The long-term outcome of patients with coronary disease and atrial fibrillation undergoing the Cox maze procedure

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Background: A significant number of patients presenting for coronary revascularization have chronic atrial fibrillation. Although the Cox maze III procedure is the gold standard for the surgical treatment of this arrhythmia, few of these patients undergo atrial fibrillation operations at the time of their coronary bypass grafting. This study examined the long-term outcome of patients with ischemic heart disease who underwent the Cox maze procedure at our institution.

Methods: From 1990 to 2002, 47 patients undergoing operations for ischemic heart disease underwent a concomitant Cox maze III procedure. All patients underwent coronary bypass grafting, and 7 (15%) patients underwent coronary bypass grafting plus a mitral valve repair. Follow-up was performed by means of mail and telephone questionnaires with both the patients and their cardiologists. All patients who had any history of arrhythmia or who were taking medications had their rhythm documented by electrocardiogram.

Results: The mean age of these patients was 62 ± 8 years, with a marked male predominance (45 men and 2 women). Twenty-eight (60%) of the patients had paroxysmal atrial fibrillation, and the remainder had persistent arrhythmias. The mean duration of atrial fibrillation was 7.6 ± 6.5 years. The operative mortality in this series was 2%. Nine (19%) patients required postoperative pacemakers. At last follow-up (mean of 5.7 ± 3.3 years), 98% of patients were free of atrial fibrillation.

Conclusion: The Cox maze III procedure has a low operative mortality and excellent long-term efficacy in patients with ischemic heart disease. These data suggest a more widespread use of this procedure in these patients.

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The Cox maze procedure was introduced in 1987 by Dr James Cox. The final iteration of this procedure, the Cox maze III procedure, was performed in 1988 and since that time has been our standard of therapy for the surgical treatment of this arrhythmia.[1] The operation was designed to interrupt the multiple macroreentrant circuits in the atria believed to be responsible for atrial fibrillation (AF). This operation creates a maze-like series of incisions in both atria to prevent the formation of AF. In this operation the pulmonary veins are completely isolated, and both appendages are removed. In 2000, we modified this procedure and replaced some of the incisions with linear lines of ablation. However, the basic lesion set has remained unchanged. This procedure has proved to be extremely effective, with a high success rate and the virtual elimination of late stroke.[2,3] Unfortunately, the requirement for cardiopulmonary bypass and the technical difficulty of the procedure have limited its use. The recent introduction of ablation technology to simplify

and shorten the operation has encouraged surgeons throughout the world to liberalize the indications for the Cox maze procedure.

More than 500,000 patients undergo surgical revascularization for ischemic heart disease every year in the United States.[4] It has been estimated that up to 15% of these patients might have chronic or permanent AF.[5] At our institution, 1.8% of patients undergoing elective coronary artery bypass grafting (CABG) had preoperative AF.[6] Few of these patients presently undergo a concomitant Cox maze procedure. Unfortunately, there have been no reports examining the late results of the Cox maze procedure in this specific group of patients that would allow surgeons to determine whether a more widespread adoption of this procedure is warranted. The purpose of this study was to examine the long-term efficacy of the Cox maze procedure in patients with ischemic heart disease undergoing coronary bypass grafting with or without mitral valve repair for ischemic mitral regurgitation.

Methods

From November 1990 to October 2002, 47 patients with ischemic heart disease underwent a Cox maze procedure with CABG. Seven patients also underwent mitral valve repair for ischemic mitral regurgitation in addition to CABG. All patients with nonischemic valvular heart disease were excluded from this study. This study cohort represented 18% (74/265) of the total number of patients who underwent a Cox maze procedure for AF at our institution during this time period. The full lesion set of the Cox maze procedure was performed in all cases. In each instance the patient underwent a median sternotomy, cardiopulmonary bypass with bicaval cannulation, and cardioplegic arrest. In the last 6 patients, either microwave ablation (n = 1) or bipolar radiofrequency ablation (n = 5) was used to replace several of the atrial lesions. The microwave device consisted of a flexible 4-cm antenna (AFx Inc, Fremont, Calif). The bipolar radiofrequency device had 1 mm $\times$ 5 cm electrodes mounted in the jaws of a clamp (Atricure, Inc, Cincinnati, Ohio).

