Cryoablation for surgical treatment of chronic atrial fibrillation combined with mitral valve surgery: a clinical observation

Alireza Alizadeh Ghavidel*, Hossein Javadpour, Massoud Shafiee, Mohammad-Bagher Tabatabaie, Kamal Raiesi, Saeed Hosseini

Department of Cardiovascular Surgery, Rajaee Heart Centre, Vali e Asr Avenue, Tehran, Iran

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Abstract

Objective: Although the classical Cox-Maze III is the gold standard surgical therapy with a proven efficacy in the treatment of atrial fibrillation (AF), complexity of this procedure has resulted in a search for a simpler, less invasive and more cost-effective method. In this study we evaluated the results of cryosurgical ablation in the treatment of chronic AF in patients undergoing concomitant mitral valve surgery.

Methods: Ninety patients (mean age: 50.9 ± 12 years) with chronic AF who were having mitral valve surgery as the main procedure underwent cryoablation with a newly designed N2O-based cryotherapy device. Pulmonary vein isolation with or without left atrial appendage closure (group A) was carried out in 65 cases and cryoablative bi-atrial Cox-Maze III (group B) in 25 patients. This additional procedure took only an extra 10 min for group A and about 20 min for group B. Half of the patients received a beta-blocker following the procedure.

Results: The overall success rate of cryoablation was 65.5%. Normal sinus rhythm was achieved in 26.7% in the operating room, 10% in ICU and the remaining cases reverted to sinus rhythm during the follow-up period. There were no major ablation-related complications such as bleeding, thromboembolic events or A-V block. The only predictor for failure of ablative procedure was left atrial size of greater than 6 cm.

Conclusion: Although in this study the efficacy rate of cryoablative surgery was not the same as classical Cox-Maze III, it seems that this procedure is safe, simple, cost-effective and at the same time does not increase the operative time significantly. Using cryoablation may enhance the cure rate of chronic AF during mitral valve surgery.

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Keywords: Atrial fibrillation; Cox-Maze III; Cryoablation; Mitral valve disease

1. Introduction

Atrial fibrillation (AF) is the most commonly sustained cardiac arrhythmia that presents in 0.4% of the general population and up to 60–80% of patients undergoing mitral valve operations [1,2]. Two main therapeutic strategies includes rate and rhythm control. Rhythm control is considered more desirable because it not only relieves the patient’s symptoms but also reduces the risk of thromboembolic events and improves cardiac performance by reestablishing the synchronized atrial contractions [2,3]. Rhythm control with antiarrhythmic drugs and cardioversion is only successful in about 50% of cases [3]. Cox-Maze procedure that was introduced by James L. Cox in 1987 as a cut-and-sew technique has been proven to be highly effective in restoring sinus rhythm in patients undergoing concomitant mitral valve procedures [1–3]. Success rates between 75% and 97% have been reported [2–5]. The classical maze is a complex and time-consuming operation and because it is an additional procedure to the main mitral valve surgery, cardiopulmonary bypass and cross-clamp times may be prolonged significantly. Different energy sources have been introduced to create transmural intra-atrial lesions similar to those used in the original cut-and-sew Maze procedure, cryoablation being one of these modalities [1,3,6].

AF is frequently initiated by triggers from the pulmonary veins (PVs). As a result, various ablative procedures have focused on electrically isolating pulmonary veins from the atria [4,7,8]. Success rate of these procedures without antiarrhythmic drugs is 57–70%. The recurrence rate of 20–60% is a result of non-PV foci or recovery of an induced lesion [4].

The aim of the present study is to evaluate the safety, feasibility and effectiveness of a modified cryoablation technique for PV isolation in patients with AF rhythm undergoing mitral valve surgery.

2. Patients and methods

2.1. Patient population

The study was approved by the hospital ethical committee. Since the device is a newly designed and manufactured...
machine, the patients were fully informed, however the device is the only cardiac ablation available at the center and the patients were given the option of not having the ablative procedure at all.

Between March 2004 and August 2005, 90 consecutive patients with chronic AF, (defined as AF lasting for more than 6 months), and rheumatic mitral valve (MV) disease who scheduled for MV repair or replacement with or without additional cardiac procedures were selected. There were 31 males (34.4%) and 59 females (65.6%) with a median age of 52 years (range: 17—74 years). The mean AF duration was 16 ± 8 months (range: 6—84 months) (Table 1). The modified Maze III procedure using Danesh Co. cryoablation machine (Danesh Medical Engineering Co., Tehran, Iran) with three different shaped probes (Fig. 1) which are reusable. Cooling temperature at the probe site reaches —60 °C. It uses three different shaped probes (Fig. 1) which are reusable. Experiments have shown in order to achieve maximum tissue penetration at the above temperature; 2 min of tissue contact is necessary. The device is approved by the Iranian health ministry. The company has more than 15 years experience in cryo-device manufacturing.

