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Preoperative Prophylaxis Can Decrease Rates of Atrial Fibrillation in Open Heart Surgery: A Retrospective Study

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ABSTRACT

Background. We investigated the effects of preoperative administration of beta-blockers on the incidence of atrial fibrillation (AF) after cardiothoracic surgery and the resulting morbidity and mortality.

Methods. We retrospectively evaluated 181 patients who underwent operations between May 2004 and December 2007. We divided the patients into 2 groups according to their preoperative use beta-blockers. Group A (n = 89) consisted of patients who did not receive beta-blockers, and group B (n = 92) consisted of patients who received 50 mg metoprolol succinate daily. All patients underwent on-pump coronary artery bypass grafting (CABG) via sternotomy.

Results. Atrial sizes and the baseline clinical and laboratory data were similar for the 2 groups. The 2 groups were also similar with respect to the numbers of grafts per patient, preoperative ejection fractions, cross-clamp times, cardiopulmonary bypass times, and postoperative inotrope use ($P > .05$). AF occurred in 39 (21.5%) of the 181 patients after the operation. Postoperative AF occurred in 30 (33.7%) of the group A patients and in 9 patients (9.7%) in group B ($P < .05$).

Conclusion. Postoperative AF increases the rates of morbidity and mortality and the length of hospital stay after CABG. The prophylactic use of beta-blockers decreases the rate of postoperative AF and thus AF-related complications.

INTRODUCTION

Atrial fibrillation (AF) and atrial flutter are arrhythmias that commonly occur following cardiac surgery. The precipitating events are not always obvious, although predisposing factors, including age, have been defined [McKeown 2005]. With the exception of sinus tachycardia, which occurs after coronary artery bypass grafting (CABG), postoperative AF is the most common arrhythmia, occurring in 10% to 65% of patients. AF is a significant cause of increased morbidity and increased length of hospital stay and significantly increases hospital costs [Kerstein 2004; Martinez 2005; McKeown 2005; Baker 2007]. The etiology of AF after open heart surgery is incompletely understood, and its prevention remains suboptimal. Some etiologic theories include neurohormonal activation, volume overload, and inflammation. Technical advances in surgery and anesthesia, as well as in different methods of myocardial protection, have not decreased the incidence of postoperative AF [Baker 2007].

Patients who undergo CABG alone have a lower incidence of postoperative AF than patients who undergo valve surgery or combined CABG/valve operations [Kerstein 2004]. Postoperative AF usually appears between 1 and 3 days after surgery and often diminishes during the first 30 postoperative days. It may be complicated by significant symptoms, hemodynamic instability, and an increased risk of stroke. Postoperative AF is also associated with an increased length of stay, both in the intensive care unit (ICU) and in rooms with less monitoring, and incurs additional costs that average several thousand dollars per patient [Bradley 2005]. In addition, postoperative AF has also been shown to independently predict postoperative delirium and neurocognitive decline [Roach 1996]. Recent guidelines of the American Heart Association and the European Society of Cardiology have recommended beta-blocker therapy as a first-line choice for the prevention of postoperative AF [Eagle 2004; Fuster 2006]. The rationale for beta-blocker therapy as prophylaxis is based on the speculation that increased sympathetic tone enhances the susceptibility of patients to postoperative dysrhythmias [Bradley 2005; Fuster 2006]. Although the efficacy of readministration of beta-blockers after cardiac surgery has been evaluated, the effectiveness of prophylactic beta-blocker treatment in patients without prior beta-blocker treatment has not been adequately studied [Baker 2007].

The purpose of this study was to investigate the effects of preoperative metoprolol administration on the incidence of AF after cardiothoracic surgery and the resulting morbidity and mortality.

PATIENTS AND METHODS

We retrospectively evaluated 181 patients who underwent operations between May 2004 and December 2007.

