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Sedation with volatile anesthetics in cardiothoracic intensive care unit patients

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ABSTRACT

Volatile anaesthetics have been reported to provide protection against myocardial ischemia and reperfusion injury. This effect has been demonstrated in experimental studies when the volatile anaesthetics were provided either before (preconditioning) or after the ischemic period (postconditioning). Clinical trials of volatile anaesthetics versus intravenous anaesthesia for coronary artery bypass grafting (CABG) have reported reduced postoperative release of troponin, a biomarker of myocardial necrosis. The most pronounced reduction was achieved when sevoflurane was administered throughout surgery. Hence, it could be of interest to investigate whether additional myocardial protection could be achieved in cardiothoracic intensive care unit (ICU) patients following CABG by prolonging administration of volatile anaesthetics to include the period of routine postoperative sedation. The AnaConDa® is an anaesthetic conserving device that enables sedation with isoflurane or sevoflurane with common ICU ventilators. This method has been demonstrated to be feasible for sedation during mechanical ventilation in the general ICU. Isoflurane has also been used clinically to provide inhaled sedation during therapeutic hypothermia following cardiac arrest, but there are no evaluations or publications of this treatment. The AnaConDa® requires scavenging of volatile anaesthetics in expired breathing air. The use of an adsorbing canister with the filtered air released in the ICU room has not been well described.

The aim of this thesis was to investigate clinical and occupational aspects of inhaled sedation with volatile anaesthetics in cardiothoracic ICU patients.

We conducted a randomized clinical trial of short-term sevoflurane sedation versus propofol following CABG. While no significant differences were found in cardiac adverse events or troponin-T values sampled 12 hours following surgery, a reduced change from pre- to postoperative troponin-T values was demonstrated in a post-hoc analysis. Wake-up times were shorter in the sevoflurane-sedated group, but did not affect ICU or hospital stay in our short-term sedation. While sevoflurane-sedated patients were able to follow verbal command earlier, memories assessed with the validated ICU-Memory Tool were similar after sedation. In a retrospective study of isoflurane sedation during therapeutic hypothermia following cardiac arrest, it appeared that the early neurologic assessment with the Glasgow Coma Scale performed within 24 hours from reaching normal body temperature was consistent with the conventional assessment following 72 hours. We conducted an observational study of occupational exposure to sevoflurane during its use to provide sedation in the ICU and demonstrated that passive scavenging with an adsorbing canister (CONTRAfluran™) provided minimal exposure to sevoflurane compared to no scavenging. Nurses in both groups had exposures below the Swedish occupational exposure limit, but only nurses working with patients without scavenging reported adverse symptoms. Smell of sevoflurane was the most frequent adverse symptom.

Keywords: sevoflurane, sedation, myocardial protection, postconditioning, occupational exposure, therapeutic hypothermia,

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their Roman numerals as indicated below:

I Hellström J, Öwall A, Bergström J, Sackey V P.
Cardiac outcome after sevoflurane versus propofol sedation following coronary bypass surgery: A pilot study.
Acta Anaesthesiologica Scandinavica 2011; 55:460–467

II Hellström J, Öwall A, Sackey V P.
Wake-up times following sedation with sevoflurane versus propofol after cardiac surgery.
Scandinavian Cardiovascular Journal 2012; 46:262-268

III Hellström J, Martling C-R, Öwall A, Sackey V P.
Inhaled isoflurane sedation during therapeutic hypothermia after cardiac arrest: A Case Series.
Critical Care Medicine 2013; 18 October, [e-pub ahead of print]

IV Hellström J, Öwall A, Lewné M, Sackey V P. (2013)
Ambient sevoflurane concentration during inhaled sedation in the Intensive Care Unit.
Manuscript submitted for publication

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LIST OF ABBREVIATIONS

AST	Aspartate transaminase
ALP	Alkaline phosphates
ATP	Adenosine triphosphate
CABG	Coronary artery bypass grafting
CK-MB	Creatinine kinase isoenzyme MB (muscle brain)
CPB	Cardiopulmonary bypass
CRP	C-reactive protein
ECG	Electrocardiogram
ICU	Intensive care unit
LDH	Lactate dehydrogenase
NIOSH	National Institute of Safety and Health (in the United Sates)
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
MRI	Magnetic resonance imaging
PCI	Percutaneous coronary intervention
ppm	Parts per million
OEL	Occupational exposure limit

INTRODUCTION

MYOCARDIAL ISCHEMIA AND REPERFUSION INJURY

Interruption of coronary blood flow results in ischemia and causes both reversible and irreversible myocardial injury depending on the duration of ischemia and the collateral blood flow[1]. Loss of contractility may be reversible[2]. Changes in myocardial electrophysiology may cause potentially life-threatening arrhythmias[3]. The irreversible cell injury is mediated via multiple pathways and mechanisms that ultimately lead to the death of cardiac myocytes. This process may be an unregulated, or partly regulated, passive event or an actively regulated chain of events leading to programmed cell death[4] (apoptosis). Mechanisms behind cell death are complex and not fully understood. Additionally, endothelial functioning and the effects of an activated immune response may further contribute to death of myocytes[5, 6].

Reversible injury

Cardiac myocytes are able to survive after up to 15 minutes following coronary artery occlusion[7]. Metabolism transits to anaerobic glycolysis[8], leading to lactate production and rise of inorganic phosphates. Hence, acidosis and increased osmosis are consequences of the changed metabolism. ECG changes[9] and impaired contractility are quickly recognized during ischemia. Post-ischemic contractile dysfunction is a reversible phenomenon called myocardial stunning[2]. This condition may last for up to several days in experimental studies[10]. Its mechanisms, leading to reduced responsiveness of contractile filaments to Ca^{2+}, are not clearly understood. Alterations in Ca^{2+} homeostasis[11] and oxygen generated free radicals[12] have been suggested and this is supported by the finding of improved contractility by scavenging of reactive oxygen species[13]. Myofibrillar oedema may also impair normal myosin-actin interaction, resulting in a poor force generation[14].

Irreversible injury

Myocardial injury becomes progressively irreversible following 15 minutes of ischemia[7], starting at the endocardium in a wave front towards the epicardium[15]. Successful reperfusion therapy obviously needs to be performed quickly. Restoring conditions with reperfusion following six hours of ischemia does not provide any salvage[7]. As stated, there are a number of different pathways and mechanisms behind the cell death of myocytes[4]. The mitochondria swell, normal crista folding becomes disorganized and the most typical cause of passive cell death is disruption of myocyte cell membrane structures[16]. Nitric oxide is an important regulator of endothelial and myocyte functioning with contrasting effects when it fuses with super oxide anions to generate highly reactive peroxynitrites ($ONOO^-$). This reactive product can cause both passive cell death and initiate apoptosis[17].

Reperfusion injury

Reperfusion can also contribute to cell injury[18]. The rapid restoration of extracellular osmolality may lead to intracellular hyperosmolality, causing lethal swelling of myocytes (oncosis)[19]. The oxidation process during reperfusion can lead to free radicals through the

formation of reactive oxygen species[20].This has been termed “the oxygen paradox” and is supported by studies of antioxidant reperfusion therapy providing myocardial protection[21]. The open state of the mitochondrial permeability transition pore can lead to swelling, loss of the electron transport chain and leakage of factors such as cytochrome C that can initiate apoptosis[22, 23]. This very large conductance channel is closed during ischemia, but overload of Ca^{2+}, reactive oxygen species and quick restoration of acidosis appear to contribute to its open state during early reperfusion with cell death as a potential consequence[24]. Aggregation of immune cells, factors and cytokines during ischemia and reperfusion can further contribute to irreversible myocardial injury and impaired contractility[25, 26].

Endothelial injury
The endothelial cells of the capillaries react slower to ischemia and reperfusion, but can also develop dysfunction and necrosis[5, 27]. Irreversible injuries of the capillary architecture can lead to a “no reflow” situation, preventing reperfusion[28, 29].

CARDIAC TROPONIN-T AS A BIOMARKER OF MYOCARDIAL NECROSIS

Cardiac troponin-T and I are structural proteins bound to the sarcomeres and also present in a small functionally free unbound cytosolic pool[30-32]. Both pools are released into the bloodstream during ischemia and reperfusion, but with different kinetics[30]. The free pool represents the very early peak. It is yet unclear whether this peak, to some extent could be part of a reversible injury[32]. The subsequent release appears from degradation of the contractile apparatus in necrotic myocytes. Different biomarkers of myocardial necrosis have been used clinically. While AST, LDH, myoglobin and CK-MB are less specific, cardiac troponin-T and I have nearly absolute myocardial tissue specificity and their elevation is considered a highly sensitive method to detect even microscopic zones of myocardial necrosis[31, 33]. In comparison to the earlier biomarkers, recent generations of troponin-T and I assays now detect myocardial necrosis in a greater number of patients at an early stage[34, 35]. The degree of troponin release further correlates to poor outcome[36, 37]. Renal failure can prolong the clearance of troponin[38], but acute elevations in troponin levels still have prognostic value regardless of renal clearance[39]. There is a good correlation between the peak of troponin release and the size of the myocardial infarction when investigated anatomically and with MRI[40, 41]. While troponin-T only has one assay, there are several assays of troponin-I with insufficient standardization[42]. The current guidelines for rapid laboratory rule-in of a myocardial infarction include a high sensitive troponin-T or I assay sampled at arrival to the hospital and a follow-up 3-6 hours later[43]. A value above the 99th percentile of a normal reference population (upper reference limit) is required to establish the diagnosis, together with a non-biomarker criterion. Cardiac troponin-T can be detected with high sensitivity from 3 hours with a peak at 6-8 hours, later decreasing to normal values within three weeks[31, 34].

CARDIAC TROPONIN-T AS BIOMARKER OF MYOCARDIAL INJURY AND PROGNOSIS IN CARDIAC SURGERY

Current guidelines state that a troponin-T or I value above 10 times the 99th percentile of the normal reference population (upper reference limit) sampled within 48 hours after CABG is indicative of a perioperative myocardial infarction in patients with normale troponin baseline before surgery[43]. The non-biomarker criteria include changes in ECG, angiographic or imaging evidence of coronary occlusion or impaired contractility. Myocardial infarction during CABG is associated with significant morbidity and mortality and may be as frequent as in 9.8% of the patients[44]. However, it is difficult to clearly define myocardial infarctions following CABG. This surgical procedure, especially with the aid of CPB, is bound to involve some myocardial necrosis which is often diffuse in its spread[45]. The myocardial injury may be due to manipulation and surgical trauma, inadequate protection with cardioplegic solution during CPB, generation of reactive oxygen species and oxidative stress during CPB, reperfusion injury following CPB, or related to micro-vascular events during reperfusion[46-48]. Postoperative troponin release appears to be less in off-pump CABG compared to conventional CABG with CPB, but peaks as demonstrated in Figure 1 at 6-8 hours in both groups[49] (n=27 in each group). Investigations of troponin release following CABG indicate that there is good correlation between its magnitude and the risk for later adverse cardiac events[50-54].

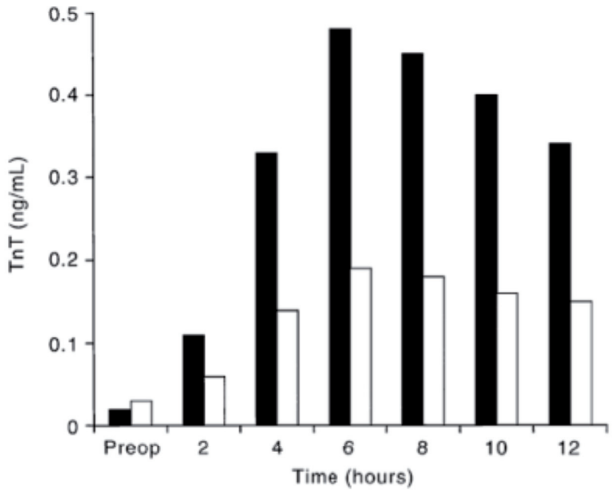

Figure 1 *Mean troponin-T release following CABG with CPB*
□ *off-pump coronary artery surgery*
■ *conventional coronary artery graft surgery*

Time, hours:	*2*	*4*	*6*	*8*	*10*	*12*
Off-pump, ng/ml:	*0.06*	*0.14*	*0.19*	*0.18*	*0.16*	*0.15*
With CPB, ng/ml:	*0.11*	*0.33*	*0.48*	*0.45*	*0.4*	*0.34*

CONDITIONING THE HEART

The meaning of "conditioning" in this context is remodelling of endogenous mechanisms to achieve protection against ischemia and reperfusion injury.

Experimentally

Murry and Jennings[55] presented a landmark study of myocardial protection in dogs by inducing short repetitive ischemic periods of five minutes before extended coronary artery occlusion of 40 minutes, an intervention that reduced infarction size by 75%. This seminal paper of ischemic preconditioning has been cited more than 4000 times and triggered a huge number of investigations. The final effector of this phenomenon is presumed to be the activation of mitochondrial ATP-sensitive K^+ channels and there seem to be some variations between species in the composition of the different pathways targeting the final effector[56, 57]. It is triggered by the release of substances such as adenosine, catecholamines, opioids, bradykinin and oxygen radicals that bind to receptors of G-proteins and phospholipases[58-60]. Stimulating these receptors leads to the epsilon isozyme of protein kinase C and many downstream messengers activating mitochondrial ATP-sensitive K^+ channels, which in turn leads to decreased membrane potential, reduced mitochondrial Ca^{2+} uptake and less high-energy phosphate consumption[61-63]. The immediate protective effect is lost if the ischemic event is longer than three hours[55]. Additionally, there appears to be a delayed, longer lasting, second window of protection related to synthesis of heat shock proteins and inducible nitric oxide synthase[64, 65]. Nitric oxide appears to be an important mediator of myocardial protection with a potential to interact on many levels[63, 66].

Preconditioning is of limited value in clinical settings where physicians cannot forecast the ischemic events. A more useful discovery was that of Zhao and Vinten-Johansen[67], namely that protection could also be achieved with three brief ischemic periods provided in the immediate reperfusion period after an extended coronary artery occlusion and therefore termed ischemic postconditioning. Mechanisms appear to be partially similar but not identical to ischemic preconditioning[68]. Preventing the open state of the mitochondrial permeability transition pore is crucial to the protective effect[69, 70]. This can be done pharmacologically with cyclosporine[71]. In this context, protection may also be provided with erythropoietin through inhibition of apoptosis in injured myocytes[72]. Myocardial remote preconditioning is another unexpected discovery first reported by Gho et al[73]. There are different models to study this phenomenon, but it usually involves transient limb ischemia applied with a blood pressure cuff, that leads to protection against ischemia and reperfusion injury in a distant organ[74]. Myocardial protection has also been demonstrated early in the reperfusion period in remote postconditioning with transient ischemia in the rat kidney[75] or in the lower limb of pigs[76]. Mechanisms are not fully understood, but may involve local release of adenosine and opioids, activating neural and/or humeral pathways[77].

Clinically

Ischemic preconditioning has been studied in a surgical context, through short periods of aortic clamping before CABG, with reduced postoperative troponin release and increased level of ATP in myocytes[78-80], but there are also contradictory results with this intervention in cardiac surgery[81]. Ischemic preconditioning with aortic clamping has moreover been investigated successfully before surgery for tetralogy of Fallot in children and in aortic valve replacement[82, 83]. Ischemic preconditioning has further been demonstrated with inflated balloons before PCI[84] and ischemic postconditioning has been described with the same method following PCI[85, 86]. A randomized trial

of cyclosporine A in patients presenting with myocardial infarction has attracted much attention. In this study, cyclosporine administration was associated with myocardial protection[87]. Remote preconditioning has been reported in experiments of brief ischemic periods in the upper limb provided before cardiac surgery with CPB[88-90]. Remote postconditioning has further been described following myocardial infarction when this intervention was conducted before PCI[91], but similar results were not found when this intervention was applied after PCI in another study[92].

CONDITIONING THE HEART WITH VOLATILE ANAESTHETICS

Experimentally

The first report[93] of anti-ischemic effects in halothane anaesthetized dogs with attenuated ST-elevations during coronary artery occlusion in comparison to intravenous anaesthesia was published in 1977. At that time, the effect was explained by potentially favourable coronary perfusion and/or reduced myocardial oxygen demand with halothane. Subsequent studies in dogs further demonstrated reduced post-ischemic myocardial stunning with quicker contractile recovery following treatment with isoflurane[94]. During 1997, three research groups described myocardial protection following coronary artery occlusion by treatment with halothane, isoflurane and enflurane in rabbits[95, 96] and dogs[97], either when provided before or during the ischemic period. These cited studies suggested adenosine, protein kinase C and ATP-sensitive K^+ channels to be involved in the mechanism. This protective effect was later confirmed in similar settings with more recent additions of volatile anaesthetics such as sevoflurane[98] and desflurane[99]. Continued research demonstrated that activating the mitochondrial subtype of ATP-sensitive K^+ channels may be the most important target in anaesthetic preconditioning[100] and that several downstream kinases and messengers are involved in this system[101]. Mechanisms resemble those reported with ischemic preconditioning. It appeared that anaesthetic preconditioning provided an immediate onset of myocardial protection lasting a few hours and a delayed, longer lasting, second window of protection with an onset after 24 hours. This later window of protection may be promoted by gene transcriptions of protective proteins[102, 103]. Furthermore, another unexpected discovery by Chiari et al[104] was that postconditioning with volatile anaesthetics in the beginning of the reperfusion period accomplished myocardial protection. Mechanisms have been suggested to involve inhibition of the mitochondrial permeability transition pore[105-108] or decreased activation of apoptosis[109]. Mechanisms in this protection are reported to involve many downstream messengers and kinases[110], often called RISK (Reperfusion Injury Salvage Kinases) and resemble those described in ischemic postconditioning. Reduced post-ischemic adhesion of inflammatory cells and platelets is another potential pathway of the protective effect by volatile anaesthetics[111-114].