The patients' clinical profiles and postoperative outcomes were recorded prospectively in a computerized database. Perioperative major complications were considered to be reoperation for bleeding, prolonged ventilatory support, renal failure requiring dialysis, mediastinitis, the placement of an intra-aortic balloon pump, perioperative transient ischemic attack or stroke, and perioperative myocardial infarction. Follow-up was conducted by means of a mailed questionnaire or telephone interview with the patient. A review of both the referring cardiologists' office charts and recent electrocardiograms was obtained on all patients who stated that they were in AF or were taking antiarrhythmic drugs or anticoagulation. Information on all out-of-hospital mortality was obtained from relatives, family physicians, and/or county death certificates. All of the patients in this series had documented AF for a duration longer than 6 months. *Paroxysmal atrial fibrillation* was defined as intermittent AF. *Persistent atrial fibrillation* was defined as continuous AF. This study was approved by the Washington University School of Medicine/Barnes-Jewish Hospital Institutional Review Board. Informed consent and permission for release of information were obtained from each participant. The closing date for enrolling patient data for this study was October 2002. Thus all patients had a minimum of 6 months' follow-up.

Late survival and outcomes were recorded and analyzed according to the Society of Thoracic Surgeons database guidelines. Data were collected and managed in Microsoft Access 2000 and analyzed with SysStat version 10.0 (SPSS Corp, Chicago, Ill). Descriptive statistics were expressed as means $\pm$ SD unless otherwise specified. Categoric data were expressed as counts and proportions. Comparisons were done with paired, 2-tailed *t* tests for means of normally distributed continuous variables and the Wilcoxon rank sum test for skewed data. χ^2 or Fisher exact tests were used to analyze differences among the categoric data. Kaplan-Meier estimates were used to depict freedom from AF.

Results

Patient Demographics

The mean age of these patients was 62 $\pm$ 8 years (range, 38-77 years). Forty-five of the patients were men, and 2 were women. There were 28 (60%) patients with paroxysmal AF and 10 (40%) with persistent AF. The mean preoperative duration of AF was 7.6 $\pm$ 6.5 years, with a range of 0.5 to 30 years.

In this group the indication for arrhythmia surgery was documented stroke or transient ischemic attack in 10 (21%) patients, medication intolerance in 4 (9%) patients, and arrhythmia intolerance in the majority of patients (70%).

All patients underwent a Cox maze procedure with CABG. The mean number of bypass grafts per patient was 1.8 $\pm$ 1.0 grafts. The average ejection fraction was 50% $\pm$ 14%, and 7 (28%) patients had an ejection fraction of less than 40%.

Of this group, there were 7 patients who also underwent mitral valve repair for ischemic mitral regurgitation. All of these patients were treated only with a ring annuloplasty. All patients whose mitral regurgitation was nonischemic in origin were excluded from the study.

Perioperative Results

The average aortic crossclamp time in this series was 111 $\pm$ 35 minutes. The mean cardiopulmonary bypass time was 204 $\pm$ 50 minutes. The median intensive care unit stay was 3 days (range, 1-11 days), and the median total length of stay was 11 days (range, 6-66 days). There was only one operative mortality (2%). This patient died on postoperative day 22 from multisystem organ failure.

In this group of patients, there was a 27% major complication rate. Three (6%) patients required reoperation for bleeding. Two patients required a postoperative intra-aortic balloon pump. There were 2 patients who required prolonged ventilation (>48 hours). One (2%) patient had mediastinitis, and there was one case of renal failure. There were no perioperative strokes. There were 2 (4%) patients with a documented postoperative myocardial infarction.

TABLE 1. Perioperative complications

	CABG/maze (%) n = 47	Isolated CABG (%) n = 1299	*P* value
Reoperation for bleeding	6	4	1.0
Renal failure	2	6	.512
IABP	4	3	.644
Mediastinitis	2	2	.577
Stroke	0	3	.629
Myocardial infarction	4	1	.105
Operative mortality	2	3	1.0

IABP, Intra-aortic balloon pump.

The incidence of these complications was not significantly different than that seen after isolated elective CABG (n = 1299) during the same period at our institution (Table 1).

The incidence of early postoperative atrial dysrhythmias was 53% (25/47 patients). All of these rhythm disturbances had resolved by the 21st postoperative day. These arrhythmias were evenly split between AF and atrial flutter, and all were transient.

A total of 9 (19%) patients required placement of a pacemaker postoperatively. Seven (78%) of these patients had a preoperative diagnosis of sick sinus syndrome.

Late Follow-up

Late follow-up was achieved in 45 (96%) of 47 patients. The mean duration of follow-up was 5.7 ± 3.3 years. There was only one late death in the entire group of patients treated with the Cox maze procedure with ischemic heart disease. This patient died from lung carcinoma and was in normal sinus rhythm. There were no late strokes in this group. All patients were discharged from the hospital with warfarin (Coumadin, DuPont Merck) for 2 to 3 months. After their postoperative clinic visits for the first several months, their medications were then managed by their referring cardiologists or family physicians. In this study 7 (16%) of the 45 patients were taking warfarin at late follow-up.

