Volatile Versus Intravenous Anesthetics in Cardiac Anesthesia: a Narrative Review

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Abstract

Purpose of the Review The present review addresses clinicians and gives an overview about the experimental rationale for pharmacological conditioning associated with volatile anesthetics, opioids, and propofol; the current clinical data; and the technical considerations regarding the clinical routine in cardiac anesthesia.

Recent Findings Volatile anesthetics have been standard of care for general anesthesia for cardiac surgery, especially while using cardiopulmonary bypass. The 2019 published MYRIAD trial was not able to show a difference in mortality or cardiac biomarkers for volatile anesthetics compared to total intravenous anesthesia (TIVA), raising the question of equivalence with respect to patient outcome.

Summary Reviewing the literature, the scientific foundation for the belief of clinically relevant conditioning by uninterrupted administration of a volatile anesthetic is weak. TIVA can also be performed safely in patients undergoing cardiac surgery.

Keywords Volatile anesthetics · Total intravenous anesthesia · Cardiac surgery · Sevoflurane · Propofol · Desflurane

Introduction

The question whether the choice of anesthetic is an outcome-determining factor in cardiac surgery has occupied generations of anesthesiologists. During the last two decades, volatile anesthetics have become the anesthetic of choice in cardiac anesthesia. Studies have found pre- and postconditioning effects of volatile anesthetics, but large clinical trials on patients undergoing coronary artery bypass graft surgery were missing for a long time. The concept of pharmacological conditioning by volatile anesthetics is not only limited to the myocardium,

suggesting beneficial effects over intravenous anesthetics with respect to the reduction of myocardial infarction [1•], acute kidney [2], and lung injury [3]. Such effects have been ascribed to different mechanisms, including inhibition of mitochondrial permeability transition pores as well as activation of complex signaling pathways in the myocardial cells [1•, 4, 5]. However, these molecular mechanisms are complex and also influenced by opioids and propofol [1•, 6•].

Clinical trials investigating the effects of pharmacological condition with volatile anesthetics compared to total intravenous anesthesia (TIVA) observed a reduction in cardiac biomarkers as well as mortality [7, 8]. The largest and most recently published MYRIAD trial was not able to show a difference in mortality or cardiac biomarkers for volatile anesthetics compared to TIVA [9••], raising the question of equivalence. However, clinicians face different technical and pharmacokinetic challenges during cardiopulmonary bypass either using volatile anesthetics or TIVA [10].

The present review addresses clinicians and gives an overview about the experimental rationale for pharmacological conditioning associated with volatile anesthetics, opioids, and propofol; the current clinical data; and the technical considerations regarding the clinical routine in cardiac anesthesia.

