K., Hergenroeder, G. W., Chang, T. R., Kim, D. H., Choi, H. A. (2019). Inflammation in delayed ischemia and functional outcomes after subarachnoid hemorrhage. *Journal of Neuroinflammation*, *16*(1), 213. doi: 10.1186/s12974-019-1578-1

Akeju, O., Loggia, M. L., Catana, C., Pavone, K. J., Vazquez, R., Rhee, J., Purdon, P. L. (2014). Disruption of thalamic functional connectivity is a neural correlate of dexmedetomidine-induced unconsciousness. *ELife*, *3*, e04499. doi: 10.7554/elife.04499

Alam, A., Hana, Z., Jin, Z., Suen, K. C., & Ma, D. (2018). Surgery, neuroinflammation and cognitive impairment. *EBioMedicine*, *37*(Suppl. 2), 547–556. doi: 10.1016/j.ebiom.2018.10.021

Alkire, M. T., Haier, R. J., Barker, S. J., Shah, N. K., Wu, J. C., & Kao, J. Y. (1995). Cerebral Metabolism during Propofol Anesthesia in Humans Studied with Positron Emission Tomography. *Anesthesiology*, *82*(2), 393–403. doi: 10.1097/00000542-199502000-00010

Angst, M. S., Ramaswamy, B., Davies, M. F., & Maze, M. (2004). Comparative analgesic and mental effects of increasing plasma concentrations of dexmedetomidine and alfentanil in humans. *Anesthesiology: The Journal of the American Society of Anesthesiologists*, *101*(3), 744–752. doi: 10.1097/00000542-200409000-00024

Armstead, W. M. (2016). Cerebral Blood Flow Autoregulation and Dysautoregulation. *Anesthesiology Clinics*, *34*(3), 465–477. doi: 10.1016/j.anclin.2016.04.002

Arnsten, A. F. T., & Pliszka, S. R. (2011). Catecholamine influences on prefrontal cortical function: relevance to treatment of attention deficit/hyperactivity disorder and related disorders. *Pharmacology, Biochemistry, and Behavior*, *99*(2), 211–216. doi: 10.1016/j.pbb.2011.01.020

Arulvelan, A., Manikandan, S., Easwer, H. V., & Krishnakumar, K. (2015). Effect of Loading Dose of Dexmedetomidine on Dynamic Cerebral Blood Flow Autoregulation in Patients With Intracranial Glial Neoplasms. *Journal of Neurosurgical Anesthesiology*, *27*(4), 289–294. doi: 10.1097/ana.0000000000000159

Baron, J. C., Rougemont, D., Soussaline, F., Bustany, P., Crouzel, C., Bousser, M. G., & Comar, D. (1984). Local interrelationships of cerebral oxygen consumption and glucose utilization in normal subjects and in ischemic stroke patients: a positron tomography study. *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *4*(2), 140–149. doi: 10.1038/jcbfm.1984.22

Beek, A. H. van, Claassen, J. A., Rikkert, M. G. O., & Jansen, R. W. (2008). Cerebral autoregulation: an overview of current concepts and methodology with special focus on the elderly. *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *28*(6), 1071–1085. doi: 10.1038/jcbfm.2008.13

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society Series B (…*. doi: 10.2307/2346101

Bianchi, M. E., & Manfredi, A. A. (2007). High-mobility group box 1 (HMGB1) protein at the crossroads between innate and adaptive immunity. *Immunological Reviews*, *220*, 35–46. doi: 10.1111/j.1600-065x.2007.00574.x

Blaudszun, G., Lysakowski, C., Elia, N., & Tramèr, M. R. (2012). Effect of perioperative systemic α2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. *Anesthesiology*, *116*(6), 1312–1322. doi: 10.1097/aln.0b013e31825681cb

Bloor, B. C., Ward, D. S., Belleville, J. P., & Maze, M. (1992). Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology: The Journal of the American Society of Anesthesiologists*, *77*(6), 1134–1142. doi: 10.1097/00000542-199212000-00014

Bosch, D. J., Meurs, M. V., Jongman, R. M., Heeringa, P., Abdulahad, W. H., & Struys, M. M. R. F. (2020). Effects of propofol and dexmedetomidine with and without remifentanil on serum cytokine concentrations in healthy volunteers: a post hoc analysis. *British Journal of Anaesthesia*, *125*(3), 267–274. doi: 10.1016/j.bja.2020.05.039

Budohoski, K. P., Czosnyka, M., & Kirkpatrick, P. J. (2015). The Role of Monitoring Cerebral Autoregulation After Subarachnoid Hemorrhage. *Neurosurgery*, *62*(CN_suppl_1), 180–184. doi: 10.1227/neu.0000000000000808

Budohoski, K. P., Czosnyka, M., Kirkpatrick, P. J., Smielewski, P., Steiner, L. A., & Pickard, J. D. (2013). Clinical relevance of cerebral autoregulation following subarachnoid haemorrhage. *Nature Reviews. Neurology*, *9*(3), 152–163. doi: 10.1038/nrneurol.2013.11

Budohoski, K. P., Czosnyka, M., Smielewski, P., Kasprowicz, M., Helmy, A., Bulters, D., … Kirkpatrick, P. J. (2012). Impairment of cerebral autoregulation predicts delayed cerebral ischemia after subarachnoid hemorrhage: a prospective observational study. *Stroke*, *43*(12), 3230–3237. doi: 10.1161/strokeaha.112.669788

Budohoski, K. P., Czosnyka, M., Smielewski, P., Varsos, G. V., Kasprowicz, M., Brady, K. M., … Kirkpatrick, P. J. (2013). Cerebral autoregulation after subarachnoid hemorrhage: comparison of three methods. *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *33*(3), 449–456. doi: 10.1038/jcbfm.2012.189

Calzada, B. C., & Artiñano, A. A. de. (2001). Alpha-adrenoceptor subtypes. *Pharmacological Research*, *44*(3), 195–208. doi: 10.1006/phrs.2001.0857

Carr, Z. J., Cios, T. J., Potter, K. F., & Swick, J. T. (2018). Does Dexmedetomidine Ameliorate Postoperative Cognitive Dysfunction? A Brief Review of the Recent Literature. *Current Neurology and Neuroscience Reports*, *18*(10), 64–67. doi: 10.1007/s11910-018-0873-z

Cata, J. P., Singh, V., Lee, B. M., Villarreal, J., Mehran, J. R., Yu, J., Ben-Eliyahu, S. (2017). Intraoperative use of dexmedetomidine is associated with decreased overall survival after lung cancer surgery. *Journal of Anaesthesiology Clinical Pharmacology*, *33*(3), 317–323. doi: 10.4103/joacp.joacp_299_16

Chan, J. K., Roth, J., Oppenheim, J. J., Tracey, K. J., Vogl, T., Feldmann, M., Nanchahal, J. (2012). Alarmins: awaiting a clinical response. *The Journal of Clinical Investigation*, *122*(8), 2711–2719. doi: 10.1172/jci62423

Chen, K., Lu, Z., Xin, Y. C., Cai, Y., Chen, Y., & Pan, S. M. (2015). Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients. *The Cochrane Database of Systematic Reviews*, *1*, CD010269. doi: 10.1002/14651858.cd010269.pub2

Chen, L., Cao, J., Cao, D., Wang, M., Xiang, H., Yang, Y., Cong, H. (2019). Protective effect of dexmedetomidine against diabetic hyperglycemia-exacerbated cerebral ischemia/reperfusion injury: An in vivo and in vitro study. *Life Sciences*, *235*, 116553. doi: 10.1016/j.lfs.2019.116553

Chen, W., Liu, B., Zhang, F., Xue, P., Cui, R., & Lei, W. (2015). The effects of dexmedetomidine on post-operative cognitive dysfunction and inflammatory factors in senile patients. *International Journal of Clinical and Experimental Medicine*, *8*(3), 4601–4605.

Cheng, S. S., Lukacs, N. W., & Kunkel, S. L. (2002). Eotaxin/CCL11 is a negative regulator of neutrophil recruitment in a murine model of endotoxemia. *Experimental and Molecular Pathology*, *73*(1), 1–8.

Cho, J. S., Lee, M.-H., Kim, S. I., Park, S., Park, H. S., Oh, E., Koo, B.-N. (2017). The Effects of Perioperative Anesthesia and Analgesia on Immune Function in Patients Undergoing Breast Cancer Resection: A Prospective Randomized Study. *International Journal of Medical Sciences*, *14*(10), 970–976. doi: 10.7150/ijms.20064

Choi, S.-H., Lee, H., Chung, T.-S., Park, K.-M., Jung, Y.-C., Kim, S. I., & Kim, J.-J. (2012). Neural network functional connectivity during and after an episode of delirium. *The American Journal of Psychiatry*, *169*(5), 498–507. doi: 10.1176/appi.ajp.2012.11060976

Cioccari, L., Luethi, N., Bailey, M., Shehabi, Y., Howe, B., Messmer, A. S., … Bellomo, R. (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. *Critical Care*, *24*(1), 1–13. doi: 10.1186/s13054-020-03115-x

Claassen, J., & Park, S. (2022). Spontaneous subarachnoid haemorrhage. *The Lancet*, *400*(J Crit Care 32 2016), 846–862. doi: 10.1016/s0140-6736(22)00938-2

Comtat, C., Sureau, F. C., Sibomana, M., Hong, I. K., Sjoholm, N., & Trebossen, R. (n.d.). *Image based resolution modeling for the HRRT OSEM reconstructions software*. 4120–4123. doi: 10.1109/nssmic.2008.4774188

Connolly, E. S., Rabinstein, A. A., Carhuapoma, J. R., Derdeyn, C. P., Dion, J., Higashida, R. T. (2012, June). *Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association.* Lippincott Williams & Wilkins.