Clinically

Clinicians were soon inspired by the pre-clinical findings of anaesthetic preconditioning to conduct human studies in CABG, demonstrating decreased release of postoperative biomarkers of myocardial ischemia using different perioperative treatment protocols with volatile anaesthetics compared to intravenous anaesthesia[115-117]. Meta-analyses of several performed studies in this field indicate that volatile anaesthetics in comparison to intravenous anaesthesia may reduce postoperative biomarkers of ischemia[118, 119]. Reduced mortality following cardiac surgery has also been suggested in other meta-analyses[120, 121]. DeHert et al[122] reported a finding that was especially interesting; that the most pronounced reduction of postoperative troponin release was achieved when sevoflurane was administered throughout the whole CABG surgery, compared with sevoflurane during only

parts of the surgery. This finding indicated that a protocol with prolonged administration increased the protective effect of sevoflurane compared to only pre-treatment before CPB.

CONDITIONING OTHER ORGANS WITH VOLATILE ANAESTHETICS

Experimentally
In addition to the cited studies of preconditioning with volatile anaesthetics against myocardial ischemia and reperfusion injury, protective effects with anaesthetic preconditioning has also been described in the brain[123, 124], spinal cord[125], liver[126] and the kidney[127]. Anaesthetic postconditioning has likewise been demonstrated to be protective in the brain[128, 129], kidney and intestine[130]. Volatile anaesthetics impact on the potentially harmful effects of an activated immune system is a parallel and close research field [131]. Pre-treatment with volatile anaesthetics has been investigated in a lung injury model, using endotoxin lipopolysaccharide to provoke an inflammatory response. In these studies, volatile anaesthetic administration was associated with reduced injury[132, 133].

Clinically
There are few human studies investigating potential protective effects with volatile anaesthetics in other organs than the heart. Anaesthetic pre- and postconditioning in the liver has been demonstrated during liver surgery[134, 135]. Anaesthetic preconditioning has moreover been reported in the kidney[116, 136]. In one study, the mechanism was suggested to be an anti-inflammatory effect accomplished by volatile anaesthetics[127]. However, renal protective effects could not be confirmed in a retrospective study of volatile anaesthesia during CABG with CPB compared to intravenous anaesthesia[137]. Anti-inflammatory effects of volatile anaesthetics have been demonstrated in one-lung ventilation during pulmonary surgery[138] and following CABG with the aid of CPB[139].

MYOCARDIAL CONDITIONING WITH OTHER SEDATIVES

Experimentally
Propofol has been reported to possess protective effects against myocardial ischemia and reperfusion injury in Langendorff rat preparations[140]. Propofol is a scavenger and is quite similar to the scavenger alfa-tocopherol (vitamin E) in its structure[141]. In experimental conditions, the concentrations required for propofol to be effective as a scavenger are normally higher than what is used in clinical anaesthesia[142, 143]. An investigation of scavenging superoxide dismutase with propofol in comparison to sevoflurane did not reveal any differences[144]. Propofol does not appear to have an effect on the mitochondrial ATP-sensitive K^+ channels[145], but a weaker effect on the mitochondrial permeability transition pore than sevoflurane[146, 147]. Propofol treatment is reported to modulate the immune response[148]. In this context, propofol has been described to attenuate endotoxin lipopolysaccharide induced acute lung injury in rats compared to no treatment[149]. This effect was greater with sevoflurane than propofol in a similar study in pigs[150].
Midazolam inhibits both ischemic and flumazenil- (its antidote) induced preconditioning[151-153].
Dexmedetomidine has been demonstrated to possess preconditioning effects against myocardial ischemia and reperfusion injury and it may be mediated through alfa-2 adrenergic stimulation[154].
Opioids have been demonstrated to provide both immediate and delayed myocardial protection involving similar mechanisms as ischemic preconditioning[155-157]. Delta and kappa opioid receptors can trigger second messengers activating mitochondrial ATP-sensitive

K^+ channels[158, 159]. Opioids also exert postconditioning effects via second messengers inhibiting the open state of the mitochondrial permeability transition pore[160-162]. Opioid receptors are also suggested to be involved in remote myocardial preconditioning[163].
Ketamine, but not the ketamine S^+ isomer, inhibits ischemic preconditioning[164].

Clinically
Propofol reduced postoperative troponin release following CABG when provided during the CPB period in a high dose compared to a low dose or isoflurane[165]. Another study demonstrated scavenging effects with propofol even in normal anaesthetic doses during CABG with CPB[166].
Dexmedetomidine has been reported to provide myocardial protection in off-pump CABG[167]. Another study of dexmedetomedine in CABG with CPB could not confirm myocardial protection[168]. A questioned retrospective study has suggested reduced mortality and less delirium in the ICU with dexmedetomidine applied during CABG, including postoperative sedation[169, 170]. Whether reduced mortality was related to less delirium or potential myocardial protective effects is unknown.
Opioids have been studied in CABG with CPB where the use of remifentanil infusion reduced postoperative troponin release[171], even when the remifentanil infusion was added to normal doses of fentanyl[172].

INHALED SEDATION WITH VOLATILE ANAESTHETICS IN THE ICU

Historical perspective
Early investigations of inhaled volatile anaesthetic sedation described shorter wake-up times with inhaled isoflurane sedation in the ICU[173, 174]. Delivery of the volatile anaesthetic was dependent on anaesthesia machines for its delivery, a method that was costly and complicated, and never became much of a clinical practice of sedation. Volatile anaesthetics have been reported to reduce airway resistance[175] and there are numerous case-reports of its successful use in status asthmaticus described in a recent review article of this treatment[176]. Historically, inhaled sedation with volatile anaesthetics had also been successfully used in therapy-resistant seizures[177, 178], tetanus[179] and congenital myasthenia[180].

AnaConDa®
The Anaesthetic Conserving Device (AnaConDa®) is a Swedish invention first described by Enlund et al in 2001[181]. It enables delivery of vaporized isoflurane or sevoflurane via a miniature evaporator rod into the breathing unit of common ICU ventilators[182, 183]. This disposable device is placed between the Y-piece of the respiratory circuit and the endotracheal tube. It has an antimicrobial and a conserving active charcoal filter that adsorbs approximately 90 % of the volatile anaesthetic at expiration. The adsorbed anaesthetic is recycled to the patient with the next breath. The AnaConDa® has a sampling port on the outlet to enable sampling of air to a gas-analyser (see Figure 2A and B). Sackey et al[184] were the first to publish a proof of concept study utilizing the AnaConDa® with isoflurane to provide sedation in ICU patients[184]. After the first publication, more studies of sedation with the AnaConDa® in ICU patients using inhaled isoflurane[185, 186] and sevoflurane[187-189] have followed.

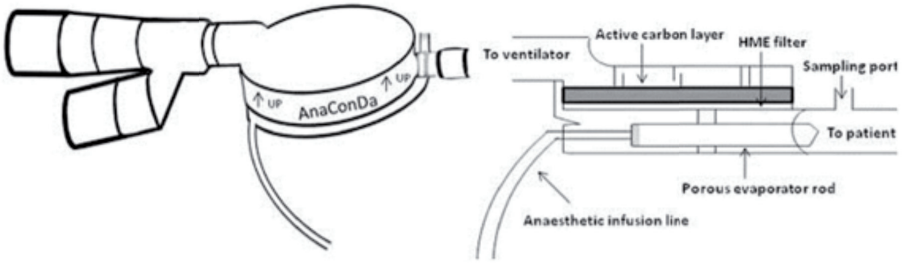

Figure 2 *A The AnaConDa®*

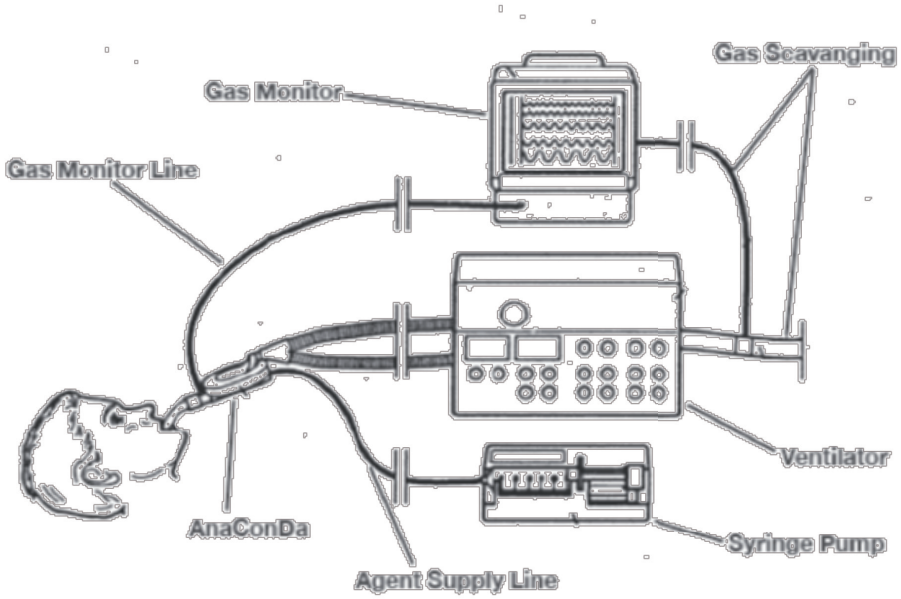

Figure 2 *B Setting of inhaled sedation in the ICU*

VOLATILE ANAESTHETICS AND OCCUPATIONAL HAZARDS

Concerns

Occupational exposure to trace concentrations of anaesthetic waste gases has been a concern for a long time[190, 191]. Epidemiological studies reported higher incidence of spontaneous abortions[192], infertility and congenital malformations in children of anaesthesia staff[193, 194]. These studies were criticised for methodological problems and flaws[195, 196] and prospective studies have not been able to confirm these concerns[197], except in occupational studies of nitrous oxide use in dental praxis without scavenging when staff were exposed to very high concentrations[198]. Occupational exposure to trace concentrations of anaesthetic gases is discussed in review articles[190, 191] and consensus in these publications is that the mentioned concerns have not been confirmed in areas where scavenging is provided[199].

Reports of psychomotor effects by exposure to trace concentrations of anaesthetic waste gases among anaesthesiologists was first published 1967 in a Russian study[200]; proposing fatigue, exhaustion and headache. Scavenging waste gases and rate of air changes in surgical theatres has improved since then. In the 1970´s, Bruce et al[201] performed experimental studies in volunteers indicating impaired performance in psychological tests by exposure to trace concentrations of enflurane and halothane in an air mix with nitrous oxide[201]. Bruce et al[202] were able to detect this effect in as low concentrations as 50 ppm of nitrous oxide and 1 ppm of halothane, but not in lower concentrations. This finding could not be reproduced in other studies using the same gas mix even in higher concentrations[203-205]. Furthermore, an occupational exposure study in surgical theatres with scavenging could not confirm decreased performance when the ambient air had trace concentrations of 48 ppm nitrous oxide and 1.4 ppm halothane[206]. More recent occupational studies by Lucchini et al[207, 208] with isoflurane and enflurane provided dual findings, both suggesting and contradicting these concerns. There are no published studies of sevoflurane. In the United States, NIOSH guideline[209] from 1977 regarding OEL is to a large extent based on the findings of Bruce et al[201, 202]. With this stated, data from other published studies give at hand that impaired psychomotor performance would require much higher concentrations of nitrous oxide and/or volatile anaesthetics[191, 210] and the threshold concentration of sevoflurane to cause psychomotor effects is yet to be determined.

Long- and short-term limits
NIOSH recommends scavenging in all areas where inhalational anaesthetics are used[209]. This recommendation includes a long-term OEL of two ppm of any volatile anaesthetics, over an eight-hour work shift with lunch break. The short-term OEL is six ppm, permitted for 15 minutes per hour. There are different recommendations within Europe. The European Community has yet to determine a general recommendation and therefore refers to each member's own legislation. The Swedish Work Environment Authorities has a long-term OEL of 10 ppm and a short-limit of 20 ppm[211].

SCAVENGING VOLATILE ANAESTHETICS IN THE ICU

Scavenging should, as cited above be applied when volatile anaesthetics are used for sedation in the ICU. With this stated, there are studies of isoflurane and sevoflurane sedation in the ICU without scavenging – only relying on room air changes – where exposures levels never rose above the Swedish long-term OEL[212, 213].

When using volatile anaesthetics for sedation, expired air from the ventilator and gas-analyser need to be connected to a scavenging system to minimize contamination of the ambient air. There are two ways of providing this, namely either using an active suction scavenging to the hospital gas waste system or passive scavenging with an adsorbing filter in a canister (see Figure 3A and B). Nurses exposure to volatile anaesthetics in the ICU has been sampled with dosimeters during isoflurane sedation[212] (exposure range between 0.06-0.16 ppm) and sevoflurane sedation[187] (exposure mean was 0.23 ppm +/-0.29) applying active suction scavenging to the hospital gas waste system. Commercially available canisters with gas adsorbing filters are an alternative. This method of scavenging has the advantage of not depending of the presence of on an active suction to the hospital gas waste system (but could of course be connected), so the filtered air can be released in the ICU room. Air passes passively through the canister where the volatile anaesthetic

is adsorbed. There are no published scientific studies of these systems with the filtered air released in the ICU room. A Canadian study combined the adsorbing canister and the active suction system to provide scavenging in the ICU[214], with the expected finding of low ambient sevoflurane concentrations. A closed suction system is recommended by the manufacturer of the AnaConDa®, but its use and scavenging from the tracheal suction air outlet has not been studied or described in above cited publications.

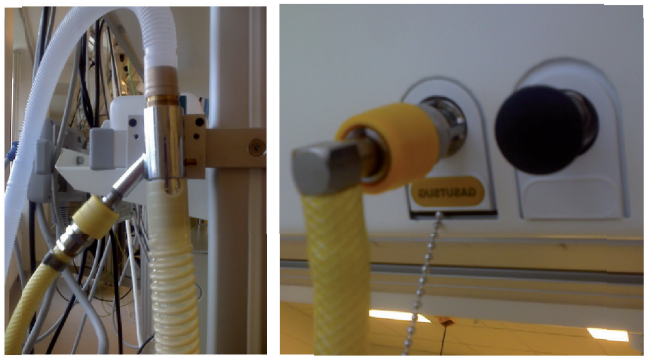

Figure 3 A. *Active suctioning scavenging*

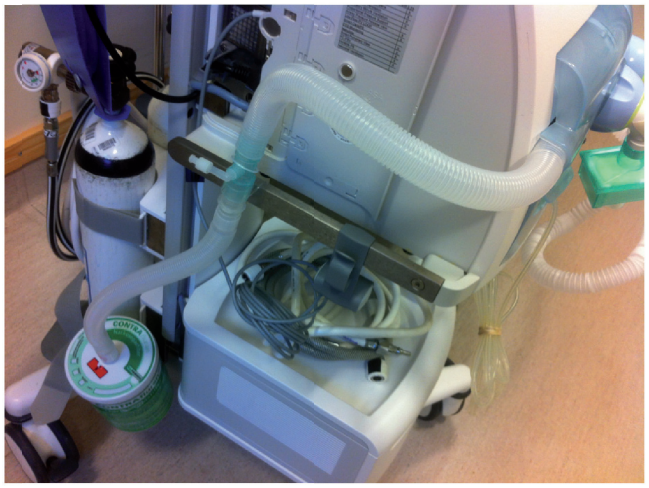

Figure 3 B. *CONTRAfluran™ scavenging connected to the ventilator*

CHARACTERISTICS OF SEDATIVE DRUGS TO FACILITATE MECHANICAL VENTILATION

Sedative drug options

The main reason to utilize intravenous sedative drugs in the ICU is to relieve discomfort during mechanical ventilation of intubated patients. Limited options of sedative drugs are available to provide sedation during mechanical ventilation[215, 216], besides off-label inhaled sedation with volatile anaesthetics. Propofol and benzodiazepines (midazolam and lorazepam) are unquestionably the most studied and frequently used alternatives. There are now also quite a few studies of dexmedetomedine to provide sedation in the ICU[217-219]. Ketamine sedation in the ICU is not well studied. Remifentanil is a short-acting opioid analgesic frequently used in combination with midazolam or propofol sedation to replace longer acting opioids[218, 220]. This regimen may reduce the sedative dose and shorten wake-up times. There are few studies of remifentanil alone (analgosedation) to relieve discomfort during mechanical ventilation[221].

