The Heart Surgery Forum #2013-286
17 (1), 2014
doi: 10.1532/HSF98.2013286

Online address: http://cardenjennings.metapress.com

Prophylactic Effects of Metoprolol on the Prevention of Atrial Fibrillation after Cardiac Surgery Are Dose Dependent

Nan Cheng, Changqing Gao

Department of Cardiovascular Surgery, Chinese People's Liberation Army General Hospital, Beijing, China

INTRODUCTION

Atrial fibrillation (AF) is one of the most common complications after cardiac surgery. Many studies have reported an incidence of 20%-40% in patients undergoing open heart surgery, and the peak incidence usually occurs between the postoperative days [Fuller 1989; Aranki 1996; Svedjeholm 2000; Maisel 2001]. AF is commonly self-limited and rarely results in postoperative death. However, postoperative AF (POAF) is often associated with complications, including stroke, heart failure, prolonged hospital stay, and increased costs [Maisel 2001; Bramer 2010]. Many pharmacological methods have been used to prevent this complication, and beta-blockers, which have been investigated in several studies, have demonstrated effectiveness [Ali 1997; Connolly 2003; Crystal 2004; Halonen 2006; Imren 2007]. There is currently a consensus in the use of beta-blockers for the prevention of POAF. However, whether the effect of beta-blockers on POAF is dose dependent has not been widely studied [Coleman 2004; Lucio 2004]. In addition, patients with different racial backgrounds have a different response to metoprolol based on body shape. In addition, the CYP2D6 genotypes are different among white and Asian patients. In this study dose-dependent prophylactic effects of beta-blockers, which were obtained in a single center.

METHODS

Patients

The study had been previously approved by the institutional review board, and all of the patients provided informed consent. A total of 680 consecutive patients underwent coronary artery bypass graft (CABG) and/or valve surgery at the General Hospital of the People's Liberation Army (PLA) between February 2009 and November 2012. Of these patients, 66 were excluded because of existing permanent preoperative AF (34 patients), missing (or incomplete) electrocardiograms (ECGs) (20 patients), or preoperative heart rates of <60 beats/min. Thus a total of 614 patients were included in the final analysis.

Received November 16, 2013; accepted March 6, 2013.

Correspondence: Changqing Gao, Department of Cardiovascular Surgery, the People's Liberation Army General Hospital, No.28. Fuxing Road, Haidian District, Beijing, China, 100853; +86-10-66938035, Fax: +86-10-88211280.

Principles of Beta-Blocker Usage

Patients with complaints of palpitations or ischemic-type chest pain, a history of myocardial infarction (MI) or ST-segment elevation, heart rate higher than 100 beats/min (bpm), systolic blood pressure higher than 120 mmHg, and/or heart failure classified as New York Heart Association (NYHA) class II to IV were subjected to metoprolol intervention. Patients diagnosed with severe aortic valve regurgitation or stenosis with a fast heart rate were cautiously administered metoprolol to attain the optimum target heart rate range of 70 to 80 bmp. The exclusion criteria included: heart rate ≤60 bpm, systolic arterial pressure ≤100 mmHg, second- or third-degree atrioventricular block, severe chronic obstructive pulmonary disease (COPD), history of asthma, and severe peripheral vascular disease. The initial dosage of 6.25 mg twice a day was adjusted to obtain a dosage that induced a controlled resting heart rate of at most 80 bpm (but not less than 55-60 bpm), a systolic blood pressure between 100 and 120 mmHg, and improvement in associated symptoms. Those patients that received the oral metoprolol therapy preoperatively continued receiving the same dosage after extubation. We compared the incidence of postoperative AF in patients who were administered metoprolol with that in patients who did not receive metoprolol. All of the patients were further divided into 4 groups according to the daily dosage of metoprolol: the no metoprolol group (n = 173), the 12.5-mg metoprolol group (n = 206), the 25-mg metoprolol group (n = 132), and the 50-mg metoprolol group (n = 103). Eight additional patients were further excluded because they received an unusual metoprolol dose (metoprolol 18.75 mg, 3 patients; metoprolol 37.5 mg, 3 patients; metoprolol 75 mg, 2 patients). These unusual metoprolol subgroups were excluded in the comparison of the groups that received different doses of metoprolol with the no metoprolol group.