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We divided the patients into 2 groups. Group A (n = 89) received no beta-blocker agent preoperatively, and group B (n = 92) received daily treatment with 50 mg metoprolol succinate (Beloc-ZOK; AstraZeneca, London, UK), which was initiated a minimum of 5 days before surgery. All patients received their last preoperative dose on the morning of surgery. Metoprolol succinate therapy was reinitiated in group B patients at the same dosage 1 day after the operation. Clinical demographic data and risk factors are summarized in Table 1.

The exclusion criteria were preoperative AF, a history of supraventricular or atrioventricular rhythm disturbances, reoperations, coexisting valvular disease, a noninterpretable electrocardiogram (ECG) for P-wave assessment, and a history of cardiogenic shock.

All of the operations were performed by the same surgical group.

Surgical Technique

With the patient under general anesthesia, we harvested the left internal mammary artery following a median sternotomy and prepared the saphenous vein if necessary. After full heparinization, cardiopulmonary bypass (CPB) was done via cannulation of the ascending aorta and the right atrium. Moderate hypothermia (28°C-30°C) was induced in all patients. We initiated cardiac arrest with crystalloid cardioplegia (Plegisol, 15 mL/kg) and supported myocardial preservation with 400 mL of cold blood cardioplegia every 20 minutes.

Table 1. Demographic Features and Preoperative Risk Factors of the Patients*

Parameter	Group A (n = 89)	Group B (n = 92)	*P*
Age, y†	59.16 ± 10.34 (32-78)	58.49 ± 10.55 (30-77)	NS
Male/female sex, n	50/39	51/41	NS
Thyroid-stimulating hormone, μIU/mL	0.12-3.9	0.65-3.1	NS
Chronic obstructive pulmonary disease, n	11	10	NS
Preoperative use of antiaggregant agents, n	42	44	NS
Left atrial diameter, cm‡	3.4 ± 0.7	3.3 ± 0.6	NS
Preoperative NYHA class, n			
I-II	58	60	NS
III-IV	31	32	
Left ventricular ejection fraction, %†	51.77 ± 10.33 (30-65)	50.61 ± 9.87 (30-65)	NS
Operation type, n			
Urgent	15	17	NS
Elective	74	75	NS
EuroScore‡	4.12 ± 1.90	4.29 ± 1.87	NS

*NS indicates not statistically significant; NYHA, New York Heart Association.

†Data are presented as the mean ± SD (range).

‡Data are presented as the mean ± SD.

Following the completion of all anastomoses, we completed proximal anastomoses with aortic side-clamping at the end of surgery.

Monitoring

All patients were continuously monitored by ECG in the ICU, with 3-channel pressure monitoring and a finger probe for oxygen saturation instituted within 48 hours. After the patients were transferred to the ward, we carried out continuous ECG monitoring and recorded blood pressure noninvasively every 30 minutes until patient discharge.

Evaluated Parameters

We used an ECG system (Datascope, Montvale, NJ, USA) to continuously monitor for perioperative myocardial infarction (MI), postoperative MI, transient atrioventricular block, postoperative ventricular fibrillation (VF), and AF from the time of the operation through the first postoperative week, with the possibility of an analysis of rhythm disturbances during the patient's stay in the ICU. We measured levels of blood electrolytes, including potassium and magnesium, and corrected any deficiencies. The groups were compared with respect to the need for an intra-aortic balloon pump, mortality rates, length of ICU stay, and time to discharge from the hospital. The patients were followed up for 30 days for de novo or permanent AF. Electrical cardioversion was performed in patients who developed AF after or just before cessation of CPB. If a patient developed AF in the immediate postoperative period, the electrical cardioversion was repeated. Medical cardioversion was done in patients who had AF or who continued to have AF at the end of first week. Anticoagulation therapy was initiated for patients who were unable to maintain sinus rhythm (persistent AF).