Correa-Sales, C., Rabin, B. C. (1992). A Hypnotic Response to Dexmedetomidine, an α2 Agonist, Is Mediated in the Locus Coerüleus in Rats. *Anesthesiology*, *76*(6), 948–952.

Cossu, M., Gennaro, S., Rossi, A., Balestrero, M. A., Cella, F., & Viale, G. L. (1999). Autoregulation of cortical blood flow during surgery for ruptured intracranial aneurysms. *Journal of Neurosurgical Sciences*, *43*(2), 99–105; discussion 105.

Coughlan, M. G., Lee, J. G., Bosnjak, Z. J., Schmeling, W. T., Kampine, J. P., & Warltier, D. C. (1992). Direct coronary and cerebral vascular responses to dexmedetomidine. Significance of endogenous nitric oxide synthesis. *Anesthesiology*, *77*(5), 998–1006.

Crowe, Gillian, & Moran, L. (2022, April 5). Perioperative Applications of Dexmedetomidine [Anesthesia Tutorial of the Week 469]. Retrieved June 16, 2022, from Perioperative Applications of Dexmedetomidine website: https://resources.wfsahq.org/atotw/perioperative-applications-of-dexmedetomidine-atotw-469/

Czosnyka, M., Brady, K., Reinhard, M., Smielewski, P., & Steiner, L. A. (2009). Monitoring of cerebrovascular autoregulation: facts, myths, and missing links. *Neurocritical Care*, *10*(3), 373–386. doi: 10.1007/s12028-008-9175-7

Dardalas, I., Stamoula, E., Rigopoulos, P., Malliou, F., Tsaousi, G., Aidoni, Z., Pourzitaki, C. (2019). Dexmedetomidine effects in different experimental sepsis in vivo models. *European Journal of Pharmacology*, *856*(Suppl. 2), 172401. doi: 10.1016/j.ejphar.2019.05.030

Deiner, S., Luo, X., Lin, H.-M., Sessler, D. I., Saager, L., Sieber, F. E., … Rock, P. (2017). Intraoperative Infusion of Dexmedetomidine for Prevention of Postoperative Delirium and Cognitive Dysfunction in Elderly Patients Undergoing Major Elective Noncardiac Surgery: A Randomized Clinical Trial. *JAMA Surgery*, *152*(8), e171505. doi: 10.1001/jamasurg.2017.1505

de-Lima-Oliveira, M., Salinet, A. S. M., Nogueira, R. C., Azevedo, D. S. de, Paiva, W. S., Teixeira, M. J., & Bor-Seng-Shu, E. (2018). Intracranial Hypertension and Cerebral Autoregulation: A Systematic Review and Meta-Analysis. *World Neurosurgery*, *113*, 110–124. doi: 10.1016/j.wneu.2018.01.194

Dernbach, P. D., Little, J. R., Jones, S. C., & Ebrahim, Z. Y. (1988). Altered Cerebral Autoregulation and CO2 Reactivity after Aneurysmal Subarachnoid Hemorrhage. *Neurosurgery*, *22*(5), 822–826. doi: 10.1227/00006123-198805000-00003

Ding, Q., Lu, P., Xia, Y., Ding, S., Fan, Y., Li, X., Liu, M. (2016). CXCL9: evidence and contradictions for its role in tumor progression. *Cancer Medicine*, *5*(11), 3246–3259. doi: 10.1002/cam4.934

Diringer, M. N., Dhar, R., Scalfani, M., Zazulia, A. R., Chicoine, M., Powers, W. J., & Derdeyn, C. P. (2016). Effect of High-Dose Simvastatin on Cerebral Blood Flow and Static Autoregulation in Subarachnoid Hemorrhage. *Neurocritical Care*, *25*(1), 56–63. doi: 10.1007/s12028-015-0233-7

Domino, E. F., Domino, S. E., Smith, R. E., Domino, L. E., Goulet, J. R., Domino, K. E., & Zsigmond, E. K. (1984). Ketamine kinetics in unmedicated and diazepam-premedicated subjects. *Clinical Pharmacology and Therapeutics*, *36*(5), 645–653.

Dong, W., Chen, M.-H., Yang, Y.-H., Zhang, X., Huang, M.-J., Yang, X.-J., & Wang, H.-Z. (2017). The effect of dexmedetomidine on expressions of inflammatory factors in patients with radical resection of gastric cancer. *European Review for Medical and Pharmacological Sciences*, *21*(15), 3510–3515.

Doze, V. A., Chen, B. X., Society, M. M. T. J. of the A., & 1989. (1989). Dexmedetomidine produces a hypnotic–anesthetic action in rats via activation of central alpha-2 adrenoceptors. *Anesthesiology*, *71*(1), 75–79.

Drake, C. G. (1988). Report of World Federation of Neurological Surgeons Committee on a universal subarachnoid hemorrhage grading scale. *Journal of Neurosurgery*, *68*, 985–986.

Drake, C. G., & Peerless, S. J. (1997). Giant fusiform intracranial aneurysms: review of 120 patients treated surgically from 1965 to 1992. *Journal of Neurosurgery*, *87*(2), 141–162. doi: 10.3171/jns.1997.87.2.0141

Drummond, John C, Dao, A. V., Roth, D. M., Cheng, C.-R., Atwater, B. I., Minokadeh, A., Patel, P. M. (2008). Effect of dexmedetomidine on cerebral blood flow velocity, cerebral metabolic rate, and carbon dioxide response in normal humans. *Anesthesiology*, *108*(2), 225–232. doi: 10.1097/01.anes.0000299576.00302.4c

Drummond, John Cornell, & Sturaitis, M. K. (2010). Brain tissue oxygenation during dexmedetomidine administration in surgical patients with neurovascular injuries. *Journal of Neurosurgical Anesthesiology*, *22*(4), 336–341. doi: 10.1097/ana.0b013e3181e4b7e3

D'Souza, S. (2015). Aneurysmal Subarachnoid Hemorrhage. *Journal of Neurosurgical Anesthesiology*, *27*(3), 222–240. doi: 10.1097/ana.0000000000000130

Duan, X., Coburn, M., Rossaint, R., Sanders, R. D., Waesberghe, J. V., & Kowark, A. (2018). Efficacy of perioperative dexmedetomidine on postoperative delirium: systematic review and meta-analysis with trial sequential analysis of randomised controlled trials. *British Journal of Anaesthesia*, *121*(2), 384–397. doi: 10.1016/j.bja.2018.04.046

Ebert, T. J., Hall, J. E., Barney, J. A., Uhrich, T. D., & Colinco, M. D. (2000). The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology: The Journal of the American Society of Anesthesiologists*, *93*(2), 382–394.

EMA. (2021, May 6). EMA Dexmedetomidine. Retrieved May 6, 2021, from Dexmedetomidine website: https://www.ema.europa.eu/en/medicines/human/EPAR/dexdor

Engelhard, K., Werner, C., Möllenberg, O., & Kochs, E. (2001). S(+)-ketamine/propofol maintain dynamic cerebrovascular autoregulation in humans. *Canadian Journal of Anaesthesia*, *48*(10), 1034. doi: 10.1007/bf03016597

Engquist, H., Lewén, A., Howells, T., Johnson, U., Ronne-Engström, E., Nilsson, P., Rostami, E. (2018). Hemodynamic Disturbances in the Early Phase After Subarachnoid Hemorrhage: Regional Cerebral Blood Flow Studied by Bedside Xenon-enhanced CT. *Journal of Neurosurgical Anesthesiology*, *30*(1), 49–58. doi: 10.1097/ana.0000000000000395

Enlund, M., Berglund, A., Andreasson, K., Cicek, C., Enlund, A., & Bergkvist, L. (2014). The choice of anaesthetic--sevoflurane or propofol--and outcome from cancer surgery: a retrospective

analysis. *Upsala Journal of Medical Sciences*, *119*(3), 251–261. doi: 10.3109/03009734.2014.922649

Fajardo-Puerta, A. B., Prado, M. M., Frampton, A. E., & Jiao, L. R. (2016). Gene of the month: HGF. *Journal of Clinical Pathology*. doi: 10.1136/jclinpath-2015-203575

FDA, U. (2021, May 6). FDA Dexmedetomidine. Retrieved May 6, 2021, from FDA Dexmedetomidine website: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206628s000lbl.pdf

Fisher, C. M., Kistler, J. P., Neurosurgery, J. D., & 1980. (n.d.). Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. *Ars-Neurochirurgica.De*.

