Long-term results of radiofrequency maze procedure for persistent atrial fibrillation with concomitant mitral surgery

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Background: The radiofrequency (RF) maze procedure can effectively restore sinus rhythm in most patients with persistent atrial fibrillation (AF) and mitral disease. However, long-term results and predictors for late AF recurrence are still under investigation.

Methods: From December 1995 to November 2011, 207 consecutive patients with persistent AF and mitral disease underwent RF maze procedure and concomitant mitral surgery. The mean age was 54±12.4 year-old. Mitral surgery was performed in all patients and concomitant procedures including tricuspid surgery, aortic valve surgery, and atrial septal defect closure were carried on 164 patients.

Results: The in-hospital mortality was 3.9% (n=8) and late mortality was 8.2% (n=17). After a mean follow-up period of 101±50.9 months, 154 patients (74.4%) had long-term sinus conversion. A permanent pacer was implanted in 8 patients (3.9%). By Cox multivariate survival regression analysis, predictors for long-term sinus conversion were identified to be the duration of persistent AF, preoperative left atrial (LA) diameter, preoperative right atrial (RA) area, and preoperative beta-blocker use. The receiver operating characteristic (ROC) curve analysis showed that the best cutoff value for persistent AF duration, preoperative LA diameter, and preoperative RA area were 59.5 months, 59.85 mm, and 25.65 cm².

Conclusions: Longer persistent AF duration, larger preoperative LA diameter, larger preoperative RA area and preoperative beta-blocker use were the predictors for negative long-term outcome of RF maze procedure for the patients with persistent AF underwent concomitant mitral surgery. Timely referral of patients for surgery is mandatory.

Keywords: Atrial fibrillation (AF); maze procedure; mitral surgery; radiofrequency (RF)

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Introduction

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia and present in 0.4% of the general population (1). The risk of systemic embolization, cardiac morbidities and mortality are increased in the patients with AF (2,3). In patients undergoing off-pump coronary artery bypass grafting, postoperative AF could even cause delayed stroke (4). Anticoagulation therapy has been recommended for prevention of systemic embolization. However, the attitude for anticoagulation therapy for the patients with AF at peri-stroke period is rather conservative due to the concern regarding the late hemorrhagic complication (5). In the patients underwent mitral surgery, concomitant AF is present in as high as 50% of patients (6). Cox *et al.* developed Cox Maze procedure and successfully treated

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Table 1	Demographic	data of the	199	patients
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Variables	Success (n=154)	Failure (n=45)	P value
Age (year)	52.7±12.3	55.4±12.5	0.865
Gender (male), n (%)	74 (48.1)	21 (46.7)	0.500
Persistent AF duration (month)	30.5±41.3	98.2±64.9	<0.001
Hypertension, n (%)	23 (14.9)	9 (20.0)	0.480
Diabetes mellitus, n (%)	13 (8.4)	5 (11.1)	0.770
Hyperlipidemia, n (%)	11 (7.1)	2 (4.4)	0.740
CAD, n (%)	7 (4.5)	0 (0)	0.200
CVA, n (%)	9 (5.8)	1 (2.2)	0.460
Hyperthyroidism, n (%)	5 (3.2)	2 (4.4)	0.660
Digitalis, n (%)	126 (81.8)	38 (84.4)	0.830
Beta-blocker, n (%)	34 (22.1)	13 (28.9)	0.500
Calcium blocker, n (%)	22 (14.3)	8 (17.8)	0.640
ACEI, n (%)	90 (58.4)	22 (48.9)	0.450
Preoperative NYHA Fc class, n		0.015	
I	1 (0.6)	0 (0)	
II	35 (22.7)	1 (2.2)	
III	96 (62.3)	39 (86.7)	
IV	22 (14.3)	5 (11.1)	
Preoperative LA size (mm)	52.2±8.8	61.1±10.5	0.030
Preoperative LA area (cm ²)	43.2±15.6	61.1±25.7	< 0.001
Preoperative RA area (cm ²)	24.3±8.5	30.5±9.5	0.230
Preoperative LVEDD (mm)	55.4±10.0	53.4±7.4	0.032
Preoperative LVESD (mm)	36.0±9.4	35.0±6.2	0.013
LV EF (%)	62.6±13.3	62.2±9.1	0.008
MVD, n (%)			0.480
MS	19 (12.3)	11 (24.4)	
MR	74 (48.1)	16 (35.6)	
MS + MR	61 (39.6)	18 (40.0)	
AVD, n (%)	33 (21.4)	8 (17.8)	0.680
TVD, n (%)	100 (64.9)	37 (82.2)	0.029
ASD, n (%)	11 (7.1)	3 (6.7)	1.000

ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ASD, atrial septal defect; AVD, aortic valve disease; CAD, coronary artery disease; CVA, cerebral vascular disease; EF, ejection fraction; Fc, functional; LA, left atrial; LV, left ventricle; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; RA, right atrial; MR, mitral regurgitation; MS, mitral stenosis; MVD, mitral valve disease; NYHA Fc class, New York Heart Association Functional Classification; TVD, tricuspid valve disease. the patients with drug-refractory AF (7,8). Since the original maze procedure required extensive cut-and-saw in both atria, modified maze procedure using variable energy sources to achieve the ablative purpose were developed (9-14). However, the long-term results and predictors for late AF recurrence are still under investigation. This study investigated the long-term results and the predictive values for late AF recurrence in 207 consecutive patients after mitral surgery and radiofrequency (RF) maze procedure for persistent AF.

Methods

Patient selection

A single-center retrospective clinical database analysis of 207 consecutive patients who underwent the RF maze procedure for persistent AF concomitant to the mitral surgery from December 1995 to November 2011 was conducted. Associated procedures including tricuspid surgery, aortic valve surgery, and atrial septal defect closure were carried on 164 patients (*Table 1*). There were 106 female. The mean age was 54±12.4 (ranged from 21 to 81) years old. This study was approved by the Institutional Review Board of Chang Gung Medical Foundation (IRB number 201600911B0), and the need for written informed consent from the patients was waived.

RF maze procedure

The RF maze procedure was initially conducted with a handmade saline-irrigated quadripolar steerable electrode catheter (Mansfield, Watertown, MA, USA) and a RF generator (EPT-1000; EP Technologies, Inc., Sunnyvale, CA, USA) guided by direct visualization during the period when the commercialized surgical ablation device was not available. Subsequently, since May 2005, the same procedure was carried with Cardioblate Monopolar RF ablator (Medtronic, Parkway, MN, USA). This technique was described elsewhere in detail and has been demonstrated to create transmural and continuous lesions (12-14).

Postoperative protocol

Both atrial and ventricular temporary pacing wires were employed in case of perioperative dysrhythmia. Cardiac rhythm was constantly monitored in the intensive care unit. In the general ward, a 12-lead electrocardiogram (ECG) was performed once each day and whenever subjective symptoms of dysrhythmias were noted. In contrast to other reports, any class I or III antiarrhythmics were not used in our practice in order to exclude chemical conversion. The patient was discharged after 2 weeks of heparinization. Persistent sinus restoration or spontaneous sinus conversion was considered as successful sinus conversion at discharge after 2 weeks of postoperative monitoring. Any atrial dysrhythmia was not converted either electrically or chemically during this period. Warfarin was administered in all patients and stopped 6 weeks later only in patients with successful sinus rhythm and atrial contraction restoration following reparative surgery or tissue valve replacement.

Cardiac rbythm and dimensions at follow-up

After hospital discharge, patients received monthly to trimonthly follow-up for medication adjustment, rhythm analysis, and chamber size evaluation with 12-lead ECG and two-dimensional echocardiogram. A 24-hour Holter ECG monitor was performed whenever symptoms or signs of dysrhythmia were noted or detected during the routine ECG and echocardiographic follow-up. M-mode measurements were performed following the recommendations of the American Society of Echocardiography for atrial dimensions (15). Atrial areas were measured by planimetry in a 4-chamber view. The maximum areas were the average of measurements over 5 beats. Early diastolic ventricular filling, filling by atrial contraction across the tricuspid and mitral valves, and total time-velocity integrals were recorded for analysis, as well.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows software system, Version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous variables acquired from the clinical characteristics were expressed as the mean ± standard deviation and were compared using the student *t*-test. The chi-squared test or Fisher's exact test according to the number of events for variables appraised was used for comparisons made between categorical variables. Cox survival regression model was used to determine factors of AF recurrence after surgical ablation. Factors for which the univariable analysis gave a p value of less than 0.1 were included in the multivariable analysis. Hazard ratio (HR) and 95% confidence interval (CI) were calculated. Youden index (sensitivity + specificity - 1) of receiver operating characteristic (ROC) curve was calculated to find out the best cutoff values of persistent AF duration, preoperative left atrial (LA) diameter and preoperative right atrial (RA) area to predict late AF recurrence. Sensitivity, specificity and accuracy were investigated by the Fisher's exact test. Survival curves for the incidence of AF recurrence by persistent AF duration, preoperative LA diameter, and preoperative RA area were calculated with the Kaplan-Meier method and a log-rank test was used to assess the statistical significance. A two-tailed probability value of less than 0.05 was considered statistically significant.

