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Article

## Long-Term Results after the Box Pulmonary Vein Isolation Procedure for Chronic Atrial Fibrillation in Mitral Valve Surgery

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**Background:** We hypothesized that chronic atrial fibrillation (AF) originated from the pulmonary veins, and was maintained by irregular activations of the posterior left atrium. We had performed the box pulmonary vein isolation procedure for the elimination of chronic AF associated with solitary mitral valve disease from 1999 to 2004. This paper evaluated the long-term results of this procedure over more than 6 years, and discussed the role of the pulmonary veins and posterior left atrium in maintaining AF.

**Methods:** Fifty-three patients were examined after box pulmonary vein isolation procedure concomitant with solitary mitral valve surgery retrospectively. We divided the patients into two groups with or without the elimination of AF (AF group and non-AF group). The disappearance of AF was determined by electrocardiography, and atrial function was evaluated by transthoracic echocardiography. The elimination of chronic AF and the recovery of atrial systolic function after surgery were evaluated over more than 6 years of follow-up.

**Results:** In a total of 462.8 patient years of follow-up (range 6.3 to 11.5 years, mean:  $8.9 \pm 2.7$  years), AF disappeared in 77.3% of the patients (41/53) at 3 months and in 70.6% (36/51) of the patients at 6 years after the box pulmonary vein isolation, respectively. Among the preoperative variables, a long duration of AF and a large diameter of the left atrium were the predictive factors for recurrences of AF ( $p < 0.05$ ). There was no left atrial tachycardia even though we did not perform ablation towards the mitral valve annulus.

**Conclusions:** The box pulmonary vein isolation procedure can terminate chronic AF associated with solitary mitral valve disease, and maintain a sinus rhythm for more than 6 years in 70% of chronic AF patients. This study implicates the pulmonary veins and posterior left atrium in maintaining chronic AF associated with mitral valve disease.

**Keywords:** atrial fibrillation, box pulmonary vein isolation, maze procedure, atrial tachycardia

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### Introduction

Although the pathogenesis of chronic atrial fibrillation (AF) associated with mitral valve disease is still equivocal, most investigators agree that an increased hemodynamic burden due to inflammation or degeneration of mitral valve can increase tissue fibrosis in the atria, resulting in a non-homogenous distribution of diastolic depolarization potentials, refractory periods, and conduction properties within the atrial muscle.<sup>1,2)</sup> Most surgeons

subscribe to the multiple re-entry theory as the mechanism responsible for AF,<sup>3)</sup> which is the basic theory of the Cox maze procedure.<sup>4)</sup> The Cox maze procedure was devised as a radical procedure for lone AF, but this procedure was effective for all kinds of AF. The Cox maze procedure and its modifications<sup>5,6)</sup> have shown effective results in both short-term and mid-term follow-ups. The modified Cox maze procedure using a bipolar radiofrequency device was also devised instead of the cut-and-sew maze procedure from 2004 onwards.<sup>7)</sup> Our previous study performed on mitral valve disease showed a shortened refractory period for the left atrial wall, and that the simple left atrial procedure was adequate in eliminating the AF associated with isolated mitral disease.<sup>8)</sup> We performed the simple left atrial procedure for chronic AF during mitral valve surgery from 1993 to 1998,<sup>9)</sup> and reported our mid-term<sup>10)</sup> and long-term<sup>11)</sup> results.

Following the discovery by Haissaguerre and colleagues,<sup>12)</sup> the etiology of paroxysmal AF was well investigated. Over 80% of paroxysmal AF occurs via ectopic foci from the pulmonary veins, and it sustained by irregular activation of the posterior left atrium. This discovery opened the door for catheter ablation for paroxysmal and persistent AF and gave key insights into the mechanism of AF occurrence. We hypothesized that chronic AF also occurred via ectopic foci from the pulmonary veins and was maintained by the irregular activations of the posterior left atrium itself. Therefore, we retrospectively reviewed the records of patients who underwent the box procedure for the isolation of pulmonary vein in chronic AF, associated with solitary mitral disease without any ablation lines on the right atrium and the mitral valvular annulus. We have already reported the clinical outcome.<sup>13,14)</sup> The purpose of this study was to examine the late occurrence of atrial tachycardia, including AF and atrial flutter, after this procedure over a 6-years follow-up period, and to discuss the role of box pulmonary vein isolation for the elimination of chronic AF.

