Original Article

The impact of beta-blocker use on postoperative atrial fibrillation after aortic valve replacement

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Background: Current guidelines recommend perioperative use of beta-blocker (BB) in patients undergoing cardiac surgery to prevent postoperative atrial fibrillation (POAF). However, this recommendation is mainly based on studies those exclusively enrolled patients undergoing coronary artery bypass grafting. This study was conducted to evaluate the impact of perioperative BB use on the occurrence of POAF after aortic valve replacement (AVR).

Methods: From January 2015 to June 2018, 296 patients (male: female = 163:133) who underwent AVR at our institution were retrospectively reviewed. Patients who underwent concomitant valve surgery other than AVR or patients with preoperative arrhythmia were excluded. Mean age at the operation was 67±12 years. All patients were continuously tele-monitored for the occurrence of AF until discharge. Occurrence of any short runs of AF during the hospital stay was treated as POAF. Early outcomes were evaluated and perioperative factors associated with POAF were analyzed using a multivariable logistic regression model.

Results: Early mortality rate was 3.7% (11 of 296 patients). The POAF occurred in 154 patients (52.0%). Univariate analyses demonstrated that postoperative use of BB as well as age, type of prosthesis, history of stroke, body surface area, and chronic kidney disease were associated with the occurrence of POAF. The multivariable model showed that postoperative use of BB within 24 hours after AVR was a preventive factor of POAF (odds ratio, 0.354; 95% CI, 0.163 to 0.770; P=0.009).

Conclusions: Postoperative use of BB within 24 hours after AVR rather than preoperative use might be effective in prevention of POAF.

Keywords: Aortic valve replacement (AVR); beta-blocker (BB); atrial fibrillation (AF)

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Introduction

Postoperative atrial fibrillation (POAF) is the most common complication after cardiac surgery with the reported incidence from 20% to 50%, depending on the type of surgery, definition and the diagnostic tools (1-4). The POAF is associated with increased risks of morbidity and mortality from hemodynamic instability, heart failure, thromboembolism and bleeding from anticoagulation (1-4). The pathophysiologic mechanisms of POAF have been considered to be multi-factorial. These included postoperative inflammatory reaction, surge of catecholamines, imbalance of autonomic nervous system, changes in intravascular volume status and substrates

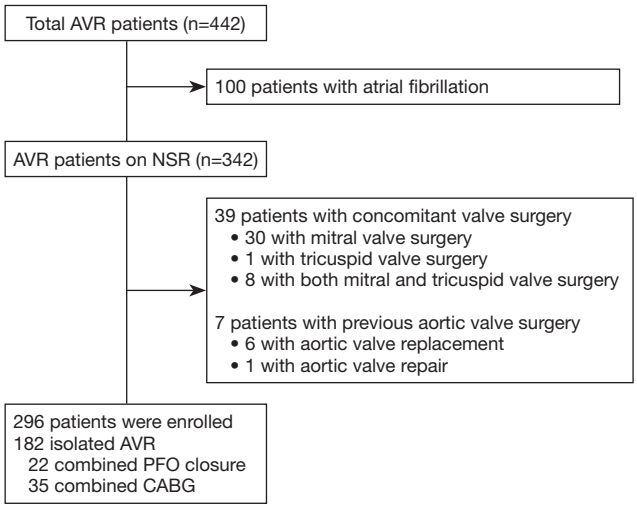

Figure 1 A flowchart of the patients enrolled in the study. AVR, aortic valve replacement; ECG, electrocardiogram.

created by surgical procedure itself such as alterations in cardiac structures and perioperative ischemia (5-10).

Previous studies have evaluated the effect of different pharmacologic and non-pharmacologic interventions to prevent POAF after cardiac surgery. Among them, perioperative use of anti-arrhythmic drugs or a beta-blocker (BB) have been reported to be helpful (1-4,7). Current European guidelines on the prevention of POAF after cardiac surgery recommended perioperative use of BB as a class I recommendation with a level of evidence B (4). However, this recommendation is mainly based on studies those exclusively enrolled patients undergoing coronary artery bypass grafting (CABG) (11,12). Therefore, current American guidelines recommend perioperative administration of BB to prevent POAF for CABG patients but not for overall cardiac surgical patients (2,13).

This study was conducted to evaluate the impact of perioperative BB use on the occurrence of POAF after aortic valve replacement (AVR).

