

# Long-term results and reliability of cryothermic ablation based maze procedure for atrial fibrillation concomitant with mitral valve surgery<sup>☆</sup>

Toshihiro Funatsu, Junjiro Kobayashi<sup>\*</sup>, Hiroyuki Nakajima, Yutaka Iba, Yusuke Shimahara, Toshikatsu Yagihara

*Department of Cardiovascular Surgery, National Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan*

Received 6 September 2008; received in revised form 15 March 2009; accepted 16 March 2009; Available online 2 May 2009

## Abstract

**Objective:** Atrial fibrillation (AF) is the common arrhythmia associated with valvular heart disease, and surgical ablation to treat AF is reported to contribute to eliminate mortality and morbidity. We report our clinical results of cryomaze procedure obtained in over 10-years' experience. **Method:** Since 1998 when we introduced cryoablation to reduce cut-and-sew line, 268 patients (145 males and 123 females, mean age of 61.2-year old) underwent cryomaze procedure concomitant with mitral valve surgery. We retrospectively obtained preoperative and follow-up data from medical records, and investigated survival rate, freedom from permanent AF recurrence rate and risk factors for recurrence. **Results:** Three in-hospital deaths were noted (1.1%), and 243 patients (91.8% of survived patients) were discharged restoring to sinus rhythm. Pacemaker implantation during hospital stay was required in 12 cases (4.5%). There were five late deaths, and 5- and 10-year cumulative survival rates were both 93.2%. Multivariate analysis revealed that huge left atrium, longer history of AF and smaller f-wave in electrocardiogram were the independent risk factors for recurrence of permanent AF. Older age and re-do cardiac surgery were not significant factors. **Conclusion:** Cryoablation based maze procedure for AF adjunct to mitral valve surgery is an effective and long-term promising solution for restoring sinus rhythm. Patient selection criterion concerning left atrial size, duration of AF and f-wave voltage might be reasonable to improve the results. © 2009 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.

**Keywords:** Atrial fibrillation; Mitral valve; Cryoablation

## 1. Introduction

Atrial fibrillation (AF) is most the common arrhythmia associated with valvular heart disease, especially with mitral valve (MV) lesion. It is also important as a contributor to symptoms and mortality in patients with valvular disease [1,2]. More than 40% of patients referred for mitral valve surgery have persistent AF [3,4], which was reported to have the potential risk to induce stroke [1,5]. Cox maze III procedure is well known to be a reliable surgical option to eliminate AF [6], however, the original cut-and-sew method tends to be time-consuming and invasive with some complications. To simplify this procedure preserving its effectiveness, ablation with a variety of energy sources such as cryotherapy [1,7–9] or radiofrequency [10,11] as alternatives to the cut-and-sew method have been developed and those mid-term results have been reported to be satisfactory [9,11].

In 1998, we introduced cryoablation into Kosakai maze procedure [12] aiming to reduce the cut-and-sew line. Since then, we have adopted cryoablation based maze procedure as the first option of surgical treatment for AF in the patients with valvular heart disease.

In this article, we sought to investigate the long-term effectiveness of cryoablation based maze procedure and its risk factors for recurrence of AF in patients who underwent concomitant MV surgery.

## 2. Patients and methods

### 2.1. Patients

Between 1998 and December 2006, 268 consecutive patients, who underwent cryotherapy-based ablation for AF concomitant with mitral valve surgery, were enrolled in this study. In same period, radiofrequency ablation combined with MV surgery was carried out in 24 patients, mainly as surgeon's choice. Preoperative variables of the patients enrolled are demonstrated in Table 1. There were 145 males and 123 females with a mean age of 61.2-year old (range 26–82). Other preoperative patient characteristics were summarized in

<sup>☆</sup> Presented at the 22nd Annual Meeting of the European Association for Cardio-thoracic Surgery, Lisbon, Portugal, September 14–17, 2008.

<sup>\*</sup> Corresponding author. Tel.: +81 6 6833 5012; fax: +81 6 6872 7486.

E-mail address: jkobayas@hsp.ncvc.go.jp (J. Kobayashi).

Table 1  
Preoperative characteristics.