Results

Surgical outcomes

Among the 207 patients, there were 8 in-hospital deaths (3.9%). The remaining 199 patients including 109 rheumatic and 90 degenerative patients were divided into success sinus restoration (success, n=154) and failed sinus restoration (failure, n=45) groups according to the rhythm at discharge after 2 weeks of postoperative continuous monitoring (Table 1). The follow-up was 100% complete. During the mean follow-up period of 101±50.9 months, stroke was documented in 3 patients (1.4%), 8 patients (3.9%) developed sick sinus syndrome and received dual chamber permanent pacemaker implantation. There was no any sustained atrial arrhythmia documented over the whole course till the last follow-up of this study in 154 of 207 patients (74.4%). There were no complications associated with the RF maze procedure. The Failure group had longer persistent AF duration, worse preoperative New York Heart Association functional class, larger preoperative LA diameter, poorer left ventricular ejection fraction, larger preoperative left ventricular end systolic and end diastolic diameters. Late mortality occurred in 17 patients (8.2%). In these 17 patients, 13 patients (76.5%) restored sinus rhythm.

Predictors of late AF recurrence

In the Cox univariate regression analysis, significant predictors of late AF recurrence were persistent AF duration, preoperative New York Heart Association functional class, preoperative LA diameter, preoperative RA area, tricuspid valve disease, and preoperative beta-blocker use (*Table 2*). In the multivariable analysis, persistent AF duration, preoperative LA diameter, preoperative RA area and preoperative beta-blocker use remained statistically significant for AF recurrence (*Table 3*). According to the ROC curve analysis, the best cutoff value for persistent AF

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Table 2 Predictors of AF recurrence in Cox univariate survival regression analysis

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Variables	β	SEM	HR	95% CI	P value
Age (in year)	0.020	0.016	0.228	0.988–1.053	0.228
Female gender	0.167	0.301	1.181	0.654-2.133	0.580
Persistent AF duration (month)	0.017	0.002	1.018	1.013-1.023	<0.001
History of embolism	-0.043	0.527	0.957	0.341-2.690	0.934
Preoperative NYHA Fc class	0.507	0.261	1.660	0.995-2.768	0.049
Preoperative LA diameter (mm)	0.068	0.015	1.070	1.040-1.101	<0.001
Preoperative RA area (cm ²)	0.042	0.013	1.043	1.017-1.070	0.001
Preoperative EF	0.006	0.012	1.006	0.982-1.031	0.641
TVD	1.206	0.420	3.341	1.466–7.612	0.004
Preoperative beta-blocker	0.716	0.338	2.046	1.056-3.966	0.034
Preoperative calcium blocker	0.334	0.393	1.410	0.653-3.046	0.382
Preoperative digoxin	-0.448	0.417	0.639	0.282-1.446	0.283
Preoperative ACEI	-0.178	0.300	0.837	0.465-1.505	0.551

ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; β, regression coefficient; CI, confidence interval; EF, ejection fraction; Fc, functional; HR, hazard ratio; LA, left atrial; NYHA Fc class, New York Heart Association Functional Classification; RA, right atrial; SEM, standard error of the mean; TVD, tricuspid valve disease.

Table 3 Predictors of AF recurrence in Cox multivariate survival regression analysis

Variables	β	SEM	HR	95% CI	P value
Persistent AF duration (month)	0.014	0.003	1.014	1.008-1.020	<0.001
Preoperative LA diameter (mm)	0.071	0.019	1.073	1.033–1.115	<0.001
Preoperative RA area (cm ²)	0.036	0.015	1.037	1.006–1.068	0.020
Preoperative beta-blocker	1.173	0.413	3.231	1.438–7.259	0.005

AF, atrial fibrillation; β, regression coefficient; LA, left atrial; RA, right atrial; SEM, standard error of the mean; HR, hazard ratio; CI, confidence interval.