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Experimental Data

Myocardial Protection

In experimental studies, the volatile anesthetics sevoflurane [11], desflurane [12], and isoflurane [13] have been shown to reduce the size of myocardial infarction. Such effects have been ascribed to cardioprotective effects by volatile anesthetics, the so-called conditioning. Traditional approaches to cardioprotection focused mainly on optimizing the oxygen supply/demand ratio. The pharmacological "conditioning" by volatile anesthetics is based on an activation of an endogenous "protection program" in the heart which results in long-term protection/resistance against ischemia-reperfusion-injury [1•]. The concept of "conditioning" itself refers to a combination of pre- and postconditioning, which exerts synergistic interactions [1•] (Figure 1). After the first stimulus, a second window of protection occurs hours later, being a result of activated transcriptional factors which alter gene expression [14, 15]. The molecular mechanisms of conditioning itself are complex and have been summarized in previous reviews [1•, 5, 16]. Briefly, the basic mechanism is the increase of the resistance of the cell against ischemia, or in other words an elongation of the time of tolerance of anaerobic metabolism in the myocardium. Physiologically, the adenosine triphosphate (ATP) production in the cardiomyocyte is realized by anaerobic glycolysis in the cytosol. ATP is transported into the mitochondria to maintain the mitochondrial membrane potential. The protons generated with this reaction lower the intracellular pH and activate proton/sodium and sodium/calcium channels resulting in an increasing level of cytosolic calcium which is transported into the mitochondria [5]. Together with reactive oxygen species, the calcium activates mitochondrial permeability transition pores (mPTPs), which result in a decoupling of the respiratory chain and swelling of the mitochondria, furthermore triggering apoptotic and necrotic mechanisms [4, 17, 18]. Volatile anesthetics as well as opioids
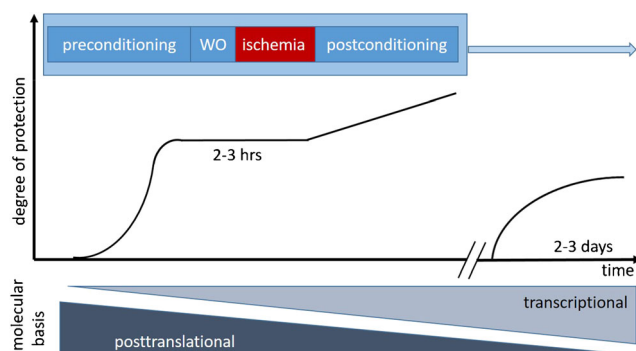

Figure 1 Concept of pharmacological conditioning. Modified from Zaugg et al. [1•]. "Pharmacological conditioning" refers to a combination of pre- and postconditioning. Due to its anti-inflammatory and anti-apoptotic effects, a prolonged protection over days is provided. WO, washout

activate via G-protein-coupled receptors, an intracellular signal cascade which results in less mitochondrial calcium and a higher mitochondrial potassium level, less reactive oxygen species (ROS), and a direct inhibition of the mPTPs. In addition, the gene expression in the cardiomyocyte is altered, leading to a transcription of anti-apoptotic genes and opening the "second window" of protection [1•].

Propofol, on the other hand, does not show typical features of conditioning [5]. It does not induce a second window of protection. Presumably, this is caused by inhibition of the protective signaling pathway initiated by volatile anesthetics and opioids through scavenging of reactive oxygen species and therefore activating the mPTP channels [19] and inhibition of K_{ATP} channels [1•, 5, 16]. However, some trials suggest protective effects of propofol due to its pronounced antioxidant properties mimicking some "pre- or postconditioning-like" effects [20–22]. Yet, the doses used in these trials were very high and out of the clinical routine range [21, 22]. It remains open, whether the scavenging effect of ROS or other mechanisms are causing those "pre- or postconditioning-like" effects [1•].

As essential partners to hypnotic agents in the clinical routine, opioids are often neglected in the discussion regarding volatile versus TIVA. Experimental data suggests protective and anti-apoptotic effects on the heart [6•]. Cardiac myocytes are capable of synthesis, storage, and release of opioid receptor peptides [6•, 23]. The therapeutic effects of clinically relevant opioids like morphine, fentanyl, remifentanil, or sufentanil mainly rely on activation of the µ-receptor. However, there are investigations questioning the existence of µ-receptor in the cardiac tissue [6•, 24]. Despite that, effects of these opioids are also mediated via κ- and δ-receptors, both found on cardiomyocytes [6•]. In addition, two studies suggested a possible µ-receptor expression in human heart tissue [25, 26]. However, the opioid-induced cardioprotection is also facilitated through the inhibition of mitochondrial transition pores similar to volatile anesthetics. Furthermore, a complex signal cascade involving sarcolemmal K_{ATP} channels, reactive oxygen species, protein kinase C, inducible nitric oxide synthetase and others are induced by opioid receptor activation in the cardiomyocyte contributing to cardioprotection by inhibition of apoptotic pathways [6•].

In summary, our knowledge on the molecular mechanisms of cardioprotective effects of propofol and opioids is still limited and more studies are warranted.