### 2.2.2. Procedure

The heart was exposed through a standard median sternotomy under general anesthesia. Cardiopulmonary bypass was established with the use of ascending aortic and bicaval cannulations with moderate hypothermia (32 °C). The mitral valve was either repaired or replaced with a suitably sized prosthetic valve. Additional procedures including coronary artery bypass grafting or other valvular surgery was carried out accordingly. The cryoablative Cox-Maze III procedure was performed during the re-warming phase with the heart still under cardioplegic arrest. In group A cryoablation was done with three linear lesions to create isolation of PVs. A linear full thickness lesion was created extending from the lateral side of right superior PV to the posterior aspect of left atrium using the T-shaped probe. Then LAA was ligated with a non-absorbable suture in case of clot or where the appendage had a wide base; this was done after removal of the aortic cross-clamp.

In group B bi-atrial cryoablation was performed as a modified Cox-Maze III. Left atrial cryoablation was performed in the arrested heart after the MV procedure. In addition to the left atriotomy incision in the inter-atrial groove, isolation of the right PVs was completed by a unilateral ablation line. Then the left PVs were encircled, and a transverse connecting line was drawn between both sides PVs. Two additional ablation lines extended from the ablation line of the left PVs to the base of left atrial appendage (LAA) and to the posterior MV annulus. The LAA was resected in these patients.

The right-sided cryoablation was carried out during the re-warming phase after removing the aortic cross-clamp. The

### Table 1

<table>
<thead>
<tr>
<th>Patient’s characteristics</th>
<th>Group A</th>
<th>Group B</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (year)</td>
<td>50 ± 12.4</td>
<td>49 ± 12.6</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>24/41</td>
<td>7/18</td>
<td>NS</td>
</tr>
<tr>
<td>AF* rhythm duration (months)</td>
<td>9.4 ± 14</td>
<td>14.8 ± 20</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Preoperative LVEF (%)</td>
<td>47 ± 5.8</td>
<td>45 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Postoperative LVEF (%)</td>
<td>42 ± 7.2</td>
<td>39 ± 5.5</td>
<td>NS</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>120 ± 37</td>
<td>141 ± 40</td>
<td>0.05</td>
</tr>
<tr>
<td>LA* size &gt; 6 cm</td>
<td>10 (15.4%)</td>
<td>4 (16%)</td>
<td>NS</td>
</tr>
<tr>
<td>Thromboembolic event</td>
<td>1 (1.5%)</td>
<td>3 (12%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Preoperative beta blocker use</td>
<td>20/65</td>
<td>8/25</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Atrial fibrillation.

### Table 2

<table>
<thead>
<tr>
<th>Different types of surgical procedures</th>
<th>Group A</th>
<th>Group B</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVR*</td>
<td>20 (30.7)</td>
<td>7 (28.0)</td>
<td>0.5</td>
</tr>
<tr>
<td>MV repair</td>
<td>2 (3.0)</td>
<td>1 (4.0)</td>
<td>0.6</td>
</tr>
<tr>
<td>OMVC*</td>
<td>5 (7.7)</td>
<td>1 (4.0)</td>
<td>0.46</td>
</tr>
<tr>
<td>Re-do MVR</td>
<td>6 (9.2)</td>
<td>2 (8.0)</td>
<td>0.6</td>
</tr>
<tr>
<td>MVR + CABG*</td>
<td>3 (4.6)</td>
<td>1 (4.0)</td>
<td>0.69</td>
</tr>
<tr>
<td>MVR + LA clot removal</td>
<td>3 (4.6)</td>
<td>0</td>
<td>0.37</td>
</tr>
<tr>
<td>MVR + TV repair</td>
<td>12 (18.5)</td>
<td>6 (24.0)</td>
<td>0.37</td>
</tr>
<tr>
<td>MVR + AVR*</td>
<td>4 (6.1)</td>
<td>3 (12.0)</td>
<td>0.29</td>
</tr>
<tr>
<td>MVR + AVR + TV repair</td>
<td>8 (12.3)</td>
<td>3 (12)</td>
<td>0.6</td>
</tr>
<tr>
<td>MVR + LA clot removal + TV repair</td>
<td>2 (3.0)</td>
<td>1 (4.0)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

The numbers in parentheses are percentages.