Statistical Analysis

All analyses were carried out with the Statistical Package for the Social Sciences, version 13 (SPSS, Chicago, IL, USA). All continuous data are presented as the mean ± SD. The unpaired Student *t* test was used to analyze the effects of normally distributed continuous variables on the occurrence of postoperative AF before, during, or after surgery. We used the Kolmogorov-Smirnov test to check the distributions of variables. Between-group differences in incidences were analyzed by analysis of variance. All *P* values <.05 were considered statistically significant.

RESULTS

CABG was performed with CPB in 181 patients. The baseline clinical and laboratory data were similar for the 2 groups (Table 1). Levels of thyroid hormone were within the normal range in both groups throughout the study. The 2 groups did not differ with respect to atrial size and were also similar with respect to the number of grafts per patient, cross-clamp times, CPB times, the postoperative use of inotropic agents, and the use of the internal mammary artery (Table 2; *P* > .05). Table 2 summarizes the

Table 2. Intraoperative and Postoperative Data of the Patients*

Parameter	Group A	Group B	*P*
No. of grafts, n			
1	3	2	NS
2	20	22	NS
3	39	38	NS
4	25	27	NS
5	2	3	NS
No. of grafts/patient†	3.03 ± 0.82	3.07 ± 0.79	NS
Graft type			
Internal mammary artery	89	92	NS
Radial artery	6	8	NS
Saphenous vein	175	183	NS
Bypass pump time, min†	75.02 ± 13	78.40 ± 19	NS
Aorta cross-clamp time, min†	44.3 ± 11	46.2 ± 13	NS
Duration of operation, h†	3.81 ± 0.2	3.77 ± 0.3	NS
Postoperative use of inotropes, n	33	34	NS
Postoperative blood data			
White blood cells, $\times 10^9$/L‡	10.2 ± 4.1 (9.2-18.1)	5.3 ± 2.8 (6.7-10.5)	<.05
Thrombocytes, $\times 10^9$/L	122-219	111-208	NS
Creatinine, mg/dL	0.8-1.5	0.9-1.6	NS
C-reactive protein, mg/dL‡	4.8 ± 3.3 (3.8-8.1)	1.1 ± 0.9 (1.3-4.8)	<.05

*NS indicates not statistically significant.
†Data are presented as the mean ± SD.
‡Data are presented as the mean ± SD (range).

intraoperative data. Patients in group A had significantly higher white blood cell counts, and C-reactive protein concentrations were significantly higher in group A than in group B ($P < .05$).

AF occurred in 39 (21.5%) of the 181 patients after the operation. Postoperative AF occurred in 30 patients (33.7%) in group A and in 9 patients (9.7%) in group B ($P < .05$). The 2 groups were also different with respect to the length of ICU stay and the time to discharge from the hospital ($P < .05$). The occurrence of an unfavorable hemodynamic status in 11 patients in group A and 10 patients in group B prompted the use of intra-aortic balloon counterpulsation. With the exception of postoperative VF, the groups were not significantly different with respect to morbidities. A higher incidence of postoperative VF occurred in the patients who did not receive beta-blocker prophylaxis ($P < .05$). Postoperative VF was seen in 9 patients (9%) in group A and in 1 patient (1%) in group B. Sinus rhythm was seen following defibrillation in all patients who had postoperative VF. The patients were administered beta-blocker or amiodarone treatment after a sinus rhythm was achieved. Table 3 summarizes the complications and the frequencies of morbidities and mortality that occurred following surgery. In addition, there was a significant difference in overall mortality between the 2 groups ($P < .05$). Four patients in group A died of postoperative MI, and 1 patient died of a cerebral embolus. One patient in group B died of low cardiac output. None of the patients developed AF prior to the cannulation before preoperative CPB.