Confirmation of Postoperative Atrial Fibrillation

After the patients were transferred to the intensive care unit (ICU) after surgery, all the patients were connected to

monitors for continuous ECG monitoring for the first 5 days after surgery. The monitors stored the ECG recordings, which were analyzed offline. Twelve-lead ECG recordings were obtained from all of the patients before their discharge from the hospital. The primary end point was the occurrence of postoperative AF (an irregular rhythm denoted by absence of *P* waves and irregular RR interval spacing) or atrial flutter (each QRS complex was accompanied by multiple monomorphic *P* waves and an accelerated atrial rate) during the hospital stay. After the first episode of AF, the study protocol was discontinued. All of the ECGs were interpreted by at least 2 clinicians. Additional diagnostic revisions were performed by a cardiologist when necessary.

DATA COLLECTION

All of the patients' demographic characteristics, medical history, cardiac history, and drug therapy were evaluated. The evaluation of the operative status and postoperative events focused on the occurrence of AF, the length of ICU stay, and the length of hospital stay. The clinical data were extracted from the patients' electronic medical records, daily ECG, and computer database in the cardiac surgery unit at PLA General Hospital.

Statistical Analysis

The continuous data are presented as mean ± standard deviation (SD) and the continuous variables were compared using the Student's t-test. The categorical variables were compared with the χ^2 test. The metoprolol dosage and odds ratio (OR) for postoperative AF (*P* for trend) were determined. The potential predictors of AF were analyzed using univariate logistic regression. The subsequent multivariate logistic regression included those factors that were found to be significant or nearly significant ($P < .10$) in the univariate analysis. All of the tests were 2-sided, and differences with $P < .05$ were defined as statistically significant. The SPSS software (version 13.0) was used for statistical analysis(SPSS, Inc., Chicago, IL).

RESULTS

Of all the 614 patients studied, 374 (60.9%) underwent a CABG procedure, 193 (31.4%) underwent aortic valve replacement (AVR), and 47 patients underwent both procedures. In addition, 437 (71.2%) patients received beta-blocker therapy, and 177 (28.8%) of the patients did not receive beta-blocker therapy. The characteristics and perioperative variables for the patients in the treated (with beta-blocker) and the untreated groups are reported in Table 1. The univariate analyses of the following variables demonstrated no significant differences: mean age, male sex, body mass index (BMI), cigarette smoking, hypertension, hypercholesterolemia, diabetes mellitus, COPD, history of MI, history of percutaneous coronary intervention (PCI), New York Heart Association (NYHA) class III-IV, right coronary artery (RCA) stenosis, 3-vessel coronary artery disease (CAD), left main coronary artery (LMCA) stenosis, left ventricular ejection fraction (LVEF), and the use of amiodarone, a calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), and statins. Moreover, the following intraoperative characteristics were similar in both groups: number of anastomoses, cardiopulmonary bypass (CPB), and procedure type (CABG and/or AVR). The length of the ICU stay, the length of the hospital stay, and the development of stroke, ventricular arrhythmia, and wound infection exhibited no significant differences between the2 groups. The only variable that was significantly different between the 2 groups was the incidence of AF, which developed in 101 (23.1%) of the 437 patients who were administered the beta-blocker and in 61 (34.5%) of the 177 patients who did not receive the beta-blocker ($P = .004$).

Further univariate analysis of the variables with the occurrence (or not) of postoperative AF revealed no significant differences in most of the preoperative and operative variables, with the exception of age ($P = .001$), history of MI ($P = .044$), and administration of beta-blocker therapy ($P = .004$) (Table 2). Moreover, the patients who developed AF required a longer ICU stay (2.96 ± 0.78 days versus 2.77 ± 0.69 days, $P = .003$) and a longer hospital stay (14.02 ± 1.35 days versus 13.03 ± 1.18 days, $P < .001$).