Flanders, C. A., Rocke, A. S., Edwardson, S. A., Baillie, J. K., & Walsh, T. S. (2019). The effect of dexmedetomidine and clonidine on the inflammatory response in critical illness: a systematic review of animal and human studies. *Critical Care*, *23*(1), 402–411. doi: 10.1186/s13054-019-2690-4

Fog, M. (1937). CEREBRAL CIRCULATION: THE REACTION OF THE PIAL ARTERIES TO A FALL IN BLOOD PRESSURE. *Archives of Neurology & Psychiatry*, *37*(2), 351–364. doi: 10.1001/archneurpsyc.1937.02260140137007

Forbes, H. S. (1928). THE CEREBRAL CIRCULATION: I. OBSERVATION AND MEASUREMENT OF PIAL VESSELS. *Archives of Neurology & Psychiatry*, *19*(5), 751–761. doi: 10.1001/archneurpsyc.1928.02210110003001

Forster, A., Juge, O., & Morel, D. (1982). Effects of Midazolam on Cerebral Blood Flow in Human Volunteers. *Anesthesiology*, *56*(6), 453–455. doi: 10.1097/00000542-198206000-00009

FreeSurfer Software. (2021, October 21). Retrieved October 21, 2021, from FreeSurfer Software website: http://surfer.nmr.mgh.harvard.edu/

Geraghty, J. R., Davis, J. L., & Testai, F. D. (2019). Neuroinflammation and Microvascular Dysfunction After Experimental Subarachnoid Hemorrhage: Emerging Components of Early Brain Injury Related to Outcome. *Neurocritical Care*, *31*(2), 373–389. doi: 10.1007/s12028-019-00710-x

Gigante, P., Hwang, B. Y., Appelboom, G., Kellner, C. P., Kellner, M. A., & Connolly, E. S. (2010). External ventricular drainage following aneurysmal subarachnoid haemorrhage. *British Journal of Neurosurgery*, *24*(6), 625–632. doi: 10.3109/02688697.2010.505989

Giller, C. A. (1991). A bedside test for cerebral autoregulation using transcranial Doppler ultrasound. *Acta Neurochirurgica*, *108*(1–2), 7–14. doi: 10.1007/bf01407660

Goettel, N., Patet, C., Rossi, A., Burkhart, C. S., Czosnyka, M., Strebel, S. P., & Steiner, L. A. (2016). Monitoring of cerebral blood flow autoregulation in adults undergoing sevoflurane anesthesia: a prospective cohort study of two age groups. *Journal of Clinical Monitoring and Computing*, *30*(3), 255–264. doi: 10.1007/s10877-015-9754-z

Guo, T. Z., Tinkienberg, J., & the, R. O. T. J. of. (1991). Central α1-Adrenoceptor Stimulation Functionally Antagonizes the Hypnotic Response to Dexmedetomidine, an α2-Adrenoceptor Agonist. *Anesthesiology*, 75:252-256.

Gupta, S., Heath, K., & Matta, B. F. (1997). Effect of incremental doses of sevoflurane on cerebral pressure autoregulation in humans. *BJA: British Journal of Anaesthesia*, *79*(4), 469–472. doi: 10.1093/bja/79.4.469

Harper, A. M., Deshmukh, V. D., Sengupta, D., Rowan, J. O., & Jennett, W. B. (1972). The effect of experimental spasm on the CO2 response of cerebral bloodflow in primates. *Neuroradiology*, *3*(3), 134–136. doi: 10.1007/bf00341495

Harper, A. M., & Glass, H. I. (1965). Effect of alterations in the arterial carbon dioxide tension on the blood flow through the cerebral cortex at normal and low arterial blood pressures. *Journal of Neurology, Neurosurgery & Psychiatry*, *28*(5), 449. doi: 10.1136/jnnp.28.5.449

Harrison, J. M., Girling, K. J., & Mahajan, R. P. (1999). Effects of target-controlled infusion of propofol on the transient hyperaemic response and carbon dioxide reactivity in the middle cerebral artery. *BJA: British Journal of Anaesthesia*, *83*(6), 839–844.

Hess, W. E. H. and R. M., & Hess, R. M. (1968). Surgical Risk as Related to Time of Intervention in the Repair of Intracranial Aneurysms. *Journal of Neurosurgery*, *28*(1). doi: https://doi.org/10.3171/jns.1968.28.1.0014

Hofer, S., Steppan, J., Wagner, T., Funke, B., Lichtenstern, C., Martin, E., Weigand, M. A. (2009). Central sympatholytics prolong survival in experimental sepsis. *Critical Care*, *13*(1), R11. doi: 10.1186/cc7709

Hsu, Y.-W., Cortinez, L. I., Robertson, K. M., Keifer, J. C., Sum-Ping, S. T., Moretti, E. W., Somma, J. (2004). Dexmedetomidine Pharmacodynamics: Part I. *Anesthesiology: The Journal of the American Society of Anesthesiologists*, *101*(5), 1066–1076. doi: 10.1097/00000542-200411000-00005

Hughes, C. G., Mailloux, P. T., Devlin, J. W., Swan, J. T., Sanders, R. D., Anzueto, A.(2021). Dexmedetomidine or Propofol for Sedation in Mechanically Ventilated Adults with Sepsis. *New England Journal of Medicine*, *384*(15), 1424–1436. doi: 10.1056/nejmoa2024922

Huupponen, E., Maksimow, A., Lapinlampi, P., Särkelä, M., Saastamoinen, A., Snapir, A., Jääskeläinen, S. (2008). Electroencephalogram spindle activity during dexmedetomidine sedation and physiological sleep. *Acta Anaesthesiologica Scandinavica*, *52*(2), 289–294. doi: 10.1111/j.1399-6576.2007.01537.x

Iirola, T., Aantaa, R., Laitio, R., Kentala, E., Lahtinen, M., Wighton, A., Olkkola, K. T. (2011). Pharmacokinetics of prolonged infusion of high-dose dexmedetomidine in critically ill patients. *Critical Care*, *15*(5), R257-10. doi: 10.1186/cc10518

Ishii, H., Kohno, T., Yamakura, T., Ikoma, M., & Baba, H. (2008). Action of dexmedetomidine on the substantia gelatinosa neurons of the rat spinal cord. *The European Journal of Neuroscience*, *27*(12), 3182–3190. doi: 10.1111/j.1460-9568.2008.06260.x

Ivanovska, M., Abdi, Z., Murdjeva, M., Macedo, D., Maes, A., & Maes, M. (2020). CCL-11 or Eotaxin-1: An Immune Marker for Ageing and Accelerated Ageing in Neuro-Psychiatric Disorders. *Pharmaceuticals*, *13*(9), 230. doi: 10.3390/ph13090230

Jaeger, M., Schuhmann, M. U., Soehle, M., Nagel, C., & Meixensberger, J. (2007). Continuous monitoring of cerebrovascular autoregulation after subarachnoid hemorrhage by brain tissue oxygen pressure reactivity and its relation to delayed cerebral infarction. *Stroke*, *38*(3), 981–986. doi: 10.1161/01.str.0000257964.65743.99

Jaeger, M., Soehle, M., Schuhmann, M. U., & Meixensberger, J. (2012). Clinical significance of impaired cerebrovascular autoregulation after severe aneurysmal subarachnoid hemorrhage. *Stroke*, *43*(8), 2097–2101. doi: 10.1161/strokeaha.112.659888

Jakob, S. M., Ruokonen, E., Grounds, R. M., Sarapohja, T., Garratt, C., Pocock, S. J. (2012). Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA*, *307*(11), 1151–1160. doi: 10.1001/jama.2012.304

Johansson, J., Keller, S., Tuisku, J., & Teräs, M. (2016). *Performance of an image-based motion compensation algorithm for the hrrt: A striatum-phantom study with true motion*. 1–3. doi: 10.1109/nssmic.2016.8069586

Jong, H. W. A. M. de, Velden, F. H. P. van, Kloet, R. W., Buijs, F. L., Boellaard, R., & Lammertsma, A. A. (2007). Performance evaluation of the ECAT HRRT: an LSO-LYSO double layer high resolution, high sensitivity scanner. *Physics in Medicine and Biology*, *52*(5), 1505–1526. doi: 10.1088/0031-9155/52/5/019

Jung, H. S., Sung, T.-Y., Kang, H., Kim, J. S., & Kim, T.-Y. (2014). Cerebral blood flow change during volatile induction in large-dose sevoflurane versus intravenous propofol induction: transcranial Doppler study. *Korean Journal of Anesthesiology*, *67*(5), 323–328. doi: 10.4097/kjae.2014.67.5.323

Kadoi, Y., Kawauchi, C. H., Ide, M., Saito, S., & Mizutani, A. (2009). Differential Increases in Blood Flow Velocity in the Middle Cerebral Artery after Tourniquet Deflation during Sevoflurane,

Isoflurane or Propofol Anaesthesia. *Anaesthesia and Intensive Care*, *37*(4), 598–603. doi: 10.1177/0310057x0903700412

Kadoi, Yuji, Kawauchi, C., Saito, S., & Takahashi, K. (2009). The comparative effects of equipotent Bispectral Index dosages of propofol and sevoflurane on cerebrovascular carbon dioxide reactivity in elderly patients. *Journal of Clinical Anesthesia*, *21*(3), 173–177. doi: 10.1016/j.jclinane.2008.06.036

Kaisti, K. K., Långsjö, J. W., Aalto, S., Oikonen, V., Sipilä, H., Teräs, M., Scheinin, H. (2003). Effects of Sevoflurane, Propofol, and Adjunct Nitrous Oxide on Regional Cerebral Blood Flow, Oxygen Consumption, and Blood Volume in Humans. *Anesthesiology*, *99*(3), 603–613. doi: 10.1097/00000542-200309000-00015

Kaisti, K. K., Metsähonkala, L., Teräs, M., Oikonen, V., Aalto, S., Jääskeläinen, S., Scheinin, H. (2002). Effects of Surgical Levels of Propofol and Sevoflurane Anesthesia on Cerebral Blood Flow in Healthy Subjects Studied with Positron Emission Tomography. *Anesthesiology*, *96*(6), 1358–1370. doi: 10.1097/00000542-200206000-00015

Karlsson, B. R., Forsman, M., Roald, O. K., Heier, M. S., & Steen, P. A. (1990). Effect of dexmedetomidine, a selective and potent alpha 2-agonist, on cerebral blood flow and oxygen consumption during halothane anesthesia in dogs. *Anesthesia & Analgesia*, *71*(2), 125–129.