Variables	
Age (years old)	60.6 ± 10.2
Male/female	145/123
NYHA III–IV	25 (9.3%)
Paroxysmal AF	22 (8.2%)
Duration of AF (years)	5.6 ± 4.9
f-wave in V1 lead (mV)	0.16 ± 0.05
f-wave in V1 <0.1 mV	15 (5.6%)
Cardiothoracic ratio (%)	58.8 ± 6.4
Echocardiography	
LA diameter (mm)	57 ± 12
LVDd (mm)	53.9 ± 9.5
Fraction shortening (%)	33.7 ± 1.2
Mitral valve lesion	
MR	121 (45.1%)
MS	104 (38.8%)
MSR	43 (16.0%)
Comorbidity	
Renal dysfunction	28 (10.4%)
Cerebral infarction	12 (4.5%)
Diabetes melitus	30 (11.1%)

AF: atrial fibrillation, LA: left atrium, LVDd: left ventricular dimension in diastolic; MR: mitral valve regurgitation, MS: mitral valve stenosis, MSR: mitral valve stenosis and regurgitation. Renal dysfunction: serum creatinine >1.5 mg/dl.

**Table 1.** Sustained AF was 246 and paroxysmal AF was 22. In sustained AF patients, mean duration of AF was 5.6 years (range 2–16 years). Types of MV disease were regurgitation in 121, stenosis in 104, and combination of those in 43. All data were retrospectively obtained from medical records.

## 2.2. Surgical procedure

Standard cardiopulmonary bypass was established through median sternotomy via bicaval drainage, and cardiac arrest was obtained under aortic cross-clamping and repeated antegrade and retrograde cold blood cardioplegia. Surgery consisted of MV replacement or repair associated with endocardial cryothermic maze procedure to left and right atriums. Cryomaze procedure was achieved before valve surgery as described below. Anatomic exclusion of the left atrial appendage was performed in most patients by either oversewing the orifice of the appendage from within the atrium or by amputating the appendage externally.

## 2.3. Cryoablation

Our detailed procedure of cryoablation in maze procedure was reported previously [8]. In short, we incised right-sided left atrium as a usual MV exposure, and completed box typed PV isolation line using cryoablation. Additional cryoablation line is also made from PV isolation line to mitral annulus and left atrial appendage. To right atrium, cryoablation was performed between right atrial incision margin and each of the fossa ovalis, tricuspid valve annulus and orifice of inferior vena cava. Cryoablation was applied on the atrial endocardium at the target temperature of  $-80^{\circ}\text{C}$  cold for 2 min using two types of probe, linear and T-shaped, and  $\text{N}_2\text{O}$  system (CCS-200, Cooper Surgical, Shelton, CT).

## 2.4. Postoperative management

Electrocardiogram monitoring was continued to check cardiac rhythm until hospital discharge. Atrial pacing using a temporary lead placed during operation was maintained for several days. During the hospital stay, recurrence of AF or atrial flutter was treated with intravenous infusion of group Ia or Ic anti-arrhythmic drug. If those were ineffective, oral administration of either drug was initiated and cardioversion was attempted 4–5 days later. To treat own high ventricular rate, beta blocker or calcium blocker was added if necessary. All patients routinely received oral coumadin administration for at least 3 months regardless of the type of mitral valve surgery and postoperative rhythm. It was discontinued within 3–6 months in the patients who underwent valve plasty or replacement using bioprosthesis and had no recurrence of AF. After hospital discharge, ECG was routinely checked in outpatient clinic every 6–12 months regardless of symptoms. If a patient came with any symptoms including palpitation or faintness, Holter ECG was carried out to detect arrhythmic event.

## 2.5. Statistical analysis

Continuous data are expressed as mean ± standard deviation. Categorical data are expressed as frequency and percentage. The Kaplan–Meier method was used to depict cumulative survival and freedom from the recurrence of permanent AF. Fisher's exact test was used to make statistical comparison between groups for categorical items. Logistic regression was used to examine predictors of the recurrence of permanent AF and was reported as odds ratio and 95% confidence intervals. The differences were estimated as significant at a *p* value less than 0.05.

## 3. Results

### 3.1. Intraoperative results

As a concomitant MV operation, valve replacement was performed in 170 cases (mechanical valve 153, biological valve 17), MV plasty in 94 and open MV commissurotomy in 4. As other concomitant operations, aortic valve replacement was done in 70 patients, tricuspid annuloplasty in 62 and coronary artery bypass grafting in 15. Eighteen of 268 cases were re-do cardiac surgery. Cardiopulmonary bypass time was  $165 \pm 52$  min and aortic cross-clamping was  $121 \pm 40$  min (Table 2).