 Table 4 Predictive values for AF recurrence by receiver-operating characteristic curve

Variables	Best cut-off value	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Accuracy (%)
Persistent AF duration (month)	59.50	0.799 (0.717–0.882)	79.9	73.3	74.9
Preoperative LA diameter (mm)	59.85	0.732 (0.643–0.822)	55.8	80.8	75.2
Preoperative RA area (cm ²)	25.65	0.709 (0.616–0.802)	75.0	65.5	67.4

Best cut-off value is equal to the biggest Youden index, Youden index, sensitivity + specificity – 1; AF, atrial fibrillation; AUC, area under the curve; CI, confidence interval; LA, left atrial; RA, right atrial.

duration, preoperative LA diameter and preoperative RA area were 59.5 months (sensitivity 79.9%, specificity 73.3% and accuracy 74.9%), 59.85 mm (sensitivity 55.8%, specificity 80.8% and accuracy 75.2%) and 25.65 cm² (sensitivity 75.0%, specificity 65.5% and accuracy 67.4%) respectively (*Table 4*).

Kaplan-Meier survival estimates also verified that patients with persistent AF duration \geq 59.5 months, preoperative LA diameter \geq 59.85 mm, preoperative RA area \geq 25.65 cm², and preoperative beta-blocker use had significant predictive value of AF recurrence (*Figures 1-4*).



Figure 1 The Kaplan-Meier curve demonstrated the cumulative freedom from atrial fibrillation according to the persistent atrial fibrillation durations (months). AF, atrial fibrillation.



Figure 3 The Kaplan-Meier curve demonstrated the cumulative freedom from atrial fibrillation according to the preoperative right atrial area (cm^2). AF, atrial fibrillation; RA, right atrial.

Discussion

Catheter ablation versus surgical ablation

Currently, catheter ablation of paroxysmal or persistent AF is a common practice although the primary success rate even including the recent state-of-art technology of cryoballoon could only achieve 60% at 12 months and this could be improved to 76.9% after repetitive procedures (16). In contrast, we demonstrated the primary success rate of 74.4% in a cohort of mitral disease with persistent AF during follow-up period of 101 ± 50.9 months by RF maze procedure with concomitant mitral surgery. Similarly, in a case-matched

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Figure 2 The Kaplan-Meier curve demonstrated the cumulative freedom from atrial fibrillation according to the preoperative left atrial diameter (mm). AF, atrial fibrillation; LA, left atrial.



Figure 4 The Kaplan-Meier curve demonstrated the cumulative freedom from atrial fibrillation according to the preoperative betablocker use. AF, atrial fibrillation.

comparison of catheter-based techniques and Cox-Maze III operation conducted by Stulak *et al.*, the superiority of surgical ablation including better free of AF, less antiarrhythmics and anticoagulation use were reported (17). Several catheter ablation related adverse events like pulmonary vein stenosis, esophageal injury, and cardiac perforation related tamponade were all well-known complications. In between, pulmonary vein stenosis is a serious issue which may require later catheter intervention or even pulmonary resection procedures. In addition, 3% of vascular access complication was not negligible (17). These complications were seldom reported in the surgical ablation groups.

Modified monopolar RF saline irrigated AF ablation

Various energy sources including RF, microwave, highintensity focused ultrasound, and cryothermia have been introduced to replace the conventional cut-and-saw maze procedure (18-20). These modifications made the AF ablation safer and easier resulted in versatile concomitant application of surgical AF ablation in various cardiac procedures, especially in mitral surgery. In this study, RF ablation was performed using a monopolar RF ablator delivering a continuous, quasi-sinusoidal, unmodulated RF output at 500 kHz. During the point-to-point ablation, saline irrigation was used continuously and transmural discoloration of each lesion was confirmed to ascertain the adequate continuity and depth of the ablation line. As an adjunction, cryoablative lesions were also made at some particular anatomical sites (12). By this monopolar saline irrigated RF maze procedure, we achieved the results of 2.9% of the 30-day mortality, 3.9% of the in-hospital mortality, 1.4% of stroke rate, and 3.9% of permanent pacer implantation rate. These results are comparable to that of the current state-of-art results reported as 4.4% of 30-day mortality, 5.5% of stroke rate, and 7.0% of permanent pacer implantation rate (21).

Heterogeneity of modified RF AF ablation

The incidence of AF increased in the patients indicated for cardiac surgery and AF was also reported to be a significant risk factor of surgical mortality (22-23). Therefore, concomitant AF ablation was inferred and justified for reducing the mortality and improving the quality of life. However, it is noteworthy that concomitant AF ablation in different cardiac surgeries demonstrated heterogeneous outcomes. According the report from Budera *et al.*, mitral surgery showed superior benefit than coronary and aortic valve surgeries (24).