## Patients and Methods

### Informed consent and ethics approval

Informed consent for this surgery and the postoperative follow-up study was obtained from every patient according to the manual of informed consent of the Hiroshima University Hospital. The Ethics Committee of Hiroshima University Hospital approved this clinical study in every patient. There was no conflict with any medical company.

### Patient population

We reviewed records between January 1999 to November 2004 of patients who underwent the box isolation procedure on the pulmonary vein in 53 patients with chronic AF associated with solitary mitral valve disease. A postoperative follow-up for longer than 6 years was available in 51 of those patients in whom the analysis could be performed. The latest consultation was performed from November 2009 until December 2010 at the out-patient clinic of the Hiroshima University Hospital. The follow-up period from surgery to the latest consultation ranged from 6.3 years to 11.5 years (mean:  $8.9 \pm 2.7$  years). **Table 1** shows the profiles of these patients. All patients had chronic AF refractory to medical treatments for 5 months to 10 years (average: 5.2 years). Chronic AF was diagnosed by electrocardiography by their medical records. There were no patients with paroxysmal AF. There were 25 men (47%) and 28 women (53%), with an average age of 61.2 years (range, 48 to 71 years old) at surgery. Twenty-eight of these patients had rheumatic mitral stenosis with or without mitral regurgitation, and 25 had pure mitral regurgitation that was secondary to degenerative valvular disease. In forty-six patients (87%), the concomitant surgical intervention consisted only of mitral valve replacement or plasty, whereas in the other patients, it involved two organic left atrial thrombectomies (3.8%) and five coronary artery bypass grafts (9.4%), in addition to mitral valve surgery. Two of the 53 patients (3.8%) had already received permanent pacemaker implantation because of symptomatic bradycardia before the operation.

### Surgical procedure

The operations were performed with the use of cardiopulmonary bypass with mild hypothermia (34°C) and cold blood cardioplegia. Before aortic cross clamping, distal coronary arterial anastomoses were performed during an on-pump beating heart in cases which required coronary artery bypass grafting. A proximal anastomosis using saphenous vein graft was performed during re-warming. After aortic cross clamping and the infusion of blood cardioplegia, a vertical left atriotomy was extended to the left margin of the left pulmonary veins. The left atrial appendage was then excised and/or closed from the inside. Cryoablation ( $-60^{\circ}\text{C}$  for 3 minutes) with a T-shaped cryoprobe (20 mm in length and 8 mm in width, Tonokura, Tokyo) was applied towards the posterior wall of the left atrium between the upper and lower incision

**Table 1** Baseline profiles of 53 patients

Profiles	No. of profiles
Male/female	25/28
Age at surgery (yrs)	61.2 ± 10.5
Duration of preoperative atrial fibrillation (yrs)	5.2 ± 4.7
Associated mitral valve disease	
Stenosis	18
Regurgitation	24
Stenosis and regurgitation	11
Mitral valve with surgical interventions	
MVR	29
MVP	24
Other procedures	
CABG	5
LA thrombectomy	2

All values are expressed as means ± standard deviation or as numbers of patients.  
MVR: mitral valve replacement; MVP: mitral valve plasty;  
CABG: coronary artery bypass grafting; LA thrombectomy: left atrial thrombectomy

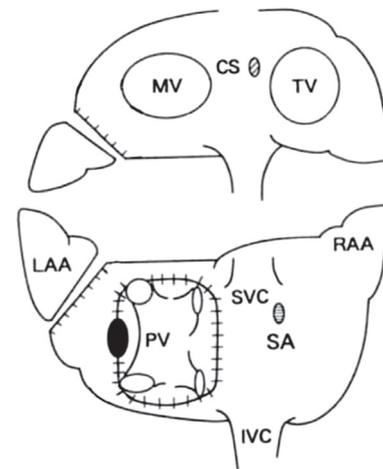
ridges (**Fig. 1**). After the isolation of all pulmonary veins with surgical incisions and cryoablation, the mitral valve procedure was completed. We did not perform the ablation towards the mitral valve annulus. No further atriotomy was performed on the atrial septum or right atrium. After completion of these AF procedures, the left atriotomy was closed by a running suture. All patients in this series were operated on by the same surgical team.

