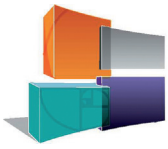
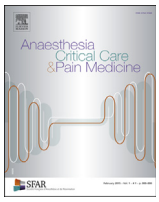
Anaesth Crit Care Pain Med xxx (2017) xxx–xxx



SFAR
Société Française d'Anesthésie et de Réanimation



Original Article

Sevoflurane-induced cardioprotection in coronary artery bypass graft surgery: Randomised trial with clinical and ex-vivo endpoints

Sandrine Lemoine [a,*,1], Lan Zhu [a,1], Jean-Louis Gérard [a], Jean-Luc Hanouz [a,b]

[a] Department of Anaesthesiology and Intensive Care, Université Caen-Normandie, Centre Hospitalier Universitaire de Caen, 14033 Caen, France
[b] EA 4650, Université Caen-Normandie, Centre Hospitalier Universitaire de Caen, 14033 Caen, France

ARTICLE INFO

Article history:
Available online xxx

Keywords:
Sevoflurane
Preconditioning
Cardiac surgery
Troponin
Inotropic drug support
Isolated trabeculae contractility

ABSTRACT

Background: Myocardial ischaemia reperfusion injury following cardiac surgery with cardiopulmonary bypass (CPB) increases postoperative mortality. Setting techniques to protect the heart during this critical period therefore represents a considerable challenge.
Method: A randomised controlled study in Caen University Hospital Centre, investigated whether the clinical cardio protective effects of administration sevoflurane before cardiopulmonary bypass during coronary artery bypass graft surgery (CABG) could translate into protected atrial trabeculae contractility against hypoxia–reoxygenation in vitro. Patients undergoing elective on-pump CABG surgery were allocated to receive either sevoflurane ($n = 24$) or no halogenated volatile anaesthetic ($n = 21$). Main outcome measures: the relationship between sevoflurane exposure before CPB and the incidence of major adverse cardiac events, with primary endpoint: the postoperative troponin I peak level, and secondary endpoints: the inotropic support, and the duration of stay in intensive unit and in-hospital stay were chosen as study endpoints. The right atrial was collected at the beginning of bypass surgery for the in vitro experimentation. Isometrically contracting isolated human right atrial trabeculae obtained from the two groups were exposed to 30-min hypoxia followed by 60-min reoxygenation.
Results: The patients receiving sevoflurane prior to aortic clamping significantly exhibited less cardiac Troponin I (1.39 [0.34–2.97] vs. 2.80 [2.54–3.64] $ng{\cdot}mL^{-1}$ in Control; $P = 0.03$) and required a reduced inotropic drug support ($P < 0.001$). Isolated trabeculae from patients receiving sevoflurane enhanced the recovery of force after reoxygenation compared to the Control group ($79 \pm 5\%$ vs. $53 \pm 8\%$ of baseline in Control; $P < 0.001$).
Conclusions: Administration of sevoflurane before CPB induced cardioprotection in patients undergoing CABG and preconditioned human myocardium against hypoxia-reoxygenation in vitro.

1. Introduction

In the perioperative period, the myocardium may suffer from ischaemia reperfusion either because of the surgical procedure (surgery with cardiopulmonary bypass [CPB]) or because of a mismatch between oxygen consumption and oxygen supply. Following coronary artery bypass grafting (CABG) surgery with CPB, myocardial contractile dysfunction remains frequent and may require inotropic and mechanical circulatory support, which has been suggested to be associated with increased morbidity and mortality [1,2]. Meta-analysis suggested that during CABG surgery, volatile anaesthetics may afford myocardial protection resulting in a significant increase in post-bypass cardiac index and reduction in postoperative plasma concentration of cardiac troponin I (TnIc) [3–5], inotrope administration, and duration of mechanical ventilation [3]. Nevertheless, the meta-analysis of Yao et al., which specifically analysed studies using sevoflurane, did not report difference in postoperative mechanical ventilation time and inotropic support [6].

Few studies have examined the effects of volatile anaesthetics administered during cardiac surgery with CPB on isolated myocardium obtained from patients during surgery. These studies focused on biochemical endpoints and strongly suggested that the biochemical cascade of preconditioning was activated [7–9]. Nevertheless, a direct link between the clinical administration of sevoflurane and its preconditioning effect on the contractile force in vitro has never been investigated.

* Corresponding author. Pôle réanimations anesthésie SAMU, Niveau 6, CHU de Caen, avenue Cote-de-Nacre, 14033 Caen cedex, France. Fax: +33 2 31 06 51 37.
E-mail address: sand.lemoine2@wanadoo.fr (S. Lemoine).
[1] Equal contribution.

http://dx.doi.org/10.1016/j.accpm.2017.05.009

The aim of our study was to investigate if administration of sevoflurane before cardiopulmonary bypass (preconditioning) could protect patient's heart against future ischaemia reperfusion injury. For the first time, the present randomised study combines an indirect proof of the preconditioning effect (postoperative troponin release which has also been shown to result from direct surgical tissue damage during surgery) and a direct proof based on the contractile performance of atrial sample obtained from the patients and exposed to hypoxia-reoxygenation in vitro.

