The Cox maze procedure in mitral valve disease: Predictors of recurrent atrial fibrillation

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Objectives: The Cox maze procedure is the gold standard for ablation of atrial fibrillation in patients undergoing mitral valve surgery, and new approaches to atrial fibrillation ablation must be compared with it. Therefore, we sought to determine the time-related prevalence of atrial fibrillation and its risk factors after combined Cox maze and mitral valve surgery.

Methods: From November 1991 through January 2004, 263 patients (mean left atrial diameter, 5.8 ± 1.2 cm) underwent combined mitral valve surgery (repair in 71%) and a cut-and-sew Cox maze procedure for atrial fibrillation (permanent, 74%; persistent, 7%; paroxysmal, 16%). Rhythm documented on 2367 postoperative electrocardiograms was used to estimate the prevalence of atrial fibrillation across time.

Results: Hospital mortality was 1.9%. Postoperative atrial fibrillation prevalence peaked at 36% at 2 weeks, decreasing to 21% at 5 years. Risk factors for higher postoperative atrial fibrillation prevalence varied with time and included longer duration of preoperative atrial fibrillation ($P = .003$), larger left atrial diameter ($P = .01$), older age ($P = .0002$), and higher left ventricular mass index ($P = .02$).

Conclusions: In some patients undergoing mitral valve surgery and a Cox maze procedure, atrial fibrillation recurs over time, mandating close, long-term follow-up of heart rhythm. Earlier operation and left atrial size reduction should be considered to improve results in selected patients.

The Cox maze procedure, which is designed to interrupt the macroreentrant circuits that characterize atrial fibrillation (AF) and atrial flutter,¹⁻³ serves as the basis for new surgical and catheter-based approaches to AF ablation.⁴⁻⁶ Validation of these new approaches requires comparing their results with those of patients undergoing a cut-and-sew Cox maze procedure.⁷ In cardiac surgical practice AF is most frequently encountered in patients with mitral valve disease. Although reports document the effectiveness of the Cox maze procedure in such patients, the operation does not cure AF in all.⁸⁻¹² Therefore, we sought to determine the time-related prevalence of AF and its risk factors after combined Cox maze and mitral valve surgery.

Abbreviations and Acronyms

AF = atrial fibrillation
CL = confidence limit
ECG = electrocardiogram

Patients and Methods**Patients**

From November 1991 through January 2004, 263 patients underwent combined mitral valve surgery (repair in 71% and replacement in 29%) and a Cox maze procedure (Cox maze II in 4 and Cox maze III in 259) at The Cleveland Clinic Foundation. All Cox maze procedures were performed with cut-and-sew and cryothermy techniques, as described by Cox and associates,¹ and included an incision to the mitral annulus and cryolesions at the mitral annulus and coronary sinus. Left atrial size reduction was not used routinely in those with left atrial dilatation. Patients were identified from the Cardiovascular Information Registry, and preoperative, operative, and postoperative variables were retrieved; the registry has been approved for research by the institutional review board. Mean patient age was 62 ± 11 years, and 61% had degenerative, 26% had rheumatic, and 3.8% had ischemic mitral valve disease (Table 1).

AF was classified as paroxysmal (16%), persistent (7%), or permanent (74%) according to established guidelines.¹³ The median duration of preoperative AF was 48 months, and 85% of patients had AF of 1 years' duration or greater. Mean left atrial diameter was 5.8 ± 1.2 cm, and left atrial diameter was greater than 6 cm in 41%. Preoperative treatment of AF consisted of antiarrhythmic medications in 25% and warfarin in 39%. Preoperative thromboembolic events included transient ischemic attack, stroke, and other systemic embolism in 18%.