### 3.2. Short-term results

In-hospital mortality occurred in three patients (1.1%), and the causes of death were cerebral bleeding, myocardial infarction and mediastinitis, respectively. During hospital stay, 135 of survived 265 patients (50.9%) experienced recurrence of AF or atrial flutter. After treating by anti-arrhythmic drug or cardioversion as described above, 243 patients (91.8% of survived patients) discharged with sinus rhythm. Pacemaker implantation during hospital stay was required in 12 cases (4.5%).

Table 2  
Operative variables.

Variables	
Concomitant procedure	
MV replacement	170 (63.4%)
Mechanical/biologic	153/17
MV plasty	94 (36.6%)
Open commissurotomy	4 (1.5%)
Aortic valve surgery	70 (26.1%)
Tricuspid annuloplasty	62 (23.1%)
CABG	15 (5.6%)
Re-do heart surgery	18 (6.7%)
CPB time (min)	165 ± 52
AXC time (min)	121 ± 40
Blood loss in operation (ml)	890 ± 440

MV: mitral valve, CABG: coronary artery bypass grafting, CPB: cardio-pulmonary bypass, AXC: aortic cross-clamp.

### 3.3. Late outcome

Among 265 patients who were discharged from hospital, long-term follow-up was achieved in 247 patients (93.2%), and averaged follow-up period was 3.8 years. There were five late deaths, and the causes of those were cerebral infarction in two, cancer in two and heart failure in one, and 5-year and 10-year cumulative survival rate were 93.2%. Thirty-one patients experienced AF during follow-up and cardioversion was successful to obtain sinus rhythm in 10 patients. Therefore, conversion to permanent AF in follow-up period was detected in 21 patients. The actuarial freedom rate from recurrence of permanent AF at three years and five years was 84.1% and 80.2%, respectively. Pacemaker implantation in follow-up period was performed in 10 patients; therefore overall implantations were 22 cases (8.3%).

### 3.4. Risk analysis for recurrence of permanent AF

Comparison of variables between patients with and without recurrence of permanent AF postoperatively is shown in Table 3, and some variables were revealed as a risk factor of recurrence. In multivariate risk analysis with a logistic regression model, left atrium larger than 70 mm (OR = 4.9,  $p = 0.0016$ ), f-wave in V<sub>1</sub> lead smaller than 0.1 mV (OR = 6.1,  $p < 0.001$ ) and AF duration longer than 10 years (OR = 5.2,  $p = 0.046$ ) were demonstrated to be significant risk factors for recurrent AF (Table 4). Although patients older

Table 3  
Univariate analysis for permanent AF recurrence.

Variables	AF rec. (-) N = 204 (%)	AF rec. (+) N = 43 (%)	p value
Age >70 years old	27 (13.2)	10 (23.3)	0.079
Gender (male)	111 (54.4)	19 (44.2)	0.300
NYHA III–IV	19 (9.3)	6 (13.6)	0.083
Fraction shortening <20%	4 (2.0)	2 (4.7)	0.102
Renal dysfunction	22 (9.2)	3 (6.8)	0.091
Cerebral infarction	6 (2.9)	2 (4.7)	0.221
Re-do surgery	12 (5.9)	6 (13.6)	0.045
Duration of AF >10 years	8 (39.2)	7 (16.3)	0.0016
LA diameter >70 mm	12 (5.9)	9 (20.9)	0.0011
f-wave in V <sub>1</sub> lead <0.1 mV	3 (1.5)	12 (27.9)	<0.001
Fraction shortening <25%	8 (3.9)	3 (6.9)	0.088

AF rec.: permanent atrial fibrillation recurrence, LA: left atrium. Renal dysfunction: serum creatinine >1.5 mg/dl.

Table 4  
Multivariate risk analysis for recurrence of permanent AF.

