

Incidence of atrial fibrillation early after cardiac surgery : can choice of the anesthetic regimen influence the incidence ?

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Summary : Occurrence of atrial fibrillation is a common complication after coronary surgery. This study aimed to identify the perioperative factors that are associated with its occurrence with specific attention to the possible influence of the choice of the anesthetic regimen after elective coronary surgery.

A retrospective chart analysis was performed in 460 patients who underwent elective coronary artery surgery with cardiopulmonary bypass using the standard institutional anesthetic, surgical and postoperative protocols. The only difference in management was the choice of the primary anesthetic regimen. 110 patients had a total intravenous anesthesia with propofol, 90 patients had a total intravenous anesthesia with midazolam, 150 patients were anesthetized with sevoflurane and 110 patients with desflurane. The primary outcome variable was the incidence of atrial fibrillation within the first 24 postoperative hours.

Atrial fibrillation occurred in 64 of the 460 patients included (13.9%). Multiple logistic regression analysis identified increased age (> 70 years), EuroSCORE > 4, prolonged CPB time (> 100 min) and need for prolonged inotropic support (> 6 hours) as the significant independent risk factors for the occurrence of postoperative atrial fibrillation. The incidence of postoperative atrial fibrillation differed among the different anesthetic groups with the lowest incidence in the sevoflurane group (propofol : 17 / 110 ; midazolam : 15 / 90 ; sevoflurane : 9 / 150 ; desflurane : 23 / 110) (p = 0.004). This finding should be further confirmed in a prospective sufficiently powered multicenter study.

pendent risk factors have been associated with an increased incidence of postoperative atrial fibrillation. Among these advanced age (4-6, 10, 11), presence of associated pathology (4-6), and surgical factors such as bicaval venous cannulation and pulmonary venting (4, 6) or myocardial preservation techniques (12, 13) have been reported. Although some data have related cardiopulmonary bypass and cardioplegic arrest to the occurrence of postoperative atrial fibrillation (14), most reports indicate that the use of minimally invasive techniques for coronary surgery apparently has not reduced the incidence of postoperative atrial fibrillation (15-19). This suggests that measures to reduce this complication should be focused on factors unrelated to surgical techniques. Several pharmacological agents have been studied with respect to their capacity of reducing postoperative atrial arrhythmias but only beta-blocking agents and amiodarone appeared to be effective in reducing the incidence of this complication (20-26). Administration of magnesium has also been claimed to reduce the incidence of atrial tachyarrhythmias after cardiovascular surgery (27, 28) although its administration in addition to beta-blocking therapy does not seem to further decrease the incidence of postoperative atrial tachyarrhythmias (29).

Although atrial fibrillation has been extensively studied, its underlying pathophysiological mechanisms remain to be determined. It has been

INTRODUCTION

Atrial fibrillation is a common complication after cardiac surgery, with quoted incidences between 11% and 40% after coronary artery bypass grafting surgery and even more after valvular surgery (1-3). Although this type of arrhythmia is usually not life-threatening, it may be responsible for significant morbidity in cardiac surgery patients. Indeed atrial fibrillation has been identified as an independent risk factor for increased hospital and intensive care unit length of stay after coronary surgery (4-9). Over the years several inde-

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suggested that myocardial bioenergetic deficits may constitute one of components in the substrate for atrial fibrillation (30). Similarly, the occurrence of atrial ischemia – reperfusion injury and oxidative stress after cardiac surgery have been implicated in the occurrence of postoperative atrial fibrillation (31-33). Recently evidence has indicated that volatile anesthetic agents exhibit a direct cardioprotective effect in the course of myocardial ischemia. These effects have been attributed to an anesthetic preconditioning effect but also to an effect on the extent of reperfusion injury (34, 35). These effects were apparent from a better myocardial function and a lower release in troponin I after coronary surgery. The present study investigated whether these cardioprotective effects would also be associated with a lower incidence of postoperative atrial fibrillation. To address this hypothesis, the incidence of atrial fibrillation after coronary surgery was evaluated and related to the choice of anesthetic regimen as possible independent predictor.