Methods

Patient characteristics

The study protocol was reviewed by the Institutional Review Board and approved as a minimal risk retrospective study (approval number: H-1812-149-997) that did not require individual consent based on the institutional guidelines for waiving consent. Four hundred forty two patients who underwent AVR between January 2015 and June 2018 at our institution were retrospectively screened. Patients who underwent concomitant valve surgery other than AVR, who had preoperative arrhythmia and those with history of previous aortic valve surgery were excluded and 296 patients were enrolled in the present study (*Figure 1*). Mean age at the operation was 67.2±11.7 years, and 163 patients (55.1%) were male. The EuroSCORE II and STS scores were 2.97±3.10 and 2.88±3.28, respectively. Etiology of AV disease was degenerative, bicuspid, rheumatic and others in 129 (43.6%), 135 (45.6%), 11 (3.7%) and 21 (7.1%) patients, respectively (*Table 1*).

Surgical procedures

All operations were performed through median sternotomy and aorto-bicaval cannulation. Mechanical valves and bioprostheses were used in 71 (24.0%) and 225 (76.0%) patients, respectively. Concomitant procedures included CABG (n=35), replacement of the ascending aorta (n=71), replacement of total arch (n=2), closure of patent foramen ovale (n=22) and closure of ventricular septal defect (n=1). Mean cardiopulmonary bypass and aortic cross-clamp times were 179±110 and 111±41 minutes, respectively (*Table 2*).

Perioperative medications

BBs were used in preoperative, postoperative (<24 hours after surgery) and both pre- and postoperative periods in 90, 37 and 14 patients, respectively. Non-dihydropyridine calcium channel blockers and statins were administered at preoperative period in 16 (5.4%) and 145 (49.0%) patients, respectively (*Table 3*).

Evaluation of the clinical outcomes

Early mortality was defined as any death within 30 days or during the same hospitalization. All patients were continuously monitored to detect the occurrence of any arrhythmia using five-lead cardiac telemetry until the day of discharge. The occurrence of any short runs of AF was considered as POAF.

Statistical analysis

The statistical analyses were performed using the IBM SPSS (Version 23.0, IBM Corporation, Armonk, NY, USA) and the SAS software package (Version 9.4, SAS Institute,

Table 1 Study characteristics

Variables	Total (n=296)
Age, years	67.2±11.7
Male/female	163/133
Body surface area, m^2	1.64±0.18
Overweight (BMI >25 kg/m^2)	97 (32.8)
Risk factors	
Smoking	64 (21.6)
Hypertension	154 (52.0)
Diabetes mellitus	72 (24.3)
Dyslipidemia	87 (29.4)
History of stroke	31 (10.5)
Chronic kidney disease (GFR <60 mL/min)	69 (23.3)
ESRD on dialysis	13 (4.4)
COPD	12 (4.1)
Peripheral vascular disease	18 (6.1)
NYHA class ≥3	52 (17.6)
LV dysfunction (ejection fraction <0.50)	36 (12.2)
Coronary artery disease	84 (28.4)
EuroSCORE II	2.97±3.10
STS score	2.88±3.28
Etiology of aortic valve disease	
Rheumatic	11 (3.7)
Degenerative	129 (43.6)
Bicuspid	135 (45.6)
Others	21 (7.1)

Values are n (%) or mean ± SD. BMI, body mass index; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; GFR, glomerular filtration rate; LV, left ventricle; NYHA, New York Heart Association; STS, The Society of Thoracic Surgeons.

Cary, NC, USA). Continuous and dichotomous variables were expressed as mean ± standard deviation and number with proportion, respectively. Factors associated with the occurrence of POAF were analyzed; Variables with a P value <0.050 in univariate logistic regression analyses were entered into a multivariable logistic regression model. Multi-collinearity was controlled using the backwards stepwise selection. Results of the multivariable analysis were expressed as P value, odd ratio (OR) and its 95% confidence interval (CI). A P value <0.050 was considered to be statistically significant.

To confirm the impact of BB use on POAF, a propensity score matching (PSM) was also performed by including all preoperative variables. With the use of the caliper-matching method, pairs of patients were matched using a nearest neighborhood (greedy matching) within a caliper width of 0.1 in propensity scores, with a ratio of 1:1. Comparison between the two groups was performed using the χ^2 test or Fisher exact test for categorical variables and Student *t*-test for continuous variables. For the comparison of categorical and continuous variables between the matched group patients, the McNemar test and paired Student *t*-test were used. The balance of covariates between the two groups was evaluated with standardized mean differences (SMD).