Table 3 shows the results of the multivariate logistic regression analysis, which identified the patients' age (OR = 1.04, 95% confidence interval [CI] = 1.02-1.07, $P = .001$) and the administration of the beta-blocker therapy (OR = 0.57, 95% CI = 0.38-0.84, $P = .004$) as separate factors that influence the postoperative AF outcome.

Comparison of the incidences of AF in the subgroups is shown in Table 4. An increase in the beta-blocker dosage decreased the incidence of AF, and this trend holds for all of the doses of metoprolol used in this study (the highest dose was 50 mg metoprolol). Furthermore, with the exception that the comparison of the incidence of AF in the subgroup that received 12.5 mg metoprolol showed no significant differences with the group that did not receive the beta blocker, a reduction in the occurrence of AF was observed in the patients who received 25 mg metoprolol (OR = 0.56, 95% CI = 0.93-0.34, $P = .025$) and 50 mg of metoprolol (OR = 0.33, 95% CI = 0.63-0.18, $P = .001$).

DISCUSSION

Postoperative AF is a common complication after cardiac surgery and has long been thought to be a nuisance that clearly increases the length of hospital stay, length of ICU stay, morbidity, and even mortality [Jideus 2000; Maisel 2001; Baker 2007; Mariscalco 2008]. It is widely believed that enhanced sympathetic nervous system activity, which is highest during the first 24 h after an operation, increases the susceptibility to postoperative AF, whereas the onset of AF often occurs in the second and third days after the operation [Imren 2007]. Approximately 70% (114/162) of the patients in our study developed postoperative AF during this period. The mean duration of the AF event was <5 hours because a beta-blocker (e.g., metoprolol and esmolol) or amiodarone was immediately used to control the heart rate once the AF onset occurred.

Table 1. Patient Characteristics and Perioperative Variables for Beta-Blocker and No Beta-Blocker Groups

Variables*	Beta-Blocker Group (n = 437)	No Beta-Blocker Group (n = 177)	*P*
Male/female ratio	233/204	109/68	.062
Age, years	63.11 ± 8.11	62.93 ± 7.68	.802
BMI	25.95 ± 2.94	25.68 ± 2.90	.284
Cigarette smoking	200 (45.8%)	80 (45.2%)	.898
Medical history			
Hypertension	257 (58.8%)	111 (62.7%)	.371
Hypercholesterolemia	101 (23.1%)	39 (22%)	.773
Diabetes mellitus	189 (43.2%)	68 (38.4%)	.272
COPD	25 (5.7%)	10 (5.6%)	.973
Cardiac history			
History of MI	125 (28.6%)	64 (36.2%)	.066
PCI history	54(12.4%)	22 (12.4%)	.980
NYHA class III-IV	209 (47.8%)	79 (44.6%)	.473
RCA stenosis	172 (39.4%)	75 (42.4%)	.490
3-Vessel CAD	215 (49.2%)	86 (48.9%)	.940
LMCA stenosis	109 (24.9%)	48 (27.1%)	.576
LVEF, %	54.95 ± 11.48	55.12 ± 11.25	.860
Medical therapy			
Amiodarone	11 (2.5%)	4 (2.3%)	.852
CCB	91 (20.8%)	37 (20.9%)	.982
ACEI	228 (52.2%)	92 (52%)	.965
Statins	268 (61.3%)	106(59.9%)	.740
Operative characteristics			
No. of anastomoses	2.73 ± 0.79	2.76 ± 0.78	.665
CPB time, min	121.84 ± 18.94	121.57 ± 18.65	.871
CABG	268 (61.3%)	106 (59.9%)	.740
AVR	134 (30.7%)	59 (33.3%)	.519
CABG + AVR	35 (8%)	12 (6.8%)	.604
Postoperative characteristics			
Length of ICU stay, days	2.84 ± 0.72	2.78 ± 0.72	.367
Length of hospital stay, days	13.26 ± 1.29	13.37 ± 1.33	.322
AF	101 (23.1%)	61 (34.5%)	.004