Follow-up

Postoperative electrocardiograms (ECGs) were used to assess AF. They were performed routinely before discharge and at the discretion of referring physicians during follow-up. Recommended ECG follow-up intervals were 1 month, 3 months, 6 months, 1 year, and annually thereafter. A total of 2367 postoperative ECGs were retrieved, and every patient had at least one record available for analysis (range, 1 day to 12 years). Among surviving patients, 210 (83%) had an ECG 6 months or more after the operation, and 181 (72%) had one 12 months or more after the operation (Figure 1). For purposes of analysis, any one of the following 3 rhythms was considered postoperative AF: AF, atrial flutter, or a paced rhythm with underlying AF or atrial flutter.

Clinical follow-up for survival, morbid events, and medication history was obtained by means of patient visit and systematic telephone or mailed questionnaires. Median clinical follow-up was 2.6 years, with a total of 918 patient-years available for analysis. Mean clinical follow-up was 3.5 ± 2.8 years (range, 6 days to 12 years). Clinical follow-up was available in 98% of patients at 6 months and 94% at 12 months. Use of class I and class III antiarrhythmic drugs and warfarin was recorded at each follow-up.

TABLE 1. Patient characteristics

Characteristic	n*	No.	%
Atrial fibrillation	263		
Duration (mo)		12, 48, 144†	
Paroxysmal		41	16
Persistent		18	7
Permanent		196	74
Flutter		8	3.0
Preoperative cardioversion		22	8.4
Mitral valve disease cause	263		
Degenerative		160	61
Rheumatic		67	26
Ischemic		10	3.8
Functional		15	5.7
Other		11	3.8
Demography	263		
Male sex		143	54
Age (y)		62 ± 11 ‡	
Symptomatology			
NYHA functional class	263		
I		37	14
II		160	61
III		56	21
IV		10	3.8
Transient ischemic attack§	263	32	12
CVA§	263	23	8.7
Embolus§	263	2	0.8
Other cardiac comorbidity			
Coronary artery disease			
Left main trunk disease	252	6	2.4
LAD disease	252	37	15
Circumflex disease	251	29	12
Right coronary disease	252	28	11
Previous cardiac operation	263		
0		224	85
1		34	13
2		5	1.9
Cardiac structure and function			
LV end-diastolic diameter (cm)	231	5.1 ± 1.0 ‡	
LV end-systolic diameter (cm)	229	3.5 ± 0.91 ‡	
LA diameter (cm)	222	5.8 ± 1.2 ‡	
Fractional shortening	229	0.35 ± 0.11 ‡	
Ejection fraction (%)	229	62 ± 15 ‡	
Previous myocardial infarction	263	40	15
Noncardiac comorbidity			
Hematocrit (%)	231	40 ± 5 ‡	
Creatinine ($\text{mg} \cdot \text{dL}^{-1}$)	261	0.8, 1, 1.2†	
Procedure	263		
Mitral valve repair		186	71
Mitral valve replacement		77	29
Tricuspid valve repair		66	25
Tricuspid valve replacement		1	0.4
Aortic valve repair		2	0.8
Aortic valve replacement		11	4.2
CABG		48	18

NYHA, New York Heart Association; CVA, cerebrovascular accident; LAD, left anterior descending coronary artery; LV, left ventricle; LA, left atrium; CABG, coronary artery bypass grafting. *Data available. †Median and 15th and 85th percentiles. ‡Mean $\pm$ standard deviation. §Not mutually exclusive. ||>50% stenosis.

Figure 1. Number of patients with electrocardiographic (ECG) follow-up available at and beyond various time points and number of ECGs available for analysis at and beyond these same time points.

Patients were questioned concerning recurrence of symptomatic AF and palpitations, and those with symptoms suggesting arrhythmias were referred for ECG confirmation; only AF documented by means of ECG was analyzed.

