

Sevoflurane causes less arrhythmias than desflurane after off-pump coronary artery bypass grafting: A pilot study

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ABSTRACT

Background: Volatile anesthetics provide myocardial protection during cardiac surgery. Sevoflurane and desflurane are both efficient agents that allow immediate extubation after off-pump coronary artery bypass grafting (OPCABG). This study compared the incidence of arrhythmias after OPCABG with the two agents. **Materials and Methods:** Forty patients undergoing OPCABG with immediate extubation and perioperative high thoracic analgesia were included in this controlled, double-blind study; anesthesia was either provided using 1 MAC of sevoflurane (SEVO-group) or desflurane (DES-group). Monitoring of perioperative arrhythmias was provided by continuous monitoring of the EKG up to 72 hours after surgery, and routine EKG monitoring once every day, until time of discharge. Patient data, perioperative arrhythmias, and myocardial protection (troponin I, CK, CK-MB-ratio, and transesophageal echocardiography examinations) were compared using t-test, Fisher's exact test or two-way analysis of variance for repeated measurements; $P < 0.05$. **Results:** Patient data and surgery-related data were similar between the two groups; all the patients were successfully extubated immediately after surgery, with similar emergence times. Supraventricular tachycardia occurred only in the DES-group (5 of 20 patients), atrial fibrillation was significantly more frequent in the DES group versus SEVO-group, at five out of 20 versus one out of 20 patients, respectively. Myocardial protection was equally achieved in both groups. **Discussion:** Ultra-fast track anesthesia using sevoflurane seems more advantageous than desflurane for anesthesia, for OPCABG, as it is associated with significantly less atrial fibrillation or supraventricular arrhythmias after surgery.

Key words: Arrhythmias, immediate extubation, respiratory function, ultra-fast track anesthesia, volatile anesthetics

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INTRODUCTION

Fast track cardiac anesthesia plays an important role in modern cardiac surgery.^[1,2] It helps to avoid postoperative complications, and has the potential to decrease Intensive Care Unit (ICU) and hospital stay.^[3] Some studies have advocated the use of regional anesthesia^[4-6] and short-acting anesthetic agents such as sevoflurane or desflurane, to achieve the earliest extubation time, including

immediate extubation after surgery (Ultra-fast track anesthesia^[5,7]). Immediate extubation is especially achievable when off-pump coronary artery bypass grafting (OPCABG) is used,^[3,7] as it decreases operating time and avoids important pathophysiological changes usually induced by extracorporeal circulation.^[8] In the context of superior myocardial protection, several studies have advocated the use of volatile anesthetics instead of propofol-based anesthesia.^[7,9-12] Sevoflurane and

desflurane would be ideally suited for ultra-fast tracking anesthesia, as both allow rapid extubation even as they provide similar myocardial protection. However, some studies indicate the risk of catecholamine stimulation^[13] with desflurane. This might have an influence on the incidence of arrhythmia after cardiac surgery as well as prolong the ICU or hospital stay.

We conducted a randomized, controlled, double-blind pilot study comparing the effect of sevoflurane and desflurane on perioperative arrhythmias in ultra-fast track OPCABG.

MATERIALS AND METHODS

After obtaining approval from the local Ethics Committee and written patient consent, 40 patients with a left ventricular ejection fraction (LVEF) of at least 30%, undergoing OPCABG (left mammary artery, where possible, and saphenous vein grafts) with complete median sternotomy (same surgical team) were included in this trial. They were randomized to undergo general anesthesia using sevoflurane ($n = 20$, SEVO-group) or desflurane ($n = 20$, DES-group). All patients were consented for perioperative pain control using high thoracic epidural anesthesia (TEA) and operating room extubation.^[14-16] Exclusion criteria were patient refusal to participate, pregnant women, patients without TEA (contraindication, impossible insertion or refusal of TEA), patients with insulin-treated diabetes, unstable angina or emergency surgery, on corticosteroid therapy and with a myocardial infarction three months before surgery. Routine monitoring included 5-lead electrocardiography, invasive blood pressure monitoring via a femoral artery catheter, central venous pressure monitoring via a subclavian central venous catheter, peripheral pulse oximetry, and transesophageal echocardiography. Ejection fraction and wall activity anomalies were noted using the standard bull eye diagram and segmental nomenclature. The same anesthesia approach was used for all patients: On arrival at the operating room, an epidural catheter was inserted at T2 – T4 under local anesthesia. The catheter was inserted using a midline approach in all patients. Exclusion of spinal or intravascular placement was performed using 4 ml lidocaine 1.5% with epinephrine 5 $\mu\text{g}/\text{ml}$. Anesthesia induction was performed by fentanyl 3 $\mu\text{g}/\text{ml}$, followed by propofol 1 – 2 $\text{mg}\cdot\text{kg}^{-1}$, and endotracheal intubation was facilitated by rocuronium 0.6 $\text{mg}\cdot\text{kg}^{-1}$. Intermittent positive pressure ventilation was used to maintain an