Table 2. Patient Characteristics and Perioperative Variables in the AF and No AF Groups

Variables*	AF (n = 162)	No AF (n = 452)	*P*
Male/female ratio	85/77	257/195	.335
Age, years	64.84 ± 7.16	62.41 ± 8.17	.001
BMI	26.25 ± 2.83	25.74 ± 2.96	.057
Cigarette smoking	68 (42%)	212 (46.9%)	.280
Medical history			
Hypertension	104 (64.2%)	264 (58.4%)	.197
Hypercholesterolemia	41 (25.3%)	99 (21.9%)	.375
Diabetes mellitus	64 (39.5%)	193 (42.7%)	.480
COPD	13 (8%)	22 (4.9%)	.137
Cardiac history			
History of MI	60 (37%)	129 (28.5%)	.044
PCI history	24 (14.8%)	52 (11.5%)	.272
NYHA class III-IV	80 (49.4%)	208 (46.0%)	.462
RCA stenosis	70 (43.2%)	177 (39.2%)	.367
3-Vessel CAD	81 (50%)	220 (48.8%)	.790
LMCA stenosis	37 (22.8%)	120 (26.5%)	.353
LVEF, %	55.97 ± 10.70	54.65 ± 11.64	.206
Medical therapy			
Amiodarone	3 (1.9%)	12 (2.7%)	.570
Beta-blockers	101 (62.3%)	336 (74.3%)	.004
CCB	41 (25.3%)	87 (19.2%)	.103
ACEI	84 (51.9%)	236 (52.2%)	.937
Statins	100 (61.7%)	274 (60.6%)	.804
Operative characteristics			
No. of anastomoses	2.75 ± 0.82	2.74 ± 0.77	.821
CPB time, min	122.04 ± 18.69	121.67 ± 18.91	.827
CABG	99 (61.1%)	275 (60.8%)	.952
AVR	45 (29.6%)	145 (32.1%)	.564
CABG + AVR	17 (9.3%)	32 (7.1%)	.371
Postoperative characteristics			
Length of ICU stay, days	2.96 ± 0.78	2.77 ± 0.69	.003
Length of hospital stay, days	14.02 ± 1.35	13.03 ± 1.18	<.001
Stroke	18 (11.1%)	48 (10.6%)	.862
Ventricular arrhythmia	41 (25.3%)	72 (15.9%)	.008
Wound infection	14 (8.6%)	35 (7.7%)	.717

*Categorical data are numbers; continuous data are means ± SD.

Table 3. Multivariate Logistic Regression Analysis of Factors Influencing the Incidence of Postoperative AF