Data Analysis

Prevalence of AF and its risk factors. Because there is no practical method for continuous heart rhythm assessment, a novel statistical technique was developed to depict prevalence of AF versus time on the basis of discrete ECG recordings. We attempted to solve multiple challenges simultaneously: repeated ECG recordings for each patient (repeated measures), variable recording times, censoring by death, and a complex temporal pattern of AF prevalence that likely represented the variable effect of different modulating factors across time. The analytic approach taken was temporal decomposition with several simple additive components.^{14,15} Multivariable analysis was performed in the odds domain to identify risk factors for each component and overall (Electronic Appendix).^{16,17}

Presentation

Continuous variables are presented as means $\pm$ standard deviation or equivalently as 15th, 50th (median), and 85th percentiles when the distribution of values was skewed. Non-time-related event data and time-related prevalences are presented as percentages with asymmetric 68% confidence limits (CLs) comparable with ± 1 standard error. The CLs for the prevalence of AF were obtained with the bootstrap percentile method.¹⁸

Results

In-hospital Results

Hospital morbidity included stroke in 3 (1.1%) patients, transient ischemic attack in 2 (0.8%) patients, and reoperation for bleeding in 15 (5.7%) patients. New permanent

pacemakers were required in 18 (6.8%) patients, and freedom from pacemaker implantation was 91% (CL, 89%-93%) at 6 months. Direct-current cardioversion of perioperative AF was performed on 56 (21%) patients before hospital discharge. There were 5 hospital deaths (1.9%; CL, 1.1%-3.2%).

Heart Rhythm

Prevalence of AF and its risk factors. Time-related predicted prevalence of AF or atrial flutter after the operation peaked at 36% (CL, 31%-42%) at 2 weeks (Figure 2,A). By 6 months, the prevalence had fallen to 13% (CL, 11%-17%). At 3 years, it was 20% (CL, 16%-24%), and thereafter it remained relatively constant. Ten percent of patients were taking antiarrhythmic medications 3 years postoperatively, and 45% were taking warfarin; these figures were similar at 5 years.

Figure 2. Temporal pattern of atrial fibrillation (AF) after ablation on the basis of postoperative electrocardiograms. **A**, Estimated prevalence of AF. The solid line represents mean prevalence, and dashed lines represent 68% confidence limits. **B**, Temporal decomposition of prevalence demonstrating 3 additive phases: an early peaking phase, a late phase, and a constant phase.

TABLE 2. Incremental risk factors for higher prevalence of atrial fibrillation

Risk factor	Estimate $\pm$ SE	P value
Overall		
Longer duration of preoperative AF*	0.14 ± 0.047	.003
Older age†	1.02 ± 0.27	.0002
Lower creatinine‡	0.62 ± 0.42	.1
Early phase		
Higher hematocrit§	4.3 ± 1.04	<.0001
Constant phase		
Higher LV mass index	0.38 ± 0.16	.02
Larger LA diameter	0.35 ± 0.14	.01
Late phase		
Larger LA diameter¶	2.6 ± 1.1	.02
Right coronary disease#	1.2 ± 0.36	.002
Higher hematocrit§	3.1 ± 0.85	.0003

SE, Standard error; AF, atrial fibrillation; LV, left ventricular; LA, left atrial.

*[Duration of preoperative AF/40], rescaled. †Exp(age/70), exponential transformation. ‡(1/Creatinine), inverse transformation. §(Hematocrit/40)², squared transformation. ||(LV mass index/125)², squared transformation. ¶Ln(LA diameter), logarithmic transformation. #Disease greater than 0%.

Temporal decomposition of AF prevalence yielded 3 components, and multivariable analysis identified different factors modulating each (Table 2), as well as overall prevalence (Figure 2,B). Longer duration of preoperative AF ($P = .003$) and older age ($P = .0002$) increased the overall prevalence of AF, whereas larger left atrial diameter increased the prevalence of AF in both the late ($P = .02$) and constant time phases ($P = .01$, Figure 3). Five years after the operation, the predicted prevalence of AF was only 5% in a patient with a 4-cm left atrium; in contrast, the predicted prevalence was 15% in a patient with a 6-cm left atrium. The type of AF and the cause of mitral valve disease did not affect the prevalence of postoperative AF.

