Volatile anesthetics for lung protection: a bridge between operating rooms and intensive care units?

Giovanni Landoni[1,2], Omar Saleh[1], Elena Scarparo[1], Alberto Zangrillo[1,2]

[1]Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy; [2]Vita-Salute San Raffaele University, Milan, Italy

Correspondence to: Professor Giovanni Landoni. IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy.
Email: landoni.giovanni@hsr.it.

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In spite of their worldwide popularity as a cornerstone of general anesthesia maintenance, inhalational anesthetics (IAs) never fail to intrigue and surprise even experienced clinicians with their diverse effects.

A very recent prospective trial by Grabitz *et al*. on a large cohort of patients undergoing non-cardiac surgical procedures strongly suggests that use of high IA doses protects against postoperative respiratory complications and mid-term mortality (1).

Organ protective effects of IAs are known and much evidence is available to date, albeit clinical implications have been properly investigated only in cardiac surgery. The best insights in this setting come from eight studies that showed a significant decrease in mortality when comparing IAs versus total intravenous anesthesia (TIVA) (2-9).

Until now, if we had stepped out of the cardiac surgical operating room we would have found a discouraging situation: three medium/small randomized clinical trials (RCTs) investigating the effect of IAs in non-cardiac surgical interventions found no evidence of cardiac protection defined as a reduction in troponin release, natriuretic peptide levels or major cardiac events and reported also a similar incidence of delirium (10-12), while only a small RCT found a reduction in cardiac troponin and duration of ischemia in patients receiving IAs (13).

Reception of this evidence in clinical practice has been mixed. The American Heart Association guidelines published in 2009 attributed a GRADE score IIa to the following: "*It can be beneficial to use volatile anesthetic agents during noncardiac surgery for the maintenance of general anesthesia in hemodynamically stable patients at risk for myocardial ischemia (level of evidence: B)*" (14). This statement was eliminated in the subsequent update in 2014, in favor of a more cautious approach: "*Use of either a volatile anesthetic agent or total intravenous anesthesia is reasonable for patients undergoing noncardiac surgery, and the choice is determined by factors other than the prevention of myocardial ischemia and MI (level of evidence: A)*" (15).

In this barren landscape, Grabitz's study stands out and brings new answers and questions that experts will have to discuss in its vast shadow.

The authors analyzed 124,497 adult patients undergoing noncardiac surgical procedures and requiring general anesthesia with endotracheal intubation over an 8 years' period. As primary endpoint, they analyzed the relationship between the mean sums of age-adjusted minimum alveolar concentration (MAC) multiples and the incidence of major respiratory complications developed within 7 days of surgery (a composite of respiratory failure, pulmonary edema, reintubation, or pneumonia). Thirty-day postoperative mortality was a secondary outcome. After adjusting for covariates, Grabitz *et al*. found that IAs were dose-dependently and linearly associated with reduced risk of postoperative respiratory complications, an effect growing

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with the increase of equivalent dose ranges. Furthermore, higher dose IAs were linearly associated with significantly reduced risk of 30-day mortality with respiratory complications being the most frequent postoperative event associated with death. Progressively higher IAs dose ranges were also associated with reduced costs and hospital length of stay.

Grabitz *et al*. conclude that various known effects of IAs could have led to these results: favorable respiratory effects of IAs include short onset and offset compared to intravenous anesthetics, immunomodulation, and bronchodilation. Any of these is a potential candidate for the observed protective power of IAs.

But there is more. They also "*speculate, based on these data, that sedation with inhalational anesthetics outside of the operating room may likewise have protective effects that decrease the risk of respiratory complications in vulnerable patients*". Volatile anesthetics are effective bronchodilators, antiepileptics and immunomodulators, and this may be sufficient to prompt intensive care units (ICU) to equip themselves with vaporizers to administer halogenated-based sedation, at least to patients with special needs. For routine use, we possess still too little information: a meta-analysis of all the 12 RCTs performed in the ICU so far showed that, among various endpoints, only time to extubation was shorter in ICU patients sedated with halogenated agents (16). This is an entirely new direction, warranting further insight.

We can conclude that inhalational agents have a truly pleiotropic range of effects. New paths reveal every now and then a new beneficial outcome. Many results are coming from preclinical research where, for example, they were found capable to halve mortality in septic mice (17-19).

Given the proven and potential organ protective effects of IAs in cardiac surgery, is this the moment we throw a bridge to other surgery settings and critical care, changing our habits and suggesting a routine and widespread use of IAs in all anesthesia and sedations? In the authors' opinion, this is not the case yet. It is still time to study this topic further and to allow those who are performing trials to complete them quickly and those who are not performing studies to deliver the anesthesia plan they prefer.

It is imperative to promote new high quality, randomized trials in surgical or better in critical care settings to produce further insights on this potentially life-saving strategy. For this reason, the largest randomized trial ever planned on anesthetic drugs is randomizing 10,600 patients to volatile *vs.* TIVA anesthesia for coronary bypass surgery, with the aim to identify differences in mortality (on Clinicaltrials.gov: NCT02105610).

At the same time, new evidence and hypotheses are already accumulating fast and in the opposite direction, driven by a diverse and interesting environment concerning IAs effects. Just as an example of how the debate is far from resolved, a Finnish ongoing RCT is planning to include 8,000 oncologic patients undergoing surgery randomized either to propofol or IAs to test the idea that propofol anesthesia contributes to survival (on Clinicaltrials.gov: NCT01975064).

We are not currently walking on a bridge to future: rather we stand in the middle of a crossroads, having already explored some directions but otherwise barely seeing promising landscapes in the distance.

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Footnote

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