Variables	Univariate		Multivariate	
	P	OR (95% CI)	*P*	OR (95% CI)
Beta-blockers	.004	0.57 (0.39-0.84)	.004*	0.55 (0.37-0.82)
Male/female ratio	.335	1.19 (0.83-1.71)	.459	1.16 (0.79-1.71)
Hypertension	.197	1.28 (0.88-1.85)	.132	1.36 (0.91-2.04)
Age, years	.001	NA†	<.001*	1.06 (1.03-1.08)
BMI	.057	NA	.063	1.07 (1.00-1.14)
COPD	.137	1.71 (0.84-3.47)	.127	1.80 (0.85-3.84)
RCA stenosis	.367	1.18 (0.82-1.70)	.453	1.16 (0.78-1.73)
NYHA class III-IV	.462	1.14 (0.80-1.64)	.813	1.05 (0.71-1.56)
History of MI	.044	1.47 (1.01-2.15)	.064	1.48 (0.98-2.23)
Cigarette smoking	.280	0.82 (0.57-1.18)	.278	0.81 (0.55-1.19)
Diabetes mellitus	.480	0.88 (0.61-1.26)	.408	0.85 (0.57-1.26)
Hypercholesterolemia	.375	1.21 (0.80-1.84)	.292	1.29 (0.81-2.06)
LMCA stenosis	.353	0.82 (0.54-1.25)	.244	0.76 (0.49-1.20)
Three-vessel CAD	.790	1.05 (0.73-1.50)	.285	0.80 (0.53-1.20)
PCI history	.272	1.34 (0.80-2.25)	.100	1.63 (0.91-2.90)
No. of anastomoses	.821	NA	.563	1.08 (0.84-1.39)
CABG	.952	1.01 (.070-1.46)	.180	0.62 (0.31-1.25)
AVR	.564	0.89 (0.60-1.32)	.118	0.55 (0.26-1.16)
ACEI	.937	0.99 (0.69-1.41)	.970	0.99 (0.68-1.45)
Statins	.804	1.05 (0.73-1.52)	.865	0.97 (0.65-1.43)
CPB time, min	.827	NA	.833	1.00 (0.99-1.01)
LVEF, %	.206	NA	.391	1.01 (0.99-1.02)
Amiodarone	.570	0.69 (0.19-2.48)	.496	0.63 (0.17-2.39)
CCB	.103	1.42 (0.93-2.17)	.183	1.36 (0.87-2.14)

*$P < .05$.

†NA, data not applicable.

Table 4. Incidence of Postoperative Atrial Fibrillation in Each Beta-Blocker Group Compared with No-Beta-Blocker Group

Blocker Dose, mg	No. of Patients	AF, n (%)	OR	95% CI	*P*
No beta-blockers	175	59 (33.7)			
Beta-blockers					
12.5	208	55 (26.4)	0.71	1.10-0.46	.121
25	130	28 (21.5)	0.54	0.91-0.32	.020*
50	93	12 (12.9)	0.29	0.56-0.15	<.001*

*$P < .05$.

There are many factors that may contribute to the development of postoperative AF. Increased age, poor left ventricular function, prolonged operative ischemic time, electrolyte changes, and postoperative redistribution of interstitial fluids may independently or interactively influence the outcome. Furthermore, sympathetic nerve activation can increase the susceptibility to postoperative AF [Baker 2007]. Mechanical stretching, which alters the atrial cellular electrophysiological properties, may contribute to the development of AF, which suggests that the increased postoperative intravascular fluid volume is also an important risk factor [Likosky 2004; Imren 2007].

Several studies have shown that the prophylactic use of a beta-blocker can prevent postoperative AF to a certain extent [Coleman 2004; Lucio 2004; Haghjoo 2007; Imren 2007]. Our observed AF rate (26.4%) was similar to that reported for several previous studies [Martinez 2005; Halonen 2006; Imren 2007]. The use of metoprolol caused a 33% reduction in the risk of arrhythmias, and this finding was similar to that obtained by Connolly in a double-blind study called the BLOS (Beta-Blocker Length of Stay) trial (n = 1,000) [Connolly 2003], which showed a 20% reduction in the risk of arrhythmias in randomized patients.

Although beta-blockers can be broadly used in the treatment of cardiovascular diseases, such as atrial or ventricular arrhythmias, hypertension, and heart failure, the mechanism through which metoprolol treatment decreases the incidence of AF has not yet been fully elucidated. Salameh and colleagues [Salameh 2010] found that the antiarrhythmic effects of metoprolol may be due to its influence on the remodeling of connexin43 (Cx43), which is the most important protein for intercellular electrical communication in the heart. Dhein et al. [Dhein 2011] also demonstrated the antagonistic effect of metoprolol on alterations in the localization of Cx43 and conduction changes, which may be helpful for the development of new antiarrhythmic drugs that can pharmacologically modulate the remodeling of the gap junction.

