Efficacy of Cox Maze IV Procedure Using Argon-Based Cryoablation: A Comparative Study with N$_2$O-Based Cryoablation

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Background: We compared the mid-term results of the Cox maze IV procedure using argon-based cryoablation with a procedure using N$_2$O-based cryoablation. Methods: From May 2006 to June 2012, 138 patients (mean age, 58.2±11.0 years) underwent the Cox maze IV procedure. Eighty-five patients underwent the maze procedure using an N$_2$O-based cryoprobe (group N), and 53 patients underwent the maze procedure using an argon-based cryoprobe (group A). Bipolar radiofrequency ablation was concomitantly used in 131 patients. The presence of atrial fibrillation immediately, 6 months, 1 year, and 2 years after surgery was compared. Results: Early mortality occurred in 6 patients (4.3%). There were no differences in early mortality or postoperative complications between the two groups. Nineteen of 115 patients (16.5%) remained in atrial fibrillation at postoperative 12 months (14 of 80 patients (17.5%) in group N and 5 of 35 patients (14.3%) in group A, $p=0.669$). There were no differences in the number of patients who remained in atrial fibrillation at any of the time periods except in the immediate postoperative period. A multivariable analysis revealed that the energy source of cryoablation was not associated with the presence of atrial fibrillation at 1 year ($p=0.862$) and that a fine F wave (<0.1 mV) was the only risk factor predicting the presence of atrial fibrillation at 1 year ($p<0.001$, odds ratio=20.287). Conclusion: The Cox maze IV procedure using an argon-based cryoprobe was safe and effective compared with the maze procedure using an N$_2$O-based cryoprobe in terms of operative outcomes and the restoration of sinus rhythm for up to 2 years after surgery.

Key words: 1. Arrhythmia surgery  
2. Arrhythmia  
3. Atrial fibrillation  
4. Ablation  
5. Cryosurgery

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, accounting for one-third of the rhythm disturbances, and is associated with substantial morbidity and mortality [1]. AF is related to systemic or pulmonary thromboembolism due to a slow and stagnant blood flow in the atria. The risk of stroke associated with AF is 5% to 8% per year, and AF is associated with a five- to seven-fold increase in the overall risk of stroke [1-3].
In recent years, the management of AF has rapidly evolved, with many available options to achieve either rate or rhythm control [4,5]. The traditional goals of treatment were to control the ventricular response rate by using pharmacological agents and to prevent thromboembolic events. However, medical treatments have limited efficacy in maintaining the sinus rhythm and may exhibit serious adverse effects [6-8].

Since the Cox maze procedure was first introduced in 1987, it has been considered the gold standard for the surgical treatment of AF. After the late 1990s, by means of various energy sources, the procedure was modified into the Cox maze IV procedure, which is less invasive and uses various energy sources to shorten the procedure time [9]. In our previous study, it was reported that the Cox maze IV procedure using N₂O-based cryoablation and bipolar radiofrequency is safe and comparable to various other maze procedures [10].

In our institution, we use an argon-based cryoprobe as well as an N₂O-based cryoprobe. The advantage of argon-based cryoablation over N₂O-based cryoablation is that the argon-based technique can reach a temperature of -140°C to -160°C compared with -60°C for N₂O, allowing for a faster and more reliable ablation lesion [11]. In this study, we compared the mid-term results of the Cox maze IV procedure using argon-based cryoablation with the same procedure using N₂O-based cryoablation.

**METHODS**

From May 2006 to June 2012, 138 consecutive patients (mean age, 58.2±11.0 years) underwent the Cox maze IV procedure at Seoul National University Hospital. Eighty-five patients underwent the maze procedure using an N₂O-based cryoprobe (Frigitronics, cardiac cryosurgical system-200; Atricure Inc., Chester, OH, USA) (group N), and 53 patients underwent a maze procedure using an argon-based cryoprobe (ATS CryoMaze surgical ablation system, Medtronic Inc., Minneapolis, MN, USA) (group A). The operation was performed by a single surgeon (KH Kim).

All patients had valvular heart disease requiring open heart surgery. All operations were performed using an aorto-bicaval cannulation under moderate hypothermia and cold crystalloid cardioplegic arrest via a median sternotomy.

