

Randomized Study of Surgery for Patients With Permanent Atrial Fibrillation as a Result of Mitral Valve Disease

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Background. The Cox Maze procedure has been used to treat atrial fibrillation in patients with mitral valve disease. Recently, ectopic foci, originating in the pulmonary veins, were demonstrated in patients with atrial fibrillation, and the indication was that their arrhythmia could have a focal origin. In the light of this new evidence, a simplified surgical technique to isolate the pulmonary veins was developed to eliminate permanent atrial fibrillation in patients undergoing mitral valve surgery. This study compares three surgical procedures proposed to maintain sinus rhythm after mitral valve surgery.

Methods. A prospective clinical trial of 30 patients with mitral valve disease and permanent atrial fibrillation who had undergone mitral valve surgery were randomized in accordance with the type of surgery used on each: (1) associated en bloc isolation of pulmonary veins, (2) the Maze procedure, or (3) mitral valve correction alone. The preoperative clinical characteristics were similar in the three groups.

Results. The overall postoperative complications were similar in all three groups. The cardiopulmonary bypass time and the aortic cross-clamping time were shorter in the control group, but this factor bore no relation to increased morbidity in the intervention groups. The relative risk of atrial fibrillation after surgery was 0.08 in the group undergoing isolation of pulmonary veins ($p = 0.010$; 95% confidence interval, 0.01 to 0.71) and 0.20 in the Maze group ($p = 0.044$; 95% confidence interval, 0.04 to 1.02) compared with the control group.

Conclusions. En bloc isolation of pulmonary veins associated with mitral valve surgery appears to be safe and just as effective as the Maze procedure in maintaining sinus rhythm in patients with permanent atrial fibrillation.

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Atrial fibrillation (AF) is a common arrhythmia and often occurs in patients with mitral valve disease. Surgical correction of the valve rarely eliminates the arrhythmia [1–3]. Approximately 75% of patients who had permanent AF before their mitral valves were corrected continued to suffer from AF after the surgery [1, 2, 4, 5].

Harada and colleagues [6] suggested that AF is initiated by electrical discharges from the left atrium (LA) in patients with mitral valve disease. Morillo and associates [7] demonstrated that cryoablation limited to the LA posterior wall was sufficient to eliminate chronic AF in dogs. Haïssaguerre and coworkers [8] showed that ectopic trigger points inside the pulmonary veins provoke paroxysmal AF and that the ablation of these foci can eliminate the arrhythmia. Therefore, since the Maze procedure was developed [9], simpler surgical approaches have emerged for the treatment of AF. For instance, Sueda and colleagues [10] and Melo and co-

workers [11] used limited incisions to the LA posterior wall for isolation of the pulmonary veins. However, such approaches to restore sinus rhythm have not been thoroughly evaluated.

We took as a starting premise that permanent AF in patients with mitral valve disease can be eliminated by isolation of the pulmonary veins during the valve surgery. The present randomized study investigates this premise by comparing the relative effectiveness in maintaining sinus rhythm in patients undergoing (1) en bloc isolation of the pulmonary veins (PVI), (2) the Maze procedure, and (3) mitral valve surgery by itself.

Patients and Methods

Sample and Designs

Patients referred to mitral valve surgery who fulfilled the clinical and hemodynamic criteria for elective mitral surgery were selected. We chose those between 18 and 75 years of age who had had permanent AF lasting for more than 6 months before the surgery. Patients who had undergone previous cardiac surgery, who were pregnant, or whose ventricular ejection fraction was less than 0.20

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were excluded. Every patient understood and signed a consent and release form before participating in the study. The approval of the institutional ethical committee was August 9, 1999.