end-tidal PETCO_2 between 4 and 4.7 kPa. In the SEVO-group, intraoperative anesthesia was maintained by 1 MAC of sevoflurane; in the DES-group, intraoperative anesthesia was maintained by 1 MAC of desflurane in oxygen air ($\text{FiO}_2 = 50\%$). The anesthesiologist in charge of the case was blinded for group assignment. Fluid treatment consisted of Ringer's lactate at 6 – 10 ml/kg/h. All patients received an epidural bolus of 6 – 10 ml of bupivacaine 0.25%, 15 minutes before skin incision and 15 minutes before extubation. During surgery, the epidural infusion rate was kept at bupivacaine 0.1% 8 – 10 ml/h. The epidural catheter was discontinued 48 hours after surgery. Transesophageal echocardiography was carried out before the start of surgery, immediately after completion of the grafts, and before skin closure. Active temperature control was achieved with an increased room temperature (22°C or more) and forced air warming therapy (Bair Hugger blankets for the lower body and head, Augustine Medical Company, Eden Prairie, MN, USA). During the ischemic period, treatable bradycardia was defined as a heart rate (HR) lower than $40\cdot\text{min}^{-1}$ and was treated with increment doses of IV ephedrine 5 mg or epicardial atrial pacing. Hypotension was defined as a systolic blood pressure inferior to 70 mmHg and was treated with increments of IV phenylephrine 50 mg. Heparin 150 $\text{IU}\cdot\text{kg}^{-1}$ was given five minutes before ischemia and at least one hour after epidural catheter placement. Heparin was antagonized using protamine after completion of the grafts on a 1:1 ratio. In each group, the volatile agent was stopped immediately after skin closure, and the time to extubation was noted then. Extubation criteria were a cooperative and alert patient; complete neuromuscular function assessed by train-of-four (TOF) > 0.9 at the adductor pollicis muscle, pulse oximetry superior to 96% on FiO_2 of 100%, PETCO_2 less than 6 kPa, stable hemodynamic and core (bladder) temperature superior to 35°C.

Surgical access was provided by complete median sternotomy. During coronary artery grafting, the heart was luxated using two posterior pericardial sutures and the coronary artery to be grafted was stabilized using a special system (Coro-Neo Medical Systems, Montreal, Canada). The anastomosis site was isolated using two blunt vascular slings passed above and below the arteriotomy site. Distal anastomoses were performed using a running 7-0 suture. No intraluminal shunts were used. Ischemia time was calculated from the tightening of the snares to their release. The culprit lesion was anastomosed first, if possible, with the left

internal mammary artery. This allowed immediate supplementary blood flow to the myocardium during the next ischemic period. After extubation in the operating room, the patients were transferred to the post-anesthesia care unit (PACU). Specially trained nurses, familiar with immediate extubation after cardiac surgery, took care of the patients on a ratio of one nurse for each patient for at least two hours, after which the patients were transferred to the intensive care unit (ICU). Patients received twice-daily heparin 5000 IU subcutaneously (s.c.) as thromboprophylaxis for three days, post surgery. Postoperative pain control was started with bupivacaine at 10 ml/h, and adjusted depending on the pain of the patient, at a rate of 6 – 14 ml/h. Pain scores were assessed using a numeric pain score (NPS) (0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable). The epidural rate was increased if the patients had pain of at least 4 on the NPS at the thoracic area by increment of 1 ml/h every two hours and a bolus of 3 – 5 ml was given. The rate was decreased in case of paresthesia in dermatome C8 or higher in a patient with no pain. Doses of morphine 5 mg s.c. were available for pain in areas not covered by the epidural catheter.