Recurrence of AF

All patients who identified themselves as being in AF were considered failures unless their cardiologist or an electrocardiogram or Holter recording documented otherwise. There were no late recurrences of atrial flutter, and only 1 (2%) patient had recurrent AF at late follow-up. This patient had his recurrence 10.5 years after his Cox maze procedure. Of the entire group, 38 (84%) patients were in sinus rhythm and completely free of antiarrhythmic drugs. Six (13%) patients were in normal sinus rhythm but were taking antiarrhythmic drugs.

Overall, the Kaplan-Meier estimate for freedom from AF for patients undergoing a Cox maze procedure and concomitant surgical intervention for ischemic heart disease was 100% at 10 years.

Discussion

The late results of the Cox maze procedure have been excellent in patients with lone AF or with AF in association with valvular heart disease.[3] The long-term efficacy of this operation in patients with ischemic heart disease in unknown. This is pertinent information for a number of reasons. First of all, there are thousands of patients undergoing coronary revascularization each year in the United States who have documented AF.[5,6] The great majority of these patients do not undergo a concomitant Cox maze procedure and are thus denied a chance to cure their arrhythmia. Second, it has been suggested that the underlying pathophysiology responsible for the genesis of AF might be different in patients with ischemic heart disease.[7,8] Thus the excellent results seen in other patient populations might not be readily applicable to patients with coronary artery disease.

This study examined the long-term efficacy of the Cox maze procedure in patients with ischemic heart disease. The long-term success of the Cox maze procedure was excellent in these patients. The overall freedom from AF at 10 years was 100%. There was only one late recurrence of AF at 10.5 years. All other patients were in normal sinus rhythm or paced atrioventricular rhythm at last follow-up. Moreover, the great majority of these patients were no longer taking both warfarin and antiarrhythmic drugs. With this superb long-term cure rate and the benefits of being able to stop warfarin, why is the Cox maze procedure so seldom performed in patients with AF presenting for surgical treatment of their coronary artery disease?

One of the principal reasons is the invasiveness and morbidity of this procedure. However, our data would argue for a more aggressive surgical approach. AF, antiarrhythmic drugs, and chronic anticoagulation all have documented and significant complications.[9-11] This study demonstrated that adding the Cox maze procedure to bypass grafting with or without mitral valve repair in this population was associated with a low mortality (2%), while offering the patient an almost certain chance of cure and eliminating the risk of late stroke. At our institution, our comparative mortality over a similar time period for elective coronary bypass grafting was 2.8%. The incidence of reoperation for bleeding, mediastinitis, and renal failure were also similar to that of the larger population undergoing isolated elective CABG at our institution. Although the addition of the Cox maze procedure did not increase perioperative mortality, it did lengthen hospital length of stay (median, 11 days). Our comparative median length of stay in isolated coronary bypass grafting during this period was 6 days.

Late complications were virtually nonexistent in this patient population. No patient had a stroke or transient ischemic attack during the follow-up period. Impressively, only one patient had recurrent AF in the entire group. Moreover, the majority of patients were able to discontinue warfarin, which carries its own long-term risk of morbidity in these patients.

Nine (19%) patients in this study required a postoperative pacemaker. The majority of these patients had a preoperative diagnosis of sick sinus syndrome, which is a known risk factor for this complication. This is very similar and not statistically significant when compared with our overall incidence of pacemaker implantation in our recently published series of 198 patients undergoing the Cox maze III procedure.[3]

The study has limitations. There were only 47 patients in our series. These were highly selected patients and represent only a small fraction of all patients seen with ischemic heart disease during this time period at Barnes-Jewish Hospital. These patients had relatively limited coronary artery disease and were, on the whole, low-risk healthy patients. It is difficult to estimate the effect of this selection bias on our results.

Another major limitation of this study was that it might have underestimated the failure rate. Electrocardiographic follow-up was not obtained on patients who stated that they were in normal sinus rhythm and were not taking any medications. However, our follow-up of all patients who identified themselves as having any atrial dysrhythmia should have captured the majority of treatment failures. It is possible, though, that a patient might have had asymptomatic episodes of AF. Unfortunately, the logistics of continuously monitoring patients for years is extremely difficult. If patients were indeed in AF, one would have expected a higher incidence of stroke.

In summary, the excellent long-term success rates would argue for a more widespread adoption of the Cox maze procedure in patients with ischemic heart disease. These data support a policy of offering the curative Cox maze procedure to patients with refractory permanent AF undergoing CABG. The results of other, more limited operations in this cohort of patients is unknown and in our opinion should only cautiously be offered to patients when there is a well-described operation that offers an extremely high cure rate without increasing the mortality and morbidity of elective coronary revascularization.