Another issue regarding the heterogeneity of RF ablation is the adoption of different device, technique, and lesion set which inevitably resulted in varied outcomes. The transmurality and continuity of lesions are important but tricky terms without objective consensus. The "ablation factors" including delivered energy, ablation duration, lesion set, lesion depth, lesion width, and even saline irrigation amount are all varied between operators. Consequently, the results of RF maze procedure varied between surgeons. In our practice, we standardize the procedure by creating the point to point continuous RF lesions with precise protocol regarding the "ablation factors" to achieve the consistent ablation result as possible (12-14). Certainly, a method for real-time confirmation of complete conduction block between the RF lesions in a beating heart is the most demanding facility for refinement of the RF maze procedure.

Post-ablative permanent pacemaker implantation

Gillinov *et al.* reported a greater incidence of pacemaker implantation in ablation group mostly for the heart block and sinus node dysfunction compared to mitral surgery alone group (25). Aggressive implantation strategies have been advocated for atypical bradydysrhythmias in rheumatic population after AF ablation (26,27). In contrast, high degree atrioventricular block or bundle branch block was considered as the indication in different studies (28,29). In our study, high degree atrioventricular block was seldom occurred and the permanent pacemaker implantation rate was low for the sinoatrial node sparing lesion set was adopted in our practice (13).

Thromboembolism after AF ablation

In the surgical group, obliteration of LA appendage and LA thrombectomy could be performed effectively. In addition, surgical ablation also achieved superior long-term sinus restoration. These surgical advantages might reflect on the observations made by Boersma *et al.* that lower incidence of stroke and thrombus formation were noted in the surgical ablation group than catheter ablation group at 12-month follow-up (30). In our practice, after routine 6-week of anticoagulation therapy, warfarin was discontinued if sinus rhythm had been restored in patients after successful valvular repair or bioprosthetic replacement. During the mean follow-up period of 101 ± 50.9 months, stroke was documented in only 3 patients (1.4%; 2 in failure group).

Predictors

In our previous study, we demonstrated that sinus conversion rate was significantly lower in the patients with preoperative LA diameter >56.8 mm and AF duration >66 months (31). In present investigation, in addition to the preoperative LA diameter (>59.85 mm) and the persistent AF duration (>59.5 months), a larger preoperative RA area (>25.65 cm²) and preoperative beta-blocker use were identified as the negative predictors for the successful sinus conversion. Theoretically, with increasing RA area, the electrical substrate of RA tissue

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might become more vulnerable to propagate AF recurrence. This additional finding in our study will be important to predict the patient with AF recurrence after sole left side maze operation. Preoperative beta-blocker use is another novel predictor of late AF recurrence detected in this study. Beta-blockers act by blocking the beta 1-adrenergic receptor, thereby reducing sympathetic activity for AF control. Consequently, preoperative beta-blocker use might suggest that the patients were under higher sympathetic status that might vulnerable to postoperative late AF recurrence.

Limitations of the study

The nature of retrospective, non-randomized, and heterogeneity of this study constitutes the inevitable weakness. Although, this cohort might demonstrate one of the longest follow-up studies in a significant number of patients, a larger prospective randomized study is mandatory for determining the best lesion set and predicting the precise risk factors of AF recurrence. Although we demonstrated that the longer persistent AF duration, larger preoperative LA diameter, larger preoperative RA area and preoperative beta-blocker use were the predictors for negative long-term outcome of RF maze procedure for the patients with persistent AF, we cannot propose the solution to improve the sinus conversion rate in patients with those negative predictors. Lack of modality to document the continuous heart rhythm is the universal weakness in dysrhythmia study. Rapid refinement of portable electronic device for continuous monitoring of heart rhythm will circumvent this predicament in the near future.

Conclusions

In conclusion, monopolar saline irrigated RF maze procedure with concomitant mitral valve surgery demonstrated acceptable sinus conversion rate with low incidences of postoperative stroke and permanent pacemaker implantation in a long-term follow-up. Longer persistent AF duration, larger preoperative LA diameter, larger preoperative RA area and preoperative beta-blocker use were the predictors for negative long-term outcome. Timely referral of patients for surgery is mandatory.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Institutional Review Board of Chang Gung Medical Foundation (IRB number 201600911B0), and the need for written informed consent from the patients was waived.

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