The frequency and types of arrhythmias were monitored continuously up to 72 hours after surgery using 2-lead electrocardiography. All EKG traces were recorded and analyzed for any arrhythmias. Arrhythmias were classified into atrial or ventricular arrhythmias; they were further separated into atrial flutter, atrial fibrillation, ventricular or atrial tachycardia or bradycardia. In addition, 12-lead electrocardiograms were obtained in all patients once every day until discharge from the hospital.

We recorded data on the patients' characteristics, preoperative medical status, current medications, left ventricular function, as well as, operative data (number of grafts, time of ischemia and hemodynamic data), any complications, and time to extubation. Pain was measured by a numeric pain score at rest and recorded immediately after surgery, and six, 24, and 48 hours after surgery. Postoperative blood pressure and heart rate were documented for the first six hours after surgery. Blood samples were obtained immediately before and after surgery, and three, 12, 24, 48, and 72 hours after surgery. These blood samples served to measure the levels of troponin-I and creatine kinase MB (CK-MB). Complications such as bleeding, hemodynamic instability, arrhythmias, and respiratory

dysfunction (peak expiratory flow measurements — in the sitting position — and arterial blood gases before surgery, immediately after surgery, and two, six, and 12 hours after surgery) were also noted. Nausea, pruritus, and episodes of paresthesia during the whole stay in the hospital were recorded. Neurological symptoms, such as muscle weakness in the legs or arms, were noted, which led to discontinuation of TEA, followed by neurological investigations.

All data collection and postoperative management was performed by personnel unaware of the group assignment. Data were analyzed using the Stata software (Stata version 10.1, STATA Corporation, College Station, TX). Patient characteristics (sex, age, weight, ASA class, ejection fraction, number of grafts, duration of grafting, duration of anesthesia and surgery) between the two groups were compared using t-test and Fisher's exact test. Biochemical serum markers and hemodynamic data were compared by two-way analysis of variance techniques for repeated measurements. $P < 0.05$ was considered to show a statistical difference. Prior to this study, we determined the incidence of arrhythmias (atrial fibrillation, bradycardia $< 45/\text{min}$ or necessitating temporary pacing, tachycardia $> 100/\text{min}$) in our population as 40% of arrhythmias, within the first 48 hours after surgery. Group size of the study was chosen to obtain a power of at least 80% ($\alpha = 0.05$), for showing a significant reduction of these arrhythmias to an overall incidence of 10% when using sevoflurane.

RESULTS

There were no significant differences between the two groups for age, weight, time to extubation, ejection fraction, number of grafts, and ischemic time [Tables 1 and 2]. The incidence of past myocardial infarction, stroke, hypertension, diabetes, chronic obstructive pulmonary disease or renal insufficiency was also similar. Room and body temperatures at the beginning of the surgery and at the moment of extubation were not different between the two groups. All patients were successfully extubated at the end of surgery and none required re-intubation. Extubation time in the two groups was similar [Table 2]. PO_2 and PCO_2 immediately after intubation and immediately after extubation (on FiO_2 of 100% by face mask) were similar in both groups [Table 3]. There was no difference in arterial PCO_2 or PO_2 between the two groups for the first 12 hours after surgery. Peak flow values were similar in the two groups during the perioperative period [Figure 1]. Phenylephrine was used equally in the

Table 1: Patients data

	SEVO-group (n = 20)	DES-group (n = 20)	P
Age (years)	61 (53 – 71; 41 – 78)	68 (58 – 76; 49 – 80)	NS
Sex (m/f)	12/8	17/3	< 0.05
Weight (kg)	73 (61 – 87; 46 – 111)	79 (70 – 88; 66 – 98)	NS
Beta blockers (n)	17	15	NS
Calcium antagonists (n)	8	5	NS
Statins (n)	17	16	NS
Nitrates (n)	14	11	NS
ACE-inhibitors (n)	9	6	NS
ASA (aspirin) (n)	9	8	NS
Proton inhibitors (n)	4	5	NS
Angiotensin-II recant (n)	1	0	NS
Diabetes (type I or II) (n)	7	11	NS
Hypertension (n)	12	12	NS
Asthma-COPD (n)	0	3	NS
PTCA prior to surgery	1	1	NS