* Mitral valve replacement.

### 2.2.1. Device

The cryoablative device C.A. 2001 T.B.T. was designed and manufactured by Danesh Medical Engineering Co., Tehran, Iran. It uses nitrous oxide (N₂O) as the cooling agent and the cooling temperature at the probe site reaches —60 °C. It uses three different shaped probes (Fig. 1) which are reusable. Experiments have shown in order to achieve maximum tissue penetration at the above temperature; 2 min of tissue contact is necessary. The device is approved by the Iranian health ministry. The company has more than 15 years experience in cryo-device manufacturing.

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**Fig. 1.** Different probes used in cryoablation.
first ablation line was created between superior and inferior vena cava. Additional lines were drawn from the medial aspect of the base of the excised right atrial appendage (RAA) into the annulus of tricuspid valve, and from the caudal end of the surgical right atriotomy to the posterior part of tricuspid valve. The fourth ablation line was drawn on the right atrial side of inter-atrial septum from the middle of the right atriotomy up to the caudal aspect of the coronary sinus. The last line was extended from coronary sinus near the fourth line to the inferior vena cava cannulation site.

Intraoperative transesophageal echocardiography was done for the majority of patients. Two right ventricular and two right atrial epicardial pacing wires were placed in all patients for dual-chamber pacing when needed.

2.3. Postoperative management

All survivors were followed up closely during the first admission and 1, 3, 6 and 12 months after the operation. All patients received anticoagulants including heparin for the first few days and Warfarin to maintain the international normalized ration (INR) value of 2.5—4 based on the type of surgery and cardiac rhythm. Antiarrhythmic drugs were continued for at least 6 months using propranolol (20—80 mg/day) or metoprolol (25—100 mg/day). At each follow-up date a medical and clinical history and an electrocardiogram (ECG) was carried out. Holter monitoring was performed for patients with normal sinus rhythm and postoperative palpitation. Electrical or medical cardioversion was not performed for patients in whom the procedure had failed. Transthoracic echocardiographic assessment was carried out for all survivors on the 4th—7th postoperative days and at the first follow-up visit. Postoperative TEE was performed in patients with suspicious prosthetic valve malfunction and those with valve repair.

2.4. Statistical analysis

The statistical analysis was performed using the SPSS version 11 software package.

Continuous variables were expressed as mean ± standard deviation. Differences of frequencies were compared using chi-squared test and Fisher’s exact test. A p-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Patient demographics

Patients in group A (n = 65) and patients in group B (n = 25) did not differ with regard to age, sex, preoperative left ventricular ejection fraction (LVEF) and left atrial size. Table 1 shows the clinical characteristics of patients in the two groups. Group B had significantly more preoperative thromboembolic episodes (12% vs 1%) and a longer duration of atrial fibrillation (14.8 months vs 9.4 months). Mean postoperative follow-up duration was 10 ± 2.8 months in group A and 8 ± 1.3 months in group B (p = 0.72). The additional cardiopulmonary bypass time required to perform the cryoablation was 14 ± 2.8 min for group A patients and 22 ± 5.3 min in group B. The additional ischemic time needed to perform the ablation procedures in group A and B was 10 ± 3.5 min and 13 ± 5.1 min, respectively (p < 0.05).

The antiarrhythmic medications were prescribed as necessary by the reviewing cardiologist. At follow-up we could ascertain medications in only 45 patients (52.2%), 24 were taking B-blockers and only 3 were taking amiodarone.

3.2. Mortality and major complications

The overall mortality rate was 3.3% (three patients). The in-hospital death rate was zero in group A and 1.2% (one case) in group B (p = 0.78). This was a 65-year-old woman who had mitral and aortic valve replacement plus tricuspid valve repair. The cause of death was multiple organ failure secondary to low cardiac output.

The late mortality rate was 2.3% (two patients). A 63-year-old woman in group A died 3 months after mitral and tricuspid valve replacement due to congestive heart failure. The second case was a 68-year-old man in group B who died 7 months after mitral valve replacement as a result of rightsided heart failure.