Discussion

Maze Procedure in Patients With Mitral Valve Disease

In patients undergoing combined mitral valve and Cox maze surgery, Cox and colleagues reported 98% cure of AF.^{3,19} Prasad and associates²⁰ observed a greater than 90% freedom from AF in patients having a Cox maze procedure with concomitant surgery. In contrast, others have used a classic cut-and-sew technique and reported less success. Raanani and coworkers⁸ recorded sinus rhythm in only 75% of patients a mean of 26 months after Cox maze and mitral valve surgery, which is similar to the Mayo Clinic experience of 74% freedom from AF at 2 years.⁹ These results are similar to Japanese experiences with modified lesion sets.¹⁰⁻¹² Results from these groups are consistent with our 18% prevalence of AF at 2 years.

Figure 3. Prevalence at 5 years of postoperative atrial fibrillation (AF) demonstrating effects of factors identified by multivariable analysis (Table 2). Except for the variables depicted, values for other risk factors were set as follows: duration of preoperative AF, 48 months; age, 62 years; creatinine, $1.0 \text{ mg} \cdot \text{dL}^{-1}$; hematocrit, 40%; left ventricular mass index, $125 \text{ g} \cdot \text{m}^{-2}$; left atrial (LA) diameter, 5.6 cm; right coronary artery stenosis, 0%. A, LA diameter. B, Duration of preoperative AF. C, Patient age.

Return of AF After the Maze Procedure in Patients With Mitral Valve Disease

No patient in this study had a postoperative electrophysiologic study. Without such studies to investigate the causes of AF after a Cox maze procedure, it is impossible to identify all the reasons for disparate results from different groups. However, some of these failures and disparities might be related to (1) possible variance in conduct of the Cox maze operation, (2) patient selection, and (3) differences in follow-up methodology, data analysis, and reporting.

Conduct of the Cox maze operation. The Cox maze III procedure includes accurately placed surgical incisions and cryolesions in both atria.¹ Thus, results of modifications of this procedure report data on similar, but different, operations.¹⁰ We have adhered strictly to the lesion set and techniques of the Cox maze III procedure, including creation of lesions at the mitral annulus and coronary sinus; alternative energy sources were not used. As noted previously, left atrial reduction was not performed.

Patient selection. As demonstrated in this and previous studies,²¹⁻²⁴ patient characteristics influence outcomes. Risk factors for return of AF after the Cox maze procedure include duration of preoperative AF, left atrial enlargement, reduced left ventricular function, and lower f-wave voltage.²¹⁻²⁴

Our data demonstrate that the association between left atrial diameter and return of AF is a continuous relationship; there is no clear cut-off value beyond which restoration of sinus rhythm is impossible. In patients with left atrial dilatation, Romano and colleagues²⁵ have demonstrated that combining atrial reduction plasty with a Cox maze III procedure resulted in 89% of patients being in sinus rhythm at a mean follow-up of 19 months. During the time of our study, we did not perform routine atrial reduction plasty in patients with left atrial enlargement, and this might be an important factor explaining our results.

Follow-up methodology, data analysis, and reporting. Differences in follow-up methodology, data analysis, and reporting render comparisons between reports problematic. All studies of heart rhythm are limited by data collection. Although symptomatic status related to heart rhythm is important, there is no substitute for electrical documentation of heart rhythm. Furthermore, asymptomatic AF is common after ablation, even in patients who previously experienced symptoms with AF,²⁶⁻²⁸ rendering patient-initiated event records of questionable sensitivity and specificity. Many reports rely on “heart rhythm at last follow-up” or patients’ self-reported rhythms without ECG verification⁸⁻¹⁰; such methodology might underestimate the prevalence of postoperative AF and, by focusing on a single time point, does not enable depiction of heart rhythm over time.