Variables	Odds ratio	95% CI	p value
Age >70 years old	1.7	0.7–4.1	0.244
Re-do surgery	1.8	0.8–6.5	0.091
Duration of AF >10 years	5.2	3.8–16.2	0.046
LA diameter >70 mm	4.9	2.8–13.1	0.0016
f-wave in V <sub>1</sub> lead <0.1 mV	6.1	4.8–15.2	<0.001

LA: left atrium.

than 70 years old or those who underwent re-do cardiac surgery were recognized as being high risk for the post-operative recurrence of permanent AF by univariate test, those were not significant by subsequent multivariate analysis ( $p = 0.244$  and  $p = 0.921$ ).

## 4. Discussion

The rationale for restoring sinus rhythm includes improving survival, lessening the risk of thromboembolism, eliminating the necessity for oral anticoagulation, preserving atrial contraction and improving cardiac output. To achieve this, Cox and colleagues promoted surgical ablation of AF [6,13]. After that, some major modifications, such as cryoablation [1,7–9], radiofrequency [10,11], microwave [14] so on, were launched to minimize the invasive, time consuming and complicating aspects of the cut-and-sew technique.

In this report, we document the mid- to long-term results of the introduction of cryoablation to treat AF in patients undergoing mitral valve surgery. Among the enrolled 268 patients, 22 patients failed to be converted to sinus rhythm during hospital stay, and the others (91.8%) were discharged restoring sinus rhythm. Freedom from AF recurrent rate at three and five years was 84.1 and 80.2%, respectively. Khargi and colleagues who reviewed clinical results of 48 manuscripts, reported postoperative SR conversion rate in the group, which was treated using an alternative energy source, was 84.9% (ranged 42–92%), whereas those in Cox maze III group was 78.3% [15]. Compared to those results, our short-term as well as long-term clinical achievement is satisfactory (Figs. 1 and 2).

Some patients have a higher risk for failure or recurrence even though the maze procedure is carried out precisely. We previously reported risk factors for recurrence of AF after Cox

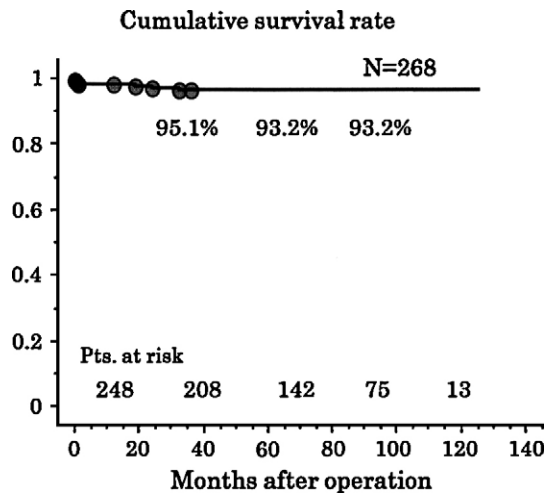


Fig. 1. Cumulative survival curve.

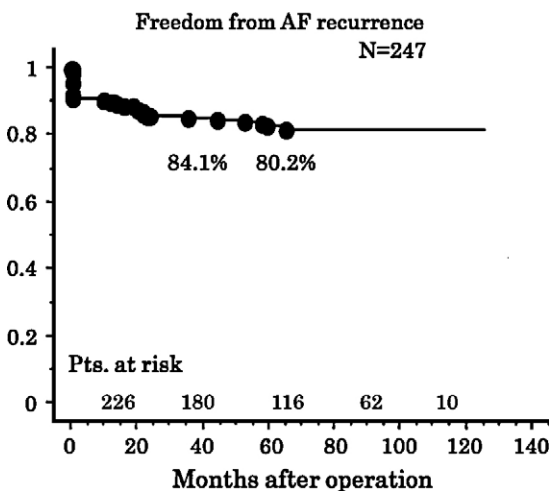


Fig. 2. Freedom from permanent AF recurrence curve.

maze III or its Kosakai modification as huge left atrium and lower voltage of f-wave in electrocardiogram [16]. According to these results, we established the patient selection criterion as follows; (1) left atrium diameter in echocardiography <70 mm, (2) cardiothoracic ratio in chest X-ray <70% and (3) f-wave voltage in V1 lead >0.1 mV [16]. In addition, we set relative indication criterion as (1) younger patients than 70 years old, (2) primary cardiac surgery cases and (3) shorter than 10 years AF duration. Since 1998, we applied the criterion basically to indicate maze procedure. However, we were encouraged to perform cryomaze on border line cases or younger patients who were out of criterion, because the introduction of cryomaze procedure had successfully reduced operation time and related morbidity with successful clinical results [8,9]. Therefore, in this series of cryomaze procedure, some patients who were out of the criterion were included.