Effects on the cardiovascular system

Hypotension is a common consequence of intravenous sedative drugs. This may be related to vasodilation, reduced contractility or bradycardia. Hypotension appears to be more pronounced with propofol, volatile anaesthetics, dexmedetomidine and remifentanil[219, 222-224], and bradycardia appears to be more frequent with remifentanil, dexmedetomedine and propofol[225-227]. Sevoflurane is reported to have a similar hemodynamic profile as remifentanil/propofol sedation[187], although heart rate was reported to be higher with sevoflurane. The cardiovascular effect of sevoflurane and isoflurane appears to be similar[228]. Dexmedetomidine is reported to have similar hemodynamic properties as propofol sedation[218], but heart rate was described as being lower with dexmedetomidine. Although this drug is associated with pronounced hypotension, rebound hypertension has been described following discontinuation. Hypotension appears to be less with midazolam and ketamine[229-231]. Ketamine may even possess inotropic effects and heart rate is often increased[232-234]. There are case reports with severe bradycardia with dexmedetomedine and remifentanil[235, 236]. The rare "propofol infusion syndrome" can lead to cardiogenic shock with impaired contractility and lactate acidosis and sudden death, associated with higher propofol doses, long-term sedation and catecholamine use[237].

Wake-up times and recovery qualities following sedation

Continuous infusion of sedative drugs during mechanical ventilation has been associated with prolonged mechanical ventilation[238, 239] and led to interest in daily interruption of sedative drugs[240]. In this context, midazolam is well known to have longer wake-up times than propofol[238]. The strategy of daily interruption of intravenous sedative infusions was means of avoiding over-sedation[240]. Daily "wake-up" was not associated with increased psychological consequences such as posttraumatic stress disorder[241], although less fluctuation in the sedation level has been proposed to reduce this disorder[242]. Recent studies suggest similar or improved outcome by only applying a better clinical protocol to titrate the intravenous sedative drug[243, 244] or even by applying a protocol of no sedation[245]. Newer drugs such as remifentanil and dexmedetomidine may have advantages in this context. The latter is reported to cause less delirium than previous standard of care sedatives[246] and both these options may contribute to shorter wake-up times compared to continuous infusion of midazolam[217, 220]. Wake-up times following dexmedetomedine sedation seemed to be similar to propofol in one study[247]. Prior to the studies in the thesis, isoflurane and desflurane sedation had been studied in ICU patients, with regard to wake-up times. These studies indicated that isoflurane sedation of critically ill patients led to shorter wake-up times than midazolam[184],

and that desflurane was associated with slightly shorter wake-up times in postoperative patients than propofol[248]. It is likely that the airway route of volatile anaesthetics elimination - being independent of renal and hepatic function - contributes to shorter wake-up times following sedation compared to conventional intravenous sedative drugs.

There has been an interest in the memory panorama following sedation. Delusional memories have been associated with the development of posttraumatic stress disorder[249]. Clear memories in the early period following sedation may be important to reduce posttraumatic stress disorder[250]. Withdrawal symptoms following sedation are more frequently reported with remifentanil and midazolam infusions[251, 252]. Opioid tolerance has been reported following short-term use of remifentanil infusion, contributing to increased postoperative pain and hyperalgesia[253, 254]. The latter adverse effects may be prevented with small doses of ketamine[255]. Midazolam sedation seems to affect memory more than propofol[256]. There is some evidence that delusional memories following long-term sedation may be less frequent with volatile anaesthetics compared to propofol or midazolam[257, 258]. Moreover, high doses of propofol have been associated with more delusional memories than lower doses[259]. Cognitive effects of ICU sedation are sparsely studied. Studies of general anaesthesia versus regional anaesthesia for surgical operations have not confirmed any differences in postoperative cognitive performance[260, 261], and there are no substantial differences between volatile anaesthesia and intravenous anaesthesia[262]. Nevertheless, sevoflurane anaesthesia in CABG with CPB appeared to provide better cognitive outcome compared to intravenous anaesthesia[263]. Findings from these cited studies are difficult to interpret in a setting of ICU sedation. The trauma necessitating ICU stay may in itself be a potential factor affecting cognitive performance.

SEDATION DURING THERAPEUTIC HYPOTHERMIA FOLLOWING CARDIAC ARREST

Therapeutic hypothermia following cardiac arrest was a standard treatment during the thesis[264], but has very recently been challenged with a protocol of 36 degree Celsius[265]. Residual sedation is acknowledged to contribute to confounding effects in the early neurological assessment after hypothermia[266, 267]. Hypothermia reduces drug metabolism and may contribute to drug accumulation[268-272]. Post-ischemic multi-organ dysfunction may further contribute to impaired metabolism. Seizures are frequent in this patient group and may clinically require higher doses of sedatives and/or benzodiazepines such as clonazepam. Considering inhaled sedation, isoflurane may be a better alternative than sevoflurane in patients with seizures[273]. Blood concentrations of intravenous sedatives are not measured clinically and it is difficult to judge when patients are free from lingering sedation. Intravenous sedation with propofol and remifentanil may be good options due to relatively short action[274]. Following the introduction of hypothermia treatment, it has been recommended to wait for at least 72 hours after regaining normal body temperature to conduct reliable neurologic assessments including neurophysiological objective methods[275, 276]. The risk of confounding from residual sedation is one reason for this late time point of neurological assessment. It appears that Glasgow Coma Scale scoring[277] has better predictability of good outcome at 72 hours[278], although scores were of predicable value already following 48 hours in a retrospective study conducted before the era of hypothermia[279].

AIMS

The principal objective in this thesis was to investigate clinical and occupational aspects of volatile anaesthetic sedation provided via the AnaConDa® in cardiothoracic ICU patients.

The specific aims were:

1. To compare biomarkers of myocardial damage and adverse cardiac events following CABG in patients postoperatively sedated with inhaled sevoflurane or intravenous propofol.

2. To compare recovery, ICU memories and length of ICU/hospital stay between patients sedated with sevoflurane or intravenous propofol following CABG.

3. To study early neurological assessment and outcome in patients treated with isoflurane sedation during therapeutic hypothermia following cardiac arrest.

4. To investigate occupational exposure to sevoflurane during its administration via the AnaConDa® to provide sedation in the ICU with or without passive scavenging.

ETHICS

The studies were performed in accordance with the declaration of Helsinki. The Regional Ethical Review Board of Stockholm, Sweden, approved all studies (I-IV). Patients in study I-II and IV gave written informed consent to be included. The Regional Ethical Review board waived the need to obtain consent from relatives to dead patients and surviving patients/ relatives gave consent to be included in the retrospective study III. The prospective studies I-II and IV were approved by The Swedish Medical Products Agency. Nursing staff gave consent to participate in study IV and pregnant nurses were excluded.

MATERIAL AND METHODS

PATIENTS

Paper I-II
In total, 100 patients scheduled to undergo elective or subacute CABG with the aid of CPB were enrolled in a prospective non-blinded randomized study of routine postoperative sedation during mechanical ventilation in the cardiothoracic ICU until criteria to extubate were met.

Paper III
In total, 12 resuscitated patients treated with inhaled isoflurane sedation during therapeutic hypothermia in the general ICU between the years 2008-2011 were identified. These patients were all included in a retrospective chart study to yield a case series of the treatment and outcome.

Paper IV
In total, 10 patients were enrolled in a non-blinded prospective randomized observational study of ambient air concentrations and occupational exposure to sevoflurane in the ICU with different means of scavenging the expired breathing air during inhaled sevoflurane sedation via the AnaConDa® following CABG.

INTERVENTIONS

Paper I-II
Perioperative anaesthesia was provided according to the local clinical protocol, including sevoflurane throughout CABG, except during the CPB period when intravenous propofol infusion was used. Randomization took place in the end of surgery through the selection of a sealed envelope by an ICU nurse in the ICU not participating in the treatment.

Patients were randomized to either receive inhaled sevoflurane (Sevorane®, Abbott Scandinavia AB, Solna, Sweden) with the anaesthetic conserving device (AnaConDa®, Sedana Medical AB, Uppsala, Sweden), or conventional intravenous propofol (Propofol 20mg/ml, Braun Medical AB, Danderyd, Sweden) sedation during routine delayed extubation in the ICU.

The intervention started upon arrival to the ICU. Patients randomized to sevoflurane received inhaled sedation via the AnaConDa® (see introduction, subsection "AnaConDa®"), aiming for a desired end-tidal concentration of 0.5-1%. The initial infusion rate was prescribed from a nomogram based on minute ventilation with adjustments of 10-20% of the infusion rate, aiming for the target end-tidal concentration and a Motor Activity Assessment Scale score[280] of 2–3 for a minimum of two hours and thereafter until defined criteria for extubation were met. These criteria included acceptable blood gases with an inspired oxygen fraction of no more than 0.4 and a positive end-expiratory pressure of no more than 5 cmH_2O, body temperature $\geq$36.5 degrees Celsius and bleeding in drains $\leq$100 ml/hour for two consecutive hours.

Patients randomized to receive propofol were sedated with continuous infusion, starting at a rate of 2 mg/kg/hour and adjusted to reach the same sedation level as in the sevoflurane-sedated group.

After the minimum postoperative sedation and observation, the AnaConDa® was removed or the propofol infusion stopped once extubation criteria were met. Patients were extubated provided they had a spontaneous respiratory rate of 10 per minute, tidal volume of 5 ml/kg and were able to open their eyes and squeeze their hand on verbal demand.

Paper III

This was a retrospective chart review and thus the treatment with isoflurane was not part of a research protocol. Patients had independently all been treated - off label - with inhaled isoflurane sedation during therapeutic hypothermia following cardiac arrest, according to the General ICU protocol for sedation options during this treatment.

Paper IV

These patients were treated with sevoflurane via the AnaConDa® as described in paper I-II, but in a designated single ICU room with six air changes per hour. This was an observational study of occupational exposure to sevoflurane and patients were randomised in the end of surgery to a non-blinded trial of different scavenging with a closed envelope drawn by a nurse who did not participate in the treatment. Randomisation led to either no scavenging of volatile anaesthetics or scavenging from all breathing air outlets to an adsorbing cylinder/canister (CONTRAfluran™, ZeoSys GmbH, Berlin, Germany). The expired breathing air passes through the canister passively with a low flow resistance and the volatile anaesthetic is adsorbed selectively before filtered air is released in the ICU room. A closed suctioning system (AirLife™ and Verso™ airway access adapter, CareFusion, Yorba Linda, USA) (see Figure 4 A) with scavenging of volatile anaesthetics in air from the suction air outlet was used in the scavenging group (see Figure 4 B).

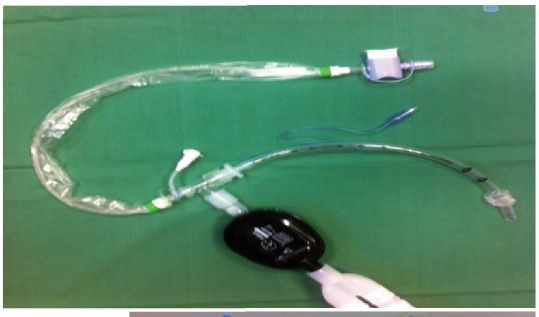

Figure 4 A *Closed suction system*

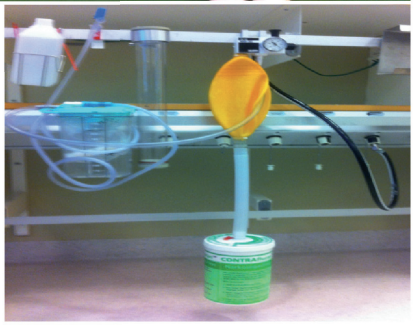

Figure 4 B *Scavenging connected to the suction air outlet*

MEASUREMENTS AND DATA COLLECTION

Paper I
The primary endpoint was a third generation high sensitive cardiac troponin-T assay (Roche Diagnostics AB, Bromma, Sweden) with sampling at 12 hours following arrival to the ICU. Secondary endpoints were cardiac adverse events; defined as any of the following: ventricular arrhythmias and cardiac arrest, atrial fibrillation or flutter, need of vasopressor/inotropic drugs, mechanical circulatory support or death within 30 days.
Secondary laboratory endpoints were CRP, AST, ALT, NT-proBNP, cystatin-C and creatinine.
Hemodynamic parameters were monitored per clinical routine, including five-lead ECG, invasive arterial and central venous line.

Paper II
The primary endpoint was time from sedative drug stop to extubation. Secondary endpoints were time to follow verbal command (providing social security number), minor adverse events (nausea, pain, agitation etc.), and adverse memories from the ICU, ICU and hospital length of stay. Technical problems with the AnaConDa® were noted. The ICU Memory Tool[281, 282] was followed up before discharge from hospital. The ICU Memory Tool is a test of memories from the ICU stay. These memories are classified into factual memories (real memories), memories of unpleasant feelings and delusional memories (hallucinations, paranoia, nightmares etc.)

Paper III
This was a retrospective study and data was collected from ICU monitoring via the patient data management system, hospital charts, emergency service charts and national death index. We searched for all relevant data regarding the medical background, resuscitation, time to therapeutic goal temperature and length of rewarming, hemodynamic parameters and inotropic/vasopressor therapy during treatment, as well as, laboratory and imaging investigations, Glasgow Coma Score[277, 283] and neurologic assessments, wake-up times and outcome. Data was consolidated and interpreted to yield a case series.

Paper IV
The primary endpoint was occupational exposure to sevoflurane sampled with dosimeters (SKC 575-0022, SKC Ltd, Dorset, U.K.) attached to nurses and fixed near the patient. These dosimeters were later analysed with gas chromatography (Environmental Laboratory of Occupational and Environmental Medicine, University of Gothenburg, Sweden). Additionally, we used an infrared spectrophotometer (Miran 1, ThermoFisher, Walthham, USA) to measure on-line sevoflurane concentration in the ambient air of the ICU room and in air outlets of the CONTRAfluran™ canister and the ventilator. We also used this equipment to measure on-line concentrations during certain procedures involving a disconnected breathing unit (suctioning, extubation ect.). We continuously measured end-tidal sevoflurane from the AnaConDa® sampling port as per clinical standard. Following extubation, on-line concentrations of sevoflurane were measured near patient for 50 minutes or until concentrations were below 1 ppm.
A secondary endpoint was possible adverse symptoms while caring for the patient. Nurses received a short written questionnaire regarding such symptoms after the work shift. They were asked if

they had felt just as during a corresponding workload with a patient on intravenous sedation. They were further specifically asked about having headache, feeling nausea, sevoflurane smell, dizziness, fatigue and concentration difficulties. They were able to explain any other symptoms in free text.

STATISTICS

Paper I
A power analysis yielded a required number of 47 patients in each group to detect a cardiac troponin-T difference of 0.1µg/l. The primary endpoint sampled 12 hours after arrival to the ICU was not normally distributed. Data was therefore compared with the Mann–Whitney U-test. Additionally, preoperative troponin-T values were elevated in a number of patients in both groups, which led us to perform a post hoc Mann–Whitney U-test analysis of the change between pre- and postoperative values.
The statistical analyses were performed according to "intention to treat". Secondary outcome data were analysed with Student's T-test for continuous parameters, with the Mann–Whitney U-test for non-normal data and Fisher's exact test for dichotomous outcomes using SPSS (IBM SPSS 18.0 (SPSS Inc., Chicago, IL).

Paper II
Based on wake-up data from a previous trial, we calculated a power of 90% at a 5% significance level for a 5-minute difference in the time to extubation from sedative drug stop. Data was analysed per protocol in order to best describe the drug efficacy. Wake-up data was not normally distributed. Primary and secondary endpoints were analysed with Mann–Whitney U-test and continuous (normally distributed) parameters were analysed with Student' s T-test and binominal data with Fisher' s exact test using SPSS (IBM SPSS 18.0 (SPSS Inc., Chicago, IL).

Paper III
Case series with descriptive data.

Paper IV
Mann Whitney U-test was applied on the primary endpoint: nurses level of exposure to sevoflurane.
Fisher´s exact test was applied on the secondary outcome from the questionnaire, with two columns of symptoms versus no symptoms. SPSS was used for both analyses (IBM SPSS 18.0 (SPSS Inc., Chicago, IL).

RESULTS

Paper I

There was no significant difference between groups in the primary endpoint cardiac troponin-T sampled 12 hours following arrival to the ICU (p=0.104) (Figure 5).

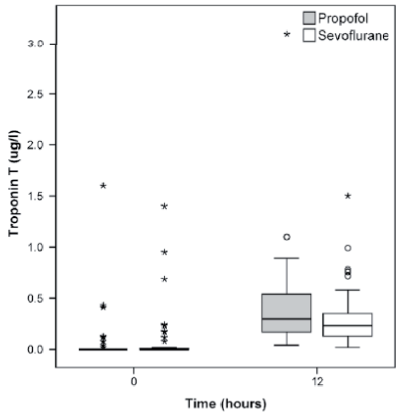

Figure 5. *Boxplot of pre-operative and 12 hours post-operative cardiac troponin-T values.*
*°, outlying point more than 1.5 box widths from edge of box, *extreme outlying point.*

Eighteen patients in the sevoflurane group and sixteen patients in the propofol group had preoperatively elevated troponin-T values above 0.033µg/l. The post-hoc analysis of the change from pre- to postoperative cardiac troponin-T value demonstrated a less pronounced change in the sevoflurane group (p=0.008). Data are presented in Table 1.