Values are presented as median (twenty-fifth to seventy-fifth percentile; range). $P < 0.05$ was considered statistically significant

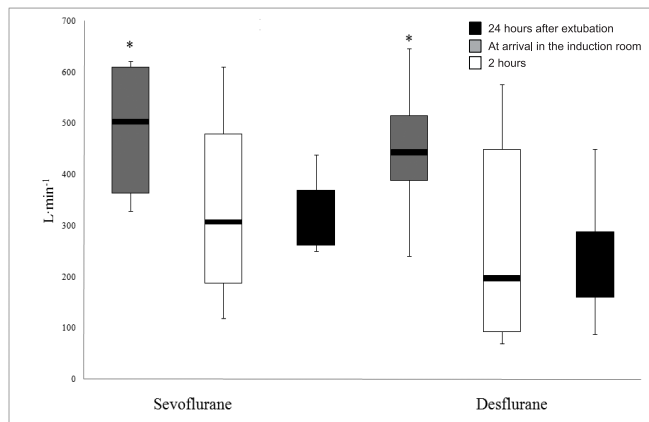


Figure 1: Peak expiratory flow measurements shown in figure. Patients were familiarized with peak flow measurements the night before surgery; * $P < 0.05$ preoperative versus postoperative value

two groups. There was no difference in systolic or diastolic pressure between the two groups during or after surgery. The rates of infusion of epidural solutions were also similar. There was no postoperative myocardial infarction. The markers of myocardial lysis were not significantly different between the two groups [Figures 2-4]. Ejection fraction was preserved in both groups throughout the surgery [Table 2]. There were no regional wall motion abnormality changes observed in any patient after grafting. Pain scores at six, 24, and 48

Table 2: Surgery-relevant data

	SEVO-group (n = 20)	DES-group (n = 20)	P
Duration of surgery (min)	150 (137 – 172; 126 – 212)	160 (145 – 197; 130 – 265)	NS
Grafts (number)	3 (2 – 4; 1 – 4)	3 (3 – 4; 2 – 6)	NS
Ischemic time (min)	20 (17 – 20; 16 – 37)	21 (17 – 26; 11 – 43)	NS
Extubation time (min)	12 (1 – 31; 8 – 18)	11 (7 – 19; 2 – 25)	NS
Post-op agitation	1	6	< 0.05
Hospitalization (days)	6 (5 – 7; 4 – 10)	6 (5 – 7; 4 – 16)	NS
Ejection fraction (%)	60 (51 – 69; 30 – 80)	56 (50 – 68; 35 – 77)	NS
Prolonged inotropic support	0	0	NS
LAD stenosis > 70% (n)	18	16	NS
Cx stenosis > 70% (n)	14	17	NS
RCA stenosis > 70% (n)	16	14	NS

Values are presented as median (twenty-fifth to seventy-fifth percentile; range). $P < 0.05$ was considered statistically significant

hours after surgery remained low (NPS < 4/10) in the two groups and were not statistically different between groups.

Six patients in the DES-group in comparison to only one patient in the SEVO-group showed an agitated state immediately after surgery, which settled spontaneously within two hours [Table 2].

There were significantly more patients with arrhythmias in the DES-group than in the SEVO-group at 50% versus 5%, respectively; five patients experienced supraventricular tachycardia and five patients developed atrial fibrillation in the DES-group, whereas, only one patient in the SEVO-group developed atrial fibrillation [Table 4]. Before being discharged from the hospital, atrial fibrillation converted spontaneously, or was converted electrically or pharmacologically to sinus rhythm in all patients. In no patient was there a neurological sign or symptom of epidural hematoma. No re-intervention was necessary in any of these patients.

