Myocardial Damage Prevented by Volatile Anesthetics: A Multicenter Randomized Controlled Study

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Objective: **The purpose of this study was to evaluate the effects of volatile anesthesia versus total intravenous anesthesia on cardiac troponin release in off-pump coronary artery bypass grafting (OPCAB).**

Design: **The authors performed a multicenter randomized controlled study to compare cardiac troponin release in patients receiving either volatile anesthetics or total intravenous anesthesia for cardiac surgery on the beating heart, which is an excellent model of human myocardial ischemia.**

Setting: **Three university hospitals.**

Participants: **The authors randomly assigned 57 patients to desflurane (volatile anesthetic) and 55 patients to propofol (intravenous anesthetic) in addition to an opiate-based anesthesia for OPCAB.**

Interventions: **The 2 groups of patients received either desflurane (volatile anesthetic) or propofol in addition to an opiate-based anesthesia for OPCAB. Peak postoperative troponin I release was measured as a marker of myocardial necrosis. Prolonged hospitalization was considered as a secondary outcome.**

Measurements and Main Results: **Patient mean age was 69 years, and 82% were men. There was a significant ($p < 0.001$) reduction in postoperative median (25th-75th percentiles) peak of troponin I in patients receiving volatile anesthetics, 1.2 (0.9-1.9) ng/dL, compared with patients receiving total intravenous anesthesia, 2.7 (2.1-4.0) ng/dL. This myocardial protection resulted in a reduced ($p = 0.04$) number (percentage) of patients requiring postoperative inotropes, 20 (35%) versus 31 (56%), and a reduced number (percentage) of patients submitted to prolonged hospitalization (≥7 days), 7 (12%) versus 20 (36%) in the 2 groups ($p = 0.005$). One patient receiving total intravenous anesthesia died within 30 days of surgery.**

Conclusions: **Myocardial damage measured by cardiac troponin release could be reduced by volatile anesthetics during OPCAB. Because patients underwent cardiac surgery on the beating heart, these results could have implications for cardiac patients undergoing noncardiac surgery.**

KEY WORDS: volatile anesthetics, off-pump, troponin, coronary artery bypass grafting, cardiac anesthesia, cardiac biomarker, preconditioning

AN INCREASE OF cardiac biomarkers occurs after all cardiac surgical procedures and is indicative of cell death. At present, the most popular biomarker for myocardial damage is cardiac troponin (cTn), with nearly total myocardial tissue specificity and extreme sensitivity, reflecting even very small amounts of myocardial necrosis.[1] cTn predicts short- and long-term outcome after coronary artery bypass graft (CABG) surgery,[2-4] noncardiac surgery,[5] stenting procedures,[6,7] acute coronary syndromes,[6] and advanced heart failure[8]; there is no discernible threshold below which an elevated value for cTn would be deemed harmless.[1] Both surgical[9] and percutaneous[7] revascularization patients showing postprocedural elevations in troponin have evidence of new irreversible myocardial injury on delayed-enhancement magnetic resonance imaging. The magnitude of this injury correlates directly with the extent of troponin elevation.

Coronary artery disease remains the most common cause of death in the western world and significantly influences the use of health care resources; in the United States alone, it results in more than 519,000 CABG surgeries per year.[10] The potential benefits gained by reducing cardiac damage have led to a renewed interest in cardiac protection strategies, including pharmacologic preconditioning.[11-17]

Volatile anesthetics, commonly used in general anesthesia to induce and maintain hypnosis, analgesia, amnesia, and muscle relaxation, improve postischemic recovery at the cellular level, in isolated hearts, and in animals,[14-16,18] mainly through pharmacologic preconditioning. Few studies have been performed on human patients undergoing CABG surgery with cardiopulmonary bypass (CPB),[19-23] and only 2 small single-center randomized studies have evaluated the effects of volatile anesthetics in off-pump CABG (OPCAB),[24,25] with conflicting results as far as cardiac biomarker release is concerned. Patients un-

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Desflurane (Suprane) was provided free of charge by the producer (Baxter).

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dergoing OPCAB do not require CPB, have a predictable ischemic zone during surgery, and represent an extremely interesting and safe[26,27] model for the study of ischemia and cardiac damage in humans. Cardiac damage in OPCAB, measured by cTn, is caused by the surgeon who must briefly block the diseased coronary artery, and it is attributable to ischemia-reperfusion (I/R) injury. Indeed, OPCAB is one of the few controlled models of human myocardial ischemia and offers the opportunity to study preventive measures that, if effective, could be transferred to all ischemic patients undergoing procedures that could trigger ischemia and myocardial damage.

Because 2 small randomized controlled studies[24,25] yielded conflicting results with respect to the effects of volatile anesthetics on the extent of myocardial damage as assessed by measurements of postoperative cTn release after OPCAB, the authors performed a multicenter randomized trial comparing volatile anesthetics to total intravenous anesthesia in OPCAB, testing the hypothesis that volatile anesthetics would decrease perioperative myocardial damage as measured by cTn release when compared with total intravenous anesthesia.

METHODS

The study was performed according to Declaration of Helsinki principles. The ethical committees of each center approved the study, and written informed consent was obtained from each patient. Consecutive patients scheduled for elective CABG surgery with the OPCAB technique at 3 university hospitals were randomly assigned to receive volatile anesthetics or total intravenous anesthesia including an opioid.