Table 1 Pre-operative and 12 hours post-operative troponin-T values (µg/l)

Pre-operative and 12h post-operative cTnT values (µg/l) in propofol and sevoflurane groups

Data	Propofol ($n=50$)		Sevoflurane ($n=50$)	
	Preop	12h	Preop	12h
Minimum	0.00	0.040	0.00	0.020
10th percentile	0.00	0.101	0.00	0.081
25th percentile	0.00	0.165	0.00	0.130
Median	0.00	0.295	0.00	0.230
75th percentile	0.05	0.545	0.01	0.370
90th percentile	0.116	0.796	0.225	0.706
Maximum	1.600	3.100	1.400	1.500

cTnT = cardiac troponin-T

Hemodynamic parameters during the first 12 hours were similar in both groups.
Adverse cardiac events - 25 events in the sevoflurane group and 29 events in the propofol group - were also similar in both groups (p=0.55).
There were no differences in secondary biochemical endpoint as CRP, AST, ALT, NT-ProBNP, creatinine and cystatin-C.
Sevoflurane sedated patient were treated for an average of 176 minutes with mean end-tidal concentration of 0.8%, while propofol-sedated patients were treated for an average 221 minutes with a mean dose of 2 mg/kg/hour the propofol groups (p=0.03).

Paper II

The time from sedative drug stop to extubation was shorter in the sevoflurane group, median time 10 minutes (interquartile (IQR) 10 minutes / range 100 minutes) versus 25 minutes (IQR 21 minutes / range 240 minutes) in the propofol group (see Figure 6) (p=0.001).
The mean end-tidal sevoflurane concentration was 0.8 with a standard deviation of 0.18. Mean propofol infusion rate was 2 mg/hour/kg with a standard deviation of 0.7.
Due to a misinterpretation of the study protocol, one patient in the sevoflurane group did not have the AnaConDa® removed, but only the sevoflurane infusion stopped, leading to rebreathing of sevoflurane and slower washout of sevoflurane. This patient represents the utmost outlier in the sevoflurane group. The outlier in the propofol group had a BMI of 38.

Following extubation, sevoflurane-sedated patients were able to follow verbal command earlier than propofol-sedated patients (p=0.036) (see Figure 7).
"Minor adverse events" as severe pain following extubation, nausea, agitation etc. were similar in both groups. Outcome from the ICU Memory Tool were also similar in groups as was the length of the ICU/hospital stay and the rate of re-admission to the ICU.

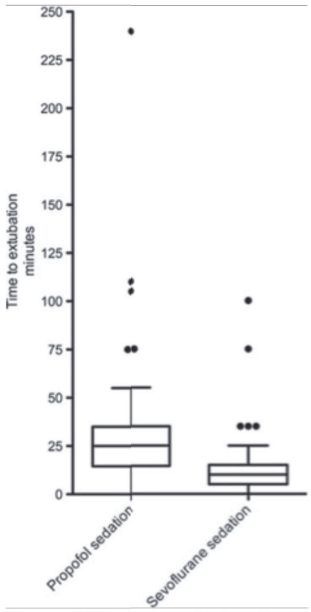

Figure 6 *Time to extubation from drug stop*

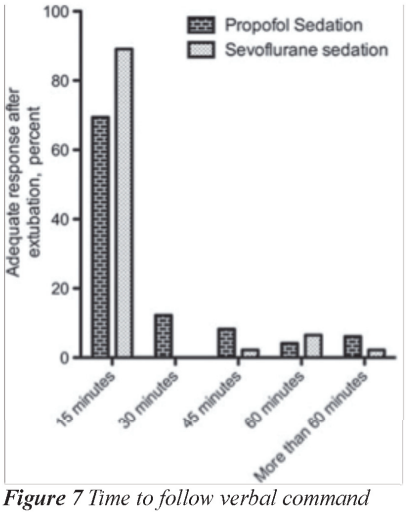

Figure 7 *Time to follow verbal command*

Paper III

Data from this patient series are presented in Table 2. We found that the early Glasgow Coma Scale assessment within 24 hours from rewarming was consistent with repeated assessment following 72 hours. Six patients survived and were later discharged to home with a good outcome. Six patients with poor outcome died within a week.

Table 2 Time to Return of Spontaneous Circulation and Hospital Clinical Outcome Data

	Patients											
Variables	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Return of spontaneous circulation, min	22	13	10	31	15	15	5	43	8	28	12	12
GCS at emergency department, score	3	3	3	3	4	4	4	3	3	3	3	4
Isoflurane, hr	41	15	28	42	23	10	35	57	29	35	26	28
GCS ≤ 24 hr after rewarming, score	4	3	14	3	5	7	14	11	10	6	14	15
GCS ≥ 72 hr after rewarming, score	4	5	14	3	5	7	15	11	14	6	15	15
Extubated at first wake-up test	No	No	Yes	No	No	No	Yes	No	No	No	Yes	Yes
Cardiac troponin-T peak, μg/L	0.37	2.8	0.24	0.37	2.66	8.09	2.51	0.82	0.24	0.12	1.47	0.30
Echo in ICU, ejection fraction %	50	10	30	10	20	30	30	45	25	45	45	40
Cystatin-C at arrival	0.54	1.36	1.01	0.74	0.87	2.04	0.68	0.82	0.6	0.69	1.02	0.92
Cystatin-C after treatment[a]	0.79	2.12	–	0.96	1.32	3.07	0.92	1.07	1.07	0.76	0.92	1.28
Neuron-specific enolase peak, μg/L	66	11	15	175	29	17	13	16	19	38	21	–
S100B, μg/L	0.11	–	0.11	0.29	0.26	0.11	0.06	0.13	–	0.1	0.07	–
Electroencephalogram with seizures	Yes	No	–	No	No	Yes	No	No	No	Yes	No	–
Somatosensory evoked potential test abnormal	Yes	No	–	Yes	–	–	–	–	–	No	–	–
CT with anoxic brain injury	Yes	No	–	Yes	No	Yes	–	–	No	Yes	No	–
Cerebral performing categories 6 mo survivors, score			2				1	1	2		1	1

GCS = Glasgow Coma Scale, S100B = a calcium-binding protein in the CNS.
[a]Sampled on day 3.
Note–Dash (–) indicates data unavailable.

Paper IV

The primary endpoint, nurses´ exposure to sevoflurane was lower in the group with scavenging, median exposure was below the detection limit for the method of analysis in this group: ≤0.67 ppm (range ≤0.50-0.77) compared to without scavenging 2.08 ppm (range 1.83-2.81) (see Table 3) (p=0.008).

Table 3 Measurements of sevoflurane concentrations from dosimeter sampling.

No scavenging						
Patient	1	2	3	4	5	*Median*
Sampling time, *min*	140	128	127	237	123	128
Nurses, *ppm*	2.81	2.08	1.34	2.44	1.83	2.08 †
Near patient, *ppm*	3.06	2.20	2.57	3.18	2.44	2.57 †
With scavenging CONTRAfluran™						
Patient	6	7	8	9	10	*Median*
Sampling time, *min*	127	145	178	197	130	145
Nurses, *ppm*	0.77*	0.67*	0.55*	0.5*	0.75*	0.67
Near patient, *ppm*	0.77*	0.67*	0.55*	0.5*	0.75*	0.71

** = Values below the detection limit for the method of analysis. † = p-value 0.008.*
The differences in detection limit are dependent on the measuring time.
min = minutes; ppm = parts per million.

On-line ambient concentrations near the patient following two hours were ≤1 ppm with scavenging and 4-6 ppm without. Extubation resulted in the highest peaks of sevoflurane concentration (peak range 4-10 ppm in both groups) lasting up to 30-50 minutes. Mean end-tidal sevoflurane used to provide sedation in the study was 0.71 % and values from the ventilators expiratory limb was close to 10% of the values sampled from the AnaConDa®.

Nurses´ reports of adverse symptoms were a secondary endpoint. Only nurses in the non-scavenging group experienced such symptoms; four of five nurses in this group reported symptoms (p=0.024). Smell of sevoflurane was the most frequently reported symptom.

GENERAL DISCUSSION AND CLINICAL IMPLICATIONS

POSTCONDITIONING WITH VOLATILE ANAESTHETICS IN CARDIOTHORACIC ICU PATIENTS

The primary endpoint in study I, troponin-T at 12 hours following CABG with CPB, was not significantly reduced in sevoflurane-sedated patients compared to conventional propofol sedation ($p=0.104$) and cardiac outcome was similar in both groups.

Of the 100 patients included in study I, 34 patients had elevated troponin-T values the day before surgery, implying a recent myocardial infarction. Even though the study was randomized, the magnitude of these already elevated values probably led to greater variation in the primary endpoint and insufficient power in the study.

The post-hoc analysis of the troponin-T difference between pre- and postoperative values at 12 hours following CABG revealed a significant attenuation of postoperative troponin-T elevations in sevoflurane-sedated patients ($p=0.008$). This finding suggests that there may be postconditioning effects with sevoflurane in comparison to propofol for postoperative sedation following GABG with CPB and warrants further investigations. Following study I, three more randomized clinical trials of sevoflurane sedation versus propofol sedation following cardiac surgery have investigated postoperative troponin release. Sevoflurane sedation was reported to reduce troponin-T sampled at 12-18 hours following cardiac surgery ($p=0.02$) in a study by Steurer at al[284] that included valve replacement and/or CABG with CPB. Another study by Soro et al[285] could not confirm significantly decreased troponin-I at 24 hours following CABG with CPB. In the publication by Soro et al, troponin-I values in the box-whisker plot appeared attenuated in the sevoflurane group, however this was not a significant finding and the investigators did not provide p-values. Orriach et al[286] reported reduced troponin-I in sevoflurane-treated patients at 24 hours after off-pump CABG ($p<0.05$). This study applied multiple samplings up to 48 hours after surgery. There are some differences in these cited studies. Steurer only used propofol anaesthesia during surgery and compared troponin-T values following four hours of sedation with sevoflurane or propofol, which is a longer period of sedation than was used in our study. Orriach employed similar minimum length of sedation as Steurer and included three groups: propofol throughout surgery and sedation, and sevoflurane throughout surgery followed by either propofol or sevoflurane sedation. Groups that included sevoflurane in anaesthesia or sedation had significantly reduced postoperative troponin-I release compared to propofol throughout surgery and sedation. Soro compared two groups, either propofol or sevoflurane used throughout surgery and during four hours of postoperative sedation. During CPB Soro used midazolam when required in the sevoflurane group. Patients with preoperative troponin-I values above 0.5 ng/ml were excluded in this study and statistics did not compare the difference from baseline. Steurer did not include patients with preoperative myocardial infarctions and randomisation was stratified for the type of cardiac surgery. Soro reported her study as double-blinded, still it is difficult to conduct a successful blinding of sevoflurane sedation in the ICU. Our and other cited studies were non-blinded in the ICU, but surgeons and anaesthesiologists participating in the surgery were unaware of the allocated treatment.

The cited studies in this field suggest that patients receiving intravenous anaesthesia may benefit most from sevoflurane sedation following cardiac surgery to accomplish myocardial protection. Sevoflurane anaesthesia during CABG with CPB is recognized to reduce postoperative troponin release[118, 119], but additional effects by further postconditioning appear to exist in the study by Orriach and are also suggested in our post-hoc analysis. Patients with preoperative myocardial infarction represent a risk group[287] that may possibly have greater myocardial protection with sevoflurane provided for anaesthesia and sedation in conjunction to CABG with CPB. These patients were enrolled in our study and excluded in the study by Soro. In the later study midazolam was used during CPB while we used propofol. It is further possible that longer sedation than was used in study I could improve protection. The optimal dose and protocol for sevoflurane postconditioning is still unknown, as well as the clinical implications. Nevertheless, postoperative troponin release following cardiac surgery appears to predict outcome in larger studies[50-54].
Myocardial protection has been described in animal studies when ischemic[67, 70] and anaesthetic[106, 146] postconditioning was initiated in the very first minutes of the reperfusion period, with sevoflurane provided for merely three to fifteen minutes. It has recently been demonstrated that ischemic postconditioning with a 30 minute delay still can achieve comparable myocardial protection[288] as described when the intervention was provided in the first minutes of reperfusion[67]. Experimental studies of anaesthetic pre- and postconditioning indicate that mechanisms resemble those reported in ischemic pre- and postconditioning to a large extent. Several pathways of known protective mechanisms may be involved in anaesthetic postconditioning. For instance, sevoflurane has experimentally been demonstrated to interact with the mitochondrial ATP-sensitive K^+ channel[98, 106] and the mitochondrial permeability transition pore[107, 108], initiate synthesis of protective proteins[112], reduce apoptosis[109], and mitigate the inflammatory response from neutrophils during reperfusion[25, 111-113]. Sedative doses of inhaled sevoflurane affect endothelial function and decrease leukocyte adhesion following forearm ischemia in human volunteers[289]. Pre-clinical studies of anaesthetic postconditioning in rodents suggested higher doses to achieve effects, but there was no clear dose-response relationship and duration of treatment was only 15 minutes[290].

Postconditioning with volatile anaesthetics during inhaled sedation in the ICU could be an appealing concept of protection against myocardial ischemia and reperfusion injury and this could be advantageous following cardiac surgery and in many more situations. Larger studies of post-ischemic sedation with sevoflurane are warranted to investigate different protocols, the implication of delayed treatment, mechanisms and whether the potential reduction of troponin release in humans may also affect clinically relevant endpoints.

RECOVERY FOLLOWING SHORT-TERM SEDATION WITH VOLATILE ANAESTHETICS IN ICU PATIENTS

The shorter time to extubation in sevoflurane-sedated patients and the earlier response to verbal demand described in Study II suggests more predictable wake-up time and earlier cognitive recovery than following propofol sedation.

Clinical practise is moving towards shorter postoperative sedation following cardiac surgery[291]. Previous studies of iso urane sedation in ICU patients described shorter time from iso urane drug stop to extubation (extubation time) than after midazolam sedation[174, 184]. Average extubation time in

a study of long-term sedation by Sackey et al[184] was10 minutes after isoflurane sedation compared to 252 minutes following midazolam sedation. The extubation times following sevoflurane sedation in study II were very similar to the times observed after isoflurane by Sackey et al. From studies of emergence from anaesthesia, extubation time appeared shorter following sevoflurane compared to isoflurane anaesthesia[292], which is in accordance to its pharmacological properties of lower solubility in blood. In addition to the above discussed studies of sevoflurane sedation investigating myocardial protection, two more prospective randomized trials of sevoflurane sedation in comparison to intravenous sedation in adult ICU patients have investigated extubation times and ICU stays during the period of thesis[189, 257]. Extubation times in these studies are in agreement with our findings. Extubation times following long-term propofol and midazolam sedation in general ICU patients were more than four respectively thirteen times longer than following corresponding sevoflurane sedation in a study by Mesnil et al[257]. Extubation time in short-term sedation following CABG was up to seven times longer following propofol sedation compared to following sevoflurane sedation in a study by Röhm[189]. Extubation times in our and these studies also demonstrated narrower standard deviations and/or range, contributing to fairly predictable extubation times, where end-tidal sevoflurane measurements may have been of clinical help to forecast near extubation. Following verbal demand after extubation can be regarded as a rough estimate of cognitive function and there may be more advanced methods that could have been applied in study II. With this stated, we found a difference between groups with this simple measure that favoured sevoflurane-sedated patients in responding earlier to verbal demand.
Not all aspects of earlier awakening were investigated in study II. It may be that more predictable and shorter extubation times could facilitate planning and utilization of intensive care recourses. Patients may further collaborate better in the immediate recovery period following extubation, which could be of importance to improve communication, mobilize mucus, protect airways and facilitate cooperation in non-invasive ventilator therapy. Early physiotherapy in ICU patients has been demonstrated to improve outcome[293]. Theoretically, longer-term sedated patients with impaired organ function suffering accumulation of intravenous sedative drugs may be weaned from these drugs ahead of planned extubation, during sevoflurane sedation and this proposed regimen might permit faster recovery and this would be interesting to investigate.

Light versus deep sedation following cardiac surgery does not appear to impact cardiac outcome[294]. However, avoiding deep sedation and maintaining clear memories following extubation may be important in preventing psychological morbidity[250]. Long-term sedation with volatile anaesthetics appears to generate less delusional memories following extubation[257, 258]. There were no differences in ICU memories compared to propofol sedation after our short-term sedation in study II. We did not screen for delirium with validated methods, which would have been of interest in this setting.

There is fairly good evidence of preserved renal integrity and acceptable fluoride-ion concentrations in short-term sedation with sevoflurane[295]. Fluoride-ion concentrations were followed for up to four days by Mesnil et al[257] without differences in renal function or reaching toxic fluoride-ion concentrations compared to propofol and midazolam sedation[257]. Larger studies are needed in long-term sedation and in patients with impaired renal function. Recovery from intravenous sedation is clinically known to be longer-lasting in the latter patient population[296]. In the studies by Röhm and Mesnil, ICU stays were shorter in sevoflurane-sedated patients compared to propofol or midazolam sedation[189, 257]. The protocol applied by Röhm following CABG lead to mechanical ventilation lasting an average of eight hours compared to three hours in Study II. While one could

speculate about such an advantage for longer-term sedated patients, we could not confirm shorter ICU or hospital stay in our short-term sevoflurane sedation following CABG.

Volatile anaesthetics appear to be a safe option for short-term sedation and this regimen is also recommended by the German Intensive Care guidelines as one option of short-term treatment[297]. More studies are warranted in long-term sedation to investigate clinical implications, the incidence of ICU delirium following sedation, renal function and concerns of fluoride-ion generation.