Other Protective Effects

The type of anesthesia has also the potential to affect pulmonary and other postoperative complications, since several anesthetic agents may contribute to organ protection aside from the myocardium. With regard to the lungs, volatile anesthetics may protect against lung injury [27] and attenuate

inflammation [3]. Fukazawa and colleagues summarized a complex signal pathway to prevent acute kidney injury [2].

Clinical Data

A retrospective register trial by Oh et al. enrolling 10,440 patients undergoing CAGB surgery showed a lower 3-year all-cause mortality with TIVA compared to volatiles [28]. Yet, the results of this retrospective trial should be interpreted with caution, due to methodical weaknesses caused by the trial design [29]. The first larger clinical randomized controlled trials demonstrating benefits for volatile anesthetics compared to TIVA were published by the group of De Hert and colleagues in 2004 and 2009 analyzing together 934 patients [8, 30, 31]. Table 1 summarizes the six largest randomized controlled trials (RCTs) with respect to patient enrollment in cardiac surgery. In the first of this RCTs, De Hert was able to observe a shorter intensive care unit (ICU) and hospital stay, as well as less inotropic support for a sevoflurane or desflurane versus propofol or midazolam-based TIVA anesthetic regimen [31]. In a second trial, published the same year, the time point of the application of sevoflurane was investigated [30]. When administered throughout the whole on pump coronary artery bypass graft (CABG) surgery, sevoflurane reduced cardiac biomarkers, as well as length of ICU and

hospital stay compared to the isolated application as pre- or postconditioning and propofol-based TIVA [30]. A reduction in 1-year mortality as well as length of hospital stay was observed for sevoflurane and desflurane versus TIVA without affecting postoperative cardiac biomarkers [8]. Another trial by Likhvantsev et al. showed lower postoperative cardiac biomarkers and shorter hospital stay for sevoflurane versus propofol-based TIVA, but was unable to observe an effect on in-hospital or 1-year mortality [7]. All these previous mentioned clinical trials were not powered for mortality.

A Bayesian network meta-analysis including primarily trials on CABG surgery demonstrated a reduction of in-hospital mortality for volatile anesthetics favoring especially sevoflurane and desflurane [33]. Those results are mostly based on the trials published by De Hert and colleagues [8, 30, 31] ranging approximately 40% of the weight of the effect size. In another meta-analysis published by our group, analyzing the data of 3205 cardiac surgical patients volatile anesthetics were associated with a reduction of overall mortality and non-pulmonary complications (mainly cardiac events) after cardiac surgery [34]. An effect on postoperative pulmonary complications could not be found in this meta-analysis [34]. However, the risk for bias was medium to high in most trials included in the analyses and none of these trials was powered for mortality as primary outcome. Therefore, the results need to be interpreted with caution.

Table 1 Trial overview. Depicted are the six largest trials with respect to patient enrollment. *AKI*, acute kidney injury; *CABG*, coronary artery bypass graft; *Des*, desflurane; *Fent*, fentanyl; *ICU*, intensive care unit; *LOS*, length of stay; *Mida*, midazolam; *PPCs*, postoperative pulmonary complications; *Prop*, propofol; *Remi*, remifentanil; *Sevo*, sevoflurane; *Suf*, sufentanil; *TIVA*, total intravenous anesthesia; +, superior to control/TIVA group; *n.s.*, not specified; *n.a.*, not statistically analyzed