2. Methods

2.1. Study design and ethics

This was a single centre (Centre Hospitalier Universitaire of Caen, Caen, France) randomised controlled trial performed from July, 01 2005 to March, 31 2006. The present study was approved by the local research ethics committee (CPP Nord Ouest III, registration number ID: 2004-22), and the authorisation by the Commission Nationale de l'Informatique et des Libertés (CNIL) was obtained on June, 20 2005. The study was registered in the university hospital of Caen (trial identification number: 04-106).

2.2. Patients selection-eligibility criteria for participants

Patients received written and oral information on the protocol during surgery and anaesthetics consultation (usually 2 to 3 weeks before surgery). Written informed consent was obtained the day before surgery by the senior anaesthetist in charge of the patient.

Consecutive adult patients scheduled for CABG surgery with CPB were randomly assigned to Control (total intravenous anaesthesia) or Sevoflurane (anaesthesia including sevoflurane administration) groups. Patients with atrial dysrhythmias, diabetes mellitus taking oral hypoglycaemic medications and insulin, with angina within the 48 hours before surgery, and patients requiring emergent surgery were excluded.

2.3. Randomisation and experimental protocol

The evening before surgery, the anaesthesiologist in charge of the patient checked for exclusion criteria and obtained written informed consent. Then, randomisation was performed through an interactive web response system (Clinsight® software, Ennov, Paris, France) allocating patient in Control or Sevoflurane group. The anaesthesiologist in charge of the patient during surgery was not blinded because sevoflurane evaporator and gas analysis monitor cannot be masked. At the end of the surgery, the anaesthesiologist in charge of the patient sealed sheets of the peroperative period data. Thus, nurses and anaesthesiologists in charge of the patient in the postoperative period (intensive care unit and wards) were blinded for group assignment. Anaesthesia procedure common to all patients is developed in supplementary material section.

In the Control group, patients received total intravenous anaesthesia (target control administration of propofol and remifentanil) without any administration of volatile anaesthetics. Vasopressor administration was left at the discretion of the attending anaesthesiologists.

In the Sevoflurane group, patients received total intravenous anaesthesia (target control administration of propofol and remifentanil) and sevoflurane was administered at 1 MAC or more. The administration of sevoflurane started from the skin incision. The duration of administration must be at least 30 minutes at the appropriate concentration and must be followed by a 10-min washout period prior to the aortic clamping. The administration of sevoflurane could be accompanied by a concomitant decrease in the continuous intravenous infusion of propofol according to depth of anaesthesia and hemodynamic data. Vasopressor administration was left at the discretion of the attending anaesthesiologists.

2.4. Primary endpoint

The primary endpoint of the study was the plasma concentration of cardiac troponin I (cTnI) at 24 h following ICU (intensive care unit) admission. This was chosen in accordance with previous studies showing that the peak of plasma concentration of cTnI value was an independent predictor of short- and long-term adverse outcome in cardiac surgical patients [10–12]. cTnI was analysed with a sensitive and highly specific immunoenzymometric assay (AxSYM Troponin-I ADV assay; Abbott Laboratories, Rungis, France) that detects both free and complex bound troponin. The assay allows the detection of cTnI within the range of 0.02–23 $ng \cdot mL^{-1}$ with appropriate dilutions. Values greater than 0.04 $ng \cdot mL^{-1} \cdot L$ were considered abnormal. The within-run coefficient of variation was 6% and the between-run coefficient of variation was 11%.

2.5. Secondary endpoints

2.5.1. Clinical outcome

The following clinical endpoints were recorded:

- postoperative plasma concentration of creatine phosphokinase (CK) and creatinine plasma concentration measured 24 h after ICU admission;
- nonfatal major adverse cardiac events (MACE) defined by: the postoperative occurrence of malignant ventricular arrhythmia (i.e. sustained ventricular arrhythmias requiring treatment), postoperative myocardial infarction, and the need for inotropic support more than 24 h, as previously described [13];

  Diagnostic criteria for myocardial infarction were the appearance of new Q waves of more than 0.04 s and 1 mm deep or a reduction in R waves of more than 25% in at least two continuous leads of the same vascular territory and/or occurrence of postoperative severe wall motion abnormalities in the same area associated with elevated cTnI. Daily 12-lead electrocardiogram recordings and postoperative two-dimensional echocardiography (systematically performed within 5 days after surgery, according to institutional procedures) were assessed by two experienced physicians blinded to the clinical and biochemical information.

  The postoperative inotrope support was defined as use of dobutamine $> 5\ \mu g \cdot kg^{-1} \cdot min^{-1}$ more than 24 h.
- the hospital length and intensive care unit length of stay;
- in-hospital mortality defined as death of any cause occurring at any time at hospital.

2.5.2. In vitro endpoint

The in vitro endpoint was the recovery of contractile force of isolated right atrial trabeculae challenged with 30-min hypoxia and 60-min reoxygenation. Right atrial appendages were obtained during cannulation for cardiopulmonary bypass from patients included in the study.

2.5.2.1. Experimental conditions. As previously described [14,15], right atrial trabeculae (one per appendage) were dissected and suspended vertically between an isometric force transducer (MLT0202; AD Instruments, Sydney, Australia) and a stationary stainless clip in a 200-mL jacketed reservoir filled with daily

Please cite this article in press as: Lemoine S, et al. Sevoflurane-induced cardioprotection in coronary artery bypass graft surgery: Randomised trial with clinical and ex-vivo endpoints. Anaesth Crit Care Pain Med (2017), http://dx.doi.org/10.1016/j.accpm.2017.05.009