The important issue of the ablation using the alternative energy source is the accuracy of the continuity and transmural of the induced block lesions. Especially in cryoablation, it seems to be difficult to verify them in the

operation. The acceptable sinus rhythm recovery rate we achieved in this series supported the reliability of cryoablation in its continuity and transmural.

The advantage of cryoablation also exists in its economical aspect. Obviously the cut-and-sew method, which requires no special device, is most economical. Cryoablation is as economical because the probe used for it is possible to be sterilized for repeated use, while devices for radiofrequency ablation are usually disposable.

The limitations of this series of study include the essential confines of retrospective data collection. Since 24 h ECG was not performed routinely, ECG recorded at outpatient clinic was the only material to judge patients' rhythm, leading to underestimation or overestimation of the prevalence of AF.

In conclusion, surgical treatment of AF using cryoablation in patients undergoing MV surgery is a reliable option providing satisfactory sinus restoring rate and economical advantage as well. Small f-wave, long AF duration and huge left atrium are significant risk factors for recurrence of permanent AF.

## References

- [1] Kobayashi J, Sasako Y, Bando K, Niwaya K, Tagusari O, Nakajima H, Ishida M, Kitamura S. Eight-year experience of combined valve repair for mitral regurgitation and maze procedure. *J Heart Valve Dis* 2002;11:165–71.
- [2] McCarthy PM, Castle LW, Maloney JD, Trophaman RG, Simmons TW, White RD, Klein AL. Initial experience with the maze procedure for atrial fibrillation. *J Thorac Cardiovasc Surg* 1993;105:1077–87.
- [3] David TE, Armstrong S, Sun Z, Daniel L. Late results of mitral valve repair for mitral regurgitation due to degenerative disease. *Ann Thorac Surg* 1993;56:7–12.
- [4] Alvarez JM, Deal CW, Loveridge K, Brennan P, Eisenberg R, Ward M, Bhattacharya K, Atkinson SJ, Choong C. Repairing the degenerative mitral valve: ten to fifteen-year follow-up. *J Thorac Cardiovasc Surg* 1996;112:238–47.
- [5] Bando K, Kobayashi J, Kosakai Y, Hirata M, Sasako Y, Nakatani S, Yagihara T, Kitamura S. Impact of Cox maze procedure on outcome in patients with atrial fibrillation and mitral valve disease. *J Thorac Cardiovasc Surg* 2002;124:575–83.
- [6] Cox JL, Schuessler RB, Boineau JP. The development of the maze procedure for the treatment of atrial fibrillation. *Semin Thorac Cardiovasc Surg* 2000;12:2–14.
- [7] Kosakai Y, Kawaguchi AT, Isobe F. Modified maze procedure for patients with atrial fibrillation undergoing simultaneous open heart surgery. *Circulation* 1993;92:1359–64.
- [8] Nakajima H, Kobayashi J, Bando K, Niwaya K, Tagusari O, Sasako Y, Nakatani T, Kitamura S. The effect of cryo-maze procedure on early and intermediate term outcome in mitral valve disease: case matched study. *Circulation* 2002;106:146–50.
- [9] Izumoto H, Kawazoe K, Eishi K, Kamata J. Medium-term results after the modified Cox/Maze procedure combined with other cardiac surgery. *Eur J Cardiothorac Surg* 2000;17:25–9.
- [10] Mokadam NA, McCarthy PM, Giltinov AM. A prospective multicenter trial of bipolar radiofrequency ablation for atrial fibrillation. *Ann Thorac Surg* 2004;78:1665–70.
- [11] Doukas G, Samani NJ, Alexiou C, Oc M, Chin DT, Stafford PG, Ng LL, Spyt TJ. Left atrial radiofrequency ablation during mitral valve surgery for continuous atrial fibrillation. *JAMA* 2005;294:2323–9.
- [12] Kosakai Y, Kawaguchi A, Isobe F, Sasako Y, Nakano K, Eishi K, Tanaka N, Kito Y, Kawashima Y. Cox maze procedure for chronic atrial fibrillation associated with mitral valve disease. *J Thorac Cardiovasc Surg* 1994;108:1049–55.
- [13] Cox JL, Schuessler RB, Demetrios GL, Voineau JP. An 8 1/2-year clinical experience with surgery for atrial fibrillation. *Ann Surg* 1996;224:267–75.
- [14] Knaut M, Tugtekin SM, Spitzer S, Gulielmos V. Combined atrial fibrillation and mitral valve surgery using microwave technology. *Semin Thorac Cardiovasc Surg* 2002;14:226–31.