In the period between June 1999 and February 2001 30 patients with permanent AF and mitral valve disease were randomly divided into three groups of 10 patients each, using a system of 30 sealed envelopes to ensure a blind selection. These groups were to undergo one of three procedures: (1) valve correction plus surgical en bloc isolation of the pulmonary veins (PVI group); (2) valve correction plus Maze procedure without cryoablation (Maze group); and (3) mitral valve correction by itself (control group). The main effect to be observed was sinus rhythm maintenance after mitral surgery. The groups were kept under follow-up observation after the surgery during periodic visits to previously agreed outpatient clinics 2, 6, 12, 18, and 24 months after surgery. Electrocardiogram (ECG) and echocardiography were performed preoperatively and postoperatively. Exercise tolerance tests and 24-hour ECG monitoring were also performed at 6 months' follow-up.

Echocardiograms were performed throughout by a single operator (Sonos 2500 system; Hewlett Packard, Andover, MA) with a multifrequency transducer from 2 to 2.5 MHz to measure the atrial transport function using maximum and minimum volumes derived from an area over length calculation. From the results it was possible to estimate the LA ejection fraction.

Exercise tests were performed using the Bruce protocol [12] to evaluate the maximum effort each patient could attain. Patients were classified as having an adequate chronotropic response if they had attained 85% of what was predicted for their age or an inadequate if they achieved less than 70% of the predicted value.

Twenty-four-hour ECG monitoring examinations (Holter ECG) were performed using a DMI-Cardiology (Burdick, Deerfield, WI) analysis center, and analyzed by the same operator blinded for the patient group. Rhythm was analyzed and characterized based on the P-wave morphology in V_2 and V_5 leads, and rhythm stability was confirmed by the visual analysis of the overall monitoring result.

During the early postoperative period, atrial tachyarrhythmias (fibrillation or flutter) were aggressively treated by pharmacologic or electrical cardioversion, and sinus rhythm was maintained by the use of amiodarone for at least 30 days. Patients who exhibited recurrent AF were excluded from the follow-up analyses of the sinus rhythm maintenance.

Surgical Techniques

Patients from the Maze group underwent a modification of the Cox Maze III surgery [1]. All incisions in this technique were performed, but ablation of the terminal points of the incisions was performed by electrocoagulation instead of the cryoablation used in the original technique. The incisions were sutured and the valve lesion was corrected. The right side lesions of the Maze III procedure were repaired without heart arrest.

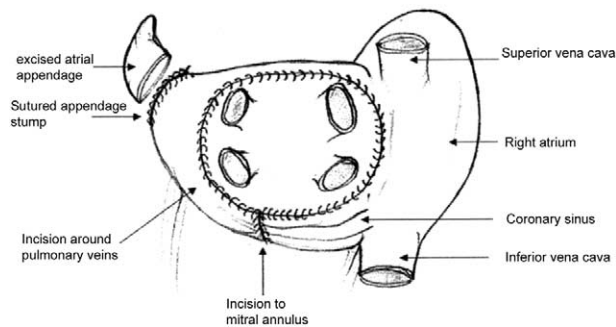


Fig 1. Posterior view of the heart after the procedure, showing the isolation of the pulmonary veins. (Reprinted with permission from The Society of Thoracic Surgeons [Ann Thorac Surg 2002, 73, 1169-73] [23].)

The following technique was used in the PVI group: left atriotomy was performed with the incision line running parallel to the interatrial sulcus. This incision was extended around the four pulmonary veins. Then the mitral valve was examined and treated according to the lesion. After valve repair, the circular incision was completed to isolate this region from the rest of the heart. Then, a right-angled incision was made, beginning at the lower border of the incision that isolates the pulmonary veins and extending to the mitral valve annulus. Electrocautery was applied to the tissues next to the mitral valve annulus. This incision in the mitral annulus was made with a pair of scissors, taking care to cut only the myocardial tissue and preserving the fat pad including the coronary arteries and coronary sinus. This incision was extended until it reached the fibrous tissue of the mitral annulus and a small area of ventricular muscle could be observed. Then, the end of the incision and the extent of the fat pad were sealed by electrocautery, trying to eliminate all remaining atrial muscle fibers. Suturing with running 3-0 propylene was then initiated from the mitral annulus back to the rest of the incision. Immediately afterward, the aortic clamp was removed, and during myocardial reperfusion, the LA appendage was amputated and sutured externally.