### Indication of surgical procedure

We performed the box pulmonary vein isolation for chronic AF associated with solitary mitral valve disease. We also performed the cryo-maze procedure for chronic AF associated with both mitral and tricuspid valvular disease during the same period because we had to incise the right atrium in patients with tricuspid valvular disease and the right atriotomy itself was arrhythmogenic. We evaluated the mid-term results of the box pulmonary vein isolation for chronic AF associated with solitary mitral valve disease in this study.

### Data acquisition and follow-up procedure

The postoperative results were collected and analyzed. To evaluate the intra-operative risk, we retrospectively reviewed the cardiopulmonary bypass time, aortic cross-clamp time, and associated mortality and morbidity. After discharge, all patients were followed up every 3 to 6 months. Anti-arrhythmic agents of class I or IV according to the Vaughan Williams classification were given to all patients postoperatively, and were discontinued at 6 months after the operation. The patients were questioned



**Fig. 1** Schema of the box pulmonary vein isolation procedure. A left-vertical atriotomy was extended to the left margin of the left pulmonary veins. After excision and closure of the left atrial appendage, cryoablation was delivered at  $-60^{\circ}\text{C}$  for 3 minutes to the posterior wall of the left atrium. The cryoablation was directed towards the incision edges between the upper and lower left pulmonary veins. black area: cryoablation; dashed lines and hatched areas: incision and suture line  
CS: coronary sinus; IVC: inferior vena cava; LAA: left atrial appendage; MV: mitral valve; PVs: pulmonary veins; RAA: right atrial appendage; SA: sinus node; SVC: superior vena cava; TV: tricuspid valve

regarding their medications at the latest follow-up, which was performed from November 2009 until December 2010 at the out-patient clinic of Hiroshima University Hospital. We divided the patients into non-AF and AF

**Table 2 Comparison of preoperative and intraoperative variables**

	Non-AF Group	AF Group	<i>p</i> value
Preoperative factors			
Male/female	17/20	7/9	0.612
Age at surgery (yrs)	60.6 ± 8.4	62.5 ± 5.8	0.842
Duration of AF (yrs)	4.4 ± 3.7	8.2 ± 4.1	0.022
Amplitude of f-wave at lead V1 (mV)	0.18 ± 0.09	0.12 ± 0.09	0.431
Cardiothoracic ratio (%)	57.2 ± 8.2	61.8 ± 4.7	0.124
Echocardiography			
Ejection fraction (%)	56.6 ± 11.1	50.0 ± 18.3	0.157
Left atrial dimensions(mm)	48.8 ± 9.4	58.3 ± 8.4	0.041
Intraoperative factors			
Duration of extracorporeal circulation (min)	110 ± 35	114 ± 38	0.712
Duration of aortic cross clamp (min)	85 ± 26	90 ± 34	0.494
Associated surgical interventions			
CABG	2	2	0.425
LA thrombectomy	1	1	0.345

All values are expressed as means ± standard deviation or as numbers of patients.

AF: atrial fibrillation; lead V1: first precordial lead

groups, based on their cardiac rhythms from the latest electrocardiograph or Holter electrocardiograph at the outpatient clinic. The non-AF group was diagnosed without AF by the latest electrocardiograph. The AF group had recurrent, persistent AF postoperatively or during the follow-up period. Postoperative occurrences of other atrial arrhythmias were also examined at the latest follow-up by electrocardiography or Holter electrocardiography. The preoperative profiles and intraoperative variables were then compared between these two groups.

The following data were collected at the latest follow-up: cardiothoracic ratio and echocardiographic indices, including Doppler flow studies (left atrial diameter, ejection fraction, and atrial kick on transmitral and transtricuspid flow). The early diastolic filling velocity (E) and atrial contraction velocity (A) were measured by pulse Doppler waves at both ventricular inflows and compared as E/A ratio.

### Statistical analysis

All values were expressed as means ± standard deviation. All collected data were entered into a database. Continuous variables were then compared using the non-parametric Mann-Whitney *U* test. The proportions were compared with Fischer's exact test. A *p* value less than 0.05 was considered to be statistically significant. Time-dependent morbidity was tabulated univariately by a Kaplan-Meier life-table with the end points of the recurrence of sustained AF diagnosed by electrocardiography. The

statistical analysis was performed using the StatView J-4.5 software package (Abacus Concepts, Inc, Berkeley, CA).