SEDATION FOLLOWING CARDIAC ARREST

Short-term sedation with volatile anaesthetics during therapeutic hypothermia following cardiac arrest seems to be a feasible regimen of short-term sedation. In this setting, volatile anaesthetics may eventually reduce lingering sedation following cessation compared to intravenous sedation.

Myocardial protection by postconditioning with sevoflurane may be more potent in sevoflurane-naïve patients as discussed earlier. Meybohm et al[298] reported improved myocardial outcome in an experimental pig study with sevoflurane sedation provided during four hours after resuscitation of electrically induced ventricular fibrillation compared to when propofol was used. Improved myocardial contractility with sevoflurane postconditioning has further been reported in a similar research model in rodents compared to untreated controls[299]. Similar experimental studies in pigs as reported by Meybohm have been conducted to investigate brain protective effects with isoflurane[300] and xenon[301] with positive results. However, results in another similar study in pigs with isoflurane or xenon did not accomplish a significant effect[302]. Experimental studies of brain protection in rodents with volatile anaesthetic postconditioning have demonstrated improved neurologic outcome in comparison to no treatment[129, 303, 304]. The previous discussion of study II suggests that emergence from sedation following sevoflurane is faster and that this finding may lead to shorter ICU stays. Hypothermia is well known to reduce metabolism of intravenous sedative drugs[268-272]. Prolonged sedation can contribute to confounding at early neurologic assessment[266, 267]. These rationales merited off-label isoflurane sedation in the general ICU. This regimen is also used in German centres and has been presented in an abstract during a German medical conference in Berlin[305], but there are still no case reports or journal publications of this treatment. We found it important to publish a case series of treated patients to attract attention and invite to discussion of conducting research in this patient group. Current legislation in the European Community requires informed consent from legal guardians of unconscious patients to be enrolled in clinical drug trials and obtaining consent to perform trials from relatives is not legal in this context[306-309]. This is a practical obstacle for us to conduct a clinical drug trial in this setting. This legislation may be revised during 2014-2015.
While the sedation was feasible in study III, no definite conclusions regarding myocardial protection or neurological outcome can be drawn from this study. There may eventually be less confounding from residual sedation during early Glasgow Coma Scale scoring, but this observation stands unchallenged as patients were few and heterogeneous and we did not have a control group. Clinical investigations in the retrospective study III were not standardized with a prospective protocol. However, patients with high Glasgow Coma Scale scores were quickly extubated in study III, which is in agreement with the short wake-up times found in Study II. Two isoflurane-sedated patients in study III with high Glasgow Coma Scale scores were only further sedated because of respiratory resons.

Early assessments in study III with Glasgow Coma Scale scoring were fairly consistent with repeated assessments following 72 hours, but it is possible that recovery processes of brain ischemia may contribute to improve Glasgow Coma Scale scores over time.

Sedation with volatile anaesthetics could be an asset in patients where neurological assessment needs to be performed during temporary sedation stop. This regimen may lead to less confounding from residual sedation. Parallel with the thesis, isoflurane sedation has been demonstrated to be feasible results in the neurosurgical ICU[186]. Investigators in this study recommended intra-cranial pressure monitoring in surgical patients, although only small and clinically insignificant differences where found in intra-cranial pressure compared to propofol-sedated patients.

Short-term sevoflurane sedation during therapeutic hypothermia following cardiac arrest is an appealing regimen of sedation that deserves to be investigated prospectively in larger randomized studies to compare wake-up times, findings in neurological assessment, neurophysiological investigations and potential differences in clinical outcome.

PASSIVE SCAVENGING OF VOLATILE ANAESTHETICS IN THE ICU

Study IV demonstrated reduced occupational exposures to sevoflurane with passive CONTRAfluran™ scavenging during its use for sedation in a moderately ventilated ICU room, compared to no scavenging from expired breathing air outlets. Occupational exposures were similar to reports of active suction scavenging to hospital gas waste system.

It has been demonstrated that active suction scavenging to hospital gas waste system provided minimal occupational exposure to isoflurane during its use for ICU sedation[212]. There are also reports[212, 213] of sedation with volatile anaesthetics without scavenging with exposure levels complying with Swedish OEL[211]. Nevertheless, the goal must be to reduce occupational exposure to a minimum and scavenging is strongly recommended even in a highly ventilated room[209]. Active suction scavenging to hospital gas waste system has been investigated during sevoflurane sedation in the ICU with a few dosimeter samplings and is reported to provide minimal occupational exposure[187, 257]. Prior to the thesis, there were no reports of passive scavenging with adsorbing gas filters, such as the commercially available CONTRAfluran™, with filtered air released in the ICU room.

Study III demonstrated low occupational exposures with passive CONTRAfluran™ scavenging as was earlier described in studies of active suction scavenging to hospital gas waste system. The system of passive scavenging is mobile and does not depend on active suction systems, which may be an advantage when these system fail or are not available, but also during transport and during interventions or diagnostic procedures outside the ICU. Study IV further demonstrated that a closed tracheal suction system with passive scavenging of air from suction air outlet could be used with minimal sevoflurane contamination in ambient air. This regimen could be considered in longer-term sedation or when tracheal suctioning is frequently needed. Extubation was the procedure in study IV that contaminated ambient air most and it lasted for up to around half an hour. Despite the observation that on-line values following extubation resulted in values below Swedish OEL, better ventilation or local exhaust ventilation could be considered in this period.

It was not the aim to investigate psychomotor effects among staff in depth in the non-blinded Study IV. Yet, the secondary finding that only nurses in the non-scavenging group reported adverse symptoms in our non-validated questionnaire is of some interest in this non-blinded study. Smell of sevoflurane was the most frequently reported symptom.

Larger blinded studies could consider investigating the latter more in depth, compare different passive scavenging systems and whether local exhaust ventilation is of any value following extubation.

CONCLUSIONS

1. There were no significant differences in the levels of cardiac troponin-T release 12 hours following CABG between short-term sedation with sevoflurane and propofol. In a post hoc analysis of the change between pre- and postoperative troponin-T release, the increase of troponin-T was less pronounced in the sevoflurane group. The incidence of cardiac adverse events was similar in both groups.

2. Wake-up times were shorter following short-term sevoflurane sedation compared to propofol and patients were able to follow verbal command earlier. The sedation regimen did not affect memories or outcome in terms of ICU or hospital length of stay.

3. Isoflurane short-term sedation may be a feasible option during therapeutic hypothermia and may possibly reduce confounding from residual sedation at early neurologic assessment

4. Scavenging with an adsorbing canister (CONTRAfluran™) with filtered air released in a moderately ventilated ICU room provided significantly less occupational exposure to sevoflurane compared to no scavenging and adverse symptoms among nurses were only reported in the latter group.

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REFERENCES

1. Jennings, R.B. Historical perspective on the pathology of myocardial ischemia/reperfusion injury. *Circ Res* **113**, 428-38 (2013).
2. Bolli, R. & Marban, E. Molecular and cellular mechanisms of myocardial stunning. *Physiol Rev* **79**, 609-34 (1999).
3. Wit, A.L. & Janse, M.J. Experimental models of ventricular tachycardia and fibrillation caused by ischemia and infarction. *Circulation* **85**, I32-42 (1992).
4. Whelan, R.S., Kaplinskiy, V. & Kitsis, R.N. Cell death in the pathogenesis of heart disease: mechanisms and significance. *Annu Rev Physiol* **72**, 19-44 (2010).
5. Lefer, A.M., Tsao, P.S., Lefer, D.J. & Ma, X.L. Role of endothelial dysfunction in the pathogenesis of reperfusion injury after myocardial ischemia. *FASEB J* **5**, 2029-34 (1991).
6. Welbourn, C.R. et al. Pathophysiology of ischaemia reperfusion injury: central role of the neutrophil. *Br J Surg* **78**, 651-5 (1991).
7. Jennings, R.B., Sommers, H.M., Smyth, G.A., Flack, H.A. & Linn, H. Myocardial necrosis induced by temporary occlusion of a coronary artery in the dog. *Arch Pathol* **70**, 68-78 (1960).
8. Ballinger, W.F., 2nd, Templeton, J.Y., 3rd & Vollenweider, H. Anaerobic metabolism of heart. *Circ Res* **11**, 681-5 (1962).
9. Li, R.A., Leppo, M., Miki, T., Seino, S. & Marban, E. Molecular basis of electrocardiographic ST-segment elevation. *Circ Res* **87**, 837-9 (2000).
10. Matsuzaki, M., Gallagher, K.P., Kemper, W.S., White, F. & Ross, J., Jr. Sustained regional dysfunction produced by prolonged coronary stenosis: gradual recovery after reperfusion. *Circulation* **68**, 170-82 (1983).
11. Kusuoka, H., Porterfield, J.K., Weisman, H.F., Weisfeldt, M.L. & Marban, E. Pathophysiology and pathogenesis of stunned myocardium. Depressed $Ca2^{+}$ activation of contraction as a consequence of reperfusion-induced cellular calcium overload in ferret hearts. *J Clin Invest* **79**, 950-61 (1987).
12. Hearse, D.J. Stunning: a radical re-view. *Cardiovasc Drugs Ther* **5**, 853-76 (1991).
13. Murphy, J.G., Smith, T.W. & Marsh, J.D. Mechanisms of reoxygenation-induced calcium overload in cultured chick embryo heart cells. *Am J Physiol* **254**, H1133-41 (1988).
14. Bragadeesh, T. et al. Post-ischaemic myocardial dysfunction (stunning) results from myofibrillar oedema. *Heart* **94**, 166-71 (2008).
15. Reimer, K.A. & Jennings, R.B. The "wavefront phenomenon" of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. *Lab Invest* **40**, 633-44 (1979).
16. Jennings, R.B. & Reimer, K.A. Lethal myocardial ischemic injury. *Am J Pathol* **102**, 241-55 (1981).
17. Pacher, P., Beckman, J.S. & Liaudet, L. Nitric oxide and peroxynitrite in health and disease. *Physiol Rev* **87**, 315-424 (2007).
18. Yellon, D.M. & Hausenloy, D.J. Myocardial reperfusion injury. *N Engl J Med* **357**, 1121-35 (2007).
19. Weerasinghe, P. & Buja, L.M. Oncosis: an important non-apoptotic mode of cell death. *Exp Mol Pathol* **93**, 302-8 (2012).
20. Hess, M.L. & Manson, N.H. Molecular oxygen: friend and foe. The role of the oxygen free radical system in the calcium paradox, the oxygen paradox and ischemia/reperfusion injury. *J Mol Cell Cardiol* **16**, 969-85 (1984).
21. Zweier, J.L. Measurement of superoxide-derived free radicals in the reperfused heart. Evidence for a free radical mechanism of reperfusion injury. *J Biol Chem* **263**, 1353-7 (1988).
22. Crompton, M. The mitochondrial permeability transition pore and its role in cell death. *Biochem J* **341 (Pt 2)**, 233-49 (1999).

23. Green, D.R. & Reed, J.C. Mitochondria and apoptosis. *Science* **281**, 1309-12 (1998).
24. Hausenloy, D.J. & Yellon, D.M. The mitochondrial permeability transition pore: its fundamental role in mediating cell death during ischaemia and reperfusion. *J Mol Cell Cardiol* **35**, 339-41 (2003).
25. Vinten-Johansen, J. Involvement of neutrophils in the pathogenesis of lethal myocardial reperfusion injury. *Cardiovasc Res* **61**, 481-97 (2004).
26. Westlin, W. & Mullane, K.M. Alleviation of myocardial stunning by leukocyte and platelet depletion. *Circulation* **80**, 1828-36 (1989).
27. Tsao, P.S., Aoki, N., Lefer, D.J., Johnson, G., 3rd & Lefer, A.M. Time course of endothelial dysfunction and myocardial injury during myocardial ischemia and reperfusion in the cat. *Circulation* **82**, 1402-12 (1990).
28. Kloner, R.A., Ganote, C.E. & Jennings, R.B. The "no-reflow" phenomenon after temporary coronary occlusion in the dog. *J Clin Invest* **54**, 1496-508 (1974).
29. Ito, H. No-reflow phenomenon and prognosis in patients with acute myocardial infarction. *Nat Clin Pract Cardiovasc Med* **3**, 499-506 (2006).
30. Remppis, A. et al. Intracellular compartmentation of troponin T: release kinetics after global ischemia and calcium paradox in the isolated perfused rat heart. *J Mol Cell Cardiol* **27**, 793-803 (1995).
31. Vasatova, M., Pudil, R., Horacek, J.M. & Buchler, T. Current applications of cardiac troponin T for the diagnosis of myocardial damage. *Adv Clin Chem* **61**, 33-65 (2013).
32. Jaffe, A.S. & Wu, A.H. Troponin release--reversible or irreversible injury? Should we care? *Clin Chem* **58**, 148-50 (2012).
33. Jaffe, A.S. et al. It's time for a change to a troponin standard. *Circulation* **102**, 1216-20 (2000).
34. Reichlin, T. et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med* **361**, 858-67 (2009).
35. Jaffe, A.S. Troponin--past, present, and future. *Curr Probl Cardiol* **37**, 209-28 (2012).
36. Ohman, E.M. et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. GUSTO IIA Investigators. *N Engl J Med* **335**, 1333-41 (1996).
37. Ottani, F. et al. Elevated cardiac troponin levels predict the risk of adverse outcome in patients with acute coronary syndromes. *Am Heart J* **140**, 917-27 (2000).
38. Li, D., Jialal, I. & Keffer, J. Greater frequency of increased cardiac troponin T than increased cardiac troponin I in patients with chronic renal failure. *Clin Chem* **42**, 114-5 (1996).
39. Aviles, R.J. et al. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *N Engl J Med* **346**, 2047-52 (2002).
40. Remppis, A. et al. Cardiac troponin T levels at 96 hours reflect myocardial infarct size: a pathoanatomical study. *Cardiology* **93**, 249-53 (2000).
41. Gallegos, R.P. et al. Infarct extent by MRI correlates with peak serum troponin level in the canine model. *J Surg Res* **120**, 266-71 (2004).
42. Labugger, R., Organ, L., Collier, C., Atar, D. & Van Eyk, J.E. Extensive troponin I and T modification detected in serum from patients with acute myocardial infarction. *Circulation* **102**, 1221-6 (2000).
43. Thygesen, K. et al. Third universal definition of myocardial infarction. *Circulation* **126**, 2020-35 (2012).
44. Yau, J.M. et al. Impact of perioperative myocardial infarction on angiographic and clinical outcomes following coronary artery bypass grafting (from PRoject of Ex-vivo Vein graft ENgineering via Transfection [PREVENT] IV). *Am J Cardiol* **102**, 546-51 (2008).
45. Selvanayagam, J.B. et al. Relationship of irreversible myocardial injury to troponin I and creatine kinase-MB elevation after coronary artery bypass surgery: insights from cardiovascular magnetic resonance imaging. *J Am Coll Cardiol* **45**, 629-31 (2005).
46. Kovacevic, R. et al. Troponin T levels in detection of perioperative myocardial infarction after coronary artery bypass surgery. *Clin Lab* **50**, 437-45 (2004).
47. Noora, J., Ricci, C., Hastings, D., Hill, S. & Cybulsky, I. Determination of troponin I release after CABG surgery. *J Card Surg* **20**, 129-35 (2005).
48. Katus, H.A. et al. Non-invasive assessment of perioperative myocardial cell damage by circulating cardiac troponin T. *Br Heart J* **65**, 259-64 (1991).
49. Bennetts, J.S., Baker, R.A., Ross, I.K. & Knight, J.L. Assessment of myocardial injury by troponin T in off-pump coronary artery grafting and conventional coronary artery graft surgery. *ANZ J Surg* **72**, 105-9 (2002).