METHODS

After obtaining institutional review board approval, a retrospective chart review was performed on 460 patients that had been included in different hemodynamic study protocols at the Department of Anesthesiology of the University Hospital Antwerp. Part of the hemodynamic data of these protocols have been reported previously (9, 36-38). For the present study, the charts were carefully checked for the occurrence of postoperative atrial fibrillation within the first 24 hours after the end of the surgical procedures. Only data from patients who were scheduled for elective coronary surgery using cardiopulmonary bypass (CPB) were included. Exclusion criteria were previous coronary or valvular heart surgery, combined operations (simultaneous valve repair, carotid endarterectomy or left ventricular aneurysm repair), unstable angina, valve insufficiency, documented myocardial infarction within the previous 6 weeks, active congestive heart failure, hemodynamic instability requiring medical or mechanical support, severe hepatic disease (alanine aminotransferase or aspartate aminotransferase > 150 international units.L⁻¹), renal insufficiency (creatinine concentration > 1.5 mg.dL⁻¹), severe chronic obstructive pulmonary disease (forced expired volume in 1 second < 50% of predicted or < 2.0.L), or history of neurological disturbances. Patients with documented rhythm

disturbances were also excluded from the present study.

Anesthetic protocols

All patients included in the present analysis were subjected to strict anesthetic and surgical protocols. All preoperative cardiac medication was continued until the morning of surgery, except for the angiotensin-converting enzyme inhibitors. Premedication was standardized for all patients (2.5 mg sublingual lorazepam (Temesta Expidet®, AHP Pharma, Louvain-la-Neuve, Belgium) 90 min before surgery and 1 µg.kg⁻¹ fentanyl + 50 µg.kg⁻¹ droperidol, given intramuscularly 60 min before surgery).

Patients were anesthetized using either a complete intravenous anesthetic regimen, based on propofol (Diprivan®, AstraZeneca, Brussels, Belgium) or midazolam (Dormicum®, Roche, Brussels, Belgium) throughout the entire procedure or by using an inhalational anesthetic regimen, based on sevoflurane (Sevorane®, Abbott, Louvain-la-Neuve, Belgium) or desflurane (Suprane®, Baxter, Lessines, Belgium) throughout the entire procedure. In all groups a continuous infusion of remifentanyl (Ultiva®, GlaxoSmithKline, Genval, Belgium) between 0.2-0.4 µg.kg⁻¹.min⁻¹ was administered throughout the operation. Muscle relaxation was obtained with pancuronium (Pavulon®, Organon, Brussels, Belgium) 0.1 mg.kg⁻¹.

In the propofol group (n = 110), anesthesia was induced with a continuous infusion of remifentanyl at 0.4 µg.kg⁻¹.min⁻¹ and a target controlled infusion (TCI) of propofol set at a target plasma concentration of 2 µg.mL⁻¹. Anesthesia was maintained with remifentanyl 0.2-0.4 µg.kg⁻¹.min⁻¹ and TCI propofol set at a plasma target concentration of 2-4 µg.mL⁻¹.

In the midazolam group (n = 90), anesthesia was induced with with a continuous infusion of remifentanyl at 0.4 µg.kg⁻¹.min⁻¹ and midazolam 0.1 mg.kg⁻¹. Anesthesia was maintained with remifentanyl 0.2-0.4 µg.kg⁻¹.min⁻¹ and midazolam 0.5-1.5 µg.kg⁻¹.min⁻¹. In the sevoflurane group (n = 150), anesthesia was also induced with with a continuous infusion of remifentanyl at 0.4 µg.kg⁻¹.min⁻¹ and midazolam 0.1 mg.kg⁻¹. Anesthesia was maintained with remifentanyl 0.2-0.4 µg.kg⁻¹.min⁻¹ and sevoflurane 0.5-2%.

In the desflurane group (n = 110), anesthesia was induced with a continuous infusion of remifentanyl at 0.4 µg.kg⁻¹.min⁻¹ and midazolam 0.1 mg.kg⁻¹.

