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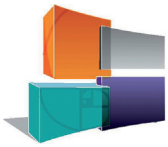

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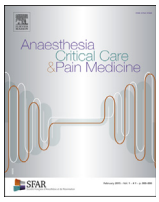

Editorial

Short-term and long-term prognosis after cardiac surgery: Do anaesthetics protect against ischemia-reperfusion injury?

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The perioperative outcome of a patient undergoing a surgical procedure under general anaesthesia is a highly complex process. In the age of Enhanced Recovery after Surgery, low complication and mortality rates are expected even after major surgery, and each specific effort designed to improve clinical outcomes must be considered [1,2]. On the bench and at the bedside, ischemia-reperfusion injuries occur in various settings, including solid organ transplantation, trauma, liver or cardiovascular surgery [3–5]. Considerable research has therefore been conducted, and attention has been paid to the impact of the anaesthesia strategy on the prevention and management of ischemia-reperfusion injury. Pharmacological conditioning before, during and after ischemia is one potential line of research. It consists of reducing injury by administering a drug before, during or after the procedure in order to reduce organ dysfunction.

Not surprisingly, cardiovascular surgery is the main field in which these strategies have been tested in a plethora of studies, conducted according to various designs with varying degrees of robustness, resulting in major or only minor benefits, ranging from decreased biomarker release to decreased mortality. More specifically, following the demonstration of the anti-ischemic effect of volatile anaesthetics by Bland and Lowenstein [6], many experimental and clinical studies on this topic have been published. The cellular and molecular mechanisms of anaesthetic preconditioning to decrease the sensitivity of cardiomyocytes to ischemia have been clearly established [7,8]. Several meta-analyses have tried to summarise the abundant small proof-of-concept studies [9], and their results generally supported the hypothesis that the use of a volatile anaesthetic was associated with decreased postoperative release of troponin, preserved left ventricular systolic function, reduced inotropic drug requirements, and a potential reduction of mortality, compared with a total intravenous anaesthetic (TIVA) technique in cardiac surgery.

Landoni et al. reported a work of major interest in a recent publication of the New England Journal of Medicine [10]. In the MYRIAD (Mortality in Cardiac Surgery Randomised Controlled Trial of Volatile Anaesthetics) randomised controlled trial, the authors designed a pragmatic multicentre prospective trial in 13 countries including 36 centres; 5400 patients undergoing elective coronary artery bypass graft (CABG) were randomly assigned to an anaesthetic regimen, which included a volatile anaesthetic (desflurane, isoflurane, or sevoflurane) or total intravenous anaesthesia. Patients with combined valvular or ascending aorta surgery were excluded. After the interim analysis led to cessation of the study for futility, no difference was observed in long-term major outcome (2.8% in 1-year all-cause mortality in the volatile anaesthetic group and 3.0% in the total intravenous anaesthesia group; relative risk: 0.94; 95% confidence interval: 0.69 to 1.29; $P = 0.71$). No trends were observed for prespecified secondary outcomes, including 30-day mortality, myocardial infarction, bleeding, neurological adverse outcomes, acute kidney injury, post-cardiotomy shock or need for mechanical support, hospital or intensive care unit stay. Biomarkers of myocardial necrosis, such as troponin or CK, which are usually the surrogate markers of pharmacological conditioning, were also equally elevated in the volatile anaesthetic and TIVA groups.

Landoni et al. conducted a well-designed study that met all of the required methodological items of a robust randomised trial. Despite negative, or at least neutral results, the authors must be congratulated for such an important study.

However, this study comprised several limitations. Firstly, this trial was designed as a pragmatic single-blind trial. Administration of volatile anaesthetics was not standardised: local investigators could choose both the agent and administration regimen (pre-, intra-, post-). In addition, patients in the volatile agents group also received propofol and opioids, two classes also known to interfere with cardioprotection. The TIVA protocol was also heterogeneous, using propofol, etomidate or benzodiazepines alone or in combination. Although this approach increased the external validity of the study, it does not exclude the possibility that another regimen would have been effective.

