Redefining the Blanking Period After Surgical Ablation For Atrial Fibrillation

Jin Hee Choi[1], Ki Won Hwang[1], Soon Myung Jung[1], Soo Yong Lee[1], Sang Hyun Lee[1], Min-Gu Chon[1], Jeong-Su Kim[1], Hyung Gon Je[1], Yong-Hyun Park[1], June Hong Kim[1], Sang Kwon Lee[1], and Kook Jin Chun[1]

[1]Pusan National University Yangsan Hospital

May 7, 2020

Abstract

Background Atrial tachyarrhythmias (ATAs) are common within the three-month blanking period following catheter ablation of atrial fibrillation (AF). However, little evidence is available regarding the current guidelines on the blanking period after surgical AF ablation. We investigate the incidence and significance of early recurrence of atrial tachyarrhythmia (ERAT) and evaluate the optimal blanking period after surgical AF ablation. Methods Data from 259 patients who underwent surgical AF ablation from 2009 to 2016 were collected. ERAT was defined as documented ATA episodes lasting for 30 seconds. A multivariate Cox proportional hazard model was constructed to evaluate the role of ERAT as a predictor of late recurrences (LR) for AF. Results In total, 127 patients (49.0%) experienced their last episodes of ERAT during the first (n=65), second (n=14), or third (n=48) month of the three-month blanking period ($p<0.001$). One-year freedom from ATAs was 97.8% in patients without ERAT compared with 95.4%, 64.3%, and 8.3% in patients with ERAT in the first, second, and third month after the index procedure, respectively ($p<0.001$). Hazard ratios of LR according to the timing of the last episode of ERAT first, second, and third month after the procedure were 2.84, 16.70, and 119.75, respectively. Conclusions The ERAT occurred in 49.0% of patients within the first three months after surgical ablation. The occurrence of ERAT within three months after surgical AF ablation was a significant independent predictor of LR. Hence, the currently accepted three-month blanking period needs to be redefined in patients with AF surgical ablation.

Introduction

Atrial fibrillation (AF) is a common preoperative arrhythmia in patients undergoing cardiac surgery. Concomitant surgical AF ablation with cardiac surgery is reasonable in selected patients with AF undergoing other cardiac surgical procedures due to valvular or coronary artery diseases.[1] Surgical AF ablation has been recognized to reduce AF-related symptoms, improve hemodynamic parameters, and reduce thromboembolic risk by restoring and maintaining sinus rhythm (SR).[2-4] Nevertheless, approximately 40% of all patients undergoing surgical AF ablation have postoperative AF.[5,6] Catheter ablation is a highly successful procedure in eliminating atrial tachyarrhythmias (ATAs) and maintaining SR after surgical AF ablation. A blanking period of three months has been universally accepted after catheter AF ablation, and AF recurrence during the blanking period is not considered a treatment failure nor is it associated with long-term AF recurrence.[7]

However, little is known about early recurrence of atrial tachyarrhythmia (ERAT), which is defined as recurrence within the first three months after surgical AF ablation. There is currently a lack of studies evaluating the optimal blanking period after surgical ablation. Therefore, we aimed to investigate the incidence and significance of ERAT after surgical AF ablation as a predictor of late recurrence (LR) and to evaluate the optimal blanking period after surgical AF ablation using receiver operating curve (ROC) analysis.

Methods

Study population

We retrospectively analyzed 259 consecutive patients who underwent open-heart surgery with concomitant surgical AF ablation in a tertiary academic referral center between October 2008 and March 2016. All patients undergoing open-heart surgery were prospectively registered in our institutional database, which contains demographics, preoperative risk factors, echocardiographic characteristics, operative details, and postoperative complications according to the established Society of Thoracic Surgeons National Adult Cardiac Surgery Database (STS ACSD) definition.[8] Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m^2 using the Modification of Diet in Renal Disease equation. We calculated the EuroSCORE II using an online calculator.[9]

All patients had follow-up information available for at least 12 months after surgical AF ablation. Twelve-lead electrocardiogram (ECG) and ambulatory Holter monitoring were retrospectively and manually analyzed by two electrophysiologists (K.W.H., J.H.C). Ethical approval was obtained from the Institutional Review Board for conducting this study.