Currently, there are no practical means for long-term, continuous heart rhythm monitoring. Data for analyzing ablation success consist of ECGs, recordings from Holter monitors, and, more recently, technology that enables either periodic transtelephonic monitoring or continuous heart rhythm monitoring for short periods.²⁶⁻²⁸ Each of these provides only a snapshot in time. The more extensive the documentation of heart rhythm, the greater the likelihood that episodes of AF will be detected.²⁶⁻²⁹ Therefore, it is possible that studies incorporating more closely spaced follow-up data points for heart rhythm will report a greater prevalence of postoperative AF than those relying on patient self-reporting or on rhythm at last follow-up assessment.

A number of techniques have been used to analyze and display heart rhythm data. Challenges related to analysis include inability in most cases to identify the onset of AF and data sets that include multiple assessments of heart rhythm at varying times. Analyses that rely on the Kaplan-Meier estimator generally use the first occurrence of AF; this strategy ignores other episodes of AF and does not account for the paroxysmal nature of AF in many patients.

In this study we estimated the prevalence of AF at any given time after ablation. In such a depiction, a given patient might have AF on one ECG and sinus rhythm on the next, unlike in time-to-event analysis. Because prevalence includes both occurrence and duration, it might produce values that appear less favorable than those from a method that assesses only the first occurrence of AF. We believe that future efforts that quantify AF burden on the basis of continuous monitoring or consistent periodic monitoring will importantly advance the assessment of therapies designed to treat AF.

Limitations

ECGs used for analysis were obtained routinely in the hospital but opportunistically after hospital discharge. Attempts were made to contact each patient and cardiologist to obtain both clinical and ECG follow-up. Two hundred ten (83%) patients had ECGs beyond 6 months postoperatively. Patients having late ECGs might be selected because they had symptomatic AF, leading to overestimation of the prevalence of AF and ablation failure. Alternatively, asymptomatic AF episodes without ECG verification might have been missed, leading to underestimation of events. Although periodic Holter monitoring and periodic transtelephonic monitoring would have provided more data for analysis, these methodologies might still have failed to capture all AF episodes.²⁶⁻²⁹ Our limited ability to document heart rhythm continuously over time led us to develop novel statistical methods that we believe provide the most accurate estimates of AF prevalence achieved to date. Although not perfect, this method rep-

resents an important improvement over analyses relying on rhythm at last follow-up or patient self-reporting.^{15,30}

Analyses of prevalence of AF do not account for antiarrhythmic medications. Prevalence of antiarrhythmic use is reported separately (Electronic Figure). Although we recommend discontinuing antiarrhythmics 3 months after ablation, continued use is at the discretion of referring cardiologists, hampering our ability to report prevalence of AF without medications.

All patients in this series received a cut-and-sew Cox maze procedure (Cox maze III procedure in 98%), with cryolesions at the coronary sinus, mitral annulus, and tricuspid annulus. Patients in this report had left atrial enlargement and mitral valve disease. Left atrial reduction was not used, and this might have affected results.^{19,20,25} These results might not be generalizable to patients with normal left atrial dimensions or to those without mitral valve disease.

Clinical Inferences

Earlier operation and left atrial size reduction should be considered in patients undergoing mitral valve surgery with longstanding AF and left atrial enlargement, respectively. Improved methodology for monitoring heart rhythm is necessary to enable assessment of AF burden after ablation.

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Discussion

Dr Ralph Damiano (*St Louis, Mo*). Dr Gillinov, I would like to congratulate you and your colleagues at the Cleveland Clinic on a beautiful study and for continuing to evaluate and examine your results in the surgical treatment of atrial fibrillation (AF). It is precisely these types of studies that are sorely needed to help us define on whom, when, and how we should perform these operations.

Your study reported predictors of failure in 263 patients who underwent mitral valve surgery and a concomitant Cox maze procedure between 1991 and 2004. The principal risk factors for late return of AF included longer duration of preoperative AF, larger left atrial volume, and lower ejection fraction. This agrees with our experience, which we presented last year here at the American Association for Thoracic Surgery, with 278 consecutive patients undergoing the Cox maze procedure in whom we found preoperative duration of AF and the type of Cox maze procedure to be the most important predictors of late recurrence. I have several questions.