The most consistent risk factor for the development of POAF is advanced age, as has been reported in many previous studies. Although the mean age of the patients in this study was no higher than 70 years, the multivariate analysis confirmed the effect of age on the incidence of POAF. The correlation between age and beta-blocker–induced AF prevention was not analyzed further because the numbers of septuagenarian and octogenarian patients were relatively small.

In this study we found that the groups administered 25 mg/day ($P < .05$) and 50 mg/day ($P < .001$) metoprolol had significant reductions in the occurrence of AF compared with the group that did not receive the therapy. However, the group that received 12.5 mg/day metoprolol did not exhibit a significant reduction. This finding suggests that the intensity of the beta-blocker may be critical both in preoperative initiation and postoperative maintenance of beta-blocker therapy. This result may be inconsistent with that obtained by the BLOS study, which showed no further reduction in the comparison of metoprolol doses of 150 and 100 mg/day. However, according to the BLOS study, at least 40% of patients in the placebo group received a different beta-blocker therapy preoperatively, which may have reduced the observed benefit of the study intervention. Thus, prophylactic use of the beta-blocker can be an effective approach to reduce the incidence of POAF, and the resulting shorter ICU and hospital stays can efficiently cut the hospital costs.

We observed no obvious side effects of metoprolol, such as severe bradycardia, hypotension, or atrioventricular block. This lack of side effects may be due to the precise regulation of the dosage through the blood pressure and heart rate and our use of conserved beta-blocker dosage in the native population, which was also lower than that used in other studies [Connolly 2003; Coleman 2004]. In the study performed by Coleman and colleagues [Coleman 2004], the incidence of AF and the length of the hospital stay were not significantly different between patients who received preoperative beta-blockers that were discontinued at the time of surgery and patients who did not receive preoperative beta-blockers. This finding may provide evidence that beta-blocker withdrawal is not a positive factor for AF, and the short withdrawal of beta-blockers at the time of surgery might have had a slight impact on the AF outcome observed in our study. The expected reduction in the length of the ICU and hospital stays due to beta-blocker–induced prevention of postoperative AF did not occur. In addition, the

preoperative use of beta-blockers did not reduce the incidence of ventricular arrhythmia. This may because the conditions of the patients were relatively good, with a mean LVEF >50% and fewer patients needing combined surgery.

Study Limitations

The main limitation of this study was its retrospective and observational design. Moreover, this study was based on a single center. Therefore, bias may have been introduced due to a lack of prospective continuous monitoring. Furthermore, the prophylactic use of metoprolol in this study was not completely for the prevention of postoperative AF. In contrast, the principle of using a beta-blocker to control blood pressure and the heart rate to standard levels was uniform, and the selection bias was likely to have been slight because the patients were consecutive. The highest dosage of metoprolol used in this study was 50 mg, which may not be a specific metoprolol dosage for AF prevention, but the dose-dependent effects of metoprolol on AF prevention were fairly obvious. Thus, a prospective randomized trial with newly initiated metoprolol treatment compared with a placebo would be needed to support the theory that metoprolol prevents AF in a dose-dependent manner.

CONCLUSION

Advanced age increases the odds of developing POAF, which may prolong the lengths of ICU and hospital stays. However, the appropriate administration of beta-blockers preoperatively for indicated patients has the potential to reduce the incidence of POAF, and this prophylactic effect is dose dependent.

ACKNOWLEDGEMENTS

Dr. Gao was the surgeon who performed all of the surgery. Dr. Cheng collected the data and analyzed the data. Dr. Gao helped revised the manuscript. This study did not receive outside financial support.

REFERENCES

Ali IM, Sanalla AA, Clark V. 1997. Beta-blocker effects on postoperative atrial fibrillation. Eur J Cardiothorac Surg 11:1154-7.

Aranki SF, Shaw DP, Adams DH, et al. 1996. Predictors of atrial fibrillation after coronary artery surgery. Current trends and impact on hospital resources. Circulation 94:390-7.