Surgical ablation procedure

The lesion sets for AF ablation consisted of left and right atrial ablation lesions. The left atrial lesion set was started with a conventional left atrial incision through the interatrial groove and extended to the inferior-posterior wall of the left atrium (LA). If the LA anteroposterior diameter was >50 mm, resection of the posterior wall of the LA was performed via LA reduction plasty. A box lesion was then made using an argon-based flexible cryoablation system, Cardioblate CryoFlex (Medtronic, Minneapolis, MN). A mitral isthmus endocardial lesion was made between the pulmonary box lesion and the mitral annulus. Additional coronary sinuses were ablated using the epicardial approach. Right-sided endocardial ablation was initiated through an oblique right atrial incision. Cavotricuspid isthmus ablation, right atrial anterior free wall ablation, and intercaval ablation were achieved using the cryoablation probe.

Concomitant bi-atrial ablation was performed in 184 patients (71 %), and others received left –sided ablation. The most common concomitant surgery was mitral valve surgery ± tricuspid annuloplasty (64.5%), followed by aortic valve surgery ± tricuspid annuloplasty (9.3%), mitral valve surgery + aortic valve surgery ± tricuspid annuloplasty (12.7%), and coronary artery bypass grafting surgery (1.2%); only 13 cases (5.0%) of isolated surgical ablation were conducted.

Post-procedure follow-up

During the first three months after surgical ablation (blanking period), administration of anti-arrhythmic drugs was allowed based on the discretion of the treating physician. The drugs were discontinued at the three-month follow-up if no documented recurrence of ATAs was observed. Patients were followed up in the outpatient clinics every month for the first three months, and every three months thereafter. Twelve-lead ECG and physical examination were performed on each visit. All patients underwent ambulatory 24-hour Holter monitoring one, three, six, and 12 months after discharge. If patients complained of symptoms suggestive of AF, they received additional 24-hour Holter monitoring. ERAT was defined as any recurrence of ATAs within the first three months after surgical ablation. Late recurrence (LR) was defined as an ATA that lasted for at least 30 seconds (s) and occurred up to 12 months after the blanking period. The timing of the last ERAT within the first three months blanking period was recorded as a continuous variable and categorized according to whether it occurred in the first, second, or third month.

Statistical analysis

All continuous variables were expressed as means ± standard deviations and compared using independent-sample Student t-tests or Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and compared using Pearson's chi-square test or Fisher's exact tests. Univariate and multivariate logistic regression models with backward elimination processes were performed to identify independent risk factors associated with the occurrence of ERAT after surgical AF ablation. The p - value for variables to enter and stay in the prediction models was set at 0.05.

Time to first LR was computed and plotted using the Kaplan-Meier method and compared using log-rank test. Cox proportional hazards regression analyses were used to estimate hazard ratio (HRs) with 95% confidence intervals (CIs). Variables reported in Tables 1 and 2 with a p - value of [?] 0.05 in the univariate analyses were candidates for the multivariable Cox proportional hazards models. The final models were determined using backward elimination processes. To redefine an ideal cut-off value for the blanking periods, a receiver operating characteristic (ROC) analysis was performed, the area under the curve (AUC) was calculated, and the possible cut-off points were selected. All statistical analyses were performed using R software version 3.5.3 (https://cran.r-project.org/).

Results

Of the 259 patients (mean age, 60.6 +- 11.4 years; 50.6% male), 127 (49%) had ERAT during the 3-month blanking periods. Among the patients with ERAT, the timing of the ERAT was during the first month post ablation in 65 patients (51.2%), during the second month in 14 (11.0%), and during the third month in 48 (37.8%). Baseline demographic and clinical characteristics of the study population are detailed in Table 1. Patients with ERAT were older (mean, 63.1 +- 9.5 and 58.2 +- 12.5 years, respectively; p <0.001) and had larger left atrial size (mean, 56.1 +- 12.1 and 52.3 +- 8.9 mm, respectively; $p = 0.004$) than those without ERAT. In addition, a significantly greater proportion of patients with ERAT had a history of persistent AF (92.1% and 74.2%, respectively; p<0.001).

The following operative and postoperative risk factors were more commonly recorded in patients with ERAT than in those without ERAT (Table 2): longer cardiopulmonary bypass (CPB) time (181.3 +- 63.3 and 154.8 +- 59.2 minutes, respectively; p =0.001) and aortic cross-clamp (ACC) time (128.1 +- 53.6 and 108.2 +- 45.3 minutes, respectively; p =0.001) and more postoperative pulmonary complications and reoperations for bleeding (11.0% and 3.0%; p= 0.022). Patients with ERAT received bi-atrial surgical AF ablation more frequently (80.3% and 62.1%, $P = 0.002$) and used more amiodarone during blanking periods (82.7% and 21.2%, P<0.001).