First, your median follow-up in this series was 2.6 years. How many of these patients in the study were lost to follow-up? More particularly, because you required electrocardiographic (ECG) evidence to confirm AF, how many patients did not have ECG follow-up at each time point? You reported in the article that only 72% of patients had ECGs at 1 year. Thus, we can assume that 28% were lost at a year. How about at 2 and 5 years, and could these patients who were lost to follow-up have influenced your findings?

What if the patient reported that he or she had AF, but you were unable to obtain ECG documentation of the arrhythmia? If you had included these patients as failures, how would this have influenced your rate of late recurrence?

My third question involves the antiarrhythmic drug use during the follow-up period. As you stated in your introduction, this is a critical piece of information that we as surgeons must begin to report in our series. Because a number of these patients might not have ever been tried on antiarrhythmic drugs preoperatively, their maintenance of sinus rhythm postoperatively might be due to more aggressive antiarrhythmic drug management after the operation. We would both agree that high success rates without antiarrhythmic drugs should be our ultimate goal as surgeons in this area.

Finally, my last question is regarding left atrial size. You mentioned that it is an important determination of failure and recurrence of AF. I was wondering whether you could elucidate on what you believe the role of atrial reduction is in these patients. In particular, at what size would you recommend an atrial reduction procedure? Also in this series, how many of the patients actually had atrial reduction procedures? Dr McCarthy, when he was at your institution, was quite a proponent of this procedure.

Once again, I would like to congratulate you on your very nice work, and I would like to thank the Association for allowing me to comment on this very important article. Thank you.

Dr Gillinov. Thank you for your comments, Ralph. Your first question gets to a key point that we are studying very intensely. How do you assess heart rhythm, and how do you follow these patients? We are subject to the same limitations as all others. We do not have continuous monitoring of heart rhythm. What did we have? At 6 months, we had clinical follow-up on 98% of patients

and ECG follow-up on 83%. At 12 months, we had clinical follow-up on 94% and ECG follow-up on 72%. Therefore, with time, more patients were certainly lost to follow-up.

I cannot tell you exactly how many had follow-up at 3 years or 5 years, although I can tell you that at 5 years we still had 40 patients with more than 5 or 6 ECGs per patient at that point and thereafter. With the new methodology devised by Dr Blackstone and his team, this provides sufficient data for analysis.

What do we do with the patient who says, "I think I am in AF but I don't have an ECG"? It is not that we do not believe the patient, but we do not count that as data. We advise the patient to get an ECG because what we want is electrical documentation of the heart rhythm. In truth, though, that was an uncommon occurrence.

Antiarrhythmic drug use certainly must influence results. It makes sense that if we have people taking antiarrhythmic drugs, our results might be influenced by them. At 3 years, 10% of the patients were taking antiarrhythmic medications, and it remained constant thereafter. Therefore, the majority were not taking antiarrhythmic agents.

Finally, what about left atrial size? We and many others have found that increasing left atrial size is associated with a decrease in succession. Some have suggested that there is a particular cutoff, 5 cm or 6 cm, beyond which you should consider doing something about the left atrial size. In fact, like most things in nature, it is a continuous relationship. That being said, I will tell you what we do now.

If the atrium is 6 cm or greater, as measured by echocardiography, in any dimension, we will cut out a portion. In this particular series, very few patients had left atrial size reduction. We became more aggressive with a strategy of size reduction only in the last year or two.