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Discussion

Dr Joseph A. Dearani *(Rochester, Minn)*. I congratulate Dr Damiano and his colleagues for another important contribution on the application of the Cox maze procedure for the treatment of AF, now in patients with coronary artery disease. They have demonstrated, in this retrospective review, that the Cox maze procedure plus CABG can be performed with low early mortality and morbidity in highly selected patients with AF and ischemic heart disease. The need for permanent pacing was approximately 20%. There were no late strokes, and the majority of patients were in sinus rhythm and free of warfarin anticoagulation at late follow-up, although electrocardiographic data were not obtained in all patients.

We, too, have had enthusiasm and success with the Cox maze procedure. Between 1993 and 2001, 367 patients underwent the Cox maze procedure at the Mayo Clinic, 62 of whom had concomitant CABG. Early mortality was 2.5%, maintenance of sinus rhythm was greater than 90% at late follow-up, late stroke was significantly reduced, and the need for permanent pacing was 5%. These favorable results have encouraged us to make an effort to apply the Cox maze procedure to many more patients with AF who undergo operations for another cardiac diagnosis.

I believe the important issue with the subject of AF and coronary artery disease is patient selection. The authors make reference and comparison to 1299 patients who underwent isolated coronary bypass surgery during the same time interval. What percentage of these 1299 patients also had AF and did not have the maze procedure and why? The average number of bypass grafts in your review was only 1.8. Specifically, how many patients had symptomatic coronary artery disease (eg, angina, dyspnea, or heart failure) that was the indication for coronary bypass surgery versus those scheduled for a maze operation and found incidentally to have coronary disease on preoperative angiography that required 1 or 2 grafts?

You noted in your article that "late complications were virtually nonexistent" in your patient population. The majority of the patients in your review had normal ventricular function, but no information was provided about comorbidity, such as diabetes or renal, pulmonary, or peripheral vascular disease. Late complications in patients with significant ischemic heart disease are well documented and are not nonexistent.

How did you select these patients for a concomitant maze procedure, and when would you simply just ligate the left atrial appendage? Would you have avoided doing the maze procedure in any of the patients who had postoperative complications or death?

Numerous groups have documented the safety and efficacy of the Cox maze procedure. What is the place of the newer, costly disposable devices? These devices were used in some of your patients. You state in your conclusions, however, that these newer devices and techniques should only "cautiously be offered." Did any of the late complications or mortality that occurred happen in any of these patients?

In principle, it appears attractive to apply the traditional maze procedure to many different cardiac diagnoses during the course of cardiac operations. As an advocate of the maze procedure, I do believe it should be offered to relatively healthy patients with coronary disease, good left ventricular function, and few comorbidities. However, in the current era, we are confronted more and more with challenging patients who require coronary revascularization or redo procedures or who have decreased left ventricular function, renal insufficiency, obstructive lung disease, the frequent use of multiple and powerful antiplatelet agents, older age, et cetera. I believe wider application of the maze procedure to all patients with ischemic heart disease will result in greater operative risk. What is your message to practicing surgeons for this group of patients?

I agree that the maze procedure has earned wider applicability in properly selected patients. Although the procedure decreases the incidence of stroke, I do not believe it eliminates the risk of stroke in this group of patients. In addition, I disagree with the conclusion in your article that it should be a policy to offer the traditional Cox maze procedure to all patients undergoing coronary bypass surgery at this time. Newer devices in the future, if proved effective, might allow more widespread application of the technique.

Dr Damiano. Thank you, Dr Dearani, and those are excellent comments. First of all, I agree completely with you. This is a very selected series and a relatively small series of patients, and I think you cautiously should draw large conclusions regarding the entire universe of patients coming for CABG.

First of all, the incidence of AF in patients coming for elective coronary bypass grafting at our institution is 1.8%. Interestingly, in the Cleveland Clinic the number of patients was just under 1%. Therefore it is a relatively small number of total patients. However, if you look nationwide, we are dealing with thousands of patients who do present with chronic AF. No patient was considered for a Cox maze procedure at our institution unless they had AF for at least 6 months. All of these patients met the standard indication for the Cox maze procedure of drug failure, arrhythmia intolerance, or both, with a small subset, as I said, having neurologic complications. These patients represented a relatively small percentage of the total patients with AF who underwent CABG at our institution during this time period.