The factors independently associated with ERAT after multivariate logistic analyses are shown in Table 3. Older age (per year: odds ratio [OR], 1.03; 95% CI, 1.00-1.06; p =0.012), history of coronary artery disease (CAD) (OR, 6.98; 95% CI, 1.38-35.36; p =0.019), history of persistent AF (OR, 3.18; 95% CI 1.36-7.43; p =0.008), larger left atrial size (OR, 1.03; 95% CI, 1.00-1.06; p =0.022), longer CPB time (OR, 1.00; 95% CI, 1.00-1.01; p =0.033), and reoperation for bleeding after cardiac surgery (OR, 3.00; 95% CI, 1.41-6.37; p =0.004) were associated with the occurrence of ERAT during the three-month blanking periods.

At the 12-month follow-up, 74 of 127 patients (58.3%) with ERAT were free from late AF recurrence compared with 129 of 132 patients (97.8%) without ERAT (p <0.001; Figure 1A). AF-free survival rate was 95.4%, 64.3%, and 8.3% among those who had ERAT in the first, second, and third months, respectively (p <0.001; Figure 1B). To evaluate the role of ERAT as a predictor contributing to LR, the univariate Cox regression model was performed according to the occurrence and timing of ERAT (classified by month) after surgical ablation. After adjustment for the occurrence of ERAT, age (per year: HR, 1.04; 95% CI, 1.00-1.07; p =0.025), male gender (HR 1.77; 95% CI, 1.02-3.09; p =0.043), larger LA size (HR, 1.04; 95% CI, 1.02-1.06; p <0.001), and the occurrence of ERAT (HR, 17.73; 95% CI 5.48-57.34; p <0.001) were shown to be independent risk factors for LR. In addition, adjusted analyses were conducted using the timing of ERAT within the blanking periods. The occurrences of ERAT during the second (HR, 16.70; 95% CI, 3.98-70.22;p =0.001) and third months (HR, 119.75; 95% CI, 36.25-395.59;p <0.001) were the most powerful independent predictors of LR (Table 4).

The ROC curve that determined the cut-off value of the blanking period is shown in Figure 2. The AUC was 0.938 (95% CI: 0.893 to 0.983,$p < 0.001$), showing excellent discrimination. The ideal cut-off value for the blanking period was 58 days. The occurrence of ERAT beyond 58 days predicted LR with a sensitivity of 93.2% and specificity of 86.8%

Discussion

The important findings from this study are as follows: (1) ERAT occurs in 49% of patients with AF after surgical ablation; (2) the predictors of ERAT include older age, history of CAD, persistent AF, larger LA size, longer CPB time, and reoperation for bleeding after cardiac surgery; (3) ERAT patients within the first three months after surgical AF ablation were more likely to have an increased incidence of LR than patients without ERAT; and (4) patients who developed ERAT within the first month had significantly better outcomes than those in whom ERAT occurred later.

Prevalence of ERAT after surgical AF ablation

There are limited data available on the occurrence of ERAT after surgical AF ablation. Our study is the first to validate the blanking period after surgical AF ablation. Few studies reported the prevalence of ERAT after surgical AF ablation. [6,10-13] Benussi et al.[13] studied the prevalence of ERAT in 132 patients undergoing surgical AF ablation. ERAT occurred in 49.2% of patients, and the one-year freedom for AF recurrence was significantly lower in patients with in-hospital postoperative arrhythmias. However, previous studies were insufficient to estimate the prevalence of ERAT after surgical AF ablation because the total number of patients was relatively small and data collection was limited to within the postoperative stay. For these reasons, unlike catheter ablation, ERAT within a 3-month blanking period after surgical AF ablation has not been established. Postoperative AF is the most common atrial arrhythmia after cardiac surgery and is usually a transient condition that resolves spontaneously.[14] Cardiac surgery itself provides extensive arrhythmogenic substrates with pre-existing cardiac fibrosis for triggering and perpetuating AF during the perioperative period.[15-17] At the same time, concomitant surgical AF ablation with cardiac surgery also causes the modification of arrhythmogenic substrates, such as triggered activity of the pulmonary veins or re-entry-promoting structural and electrical remodeling. The positive and negative effects of ERAT occurred in the immediate post-operative phase. Unlike several studies on the blanking period of catheter AF ablation,[18-20], our study included mostly patients undergoing cardiac surgery, such as valve repair or replacement and coronary artery bypass grafting. Therefore, there may be a drawback in simply accepting the blanking periods after surgical AF ablation based on the blanking periods after catheter ablation. Nevertheless, approximately half of the patients (49%) experienced ERAT within the first three months following surgical AF ablation, which is consistent with prevalence rates between 15.9% and 65% of patients with catheter AF ablation in previous studies.[16-18] Previous studies showed that ERAT occurred in the majority of patients within the first month after catheter AF ablation, and it gradually decreased; almost all ERAT occurred within the first two months. [18,20] Our data founded that ERAT occurred in more than half of the total number of patients (65 patients) within the first month and slightly rebounded up to 37.8% in the third month after the index procedure.