Trial	Type of surgery	Type of volatile (number of patients)	Type of TIVA (number of patients)	Type of opioid Volatile (number of patients)	Type of opioid TIVA (number of patients)	Outcome						
						Mortality	Cardiac events	Cardiac biomarkers	PPCs	AKI	LOS ICU	LOS hospital
De Hert I [31]	CABG	Sevo (80) Des (80)	Prop (80) Mida (80)	Remi (All groups)	Remi	= (In-hospital)	=	Sevo+ Des+	=	n.s.	Sevo + Des+	Sevo+ Des+
De Hert II [30]	CABG	Sevo (150)	Prop (50)	Remi	Remi	=	=	Sevo+		n.s.	Sevo+	Sevo+
Lorsomradee [32]	CABG	Sevo (160)	Prop (160)	Fent	Fent	=	=	=	n.s.	=	=	=
De Hert [8]	CABG	Sevo (132) Des (137)	n.s. (145)	n.s. (all groups)	n.s.	Sevo+ Des+ (1 year)	=	=	n.s.	n.s.	n.s.	n.a.
Likhvantsev [7]	CABG	Sevo (437)	Prop (431)	Fent (Both groups)	Fent	Sevo + (1 year)	n.s.	Sevo +	n.s.	n.s.	n.s.	Sevo +
Landoni [9••]	CABG	n.s. Sevo (2255) Des (248) Iso (157) Total 2709	n.s. Prop (2297) Mida (419) Other (335) Total 2691	n.s. Fent (2238) Suf (389) Remi (185)	n.s. Fent (2198) Suf (385) Remi (258)	= (1 year) = (30 days)	=	n.s.	n.s.	=	=	=

The largest and most recent trial in this field is the so-called MYRIAD trial, published by Landoni and colleagues [9••]. This multicenter RCT enrolling 5400 patients undergoing elective CABG surgery was unable to determine a statistically significant difference between volatile anesthetics and TIVA in relation to 1-year mortality, length of hospital stay, or myocardial infarction and, consequently, was stopped for futility. Since its publication, the MYRIAD trial has been discussed extensively among clinicians. First, the trial was not planned for 5400, but 10,600 patients, raising concerns about underpowering. However, considering the small difference between groups for the primary outcome "1-year mortality" of 0.2 percentage points (2.8% versus 3.0%; 75 versus 79 [number of patients]; volatile versus TIVA, respectively), a total of 372,984 patients (186,492 patients per group) would be necessary to detect a difference in 1-year mortality with 90% statistical power and alpha of 0.05, according to the authors [35]. Second, the type and dosage of the volatile and TIVA agents were at the choice of the treating clinician which may have led to "underdosing" of volatile anesthetics, especially in case of high volume use of opioids. On the other side, this pragmatic approach made this trial feasible in almost every hospital performing CABG surgery representing "real-life" conditions. Third, only 482 patients in the volatile group received volatile anesthetics during cardiopulmonary bypass. As discussed before, the timing of the administration of the volatile anesthetic is crucial, since these agents exhibit the highest protective effect when administered during cardiopulmonary bypass (CPB) [1•, 30].

A recent meta-analysis including the MYRIAD trial, accounting for 57% of included patients, showed no difference in mortality, cardiac biomarkers, and time to extubation between TIVA and volatile anesthetics [36••]. While most of the data on the administration of volatile anesthetics is published for elective CABG surgery, clinical data in patients undergoing heart valve surgery is rare. A recent meta-analysis summarizing the data for volatile anesthetics in heart valve surgery found no difference between TIVA and volatile anesthetics with respect to mortality, postoperative complications, length of ventilator support, ICU, and hospital stay [37•].

In case of one lung ventilation, De Conno and colleagues found a reduction of proinflammatory cytokines for volatile anesthetics compared to propofol-based TIVA [38]. Schilling et al. observed a reduction of alveolar cytokines and systemic inflammatory response for sevoflurane and desflurane compared to propofol [39]. Another trial by Beck-Schimmer was unable to find a difference between desflurane and propofol-based TIVA on patient outcome after lung surgery [40]. Although all of those patients had thoracic surgery, one lung ventilation is also used during lateral thoracotomy for minimally invasive cardiac surgery.

In summary, the MYRIAD study has included markedly more patients than all other studies in this field together.