Kaskinoro, K., Maksimow, A., Långsjö, J., Aantaa, R., Jääskeläinen, S., Kaisti, K., Scheinin, H. (2011). Wide inter-individual variability of bispectral index and spectral entropy at loss of consciousness during increasing concentrations of dexmedetomidine, propofol, and sevoflurane. *BJA: British Journal of Anaesthesia*, *107*(4), 573–580. doi: 10.1093/bja/aer196

Kassell, N. F., Sasaki, T., Colohan, A. R., & Nazar, G. (1985). Cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *Stroke*, *16*(4), 562–572. doi: 10.1161/01.str.16.4.562

Kauppila, T., Kemppainen, P., Tanila, H., & Pertovaara, A. (1991). Effect of systemic medetomidine, an alpha 2 adrenoceptor agonist, on experimental pain in humans. *Anesthesiology: The Journal of the American Society of Anesthesiologists*, *74*(1), 3–8. doi: 10.1097/00000542-199101000-00002

Kawazoe, Y., Miyamoto, K., Morimoto, T., Yamamoto, T., Fuke, A., Hashimoto, A., Investigators, D. for S. in I. C. U. R. E. (DESIRE) T. (2017). Effect of Dexmedetomidine on Mortality and Ventilator-Free Days in Patients Requiring Mechanical Ventilation With Sepsis: A Randomized Clinical Trial. *JAMA*, *317*(13), 1321–1328. doi: 10.1001/jama.2017.2088

Khey, K. M. W., Huard, A., & Mahmoud, S. H. (2020). Inflammatory Pathways Following Subarachnoid Hemorrhage. *Cellular and Molecular Neurobiology*, *40*(5), 675–693. doi: 10.1007/s10571-019-00767-4

Kim, Y., Kang, S.-H., Hong, T.-H., Cho, M.-L., Han, H.-J., Kwon, S.-J., & Lee, J. (2014). Effects of dexmedetomidine on the ratio of T helper 1 to T helper 2 cytokines in patients undergoing laparoscopic cholecystectomy. *Journal of Clinical Anesthesia*, *26*(4), 281–285. doi: 10.1016/j.jclinane.2013.11.018

Kirkpatrick, P. J., Turner, C. L., Smith, C., Hutchinson, P. J., Murray, G. D., & Collaborators, for the S. (2014). Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial. *The Lancet Neurology*, *13*(7), 666–675. doi: 10.1016/s1474-4422(14)70084-5

Kolbitsch, C., Lorenz, I. H., Hörmann, C., Schocke, M., Kremser, C., Zschiegner, F., Benzer, A. (2000). A Subanesthetic Concentration of Sevoflurane Increases Regional Cerebral Blood Flow and Regional Cerebral Blood Volume and Decreases Regional Mean Transit Time and Regional Cerebrovascular Resistance in Volunteers. *Anesthesia & Analgesia*, *91*(1), 156–162. doi: 10.1213/00000539-200007000-00029

Lam, J. M. K., Smielewski, P., Czosnyka, M., Pickard, J. D., & Kirkpatrick, P. J. (2000). Predicting Delayed Ischemic Deficits after Aneurysmal Subarachnoid Hemorrhage Using a Transient Hyperemic Response Test of Cerebral Autoregulation. *Neurosurgery*, *47*(4), 819. doi: 10.1097/00006123-200010000-00004

Lam, J. M., Smielewski, P., Czosnyka, M., Pickard, J. D., & Kirkpatrick, P. J. (2000). Predicting delayed ischemic deficits after aneurysmal subarachnoid hemorrhage using a transient hyperemic response test of cerebral autoregulation. *Neurosurgery*, *47*(4), 819-25-discussions 825-6.

Lands, A. M., Arnold, A., McAuliff, J. P., Luduena, F. P., & Brown, T. G. (1967). Differentiation of receptor systems activated by sympathomimetic amines. *Nature*, *214*(5088), 597–598. doi: 10.1038/214597a0

Lang, E. W. (2002). Continuous monitoring of cerebrovascular autoregulation: a validation study. *Journal of Neurology, Neurosurgery & Psychiatry*, *72*(5), 583–586. doi: 10.1136/jnnp.72.5.583

Langsjo, J. W., Alkire, M. T., Kaskinoro, K., Hayama, H., Maksimow, A., Kaisti, K. K., Scheinin, H. (2012). Returning from Oblivion: Imaging the Neural Core of Consciousness. *Journal of Neuroscience*, *32*(14), 4935–4943. doi: 10.1523/jneurosci.4962-11.2012

Långsjö, J. W., Maksimow, A., Salmi, E., Kaisti, K., Aalto, S., Oikonen, V., Scheinin, H. (2005a). S-Ketamine Anesthesia Increases Cerebral Blood Flow in Excess of the Metabolic Needs in Humans. *Anesthesiology*, *103*(2), 258–268. doi: 10.1097/00000542-200508000-00008

Långsjö, J. W., Maksimow, A., Salmi, E., Kaisti, K., Aalto, S., Oikonen, V., Scheinin, H. (2005b). S-ketamine anesthesia increases cerebral blood flow in excess of the metabolic needs in humans. *Anesthesiology*, *103*(2), 258–268.

Lassen, N. A. (1959). Cerebral blood flow and oxygen consumption in man. *Physiological Reviews*, *39*(2), 183–238. doi: 10.1152/physrev.1959.39.2.183

Lassen, N. A., & Christensen, M. S. (1976). PHYSIOLOGY OF CEREBRAL BLOOD FLOW. *BJA: British Journal of Anaesthesia*, *48*(8), 719–734. doi: 10.1093/bja/48.8.719

Lavon, H., Matzner, P., Benbenishty, A., Sorski, L., Rossene, E., Haldar, R., Ben-Eliyahu, S. (2018). Dexmedetomidine promotes metastasis in rodent models of breast, lung, and colon cancers. *British Journal of Anaesthesia*, *120*(1), 188–196. doi: 10.1016/j.bja.2017.11.004

Lee, S. H., Choi, Y. S., Hong, G. R., & Oh, Y. J. (2015). Echocardiographic evaluation of the effects of dexmedetomidine on cardiac function during total intravenous anaesthesia. *Anaesthesia*, *70*(9), 1052–1059. doi: 10.1111/anae.13084

Li, R., Liu, H., Dilger, J. P., & Lin, J. (2018). Effect of Propofol on breast Cancer cell, the immune system, and patient outcome. *BMC Anesthesiology*, *18*(1), 77. doi: 10.1186/s12871-018-0543-3

Li, X., Yang, J., Nie, X.-L., Zhang, Y., Li, X.-Y., Li, L.-H., Ma, D. (2017). Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: A randomized controlled trial. *PloS One*, *12*(2), e0170757. doi: 10.1371/journal.pone.0170757

Lim, J.-A., Oh, C.-S., Yoon, T.-G., Lee, J. Y., Lee, S.-H., Yoo, Y.-B., Kim, S.-H. (2018). The effect of propofol and sevoflurane on cancer cell, natural killer cell, and cytotoxic T lymphocyte function in patients undergoing breast cancer surgery: an in vitro analysis. *BMC Cancer*, *18*(1), 159–8. doi: 10.1186/s12885-018-4064-8

Liu, D., Sun, X., Du, Y., & Kong, M. (2018). Propofol Promotes Activity and Tumor-Killing Ability of Natural Killer Cells in Peripheral Blood of Patients with Colon Cancer. *Medical Science Monitor : International Medical Journal of Experimental and Clinical Research*, *24*, 6119–6128. doi: 10.12659/msm.911218

Liu, H., Tariq, R., Liu, G., & Yu, L. (2017). Pharmacological Cerebral Protection in Cardiac Surgery: An Update. *Journal of Anesthesia and Perioperative Medicine*, *4*(1), 23–37. doi: 10.24015/japm.2017.0004

Lok, J., Gupta, P., Guo, S., Kim, W. J., Whalen, M. J., Leyen, K. van, & Lo, E. H. (2007). Cell-cell signaling in the neurovascular unit. *Neurochemical Research*, *32*(12), 2032–2045. doi: 10.1007/s11064-007-9342-9

Lord, J. M., Midwinter, M. J., Chen, Y.-F., Belli, A., Brohi, K., Kovacs, E. J., Lilford, R. J. (2014). The systemic immune response to trauma: an overview of pathophysiology and treatment. *The Lancet*, *384*(9952), 1455–1465. doi: 10.1016/s0140-6736(14)60687-5

Lorenz, I. H., Kolbitsch, C., Hörmann, C., Schocke, M., Felber, S., Zschiegner, F., Benzer, A. (2001). Subanesthetic Concentration of Sevoflurane Increases Regional Cerebral Blood Flow More, but

Regional Cerebral Blood Volume Less, than Subanesthetic Concentration of Isoflurane in Human Volunteers. *Journal of Neurosurgical Anesthesiology*, *13*(4), 288–295. doi: 10.1097/00008506-200110000-00002

Lublinsky, S., Major, S., Kola, V., Horst, V., Santos, E., Platz, J., Friedman, A. (2019). Early blood-brain barrier dysfunction predicts neurological outcome following aneurysmal subarachnoid hemorrhage. *EBioMedicine*, *43*, 460–472. doi: 10.1016/j.ebiom.2019.04.054

Lucke-Wold, B. P., Logsdon, A. F., Manoranjan, B., Turner, R. C., McConnell, E., Vates, G. E., Simard, J. M. (2016). Aneurysmal Subarachnoid Hemorrhage and Neuroinflammation: A Comprehensive Review. *International Journal of Molecular Sciences*, *17*(4), 497. doi: 10.3390/ijms17040497

Lundar, T., Lindegaard, K. F., Frøysaker, T., Aaslid, R., Grip, A., & Nornes, H. (1985). Dissociation between cerebral autoregulation and carbon dioxide reactivity during nonpulsatile cardiopulmonary bypass. *The Annals of Thoracic Surgery*, *40*(6), 582–587. doi: 10.1016/s0003-4975(10)60353-0