Results

Early clinical outcomes

The early mortality rate was 3.7% (11 of 296 patients). The causes of death were low cardiac output syndrome (LCOS) (n=4), sepsis (n=3), acute bowel ischemia (n=3) and mediastinitis (n=1). The postoperative complications included LCOS (n=15, 5.1%), respiratory complications (n=22, 7.4%), bleeding reoperation (n=10, 3.4%), acute renal failure (n=21, 7.1%) and stroke (n=5, 1.7%). Six patients suffered from complete atrioventricular block after surgery and two of six patients needed permanent pacemaker implantation (*Table 4*).

POAF events and risk factor analysis

The POAF occurred in 154 patients (52.0%) at mean 2.8±1.8 days (range, 0 to 13) after surgery. Univariate analyses demonstrated that postoperative BB use (<24 hours) regardless of preoperative use (n=37) was significantly associated with a reduction of the occurrence of POAF (OR, 0.343; 95% CI, 0.163 to 0.724; P=0.005), whereas class of BB (OR, 0.997; 95% CI, 0.530 to 1.872; P=0.991) or preoperative BB use showed no significant association with POAF (OR, 0.949; 95% CI, 0.578 to 1.557; P=0.835). Other factors associated with the occurrence of POAF included age, history of stroke, type of aortic prosthesis, chronic kidney disease and body surface area. The multivariable logistic regression model showed that postoperative BB use within 24 hours after surgery was a

Table 2 Operative data of the study patients

Variables	Total (n=296)
CPB time, minutes	179±110
ACC time, minutes	111±41
Type of AVR	
Mechanical valve	71 (24.0)
Bioprosthesis	225 (76.0)
Concomitant procedures	
Replacement of the aorta	73 (24.7)
Ascending aorta	71 (24.0)
Total arch	2 (0.7)
CABG	35 (11.8)
PFO closure	22 (7.4)
VSD closure	1 (0.3)

Values are n (%) or mean ± SD. ACC, aortic cross clamp; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; PFO, patent foramen ovale; VSD, ventricular septal defect.

preventive factor of POAF (OR, 0.354; 95% CI, 0.163 to 0.770; P=0.009). Age was also significantly associated with the occurrence of POAF (OR, 1.056; 95% CI, 1.032 to 1.081; P<0.001) (*Table 5*).

When the patients were grouped according to the postoperative BB use, BB use group had more patients with high body surface area and overweight than did non-BB use group. The preoperative New York Heart Association functional class was worse in non-BB use group than in BB use group. After PSM, no preoperative factor was significantly different between the two groups, but the occurrence rate of POAF was still lower in the BB use group compared to non-BB use group (29.7% *vs.* 4.1%, P=0.039, *Table 6*).

Discussion

This study demonstrated that postoperative use of BB within 24 hours after AVR rather than preoperative use are effective in prevention of POAF.

Table 3 Perioperative medications

Variables	Total (n=296), n (%)	Dosage (mg), median (range)
Types of BB use	180 (60.8)	
Nonselective agents		
Carvedilol	54 (30.0)	12.5 (3.0–25.0)
Propranolol	3 (1.7)	20.0 (20.0–40.0)
β_1-selective agents		
Bisoprolol	100 (55.6)	2.5 (1.25–5.0)
Nebivolol	17 (9.4)	2.5 (1.25–5.0)
Atenolol	5 (2.8)	50 (25.0–50.0)
Betaxolol	1 (0.6)	10
Timing of BB use		
Preoperative BB use	90 (30.4)	
Postoperative BB use (<24 hours after AVR)	37 (12.5)	
Both preoperative and postoperative BB use	14 (4.7)	
Other preoperative medications		
Non-dihydropyridine CCBs	16 (5.4)	
Statins	145 (49.0)	

Values are n (%). AVR, aortic valve replacement; BB, beta-blocker; CCB, calcium channel blocker.

The POAF is one of the most common complications after cardiac surgery with an incidence ranging from 20% to 50%. It usually develops between 2 to 4 postoperative days with a peak incidence on the second postoperative day (1-4,14,15). Despite the transient and self-limiting nature of most episodes of POAF, it is an independent predictor of worse outcomes after cardiac surgery, including a 2- to 4-fold increase in stroke and a 2-fold increase in 30-day and 6-month mortalities (1,3,15-17).

