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EDITED AND REVIEWED BY
Andrea Kurz,
Cleveland Clinic, United States

*CORRESPONDENCE
Giovanni Landoni
✉ landoni.giovanni@hsr.it

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Old issues and new challenges in cardiothoracic anesthesiology: Work in progress...

Antonio Pisano[1], Matteo Angelini[2], Iliyan Vlasakov[2] and Giovanni Landoni[2,3]*

[1]Cardiac Anesthesia and Intensive Care Unit, Department of Critical Care, Azienda Ospedaliera Dei Colli, Monaldi Hospital, Naples, Italy, [2]Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy, [3]Faculty of Medicine, Vita-Salute San Raffaele University, Milan, Italy

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Present and future of cardiothoracic anesthesia: An overview

Cardiothoracic anesthesia may seem one of the most "traditionalist" subspecialties among anesthesia: cardiothoracic anesthesiologists intubate almost everyone, do very little locoregional anesthesia (especially in cardiac surgery), are still a long way from the fashionable "opioid-free anesthesia" concept [1], and are among the few who still use (and appreciate) the pulmonary artery catheter [2, 3]. Some would say it is an old dinosaur destined for extinction just like cardiac surgery itself [4], but (s)he couldn't be further from the truth. First, cardiothoracic anesthesiology has a long tradition of continuous research and innovation to improve the outcome of complex procedures, which are often associated with marked hemodynamic impairment, major bleeding, and life-threatening complications. Moreover, not rarely cardiac surgery is performed in high risk patients due to age, frailty, comorbidities, or critical status. Hence, an increasingly refined and extensive monitoring, specific pharmacological and non-pharmacological perioperative interventions, and defined organ-protection strategies may be pivotal in improving clinically relevant outcomes and increasing survival after cardiothoracic surgery. Second, cardiothoracic surgery is a constantly and rapidly evolving field. On the one hand, improvements in perioperative hemodynamic management and intensive care procedures, as well as the availability of increasingly sophisticated and effective mechanical circulatory support devices allow complex invasive cardiothoracic surgery procedures to be performed relatively safely in elderly patients [5] and in patients with poor myocardial systolic function [6]. On the other hand, minimally invasive and hybrid cardiothoracic procedures are becoming increasingly more common. Cardiothoracic surgery of the future will no longer be considered as opposed to interventional cardiology, but rather it will become part (or one of the options) of a dynamic multidisciplinary approach [7] involving cardiologists, cardiothoracic surgeons, cardiac anesthesiologists, and dedicated intensive care practitioners (the last two now already often belonging to a single team of anesthesiologists/intensivists who deal with both perioperative and intensive care management). Accordingly, cardiothoracic anesthesiologists and intensivists will have to keep up with all this in order to face, at the same time, both less invasivity and greater complexity and level of risk.

Outcomes after cardiothoracic surgery

Mortality and the rate of major complications after cardiothoracic surgery have decreased in the last decades due to improvements in both surgical techniques and perioperative care (including, as mentioned, the availability of increasingly sophisticated monitoring devices). However, mortality remains non-negligible (on average, around 2%) even for the simplest procedures, and dramatically increases in combined or more complex interventions [1]. Moreover, cardiothoracic surgery remains burdened with a relatively high risk of severe complications such as low cardiac output syndrome (LCOS), neurological complications, acute kidney injury (AKI), pulmonary complications, and major bleeding [1, 8].

Despite an intense clinical research activity, many aspects of cardiothoracic anesthesia care are still rather "empirical," without strong randomized evidence clearly guiding clinical strategies and therapeutic choices (see Figure 1) [1, 8]. In the latest edition of a series of international "democracy-based" consensus conferences aimed at reporting all "ancillary" (i.e., nonsurgical) interventions widely believed to significantly affect survival in the perioperative and critical illness setting according to at least one randomized controlled trial (RCT), only four interventions relating to cardiothoracic surgery were identified [9, 10]: volatile anesthetics, levosimendan for postoperative LCOS, leukocyte-depleted red blood cells use, and aprotinin avoidance. Of these, the use of leukocyte-depleted red blood cells for blood transfusion is now considered to be best practice in most Western countries [11], while the "cold case" of aprotinin could maybe be reopened in the future following its reintroduction into the (European) market in 2016 and on the basis of a recent noninterventional, post-authorization safety study whose results seem to be in contrast to those of the RCT that led to the withdrawal of aprotinin from the market [12]. Conversely, volatile anesthetics and levosimendan are undoubtedly two hot topics of current clinical practice and research in cardiothoracic anesthesia.