Therefore, the data contributed by the MYRIAD trial dominate all meta-analyses on this topic and the conclusion based on MYRIAD data has to be considered the current state of knowledge. However, De Hert et al. have found a clinically relevant conditioning effect by volatile anesthetics only in the group with continuous/uninterrupted administration of the volatile anesthetic before, during, and after cardiopulmonary bypass, i.e., throughout anesthesia and surgery [30]. In the MYRIAD trial, the majority of patients did not receive a volatile anesthetic during CPB [9••]. Therefore, the MYRIAD trial [9••] does not provide data to investigate whether or not the results by De Hert et al. [30] are of clinical relevance or just a finding by chance in a study with a small sample size.

Technical and Pharmacokinetic Considerations

Volatile Anesthetics

Although volatile anesthetics are widely used during CPB, not all manufacturers equip their CPB circuits for the attachment of vaporizers for volatile anesthetics [10, 41]. Several considerations need to be taken into account by the anesthetists and perfusionist while using volatile anesthetics during CPB: (1) a variable uptake of volatile anesthetics depending on the oxygenator type, (2) the difficulty to maintain a steady-state plasma concentration of volatile anesthetics during different phases of CPB and variable fresh gas flow rates, (3) avoiding awareness, (4) unexpected damage to parts of the CPB [42, 43], and (5) air pollution of operating room due to inefficient scavenging of waste gas [44, 45].

The oxygenator type mainly determines the rate of transfer of volatile anesthetics. Two types of hollow fiber membrane oxygenators are currently available: the microporous polypropylene (PPL) and the plasma-tight polymethylpentene (PMP) [46]. PPL membranes are recommended by the European Association of Cardio-Thoracic Surgery/European Association of Cardiothoracic Anaesthesiology/European Board of Cardiovascular Perfusion (EACTS/EACTA/EBCP) guidelines as first choice, because this membrane type allows the best transfer of volatile anesthetics [47]. Plasma-tight PMP membrane oxygenators are less efficient for diffusion of fresh gas and volatile anesthetic agents and, therefore, have an increased risk of intraoperative awareness [48, 49]. The EACTS/EACTA/EBCP guidelines do not recommend the use of plasma-tight PMP membrane oxygenators when volatile agents are administered during CPB [47]. In case of planned TIVA during CPB, plasma-tight PMP membrane oxygenators are feasible allowing a smooth transition from balanced anesthesia with volatiles to TIVA [46, 50]. The oxygenator fresh gas flow is the carrier gas for the delivery of volatile anesthetics. An increase of the fresh gas flow rate

enhances the uptake and solubility of volatile anesthetics in the plasma [51]. Higher rates of fresh gas flow may be necessary during CPG for instance to achieve normocapnia when carbon dioxide is inflated in the pericardial space to decrease the risk of air embolism. This may result in a higher volatile plasma concentration independent of blood/gas solubility assuming the concentration of the volatile agent is maintained constant [51].

On the other hand, hemodilution through the priming solutions of the extracorporal circuit reduces the blood solubility of volatile anesthetics resulting in lower plasma concentrations [49, 52]. In case of hypothermia during CPB, the uptake and plasma solubility of volatile anesthetics increase when temperature decreases. At the commencement of CPB, this effect might be balanced by the opposing effect induced by the prime hemodilution [10]. Furthermore, during rewarming and weaning from CPB, the change in temperature is usually faster than the increase in hematocrit. This effect decreases the blood/gas solubility to the lowest level of the entire cardiac surgery, facilitating washout of volatile anesthetics and resulting in a rapid decrease in depth of anesthesia [53]. All these special pharmacokinetic characteristics are accompanied by challenges in monitoring of the delivery of volatile anesthetics. The redundant venting systems deployed at the end of the exhaust port of the membrane oxygenator to eliminate the risk of overpressurization in the oxygenator makes it difficult to measure the concentrations of volatile anesthetic agent in the exhaust port precisely [10, 52] (Figure 2). The EACTS/ EACTA/EBCP guidelines recommend the measurement of all incoming and outgoing gases should be installed and maintained [47]. In addition, the volatile anesthetic concentration at the oxygenator exhaust should be maintained at least at the same level as before CPB and greater during rewarming [47]. However, especially the measurement of volatile anesthetics

at the exhaust port is technical complex and dependent on the type of oxygenator. Processed electroencephalography, such as the bispectral index (BIS), is essential to reduce the incidence of awareness during CPB [54]. However, there are some trials showing a poor correlation between the measured volatile gas concentration at the exhaust port of the oxygenator and BIS [51, 55].