Anesthesia was maintained with remifentanyl 0.2-0.4 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and desflurane 1-4%.

Peroperative procedures

In the operating room patients received routine monitoring including 5-lead electrocardiogram, radial and pulmonary artery catheters with continuous cardiac output measurement (Swan Ganz CCO/VIP, Edwards Lifesciences LLC, Irvine, CA), pulse oxymetry, capnography, blood and urine bladder temperature monitoring.

Routine cardioprotective strategies were used in all patients. These included the intravenous administration of 1 mg/kg lidoflazine and 2 g methylprednisolone after induction of anesthesia and the high-dose aprotinin (Trasylol®, Bayer, Leverkusen, Germany) regimen (bolus of $2\cdot 10^6$ kallikrein inhibiting units followed by a continuous infusion of $5\cdot 10^5$ kallikrein inhibiting units $\cdot\text{h}^{-1}$ until the end of CPB, plus an additional $2\cdot 10^6$ kallikrein inhibiting units in the priming fluid of the CPB circuit). Patients had median sternotomy with harvesting of saphenous veins and internal thoracic arteries as conduits. All patients received 300 units $\cdot\text{kg}^{-1}$ of heparin (Heparine®, Leo Pharma, Zaventem, Belgium) before the start of CPB. Activated coagulation time (using kaolin as activator) was kept above 450 s throughout the CPB period. Systemic temperature was allowed to drift during CPB to 32° C. Hematocrit concentrations were maintained between 20 and 25% and on CPB a nonpulsatile flow was maintained between 2.2 and 2.5 $\text{l}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$. The mean perfusion pressure was kept at 50-60 mm Hg. Revascularization was performed using intermittent aortic crossclamping.

The CPB circuit used was a closed system consisting of tubing with a surface modifying additives coating, an arterial filter with heparin coating, a hollow fiber membrane oxygenator with a surface modified additives coating and a venous and cardiectomy reservoir (Cobe Cardiovascular Inc., Arvada, CO). Venous cannulation was performed using a two-stage venous canula. The priming fluid of the CPB circuit contained 1000 ml 6% hydroxyethyl starch 130/0.4 (Voluven®, Fresenius Kabi, Schelle, Belgium), 300 ml crystalloids (Plasma-Lyte®, Baxter, Lessines, Belgium), 200 ml aprotinin, 5000 units of heparin and 1 $\text{mg}\cdot\text{kg}^{-1}$ lidoflazine (a nucleoside transport inhibitor) (Johnson and Johnson, Beerse, Belgium).

After the surgical procedure, reperfusion of the heart (reperfusion time was set at 50% of the aortic crossclamping time in all patients) and

rewarming to a bladder temperature of 35° C, the heart was paced in atrioventricular sequential mode at a rate of 90 $\text{beats}\cdot\text{min}^{-1}$ and the patients were separated from CPB. After removal of the aortic cannula, heparin activity was neutralized with protamine sulphate (Protamine®, Leo Pharma, Zaventem, Belgium) at a ratio of 1 mg protamine for 100 units of heparin. Protamine administration was further guided by ACT measurements aiming at a value of 140 s. At the end of the surgical procedure, patients were transferred to the ICU. Inotropic and vasoconstrictive support such as volume replacement and transfusion strategies were performed using strict protocols which have previously been described.

Data collection

For the present study protocol, the data collected included incidence of atrial fibrillation during the first 24 hours postoperatively. Other data were gender, age, weight, height, body mass index, degree and extent of coronary disease, pre-operative ejection fraction, medical history and chronic treatment. Risk stratification was performed using the EuroSCORE risk stratification model (39). Intraoperative data collected included type of anesthesia (total intravenous vs inhalational protocol), number of bypasses, number of arterial grafts, aortic cross clamping time, and CPB duration.

Statistical analysis

The primary outcome variable in the present study was the incidence of atrial fibrillation within the first 24 postoperative hours. Patients' characteristics between groups were compared using one-way analysis of variance and chi-square analysis where appropriate. Data were expressed as mean \pm standard deviation (SD) or as median with range. Statistical significance was accepted at $p < 0.05$. All p-values were two-tailed.