Lundorf, L. J., Nedergaard, H. K., & Møller, A. M. (2016). Perioperative dexmedetomidine for acute pain after abdominal surgery in adults. *Cochrane Database of Systematic Reviews*, *19*(2), 537. doi: 10.1002/14651858.cd010358.pub2

Ma, J., Chen, Q., Li, J., Zhao, H., Mi, E., Chen, Y., Gu, J. (2020). Dexmedetomidine-Mediated Prevention of Renal Ischemia-Reperfusion Injury Depends in Part on Cholinergic Anti-Inflammatory Mechanisms. *Anesthesia & Analgesia*, *130*(4), 1054–1062. doi: 10.1213/ane.0000000000003820

Macdonald, R. L., Pluta, R. M., & Zhang, J. H. (2007). Cerebral vasospasm after subarachnoid hemorrhage: the emerging revolution. *Nature Clinical Practice. Neurology*, *3*(5), 256–263. doi: 10.1038/ncpneuro0490

Mahajan, R. P., Cavill, G., & Simpson, E. J. (1998). Reliability of the Transient Hyperemic Response Test in Detecting Changes in Cerebral Autoregulation Induced by the Graded Variations in End-Tidal Carbon Dioxide. *Anesthesia & Analgesia*, *87*(4), 843–849. doi: 10.1097/00000539-199810000-00018

Manno, E. M., Gress, D. R., Schwamm, L. H., Diringer, M. N., & Ogilvy, C. S. (1998). Effects of Induced Hypertension on Transcranial Doppler Ultrasound Velocities in Patients After Subarachnoid Hemorrhage. *Stroke*, *29*(2), 422–428. doi: 10.1161/01.str.29.2.422

Marsh, B., White, M., Morton, N., & Kenny, G. N. (1991). Pharmacokinetic model driven infusion of propofol in children. *British Journal of Anaesthesia*, *67*(1), 41–48.

Matsota, P., Kostopanagiotou, G., Kalimeris, K., Pandazi, A., Kotsaki, A., Kontogiannopoulou, S., & Giamarellos-Bourboulis, E. J. (2018). Transient Effects of Anesthesia on Leukocyte Apoptosis and Monocyte Cytokine Stimulation: A Clinical Study. *Immunological Investigations*, *47*(4), 327–334. doi: 10.1080/08820139.2018.1435690

Matta, B. F., Heath, K. J., Tipping, K., & Summors, A. C. (1999). Direct Cerebral Vasodilatory Effects of Sevoflurane and Isoflurane. *Anesthesiology*, *91*(3), 677. doi: 10.1097/00000542-199909000-00019

Matta, B. F., Mayberg, T. S., & Lam, A. M. (1995). Direct Cerebrovasodilatory Effects of Halothane, Isoflurane, and Desflurane during Propofol-induced Isoelectric Electroencephalogram in Humans. *Anesthesiology*, *83*(5), 980-985. doi: 10.1097/00000542-199511000-00011

McConnell, E. D., Wei, H. S., Reitz, K. M., Kang, H., Takano, T., Vates, G. E., & Nedergaard, M. (2016). Cerebral microcirculatory failure after subarachnoid hemorrhage is reversed by hyaluronidase. *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *36*(9), 1537–1552. doi: 10.1177/0271678x15608389

Mees, S. D., Rinkel, G. J., Feigin, V. L., Algra, A., Bergh, W. M. van den, Vermeulen, M., & Gijn, J. van. (2007). Calcium antagonists for aneurysmal subarachnoid haemorrhage. *Cochrane Database of Systematic Reviews*, *308*(3), 619. doi: 10.1002/14651858.cd000277.pub3

Memiş, D., Hekimoğlu, S., Vatan, I., Yandim, T., Yüksel, M., & Süt, N. (2007). Effects of midazolam and dexmedetomidine on inflammatory responses and gastric intramucosal pH to sepsis, in critically ill patients. *British Journal of Anaesthesia*, *98*(4), 550–552. doi: 10.1093/bja/aem017

Mielck, F., Stephan, H., Weyland, A., & Sonntag, H. (1999). Effects of One Minimum Alveolar Anesthetic Concentration Sevoflurane on Cerebral Metabolism, Blood Flow, and CO2 Reactivity in Cardiac Patients. *Anesthesia & Analgesia*, *89*(2), 364. doi: 10.1213/00000539-199908000-00022

Mohite, S., Cordeiro, T., Tannous, J., Mwangi, B., Selvaraj, S., Soares, J. C., Teixeira, A. L. (2020). Eotaxin-1/CCL11 Correlates with Left Superior Temporal Gyrus in Bipolar Disorder: A Preliminary Report suggesting Accelerated Brain Aging. *Journal of Affective Disorders*, *273*, 592–596. doi: 10.1016/j.jad.2020.05.062

Molnár, C., Settakis, G., Sárkány, P., Kálmán, S., Szabó, S., & Fülesdi, B. (2007). Effect of sevoflurane on cerebral blood flow and cerebrovascular resistance at surgical level of anaesthesia: a transcranial Doppler study. *European Journal of Anaesthesiology*, *24*(2), 179–184. doi: 10.1017/s0265021506001335

Morelli, A., Sanfilippo, F., Arnemann, P., Hessler, M., Kampmeier, T. G., D'Egidio, A., Ertmer, C. (2019). The Effect of Propofol and Dexmedetomidine Sedation on Norepinephrine Requirements in Septic Shock Patients: A Crossover Trial. *Critical Care Medicine*, *47*(2), e89–e95. doi: 10.1097/ccm.0000000000003520

Muench, E., Bauhuf, C., Roth, H., Horn, P., Phillips, M., Marquetant, N., Vajkoczy, P. (2005). Effects of positive end-expiratory pressure on regional cerebral blood flow, intracranial pressure, and brain tissue oxygenation* *Critical Care Medicine*, *33*(10), 2367–2372. doi: 10.1097/01.ccm.0000181732.37319.df

Naqvi, J., Yap, K. H., Ahmad, G., & Ghosh, J. (2013). Transcranial Doppler Ultrasound: A Review of the Physical Principles and Major Applications in Critical Care. *International Journal of Vascular Medicine*, *2013*(6), 1–13. doi: 10.1155/2013/629378

Nguyen, V., Tiemann, D., Park, E., & Salehi, A. (2017). Alpha-2 Agonists. *Anesthesiology Clinics*, *35*(2), 233–245. doi: 10.1016/j.anclin.2017.01.009

Nieminen, A., Maksimow, M., Mentula, P., Kyhälä, L., Kylänpää, L., Puolakkainen, P., Salmi, M. (2014). Circulating cytokines in predicting development of severe acute pancreatitis. *Critical Care*, *18*(3), R104. doi: 10.1186/cc13885

Ning, Q., Liu, Z., Wang, X., Zhang, R., Zhang, J., Yang, M., Zhang, X. (2017). Neurodegenerative changes and neuroapoptosis induced by systemic lipopolysaccharide administration are reversed by dexmedetomidine treatment in mice. *Neurological Research*, *39*(4), 357–366. doi: 10.1080/01616412.2017.1281197

Nishiyama, T., Matsukawa, T., Yokoyama, T., & Hanaoka, K. (1999). Cerebrovascular Carbon Dioxide Reactivity During General Anesthesia: A Comparison Between Sevoflurane and Isoflurane. *Anesthesia & Analgesia*, *89*(6), 1437. doi: 10.1097/00000539-199912000-00021

Oddo, M., Crippa, I. A., Mehta, S., Menon, D., Payen, J.-F., Taccone, F. S., & Citerio, G. (2016). Optimizing sedation in patients with acute brain injury. *Critical Care*, *20*(1), 128. doi: 10.1186/s13054-016-1294-5

Ogawa, Y., Iwasaki, K., Aoki, K., Gokan, D., Hirose, N., Kato, J., & Ogawa, S. (2010). The different effects of midazolam and propofol sedation on dynamic cerebral autoregulation. *Anesthesia & Analgesia*, *111*(5), 1279–1284. doi: 10.1213/ane.0b013e3181f42fc0

Ogawa, Y., Iwasaki, K., Aoki, K., Kojima, W., Kato, J., & Ogawa, S. (2008). Dexmedetomidine weakens dynamic cerebral autoregulation as assessed by transfer function analysis and the thigh cuff method. *Anesthesiology*, *109*(4), 642–650. doi: 10.1097/aln.0b013e3181862a33

Ogawa, Y., Iwasaki, K., Shibata, S., Kato, J., Ogawa, S., & Oi, Y. (2006). The effect of sevoflurane on dynamic cerebral blood flow autoregulation assessed by spectral and transfer function analysis. *Anesthesia & Analgesia*, *102*(2), 552–559. doi: 10.1213/01.ane.0000189056.96273.48

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. *Critical Care*, *24*(1), 493–498. doi: 10.1186/s13054-020-03207-8

Oppenheim, J. J., & Yang, D. (2005). Alarmins: chemotactic activators of immune responses. *Current Opinion in Immunology*, *17*(4), 359–365. doi: 10.1016/j.coi.2005.06.002

Oshima, T., Karasawa, F., Okazaki, Y., Wada, H., & Satoh, T. (2003). Effects of sevoflurane on cerebral blood flow and cerebral metabolic rate of oxygen in human beings: a comparison with isoflurane. *European Journal of Anaesthesiology*, *20*(7), 543–547. doi: 10.1097/00003643-200307000-00005

Otite, F., Mink, S., Tan, C. O., Puri, A., Zamani, A. A., Mehregan, A., … Sorond, F. A. (2014). Impaired cerebral autoregulation is associated with vasospasm and delayed cerebral ischemia in subarachnoid hemorrhage. *Stroke*, *45*(3), 677–682. doi: 10.1161/strokeaha.113.002630