Another important factor is the occupational hazard and air pollution of the operating room. To avoid this, a scavenging system at the outlet of the oxygenator is recommended [47, 56, 57]. Otherwise, the anesthesiologist, surgical staff, and the perfusionist will be exposed to waste volatile gas [56]. However, the occupational exposure standards are not uniform, but vary from country to country. In addition, there is no proprietary scavenging equipment specifically designed for the oxygenators available [10]. Nevertheless, adaptions to the anesthetic gas scavenging system are feasible [45, 58, 59], but often lack official certification. Also, the contribution to the greenhouse effect by depletion of the ozone layer, especially with isoflurane, should be considered [60].

Accidental spillage of liquid volatile agents over the polycarbonate shell reservoir or other CPB lines can cause severe damage and needs to be avoided [10]. The use of keyed vaporizers is recommended.

Total Intravenous Anesthesia

For anesthesia maintenance during CABG surgery with TIVA, the two most frequent drugs used are propofol (85.3%) and midazolam (15.6%) [9••]. Propofol has the advantage of improved controllability. The administration of midazolam is associated with increased risk for postoperative delirium [61, 62]. Due to its frequent use, only propofol will be discussed in this narrative review. The extracorporal circuit
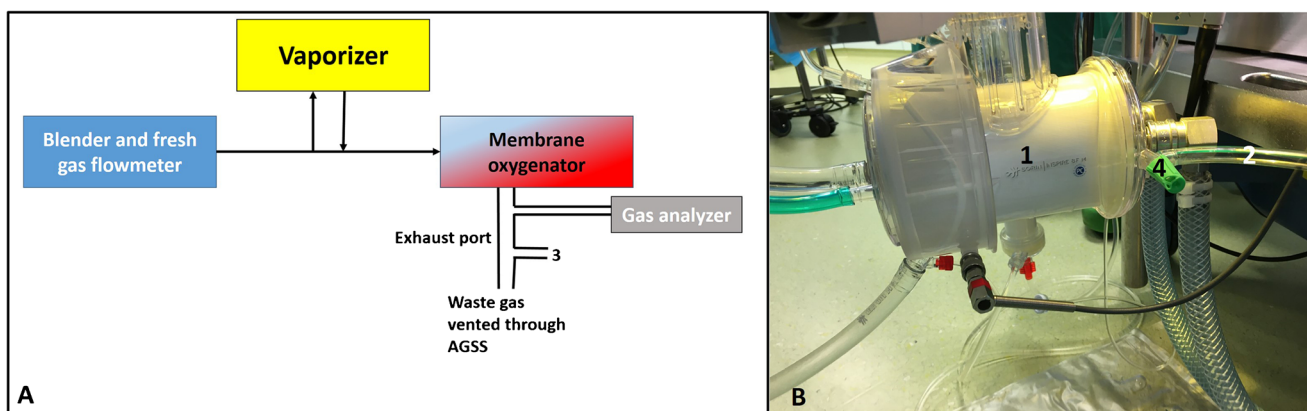