You have to remember that this is our entire experience dating back to the very early days of the Cox maze procedure. In the beginning of this experience, we were hesitant to widely apply it in patients, particularly those having extensive other concomitant procedures. Obviously this is a selected group, and you can see, compared with our overall group of patients having coronary revascularization, that this group had significantly fewer distal grafts per patient. Only time will tell what the results will be with a more aggressive application of the Cox maze procedure in this group of patients.

I do believe that the use of newer ablation devices, which have comprised our more recent experience, has led us to be significantly more aggressive. In this series our only death occurred in a patient having a traditional cut-and-sew Cox maze procedure relatively early in the experience. We have had no recent deaths or major complications in the patients in whom we have used the ablation devices. With these ablation devices, we have been able to cut more than 30 minutes off the crossclamp time required to perform the Cox maze procedure.

I certainly do not want to say that the addition of the Cox maze procedure does not add potential morbidity. All of us would agree that these are relatively long crossclamp and bypass times. Although these have been improving recently, if we did a much larger series, we might have seen a higher complication rate.

However, our data do show that the operative mortality is similar to that with isolated CABG, and we have looked at our major complications with the Society of Thoracic Surgeons database. Even with the fact that most of these patients underwent a lengthy traditional cut-and-sew Cox maze procedure, we still did not see a higher incidence of complications, albeit with this very selected group.

We do believe that with the newer ablation devices and the fact that this now adds only 10 or 15 minutes to our crossclamp time that we should be more aggressive in offering this operation to patients with chronic AF. There are some tremendous long-term benefits. Even if there was a slightly higher short-term morbidity, the ability to get these patients off warfarin and to maintain sinus rhythm would be a tremendous benefit.

As far as our current indications, we do consider patients at reasonable risk undergoing elective coronary bypass grafting to be candidates for a concomitant Cox maze procedure. Time will tell, and we will certainly have more numbers in the next 5 years with this more aggressive policy. We can then look at the question of whether we might be seeing more complications in this group.

Recently, there has been much interest around the world in simplifying and decreasing the number of the incisions of the Cox maze procedure. This study does represent long-term follow-up of the entire lesion set, whether done surgically or with an ablation device. Our data reveal that if this entire lesion set is performed, you can expect more than a 90% cure rate at 10 years.

The reason we looked at this particular group of patients was that it appears from recent experimental work that the cause of AF might be very different in patients with ischemic heart disease than in either those with valvular heart disease or with lone AF. Actually, I would have predicted that this group would have had a worse outcome because you would consider that they would probably have recurrent ischemic heart disease during follow-up. However, the long-term results were excellent.

Dr Paul A. Kurlansky *(Miami Beach, Fla)*. I congratulate you on a very provocative and beautifully performed study. As you know from the AFFIRM study, which randomized patients with chronic AF to either rate control or rhythm control, absolutely no difference in late mortality was found. In fact, there was a suggestion that there was higher stroke-related morbidity in the rhythm control group and that was hypothesized to be perhaps because the patients who were in sinus rhythm were intermittently in AF and had cerebrovascular events or cerebroembolic events at that time. But it also raised the possibility that perhaps this subgroup of patients who have AF require chronic anticoagulation, even after they are converted to sinus rhythm.

Your study, which had a zero stroke rate at follow-up both at 5 and 10 years is extremely revealing in this regard in that it suggests that even in this subgroup of patients with AF, once they are in sinus rhythm, at least with this procedure, they no longer have a need for anticoagulation, which is an extremely valuable contribution in and of itself.

A certain percentage of patients were receiving anticoagulation, and therefore I have 2 questions. What were the indications for the anticoagulation in those patients who were receiving it? For the patients who were not receiving anticoagulation, were they receiving any form of treatment (eg, Plavix or antiplatelet agents) other than the aspirin that they would normally receive for having coronary artery disease?

Dr Damiano. Thank you, and those are excellent questions. In terms of our indications for anticoagulation, virtually none of these patients were under our own care. Most of these were referred from around the country, around the world, and anticoagulation was based solely on the discretion of their referring physician. Some referring physicians maintained chronic anticoagulation, and we do not have information on their rationale. We just recorded which patients were receiving anticoagulation. Whether it was appropriate I can not tell you. Most of the patients were taking aspirin. As far as other antiplatelet drugs, I do not have that information, but it would be interesting to look it up.

Actually, when we presented the full Cox maze III experience last year, these patients virtually never had a stroke. In our whole series, since the Cox maze III procedure was introduced in 1998, we have only seen one late stroke, and that patient had a cerebral atrioventricular malformation. Obviously, that is probably a testimony to the fact that this operation is very good at maintaining sinus rhythm. It might also be due to the fact that we ligate the left atrial appendage.