For all patients the presence of the following variables was noted : *preoperative* : female gender, age > 70 years, ejection fraction < 50%, diabetes, EuroSCORE > 4, daily intake of β -blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, nitrates, and diuretics, *intraoperative* : anesthetic regimen used (total intravenous or volatile anesthetic agent), CPB time > 100 min, and need for prolonged (> 6 hours) inotropic support. These variables were entered as independent variables into a multiple logistic regression model with occurrence of atrial fibrillation as the dependent

Table 1

Multiple logistic regression analysis of the different independent variables associated with early postoperative atrial fibrillation in the study population

variable	prevalence	Odds ratio	5% and 95% confidence limits	P-value
<u>preoperative</u>				
female gender	18.5%	0.57	0.23 – 1.46	0.242
age > 70 years	39.3%	16.78	7.65 – 44.37	< 0.001
ejection fraction < 50%	8.7%	1.10	0.62 – 3.03	0.829
diabetes	27.8%	1.71	0.75 – 3.90	0.460
EuroSCORE > 4	42.6%	27.77	8.83 – 87.35	< 0.001
<u>preoperative medication</u>				
β -blockers	78.7%	1.39	0.61 – 3.19	0.438
calcium channel blockers	29.6%	0.67	0.29 – 1.54	0.344
ACE inhibitors	30.0%	0.80	0.36 – 1.81	0.599
nitrates	42.2%	1.20	0.55 – 2.60	0.644
diuretics	22.6%	0.75	0.31 – 1.81	0.519
<u>intraoperative</u>				
volatile anesthetic	56.5%	1.02	0.49 – 2.11	0.439
CPB time > 100 min	35.7%	24.31	10.41 – 56.78	< 0.001
inotropic support	36.2%	2.53	1.02 – 6.30	0.034

P = statistical significance ; ACE = angiotensin converting enzyme ; CPB = cardiopulmonary bypass.

variable. Statistical analysis was performed using SigmaStat 2.03 software package (SPSS, Leuven, Belgium) and GraphPad Prism 4 software package (GraphPad Software Inc, San Diego, Ca).

RESULTS

Atrial fibrillation occurred in 64 of the 460 patients included (13.9%). The occurrence of atrial fibrillation was similar in the group of patients who underwent surgery under a complete intravenous anesthetic regimen (32 / 200 ; 16.0%) and in those who had anesthesia with a volatile anesthetic regimen (32 / 260 ; 12.3%). Multiple logistic regression analysis identified increased age (> 70 years), EuroSCORE > 4, prolonged CPB time (> 100 min) and need for prolonged inotropic support (> 6 hours) as the significant independent risk factors for the occurrence of postoperative atrial fibrillation in the present study population (Table 1). None of the other variables analyzed – including the type of anesthetic regimen – was identified as an independent risk factor for the occurrence of postoperative atrial fibrillation after coronary surgery. The incidence of postoperative atrial fibrillation however differed ($p = 0.004$) among the different anesthetic groups with the lowest incidence in the sevoflurane group (propofol : 17 / 110 ; midazolam : 15 / 90 ; sevoflurane : 9 / 150 ; desflurane : 23 / 110) (Fig. 1). Pre-operative and intraoperative patient characteristics

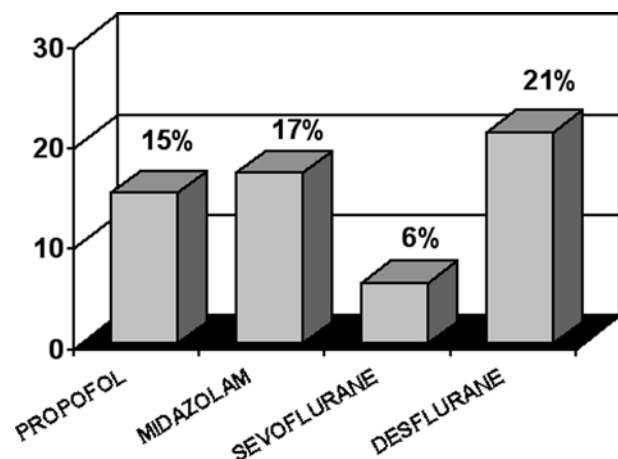


Fig. 1. — Incidence of postoperative atrial fibrillation with the different anesthetic regimens.

were similar in the different groups (Table 2) but the need for prolonged inotropic support was different (propofol : 19 / 110 ; midazolam : 18 / 90 ; sevoflurane : 9 / 150 ; desflurane : 10 / 110 ; $p = 0.0049$).