50. Costa, M.A. et al. Incidence, predictors, and significance of abnormal cardiac enzyme rise in patients treated with bypass surgery in the arterial revascularization therapies study (ARTS). *Circulation* **104**, 2689-93 (2001).
51. Domanski, M.J. et al. Association of myocardial enzyme elevation and survival following coronary artery bypass graft surgery. *JAMA* **305**, 585-91 (2011).
52. Croal, B.L. et al. Relationship between postoperative cardiac troponin I levels and outcome of cardiac surgery. *Circulation* **114**, 1468-75 (2006).
53. Fellahi, J.L. et al. Short- and long-term prognostic value of postoperative cardiac troponin I concentration in patients undergoing coronary artery bypass grafting. *Anesthesiology* **99**, 270-4 (2003).
54. Mohammed, A.A. et al. Prospective, comprehensive assessment of cardiac troponin T testing after coronary artery bypass graft surgery. *Circulation* **120**, 843-50 (2009).
55. Murry, C.E., Jennings, R.B. & Reimer, K.A. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* **74**, 1124-36 (1986).
56. Gross, G.J. & Auchampach, J.A. Blockade of ATP-sensitive potassium channels prevents myocardial preconditioning in dogs. *Circ Res* **70**, 223-33 (1992).
57. Gross, G.J. & Fryer, R.M. Sarcolemmal versus mitochondrial ATP-sensitive K+ channels and myocardial preconditioning. *Circ Res* **84**, 973-9 (1999).
58. Liu, G.S. et al. Protection against infarction afforded by preconditioning is mediated by A1 adenosine receptors in rabbit heart. *Circulation* **84**, 350-6 (1991).
59. Cohen, M.V. et al. Phospholipase D plays a role in ischemic preconditioning in rabbit heart. *Circulation* **94**, 1713-8 (1996).
60. Downey, J.M., Davis, A.M. & Cohen, M.V. Signaling pathways in ischemic preconditioning. *Heart Fail Rev* **12**, 181-8 (2007).
61. Cohen, M.V., Baines, C.P. & Downey, J.M. Ischemic preconditioning: from adenosine receptor to KATP channel. *Annu Rev Physiol* **62**, 79-109 (2000).
62. Murphy, E. & Steenbergen, C. Mechanisms underlying acute protection from cardiac ischemia-reperfusion injury. *Physiol Rev* **88**, 581-609 (2008).
63. Sasaki, N., Sato, T., Ohler, A., O'Rourke, B. & Marban, E. Activation of mitochondrial ATP-dependent potassium channels by nitric oxide. *Circulation* **101**, 439-45 (2000).
64. Marber, M.S., Latchman, D.S., Walker, J.M. & Yellon, D.M. Cardiac stress protein elevation 24 hours after brief ischemia or heat stress is associated with resistance to myocardial infarction. *Circulation* **88**, 1264-72 (1993).
65. Bolli, R. et al. The protective effect of late preconditioning against myocardial stunning in conscious rabbits is mediated by nitric oxide synthase. Evidence that nitric oxide acts both as a trigger and as a mediator of the late phase of ischemic preconditioning. *Circ Res* **81**, 1094-107 (1997).
66. Jones, S.P. & Bolli, R. The ubiquitous role of nitric oxide in cardioprotection. *J Mol Cell Cardiol* **40**, 16-23 (2006).
67. Zhao, Z.Q. et al. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol Heart Circ Physiol* **285**, H579-88 (2003).
68. Hausenloy, D.J., Ong, S.B. & Yellon, D.M. The mitochondrial permeability transition pore as a target for preconditioning and postconditioning. *Basic Res Cardiol* **104**, 189-202 (2009).
69. Halestrap, A.P., Clarke, S.J. & Javadov, S.A. Mitochondrial permeability transition pore opening during myocardial reperfusion--a target for cardioprotection. *Cardiovasc Res* **61**, 372-85 (2004).
70. Argaud, L. et al. Postconditioning inhibits mitochondrial permeability transition. *Circulation* **111**, 194-7 (2005).
71. Crompton, M., Ellinger, H. & Costi, A. Inhibition by cyclosporin A of a Ca2+-dependent pore in heart mitochondria activated by inorganic phosphate and oxidative stress. *Biochem J* **255**, 357-60 (1988).
72. Maiese, K., Li, F. & Chong, Z.Z. New avenues of exploration for erythropoietin. *JAMA* **293**, 90-5 (2005).
73. Gho, B.C., Schoemaker, R.G., van den Doel, M.A., Duncker, D.J. & Verdouw, P.D. Myocardial protection by brief ischemia in noncardiac tissue. *Circulation* **94**, 2193-200 (1996).

74. Kharbanda, R.K., Nielsen, T.T. & Redington, A.N. Translation of remote ischaemic preconditioning into clinical practice. *Lancet* **374**, 1557-65 (2009).
75. Kerendi, F. et al. Remote postconditioning. Brief renal ischemia and reperfusion applied before coronary artery reperfusion reduces myocardial infarct size via endogenous activation of adenosine receptors. *Basic Res Cardiol* **100**, 404-12 (2005).
76. Andreka, G. et al. Remote ischaemic postconditioning protects the heart during acute myocardial infarction in pigs. *Heart* **93**, 749-52 (2007).
77. Saxena, P., Newman, M.A., Shehatha, J.S., Redington, A.N. & Konstantinov, I.E. Remote ischemic conditioning: evolution of the concept, mechanisms, and clinical application. *J Card Surg* **25**, 127-34 (2010).
78. Szmagala, P., Morawski, W., Krejca, M., Gburek, T. & Bochenek, A. Evaluation of perioperative myocardial tissue damage in ischemically preconditioned human heart during aorto coronary bypass surgery. *J Cardiovasc Surg (Torino)* **39**, 791-5 (1998).
79. Yellon, D.M., Alkhulaifi, A.M. & Pugsley, W.B. Preconditioning the human myocardium. *Lancet* **342**, 276-7 (1993).
80. Jenkins, D.P. et al. Ischaemic preconditioning reduces troponin T release in patients undergoing coronary artery bypass surgery. *Heart* **77**, 314-8 (1997).
81. Perrault, L.P. et al. Ischemic preconditioning in cardiac surgery: a word of caution. *J Thorac Cardiovasc Surg* **112**, 1378-86 (1996).
82. Luo, W., Li, B., Lin, G. & Huang, R. Postconditioning in cardiac surgery for tetralogy of Fallot. *J Thorac Cardiovasc Surg* **133**, 1373-4 (2007).
83. Luo, W., Li, B., Chen, R., Huang, R. & Lin, G. Effect of ischemic postconditioning in adult valve replacement. *Eur J Cardiothorac Surg* **33**, 203-8 (2008).
84. Tomai, F. et al. Ischemic preconditioning during coronary angioplasty is prevented by glibenclamide, a selective ATP-sensitive K+ channel blocker. *Circulation* **90**, 700-5 (1994).
85. Thibault, H. et al. Long-term benefit of postconditioning. *Circulation* **117**, 1037-44 (2008).
86. Yang, X.C. et al. Reduction in myocardial infarct size by postconditioning in patients after percutaneous coronary intervention. *J Invasive Cardiol* **19**, 424-30 (2007).
87. Piot, C. et al. Effect of cyclosporine on reperfusion injury in acute myocardial infarction. *N Engl J Med* **359**, 473-81 (2008).
88. Hausenloy, D.J. et al. Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial. *Lancet* **370**, 575-9 (2007).
89. Cheung, M.M. et al. Randomized controlled trial of the effects of remote ischemic preconditioning on children undergoing cardiac surgery: first clinical application in humans. *J Am Coll Cardiol* **47**, 2277-82 (2006).
90. Thielmann, M. et al. Cardioprotective and prognostic effects of remote ischaemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial. *Lancet* **382**, 597-604 (2013).
91. Botker, H.E. et al. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *Lancet* **375**, 727-34 (2010).
92. Carrasco-Chinchilla, F. et al. Remote ischaemic postconditioning: does it protect against ischaemic damage in percutaneous coronary revascularisation? Randomised placebo-controlled clinical trial. *Heart* **99**, 1431-7 (2013).
93. Bland, J.H. & Lowenstein, E. Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. *Anesthesiology* **45**, 287-93 (1976).
94. Warltier, D.C., al-Wathiqui, M.H., Kampine, J.P. & Schmeling, W.T. Recovery of contractile function of stunned myocardium in chronically instrumented dogs is enhanced by halothane or isoflurane. *Anesthesiology* **69**, 552-65 (1988).
95. Cason, B.A., Gamperl, A.K., Slocum, R.E. & Hickey, R.F. Anesthetic-induced preconditioning: previous administration of isoflurane decreases myocardial infarct size in rabbits. *Anesthesiology* **87**, 1182-90 (1997).
96. Cope, D.K., Impastato, W.K., Cohen, M.V. & Downey, J.M. Volatile anesthetics protect the ischemic rabbit myocardium from infarction. *Anesthesiology* **86**, 699-709 (1997).
97. Kersten, J.R., Schmeling, T.J., Pagel, P.S., Gross, G.J. & Warltier, D.C. Isoflurane mimics ischemic preconditioning via activation of K(ATP) channels: reduction of myocardial infarct size with an acute memory phase. *Anesthesiology* **87**, 361-70 (1997).

98. Toller, W.G., Kersten, J.R., Pagel, P.S., Hettrick, D.A. & Warltier, D.C. Sevoflurane reduces myocardial infarct size and decreases the time threshold for ischemic preconditioning in dogs. *Anesthesiology* **91**, 1437-46 (1999).
99. Hanouz, J.L. et al. Mechanisms of desflurane-induced preconditioning in isolated human right atria in vitro. *Anesthesiology* **97**, 33-41 (2002).
100. Zaugg, M., Lucchinetti, E., Spahn, D.R., Pasch, T. & Schaub, M.C. Volatile anesthetics mimic cardiac preconditioning by priming the activation of mitochondrial K(ATP) channels via multiple signaling pathways. *Anesthesiology* **97**, 4-14 (2002).
101. Ludwig, L.M., Weihrauch, D., Kersten, J.R., Pagel, P.S. & Warltier, D.C. Protein kinase C translocation and Src protein tyrosine kinase activation mediate isoflurane-induced preconditioning in vivo: potential downstream targets of mitochondrial adenosine triphosphate-sensitive potassium channels and reactive oxygen species. *Anesthesiology* **100**, 532-9 (2004).
102. Sergeev, P. et al. Trigger-dependent gene expression profiles in cardiac preconditioning: evidence for distinct genetic programs in ischemic and anesthetic preconditioning. *Anesthesiology* **100**, 474-88 (2004).
103. Tanaka, K. et al. Isoflurane produces delayed preconditioning against myocardial ischemia and reperfusion injury: role of cyclooxygenase-2. *Anesthesiology* **100**, 525-31 (2004).
104. Chiari, P.C. et al. Isoflurane protects against myocardial infarction during early reperfusion by activation of phosphatidylinositol-3-kinase signal transduction: evidence for anesthetic-induced postconditioning in rabbits. *Anesthesiology* **102**, 102-9 (2005).
105. Feng, J. et al. Isoflurane postconditioning prevents opening of the mitochondrial permeability transition pore through inhibition of glycogen synthase kinase 3beta. *Anesthesiology* **103**, 987-95 (2005).
106. Obal, D. et al. The influence of mitochondrial KATP-channels in the cardioprotection of preconditioning and postconditioning by sevoflurane in the rat in vivo. *Anesth Analg* **101**, 1252-60 (2005).
107. Huhn, R. et al. Hyperglycaemia blocks sevoflurane-induced postconditioning in the rat heart in vivo: cardioprotection can be restored by blocking the mitochondrial permeability transition pore. *Br J Anaesth* **100**, 465-71 (2008).
108. Yao, Y.T. et al. Sevoflurane postconditioning protects isolated rat hearts against ischemia-reperfusion injury: the role of radical oxygen species, extracellular signal-related kinases 1/2 and mitochondrial permeability transition pore. *Mol Biol Rep* **37**, 2439-46 (2010).
109. Inamura, Y., Miyamae, M., Sugioka, S., Domae, N. & Kotani, J. Sevoflurane postconditioning prevents activation of caspase 3 and 9 through antiapoptotic signaling after myocardial ischemia-reperfusion. *J Anesth* **24**, 215-24 (2010).
110. Hausenloy, D.J. & Yellon, D.M. Reperfusion injury salvage kinase signalling: taking a RISK for cardioprotection. *Heart Fail Rev* **12**, 217-34 (2007).
111. Heindl, B., Reichle, F.M., Zahler, S., Conzen, P.F. & Becker, B.F. Sevoflurane and isoflurane protect the reperfused guinea pig heart by reducing postischemic adhesion of polymorphonuclear neutrophils. *Anesthesiology* **91**, 521-30 (1999).
112. Chappell, D. et al. Sevoflurane reduces leukocyte and platelet adhesion after ischemia-reperfusion by protecting the endothelial glycocalyx. *Anesthesiology* **115**, 483-91 (2011).
113. Kowalski, C. et al. Halothane, isoflurane, and sevoflurane reduce postischemic adhesion of neutrophils in the coronary system. *Anesthesiology* **86**, 188-95 (1997).
114. Mobert, J., Zahler, S., Becker, B.F. & Conzen, P.F. Inhibition of neutrophil activation by volatile anesthetics decreases adhesion to cultured human endothelial cells. *Anesthesiology* **90**, 1372-81 (1999).
115. Belhomme, D. et al. Evidence for preconditioning by isoflurane in coronary artery bypass graft surgery. *Circulation* **100**, II340-4 (1999).
116. Julier, K. et al. Preconditioning by sevoflurane decreases biochemical markers for myocardial and renal dysfunction in coronary artery bypass graft surgery: a double-blinded, placebo-controlled, multicenter study. *Anesthesiology* **98**, 1315-27 (2003).
117. Tomai, F. et al. Beneficial impact of isoflurane during coronary bypass surgery on troponin I release. *G Ital Cardiol* **29**, 1007-14 (1999).
118. Symons, J.A. & Myles, P.S. Myocardial protection with volatile anaesthetic agents during coronary artery bypass surgery: a meta-analysis. *Br J Anaesth* **97**, 127-36 (2006).

119. Yu, C.H. & Beattie, W.S. The effects of volatile anesthetics on cardiac ischemic complications and mortality in CABG: a meta-analysis. *Can J Anaesth* **53**, 906-18 (2006).
120. Bignami, E. et al. Volatile anesthetics reduce mortality in cardiac surgery. *J Cardiothorac Vasc Anesth* **23**, 594-9 (2009).
121. Landoni, G. et al. Desflurane and sevoflurane in cardiac surgery: a meta-analysis of randomized clinical trials. *J Cardiothorac Vasc Anesth* **21**, 502-11 (2007).
122. De Hert, S.G. et al. Cardioprotective properties of sevoflurane in patients undergoing coronary surgery with cardiopulmonary bypass are related to the modalities of its administration. *Anesthesiology* **101**, 299-310 (2004).
123. Xiong, L. et al. Preconditioning with isoflurane produces dose-dependent neuroprotection via activation of adenosine triphosphate-regulated potassium channels after focal cerebral ischemia in rats. *Anesth Analg* **96**, 233-7, table of contents (2003).
124. Kehl, F., Payne, R.S., Roewer, N. & Schurr, A. Sevoflurane-induced preconditioning of rat brain in vitro and the role of KATP channels. *Brain Res* **1021**, 76-81 (2004).
125. Park, H.P. et al. Isoflurane preconditioning protects motor neurons from spinal cord ischemia: its dose-response effects and activation of mitochondrial adenosine triphosphate-dependent potassium channel. *Neurosci Lett* **387**, 90-4 (2005).
126. Schmidt, R. et al. Heme oxygenase-1 induction by the clinically used anesthetic isoflurane protects rat livers from ischemia/reperfusion injury. *Ann Surg* **245**, 931-42 (2007).
127. Lee, H.T., Ota-Setlik, A., Fu, Y., Nasr, S.H. & Emala, C.W. Differential protective effects of volatile anesthetics against renal ischemia-reperfusion injury in vivo. *Anesthesiology* **101**, 1313-24 (2004).
128. Lee, J.J., Li, L., Jung, H.H. & Zuo, Z. Postconditioning with isoflurane reduced ischemia-induced brain injury in rats. *Anesthesiology* **108**, 1055-62 (2008).
129. Wang, J.K. et al. Postconditioning with sevoflurane protects against focal cerebral ischemia and reperfusion injury via PI3K/Akt pathway. *Brain Res* **1357**, 142-51 (2010).
130. Kim, M., Park, S.W., Kim, M., D'Agati, V.D. & Lee, H.T. Isoflurane post-conditioning protects against intestinal ischemia-reperfusion injury and multiorgan dysfunction via transforming growth factor-beta1 generation. *Ann Surg* **255**, 492-503 (2012).
131. Kurosawa, S. & Kato, M. Anesthetics, immune cells, and immune responses. *J Anesth* **22**, 263-77 (2008).
132. Suter, D. et al. The immunomodulatory effect of sevoflurane in endotoxin-injured alveolar epithelial cells. *Anesth Analg* **104**, 638-45 (2007).
133. Shayevitz, J.R., Rodriguez, J.L., Gilligan, L., Johnson, K.J. & Tait, A.R. Volatile anesthetic modulation of lung injury and outcome in a murine model of multiple organ dysfunction syndrome. *Shock* **4**, 61-7 (1995).
134. Beck-Schimmer, B. et al. A randomized controlled trial on pharmacological preconditioning in liver surgery using a volatile anesthetic. *Ann Surg* **248**, 909-18 (2008).
135. Beck-Schimmer, B. et al. Protection of pharmacological postconditioning in liver surgery: results of a prospective randomized controlled trial. *Ann Surg* **256**, 837-44; discission 844-5 (2012).
136. Kim, M. et al. The volatile anesthetic isoflurane induces ecto-5'-nucleotidase (CD73) to protect against renal ischemia and reperfusion injury. *Kidney Int* **84**, 90-103 (2013).
137. Sindhvananda, W., Phisaiphun, K. & Prapongsena, P. No renal protection from volatile-anesthetic preconditioning in open heart surgery. *J Anesth* **27**, 48-55 (2013).
138. De Conno, E. et al. Anesthetic-induced improvement of the inflammatory response to one-lung ventilation. *Anesthesiology* **110**, 1316-26 (2009).
139. Kawamura, T. et al. Effects of sevoflurane on cytokine balance in patients undergoing coronary artery bypass graft surgery. *J Cardiothorac Vasc Anesth* **20**, 503-8 (2006).
140. Xia, Z., Godin, D.V., Chang, T.K. & Ansley, D.M. Dose-dependent protection of cardiac function by propofol during ischemia and early reperfusion in rats: effects on 15-F2t-isoprostane formation. *Can J Physiol Pharmacol* **81**, 14-21 (2003).
141. Murphy, P.G., Myers, D.S., Davies, M.J., Webster, N.R. & Jones, J.G. The antioxidant potential of propofol (2,6-diisopropylphenol). *Br J Anaesth* **68**, 613-8 (1992).
142. Green, T.R., Bennett, S.R. & Nelson, V.M. Specificity and properties of propofol as an antioxidant free radical scavenger. *Toxicol Appl Pharmacol* **129**, 163-9 (1994).
143. Gulcin, I., Alici, H.A. & Cesur, M. Determination of in vitro antioxidant and radical scavenging activities of propofol. *Chem Pharm Bull (Tokyo)* **53**, 281-5 (2005).