Predictors of ERAT after Surgical AF ablation

In our study, the occurrence of ERAT was associated with older age, persistent AF, larger LA size, and history of CAD; these have been identified as predictors of ERAT after catheter AF ablation. Furthermore, longer CPB time and reoperation for bleeding probably reflect co-morbidities and the presence of concomitant valve diseases that further contribute to the development of ERAT. Paradoxically, ERAT is seen more often in patients who underwent bi-atrial surgical AF ablation. These observations suggest that bi-atrial surgical ablation might be preferentially selected in a fragile cohort of patients with late AF recurrence. More extensive bi-atrial ablation led to sinus node dysfunction due to surgical damage.[21] Transient pacemaker implantation or use of inotropic agents resulted in the development of AF in early postoperative periods.

Significance of the occurrence and timing of ERAT

It is difficult to discriminate early ablation failure from transient ERAT, which may be related to acute myocardial injury, subsequent inflammation response following radiofrequency ablation or cryoablation, and temporary abnormality in cardiac autonomic function.[7,19,22-24] ERAT should not be classified as an ablation failure if it occurred during the blanking periods. However, several studies have shown that the presence of ERAT was associated with LR of AF in patients undergoing catheter AF ablation.[18-20,25] The timing and frequency of ERAT within the blanking period are also important predictors of LR.

Several studies reported that early repeat ablation in patients who experience ERAT led to improved AF-free survival.[26,27]DAS[28] et al. found that reconnection of the pulmonary veins was significantly higher in patients who experience ERAT beyond the first four weeks following catheter ablation. ERAT occurring after the first four weeks of catheter ablation was associated with an increased risk of LR. A 3-month blanking period is too long to be attributed as transient atrial changes after catheter or surgical AF ablation. There were various attempts to determine the optimal timing of the blanking period because the occurrence of ERAT in patients within three months following catheter AF ablation is associated with LR.[20,29] Alipur[29] et al. examined 636 consecutive patients who received catheter AF ablation; ERAT occurred in 31.4 % of the patients during the three- month blanking period and, most commonly, within the first two months after catheter ablation. Patients with ERAT were significantly more associated with LR than those without ERAT (73.1% vs. 24%; p =0.0001). According to the timing of ERAT, the rate of LR was one-half of the patients who experienced ERAT within the first month, whereas it was 76% within the second month, and 92% within the third month (p =0.001). Same investigators identified a cut-off of 23 days as the optimal blanking period.

Conversely, a shorter blanking period can lead to unnecessary early repeat ablation. We found that two-third of patients with ERAT occurring within the second month remained free of LR. The cut-off value in the first month could be short enough to achieve atrial reverse remodeling in maintaining sinus rhythm. Delayed maturation of the ablative lesions occurred up to two months after catheter ablation[30]; markers of inflammation continuously increase at the first week post-ablation and tend to decrease at the first month post-ablation.[22,23] The transient autonomic dysfunction in heart rate variability persisted for at least three months after AF ablation.[31] Furthermore, patients who underwent cardiac surgery had more extensive atrial scarring/fibrosis and frequent development of non-PV triggers than those who underwent catheter AF ablation.[32]

Our study provides the optimal cut-off value of blanking periods using ROC curve analysis. A cut-off value of 58 days indicated the highest discriminatory potential for the timing of ERAT that predicted LR after three months post-ablation. According to our data, ERAT within the blanking period of 58 days was associated with LR of AF (unadjusted HR 15.06, 95% CI 6.02-37.69, p <0.001). However, the purpose of the blanking period may be to reduce unnecessary repeat ablation. One-half of the patients who experienced ERAT within 58 days had AF-free survival. There is a lack of randomized clinical trials to define the optimal blanking periods in patients undergoing surgical or catheter AF ablation.