DISCUSSION

The results of the present study indicated that the presence of an increased age more than 70 years, the presence of comorbidity as assessed by an EuroSCORE more than 4, prolonged duration of CPB (> 100 min) and the prolonged need

Table 2
Pre- and intra-operative patient characteristics

	propofol (n = 110)	midazolam (n = 90)	sevoflurane (n = 150)	desflurane (n = 110)
preoperative data				
gender (male/female)	90 / 20	73 / 17	123 / 27	89 / 21
age (years)	66 ± 9	67 ± 10	66 ± 9	68 ± 8
body mass index (kg.m ⁻²)	27.4 ± 4.3	27.0 ± 5.3	26.9 ± 3.7	26.9 ± 3.2
ejection fraction (%)	68 ± 12	67 ± 10	64 ± 13	67 ± 10
diabetes	29 (26%)	27 (30%)	41 (27%)	31 (28%)
EuroSCORE (median (range))	4 (0 - 13)	4 (0 - 13)	4 (0 - 14)	4 (0 - 12)
chronic preoperative medication				
β-blockers	85 (77%)	72 (80%)	118 (79%)	87 (79%)
calcium channel blockers	33 (30%)	27 (30%)	43 (29%)	33 (30%)
ACE inhibitors	32 (29%)	28 (31%)	45 (30%)	33 (30%)
nitrates	47 (43%)	37 (41%)	64 (43%)	46 (42%)
diuretics	26 (24%)	21 (23%)	33 (22%)	24 (22%)
intraoperative data				
n° of bypasses (median (range))	4 (2 - 6)	4 (2 - 6)	4 (2 - 6)	4 (2 - 6)
n° of arterial grafts (median (range))	2 (1 - 3)	2 (1 - 3)	2 (1 - 3)	2 (1 - 3)
aortic cross-clamp time (min)	28 ± 13	28 ± 14	32 ± 15	30 ± 14
CPB time (min)	94 ± 31	101 ± 27	99 ± 25	98 ± 28

Data are mean ± SD, unless noted otherwise; ACE = angiotensin converting enzyme; CPB = cardiopulmonary bypass. There were no differences between the 4 groups in any of the pre- and intraoperative patient characteristics.

(> 6 hours) for postoperative inotropic support all constituted independent pre- and intra-operative risk factors for the development of atrial fibrillation after coronary surgery. None of the other factors, including the choice between a total intravenous anesthetic regimen or an anesthetic regimen based on a volatile agent apparently influenced the incidence of postoperative atrial fibrillation. However, when the incidence of postoperative fibrillation was compared between the four different anesthetic regimens, it appeared that postoperative atrial fibrillation was lower with sevoflurane than with the other anesthetic agents.

Many studies have already addressed the risk stratification for the development of atrial fibrillation after coronary surgery. A very recent prospective multicenter study on 4657 coronary surgery patients identified older age, the presence of associated pathology such as congestive heart failure and chronic obstructive pulmonary disease as preoperative risk factors for the development of atrial fibrillation (40). The role of age and comorbidity are also apparent from the present observations and are in line with other previous reports (4-6). Reported intraoperative risk factors include prolonged aortic crossclamp time, need for an intraoperative intra-aortic balloon pump, surgical practices such as pulmonary vein venting and bicaval venous cannulation, and use of inotropic agents for more than 30 min after termination of CPB (4-6, 11, 40). In the current study population, a similar risk strat-

ification was observed with an increased risk for postoperative fibrillation with longer duration of CPB and prolonged need for inotropic support.