144. Allaouchiche, B., Debon, R., Goudable, J., Chassard, D. & Duflo, F. Oxidative stress status during exposure to propofol, sevoflurane and desflurane. *Anesth Analg* **93**, 981-5 (2001).
145. Mathur, S., Farhangkhgoee, P. & Karmazyn, M. Cardioprotective effects of propofol and sevoflurane in ischemic and reperfused rat hearts: role of K(ATP) channels and interaction with the sodium-hydrogen exchange inhibitor HOE 642 (cariporide). *Anesthesiology* **91**, 1349-60 (1999).
146. He, W. et al. Postconditioning of sevoflurane and propofol is associated with mitochondrial permeability transition pore. *J Zhejiang Univ Sci B* **9**, 100-8 (2008).
147. Javadov, S.A. et al. Protection of hearts from reperfusion injury by propofol is associated with inhibition of the mitochondrial permeability transition. *Cardiovasc Res* **45**, 360-9 (2000).
148. Marik, P.E. Propofol: an immunomodulating agent. *Pharmacotherapy* **25**, 28S-33S (2005).
149. Gao, J., Zeng, B.X., Zhou, L.J. & Yuan, S.Y. Protective effects of early treatment with propofol on endotoxin-induced acute lung injury in rats. *Br J Anaesth* **92**, 277-9 (2004).
150. Ferrando, C. et al. Sevoflurane, but not propofol, reduces the lung inflammatory response and improves oxygenation in an acute respiratory distress syndrome model: a randomised laboratory study. *Eur J Anaesthesiol* **30**, 455-63 (2013).
151. Yao, Z. et al. Signal transduction of flumazenil-induced preconditioning in myocytes. *Am J Physiol Heart Circ Physiol* **280**, H1249-55 (2001).
152. Rivo, J. et al. Flumazenil mimics whereas midazolam abolishes ischemic preconditioning in a rabbit heart model of ischemia-reperfusion. *Anesthesiology* **105**, 65-71 (2006).
153. Gomes, O.M., Valladares, U.F., Santos, C.H. & Abrantes, R.D. Preconditioning abolishion by midazolam in isolated hearts of rats. *Acta Cir Bras* **24**, 173-6 (2009).
154. Okada, H., Kurita, T., Mochizuki, T., Morita, K. & Sato, S. The cardioprotective effect of dexmedetomidine on global ischaemia in isolated rat hearts. *Resuscitation* **74**, 538-45 (2007).
155. Schultz, J.E. & Gross, G.J. Opioids and cardioprotection. *Pharmacol Ther* **89**, 123-37 (2001).
156. Gross, G.J. Role of opioids in acute and delayed preconditioning. *J Mol Cell Cardiol* **35**, 709-18 (2003).
157. Zhang, Y., Irwin, M.G. & Wong, T.M. Remifentanil preconditioning protects against ischemic injury in the intact rat heart. *Anesthesiology* **101**, 918-23 (2004).
158. Bell, S.P., Sack, M.N., Patel, A., Opie, L.H. & Yellon, D.M. Delta opioid receptor stimulation mimics ischemic preconditioning in human heart muscle. *J Am Coll Cardiol* **36**, 2296-302 (2000).
159. Wong, T.M. & Wu, S. Roles of kappa opioid receptors in cardioprotection against ischemia: the signaling mechanisms. *Sheng Li Xue Bao* **55**, 115-20 (2003).
160. Fuardo, M., Lemoine, S., Lo Coco, C., Hanouz, J.L. & Massetti, M. [D-Ala2,D-Leu5]-enkephalin (DADLE) and morphine-induced postconditioning by inhibition of mitochondrial permeability transition pore, in human myocardium. *Exp Biol Med (Maywood)* **238**, 426-32 (2013).
161. Gross, E.R., Hsu, A.K. & Gross, G.J. Opioid-induced cardioprotection occurs via glycogen synthase kinase beta inhibition during reperfusion in intact rat hearts. *Circ Res* **94**, 960-6 (2004).
162. Xi, J., Tian, W., Zhang, L., Jin, Y. & Xu, Z. Morphine prevents the mitochondrial permeability transition pore opening through NO/cGMP/PKG/Zn2+/GSK-3beta signal pathway in cardiomyocytes. *Am J Physiol Heart Circ Physiol* **298**, H601-7 (2010).
163. Zhang, S.Z. et al. Kappa-opioid receptors mediate cardioprotection by remote preconditioning. *Anesthesiology* **105**, 550-6 (2006).
164. Mullenheim, J., Frassdorf, J., Preckel, B., Thamer, V. & Schlack, W. Ketamine, but not S(+)-ketamine, blocks ischemic preconditioning in rabbit hearts in vivo. *Anesthesiology* **94**, 630-6 (2001).
165. Xia, Z., Huang, Z. & Ansley, D.M. Large-dose propofol during cardiopulmonary bypass decreases biochemical markers of myocardial injury in coronary surgery patients: a comparison with isoflurane. *Anesth Analg* **103**, 527-32 (2006).

166. Corcoran, T.B. et al. The effects of propofol on lipid peroxidation and inflammatory response in elective coronary artery bypass grafting. *J Cardiothorac Vasc Anesth* **18**, 592-604 (2004).
167. Ren, J. et al. Protective effect of dexmedetomidine in coronary artery bypass grafting surgery. *Exp Ther Med* **6**, 497-502 (2013).
168. Tosun, Z. et al. Does dexmedetomidine provide cardioprotection in coronary artery bypass grafting with cardiopulmonary bypass? A pilot study. *J Cardiothorac Vasc Anesth* **27**, 710-5 (2013).
169. Ji, F. et al. Perioperative dexmedetomidine improves outcomes of cardiac surgery. *Circulation* **127**, 1576-84 (2013).
170. Ji, F. et al. Response to letters regarding article, "perioperative dexmedetomidine improves outcomes of cardiac surgery". *Circulation* **128**, e339-40 (2013).
171. Greco, M. et al. Remifentanil in cardiac surgery: a meta-analysis of randomized controlled trials. *J Cardiothorac Vasc Anesth* **26**, 110-6 (2012).
172. Wong, G.T., Huang, Z., Ji, S. & Irwin, M.G. Remifentanil reduces the release of biochemical markers of myocardial damage after coronary artery bypass surgery: a randomized trial. *J Cardiothorac Vasc Anesth* **24**, 790-6 (2010).
173. Spencer, E.M. & Willatts, S.M. Isoflurane for prolonged sedation in the intensive care unit; efficacy and safety. *Intensive Care Med* **18**, 415-21 (1992).
174. Kong, K.L., Willatts, S.M. & Prys-Roberts, C. Isoflurane compared with midazolam for sedation in the intensive care unit. *BMJ* **298**, 1277-80 (1989).
175. Rooke, G.A., Choi, J.H. & Bishop, M.J. The effect of isoflurane, halothane, sevoflurane, and thiopental/nitrous oxide on respiratory system resistance after tracheal intubation. *Anesthesiology* **86**, 1294-9 (1997).
176. Vaschetto, R. et al. Inhalational anesthetics in acute severe asthma. *Curr Drug Targets* **10**, 826-32 (2009).
177. Kofke, W.A. et al. Isoflurane for refractory status epilepticus: a clinical series. *Anesthesiology* **71**, 653-9 (1989).
178. Hilz, M.J., Erbguth, F., Stefan, H. & Neundorfer, B. Isoflurane for 7 days in refractory status epilepticus. *Eur J Neurol* **2**, 95-9 (1995).
179. Stevens, J.J., Griffin, R.M. & Stow, P.J. Prolonged use of isoflurane in a patient with tetanus. *Br J Anaesth* **70**, 107-9 (1993).
180. McBeth, C. & Watkins, T.G. Isoflurane for sedation in a case of congenital myasthenia gravis. *Br J Anaesth* **77**, 672-4 (1996).
181. Enlund, M., Wiklund, L. & Lambert, H. A new device to reduce the consumption of a halogenated anaesthetic agent. *Anaesthesia* **56**, 429-32 (2001).
182. Meiser, A. & Laubenthal, H. Inhalational anaesthetics in the ICU: theory and practice of inhalational sedation in the ICU, economics, risk-benefit. *Best Pract Res Clin Anaesthesiol* **19**, 523-38 (2005).
183. Misra, S. & Koshy, T. A review of the practice of sedation with inhalational anaesthetics in the intensive care unit with the AnaConDa(R) device. *Indian J Anaesth* **56**, 518-23 (2012).
184. Sackey, P.V., Martling, C.R., Granath, F. & Radell, P.J. Prolonged isoflurane sedation of intensive care unit patients with the Anesthetic Conserving Device. *Crit Care Med* **32**, 2241-6 (2004).
185. L'Her, E. et al. Feasibility and Potential Cost/Benefit of Routine Isoflurane Sedation Using an Anesthetic-Conserving Device: a Prospective Observational Study. *Respiratory Care* **53**, 1295-1303 (2008).
186. Bosel, J. et al. Volatile isoflurane sedation in cerebrovascular intensive care patients using AnaConDa(R): effects on cerebral oxygenation, circulation, and pressure. *Intensive Care Med* **38**, 1955-64 (2012).
187. Migliari, M. et al. Short-term evaluation of sedation with sevoflurane administered by the anesthetic conserving device in critically ill patients. *Intensive Care Med* **35**, 1240-6 (2009).
188. Mesnil, M. et al. Long-term sedation in intensive care unit: a randomized comparison between inhaled sevoflurane and intravenous propofol or midazolam. *Intensive Care Med* (2011).
189. Röhm, K.D. et al. Short-term sevoflurane sedation using the Anaesthetic Conserving Device after cardiothoracic surgery. *Intensive Care Med* **34**, 1683-9 (2008).

190. Byhahn, C., Wilke, H.J. & Westpphal, K. Occupational exposure to volatile anaesthetics: epidemiology and approaches to reducing the problem. *CNS Drugs* **15**, 197-215 (2001).
191. Nilsson, R. et al. Health risks and occupational exposure to volatile anaesthetics--a review with a systematic approach. *J Clin Nurs* **14**, 173-86 (2005).
192. Cohen, E.N., Bellville, J.W. & Brown, B.W., Jr. Anesthesia, pregnancy, and miscarriage: a study of operating room nurses and anesthetists. *Anesthesiology* **35**, 343-7 (1971).
193. Knill-Jones, R.P., Rodrigues, L.V., Moir, D.D. & Spence, A.A. Anaesthetic practice and pregnancy. Controlled survey of women anaesthetists in the United Kingdom. *Lancet* **1**, 1326-8 (1972).
194. Askrog, V. & Harvald, B. [Teratogenic effects of inhalation anesthetics]. *Nord Med* **83**, 498-500 (1970).
195. Buring, J.E. et al. Health experiences of operating room personnel. *Anesthesiology* **62**, 325-30 (1985).
196. Tannenbaum, T.N. & Goldberg, R.J. Exposure to anesthetic gases and reproductive outcome. A review of the epidemiologic literature. *J Occup Med* **27**, 659-68 (1985).
197. Spence, A.A. Environmental pollution by inhalation anaesthetics. *Br J Anaesth* **59**, 96-103 (1987).
198. Rowland, A.S. et al. Reduced fertility among women employed as dental assistants exposed to high levels of nitrous oxide. *N Engl J Med* **327**, 993-7 (1992).
199. McGregor, D.G. Occupational exposure to trace concentrations of waste anesthetic gases. *Mayo Clin Proc* **75**, 273-7 (2000).
200. Vaisman, A.I. Working conditions in the operating room and their effect on the health of anesthetists. *Eksp Khir Anesteziol* **12**, 44-9 (1967).
201. Bruce, D.L., Bach, M.J. & Arbit, J. Trace anesthetic effects on perceptual, cognitive, and motor skills. *Anesthesiology* **40**, 453-8 (1974).
202. Bruce, D.L. & Bach, M.J. Effects of trace anaesthetic gases on behavioural performance of volunteers. *Br J Anaesth* **48**, 871-6 (1976).
203. Cook, T.L., Smith, M., Starkweather, J.A., Winter, P.M. & Eger, E.I., 2nd. Behavioral effects of trace and subanesthetic halothane and nitrous oxide in man. *Anesthesiology* **49**, 419-24 (1978).
204. Frankhuizen, J.L., Vlek, C.A., Burm, A.G. & Rejger, V. Failure to replicate negative effects of trace anaesthetics on mental performance. *Br J Anaesth* **50**, 229-34 (1978).
205. Smith, G. & Shirley, A.W. Failure to demonstrate effect of trace concentrations of nitrous oxide and halothane on psychomotor performance. *Br J Anaesth* **49**, 65-70 (1977).
206. Stollery, B.T. et al. Mood and cognitive functions in anaesthetists working in actively scavenged operating theatres. *Br J Anaesth* **61**, 446-55 (1988).
207. Lucchini, R. et al. Neurobehavioral functions in operating theatre personnel exposed to anesthetic gases. *Med Lav* **86**, 27-33 (1995).
208. Lucchini, R. et al. Neurobehavioral functions in operating theatre personnel: a multicenter study. *Med Lav* **88**, 396-405 (1997).
209. Woebkenberg, M.L. & Doemeny, L.J. NIOSH's criteria for a recommended standard--occupational exposure to waste anesthetic gases and vapors. *Am Ind Hyg Assoc J* **39**, 598-600 (1978).
210. Smith, G. & Shirley, A.W. A review of the effects of trace concentrations of anaesthetics of performance. *Br J Anaesth* **50**, 701-12 (1978).
211. Arbets miljöverket, författning:AFS 2011:18. Hygieniska grändvärden. Arbetsmiljöverkets författningssamling. 2011.
212. Sackey, P.V., Martling, C.R., Nise, G. & Radell, P.J. Ambient isoflurane pollution and isoflurane consumption during intensive care unit sedation with the Anesthetic Conserving Device. *Crit Care Med* **33**, 585-90 (2005).
213. Marbini HD & P.E., Chantler J. Active gas scavenging is unnecessary when using the AnaConDa volatile agent delivery system. *Intensive Care Soc* **10**, 26-28 (2009).
214. Pickworth, T., Jerath, A., DeVine, R., Kherani, N. & Wasowicz, M. The scavenging of volatile anesthetic agents in the cardiovascular intensive care unit environment: a technical report. *Can J Anaesth* **60**, 38-43 (2013).
215. Patel, S.B. & Kress, J.P. Sedation and analgesia in the mechanically ventilated patient. *Am J Respir Crit Care Med* **185**, 486-97 (2012).
216. Jacobi, J. et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* **30**, 119-41 (2002).

217. Riker, R.R. et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA* **301**, 489-99 (2009).
218. Venn, R.M. et al. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. *Anaesthesia* **54**, 1136-42 (1999).
219. Jakob, S.M. et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA* **307**, 1151-60 (2012).
220. Breen, D. et al. Decreased duration of mechanical ventilation when comparing analgesia-based sedation using remifentanil with standard hypnotic-based sedation for up to 10 days in intensive care unit patients: a randomised trial [ISRCTN47583497]. *Crit Care* **9**, R200-10 (2005).
221. Tipps, L.B., Coplin, W.M., Murry, K.R. & Rhoney, D.H. Safety and feasibility of continuous infusion of remifentanil in the neurosurgical intensive care unit. *Neurosurgery* **46**, 596-601; discussion 601-2 (2000).
222. Xuan, Y.T. & Glass, P.S. Propofol regulation of calcium entry pathways in cultured A10 and rat aortic smooth muscle cells. *Br J Pharmacol* **117**, 5-12 (1996).
223. Hanley, P.J., ter Keurs, H.E. & Cannell, M.B. Excitation-contraction coupling in the heart and the negative inotropic action of volatile anesthetics. *Anesthesiology* **101**, 999-1014 (2004).
224. Darrouj, J., Karma, L. & Arora, R. Cardiovascular manifestations of sedatives and analgesics in the critical care unit. *Am J Ther* **16**, 339-53 (2009).
225. Ma, D., Chakrabarti, M.K. & Whitwam, J.G. Propofol, bradycardia and the Bezold-Jarisch reflex in rabbits. *Br J Anaesth* **82**, 412-7 (1999).
226. Shinohara, K., Aono, H., Unruh, G.K., Kindscher, J.D. & Goto, H. Suppressive effects of remifentanil on hemodynamics in baro-denervated rabbits. *Can J Anaesth* **47**, 361-6 (2000).
227. Belleville, J.P., Ward, D.S., Bloor, B.C. & Maze, M. Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. *Anesthesiology* **77**, 1125-33 (1992).
228. Malan, T.P., Jr. et al. Cardiovascular effects of sevoflurane compared with those of isoflurane in volunteers. *Anesthesiology* **83**, 918-28 (1995).
229. Pappagallo, S. et al. [Propofol-midazolam in continuous infusion for sedation in intensive care]. *Minerva Anestesiol* **59**, 441-6 (1993).
230. Stowe, D.F., Bosnjak, Z.J. & Kampine, J.P. Comparison of etomidate, ketamine, midazolam, propofol, and thiopental on function and metabolism of isolated hearts. *Anesth Analg* **74**, 547-58 (1992).
231. Win, N.N., Fukayama, H., Kohase, H. & Umino, M. The different effects of intravenous propofol and midazolam sedation on hemodynamic and heart rate variability. *Anesth Analg* **101**, 97-102, table of contents (2005).
232. Gelissen, H.P. et al. Inotropic effects of propofol, thiopental, midazolam, etomidate, and ketamine on isolated human atrial muscle. *Anesthesiology* **84**, 397-403 (1996).
233. Cook, D.J., Carton, E.G. & Housmans, P.R. Mechanism of the positive inotropic effect of ketamine in isolated ferret ventricular papillary muscle. *Anesthesiology* **74**, 880-8 (1991).
234. Inoue, K. & Arndt, J.O. Efferent vagal discharge and heart rate in response to methohexitone, althesin, ketamine and etomidate in cats. *Br J Anaesth* **54**, 1105-16 (1982).
235. Zhang, X., Schmidt, U., Wain, J.C. & Bigatello, L. Bradycardia leading to asystole during dexmedetomidine infusion in an 18 year-old double-lung transplant recipient. *J Clin Anesth* **22**, 45-9 (2010).
236. DeSouza, G., Lewis, M.C. & TerRiet, M.F. Severe bradycardia after remifentanil. *Anesthesiology* **87**, 1019-20 (1997).
237. Vasile, B., Rasulo, F., Candiani, A. & Latronico, N. The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. *Intensive Care Med* **29**, 1417-25 (2003).
238. Barrientos-Vega, R. et al. Prolonged sedation of critically ill patients with midazolam or propofol: impact on weaning and costs. *Crit Care Med* **25**, 33-40 (1997).
239. Bauer, T.M. et al. Prolonged sedation due to accumulation of conjugated metabolites of midazolam. *Lancet* **346**, 145-7 (1995).