This study has several limitations that need to be addressed. First, we did not use intensive monitoring systems such as implantable loop recorder or transtelephonic monitoring to rule out asymptomatic ATA recurrences during the third month post-maze procedure. Second, our data did not include histories of medications that might influence clinical outcomes. Finally, our study was a small, observational, and non-randomized single-center study. Thus, large-scale studies are needed in the future to fully evaluate the relationship between the blanking period and LR in post-maze procedure patients.

Conclusions

ERAT occurred in 49.0 % of patients within the first three months after surgical ablation. Patients with ERAT that occurred within three months after surgical AF ablation were significantly more likely to have an increased incidence of LR than patients without ERAT. Most importantly, the patients in whom ERAT occurred within the first month had significantly better outcomes than those in whom ERAT occurred later, and two-thirds of patients who had ERAT within the first two months remained free of LR. Therefore, the currently accepted three-month blanking period needs to be redefined in patients with surgical ablation for AF.

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Table 1. Demographic and pre-operative risk factors by occurrence of early recurrence of atrial tachyarrhythmia (ERAT)

	Overall (n=259)	ERAT (n=127)	No ERAT (n=132)	p-value
Age, years	60.6 ± 11.4	63.1 ± 9.5	58.2 ± 12.5	<0.001
Male gender	131 (50.6)	66 (52.0)	65 (49.2)	0.753
Body Mass Index (kg/m^2)	23.4 ± 3.4	23.7 ± 3.4	23.2 ± 3.4	0.240
Cardiac or coexisting conditions				
Hypertension	119 (45.9)	62 (48.8)	57 (43.2)	0.432
Diabetes mellitus	41 (15.8)	24 (18.9)	17 (12.9)	0.248
Chronic lung disease	55 (21.2)	30 (32.6)	25 (18.9)	0.442
Previous CAD	11 (4.2)	9 (7.1)	2 (1.5)	0.056
Congestive heart failure	61 (23.6)	29 (22.8)	32 (24.2)	0.904
Previous CVA	56 (21.6)	26 (20.5)	30 (22.7)	0.772
Current Smoker	36 (13.9)	18 (14.2)	18 (13.6)	1.000
Chronic kidney disease	67 (25.9)	38 (29.9)	29 (22.0)	0.187
Dyslipidemia	150 (58.0)	75 (59.1)	75 (56.8)	0.811
NYHA functional class [?] 3	71 (55.9)	71 (55.9)	60 (45.5)	0.119
CHA_2DS_2-VASc score	2.3 ± 1.6	2.4 ± 1.6	2.2 ± 1.7	0.317
Persistent AF	215 (83.0)	117 (92.1)	98 (74.2)	<0.001
Left atrial size, mm	54.2 ± 10.8	56.1 ± 12.1	52.3 ± 8.9	0.004
Left ventricular ejection fraction, %	58.9 ± 10.5	58.9 ± 10.2	58.8 ± 10.9	0.952
EuroSCORE II, %	5.7 ± 7.0	6.2 ± 6.5	5.2 ± 7.4	0.262

Values are mean ± SD or n (%) unless otherwise noted.

AF = atrial fibrillation; CAD = coronary artery disease; CVA = cerebrovascular accident; EuroSCORE = European system for cardiac operative risk evaluation; ERAT= early recurrence of tachyarrhythmia; NYHA = New York Heart Association.

Table 2. Operation and post-operative risk factor by occurrence of early recurrence of atrial tachyarrhythmia (ERAT)

	Overall (n=259)	ERAT (n=127)	No ERAT (n=132)	p-value
Status of Surgery				0.450
Urgent or Emergent	63 (24.3)	34 (26.8)	29 (22.0)	
Elective	196 (75.7)	93 (73.2)	103 (78.0)	
Surgical AF ablation				
Bi-atrial ablation	184 (71.0)	102 (80.3)	82 (62.1%)	0.002
Concomitant LAA resection/obliteration	110 (42.4)	59 (46.5)	51 (38.6)	0.251
CPB Time, min	167.8 ± 62.5	181.3 ± 63.3	154.8 ± 59.2	0.001
ACC Time, min	116.5 ± 51.7	128.1 ± 53.6	108.2 ± 45.3	0.001
Post-operative stroke	5 (1.9)	2 (1.6)	3 (2.3)	1.000
Post-operative AKI	3 (1.2)	3 (2.4)	0 (0.0)	0.232

	Overall (n=259)	ERAT (n=127)	No ERAT (n=132)	p-value
Post-operative lung complication	49 (18.9)	35 (27.6)	14 (10.6)	0.001
Reoperation for bleeding	18 (6.9)	14 (11.0)	4 (3.0)	0.022

Values are mean ± SD or n (%) unless otherwise noted.