Secondly, the primary objective was 1-year mortality, which is a questionable choice, as a combination of outcomes would have been preferable, especially in the setting of cardiac surgery in which mortality is now very low. In addition, patients were not severely ill: although the EuroSCORE II was not reported, the median left ventricular ejection fraction was 58% in the volatile

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anaesthetics group and 57% in the TIVA group, and the incidence of postoperative low output syndrome or need for mechanical support were quite low. It is likely that higher surgical risk patients undergoing combined surgery, or with poorer ventricular function, may have derived greater benefit from perioperative optimisation including volatile anaesthetics. Inclusion of patients undergoing valve surgery would also have provided valuable data. No details concerning the type of cardioplegia and cardiopulmonary bypass management were reported. Importantly, about 40% of CABG procedures were performed off-pump, whereas the long-term adverse outcomes of off-pump surgery have been recently demonstrated [11].

Thirdly, postoperative serum troponin level was not specifically evaluated as a secondary outcome. Various types of troponin were non-systematically assayed according to each participating centre's usual practice, and did not reveal any significant differences. Troponin is a specific marker of cardiomyocyte injury and a proven predictor of mortality in cardiac surgery [12]. The authors targeted hard clinical outcomes, but in the context of the neutral results of the study, strictly timed quantitative evaluation of troponin kinetics could have provided more insight into subclinical myocardial injury.

Promising preclinical studies, observational studies, and moderate-sized randomised controlled trials in anaesthesiology and critical care medicine have been largely discarded by large-scale randomised trials, such as corticosteroids in sepsis [13], cyclosporine in myocardial infarction [14] or levosimendan in cardiac surgery [15–17]. Does this mean that we are going back to the stone age of our specialty? Certainly not. But it highlights the need to define more clearly the optimal target of each specific intervention, such as the most severe septic patients [18] or cardiogenic shock treated by veno-arterial ECMO [19,20].

Cardiac surgery-related morbidity has decreased over recent decades as a result of multifactorial improvements, such as cardioplegia composition, better surgical techniques, new drugs, development of more adequate biomaterial, and continuous optimisation of perioperative haemodynamic, ventilation or transfusion/haemostasis strategies. This progressive multimodal improvement in outcomes could also partially explain the neutral results reported by Landoni et al. after years of hopeful research. The current practice of cardiac anaesthesiologists is certainly very different from that before the discussion of this topic. The rules of the game have changed. A legitimate question in the field of anaesthesiology research would be: are the strategies effective per se individually or only when they are combined? In other words, are single interventions drowned in a global strategy? In this context, another neutral result might be disappointing for researchers, but it would probably be good news for clinical practice. We have reached a degree of improvement at which it is difficult to demonstrate any major improvements based on single interventions.

Finally, is the debate about volatile anaesthetics closed? It would be unwise to end 30 years of research into volatile anaesthetics on the basis of these results. The MYRIAD study addresses a major issue in cardiac anaesthesiology and constitutes a significant step forward. No difference in terms of outcome was observed between volatile anaesthesia and TIVA in the routine clinical practice of the 36 participating centres. However, would a more standardised volatile anaesthetic administration approach make a difference in the most severe patients? We do not know the answer to this question. Clinical practice confers a less controlled environment compared to an experimental setting. Is "common practice" enough in the most severely ill population?

At this stage, it might be premature to conclude on the complete lack of benefit of volatile anaesthetics in all patients based on the results of a single study. This question needs to be addressed by a strict comparison of volatile anaesthesia with a single administration strategy. The upcoming DELICATE trial (clinicaltrial.gov number: NCT03729011) will test the effect of volatile anaesthetics on neurological outcomes in cardiac surgery and may add another piece to the puzzle. The arrival of personalised anaesthetic management, perioperative genomics and pharmacogenetics might also change our actual paradigm [21–23].

Disclosure of interest

The authors declare that they have no competing interest.

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