Table 3. Incidences of Complications and Mortality*

Parameter	Group A	Group B	*P*
Morbidities, n			
Reoperation for bleeding	5	4	NS
Tamponade	0	1	NS
Intra-aortic balloon pump	11	10	NS
Pneumothorax	3	4	NS
Delayed wound healing	9	11	NS
Deep sternal infection	1	1	NS
Respiratory failure	1	0	NS
Perioperative MI	2	1	NS
Postoperative MI	5	4	NS
Transient AV block	4	3	NS
Postoperative VF	9	1	<.05
Renal failure	2	1	NS
Pericardial effusion	5	4	NS
Stroke/TIA	1	0	NS
Duration of ventilation, h	4.9 ± 1.4	4.8 ± 1.3	NS
ICU stay, d	3.9 ± 0.4	1.9 ± 0.2	<.05
Hospital stay, d	9.1 ± 1.9	6.3 ± 1.5	<.05
Overall mortality, n	5	1	<.05

*Data are presented as the mean ± SD where appropriate. NS indicates not statistically significant; MI, myocardial infarction; AV, atrioventricular; VF, ventricular fibrillation; TIA, transient ischemic attack; ICU, intensive care unit.

Intraoperatively, 15 patients (15%) in group A and 6 patients (6%) in group B developed AF during cannulation ($P < .05$, Table 4). After CPB, electrical cardioversion was performed in these patients. Four patients in group A and 3 patients in group B regained sinus rhythm. After the operation, 9 patients in group A and 3 patients in group B still had AF. These patients underwent cardioversion prior to sternal closure. Two patients in both groups regained sinus rhythm. Eleven patients (12.3%) in group A and 3 patients (3.2%) in group B had AF in the early postoperative period in the ICU. All of these patients underwent electrical cardioversion in the ICU. Seven patients in group A and no patients in group B had persistent AF after cardioversion. At postoperative day 3, 14 patients (11%) in group A and 4 patients (4.3%) in group B had AF. These patients were first treated with electrical cardioversion and were given medical cardioversion if they did not respond. The frequency of perioperative and postoperative

Table 4. Differences in Atrial Fibrillation (AF) Variables between Groups*

AF Occurrence	Group A, n	Group B, n	*P*
Before CPB	0	0	>.05
During cannulation	15	6	<.05
After CPB and before sternal closure	9	3	<.05
Early postoperative in ICU (new AF)	11	3	<.05
Third postoperative day (new AF)	14	4	<.05
First postoperative month (new AF)	5	2	<.05
Persistent AF	8	0	<.05

*CPB indicates cardiopulmonary bypass; ICU, intensive care unit.

AF was less in group B than in group A, and this difference was statistically significant ($P < .05$, Table 4). No shifts blood electrolyte levels were found in any of the patients, with or without AF.

DISCUSSION

AF, a common complication after cardiovascular surgery, often leads to prolonged postsurgical hospital stays and increased morbidity, compared with patients who maintain sinus rhythm. Long thought a nuisance, AF has clearly been shown to increase the length of hospital stay, ICU use, morbidity, and even mortality [Eagle 2004; Bradley 2005; Martinez 2005; Eslami 2007], as we observed in our series.

AF and CABG surgery are protagonists in a neverending story. Despite the astonishing advances that have been made in cardiac surgery over the past 40 years, new-onset AF remains its most common complication [Bradley 2005].

Many factors contribute to the development of AF in the postoperative period. An older age, hypertension, poor left ventricular function, a prolonged operative ischemic period, poor myocardial preservation, metabolic changes, temperature flux, postoperative mobilization of interstitial fluids, electrolyte changes, and ICU stress can increase the incidence of postoperative AF. Reperfusion injury, an exaggerated inflammatory response (especially involving the pericardium), and mechanical stretching of the atrium can also contribute to the development of AF. Furthermore, a heightened sympathetic activation is an established risk factor for postoperative AF [Bradley 2005; Martinez 2005; Baker 2007]. Although there are many etiologic and predisposing factors, little consensus exists regarding these factors, and it is not easy to prove a single causal factor. Perhaps interaction between these factors is important for the occurrence of AF.

Both groups (more in group A) had increased perioperative AF (Table 4).

The efficacy of pharmacologic prophylaxis in reducing the incidence of AF has been investigated in several studies, and different studies have addressed the issue of preventing AF after CABG [Martinussen 1988; Kerstein 2004; Bradley 2005; Imren 2007].