DISCUSSION

Our study shows that patients undergoing OPCABG with general anesthesia, using desflurane, experience significantly more paroxysmal tachycardia and atrial

Table 3: Arterial oxygen and carbon dioxide partial pressures immediately after intubation and immediately after extubation

	At intubation		Post-extubation	
	pO ₂	pCO ₂	pO ₂	pCO ₂
SEVO-group (n = 20)	257 (224 – 267; 106 - 381)	38 (35 – 43; 27 – 49)	170 (154 – 216; 129 – 336)	44 (39 – 4; 36 – 9)
DES-group (n = 20)	294 (239 – 335; 126 – 390)	35 (33 – 40; 26 – 0)	166 (103 – 46; 73 – 93)	44 (42 – 7; 35 – 67)
<i>P</i>	NS	NS	NS	NS

Values are presented as median (twenty-fifth to seventy-fifth percentile; range)

Table 4: Arrhythmias

	SEVO-group (n = 20)	DES-group (n = 20)	<i>P</i>
Atrial fibrillation	1	5	< 0.05
Atrial flutter	0	0	NS
Supraventricular tachycardia	0	5	< 0.05
Ventricular tachycardia	0	0	NS
Ventricular fibrillation	0	0	NS
Bradycardia	4	3	NS

fibrillation after surgery than patients where anesthesia is maintained with sevoflurane. There were also a significant number of patients showing an agitated state after extubation when desflurane was used during anesthesia. Both volatile anesthetics preserve myocardial function well during OPCABG and show no difference in terms of effect on respiratory function after surgery.

Our findings favor sevoflurane as a volatile anesthetic of choice for cardiac surgery; it can be deduced that either desflurane causes postoperative arrhythmias by the known activation of the sympathomimetic system^[17] or sevoflurane protects against arrhythmias, such as, paroxysmal tachycardia or atrial fibrillation. Desflurane has been linked to increased sympathetic stimulation,^[18-20] which some authors have related to increased intramyocardial catecholamine release in animal findings.^[21,22]

A decreased incidence of arrhythmias with sevoflurane was found in a study comparing propofol-based anesthesia with sevoflurane.^[12] Our findings are similar to a retrospective analysis of Cromheecke *et al.*,^[23] where the incidence of postoperative atrial fibrillation was lower in the group of patients who had sevoflurane-

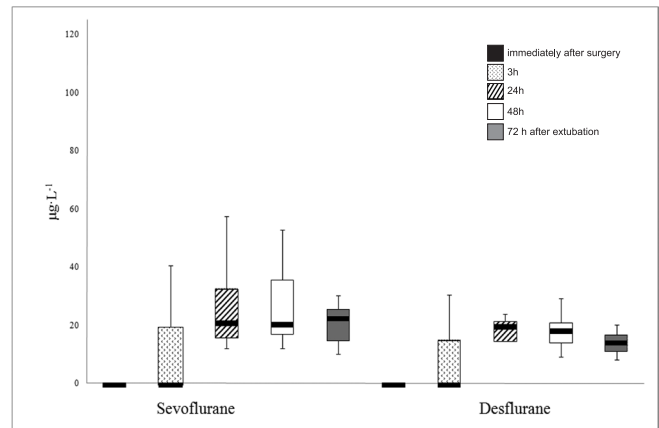


Figure 2: Levels of creatin kinase-MB determined at different time points after extubation: immediately, 3h, 12h, 24h, 48h and 72h after extubation

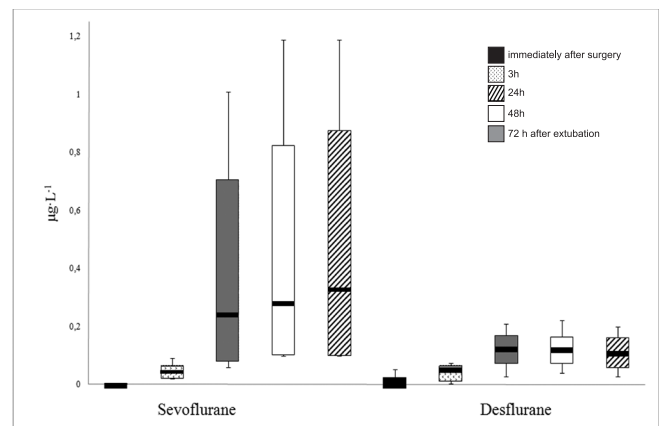


Figure 3: Levels of troponin I determined at different time points after extubation: immediately, 3h, 12h, 24h, 48h and 72h after extubation