Table 4 Early clinical outcomes

Variables	Total (n=296)
Early mortality	11 (3.7)
New onset atrial fibrillation	154 (52.0)
Other postoperative complications	
Low cardiac output syndrome	15 (5.1)
Respiratory complication	22 (7.4)
Bleeding reoperation	10 (3.4)
Acute renal failure	21 (7.1)
Complete atrioventricular block	6 (2.0)
Stroke	5 (1.7)
Mediastinitis	4 (1.4)

Current European guidelines recommend the perioperative use of oral BB for the prevention of POAF after cardiac surgery as a class I recommendation with a level of evidence B (4). However, this recommendation was based on meta-analyses in which, most of the included studies were exclusively enrolling patients who underwent isolated CABG rather than overall cardiac surgery (11,12). On the contrary, current American guidelines recommend that BB should be administered for at least 24 hours before surgery and reinstituted as soon as possible after surgery in patients who underwent CABG (13). However, this recommendation was not generalized to the other cardiac surgical patients (2).

The present study was object to complete the lack of evidence for the routine application of perioperative BB to prevent POAF after cardiac surgery other than CABG. As the first step, patients who underwent AVR without any concomitant other valve surgery were analyzed in the present study. A recent study on patients who underwent AVR reported that preoperative BB use was an independent predictor of POAF after AVR (OR, 0.310; 95% CI, 0.119 to 0.809; P<0.05), and a combination of pre- and postoperative BB administration was even more effective. However, the study is limited due to the small number of study population (n=119) (18).

The incidence of POAF in the present study might be

Table 5 Risk factor analysis for the occurrence of POAF

Variables	Univariate analysis		Multivariable analysis	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Age (years)	1.058 (1.034–1.083)	<0.001	1.056 (1.032–1.081)	<0.001
History of stroke	2.463 (1.093–5.548)	0.030	2.144 (0.912–5.042)	0.080
Type of prosthesis (bioprosthesis)	2.908 (1.656–5.107)	<0.001	–	–
Chronic kidney disease (GFR <60 mL/min)	1.728 (0.995–3.002)	0.052	–	–
Body surface area (m^2)	0.264 (0.074–0.948)	0.041	–	–
Preoperative BB use	0.949 (0.578–1.557)	0.835	–	–
Postoperative BB use*	0.343 (0.163–0.724)	0.005	0.354 (0.163–0.770)	0.009
Both preoperative and postoperative use*	0.352 (0.108–1.149)	0.084	–	–
Other preoperative medications				
Non-dihydropyridine CCBs	0.535 (0.189–1.512)	0.238	–	–
Statins	1.428 (0.903–2.258)	0.127	–	–

*, use of BB <24 hours after surgery. AVR, aortic valve replacement; BB, beta-blocker; CCB, calcium channel blocker; CI, confidence interval; GFR, glomerular filtration rate.

Table 6 Baseline characteristics and the occurrence rate of POAF for postoperative beta-blocker (BB) use group and non-BB use group