Differently from the Cox-Maze procedure, no incision was performed between the LA appendage suture line and the circular suture around the pulmonary veins. Cryoablation or radiofrequency were never used. No incision was performed in the right atrium or atrial septum (Fig 1). Mitral valve repair or replacement was performed in the control group, and LA appendage exclusion by pursestring suture was performed on patients in whom thrombi were found inside the LA appendage.

Statistical Analysis

Quantitative variables were presented as mean and standard deviation. Group comparisons were made by one-way analysis of variance followed by Duncan's post hoc test. The analysis of variance was repeated to study changes in heart rate with time. For categorical data we used frequencies, percentages, and the χ^2 or Fisher's exact test to check for statistical significance.

Table 1. Clinical Characteristics^d

Characteristics	PVI (n = 10)	Maze (n = 10)	Control (n = 10)	Total (n = 30)	p Value
Age (y)	54.1 ± 9.4	50.1 ± 15.3	50.1 ± 15.4	51.4 ± 13.3	0.754 ^a
Female (%)	70	70	40	60	0.287 ^b
AF duration (months)	23 (15–24)	14 (9–63)	16.5 (13–24)	18 (11.8–42.8)	0.656 ^c
LVEF	0.64 ± 0.12	0.643 ± 0.075	0.64 ± 0.095	0.64 ± 0.10	0.998 ^a
LA (cm)	5.3 ± 0.9	6 ± 1.6	6.2 ± 1.2	5.8 ± 1.3	0.273 ^a
NYHA	2.9 ± 0.7	2.9 ± 0.7	3.2 ± 0.8	3.0 ± 0.7	0.581 ^c
I	
II	3	3	2	8	
III	5	5	4	14	
IV	2	2	4	8	
Mitral lesion					
Stenosis	5	4	2	11	
Regurgitation	4	5	5	14	0.555 ^b
Stenosis + regurgitation	1	1	3	5	
Etiology					
Rheumatic	8	7	7	22	0.843 ^b
Degenerative	2	3	3	8	

^a Analysis of variance test. ^b χ^2 test. ^c Kruskal-Wallis test. ^d Data are presented as mean ± standard deviation, frequency (%) and median (25th–75th percentiles).

AF = atrial fibrillation; LA = left atrium; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association functional class; PVI = en bloc isolation of pulmonary veins.

To evaluate the occurrence of AF events among groups, we used incidence rates based on patient-months (incidence densities), calculating relative risks and their 95% confidence intervals. Additionally Kaplan-Meier survival curves were plotted with the significance established by log rank test. The significance level was set to $\alpha = 0.05$. Data were analyzed with SPSS for Windows version 10.0 (Chicago, IL).

Results

As shown in Table 1, clinical characteristics were similar in all groups. Number of days in the hospital of the three groups was also similar ($p = 0.240$). There was one hospital death on the 57th postoperative day, caused by sepsis, in a patient who underwent the Maze procedure. No other death occurred throughout the follow-up. One redo surgical intervention was necessary because of bleeding and hemopericardium in a patient of the control group. This patient suffered a stroke and pulmonary embolism, but exhibited a favorable clinical outcome. Four patients had previous history of stroke but only 1 had cerebral ischemia during the postoperative period. No patient required a permanent pacemaker during follow-up. There was one case of intestinal bleeding, during the second postoperative week, which required surgical intervention. There were no other major complications.

Twenty-one patients (70%) underwent mitral repair, 5 patients received a biologic prosthesis, and 4 received a mechanical prosthesis. Two patients had a biologic mitral prosthesis implanted in the PVI group, 2 in the Maze

group, and 1 in the control group. One patient had an implant of a mechanical prosthesis in the PVI group, none in the Maze group, and 3 in the control group.

Mitral repair or replacement and associated aortic or tricuspid surgeries were similar in all groups ($p = 0.62$). The mean cardiopulmonary bypass time in the PVI group (97.8 ± 3 minutes) was approximately 20 minutes shorter than in the Maze group (115.3 ± 25 minutes), but this difference was not statistically significant ($p > 0.05$). As expected, the cardiopulmonary bypass time (68.3 ± 22 minutes) and the aortic cross-clamping time (49.1 ± 19 minutes) were markedly less in the control group ($p = 0.009$).