Volatile anesthetics have been shown to exert cardioprotective effects (the so-called anesthetic preconditioning) in several single-center investigations and meta-analyses and, accordingly, their use within the anesthesia regimen for cardiothoracic procedures is suggested or recommended by current guidelines and is largely diffuse also as primary maintenance agents during cardiopulmonary bypass (CPB) in countries like United States, United Kingdom, Belgium, and The Netherlands [1, 8]. Contrarily the recent MYRIAD multicenter RCT did not confirm the favorable effects of volatile anesthetics compared to total intravenous anesthesia on overall survival among 5,400 patients undergoing isolated coronary artery bypass graft (CABG) surgery [13]. However, as discussed elsewhere [1, 8], several factors may have contributed to these "no-difference" results: first, the pragmatic design of the study, which allowed different doses of volatile anesthetics and their association with drugs (especially propofol) that might have interfered with the preconditioning effect of volatile anesthetics; second, the small representation in the study population of either high-risk patients or patients undergoing the most complex cardiac procedures, who could have benefited more from a myocardial protective effect. Indeed, the findings of a *post-hoc* analysis of the MYRIAD trial, published in 2022, demonstrate a significantly reduced risk of myocardial infarction with hemodynamic complications in the volatile arm of the study, suggesting that anesthetic preconditioning by volatile anesthetics could be a real effect with clinical relevance [14]. Probably, the chapter "volatile anesthetics and myocardial protection" has not yet concluded. Studies are currently underway to investigate the possible role of volatile anesthetics in preventing other organ injuries in patients undergoing cardiac surgery: the DELICATE multicenter RCT (http://clinicaltrials.gov/show/NCT03729011) aims at investigating the effect of volatile anesthetics on the incidence of postoperative delirium in elderly patients; the APLICS trial [15] addresses the impact of sevoflurane, as compared with propofol, on lung injury and pulmonary complications.

Levosimendan is the most studied inotropic drug ever and the only one for which there is evidence (mainly coming from meta-analyses) of mortality reduction in cardiac surgery patients with or at risk for LCOS [16, 17]. Although three large RCTs published in 2017 found no statistically significant favorable effects of levosimendan on clinically relevant outcomes after cardiac surgery when administered either preoperatively in patients with reduced left ventricular ejection fraction (LICORN [18] and LEVO-CTS [19] trials) or postoperatively in patients with high inotropic score (CHEETAH study [20]), its use in the setting of cardiothoracic surgery has not decreased [21]. The findings of a recent substudy of the LEVO-CTS trial showing that levosimendan significantly reduced both 90-day mortality and the rate of LCOS in patients undergoing isolated CABG, but not in those undergoing valve surgery or combined CABG/valve procedures suggest that subgroups of patients can benefit from levosimendan in terms of survival [22]. Moreover, it has been recently suggested that levosimendan may improve the weaning success rate and survival in patients on venoarterial extracorporeal membrane oxygenation (VA-ECMO) [23, 24], who undoubtedly represent a subgroup of patients with severe myocardial dysfunction and LCOS. The currently ongoing WEANILEVO trial aims at investigating the effectiveness of levosimendan in improving the weaning success rate (and mortality among other secondary outcomes) in adult patients who are eligible for VA-ECMO withdrawal [25].