Dr Niv Ad (*Falls Church, Va*). I enjoyed very much your presentation. With regard to left atrial size and left atrial reduction, I wonder what your comment is as for a possible explanation of high success rate early on, even with very big left atrial size and then a failure that occurs late in the follow-up. Assuming that you have transmural lesions and that there is no question about it, because in this series the cut-and-sew maze procedure was performed, then the only explanation for late failures that make sense is the sick atrial substrate. Atrial remodeling can be severe in some patients and a major factor for failure down the road, and I am personally not convinced that you can take care of this by just reducing the size of the atrium. Because you have an initial high success rate, why would they fail if you fix the mitral valve and you do not have any AF? Therefore, do you think that the atrial substrate and irreversible changes could be responsible for late failures in some patients?

Dr Gillinov. Actually, I can give you an answer that has some preliminary data to back it up.

All of these patients had their left atrial appendages removed, and for more than a decade, we have been examining these left atrial appendages. What we find is that in patients with very long-term AF, which correlates with large left atria, they tend to have a large left atrium and permanent AF of long duration, and their atria have intense inflammatory reactions, scar, and fibrosis. And I think you are right. What that patient brings to the operating room might make it such that we can never restore, at least

permanently restore, sinus rhythm, even with the operation done correctly.

Dr Ad. Maybe we should not modify the antiarrhythmic drug treatment postoperatively in such patients, keeping them on longer treatment regimens and discontinuing therapy only under very tight follow-up and monitoring.

I am convinced that some patients should be kept on antiarrhythmic drugs for life, because their atrial substrate and the changes are irreversible and their atrium is prone to recurrent atrial arrhythmia. Therefore, it is not the left atrial size as a predictor for failure. It is the atrial size as a marker for the severity of the disease, and it is all about the substrate and reverse remodeling.

Dr Gillinov. I am not sure you can separate those. They go together. But you might very well be right. A strategy of long-term antiarrhythmic therapy might improve our results in those patients.

Dr D. Craig Miller (*Stanford, Calif*). Mark, that was a splendid presentation. I congratulate you. But you admit freely and honestly that you do not have a complete radar system to follow these patients forever; you do have more complete clinical follow-up than ECG follow-up. Do you have the data on how many patients, wrongly or rightly, were still receiving warfarin anticoagulation at the various points in time? This statistic might serve as a practical surrogate for what the local physicians think is going on?

Dr Gillinov. We have those data, but I am not sure what to do with them. Forty-five percent of patients were still receiving warfarin at 3 years, and over the next several years, it was relatively constant. Now, about a quarter of those people had a mechanical valve, a few have had a deep venous thrombosis, and many of them have had no documented AF because we have contacted them, but each time they see their physician, AF comes up on their list of diagnoses, and that leads straight to warfarin. Unfortunately, we do not have control of those patients. It is possible that it is right to keep all of them on warfarin. I am not sure.

Dr Miller. Good point. My last question is to look into your crystal ball and tell us what you would speculate those freedom-from-AF curves would look like had you not done an adjunctive Cox maze procedure, such as in a legitimate control group that we all need.

Dr Gillinov. In these patients I think that 80% or more would have stayed in AF because 74% came to us with permanent AF, and 85% had AF for more than a year preoperatively. There are some data that suggest the possibility that in certain patients with new-onset AF, just fixing the mitral valves makes the AF go away.

I think in these patients with long-standing AF, it is not likely that the AF will disappear with mitral surgery alone.

Dr Takashi Nitta (*Tokyo, Japan*). Congratulations on the excellent presentation and data analyses. Early recurrence of AF might be the result of electrical remodeling caused by long-lasting AF preoperatively. This subset of patients might be treated with amiodarone, and sinus rhythm would resume when the refractory period returns to the normal range. However, the mechanism for the AF recurrence occurring midterm or late term after the operation remains unclear.

In my series the postoperative AF recurrence rate was about 11% among the patients with permanent AF and mitral valve disease. Our EP fellows are doing an EP study on the patients in whom AF recurs more than 1 month after surgical intervention. Interestingly, they found residual conduction over the coronary sinus, which is a technical failure, as the cause of recurrence of AF in about two thirds of the patients. They also found rapid activation from nonpulmonary vein foci as the cause of AF.