## Result

### Operative procedure, mortality, and morbidity

We performed a complete box isolation procedure for treating pulmonary vein in patients with chronic AF. The duration of cardiac arrest ranged from 52 to 123 minutes (mean: 86 ± 35 minutes), and the cardiopulmonary bypass time from 72 to 158 minutes (mean: 111 ± 45 minutes). No patients required postoperative circulatory support such as intraaortic balloon pumping, and there was no re-exploration for postoperative hemostasis. There was no postoperative mortality. Fifty-one cases survived during the entire follow-up period without any serious complications. Two cases died due to colon cancer and pneumonia at 8 years and 9 years after surgery. The follow-up period from surgery to the latest follow-up ranged from 6.3 to 11.5 years (mean: 8.9 ± 2.7 years) with a total of 462.8 patient-years. No patients had any severe cerebral thromboembolic complications postoperatively, even in those cases with a recurrence of AF.

### Perioperative variables in relation to postoperative status

Comparisons of the preoperative and intraoperative variables between the non-AF and AF groups are shown

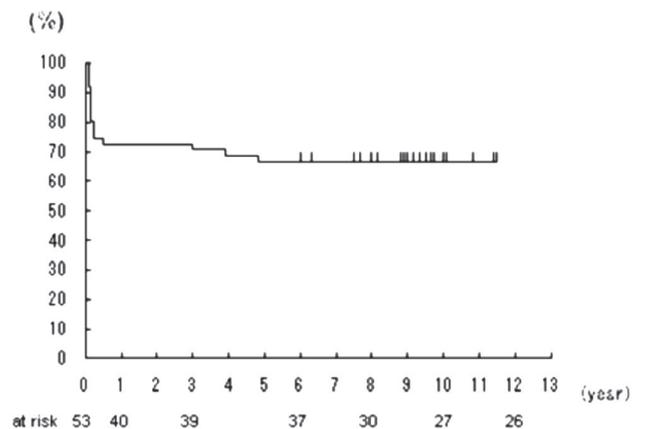
in **Table 2**. Among the preoperative variables, a long duration of AF and a large diameter of the left atrium were predisposing factors for the postoperative persistence or recurrence of AF. We defined the duration of AF by checking the actual electrocardiographic data from the medical records. It ranged from 0.5 to 8.2 years (mean:  $4.4 \pm 3.7$  years) in the non-AF group and from 4 to 12 years (mean:  $8.2 \pm 4.1$  years) in the AF group and was significantly shorter in the non-AF group ( $p = 0.022$ ). Among the intraoperative variables, there was a significant difference in the diameter of the left atrium found between the two groups ( $p = 0.041$ ).

### Recurrence of atrial fibrillation

Four of 53 patients did not recover their sinus rhythm during the operation and remained in persistent AF during the follow-up periods. Eight of 53 patients had persistent AF during the perioperative period in spite of attempts at direct cardioversion. The AF elimination rate was 77% (41/53) at 3 months after surgery. Two cases died by pneumonia and colon cancer 46 and 55 months after surgery. Four of 51 patients developed AF at a later time (1 patient within 6 months after the operation, 1 patient within 36 months after the operation and 2 patients within 48 and 58 months after the operation). On the final follow-up, 36 of 51 patients (70.6%) remained free from chronic AF. The actuarial proportion of patients without a recurrence of AF was 75.4% at 1 year after the operation, and 70.6% at 6 years after the operation (59.2% to 89.8%: 95% confidence intervals) (**Fig. 2**).

### Other postoperative atrial arrhythmias and sinus node dysfunction

Four of 53 patients (7.5%) without a recurrence of AF showed other atrial arrhythmia, such as atrial flutter or atrial tachycardia during the follow-up periods. These patients required direct current cardioversion for restoring their sinus rhythm, but 2 of these 4 patients could not have their sinus rhythm restored with direct current cardioversion and required radiofrequency catheter ablation. These two atrial tachycardias were diagnosed as atrial flutters. The atrial isthmus between the tricuspid valve and the coronary sinus orifice was ablated for common atrial flutter in two patients at 24 and 36 months after surgery. These common atrial flutter patients regained their atrial sinus rhythm after catheter ablation. However, there was no left atrial tachycardia in those cases who regained their sinus rhythm. Although we did not perform cryoablation towards the mitral valvular annulus, left



**Fig. 2** Long-term freedom from AF.

The results of the long-term follow-up on patients with successful simple left atrial procedures are shown with the actuarial proportion of patients free from AF (95% confidence intervals). The AF free rate was 75.5% at 1 year and 70.6% at 6 years after surgery ( $p = 0.083$ ).