Many approaches to preoperative and postoperative prophylaxis of AF have been attempted with varying degrees of clinical success. These strategies have included preoperative beta-blocker therapy [Martinussen 1988; Bradley 2005; Fuster 2005]. According to the American College of Cardiology/American Heart Association and the European Society of Cardiology Guidelines for AF, preoperative or early postoperative administration of beta-blockers in patients without contraindications is a class-1 indication for preventing AF after CABG [Eagle 2004]. Beta-blockers have been shown to be effective prophylactic agents and to carry a lower risk than other antiarrhythmic agents [Evrard 2000; Eagle 2004; Bradley 2005]. Our observed AF rate (21.5%) was similar to the findings of several studies [Kerstein 2004; Martinez 2005; Baker 2007; Imren 2007]; however, AF frequency was significantly reduced in our study with the prophylactic use of beta-blockers.

In the study of Evrard and colleagues [2000], the incidence of postoperative AF was 16% in the sotalol group and 48% in the control group. This report emphasized that low-dose oral sotalol provided considerable and reliable protection for patients, especially those with selected nondepressed cardiac function [Evrard 2000]. Metoprolol has been hypothesized to offer better protection than conventional beta-blockers because it blocks β_1 and β_2 receptors. It may have had a preventive effect against AF in the present study. As a proof of this preventive effect, the patients who received metoprolol did not experience persistent postoperative AF. Furthermore, we did not observe the potential side effects of beta-blockers, with the exception of 1 patient who experienced a transient atrioventricular block.

Postoperative AF increases the length of the hospital stay after CABG up to 5 days [Bradley 2005], increases the charges by as much as US $10,055 [Aranki 1996; Bradley 2005], and is associated with a 2- to 3-fold increase in the incidence of postoperative stroke [Roach 1996; Eslami 2007]. In our study, beta-blocker prophylaxis reduced ICU and hospital stays (Table 3), and this finding was consistent with the relevant literature [Aranki 1996; Bradley 2005]. Preoperative left ventricular function has been suggested to predict a risk for AF [Crozier 2003; Imren 2007]. Left ventricular ejection fractions for our 2 groups were similar (group A, 51.77% ± 10.33%; group B, 50.61% ± 9.87%). Imren et al [2007] reported that patients with poor ventricular function could not tolerate beta-blockers and that the dosing of beta-blockers should be adjusted.

The role of inflammation and oxidative stress in the pathophysiology of AF has been recognized [Boos 2006; Korantzopoulos 2007]. The first observation that related inflammation to AF after CPB was made in 1997 by Bruins et al [1997]. These investigators reported that the peak incidence of AF on the second to third postoperative day coincided with the peak in C-reactive protein concentration. Activation of the complement system and the release of proinflammatory cytokines occur after cardiac surgery, suggesting the presence of an intense inflammatory process [Bruins 1997]. Furthermore, more recent trials have shown that an elevated postoperative white blood cell count [Fontes 2005] and monocyte activation are associated with the development of AF after cardiac surgery [Fontes 2005], emphasizing the role of inflammation in this setting. In our study, the white blood cell count and C-reactive protein levels were higher postoperatively in the patients in the metoprolol group than in the group of patients who did not receive a beta-blocker. This result was statistically significant ($P < .05$). Evidence is accumulating on the role of anti-inflammatory and antioxidant drugs for reducing the incidence of postoperative AF [Likosky 2004; Boos 2006; Korantzopoulos 2007].

It must be remembered that enteral absorption of drugs might be disturbed following extracorporeal circulation. Blood levels of metoprolol were not monitored. This was one of the limitations of our study.

In conclusion, postoperative beta-adrenergic blockade at low doses is valuable for patients who receive these medications before CABG procedures. In addition, the patient's preoperative ventricular function, the length of the myocardial ischemic period, patient age, and the use of inotropic agents may play important roles in the triggering and prevention of AF.

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