I have 2 questions for you. Did you see any correlation between the phase of AF recurrence and the other risk factors, such as left atrial diameter, older age, or longer duration of preoperative AF?

Second, would you speculate the mechanism of AF recurrence in each phase?

Once again, congratulations on the excellent article.

Dr Gillinov. Thank you. What he is getting at is that the recurrence of AF occurs at different time frames. It can occur early, late, or during a constant phase of risk, and each of these clinical risk factors, like left atrial diameter, has an effect at a different time frame.

For example, older age might be more important with the constant phase, whereas it turns out, for reasons that are not entirely clear, that a higher hematocrit level is associated with early recurrence of AF. Therefore, yes, there are a variety of relationships that require further study.

As for speculating on the mechanisms of failure, actually you have the data, and we do not. Your mapping studies are going to pave the way. But I suspect it is a combination of one of 2 factors. Either we have done the procedure incompletely—for example, left a pathway near the coronary sinus as you and Dr Cox have noted—or the patient has a substrate that perhaps cannot be cured with a standard maze procedure, maybe atrial scar, fibrosis, inflammation. I think that, as with any therapy, there will be some patients who will not be amenable to it.

Electronic Appendix. Variables used in the analyses

Patient	
Atrial fibrillation types:	Permanent, persistent, paroxysmal, duration (months)
Mitral valve disease:	Cause (degenerative, rheumatic, ischemic, degenerative), pathophysiology (regurgitation)
Demography:	Age (years), sex, weight (kg), height (cm), body surface area (m ²), body mass index (kg · m ⁻²)
Symptoms:	New York Heart Association functional class (I-IV), emergency operation, transient ischemic attack, cerebrovascular accident
Other cardiac comorbidity:	Complete heart block/pacer, ventricular arrhythmia, number of previous cardiac operations Other valve pathology: Aortic valve regurgitation, tricuspid valve regurgitation Coronary artery disease: Maximum percentage stenosis in left main trunk, left anterior descending coronary artery system, right coronary artery system, left circumflex coronary artery system Left ventricular function: Ejection fraction (%), end-diastolic diameter (cm), end-systolic diameter (cm), fractional shortening, mass (g), mass index (g · m ⁻²), end-diastolic volume (mL), end-systolic volume (mL), end-diastolic volume index (mL · m ⁻²), end-systolic volume index (mL · m ⁻²), posterior wall thickness (cm), estimated wall stress (2 × posterior wall thickness/end-diastolic diameter) Right ventricular function: Estimated systolic pressure Atrial size: Left atrial (LA) diameter (cm), LA volume (mL), LA volume index (mL · m ⁻²)
Noncardiac comorbidity:	Insulin-treated diabetes, non-insulin-treated diabetes, treated diabetes, history of peripheral vascular disease, history of smoking, carotid disease, chronic obstructive pulmonary disease, hypertension, renal disease, creatinine (mg · dL ⁻¹), blood urea nitrogen (mg · dL ⁻¹), bilirubin (mg · dL ⁻¹), hematocrit (%)
Procedure	
Operation:	Internal thoracic artery grafting, coronary artery bypass grafting, tricuspid valve repair, mitral valve (MV) repair, MV replacement, MV bioprosthetic replacement, aortic valve replacement
Support:	Aortic clamp time (minutes), cardiopulmonary bypass time (minutes)
Experience:	Date of operation (years since January 1, 1991)

Electronic Figure. Prevalence of class I/III antiarrhythmic agent and warfarin use after ablation. Horizontal axis begins at 3 months, marking the first systematic follow-up of patients. Filled circles are observed prevalences but only approximate the data because of multiple follow-up inquiries per patient. The solid line represents the prevalence estimate from logistic mixed model enclosed within dashed 68% confidence limits. A, Prevalence of class I/III antiarrhythmic agent use. B, Prevalence of warfarin use.