AF: atrial fibrillation

atrial tachycardia around the mitral valve annulus did not occur during the entire follow-up period.

Two of 53 patients (3.8%) received prophylactic pacemaker implantation because of sinus bradycardia (<50 beats per minutes), although they were asymptomatic. A dual-chamber pacemaker was implanted to achieve the appropriate heart rate and atrio-ventricular sequential contraction was clearly established with atrial kick after a dual chamber pacemaker implantation in these patients (**Table 3**).

### Postoperative medication

Anti-arrhythmic agents of class I or IV according to the Vaughan Williams classification were given in all patients until 6 months after the operation. When the patients had sinus rhythm restored for more than 6 months, we terminated the anti-arrhythmic drugs gradually. We gave anti-arrhythmic agents in those cases with AF recurrence after surgery with the expectation of a late recovery of the sinus rhythm for 1 year. Forty-eight of 51 patients (94.1%) had discontinued anti-arrhythmic drugs on their latest follow-up. Three patients (5.9%) continued to take anti-arrhythmic drugs (class IV) to prevent premature ventricular contraction or paroxysmal atrial tachycardia until their latest follow-up. The final free of anti-arrhythmic drugs rate was 94.1% at 6 years after surgery.

Coumadin sodium was prescribed in every case with a recurrence of AF, and the dosage was adjusted by their

**Table 3 Other postoperative atrial arrhythmias in the non-AF group**

Event	No. of Patients
DC cardioversion (against AT or AFlu)	4 (7.7%)
Successful catheter ablation	2 (3.8%) a
Prophylactic pacemaker implantation for sinus bradycardia	2 (3.8%) b

a: right atrial ablations (tricuspid valve-coronary sinus isthmus ablation for 2 cases against common atrial flutter)

b: to increase heart rate for sinus bradycardia (<50/in) in spite of no symptom

AF: atrial fibrillation; DC: direct current cardioversion, AT: atrial tachycardia; AFlu: atrial flutter

**Table 4 Presence of atrial kick in the sinus rhythm group**

Side of atrium	Presence of atrial kick	Range of E/A ratio				(No. of patients)
		<0.75	0.75–1.5	0.1–3.0	>3.0	
Right	No. of patients 35/35 (100%)	(3)	(30)	(2)		
Left	23/36 (64%)	(8)	(6)	(4)	(5)	

E/A ratio: the ratio of the early diastolic peak velocity (E) to the peak velocity at atrial contraction (A)

serum PT-INR score. Coumadin sodium was also given in every case of concomitant mitral valve replacement with a mechanical valve (25 of 53 patients), in 3 patients with valve repair procedure and in 2 patients with a bio-prosthetic valve replacement due to the recurrence of AF. Thirty of 51 patients (58.8%) took Coumadin sodium at their latest follow-up. Twenty three of 51 patients (45.1%) could terminate their Coumadin sodium within 2 years after surgery because they had a normal sinus rhythm and did not receive a mechanical valve. They all had an uneventful course without Coumadin sodium for 6 years.

### Atrial transport function

To evaluate the postoperative atrial transport function in the sinus rhythm group, pulsed-wave Doppler examinations were carried out at the end of the follow-up.

Data for the mitral valve procedures were available in 36 patients, and data for the tricuspid valve procedures were available in 35 patients. An A wave was detected during the transmitral flow in 23 of 36 patients (64%), and during the transtricuspid flow in all 35 patients (100%) (Table 4). The E/A ratio during transmitral flow of the 23 patients were as follows: 8 patients under 0.75, 6 patients within 0.75–1.5, and 9 patients over 1.5. In 9 of 23 (39%) patients, the E/A ratio was more than 1.5, and six of them were over 3.0. The A wave was very small in these patients. In contrast, the E/A ratio during transtricuspid flow showed a good recovery, such as 2 patients

under 0.75, 31 patients within 0.75–1.5, and 2 patients over 1.5. The E/A ratio during transtricuspid flow was the same as that of healthy volunteers. In contrast, the E/A ratio during transmitral flow had rather high values because of the small A wave.