Rhythm

As Maze surgery distorts P-wave morphology on ECG, we considered both sinus rhythm and atrial rhythm as successful results.

The results showed a marked decrease in the recurrence of AF in the intervention groups with a strong protector effect for AF recurrence in the PVI (relative risk, 0.08) and Maze groups (relative risk, 0.2) compared with the control group (Table 2).

When analyzing the data by using Kaplan-Meier curve, we found the proportion of individuals free of AF events after 18 months for the control, Maze, and PVI groups to be 40%, 80%, and 90%, respectively (Fig 2).

Thromboembolic Events and Anticoagulation

Only 1 patient suffered a stroke during the postoperative period, after having undergone reintervention because of

Table 2. Recurrence of Atrial Fibrillation According to Surgical Technique

Group	AF events	Patient-months	AF incidence (per 100 patients-month)		RR	95% CI ^a	p Value ^b
			AF incidence	RR			
Control	5	61.77	8.10	1	
Maze	2	124.50	1.61	0.20	0.04-0.89	0.044	
PVI	1	148.70	0.67	0.08	0.01-0.54	0.02	

^a Cornfield method. ^b Fisher's exact test.

AF = atrial fibrillation; CI = confidence interval; PVI = en bloc isolation of pulmonary veins; RR = relative risk; SR = sinus rhythm.

surgical bleeding. This patient had a previous history of ischemic stroke.

Fifty percent of the patients received oral anticoagulants at some time during the postoperative period, as prescribed by their physician. Five patients receiving sodium warfarin at the last visit were part of the PVI group, 1 was in the Maze group, and 10 were in the control group ($p < 0.001$; Table 3).

Functional Class

Patients in all groups exhibited a significant improvement in New York Heart Association functional class. Although during the preoperative period the patients of all groups had similar classifications and none were in class I, 83% had attained this functional class when examined at the last clinical visit after the operation. Also no relevant differences were observed in functional classification when the groups ($p = 0.45$) or rhythm (sinus or AF) were evaluated during the postoperative period ($p = 0.37$). The improvement in the functional class was the result of the mitral valve corrections, and occurred in a similar manner in all three intervention groups.

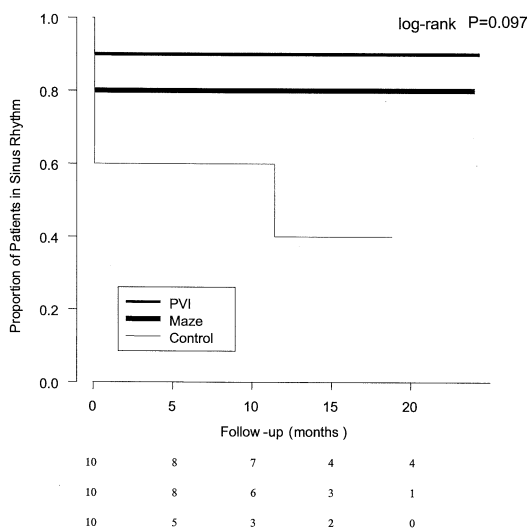


Fig 2. Kaplan-Meier chart showing the proportional number of patients in sinus rhythm as a function of time, in accordance with the surgical technique. (PVI = isolation of pulmonary veins.)

Table 3. Anticoagulants and Antiarrhythmic Agents Used at Last Visit According to Surgical Technique

Medication	PVI (n = 10)	Maze (n = 10)	Control (n = 10)	Total (n = 30)	p Value ^a
Warfarin	5	1	10	16	<0.001
Digoxin	6	4	8	18	0.248
Amiodarone	4	2	5	11	0.510

^a Fisher's exact test.

PVI = en bloc isolation of pulmonary veins.