Variables	All study patients			Propensity score-matched patients			
	BB-use (n=37)	Non-BB use (n=259)	P	BB-use (n=37)	Non-BB use (n=37)	SMD	P
Age (years)	65.4±12.2	67.5±11.6	0.307	65.4±12.2	65.2±11.5	0.016	0.939
Sex (male)	21 (56.8)	142 (54.8)	0.825	21 (56.8)	19 (51.4)	0.109	0.617
Body surface area (m^2)	1.70±0.16	1.63±0.18	0.020	1.70±0.16	1.66±0.23	0.222	0.255
Overweight (BMI >25 kg/m^2)	20 (54.1)	77 (29.7)	0.003	20 (54.1)	18 (48.6)	0.108	0.564
Risk factors, n (%)							
Smoking	9 (24.3)	55 (21.2)	0.669	9 (24.3)	7 (18.9)	0.132	0.527
Hypertension	22 (59.5)	132 (51.0)	0.333	22 (59.5)	23 (62.2)	–0.055	0.796
Diabetes mellitus	8 (21.6)	64 (24.7)	0.682	8 (21.6)	10 (27.0)	–0.126	0.617
Dyslipidemia	7 (18.9)	80 (30.9)	0.135	7 (18.9)	8 (21.6)	–0.067	0.739
History of stroke	3 (8.1)	28 (10.8)	0.779	3 (8.1)	3 (8.1)	0.000	>0.999
Chronic kidney disease (GFR <60 mL/min)	9 (24.3)	60 (23.2)	0.876	9 (24.3)	9 (24.3)	0.000	>0.999
ESRD on dialysis	0 (0.0)	13 (5.0)	0.163	0 (0.0)	0 (0.0)	0.000	>0.999
COPD	1 (2.7)	11 (4.2)	>0.999	1 (2.7)	2 (5.4)	–0.137	0.564
Peripheral vascular disease	3 (8.1)	15 (5.8)	0.480	3 (8.1)	6 (16.2)	–0.250	0.257
NYHA class ≥3	2 (5.4)	50 (19.3)	0.038	2 (5.4)	2 (5.4)	0.000	>0.999
LV dysfunction (EF <0.50)	3 (8.1)	33 (12.8)	0.593	3 (8.1)	4 (10.8)	–0.092	0.705
Coronary artery disease	11 (29.7)	73 (28.2)	0.845	11 (29.7)	11 (29.7)	0.000	>0.999
EuroSCORE II	2.60±3.06	3.02±3.11	0.449	2.60±3.06	2.36±2.32	0.088	0.694
STS score	2.23±2.71	2.98±3.36	0.250	2.23±2.71	2.09±1.85	0.060	0.697
Preoperative medications							
BBs	14 (37.8)	76 (29.3)	0.293	14 (37.8)	12 (32.4)	0.113	0.637
Calcium channel blockers	2 (5.4)	14 (5.4)	>0.999	2 (5.4)	3 (8.1)	–0.108	0.655
Statins	19 (51.4)	126 (48.6)	0.758	19 (51.4)	17 (45.9)	0.108	0.593
Etiology of aortic valve disease							
Rheumatic	1 (2.7)	10 (3.9)	>0.999	1 (2.7)	2 (5.4)	–0.137	0.564
Degenerative	16 (43.2)	113 (43.6)	0.965	16 (43.2)	16 (43.2)	0.000	>0.999
Bicuspid	16 (43.2)	119 (45.9)	0.758	16 (43.2)	13 (35.1)	0.167	0.467
Others	4 (10.8)	17 (6.6)	0.313	4 (10.8)	6 (16.2)	–0.159	0.527
POAF	11 (29.7)	143 (55.2)	0.004	11 (29.7)	20 (54.1)	–	0.039

Values are n (%) or mean ± SD. BMI, body mass index; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; GFR, glomerular filtration rate; LV, left ventricle; NYHA, New York Heart Association; SMD, standardized mean difference; STS, The Society of Thoracic Surgeons.

relatively high compared to literature. Meticulous 24-hour monitoring of all patients until discharge might be the reason for this high incidence. Contrary to the relatively high rate of POAF, the early mortality rate of the present study was comparable to those reported by the STS National Cardiac Surgery Database (3.7% *vs.* 4.5%) (19). The present study showed that the postoperative BB use resulted in a 64% reduction of the occurrence of POAF, and the preventive effect was remained statistically significant in PSM analysis. This effect was in agreement with previous meta-analyses showing 56% to 61% risk reduction of POAF (20,21). The most effective timing of BB administration to prevent POAF after cardiac surgery is uncertain. A recent meta-analysis showed that perioperative BB had consistent protective effect in postoperative supraventricular arrhythmias, irrespective of the timing of administration (21), whereas another meta-analysis showed that postoperative initiation of BB prophylaxis resulted in a statistically significant reduction of POAF incidence by 50% (12). The present study also showed that the perioperative BB use might be most effective when it was administered within 24 hours after surgery, regardless of its use in the preoperative period; when multi-collinearity was controlled by stepwise regression model, only postoperative use of BB within 24 hours after AVR showed statistically significant reduction of the POAF occurrence.

Only preoperative use of BB was not effective at all in reducing POAF after AVR. This could be explained by adverse effects associated with a rebound phenomenon caused by discontinuation of BB after surgery in patients who took them before surgery (22,23). This result is in accordance with current recommendations which suggest that patients who are already taking BB should continue to take them up to the morning of surgery and restart on the first postoperative day after surgery (24).

The present study has limitations that must be recognized. First, this study was a retrospective study although all consecutive patients who underwent AVR during the study period were enrolled. Second, protocols regarding the use of BB such as the types of drugs, dosage and timing of administration had diverse heterogeneity. Further randomized controlled trials based on the uniform protocol of BB administration might be needed to draw a definitive conclusion.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd.2020.03.30). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Institutional Review Board of the Seoul National University Hospital (H-1812-149-997). This study is based on data retrieved from a hospital medical record system. All personal data have been protected and secured according to current national and international laws.

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