The pathophysiological mechanisms underlying the occurrence of postoperative atrial fibrillation still are not definitively elucidated. It has been suggested that myocardial energetic deficits may constitute one of components in the substrate for atrial fibrillation (30). Similarly, the occurrence of atrial ischemia – reperfusion injury and oxidative stress after cardiac surgery have been implicated in the occurrence of postoperative atrial fibrillation (31-33). Recently evidence has indicated that volatile anesthetic agents exhibit a direct cardioprotective effect in the course of myocardial ischemia. These effects have been attributed to an anesthetic preconditioning effect but also to an effect on the extent of reperfusion injury (34, 35). The experimental hypothesis for the present study was that the choice for a volatile anesthetic regimen might influence the incidence of postoperative atrial fibrillation. To our knowledge, this question has not yet been addressed. Only a few reports have addressed the potential association between rhythm disturbances and different newer anesthetic drugs but only reported on ventricular rhythm disturbances (41-43). The pathophysiological background for the experimental hypothesis was that the reported cardioprotective effects of volatile anesthetic agents might result in a lower incidence of postoperative atrial fibrillation. From the present

results it appeared that this was only true for sevoflurane and that with desflurane the incidence of postoperative atrial fibrillation was similar to the incidence observed with the intravenous anesthetic regimens. This was somewhat surprising since the reported cardioprotective effects with sevoflurane and desflurane in the setting of coronary surgery were quite similar (9, 37). The explanation for this phenomenon remains to be established. Desflurane has been reported to be associated with sympathetic stimulation (44-48) and with intramyocardial catecholamine release (49, 50); both mechanisms that may result in the induction of cardiac arrhythmias. Further studies will have to elucidate which mechanisms are responsible for this phenomenon.

A number of methodologic issues deserve attention. The global incidence of postoperative atrial fibrillation in the present study (13.9%) is relatively low compared with the incidence reported in other studies. It should be noted that the routine surgical technique for coronary surgery in our centre involves the use of a two stage venous cannula inserted in the inferior caval vein and that bypasses were sutured under intermittent aortic crossclamping. All patients also routinely received 2 g of methylprednisolone, a high dose scheme of trasyolol, and the nucleoside transport inhibitor lidoflazine. Although there is no evidence that these interventions altered the incidence of postoperative atrial fibrillation (32), these elements constitute a difference with the routine surgical procedures of other reports. β -blocking therapy has been shown to have a protective action against occurrence of postoperative atrial fibrillation (21, 26, 29). Almost 80% of the patients in the different anesthetic groups received preoperative β -blocking therapy, and all patients routinely were on β -blocking therapy postoperatively. There was also no difference for the intake of other drugs. However the number of patients necessitating prolonged inotropic support differed among the groups. Although there is yet no definitive proven enhancement of arrhythmogenic effects of β -adrenergic stimulation by specific anesthetic drugs (51-53), it can not be excluded that such interaction might – at least in part – be involved in the different incidence of atrial fibrillation between groups.

The observation period for occurrence of postoperative atrial fibrillation in the current study was limited to the first 24 hours postoperatively. Earlier reports have indicated that the peak incidence of occurrence of postoperative atrial fibrillation was between the second and the fourth day after the operation (5). It can therefore be expected

that the reported incidence in the current study underestimates the true incidence of atrial fibrillation after coronary surgery and emphasizes the importance of a sufficiently long observation period.

In conclusion, the results of the current study indicated that presence of an increased age more than 70 years, the presence of comorbidity as assessed by an EuroSCORE more than 4, prolonged duration of CPB (> 100 min) and the prolonged need (> 6 hours) for postoperative inotropic support were independent pre- and intraoperative risk factors for the development of atrial fibrillation after elective coronary surgery. The incidence of postoperative atrial fibrillation was lower in the group of patients who had a sevoflurane-based anesthesia. This observation suggests that the choice of the primary anesthetic regimen might influence the incidence of atrial fibrillation after coronary surgery. Further prospective, sufficiently powered multicenter studies should now be designed to further elucidate this issue and to identify potential underlying mechanisms.

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