Antiarrhythmic Agents

Pharmacologic agents used during follow-up to control the arrhythmia were digoxin, amiodarone, and sotalol. Ten patients were receiving digoxin, 3 patients were using amiodarone, and 8 were receiving both antiarrhythmic drugs. Only 1 patient, in the control group, used sotalol during follow-up (Table 3). The other 8 patients were not using antiarrhythmic drugs. No additional β -adrenergic blocker was used in the study cohort.

Sixteen patients underwent electrical cardioversion after surgery. The time between surgery and electrical cardioversion and the number of attempts of cardioversion were similar in all groups.

Echocardiography

After surgery a reduction in the mean LA size in the three groups ($p < 0.001$) was observed. This was smaller in the PVI group (4.6 ± 0.9 cm) as compared with the Maze group (5.4 ± 1.2 cm) and the control group (5.6 ± 0.9 cm), but the difference did not attain statistical significance ($p = 0.109$). Analysis performed according to the rhythm at the postoperative period showed that those in sinus rhythm exhibited significantly smaller LAs ($p = 0.034$).

The mean LA ejection fraction after surgery was similar in the three groups ($p = 0.35$). However, those patients in sinus rhythm exhibited larger LA ejection fractions ($p = 0.036$). Multiple linear regression analysis showed that the sinus rhythm leading to an increase in the LA ejection fraction was independent of the surgical group ($p = 0.063$).

Exercise Testing

Only patients in sinus rhythm underwent exercise testing. After 12 months, the PVI group exhibited a better chronotropic response to exercise than the control group (86.2% versus 64.1%). The improvement, however, was statistically only marginally significant when measured by analysis of variance, but did show statistical significance when the Duncan test ($p < 0.05$) was used.

The Maze group had a better chronotropic response to exercise than the control group (80.5% versus 64.1%), and showed the same differences between the analysis systems as the PVI group.

Twenty-four-Hour Outpatient Electrocardiogram

Twenty patients with sinus rhythm before examination underwent the 24-hour Holter ECG. Test. The recorded results did not show any AF or atrial flutter. There were

pauses of more than 2 seconds in 2 patients, who were asymptomatic and did not require specific treatment.

The differences in heart rate variability among the three groups were not statistically relevant.

Comment

Until recently, AF treatment [4, 13] focused on self-perpetuating anatomic substrate. However, premature atrial beats may act as a trigger for early or late recurrence of the arrhythmia after cardioversion, even in patients with permanent AF [14, 15].

Studies with animals [16] and humans [8, 17] showed that ablation of certain atrial regions might cure AF. Atrial mapping data suggested that the posterior region of the LA appears to be critical for AF maintenance, even in patients with mitral valve disease [6, 10]. Several publications showed different patterns of electrical activity in different atrial regions during AF, with regular activity in the LA and irregular and chaotic activity in the right atrium [7, 10, 17]. Recently the Bordeaux group [8] showed that ablation of ectopic beats inside the pulmonary veins with a radiofrequency catheter was effective for long-term elimination of arrhythmia. Because of this nonpharmacologic treatment techniques were concentrated on the LA.

Sueda and associates [10] have developed a surgical technique for treatment of permanent AF in patients with mitral valve disease, which principally involved the posterior region of the LA. Six months after surgery, 78% of patients did not exhibit AF, and 61% had recovered LA contractility. Long-term results showed an actuarial proportion of 74% for the elimination of AF [18]. Other authors [19, 20] have also developed surgeries involving the posterior region of the LA, and using cryoablation, radiofrequency [19-22], or surgical incisions [19, 23] have succeeded in maintaining the sinus rhythm at 70% to 80% over the medium term.

In our study the PVI and Maze groups exhibited AF rates statistically lower than that found for the control group ($p < 0.05$). Despite the large differences observed, it is surprising that the analysis based on Kaplan-Meier curves and the log rank test were not statistically significant ($p = 0.097$). Incidence rate analysis (based on incidence densities) and the Kaplan-Meier method, although theoretically related, may produce slightly different results. The reason for this is that these techniques use different algorithms that can lead to discrepancies, particularly when small samples are concerned. Our results agree with previous studies that point out the importance of the LA for AF recurrence, even in patients with mitral valve disease. Thus, at least in a significant number of patients, permanent AF depends considerably on the pulmonary veins region for self-perpetuation.