Owusu, K. A., Kurczewski, L., Armahizer, M. J., Zichichi, A., Maciel, C. B., & Heavner, M. S. (2020). DEXmedetomidine compared to PROpofol in NEurocritical Care [DEXPRONE]: A multicenter retrospective evaluation of clinical utility and safety. *Journal of Critical Care*, *60*, 79–83. doi: 10.1016/j.jcrc.2020.07.021

Page, V., & McKenzie, C. (2021). Sedation in the Intensive Care Unit. *Current Anesthesiology Reports*, *11*(2), 92–100. doi: 10.1007/s40140-021-00446-5

Pan, Y., Wan, W., Xiang, M., & Guan, Y. (2022). Transcranial Doppler Ultrasonography as a Diagnostic Tool for Cerebrovascular Disorders. *Frontiers in Human Neuroscience*, *16*, 841809. doi: 10.3389/fnhum.2022.841809

Pandharipande, P. P., Sanders, R. D., Girard, T. D., McGrane, S., Thompson, J. L., Shintani, A. K.(2010). Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an a priori-designed analysis of the MENDS randomized controlled trial. *Critical Care*, *14*(2), R38. doi: 10.1186/cc8916

Panerai, R. B. (2009). Transcranial Doppler for evaluation of cerebral autoregulation. *Clinical Autonomic Research*, *19*(4), 197–211. doi: 10.1007/s10286-009-0011-8

Paulson, O. B., Strandgaard, S., & Edvinsson, L. (1990). Cerebral autoregulation. *Cerebrovascular and Brain Metabolism Reviews*, *2*(2), 161–192.

Phelps, M. E., Huang, S. C., Hoffman, E. J., Selin, C., Sokoloff, L., & Kuhl, D. E. (1979). Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: validation of method. *Annals of Neurology*, *6*(5), 371–388. doi: 10.1002/ana.410060502

Phillips, A. A., Chan, F. H., Zheng, M. M. Z., Krassioukov, A. V., & Ainslie, P. N. (2016). Neurovascular coupling in humans: Physiology, methodological advances and clinical implications. *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *36*(4), 647–664. doi: 10.1177/0271678x15617954

Pickard, J. D., Nelson, R. J., Lovick, A. H. J., Coull, R. W. B., Stanley, J. C., Read, D. H., Campbell, M. (1992). *Stimulated Cerebral Blood Flow, Experimental Findings and Clinical Significance*. 220–225. doi: 10.1007/978-3-642-77102-6_23

Pickard, John D, Matheson, M., Patterson, J., & Wyper, D. (1980). Prediction of late ischemic complications after cerebral aneurysm surgery by the intraoperative measurement of cerebral blood flow. *Journal of Neurosurgery*, *53*(3), 305–308. doi: 10.3171/jns.1980.53.3.0305

Prielipp, R. C., Wall, M. H., Tobin, J. R., Groban, L., Cannon, M. A., Fahey, F. H., Butterworth, J. (2002). Dexmedetomidine-induced sedation in volunteers decreases regional and global cerebral blood flow. *Anesthesia & Analgesia*, *95*(4), 1052-9-table of contents.

Purkayastha, S., & Sorond, F. (2012). Transcranial Doppler Ultrasound: Technique and Application. *Seminars in Neurology*, *32*(04), 411–420. doi: 10.1055/s-0032-1331812

Rabinstein, A. A., Friedman, J. A., Weigand, S. D., McClelland, R. L., Fulgham, J. R., Manno, E. M., Wijdicks, E. F. M. (2004). Predictors of cerebral infarction in aneurysmal subarachnoid hemorrhage. *Stroke*, *35*(8), 1862–1866. doi: 10.1161/01.str.0000133132.76983.8e

Raemdonck, K. V., Steen, P. E. V. den, Liekens, S., Damme, J. V., & Struyf, S. (2015). CXCR3 ligands in disease and therapy. *Cytokine & Growth Factor Reviews*, *26*(3), 311–327. doi: 10.1016/j.cytogfr.2014.11.009

Rasulo, F. A., Peri, E. D., & Lavinio, A. (2008). Transcranial Doppler ultrasonography in intensive care. *European Journal of Anaesthesiology*, *25*(Supplement 42), 167–173. doi: 10.1017/s0265021507003341

Rätsep, T., & Asser, T. (2001). Cerebral hemodynamic impairment after aneurysmal subarachnoid hemorrhage as evaluated using transcranial doppler ultrasonography: relationship to delayed cerebral ischemia and clinical outcome. *Journal of Neurosurgery*, *95*(3), 393–401. doi: 10.3171/jns.2001.95.3.0393

Riker, R. R., Shehabi, Y., Bokesch, P. M., Ceraso, D., Wisemandle, W., Koura, F. (2009). Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA*, *301*(5), 489–499. doi: 10.1001/jama.2009.56

Rooij, N. K. de, Linn, F. H. H., Plas, J. A. van der, Algra, A., & Rinkel, G. J. E. (2007). Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. *Journal of Neurology, Neurosurgery & Psychiatry*, *78*(12), 1365–1372. doi: 10.1136/jnnp.2007.117655

Rossaint, J., & Zarbock, A. (2019). Anesthesia-induced immune modulation. *Current Opinion in Anaesthesiology*, *32*(6), 799–805. doi: 10.1097/aco.0000000000000790

Rostrup, E., Knudsen, G. M., Law, I., Holm, S., Larsson, H. B. W., & Paulson, O. B. (2005). The relationship between cerebral blood flow and volume in humans. *NeuroImage*, *24*(1), 1–11. doi: 10.1016/j.neuroimage.2004.09.043

Rothenberg, M. E., & Hogan, S. P. (2006). The eosinophil. *Annual Review of Immunology*, *24*, 147–174. doi: 10.1146/annurev.immunol.24.021605.090720

Roux, A. A. le, & Wallace, M. C. (2010). Outcome and cost of aneurysmal subarachnoid hemorrhage. *Neurosurgery Clinics of North America*, *21*(2), 235–246. doi: 10.1016/j.nec.2009.10.014

Rowland, M. J., Hadjipavlou, G., Kelly, M., Westbrook, J., & Pattinson, K. T. S. (2012). Delayed cerebral ischaemia after subarachnoid haemorrhage: looking beyond vasospasm. *British Journal of Anaesthesia*, *109*(3), 315–329. doi: 10.1093/bja/aes264

Rynkowski, C. B., Manoel, A. L. de O., Reis, M. M. dos, Puppo, C., Worm, P. V., Zambonin, D., & Bianchin, M. M. (2019). Early Transcranial Doppler Evaluation of Cerebral Autoregulation Independently Predicts Functional Outcome After Aneurysmal Subarachnoid Hemorrhage. *Neurocritical Care*, *31*(2), 253–262. doi: 10.1007/s12028-019-00732-5

Sahinovic, M. M., Struys, M. M. R. F., & Absalom, A. R. (2018). Clinical Pharmacokinetics and Pharmacodynamics of Propofol. *Clinical Pharmacokinetics*, *57*(12), 1539–1558. doi: 10.1007/s40262-018-0672-3

Satterthwaite, T. D., Shinohara, R. T., Wolf, D. H., Hopson, R. D., Elliott, M. A., Vandekar, S. N., Gur, R. E. (2014). Impact of puberty on the evolution of cerebral perfusion during adolescence. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(23), 8643–8648. doi: 10.1073/pnas.1400178111

Scheinin, A. (2022). *Probing the (Un)Conscious Brain : EEG and PET Studies on Healthy Human Subjects Using Propofol, Dexmedetomidine and Natural Sleep*. University of Turku.

Scheinin, A., Kantonen, O., Alkire, M., Långsjö, J., Kallionpää, R. E., Kaisti, K., Scheinin, H. (2021). Foundations of Human Consciousness: Imaging the Twilight Zone. *The Journal of Neuroscience*, *41*(8), 1769–1778. doi: 10.1523/jneurosci.0775-20.2020

Schlünzen, L., Cold, G. E., Rasmussen, M., & Vafaee, M. S. (2006). Effects of dose-dependent levels of isoflurane on cerebral blood flow in healthy subjects studied using positron emission

tomography. *Acta Anaesthesiologica Scandinavica*, *50*(3), 306–312. doi: 10.1111/j.1399-6576.2006.00954.x

Schlünzen, L., Juul, N., Hansen, K. V., & Cold, G. E. (2012). Regional cerebral blood flow and glucose metabolism during propofol anaesthesia in healthy subjects studied with positron emission tomography. *Acta Anaesthesiologica Scandinavica*, *56*(2), 248–255. doi: 10.1111/j.1399-6576.2011.02561.x

Schlünzen, L., Vafaee, M. S., Cold, G. E., Rasmussen, M., Nielsen, J. F., & Gjedde, A. (2004). Effects of subanaesthetic and anaesthetic doses of sevoflurane on regional cerebral blood flow in healthy volunteers. A positron emission tomographic study. *Acta Anaesthesiologica Scandinavica*, *48*(10), 1268–1276. doi: 10.1111/j.1399-6576.2004.00505.x

Schmittner, M. D., Vajkoczy, S. L., Horn, P., Bertsch, T., Quintel, M., Vajkoczy, P., & Muench, E. (2007). Effects of Fentanyl and S(+)-ketamine on Cerebral Hemodynamics, Gastrointestinal Motility, and Need of Vasopressors in Patients With Intracranial Pathologies. *Journal of Neurosurgical Anesthesiology*, *19*(4), 257–262. doi: 10.1097/ana.0b013e31811f3feb

Schneemilch, C. E., Ittenson, A., Ansorge, S., Hachenberg, T., & Bank, U. (2005). Effect of 2 anesthetic techniques on the postoperative proinflammatory and anti-inflammatory cytokine response and cellular immune function to minor surgery. *Journal of Clinical Anesthesia*, *17*(7), 517–527. doi: 10.1016/j.jclinane.2004.12.017

Schneemilch, C. E., Schilling, T., & Bank, U. (2004). Effects of general anaesthesia on inflammation. *Best Practice & Research. Clinical Anaesthesiology*, *18*(3), 493–507. doi: 10.1016/j.bpa.2004.01.002

Segal, I. S., Vickery, R. G., Walton, J. K. (1988). Dexmedetomidine Diminishes Halothane Anesthetic Requirements in Rats Through a Postsynaptic Alpha2 Adrenergic Receptor. *Anesthesiology*, *69*(6), 818–823.