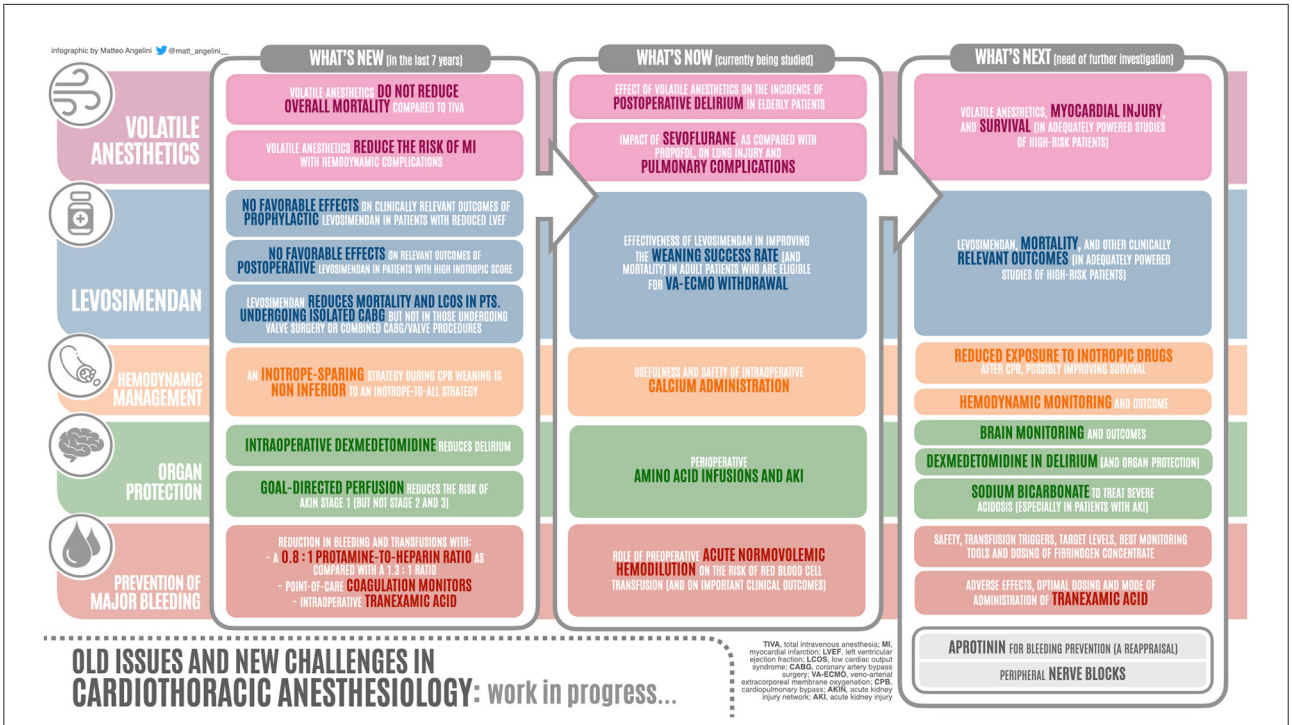

FIGURE 1
Present and future of clinical research in cardiothoracic anesthesia (only main evidences from randomized controlled trials are reported). TIVA, total intravenous anesthesia; MI, myocardial infarction; LVEF, left ventricular ejection fraction; LCOS, low cardiac output syndrome; CABG, coronary artery bypass surgery; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; CPB, cardiopulmonary bypass; AKIN, acute kidney injury network; AKI, acute kidney injury.

Hemodynamic management and outcome: Other issues looking for answers

Hemodynamic targets (e.g., mean arterial pressure during CPB), administration of inotropic drugs and calcium to aid CPB separation, parameters to be monitored, use of "goal-directed therapy" or "goal-directed perfusion" (GDP) protocols, and monitoring devices to be used during and after cardiothoracic surgery are all widely variable among centers worldwide and chosen rather empirically [8]. Dozens of small studies could be identified showing that one or another monitoring device can improve this or that outcome or, on the contrary, has no impact on outcome at all, and studies of this type will continue to be done in the future. However, if we wait for a large RCT unequivocally proving that a monitoring system improves patient survival, we could be left disappointed for life. Hemodynamic monitoring and management of hemodynamic instability are a serious affair: probably, the more information you have, the better, but how this information is used (or misused), integrated with one another, interpreted, and which action it leads to (in the individual patient you are in front of) is the heart of the difficult work of the skilled (cardiothoracic) anesthesiologist/intensivist and it can hardly be standardized.

Two topics regarding hemodynamic management for which changes in clinical practice are underway are the administration of inotropes and that of calcium during CPB weaning [8]. The traditional "inotrope-to-all" strategy is gradually giving way to an "inotrope-sparing" approach, which did not show an increased mortality in a recent relatively small RCT [26] and is worthy of further research to evaluate the hypothesis that a reduced exposure to inotropic drugs after CPB could even improve survival.

Calcium salts are often routinely administered with the aim of hemodynamic support during CPB separation, although calcium may potentially worsen the myocardial ischemia/reperfusion injury [8], and further concern comes from a 2021 RCT suggesting possible harm from calcium infusion in the setting of out-of-hospital cardiac arrest [27]). A currently ongoing large multicenter RCT (the ICARUS trial [28]) will hopefully shed some light on the usefulness and safety of calcium administration during cardiac surgery.

Organ protection during cardiothoracic surgery

The risk of neurological complications after cardiac surgery (ranging from the much more common delirium

and neurocognitive dysfunction to stroke and coma) remains relatively high [1, 29]. There is no outstanding evidence that any of the available brain monitoring devices, including processed electroencephalography, evoked potentials, transcranial Doppler, and near-infrared spectroscopy cerebral oximetry (from which anesthesiologists can potentially get a lot of useful information) may favorably affect clinically relevant outcomes after cardiac surgery. Accordingly, there is currently poor general agreement on the usefulness of routine cerebral monitoring even with a widespread and easy-to-use technology, which has been intensively studied in recent years, such as near-infrared spectroscopy [8, 29, 30]. Adequately designed and powered studies should continue to investigate the potential role of neurological monitoring (possibly associated with specific intervention protocols) in reducing the risk of brain injury, neurocognitive dysfunction, and delirium after cardiac surgery. A patient-tailored approach to mean arterial pressure targeting during CPB, based on near-infrared spectroscopy and/or transcranial Doppler to estimate the lower limit of cerebral autoregulation and aimed at reducing the risk of postoperative stroke, is particularly intriguing, but very far from entering common clinical practice [8, 29].