The use of antiarrhythmic agents in postoperative periods probably did not influence the main results. They were used in the same proportion in all the surgical groups so that any effects would be found in all the results, but there remains a possibility that they might

have interfered with the chronotropic response to exercise.

Cardiopulmonary bypass time and the aortic cross-clamping time were longer in the intervention groups than in the control group, but this was not related to higher morbidity or longer hospital stay. Cardiopulmonary bypass time was 18 minutes longer in the Maze group than in the PVI group, but this difference was not statistically significant, and was probably related to the small size of the sample.

At the last clinical visit, the patients in the control group had used more anticoagulation than those in the intervention groups. There has not been sufficient follow-up to support a firm assertion that these surgical techniques for AF really reduce the risk of thromboembolic phenomena. Although the improvements observed are almost certainly the result of better maintenance of sinus rhythm and surgical removal of the LA appendage, final proof is still to be provided.

All three procedures caused a considerable reduction in the LA size, the magnitude of which was the similar in all procedures. This was probably caused by mitral valve correction resulting in LA pressure relief. Echocardiographic analysis showed that patients in sinus rhythm during the postoperative period had a smaller LA during the preoperative period than those who remained in AF after surgery.

Patients in the PVI and Maze groups had longer periods of sinus rhythm maintenance than the control group. This was more likely the result of isolation of the arrhythmia-triggering foci than of a simple reduction in LA size. The fact that patients in sinus rhythm achieved a greater LA ejection fraction during the postoperative period than patients in AF shows the importance of this rhythm maintenance, no matter what type of surgery was used.

There was only a single death, which could not be directly attributed to surgery for AF. This death, and the complications that occurred during the study, was caused by events specifically related to valve surgery.

We consider that this simplified surgical procedure presents several advantages, such as simpler surgical technique, no need for cryoablation, and less risk of damaging the atrial myocardium and the sinus node artery. Although at this time our own experience is somewhat limited, other authors appear enthusiastic about similar simplified procedures [24]. Possibly this technique should be disseminated more widely among surgery centers as it is effective and does not require either new technical resources or additional training of surgical teams.

We believe that patients who have an indication for mitral surgery and exhibit permanent AF should be considered for concurrent AF surgery. Avoidance of the risk of arrhythmia during the postoperative period and the current success of these techniques justifies the longer surgical time. However, larger scale studies must be carried out to confirm our findings and evaluate the resulting survival and quality-of-life rates for a longer period.

Although surgeons are currently using technical improvements, such as radiofrequency catheters, which can rapidly create long blockade lines [25], and new sources

of energy, such as cryoablation, which can be used even by epicardial approach [26], in the technique used here no special device was necessary. The surgical approach seems to be familiar to all cardiac surgeons and is really simpler than the Cox Maze procedure.

Our study had some limitations. The follow-up after surgery was not blinded, ie, we knew to which group each patient belonged, and this may have caused bias. Sample size was small, which may have prevented observation of certain differences, although we have a follow-up of 100% of the initial sample. Also as a result of the sample size, there may be differences in clinical characteristics that have not been observed. However, according to the statistical inferential process, the greatest limitation of small samples refers to situations in which no statistically significant differences are found. We believe that the situations in which we found statistically significant differences are important and should be taken into account.

In conclusion, PVI procedure in patients with mitral valve disease is as effective as the Maze procedure to maintain sinus rhythm, and both techniques were more effective than isolated correction of the valve disease. We believe that our tests and the results obtained in this study form a solid basis for further investigation of this procedure for most permanent AF patients who need surgical repair or replacement of the mitral valve.

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INVITED COMMENTARY

Using a prospective randomized clinical trial, the authors of this paper evaluate the treatment of atrial fibrillation (AF) by pulmonary vein isolation in patients undergoing mitral valve surgery.

This patient population differs significantly from that with "lone" atrial fibrillation, since the left-sided origin of AF is well documented in patients with mitral valve disease. Several studies have been able to identify trigger