Baker WL, White CM. 2007. Post-cardiothoracic surgery atrial fibrillation: a review of preventive strategies. Ann Pharmacother 41:587-98.

Bramer S, van Straten AH, Soliman Hamad MA, Berreklouw E, Martens EJ, Maessen JG. 2010. The impact of new-onset postoperative atrial fibrillation on mortality after coronary artery bypass grafting. Ann Thorac Surg 90:443-9.

Crystal E, Thorpe KE, Connolly SJ, et al. 2004. Metoprolol prophylaxis against postoperative atrial fibrillation increases length of hospital stay in patients not on pre-operative beta blockers: the beta blocker length of stay (BLOS) trial. Heart 90:941-2.

Coleman CI, Perkerson KA, Gillespie EL, et al. 2004. Impact of prophylactic postoperative beta-blockade on post-cardiothoracic surgery length of stay and atrial fibrillation. Ann Pharmacother 38:2012-6.

Connolly SJ, Cybulsky I, Lamy A, et al. 2003. Double-blind, placebo-controlled, randomized trial of prophylactic metoprolol for reduction of hospital length of stay after heart surgery: the beta-Blocker Length Of Stay (BLOS) study. Am Heart J 145:226-32.

Dhein S, Rothe S, Busch A, et al. 2011. Effects of metoprolol therapy on cardiac gap junction remodelling and conduction in human chronic atrial fibrillation. Br J Pharmacol 164:607-16.

Fuller JA, Adams GG, Buxton B. 1989. Atrial fibrillation after coronary artery bypass grafting. Is it a disorder of the elderly? J Thorac Cardiovasc Surg 97:821-5.

Haghjoo M, Saravi M, Hashemi MJ, et al. 2007. Optimal beta-blocker for prevention of atrial fibrillation after on-pump coronary artery bypass graft surgery: carvedilol versus metoprolol. Heart Rhythm 4:1170-4.

Halonen J, Hakala T, Auvinen T, et al. 2006. Intravenous administration of metoprolol is more effective than oral administration in the prevention of atrial fibrillation after cardiac surgery. Circulation 114(1 Suppl):I1-4.

Imren Y, Benson AA, Zor H, et al. 2007. Preoperative beta-blocker use reduces atrial fibrillation in off-pump coronary bypass surgery. ANZ J Surg 77:429-32.

Jidéus L, Blomstrom P, Nilsson L, Stridsberg M, Hansell P, Blomström-Lundqvist C. 2000. Tachyarrhythmias and triggering factors for atrial fibrillation after coronary artery bypass operations. Ann Thorac Surg 69:1064-9.

Likosky DS, Caplan LR, Weintraub RM, et al. 2004. Intraoperative and postoperative variables associated with strokes following cardiac surgery. Heart Surg Forum 7:E271-6.

Lúcio Ede A, Flores A, Blacher C, Leães PE, Lucchese FA, Ribeiro JP. 2004. Effectiveness of metoprolol in preventing atrial fibrillation and flutter in the postoperative period of coronary artery bypass graft surgery. Arq Bras Cardiol 82:42-46, 37-41 [In Portuguese].

Maisel WH, Rawn JD, Stevenson WG. 2001. Atrial fibrillation after cardiac surgery. Ann Intern Med 135:1061-73.

Mariscalco G, Klersy C, Zanobini M, et al. 2008 Atrial fibrillation after isolated coronary surgery affects late survival. Circulation 118:1612-8.

Martinez EA, Bass EB, Zimetbaum P; American College of Chest Physicians. 2005. Pharmacologic control of rhythm: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. Chest 128(2 Suppl):48S-55S.

Salameh A, Blanke K, Dhein S, Janousek J. 2010. Cardiac gap junction channels are upregulated by metoprolol: an unexpected effect of beta-blockers. Pharmacology 85:203-10.

Svedjeholm R, Hakanson E. 2000. Predictors of atrial fibrillation in patients undergoing surgery for ischemic heart disease. Scand Cardiovasc J 34:516-21.