240. Girard, T.D. et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* **371**, 126-34 (2008).
241. Kress, J.P. et al. The long-term psychological effects of daily sedative interruption on critically ill patients. *Am J Respir Crit Care Med* **168**, 1457-61 (2003).
242. Svenningsen, H. et al. Fluctuations in sedation levels may contribute to delirium in ICU patients. *Acta Anaesthesiol Scand* **57**, 288-93 (2013).
243. Mehta, S. et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. *JAMA* **308**, 1985-92 (2012).
244. de Wit, M., Gennings, C., Jenvey, W.I. & Epstein, S.K. Randomized trial comparing daily interruption of sedation and nursing-implemented sedation algorithm in medical intensive care unit patients. *Crit Care* **12**, R70 (2008).
245. Strom, T., Martinussen, T. & Toft, P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet* **375**, 475-80 (2010).
246. Pandharipande, P.P. et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* **298**, 2644-53 (2007).
247. Venn, R.M. & Grounds, R.M. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. *Br J Anaesth* **87**, 684-90 (2001).
248. Meiser, A. et al. Desflurane compared with propofol for postoperative sedation in the intensive care unit. *Br J Anaesth* **90**, 273-80 (2003).
249. Jones, C. et al. Precipitants of post-traumatic stress disorder following intensive care: a hypothesis generating study of diversity in care. *Intensive Care Med* **33**, 978-85 (2007).
250. Granja, C. et al. Understanding posttraumatic stress disorder-related symptoms after critical care: the early illness amnesia hypothesis. *Crit Care Med* **36**, 2801-9 (2008).
251. Cammarano, W.B., Pittet, J.F., Weitz, S., Schlobohm, R.M. & Marks, J.D. Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients. *Crit Care Med* **26**, 676-84 (1998).
252. Delvaux, B., Ryckwaert, Y., Van Boven, M., De Kock, M. & Capdevila, X. Remifentanil in the intensive care unit: tolerance and acute withdrawal syndrome after prolonged sedation. *Anesthesiology* **102**, 1281-2 (2005).
253. Guignard, B. et al. Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. *Anesthesiology* **93**, 409-17 (2000).
254. Angst, M.S., Koppert, W., Pahl, I., Clark, D.J. & Schmelz, M. Short-term infusion of the mu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal. *Pain* **106**, 49-57 (2003).
255. Joly, V. et al. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology* **103**, 147-55 (2005).
256. Polster, M.R., Gray, P.A., O'Sullivan, G., McCarthy, R.A. & Park, G.R. Comparison of the sedative and amnesic effects of midazolam and propofol. *Br J Anaesth* **70**, 612-6 (1993).
257. Mesnil, M. et al. Long-term sedation in intensive care unit: a randomized comparison between inhaled sevoflurane and intravenous propofol or midazolam. *Intensive Care Med* **37**, 933-41 (2011).
258. Sackey, P.V., Martling, C.R., Carlsward, C., Sundin, O. & Radell, P.J. Short- and long-term follow-up of intensi259. Samuelson, K., Lundberg, D. & Fridlund, B. Memory in relation to depth of sedation in adult mechanically ventilated intensive care patients. *Intensive Care Med* **32**, 660-7 (2006).
259. Ringdal M. et al. Outcome after injury: memories, healthrelated quality of life, axiety, and symptoms of depression after intensive care. J Trauma **66**, 1226-33 (2009)
260. Williams-Russo, P., Sharrock, N.E., Mattis, S., Szatrowski, T.P. & Charlson, M.E. Cognitive effects after epidural vs general anesthesia in older adults. A randomized trial. *JAMA* **274**, 44-50 (1995).
261. Rasmussen, L.S. et al. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. *Acta Anaesthesiol Scand* **47**, 260-6 (2003).
262. Magni, G. et al. No difference in emergence time and early cognitive function between sevoflurane-fentanyl and propofol-remifentanil in patients undergoing craniotomy for supratentorial intracranial surgery. *J Neurosurg Anesthesiol* **17**, 134-8 (2005).

263. Schoen, J. et al. Cognitive function after sevoflurane- vs propofol-based anaesthesia for on-pump cardiac surgery: a randomized controlled trial. *Br J Anaesth* **106**, 840-50 (2011).
264. Bernard, S.A. et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* **346**, 557-63 (2002).
265. Nielsen, N. et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med* **369**, 2197-206 (2013).
266. Samaniego, E.A., Mlynash, M., Caulfield, A.F., Eyngorn, I. & Wijman, C.A. Sedation confounds outcome prediction in cardiac arrest survivors treated with hypothermia. *Neurocrit Care* **15**, 113-9 (2011).
267. Fugate, J.E. et al. Predictors of neurologic outcome in hypothermia after cardiac arrest. *Ann Neurol* **68**, 907-14 (2010).
268. Arpino, P.A. & Greer, D.M. Practical pharmacologic aspects of therapeutic hypothermia after cardiac arrest. *Pharmacotherapy* **28**, 102-11 (2008).
269. Bjelland, T.W., Klepstad, P., Haugen, B.O., Nilsen, T. & Dale, O. Effects of hypothermia on the disposition of morphine, midazolam, fentanyl, and propofol in intensive care unit patients. *Drug Metab Dispos* **41**, 214-23 (2013).
270. Empey, P.E. et al. Mild hypothermia decreases fentanyl and midazolam steady-state clearance in a rat model of cardiac arrest. *Crit Care Med* **40**, 1221-8 (2012).
271. Hostler, D. et al. Mild hypothermia alters midazolam pharmacokinetics in normal healthy volunteers. *Drug Metab Dispos* **38**, 781-8 (2010).
272. Leslie, K., Sessler, D.I., Bjorksten, A.R. & Moayeri, A. Mild hypothermia alters propofol pharmacokinetics and increases the duration of action of atracurium. *Anesth Analg* **80**, 1007-14 (1995).
273. Voss, L.J., Ludbrook, G., Grant, C., Sleigh, J.W. & Barnard, J.P. Cerebral cortical effects of desflurane in sheep: comparison with isoflurane, sevoflurane and enflurane. *Acta Anaesthesiol Scand* **50**, 313-9 (2006).
274. Chamorro, C., Borrallo, J.M., Romera, M.A., Silva, J.A. & Balandin, B. Anesthesia and analgesia protocol during therapeutic hypothermia after cardiac arrest: a systematic review. *Anesth Analg* **110**, 1328-35 (2010).
275. Cronberg, T. et al. Neurological prognostication after cardiac arrest--recommendations from the Swedish Resuscitation Council. *Resuscitation* **84**, 867-72 (2013).
276. Friberg, H. & Cronberg, T. Prognostication after cardiac arrest. *Best Pract Res Clin Anaesthesiol* **27**, 359-72 (2013).
277. Jennett, B. & Bond, M. Assessment of outcome after severe brain damage. *Lancet* **1**, 480-4 (1975).
278. Edgren, E., Hedstrand, U., Kelsey, S., Sutton-Tyrrell, K. & Safar, P. Assessment of neurological prognosis in comatose survivors of cardiac arrest. BRCT I Study Group. *Lancet* **343**, 1055-9 (1994).
279. Mullie, A. et al. Predictive value of Glasgow coma score for awakening after out-of-hospital cardiac arrest. Cerebral Resuscitation Study Group of the Belgian Society for Intensive Care. *Lancet* **1**, 137-40 (1988).
280. Devlin, J.W. et al. Motor Activity Assessment Scale: a valid and reliable sedation scale for use with mechanically ventilated patients in an adult surgical intensive care unit. *Crit Care Med* **27**, 1271-5 (1999).
281. Granja, C. et al. Patients' recollections of experiences in the intensive care unit may affect their quality of life. *Crit Care* **9**, R96-109 (2005).
282. Kiekkas, P., Theodorakopoulou, G., Spyratos, F. & Baltopoulos, G.I. Psychological distress and delusional memories after critical care: a literature review. *Int Nurs Rev* **57**, 288-96 (2010).
283. Teasdale, G. & Jennett, B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* **2**, 81-4 (1974).
284. Steurer, M.P. et al. Late pharmacologic conditioning with volatile anesthetics after cardiac surgery. *Crit Care* **16**, R191 (2012).
285. Soro, M. et al. Cardioprotective effect of sevoflurane and propofol during anaesthesia and the postoperative period in coronary bypass graft surgery: a double-blind randomised study. *Eur J Anaesthesiol* **29**, 561-9 (2012).
286. Guerrero Orriach, J.L. et al. Prolonged sevoflurane administration in the off-pump coronary artery bypass graft surgery: beneficial effects. *J Crit Care* **28**, 879 e13-8 (2013).

287. Thielmann, M. et al. Prognostic value of preoperative cardiac troponin I in patients with non-ST-segment elevation acute coronary syndromes undergoing coronary artery bypass surgery. *Chest* **128**, 3526-36 (2005).
288. Roubille, F. et al. Delayed postconditioning in the mouse heart in vivo. *Circulation* **124**, 1330-6 (2011).
289. Lucchinetti, E. et al. Sevoflurane inhalation at sedative concentrations provides endothelial protection against ischemia-reperfusion injury in humans. *Anesthesiology* **106**, 262-8 (2007).
290. Obal, D. et al. One MAC of sevoflurane provides protection against reperfusion injury in the rat heart in vivo. *Br J Anaesth* **87**, 905-11 (2001).
291. Zhu, F., Lee, A. & Chee, Y.E. Fast-track cardiac care for adult cardiac surgical patients. *Cochrane Database Syst Rev* **10**, CD003587 (2012).
292. Agoliati, A. et al. Meta-analysis of average and variability of time to extubation comparing isoflurane with desflurane or isoflurane with sevoflurane. *Anesth Analg* **110**, 1433-9 (2010).
293. Morris, P.E. et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med* **36**, 2238-43 (2008).
294. Hall, R.I. et al. Light versus heavy sedation after cardiac surgery: myocardial ischemia and the stress response. Maritime Heart Centre and Dalhousie University. *Anesth Analg* **85**, 971-8 (1997).
295. Rohm, K.D. et al. Renal integrity in sevoflurane sedation in the intensive care unit with the anesthetic-conserving device: a comparison with intravenous propofol sedation. *Anesth Analg* **108**, 1848-54 (2009).
296. Shelly, M.P., Sultan, M.A., Bodenham, A. & Park, G.R. Midazolam infusions in critically ill patients. *Eur J Anaesthesiol* **8**, 21-7 (1991).
297. Martin, J. et al. Evidence and consensus-based German guidelines for the management of analgesia, sedation and delirium in intensive care - short version. *Ger Med Sci* **8**, Doc02 (2010).
298. Meybohm, P. et al. Pharmacological postconditioning with sevoflurane after cardiopulmonary resuscitation reduces myocardial dysfunction. *Crit Care* **15**, R241 (2011).
299. Knapp, J. et al. Pre- and postconditioning effect of Sevoflurane on myocardial dysfunction after cardiopulmonary resuscitation in rats. *Resuscitation* **84**, 1450-5 (2013).
300. Derwall, M., Timper, A., Kottmann, K., Rossaint, R. & Fries, M. Neuroprotective effects of the inhalational anesthetics isoflurane and xenon after cardiac arrest in pigs. *Crit Care Med* **36**, S492-5 (2008).
301. Chakkarapani, E. et al. Xenon enhances hypothermic neuroprotection in asphyxiated newborn pigs. *Ann Neurol* **68**, 330-41 (2010).
302. Fries, M. et al. Early administration of xenon or isoflurane may not improve functional outcome and cerebral alterations in a porcine model of cardiac arrest. *Resuscitation* **80**, 584-90 (2009).
303. Table of sorbents for contaminants listed in ACGIH 1970 threshold limit values. *Am Ind Hyg Assoc J* **32**, 404-9 (1971).
304. Adamczyk, S. et al. Sevoflurane pre- and post-conditioning protect the brain via the mitochondrial K ATP channel. *Br J Anaesth* **104**, 191-200 (2010).
305. Kersten, A. Abstact at Medizinische Klinik-Intensivmedizin und Notfallmedizin in Berlin **107** 317-318 (2012)
306. Lemaire, F. et al. The European Union Directive on Clinical Research: present status of implementation in EU member states' legislations with regard to the incompetent patient. *Intensive Care Med* **31**, 476-9 (2005).
307. Druml, C. Informed consent of incapable (ICU) patients in Europe: existing laws and the EU Directive. *Curr Opin Crit Care* **10**, 570-3 (2004).
308. Perkins, G.D. et al. Proposed revisions to the EU clinical trials directive--comments from the European Resuscitation Council. *Resuscitation* **84**, 263-4 (2013).
309. Sterz, F. et al. A serious threat to evidence based resuscitation within the European Union. *Resuscitation* **53**, 237-8 (2002).

Institutionen för Molekylär Medicin och Kirurgi

Sedation with volatile anesthetics in cardiothoracic ICU patients

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ABSTRACT

Volatile anaesthetics have been reported to provide protection against myocardial ischemia and reperfusion injury. This effect has been demonstrated in experimental studies when the volatile anaesthetics were provided either before (preconditioning) or after the ischemic period (postconditioning). Clinical trials of volatile anaesthetics versus intravenous anaesthesia for coronary artery bypass grafting (CABG) have reported reduced postoperative release of troponin, a biomarker of myocardial necrosis. The most pronounced reduction was achieved when sevoflurane was administered throughout surgery. Hence, it could be of interest to investigate whether additional myocardial protection could be achieved in cardiothoracic intensive care unit (ICU) patients following CABG by prolonging administration of volatile anaesthetics to include the period of routine postoperative sedation. The AnaConDa® is an anaesthetic conserving device that enables sedation with isoflurane or sevoflurane with common ICU ventilators. This method has been demonstrated to be feasible for sedation during mechanical ventilation in the general ICU. Isoflurane has also been used clinically to provide inhaled sedation during therapeutic hypothermia following cardiac arrest, but there are no evaluations or publications of this treatment. The AnaConDa® requires scavenging of volatile anaesthetics in expired breathing air. The use of an adsorbing canister with the filtered air released in the ICU room has not been well described.

The aim of this thesis was to investigate clinical and occupational aspects of inhaled sedation with volatile anaesthetics in cardiothoracic ICU patients.

We conducted a randomized clinical trial of short-term sevoflurane sedation versus propofol following CABG. While no significant differences were found in cardiac adverse events or troponin-T values sampled 12 hours following surgery, a reduced change from pre- to postoperative troponin-T values was demonstrated in a post-hoc analysis. Wake-up times were shorter in the sevoflurane-sedated group, but did not affect ICU or hospital stay in our short-term sedation. While sevoflurane-sedated patients were able to follow verbal command earlier, memories assessed with the validated ICU-Memory Tool were similar after sedation. In a retrospective study of isoflurane sedation during therapeutic hypothermia following cardiac arrest, it appeared that the early neurologic assessment with the Glasgow Coma Scale performed within 24 hours from reaching normal body temperature was consistent with the conventional assessment following 72 hours. We conducted an observational study of occupational exposure to sevoflurane during its use to provide sedation in the ICU and demonstrated that passive scavenging with an adsorbing canister (CONTRAfluranTM) provided minimal exposure to sevoflurane compared to no scavenging. Nurses in both groups had exposures below the Swedish occupational exposure limit, but only nurses working with patients without scavenging reported adverse symptoms. Smell of sevoflurane was the most frequent adverse symptom.

Keywords:*sevoflurane, sedation, myocardial protection, postconditioning, occupational exposure, therapeutic hypothermia,*

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