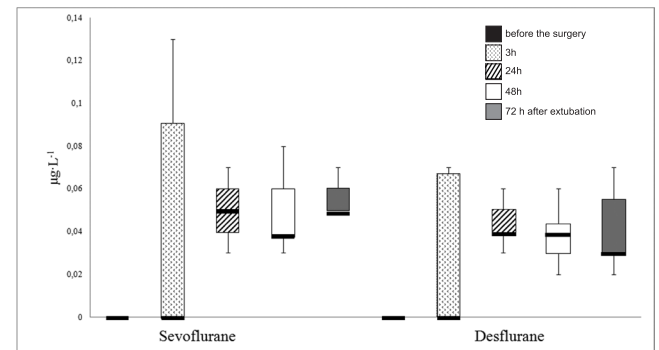


Figure 4: Ratio CK-MB/CK determined at different time points after extubation: immediately, 3h, 12h, 24h, 48h and 72h after extubation

based anesthesia in comparison with the other three groups with propofol, midazolam, and desflurane. It is interesting to note that in that retrospective analysis in patients who had undergone elective on-pump CABG, the incidence of atrial fibrillation when sevoflurane was used during anesthesia was 6% versus 21% in patients who had undergone anesthesia using desflurane. This is very similar to our own findings in OPCABG, with an incidence of 5% and 25% atrial fibrillation with sevoflurane and desflurane, respectively.

Some authors have indicated that desflurane might be potentially harmful in patients with increased airway reactivity;^[24,25] we therefore obtained pre- and postoperative peak expiratory flow measurements as a simple and feasible test in all patients to investigate this theory — more elaborate respiratory tests, such as, body plethysmography are very difficult to apply in this clinical scenario. As expected, the peak expiratory flow values decreased significantly after surgery from baseline values with very little improvement two hours and 24 hours after extubation. Arterial blood gases did not show any differences between the two volatile agents. Our study, however, might be underpowered to find significant differences in airway compromise between the two drugs.

In a similar study, we^[7] found that during OPCABG, sevoflurane and isoflurane provide the same ischemic cardioprotective effects. No difference in heart contractility or hemodynamic values was found between the two agents during and after OPCABG. Similar findings could be deducted from our study; in terms of myocardial protection, there seemed to be no difference between isoflurane, desflurane or sevoflurane. In terms of myocardial protection, all volatile anesthetic agents could be recommended equally for patients at risk for MI.^[26]

Recovery from anesthesia was equally fast with both volatile anesthetics; immediate extubation was successful in all patients without any re-intubation. It was of interest to note that there were a significant number of patients, after desflurane, showing signs of agitation immediately after surgery, which was not related to increased pain, shivering or temperature abnormalities. This was surprising, as agitation after emergence from anesthesia is mostly described in children, both with sevoflurane and desflurane.^[27,28] Clinically, it could sometimes be seen after excessive re-warming after extracorporeal circulation — which was not the case in our patients undergoing OPCABG. All patients in the present study recovered from this agitated state within two hours of surgery, without delay in postoperative recovery.

Pain relief was successfully provided using continuous TEA. There are some studies indicating a positive effect of TEA in terms of avoiding postoperative arrhythmias.^[29,30] However, a recent study from our group could not find a significant difference in the incidence of postoperative arrhythmias when TEA

was used for OPCABG with immediate extubation.^[7] Even if TEA decreased the incidence of arrhythmias after OPCABG in our patients, this would not have influenced the validity of our findings, as all our patients received TEA.

One limitation of any double-blind study using desflurane and sevoflurane is that the desflurane vaporizer can easily be recognized by the heat it generates. Therefore, the anesthesiologist managing the case did not take care about maintaining 1 MAC of sevoflurane or desflurane; this was done by an independent observer who also took care of the randomization process.

This is a small scale pilot study; future studies with a higher number of patients are needed to confirm these initial results.

In conclusion, ultra-fast track anesthesia using sevoflurane seems to be superior to desflurane as anesthesia for OPCABG, as it is associated with significantly less atrial fibrillation or supraventricular arrhythmias after surgery, while providing equally fast extubation time.

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