Continuous electrocardiographic monitoring was performed during the postoperative period until discharge. In addition, 12-lead electrocardiography (ECG) was performed daily during the hospital stay. Follow-up ECG was performed 1, 3, 6, 12, 18, and 24 months after surgery and annually thereafter. The presence of AF in the early postoperative days and 6 months, 1 year, and 2 years after surgery was compared between the two groups. ‘Free from AF’ was defined as an ECG-verified normal sinus rhythm, junctional rhythm, and atrial pacing rhythm. Maze failure was also defined as cases with recurrent or persistent AF 1 year after the surgery.

Statistical analysis was performed using the SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean±standard deviation or as proportions. Comparisons between the two groups were performed with the chi-square test or Fisher’s exact test for categorical variables and the Student t-test for continuous variables. A multivariable logistic regression model was used to identify the risk factors for AF recurrence or maze failure 1 year after the surgery. Group factor and variables with p-values less than 0.05 were entered into multivariable analyses. p-values of less than 0.05 were considered statistically significant.

**RESULTS**

1) Comparisons of the patients’ characteristics and operative data of the two groups

The etiologies of valvular heart disease included 91 rheumatic (65.9%), 30 degenerative (21.7%), and 17 other etiologies (12.3%), such as the mixed form or congenital causes. One hundred and thirty five patients exhibited longstanding persistent AF, and three patients exhibited paroxysmal AF. There were no differences in the baseline characteristics, echocardiographic parameters, or characteristics of AF between two groups except that patients in group N were older than those in group A (61.2±11.3 years and 56.4±10.4 years, respectively; p=0.011) (Table 1).

Mitral valve procedures were performed more frequently in group N than in group A (80 patients versus 43 patients, respectively; p=0.017). Other cardiac procedures included aortic valve operations (n=43, 31.1%), tricuspid valve surgery
Table 1. The demographic data, echocardiographic parameters and characteristics of atrial fibrillation of the study patients

| Variable                                      | Group N (n=85) | Group A (n=53) | p-value |
|-----------------------------------------------|----------------|----------------|---------|
| Age (yr)                                      | 61.2±11.3      | 56.4±10.4      | 0.011   |
| Sex (male:female)                             | 53:32          | 35:18          | 0.661   |
| Hypertension                                  | 10 (11.8)      | 12 (22.6)      | 0.080   |
| Diabetes mellitus                             | 14 (16.5)      | 4 (7.5)        | 0.140   |
| History of stroke                             | 11 (12.9)      | 12 (23.1)      | 0.123   |
| Etiology of valvular disease                  |                |                | 0.179   |
| Degenerative (Rheumatic, Degenerative, Other)  |                |                |         |
| Left ventricular ejection fraction (%)        | 55.2±8.9       | 56.5±8.4       | 0.405   |
| Left atrium dimension (mm)                    | 60.5±11.7      | 60.2±11.7      | 0.856   |
| Tricuspid regurgitation ≥ moderate            | 23 (27.1)      | 22 (41.5)      | 0.078   |
| AF duration (yr)                              | 7.0±6.0        | 7.7±6.2        | 0.540   |
| F wave size (mm)                              | 1.4±0.8        | 1.2±0.6        | 0.054   |

Values are presented as mean±standard deviation or number (%).

AF, atrial fibrillation.

Table 2. Operative data of the study population

| Variable                                      | Group N (n=85) | Group A (n=53) | p-value |
|-----------------------------------------------|----------------|----------------|---------|
| Aortic cross clamp time (min)                 | 151±39         | 167±43         | 0.034   |
| Cardiopulmonary bypass time (min)             | 225±48         | 245±51         | 0.019   |
| Other cardiac procedures                      |                |                |         |
| Mitral valve procedure                        | 80 (94.1)      | 43 (81.1)      | 0.017   |
| Aortic valve procedure                        | 28 (32.9)      | 15 (28.3)      | 0.567   |
| Tricuspid valve surgery                       | 75 (88.2)      | 42 (79.2)      | 0.153   |
| Aortic surgery                                | 7 (8.2)        | 6 (11.3)       | 0.562   |
| Coronary arterial bypass grafting             | 4 (4.7)        | 3 (5.7)        | >0.999  |
| Redo open heart surgery                       | 0              | 2 (3.8)        | 0.146   |
| Concomitant use of radiofrequency ablation    | 85 (100.0)     | 46 (86.8)      | 0.001   |

Values are presented as mean±standard deviation or number (%).