### Discussion

Although the Cox maze procedure and its modifications have been adopted by many surgeons, the original maze procedure required a significant elongation of the aortic cross-clamp time and postoperative hemostasis<sup>4</sup> because of the numerous incision lines on both atria and the atrial septum. The introduction of a bipolar radiofrequency ablation device for the maze procedure made the maze procedure easy to perform, and it has been adopted as the standard AF procedure now.<sup>7</sup> We previously developed the simple left atrial procedure<sup>8,9</sup> to ablate only the posterior wall of the left atrium against chronic AF. Our previous study reported the long-term results of the simple left atrial procedure for chronic AF associated with mitral valve disease. The actuarial elimination rate of AF was 73% at 5 years and 69% at 10 years after the simple left atrial procedure in a total follow-up of 702.5 patient years.<sup>11</sup> Subsequent results from the modified maze procedures against AF with organic valvular disease have seldom been reported. Kosakai and colleagues<sup>6</sup> described their outcomes with sixty-two modified Cox

maze procedures; Of 65 patients, 55 (84%) regained sinus atrial rhythm at one year follow-up.

We hypothesized that the occurrence and maintenance of chronic AF was related to the pulmonary veins and posterior wall of the left atrium itself, which Haissaguerre reported as the ectopic foci of paroxysmal AF.<sup>12)</sup> Our results revealed that isolation of the entire posterior left atrium was essential for the elimination of chronic AF during a long-term follow-up. Voeller et al.<sup>15)</sup> also reported the importance of the isolation of all pulmonary veins in the new Cox maze VI procedure, in which a complete box isolation of the whole pulmonary veins was performed using a bipolar radiofrequency clamp. The new Cox maze IV procedure improved the elimination rate of AF and decreased the occurrence of postoperative atrial tachycardia significantly as compared with the old Cox maze IV procedure (non-box pulmonary vein isolation procedure). This means that the essential procedure for AF elimination is the box isolation of the entire posterior left atrium during the Cox maze procedure.

There were no cases with mitral valve annulus tachycardia in the sinus rhythm patients, in whom we did not perform cryoablation towards the mitral valve annulus. High incidence of atrial tachycardia is reported after widespread left atrial catheter ablation. Widespread left atrial catheter ablation creates a proarrhythmic effect of an incomplete pulmonary vein isolation or a linear lesion towards the mitral valve annulus.<sup>16)</sup> Perimitral reentry can be promoted by the isthmus located between the mitral valve annulus and the encircling lesion around the left pulmonary veins.<sup>17)</sup> In contrast, surgical box pulmonary vein isolation can create a definite ablation line around all pulmonary veins. We can preserve a large and healthy atrial myocardium from 3 to 4 cm in width between the left pulmonary veins and the mitral valve annulus. This may prevent the creation of an isthmus and perimitral reentry.

The restoration of the atrial contribution to ventricular filling is another important purpose of this operation. In the non-AF group, atrial contraction was detected in 64% of the left atrium and in 100% of the right atrium. According to a study in healthy patients,<sup>18)</sup> the difference between the transmitral E/A ratio and the transtricuspid E/A ratio was not significant; however, the transmitral E/A ratio was still higher than the transtricuspid E/A ratio in our series. Although the ablation to the left atrium was limited to the orifice of the four pulmonary veins, there were no incisions added towards the right atrium or atrial septum. This could be responsible for the better preserva-

tion of right atrial function than left atrial function.

This study revealed the indication of the box pulmonary vein isolation procedure for chronic AF. We think this procedure is indicative for paroxysmal AF and chronic AF associated with solitary mitral valve disease. We continue to perform this procedure for paroxysmal AF and chronic AF associated with solitary mitral valve disease and short AF duration until now. However, we had better to choose the simple maze procedure to prevent atrial flutter or postoperative incisional atrial tachycardia in cases who require right atriotomy due to tricuspid valvular disease. We perform the simple maze procedure, consisting of left atrial ablation, tricuspid isthmus ablation and linear ablation between right atriotomy and the inferior vena cava, for chronic AF associated with both mitral and tricuspid valvular disease using radiofrequency ablation device.

In conclusion, the long-term results of the box pulmonary vein isolation procedure showed a 70.6% success rate in eliminating chronic AF with solitary mitral valve disease during a more than 6 years follow-up. However, several patients had recurrent AF during the follow-up period. The factors associated with AF occurrence were a long duration of AF history, and a large diameter of the left atrium. All patients avoided thromboembolic events, and most patients with a sinus rhythm regained the transport function of both atria.

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