All subjects undergoing isolated coronary revascularization were eligible if referred for an elective procedure, were >18 years old, and if an OPCAB procedure was deemed technically feasible. Patients were excluded in the case of CABG with CPB, myocardial infarction during the preceding 6 weeks, valve insufficiency, active congestive heart failure, any other surgical procedure during current admission, previous unusual response to an anesthetic, and use of any experimental drugs within 28 days before surgery. Patients taking sulfonylurea, theophylline, or allopurinol were also excluded.

Patients in the volatile anesthetic group received desflurane (Suprane; Baxter, Lessines, Belgium), 0.5 to 2.0 end-tidal minimum alveolar concentration, throughout the procedure; this anesthetic has known beneficial effects on postischemic mechanical and coronary function.[19,28] Patients in the total intravenous anesthesia group received propofol (Diprivan; AstraZeneca, Brussels, Belgium), 2 to 3 μg/mL plasma level (equivalent to 2-3 mg/kg/h) via target-controlled infusion, throughout the procedure; this drug represents the standard hypnotic drug in most cardiac anesthesia units but has no known pharmacologic preconditioning effect.[15] All patients received desflurane or propofol in addition to an opioid (fentanyl)-based anesthetic.

Baseline demographics and clinical characteristics were collected as described in Table 1. All preoperative medications were routinely omitted on the day of surgery. Aspirin was stopped 1 week before surgery; angiotensin-converting enzyme inhibitors were withdrawn at hospital admission (generally 1 day before surgery). Preoperative beta-blockers were continued postoperatively to avoid withdrawal on the first postoperative day if permitted by heart rate, blood pressure, and cardiac index evaluation. No other drugs were continued routinely. No other drugs were given for cardiac protection. All patients were premedicated with diazepam, 0.1 mg/kg orally, morphine, 0.1 mg/kg, and scopolamine, 0.25 mg intramuscularly, and received standard monitoring.

During anesthetic induction each patient received an intravenous bolus of midazolam (0.2 mg/kg), fentanyl (5-10 μg/kg), and pancuronium (0.1 mg/kg). Patient monitoring included invasive radial artery blood pressure measurement, continuous electrocardiographic leads II and V_5 with ST-segment analysis, pulse oximetry, central venous pressure, capnometry, and urine output. In all patients, bispectral index monitoring of sedation was used with a target of <40. Anesthesia was maintained with repeated doses of fentanyl, pancuronium, and with either volatile anesthetics or propofol as described earlier. All patients received an intraoperative infusion of tranexamic acid (1 g over 20 minutes followed by 400 mg/h). No aprotinin was administered.

Table 1. Pre- and Intraoperative Variables: Baseline Demographic and Clinical Characteristics of 112 Patients Receiving Either Volatile Anesthetics or Total Intravenous Anesthesia (TIVA) to Prevent Perioperative Myocardial Damage

Variables	Volatile Anesthetics (n = 57)	TIVA (n = 55)
Age (y)	69 ± 9.0	69 ± 8.0
Height (cm)	169 ± 8.5	169 ± 9.7
NYHA		
I-II, n (%)	38 (66.6)	36 (65.5)
III-IV, n (%)	19 (33.4)	19 (34.5)
Female sex, n (%)	8 (14.0)	12 (21.8)
Weight (kg)	74 ± 13.1	73 ± 13.5
Chronic obstructive pulmonary disease, n (%)	11 (19.3)	6 (10.9)
Diabetes mellitus on insulin, n (%)	14 (24.6)	13 (23.6)
Stroke, n (%)	3 (5.3)	4 (7.3)
Previous cardiac surgery, n (%)	2 (3.5)	2 (3.6)
Ejection fraction (%)	46 ± 10.2	46 ± 10.0
Creatinine (mg/dL)	1.3 ± 0.36	1.3 ± 0.80
Preoperative cTnI (ng/dL)	0.04 ± 0.15	0.02 ± 0.09
Non-measurable cTnI, n (%)	47 (82.5)	49 (89.1)
Number of grafts		
1	13 (22.8)	9 (16.4)
2	10 (17.5)	10 (18.2)
3	29 (50.9)	28 (50.9)
4	5 (8.8)	7 (12.7)

Abbreviations: NYHA, New York Heart Association; cTnI, cardiac troponin I.

All patients underwent OPCAB using a median sternotomy approach. In all patients, at least 1 internal mammary artery was used and it was grafted first. Additional grafts were performed after harvesting saphenous veins. After systemic heparinization (150 U/kg with additional doses to reach the target activated coagulation time >300 seconds), the target vessels were exposed with a stabilizer and occluded using bidirectional stretch elastic sutures. On completion of anastomoses, heparin activity was neutralized with protamine sulfate. Patients included in the study were treated by cardiothoracic anesthesiologists and surgeons experienced in both on-pump and off-pump bypass surgery. Filling pressures were kept constant (central venous pressure >10 mmHg) throughout the entire observation period by the administration of intravenous fluids (crystalloids and colloids). When patients showed arrhythmias or ischemia, the procedure was interrupted and continued after CPB was initiated. When patients developed systemic hypotension (systolic blood pressure <90 mmHg unresponsive to Trendelenburg position, atrial pacing, fluid infusion, and inotropes: dopamine 5-8 μg/kg/min first and norepinephrine 0.025-0.05 μg/kg/min in case of low ejection fraction patients), the procedure was interrupted and continued when CPB had been initiated.

After surgery, patients were transferred to the intensive care unit, sedated with midazolam for 2 hours, and weaned from the ventilator as