(n=117, 84.8%), ascending aorta procedures (n=13, 9.4%), and coronary artery bypass grafting (n=7, 5.1%). There were two redo open heart surgery cases, both of which belonged to group A. The maze lesion sets were standardized for all patients, as described in our previous report [10], with the exception of the energy sources for ablation. Bipolar radiofrequency ablation was concomitantly used in 131 patients (Table 2).

2) Early clinical results

Early mortality occurred in 6 patients (4.3%). Postoperative morbidities included low cardiac output syndrome (n=7, 5.1%), postoperative bleeding (n=3, 2.2%), acute renal failure (n=2, 1.4%), stroke (n=4, 2.9%), and thromboembolic event (n=1, 0.7%). There were no differences in early mortality or postoperative complications between the two groups (Table 3).

3) Rhythm status and risk factors for maze failure

Twenty-two patients (15.9%) exhibited consistent AF immediately after surgery. ECG performed 6 months and 12 months postoperatively demonstrated the AF rhythm in 18.2%
(22 of 121 patients) and 16.5% (19 of 115 patients) of the patients, respectively. In the early postoperative days, more patients in group A exhibited the AF rhythm than in group N (9 of 85 patients [10.6%] in group N vs. 13 of 53 patients [24.5%] in group A; p=0.030). At 6 months, 12 months, and 2 years postoperatively, however, there were no significant differences in the proportions of patients with AF between the two groups (Table 4, Fig. 1).

The risk factors for maze failure at 1 year postoperatively were analyzed. In univariate analyses, old age (p=0.004), large left atrial dimension (p=0.026), a preoperative F wave of less than 0.1 mV (p<0.001), and tricuspid regurgitation

Table 3. Early mortality and postoperative complications

| Variable                   | Group N (n=85) | Group A (n=53) | p-value |
|----------------------------|----------------|----------------|---------|
| Early mortality            | 2 (2.4)        | 4 (7.5)        | 0.197   |
| Postoperative complications |                |                |         |
| Low cardiac output syndrome| 4 (4.7)        | 3 (5.7)        | >0.999  |
| Bleeding reoperation       | 2 (2.4)        | 1 (1.9)        | >0.999  |
| Acute renal failure        | 0              | 2 (3.8)        | 0.139   |
| Stroke                     | 2 (2.4)        | 2 (3.8)        | 0.631   |
| Thromboembolic event       | 1 (1.2)        | 0              | >0.999  |

Values are presented as number (%).

Table 4. Rhythm status of the study patients

| Period       | Status   | Group N | Group A | p-value |
|--------------|----------|---------|---------|---------|
| Immediate    | AF-free  | 76      | 40      | 0.030   |
| 6 months     | AF       | 9       | 13      |         |
| 12 months    | AF-free  | 66      | 30      | 0.669   |
| 24 months    | AF-free  | 58      | 12      | 0.760   |
|              | AF       | 14      | 5       |         |

AF, atrial fibrillation.

Fig. 1. The proportions of patients with AF in (A) groups N and (B) A. There were no differences in the proportions between the two groups in each time period except the immediate postoperative period (p=0.030). AF, atrial fibrillation.

Table 5. Risk factor analysis for presence of atrial fibrillation at 1 year after maze operation