Sekandarzad, M. W., Zundert, A. A. J. van, Lirk, P. B., Doornebal, C. W., & Hollmann, M. W. (2017). Perioperative Anesthesia Care and Tumor Progression. *Anesthesia & Analgesia*, *124*(5), 1697–1708. doi: 10.1213/ane.0000000000001652

Shafer, S. L., Siegel, L. C., Cooke, J. E., & Scott, J. C. (1988). Testing computer-controlled infusion pumps by simulation. *Anesthesiology*, *68*(2), 261–266.

Shakhar, G., & Ben-Eliyahu, S. (1998). In vivo beta-adrenergic stimulation suppresses natural killer activity and compromises resistance to tumor metastasis in rats. *Journal of Immunology (Baltimore, Md. : 1950)*, *160*(7), 3251–3258.

Sharma, D. (2020). Perioperative Management of Aneurysmal Subarachnoid Hemorrhage. *Anesthesiology*, *133*(6), 1283–1305. doi: 10.1097/aln.0000000000003558

Shehabi, Y., Howe, B. D., Bellomo, R., Arabi, Y. M., Bailey, M., Bass, F. E.(2019). Early Sedation with Dexmedetomidine in Critically Ill Patients. *The New England Journal of Medicine*. doi: 10.1056/nejmoa1904710

Shehabi, Y., Neto, A. S., Howe, B. D., Bellomo, R., Arabi, Y. M., Bailey, M., Skelly, C. (2021). Early sedation with dexmedetomidine in ventilated critically ill patients and heterogeneity of treatment effect in the SPICE III randomised controlled trial. *Intensive Care Medicine*, *47*(4), 455–466. doi: 10.1007/s00134-021-06356-8

Silverman, A., Kodali, S., Strander, S., Gilmore, E. J., Kimmel, A., Wang, A., Petersen, N. H. (2019). Deviation From Personalized Blood Pressure Targets Is Associated With Worse Outcome After Subarachnoid Hemorrhage. *Stroke*, *50*(10), 2729–2737. doi: 10.1161/strokeaha.119.026282

Singer, R. J., Ogilvy, C. S., & Rordorf, G. (2021, September 7). UpToDate SAH grading scales. Retrieved October 14, 2022, from Subarachnoid hemorrhage grading scales website: https://www.uptodate.com/contents/subarachnoid-hemorrhage-grading-scales?search=sah%20grading%20system&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

Smielewski, P., Czosnyka, M., Kirkpatrick, P., & Pickard, J. D. (1997). Evaluation of the transient hyperemic response test in head-injured patients. *Journal of Neurosurgery*, *86*(5), 773–778. doi: 10.3171/jns.1997.86.5.0773

Soehle, M., Czosnyka, M., Pickard, J. D., & Kirkpatrick, P. J. (2004a). Continuous assessment of cerebral autoregulation in subarachnoid hemorrhage. *Anesthesia & Analgesia*, *98*(4), 1133-9-table of contents.

Soehle, M., Czosnyka, M., Pickard, J. D., & Kirkpatrick, P. J. (2004b). Continuous Assessment of Cerebral Autoregulation in Subarachnoid Hemorrhage. *Anesthesia & Analgesia*, *98*(4), 1133–1139. doi: 10.1213/01.ane.0000111101.41190.99

Sofra, M., Fei, P. C., Fabrizi, L., Marcelli, M. E., Claroni, C., Gallucci, M., Forastiere, E. (2013). Immunomodulatory effects of total intravenous and balanced inhalation anesthesia in patients with bladder cancer undergoing elective radical cystectomy: preliminary results. *Journal of Experimental & Clinical Cancer Research : CR*, *32*(1), 6. doi: 10.1186/1756-9966-32-6

Sriram, S., Cutler, C., Azab, M., Reddy, R., Peart, R., & Lucke-Wold, B. (2022). Neuroinflammation and subarachnoid hemorrhage: a revised look at the literature. *Clinical Research Communications*, *5*(3), 14. doi: 10.53388/crc20220014

Stanpump software. (2021, October 21). Retrieved October 21, 2021, from Stanpump software website: www.opentci.org/code/stanpump

Steiner, L. A., Coles, J. P., Johnston, A. J., Chatfield, D. A., Smielewski, P., Fryer, T. D., Czosnyka, M. (2003). Assessment of Cerebrovascular Autoregulation in Head-Injured Patients. *Stroke*, *34*(10), 2404–2409. doi: 10.1161/01.str.0000089014.59668.04

Steiner, L. A., Johnston, A. J., Chatfield, D. A., Czosnyka, M., Coleman, M. R., Coles, J. P., Menon, D. K. (2003). The effects of large-dose propofol on cerebrovascular pressure autoregulation in head-injured patients. *Anesthesia & Analgesia*, *97*(2), 572-6-table of contents. doi: 10.1213/01.ane.0000070234.17226.b0

Strebel, S, Lam, A. M., Matta, B., Mayberg, T. S., Aaslid, R., & Newell, D. W. (1995). Dynamic and static cerebral autoregulation during isoflurane, desflurane, and propofol anesthesia. *Anesthesiology*, *83*(1), 66–76.

Strebel, Stephan, Lam, A., Matta, B., Mayberg, T. S., Aaslid, R., & Newell, D. W. (1995). Dynamic and Static Cerebral Autoregulation during Isoflurane, Desflurane, and Propofol Anesthesia. *Anesthesiology*, *83*(1), 66-76. doi: 10.1097/00000542-199507000-00008

Su, X., Meng, Z.-T., Wu, X.-H., Cui, F., Li, H.-L., Wang, D.-X., Ma, D. (2016). Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet (London, England)*, *388*(10054), 1893–1902. doi: 10.1016/s0140-6736(16)30580-3

Talke, P., Lobo, E., & Brown, R. (2003). Systemically administered alpha2-agonist-induced peripheral vasoconstriction in humans. *Anesthesiology*, *99*(1), 65–70.

Tasdogan, M., Memis, D., Sut, N., & Yuksel, M. (2009). Results of a pilot study on the effects of propofol and dexmedetomidine on inflammatory responses and intraabdominal pressure in severe sepsis. *Journal of Clinical Anesthesia*, *21*(6), 394–400. doi: 10.1016/j.jclinane.2008.10.010

Tenjin, H., Hirakawa, K., Mizukawa, N., Yano, I., Ohta, T., Uchibori, M., & Hino, A. (1988). Dysautoregulation in Patients with Ruptured Aneurysms: Cerebral Blood Flow Measurements Obtained during Surgery by a Temperature-controlled Thermoelectrical Method. *Neurosurgery*, *23*(6), 705–709. doi: 10.1227/00006123-198812000-00003

Thorup, L., Koch, K. U., Upton, R. N., Østergaard, L., & Rasmussen, M. (2019). Effects of Vasopressors on Cerebral Circulation and Oxygenation: A Narrative Review of Pharmacodynamics in Health and Traumatic Brain Injury. *Journal of Neurosurgical Anesthesiology*, *32*(1), 18–28. doi: 10.1097/ana.0000000000000596

Tibble, R. K., Girling, K. J., & Mahajan, R. P. (2001). A comparison of the transient hyperemic response test and the static autoregulation test to assess graded impairment in cerebral

autoregulation during propofol, desflurane, and nitrous oxide anesthesia. *Anesthesia & Analgesia*, *93*(1), 171–176. doi: 10.1097/00000539-200107000-00034

Tiecks, F. P., Lam, A. M., Aaslid, R., & Newell, D. W. (1995). Comparison of static and dynamic cerebral autoregulation measurements. *Stroke*, *26*(6), 1014–1019. doi: 10.1161/01.str.26.6.1014

Tsaousi, G. G., Lamperti, M., & Bilotta, F. (2016). Role of Dexmedetomidine for Sedation in Neurocritical Care Patients. *Clinical Neuropharmacology*, *39*(3), 144–151. doi: 10.1097/wnf.0000000000000151

Tseng, M.-Y., Czosnyka, M., Richards, H., Pickard, J. D., & Kirkpatrick, P. J. (2005). Effects of acute treatment with pravastatin on cerebral vasospasm, autoregulation, and delayed ischemic deficits after aneurysmal subarachnoid hemorrhage: a phase II randomized placebo-controlled trial. *Stroke*, *36*(8), 1627–1632. doi: 10.1161/01.str.0000176743.67564.5d

Tseng, M.-Y., Czosnyka, M., Richards, H., Pickard, J. D., & Kirkpatrick, P. J. (2006). Effects of acute treatment with statins on cerebral autoregulation in patients after aneurysmal subarachnoid hemorrhage. *Neurosurgical Focus*, *21*(3), 1–6. doi: 10.3171/foc.2006.21.3.10

Tseng, M.-Y., Hutchinson, P. J., Richards, H. K., Czosnyka, M., Pickard, J. D., Erber, W. N., Kirkpatrick, P. J. (2009). Acute systemic erythropoietin therapy to reduce delayed ischemic deficits following aneurysmal subarachnoid hemorrhage: a Phase II randomized, double-blind, placebo-controlled trial: Clinical article. *Journal of Neurosurgery*, *111*(1), 171–180. doi: 10.3171/2009.3.jns081332