ACC = aorta cross clamp; AF = atrial fibrillation; AKI = acute kidney injury; CPB = cardiopulmonary bypass; LAA = left atrial appendage.

Table 3. Univariate and multivariate logistic regression analyses for predicting occurrence of early recurrence of atrial tachyarrhythmia (ERAT)

			Univariate	Univariate
		Odds ratio	Odds ratio	95% Confidence Interval
Age	Age	1.04	1.04	1.02-1.07
Previous CAD	Previous CAD	4.96	4.96	1.05-23.4
Persistent AF	Persistent AF	4.06	4.06	1.91-8.63
Left atrial size	Left atrial size	1.04	1.04	1.01-1.06
Bi-atrial ablation	Bi-atrial ablation	2.49	2.49	1.42-4.36
CPB Time	CPB Time	1.01	1.01	1.00-1.01
ACC Time	ACC Time	1.01	1.01	1.00-1.01
Post-operative lung complication	Post-operative lung complication	3.21	3.21	1.63-6.31
Reoperation for bleeding	Reoperation for bleeding	3.96	3.96	1.27-12.39

Abbreviations as in Table 1 and 2.

Table 4. Multivariable cox proportional analysis of factors related to late recurrence according to the occurrence of early recurrence of atrial tachyarrhythmia (ERAT) and timing of the last episodes of ERAT within blanking period

Variable	Hazard ratio
Analysis according to the occurrence of ERAT	**Analysis according to the occurrence of ERA**
Age	1.04
Male	1.77
Left atrial size	1.04
ERAT	17.73
Analysis according to the Timing of the last ERAT Episodes	**Analysis according to the Timing of the last**
CHADS2-VASc score	1.25
Timing of ERAT	
No ERAT	Reference
First month	2.84
Second month	16.70
Third month	119.75

Abbreviations as in Table 1.

Figure 1. (A) Freedom from atrial tachyarrhythmias (ATAs) after surgical ablation in patients with and without early recurrence of atrial tachyarrhythmia (ERAT). (B) Freedom from ATAs after surgical ablation in patients with ERAT in the first, second, and third month after surgical ablation for atrial fibrillation.