- [15] Khargi K, Hutten BA, Lemke B, Deneke T. Surgical treatment of atrial fibrillation: a systematic review. *Eur J Cardiothorac Surg* 2005;27:258–65.
- [16] Kobayashi J, Kosakai Y, Nakano K, Sasako Y, Eishi K, Yamamoto F. Improved success rate of the maze procedure in mitral valve disease by new criteria for patients' selection. *Eur J Cardiothorac Surg* 1998;13:247–52.

## Appendix A. Conference discussion

**Dr S. Benussi (Milan, Italy):** I think this is a very interesting contribution for a number of reasons. It entails a large series of patients. It comes from a center with a great experience in the field, and most importantly, it depicts long-term follow-up results, which are not very commonly described, in atrial fibrillation surgery. I have got a comment and a few questions.

Last year the Heart Rhythm Society produced a consensus statement setting the standards for reporting the results on atrial fibrillation ablation in general and also for atrial fibrillation surgery. In particular, it seemed convenient to such a consensus statement to classify preoperative atrial fibrillation as paroxysmal, persistent, or long-standing persistent, which we may define also permanent, and to follow up patients with at least, as a minimum requirement, Holter monitoring, which is definitely agreeable.

Furthermore, the consensus statement solicited to report results of the ablation in terms of freedom from arrhythmia recurrence of anti-arrhythmic drugs.

So although obviously I realize the difficulties of complying with such guidelines while dealing with patients operated 10 years before the consensus statement was actually produced, I've got a couple of issues with your follow-up results.

First of all, I'd like to know what the rate of freedom from recurrence is off drug or at least off class 1, class 3 anti-arrhythmic medications at five and ten years follow-up. Do you want to answer point by point?

**Dr Funatsu:** Yes, I answer one by one.

Class 1A or 1C drug was used if postoperative AF recurred. So after using that, average AF-free rate at five years was 80% as I said in the presentation.

**Dr Benussi:** What percentage of those patients were free of any anti-arrhythmic medication?

**Dr Funatsu:** I'm sorry?

**Dr Benussi:** Of those 80% of patients in sinus rhythm, how many are having no drugs?

**Dr Funatsu:** Okay. No drugs was about 80%, I mean, 20% of the recurrence-free patient having some kind of anti-arrhythmic drug.

**Dr Benussi:** Okay. So regarding follow-up method, I think it's key to have at least Holter recordings to assess freedom from AF recurrence after surgery especially when you deal with patients with paroxysmal atrial fibrillation, like in this series. Otherwise, how can you say those patients do not have any asymptomatic episode of paroxysmal atrial fibrillation based only on separate ECG recordings?

**Dr Funatsu:** We check the result on the ECG based in the outpatient clinic. So paroxysmal afib is very difficult to detect. In fact, it is a limitation of this study.

But if the patient had some symptom, we check the ECG, 24 h ECG, and paroxysmal afib may be detected.

**Dr Benussi:** I see. I've got one last issue. I see your pacemaker requirement intraoperatively or before discharge is consistently low. I think less than 5% is very reasonable for biatrial ablation procedure.

And actually it is remarkable that there are series dealing with standard maze III procedure in which the rate of pacemaker implantation is much higher. I should say somewhere around 8–15, even 20% in some cases.

What do you think are the reasons for such a good percentage of pacemaker implantation in your series?

**Dr Funatsu:** Regarding to pacemaker implantation, I think one reason for this small rate of pacemaker implantation is maybe our simple lesion set that we don't operate cryoablation aggressively especially to the right atrium to avoid sinus node injury. However, postoperative flutter is not frequent.

I think that pacemaker implantation correlates with AF history, so sinus node function may be impaired during a long AF history. But in our series, patients with longer AF history were not included, so this is the second reason I think.