| Variable                           | Univariate p-value | Multivariate Odds ratio (95% confidence interval) | p-value |
|------------------------------------|---------------------|---------------------------------------------------|---------|
| Age                                | 0.004               | 1.061 (0.982–1.146)                                 | 0.136   |
| Preoperative left atrium dimension | 0.026               | 1.016 (0.968–1.066)                                 | 0.519   |
| F wave size (<0.1 mV)              | <0.001              | 20.287 (4.189–96.331)                               | <0.001  |
| Preoperative tricuspid regurgitation ≥ moderate | 0.028                  | 2.352 (0.631–8.773)                                | 0.203   |
| Energy source for cryoablation     | 0.669               | 0.876 (0.199–3.866)                                 | 0.862   |
| Concomitant use of radiofrequency ablation | >0.999                 | -                                                 | -       |
greater than or equal to the moderate grade (p=0.028) were significant risk factors for maze failure. A concomitant use of RF ablation was not a significant risk factor for maze failure. Multivariate analysis revealed that the fine F wave (<0.1 mV) was the only significant risk factor predicting the presence of AF after 1 year (p<0.001, odds ratio=20.287). The energy source of cryoablation was not associated with the presence of AF after 1 year (p=0.862) (Table 5).

DISCUSSION

The original Cox maze procedure was introduced in 1987 as a cut-and-sew method [12,13]. Since then, the time-consuming and technically challenging cut-and-sew lesions have been replaced by the application of alternative energy sources. In 1999, the first non-cut-and-sew full Cox maze procedure was performed using cryothermal energy as the only ablation modality, and the Cox maze III procedure was modified into the Cox maze IV procedure, which is less invasive and requires less procedure time. In this procedure, the pulmonary veins are isolated bilaterally, and a connecting lesion is applied rather than performing the original box lesion [9]. This modification was based on the findings published in the work of Haissaguerre and his colleagues [14].

Various ablation devices have been developed using different energy sources to perform the ablation, including radiofrequency (unipolar and bipolar), microwave, laser, cryoablation, and high-frequency ultrasound [9]. With all the available energy sources, the major issue remains the reliable creation of a transmural lesion. Disagreement exists with respect to the optimal energy sources used in creating the transmural lesion with the efficacy of the cut-and-sew Cox maze III procedure [15,16]. However, experimental data demonstrate that heating a tissue with radiofrequency energy for approximately 1 minute at 70°C to 80°C produces lesions that are 3- to 6-mm deep, usually sufficient to create a transmural line of the conduction block, and the application of an N₂O-based cryoprobe to the atrial tissue for 2 minutes at -60°C reliably produces a transmural lesion [3]. In our previous report, we demonstrated that the Cox maze IV procedure using N₂O-based cryoablation and bipolar radiofrequency was a safe and effective method to terminate AF [10].

The major advantages of cryoablation are the visual confirmation of transmurality by an 'ice ball' formation; the rapid creation of a focal lesion; the preservation of the underlying tissue architecture, possibly decreasing the risk of thrombus formation; and the strong adherence of the probe to the tissue surface during freezing, which helps positioning. Among the modalities of cryoablation, argon-based cryoablation has some advantages over N₂O-based cryoablation: 1) Argon-based cryoablation can reach temperatures of -140°C to -160°C compared with -60°C for N₂O-based cryoablation, allowing for a faster and more reliable lesion. 2) Argon-based cryoablation uses a long and flexible probe, which can create long lesions relatively quickly, conforms to the cardiac contours around the heart structures, and allows the surgeon to perform other procedures during cryoablation. 3) Argon-based cryoablation uses an adjustable insulation sheath that can cover the cryoablation segment [11,17]. In the present study, however, the aortic cross-clamp and cardiopulmonary bypass times were not shorter in group A than those in group N despite the advantages of argon-based cryoablation over N₂O-based cryoablation. This might be due to the differences in operative characteristics such as more cases of redo open heart surgery and combined aortic operation, and less frequent use of RF ablation in group A patients than in group N patients.

Some investigators have reported the results of argon-based cryoablation for the AF treatment during a concomitant cardiac operation. In these reports, 81% to 89% of the patients were free from AF at 12 months, and 70% to 71% of the patients were free from AF at 24 months [17,18]. Although there were some differences in the technique and ablation lesion set, we achieved similar results in group A, with freedom from AF in 85.7% and 70.6% of the patients after 12 months and 2 years, respectively. These results were similar to those of the maze procedure using N₂O-based cryoablation. Our data confirmed that argon-based cryoablation was as effective as N₂O-based cryoablation, which has been widely used with proven safety and efficacy. Considering the advantages of argon-based cryoablation described above, our data support the use of the Cox maze IV procedure with argon-based cryoablation in patients with AF.