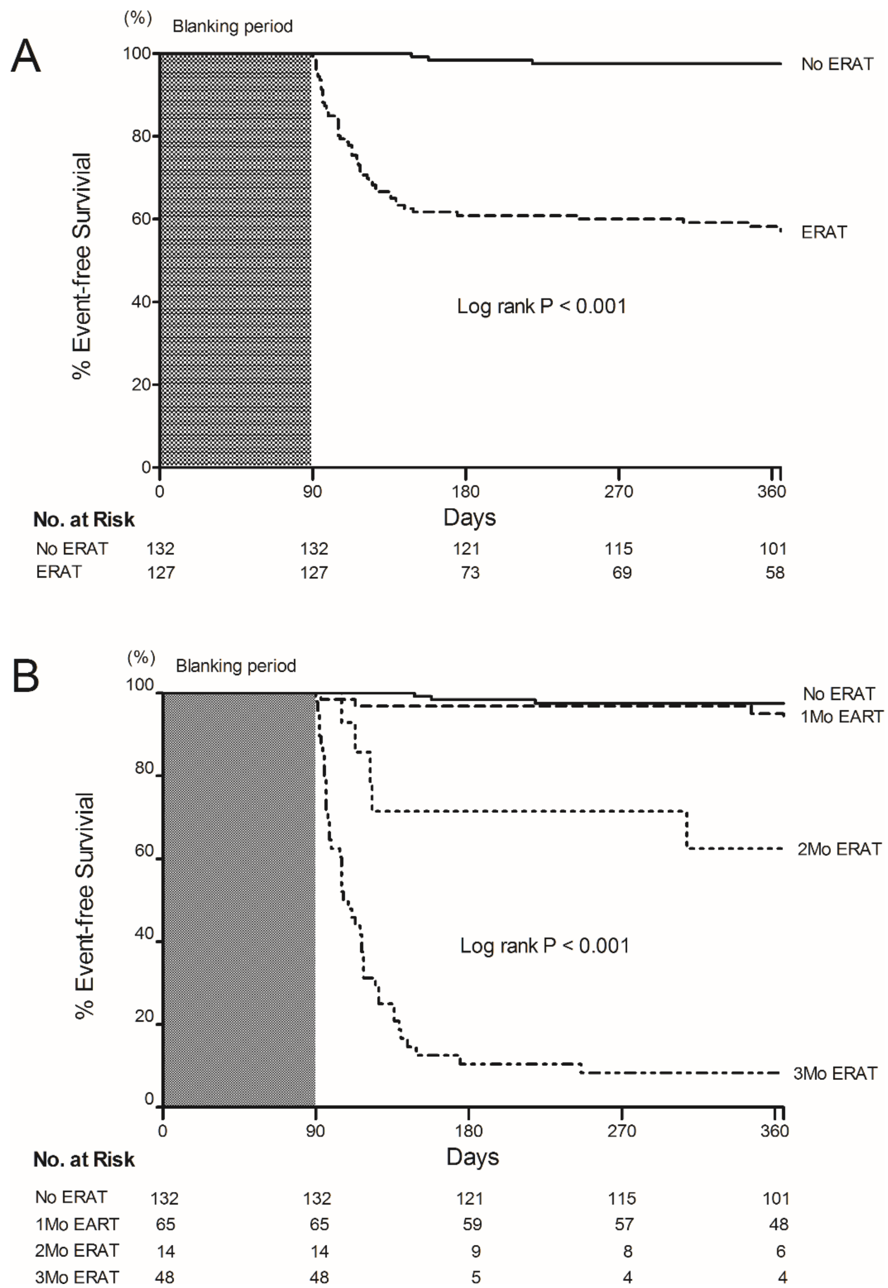
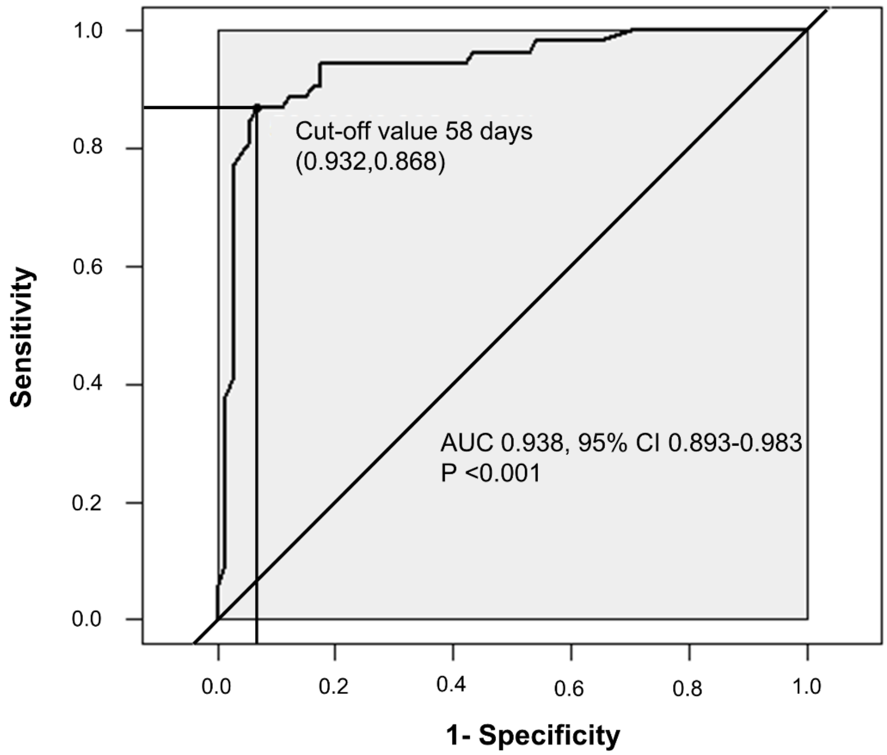


Figure 2. Receiving operator characteristic curve analysis to assess the correlation between timing of early recurrence of atrial tachyarrhythmia and late recurrence.



AUC = area under the curve.