Velly, L., & Bruder, N. (2018). *Cerebral Metabolism and Function*. In *Metabolic Disorders and Critically Ill Patients*: *Vol. 325* (pp. 285–300). doi: 10.1007/978-3-319-64010-5_12

Venn, R. M., & Grounds, R. M. (2001). Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. *British Journal of Anaesthesia*, *87*(5), 684–690. doi: 10.1093/bja/87.5.684

Venn, R. M., Hell, J., & Grounds, R. M. (2000). Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. *Critical Care*, *4*(5), 302–308. doi: 10.1186/cc712

Venn, R. M., Karol, M. D., & Grounds, R. M. (2002). Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive caret. *BJA: British Journal of Anaesthesia*, *88*(5), 669–675. doi: 10.1093/bja/88.5.669

Verbree, J., Bronzwaer, A., Buchem, M. A. van, Daemen, M., Lieshout, J. J. van, & Osch, M. van. (2017). Middle cerebral artery diameter changes during rhythmic handgrip exercise in humans. *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *37*(8), 2921–2927. doi: 10.1177/0271678x16679419

Villa, F., Iacca, C., Molinari, A. F., Giussani, C., Aletti, G., Pesenti, A., & Citerio, G. (2012). Inhalation versus endovenous sedation in subarachnoid hemorrhage patients. *Critical Care Medicine*, *40*(10), 2797–2804. doi: 10.1097/ccm.0b013e31825b8bc6

Villeda, S. A., Luo, J., Mosher, K. I., Zou, B., Britschgi, M., Bieri, G., Wyss-Coray, T. (2011). The ageing systemic milieu negatively regulates neurogenesis and cognitive function. *Nature*, *477*(7362), 90–94. doi: 10.1038/nature10357

Virtanen, R., Savola, J. M., Saano, V., & Nyman, L. (1988). Characterization of the selectivity, specificity and potency of medetomidine as an alpha 2-adrenoceptor agonist. *European Journal of Pharmacology*, *150*(1–2), 9–14. doi: 10.1016/0014-2999(88)90744-3

Vlak, M. H., Algra, A., Brandenburg, R., & Rinkel, G. J. (2011). Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. *The Lancet. Neurology*, *10*(7), 626–636. doi: 10.1016/s1474-4422(11)70109-0

Voldby, B., Enevoldsen, E. M., & Jensen, F. T. (1985). Cerebrovascular reactivity in patients with ruptured intracranial aneurysms. *Journal of Neurosurgery*, *62*(1), 59–67. doi: 10.3171/jns.1985.62.1.0059

Wang, K., Wu, M., Xu, J., Wu, C., Zhang, B., Wang, G., & Ma, D. (2019). Effects of dexmedetomidine on perioperative stress, inflammation, and immune function: systematic review and meta-analysis. *British Journal of Anaesthesia*, *123*(6), 777–794. doi: 10.1016/j.bja.2019.07.027

Wang, Xian-wang, Cao, J., Lv, B., Mi, W., Wang, Z., Zhang, C., Xu, Z. (2015). Effect of perioperative dexmedetomidine on the endocrine modulators of stress response: a meta-analysis. *Clinical and Experimental Pharmacology & Physiology*, *42*(8), 828–836. doi: 10.1111/1440-1681.12431

Wang, Xuemin, Ji, J., Fen, L., & Wang, A. (2013). Effects of dexmedetomidine on cerebral blood flow in critically ill patients with or without traumatic brain injury: a prospective controlled trial. *Brain Injury*, *27*(13–14), 1617–1622. doi: 10.3109/02699052.2013.831130

Weerink, M. A. S., Struys, M. M. R. F., Hannivoort, L. N., Barends, C. R. M., Absalom, A. R., & Colin, P. (2017). Clinical Pharmacokinetics and Pharmacodynamics of Dexmedetomidine. *Clinical Pharmacokinetics*, *56*(8), 893–913. doi: 10.1007/s40262-017-0507-7

Weiland, J., Beez, A., Westermaier, T., Kunze, E., Sirén, A.-L., & Lilla, N. (2021). Neuroprotective Strategies in Aneurysmal Subarachnoid Hemorrhage (aSAH). *International Journal of Molecular Sciences*, *22*(11), 5442. doi: 10.3390/ijms22115442

Weiss, M., Albanna, W., Conzen, C., Megjhani, M., Tas, J., Seyfried, K., … Schubert, G. A. (2022). Optimal Cerebral Perfusion Pressure During Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage. *Critical Care Medicine*, *50*(2), 183–191. doi: 10.1097/ccm.0000000000005396

Welden, B., Gates, G., Mallari, R., & Garrett, N. (2009). Effects of anesthetics and analgesics on natural killer cell activity. *AANA Journal*, *77*(4), 287–292.

Wiebers, D. O., Whisnant, J. P., Huston, J., Meissner, I., Brown, R. D., Piepgras, D. G.(2003). Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet (London, England)*, *362*(9378), 103–110. doi: 10.1016/s0140-6736(03)13860-3

Wienhard, K. (2002). Measurement of glucose consumption using [(18)F]fluorodeoxyglucose. *Methods (San Diego, Calif.)*, *27*(3), 218–225. doi: 10.2337/diab.18.7.467

Wigmore, T. J., Mohammed, K., & Jhanji, S. (2016). Long-term Survival for Patients Undergoing Volatile versus IV Anesthesia for Cancer Surgery: A Retrospective Analysis. *Anesthesiology*, *124*(1), 69–79. doi: 10.1097/aln.0000000000000936

Wu, H.-M., Bergsneider, M., Glenn, T. C., Yeh, E., Hovda, D. A., Phelps, M. E., & Huang, S.-C. (2003). Measurement of the global lumped constant for 2-deoxy-2-[18F]fluoro-D-glucose in normal human brain using [15O]water and 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography imaging. A method with validation based on multiple methodologies. *Molecular Imaging and Biology : MIB : The Official Publication of the Academy of Molecular Imaging*, *5*(1), 32–41.

Wu, Y., Liu, Y., Huang, H., Zhu, Y., Zhang, Y., Lu, F., Zhou, C. (2013). Dexmedetomidine inhibits inflammatory reaction in lung tissues of septic rats by suppressing TLR4/NF-κB pathway. *Mediators of Inflammation*, *2013*, 562154. doi: 10.1155/2013/562154

Xiang, H., Hu, B., Li, Z., & Li, J. (2014). Dexmedetomidine controls systemic cytokine levels through the cholinergic anti-inflammatory pathway. *Inflammation*, *37*(5), 1763–1770. doi: 10.1007/s10753-014-9906-1

Xu, J., Dong, H., Qian, Q., Zhang, X., Wang, Y., Jin, W., & Qian, Y. (2017). Astrocyte-derived CCL2 participates in surgery-induced cognitive dysfunction and neuroinflammation via evoking microglia activation. *Behavioural Brain Research*, *332*, 145–153. doi: 10.1016/j.bbr.2017.05.066

Yang, X.-H., Bai, Q., Lv, M.-M., Fu, H.-G., Dong, T.-L., & Zhou, Z. (2017). Effect of dexmedetomidine on immune function of patients undergoing radical mastectomy: a double blind and placebo control study. *European Review for Medical and Pharmacological Sciences*, *21*(5), 1112–1116.

Yuki, K., & Eckenhoff, R. G. (2016). Mechanisms of the Immunological Effects of Volatile Anesthetics: A Review. *Anesthesia & Analgesia*, *123*(2), 326–335. doi: 10.1213/ane.0000000000001403

Zamani, M. M., Keshavarz-Fathi, M., Fakhri-Bafghi, M. S., Hirbod-Mobarakeh, A., Rezaei, N., Bahrami, A., & Nader, N. D. (2016). Survival benefits of dexmedetomidine used for sedating

septic patients in intensive care setting: A systematic review. *Journal of Critical Care*, *32*, 93–100. doi: 10.1016/j.jcrc.2015.11.013

Zhou, C., Zhu, Y., Liu, Z., & Ruan, L. (2016). Effect of dexmedetomidine on postoperative cognitive dysfunction in elderly patients after general anaesthesia: A meta-analysis. *The Journal of International Medical Research*, *44*(6), 1182–1190. doi: 10.1177/0300060516671623

Zhou, H., Lu, J., Shen, Y., Kang, S., & Zong, Y. (2017). Effects of dexmedetomidine on CD42a(+)/CD14(+), HLADR(+)/CD14(+) and inflammatory cytokine levels in patients undergoing multilevel spinal fusion. *Clinical Neurology and Neurosurgery*, *160*, 54–58. doi: 10.1016/j.clineuro.2017.06.012

Zhu, Y.-J., Peng, K., Meng, X.-W., & Ji, F.-H. (2016). Attenuation of neuroinflammation by dexmedetomidine is associated with activation of a cholinergic anti-inflammatory pathway in a rat tibial fracture model. *Brain Research*, *1644*(1), 1–8. doi: 10.1016/j.brainres.2016.04.074

Zornow, M. H., Fleischer, J. E., Scheller, M. S., Nakakimura, K., & Drummond, J. C. (1990). Dexmedetomidine, an alpha 2-adrenergic agonist, decreases cerebral blood flow in the isoflurane-anesthetized dog. *Anesthesia & Analgesia*, *70*(6), 624–630.

Zornow, M. H., Maze, M., Dyck, J. B., & Shafer, S. L. (1993). Dexmedetomidine decreases cerebral blood flow velocity in humans. *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *13*(2), 350–353. doi: 10.1038/jcbfm.1993.45

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