Figure 2 Anesthesia gas scavenging system. Modified from Yeoh and colleagues [10]. This figure shows a diagram of anesthesia gas scavenging system (**A**) and in real life (**B**). The vaporizer is installed between the blender and fresh gas flowmeter and the oxygenator. The gas analyzer samples waste gas from the exhaust port. The incorporation of another gas inlet 1 for entrainment of atmospheric air regulates the negative pressure within the exhaust port which is generated by the anesthesia gas scavenging system (AGSS). This active scavenging will lead to underestimation of the volatile anesthetic gas concentration in the waste gas sampled by the gas analyzer. 1: membrane oxygenator, 2: anesthesia gas scavenging system, 4: exhaust port

requires no special adaption to the use of propofol as continuous infusion [10]. The depth of anesthesia should be also monitored with processed electroencephalogram like BIS [63]. The free fraction of propofol in the plasma is influenced by the plasma protein binding capacity, hemodilution, the degree of adsorption to the extracorporeal circuit/membrane, the effect of hypothermia to the hepatic clearance of propofol, and other pharmacokinetic variation throughout different age groups [10].

With initiation of the CPB, the plasma concentration of the propofol decreases as well as the concentration of albumin, α1-glycoproteine, and red blood cells, which all bind propofol, resulting in a lower and variable free fraction of propofol [64, 65]. Even when assuming a homogeneous dilution of free propofol, protein bind propofol, and the binding proteins, the increased free fraction of propofol will offset the reduction in free drug concentration to some extent [10, 47, 65]. Because of its lipid solubility propofol will be sequestrated in the extracorporal circuit very quickly contributing to lower propofol plasma concentration [64]. Uncoated and heparin- or phosphorylcholine-coated circuits bind lipophilic drugs excellently [66, 67]. These mechanisms need to be considered and counteracted by increase of propofol concentration while avoiding awareness during CPB.

Hypothermia reduces the hepatic blood flow approximately 20% resulting in a lower propofol extraction [68]. For instance, at core temperature of 34 °C, the propofol plasma concentration is 28% higher than at 37 °C [69].

Implications for Future Studies

It is worth noting that the choice of anesthetic is not the only outcome relevant factor in cardiac surgery, which could be influenced by the anesthesiologist. Thermal care, hemoglobin and coagulation management, glycemic control, a protective ventilation strategy, and heart rate control also affect the outcome of the patient [1•]. During the last years, progress in cardiac surgical techniques, anesthetic management, and postoperative care has reduced perioperative mortality. There are several reasons why the "clear" signal of pharmacological conditioning by volatile anesthetics found in several experimental studies could be less and less better translated into a clear improvement of outcome in clinical trials over time: First, the outcome parameter mortality is very robust, but also a definitive endpoint, whereas length of hospital or ICU stay may be dependent on the health care system in each country. Second, the inclusion and exclusion criteria of clinical trials often choose a "healthier" study population compared to the "real-life" cohort. Third, confounding by indication bias especially in coronary bypass surgery may have influenced the patient population undergoing CABG surgery. While in the last decade also complex percutaneous coronary interventions

have become clinical routine [70], patients selected for CABG may have higher morbidity. Fourth, the protective role of opioid-induced pharmacological conditioning could have been underestimated in the previous clinical studies. Clinical trials investigating the effects of different opioids on mortality, cardiac, and non-cardiac complications are warranted.

Conclusion

The choice of anesthetic has been considered an outcome-relevant parameter in cardiac surgery favoring pharmacological conditioning with uninterrupted administration of volatile anesthetics throughout the entire cardiac surgery. These findings are based on a trial by the Group of De Hert with small sample size. No other published study has tested and confirmed their findings. Therefore, the scientific foundation for the belief of clinically relevant conditioning by uninterrupted administration of a volatile anesthetic is weak. The selection of anesthetic should be a team decision of the anesthesiologist, the perfusionist, and the cardiac surgeon considering the technical and pharmacokinetic challenges focused on each patients' demands. Further large randomized controlled trials are warranted investigating the role of volatile anesthetics, opioids, and propofol on patient outcome in cardiac surgery.

Compliance with Ethical Standards

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Papers of particular interest, published recently, have been highlighted as:
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