Risk factors for the failure of maze procedures include old-
er age, larger left atrial size, and the presence of preoperative tricuspid regurgitation [9,10]. This analysis also observed that older age, larger left atrial size, and preoperative more than moderate tricuspid regurgitation were significant risk factors for the failure of maze procedures in the univariate analysis but not in the multivariate analysis. In the multivariate analysis, the fine F wave (≤0.1 mV) was the only significant risk factor predicting the presence of AF after 1 year.

The limitations of this study are as follows. First, the present study was designed as a retrospective study. Second, the patients’ rhythm status was evaluated using only a 12-lead ECG at each time period. Third, the number of patients was relatively small to draw definite conclusions.

In conclusion, the Cox maze IV procedure using an argon-based cryoprobe is safe and effective compared with the maze procedure using an N₂O-based cryoprobe in terms of the operative outcomes and the restoration of the sinus rhythm for up to 2 years after surgery.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Doty DB. Surgical treatment of atrial fibrillation. Heart Lung Circ 2004;13:280-7.
2. Narayan SM, Cain ME, Smith JM. Atrial fibrillation. Lancet 1997;350:943-50.
3. Gillinov AM, Blackstone EH, McCarthy PM. Atrial fibrillation: current surgical options and their assessment. Ann Thorac Surg 2002;74:2210-7.
4. Fuster V, Ryden LE, Cannon DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: executive summary. Rev Port Cardiol 2007;26:383-446.
5. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002;347:1834-40.
6. Crijns HJ, Van Gelder IC, Van Gilst WH, Hillege H, Gosselink AM, Lier KI. Serial antiarrhythmic drug treatment to maintain sinus rhythm after electrical cardioversion for chronic atrial fibrillation or atrial flutter. Am J Cardiol 1991;68:335-41.
7. Falk RH. Proarrhythmia in patients treated for atrial fibrillation or flutter. Ann Intern Med 1992;117:141-50.
8. Flaker GC, Blackshear JL, McBride R, Kronmal RA, Halperin JL, Hart RG. Antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators. J Am Coll Cardiol 1992;20:527-32.
9. Ad N. The Cox-Maze procedure: history, results, and predictors for failure. J Interv Card Electrophysiol 2007;20:65-71.
10. Kim JS, Lee JH, Chang HW, Kim KH. Surgical outcomes of Cox-maze IV procedure using bipolar irrigated radiofrequency ablation and cryotherapy in valvular heart disease. Korean J Thorac Cardiovasc Surg 2011;44:18-24.
11. Yanagawa B, Holmes SD, Henry L, Hunt S, Ad N. Outcome of concomitant Cox-maze III procedure using an argon-based cryosurgical system: a single-center experience with 250 patients. Ann Thorac Surg 2013;95:1633-9.
12. Prasad SM, Maniar HS, Camillo CJ, et al. The Cox maze III procedure for atrial fibrillation: long-term efficacy in patients undergoing lone versus concomitant procedures. J Thorac Cardiovasc Surg 2003;126:1822-8.
13. McCarthy PM, Gillinov AM, Castle L, Chung M, Cosgrove D 3rd. The Cox-Maze procedure: the Cleveland Clinic experience. Semin Thorac Cardiovasc Surg 2000;12:25-9.
14. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659-66.
15. Viola N, Williams MR, Oz MC, Ad N. The technology in use for the surgical ablation of atrial fibrillation. Semin Thorac Cardiovasc Surg 2002;14:198-205.
16. Damiano RJ Jr. Alternative energy sources for atrial ablation: judging the new technology. Ann Thorac Surg 2003;75:329-30.
17. Rahman NM, Chard RB, Thomas SP. Outcomes for surgical treatment of atrial fibrillation using cryoablation during concomitant cardiac procedures. Ann Thorac Surg 2010;90:1523-7.
18. Rahmanian PB, Filsoofi F, Salzberg S, Coppolino A, Castillo JG, Adams DH. Surgical treatment of atrial fibrillation using cryotherapy in patients undergoing mitral valve surgery. Interact Cardiovasc Thorac Surg 2008;7:990-5.