Role of Inhalational Anesthetic Agents in Reducing Perioperative Mortality

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4.1 General Principles

In a recent Consensus Conference, among the 12 maneuvers that led to improved outcome in the perioperative period, inhalational anesthetic agents were the only anesthetic agents identified as contributing to reduced postoperative surgical mortality [1, 2]. Inhalational anesthetic agents have been shown to provide short-term as well as long-term protection [3, 4]. The evidence supporting mortality reduction via inhalational anesthetic agents seems to be growing.

4.2 Published Evidence

Several randomized controlled trials suggested a reduction in cardiac troponin release in patients receiving volatile anesthetics in cardiac surgery when compared to patients receiving a total intravenous anesthesia (TIVA). A meta-analysis of randomized trials summarized these findings and also suggested a beneficial effect of volatile agents on myocardial infarction and survival [5]. Based on these results, the American College of Cardiology and the American Heart Association suggested that the use of inhalational anesthetic agents might be cardioprotective [6]. A recent meta-analysis confirmed that mortality was doubled in patients receiving TIVA in contrast to volatile agents (1.3 % in the volatile group vs 2.6 % in TIVA group, $p = 0.004$) [7].

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4.3 Pharmacological Properties

Inhalational anesthetic agents seem to protect myocardium by a mechanism known as "ischemic preconditioning," which is defined as "adaptive response to brief sublethal episodes of ischemia leading to a pronounced protection against subsequent lethal ischemia." Ischemic preconditioning provides two "protective windows": the first occurs immediately after restoration of circulation and lasts about 2 h and the second appears after 24 h, lasting up to 72 h. Intracellular signaling pathways resulting in the opening of sarcolemmal and mitochondrial adenosine-triphosphate-regulated potassium channels have now been identified to be responsible for myocardial protection, which is dose dependent. The reactive oxygen species, apoptotic cascade, nitric oxide, and calcium intracellular overload appear to play a major role in preconditioning. Myocardial protection by isoflurane triggers partial mitochondrial uncoupling and reduces mitochondrial Ca2+ uptake [8]. Availability of gene chips enabled researchers to show that ischemic preconditioning and isoflurane cardioprotection appear to modulate gene expression in rat hearts, suggesting trigger-dependent transcriptome variability [9]. However, recently a multicentric trial on remote ischemic preconditioning during cardiac surgery did not show beneficial effect [10].

4.4 Therapeutic Use

Therapeutic use of inhalational anesthetic agents for myocardial protection during cardiopulmonary bypass, beating heart surgery, percutaneous coronary interventions and noncardiac surgery is known. This protective phenomenon is predominantly pronounced during cardiac surgery using cardiopulmonary bypass and to a lesser extent during off-pump coronary artery bypass (OPCAB) surgery. Its role during percutaneous coronary interventions and noncardiac surgery appears to be even lesser.

4.4.1 Myocardial Protection in Patients Undergoing Surgery Under Cardiopulmonary Bypass

It was suggested that "a combination of alteration in contractility and metabolism, as well as a preconditioning-like effect, appears to be responsible for the protective properties against ischemia and reperfusion damage" [11].

4.4.1.1 Isoflurane

In a recent meta-analysis of role of isoflurane in comparison to propofol, Bignami and coworkers showed a trend ($p = 0.05$) toward a reduction in mortality in a subgroup of well-conducted studies [12]. Isoflurane protection activates the pro-survival signaling pathways even if the combination of ischemic preconditioning and anesthetic preconditioning by isoflurane merely increases the intracellular ATP concentration without additional benefits [13]. A recent meta-analysis of

randomized trials identified 37 studies and 3,539 patients in cardiac (16 studies) and in noncardiac surgery (21 studies). The authors found a reduction in mortality only when studies with a low risk of bias were included in the analyses (0 % in the isoflurane group versus 0.7 % in the comparator group, OR 0.13, 0.02–0.76, $p = 0.02$) with four cardiac and six noncardiac trials included and five non-inhalation and five inhalation agents as the comparator. A trend was noted when a subanalysis was performed with propofol as a comparator (0.2 % versus 1.1 %, $p = 0.05$, with 16 studies included) [12].

4.4.1.2 Sevoflurane and Desflurane

Recent data suggest that sevoflurane/desflurane use resulted in improved cardiac outcome [7]. In this meta-analysis, the authors stated that "Volatile agents were associated with a reduced time of mechanical ventilation, and duration of ICU and hospital stay. Furthermore, of 17 studies with troponin I analysis, 7 significantly favored the volatile regimen, in 6 we observe a trend in favor of volatile agents, and in 4 a trend in favor of TIVA." Landoni and coworkers also maintained that "Anesthesia with volatile agents appears to reduce mortality after cardiac surgery when compared with TIVA, especially when sevoflurane or desflurane is used. A large, multicentre trial is warranted to confirm that long-term survival is significantly affected by the choice of anesthetic" [7]. The same study group recently planned a large randomized trial to confirm the findings. [NCT02105610] The use of inhalational agents was shown to reduce 1-year mortality when compared to the TIVA group, although the markers of myocardial injury were not different between groups [14].

4.4.2 Myocardial Protection in Patients Undergoing OPCAB Surgery

It is but logical to expect a similar myocardial protection to be offered by inhalational anesthetic agents during OPCAB. Hemmerling and coworkers showed less myocardial injury during the first 24 postoperative hours in patients receiving sevoflurane for OPCAB surgery in contrast to those receiving propofol [15]. Wang and coworkers recently showed that, in a group of 48 patients, >1 MAC sevoflurane could exert a significant myocardial protective effect during OPCAB surgery [16]. However, in a large randomized controlled study, we could not demonstrate short-term benefits by the use of inhalational agents [17]. The data on this topic are still not forthcoming.

4.4.3 Myocardial Protection in Patients Undergoing Noncardiac Surgery or Percutaneous Coronary Interventions

Data about anesthetic agents in noncardiac surgery and percutaneous interventions are not supportive of the protective action [18, 19].

Conclusion

Volatile anesthetic agents decrease mortality and morbidity among cardiac surgical patients whether they undergo surgery under cardiopulmonary bypass or off-pump. The level of evidence for protection by TIVA seems lacking. Superiority of one volatile over the other has not been established, but in general, they all seem to provide clinically relevant protection. Nevertheless the dose route, duration, and type of volatile agents that might offer maximum protection with minimal side effects are still under investigation. It has now become all the more relevant to perform a large multicentric randomized control trial to better understand these intricacies.

Summary Table

Clinical summary					
Drug	Indications	Cautions	Side effects	Dosage	Notes
Inhalational agents	Myocardial protection during general anesthesia for cardiac surgery	Myocardial protection is dose and duration of inhalational anesthetic agent dependent	Common side effects of inhalational agents such as hypotension, myocardial depression, arrhythmias and effects on other solid organs	Unclear at the moment	Myocardial protection, decrease in infarct size and reduction in mortality during cardiac surgery have been well documented

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