Among the pharmacological interventions which may improve neurological outcomes after cardiac surgery [1, 8], the most promising (and certainly deserving of further studies) is intraoperative infusion of dexmedetomidine, which has been shown in a 2020 meta-analysis [31] and in a subsequent single-center RCT [32] to possibly reduce postoperative delirium in patients undergoing cardiac surgery.

Cardiothoracic anesthesiologists and intensivists have long been looking for strategies to reduce the incidence and severity of postoperative AKI (and its burden of morbidity and mortality), most of which have proved to be useless (e.g., dopamine agonists [33]) or even harmful (prophylactic sodium bicarbonate infusion [34]). More recently, a goal-directed perfusion strategy aimed at maintaining indexed oxygen delivery above 280 ml/min/m^2 during CPB was shown in a multicenter RCT (the GIFT trial [35]) to reduce the rate of acute kidney injury network (AKIN) stage 1 (but not stage 2 and 3) AKI after cardiac surgery, while the BICAR-ICU multicenter trial [36] found that administering sodium bicarbonate to maintain a pH $>$ 7.3 may reduce mortality in intensive care unit patients with severe metabolic acidosis and AKI. These findings need to be confirmed in further studies. Another possible AKI prevention strategy in cardiac surgery patients, which is under investigation by a currently ongoing large multicenter RCT (the PROTECTION trial [37]), is the intra- and postoperative infusion of amino acids.

The use of neuromuscular blocking agents and the ventilatory strategies in cardiothoracic surgery (including during CPB) are gradually changing, although there is still no evidence that avoiding neuromuscular blocking agents or any ventilatory strategy may affect postoperative pulmonary outcomes, despite a couple of RCTs recently addressed these topics [1, 8].

Prevention of major bleeding

A large number of blood products are consumed every day during cardiothoracic procedures, and reducing bleeding and transfusions (and, consequently, the quarrels with surgeons and blood banks but, primarily, the risk of associated complications and worst outcomes) is a compelling challenge in this setting. In the last few years, several RCTs have provided cardiac anesthesiologists with some evidence-based strategies to possibly achieve this goal: a 0.8:1 protamine-to-heparin ratio compared to a 1.3:1 ratio [38], the use of point-of-care coagulation monitors [39], fibrinogen concentrate supplementation (ZEPLAST trial) [40] and, above all, intraoperative administration of tranexamic acid (ATACAS trial) [41]. However, there is still a long way to go since all but ATACAS are relatively small studies and none of them shows outstanding effects on clinically relevant outcomes such as survival. Moreover, many aspects (e.g., the safety, transfusion triggers, target levels, best monitoring tools and dosing of fibrinogen [42] and the possible adverse effects, optimal dosing and mode of administration of tranexamic acid [43]) need to be further clarified. A large multicenter RCT investigating the role of preoperative acute normovolemic hemodilution on the risk of red blood cells transfusion (and on important clinical outcomes as secondary endpoints) is currently ongoing (ANH trial, http://clinicaltrials.gov/show/NCT03913481).

Along the road toward less invasivity: Loco-regional anesthesia

While neuraxial and deep regional (such as paravertebral blocks) anesthetic/analgesic techniques have long been a reality in thoracic surgery, in which even lung resections are increasingly performed without general anesthesia and one-lung mechanical ventilation [44, 45], their use in cardiac surgery is still rather limited due to concerns of potential serious complications (especially neurological sequelae due to hematoma formation), the increasingly aggressive perioperative use of antithrombotic drugs, and the lack of clear evidence of a favorable impact on outcomes [1]. However, probably additionally due to the spread and refinement of ultrasound-guided techniques and to a general tendency toward opioid sparing and optimization of the times and quality of recovery after surgery (within specific "enhanced recovery after surgery" protocols or not), there is a recent renewed enthusiasm for loco-regional anesthesia also in cardiac surgery. In particular, small studies and case reports are accumulating describing

the use of various myofascial plane blocks such as erector spinae plane block, serratus anterior plane block, or parasternal block for pain management in cardiothoracic surgery, including "conventional" (i.e., sternotomy) procedures [46–48]. These blocks may have an even greater rationale considering the growing spread of less invasive (e.g., mini-thoracotomy) cardiac surgery techniques. This will certainly be a thriving field of clinical research in cardiothoracic anesthesia in the near future.

Author contributions

GL and AP ideated and wrote the article. IV and MA collaborated to the improvement of the article. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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