There were no instances of atrial or esophageal perforation and infective endocarditis. No permanent pace-maker implantation was necessary in this series. Postoperative echocardiographic assessment showed widely patent pulmonary veins and normal pulmonary veins orifices in all patients. The incidence of re-exploration for surgical bleeding was 3.3% (3/90). Cardiac tamponade occurred in two patients (2.2%). History of preoperative thromboembolic cerebrovascular accident was recorded in three cases, but no thromboembolic event was seen postablation period. Three patients showed evidence of neurocognitive disturbances.

3.3. Success rate of cryoablation

The overall success rate of cryoablation was 65.5%. Normal sinus rhythm was achieved in 26.7% of patients in the operating room, 10% in the ICU and the remaining cases achieved sinus rhythm during the follow-up period. At the
first postoperative day, 19 patients (29.2%) from group A and five patients (20%) from group B were in sinus rhythm ($p < 0.05$). During the hospitalization period 25 patients (38.5%) in group A and 10 patients (40%) in group B converted from atrial fibrillation to sinus rhythm ($p = 0.76$). At the 6–12 month follow-up period 67.7% (45/65) in group A and 60% (15/25) in group B were in sinus rhythm, ($p = 0.68$).

Four patients (5.1%) in group A and one case in group B who had achieved sinus rhythm converted back to atrial fibrillation ($p = 0.88$). Table 3 shows the postoperative cardiac rhythms in the two study groups.

### 3.4. Predictors for failure of ablation

Patients were divided into three groups according to preoperative left atrial (LA) size using echocardiographic assessment. LA size was less than 4 cm in group I, 4–6 cm in group II and more than 6 cm in group III. Sixty percent of group I patients converted to normal sinus rhythm before hospital discharge but this rate was 35% for group II and only 14.3% for group III (Table 4). Overall success rate of cryoablation was significantly lower in group III ($p = 0.0006$ compared to group I, $p = 0.0003$ compared to group II, Fisher’s exact test). Longer duration of AF rhythm was the next important predictive factor for failure of ablative procedure. None of the patients who had AF for more than 60 months achieved sinus rhythm therefore the success rate of cryoablative procedure in these patients was zero. In comparison the success rate of the operation in patients who were in AF for less than 12 months was more than 70% ($p > 0.05$).

<table>
<thead>
<tr>
<th>No. (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation room</td>
<td>ICU*</td>
</tr>
<tr>
<td>Group A</td>
<td>19 (29.2)</td>
</tr>
<tr>
<td>Group B</td>
<td>5 (20.0)</td>
</tr>
</tbody>
</table>

The numbers in parentheses are percentages.

a Intensive care unit.
b Atrial fibrillation.
c Normal sinus rhythm.

### 4. Discussion

The aim of any surgical procedure for treating AF is to diminish uncomfortable symptoms of this arrhythmia by restoring sinus rhythm, to regain atrial kick to improve hemodynamic status, and to reduce the risk of thromboembolic events [2,6,9,10]. Spontaneous conversion to sinus rhythm after mitral valve surgery alone is 8–27%. The classical Cox-Maze III procedure has become the most successful surgical treatment for medically refractory AF but is associated with certain limitations such as poor atrial functional recovery and loss of effective atrial contraction [6,9]. Cox et al. [11] has reported a 99% success rate among 346 patients with AF. The operative mortality was 2%, and 15% needed a new pacemaker after the procedure. Others have reported less success with this procedure with late freedom from AF of about 90% [12,13]. In most series, combining mitral valve surgery with the Cox-Maze III resulted in abolition of AF in only 75–82% of patients [14,15].

The classical Cox-Maze III operation has not been widely adopted as a method for treatment of AF. This is primarily due to the operative complexity of this procedure. Even in experienced hands, this operation requires about 1 h of extra cardiopulmonary bypass time [16]. Several energy sources were developed to tackle these problems namely radiofrequency, cryotherapy and microwave energy. The introduction of new devices using alternative energy sources added some benefit including simplification and reduction of operative time without compromising the surgical outcome significantly [6,8,16].

Radiofrequency uses alternating current of 350 kHz to 1 MHz to heat tissue. Using this energy source for 1 min at 70–80°C produces lesions 3–6 mm deep, enough to create a transmural lesion. The success rate of radiofrequency in abolition of AF in patients undergoing mitral valve surgery has been 70–80% [17,18]. Microwave energy uses high-frequency electromagnetic radiation which causes oscillation of water molecules in tissue. The depth and volume of heated tissue is greater with microwaves than with radiofrequency and the probability of creating transmural lesion is greater, in addition microwave heating does not char the endocardial surface [19]. Knaut et al. reported an 80% success rate with this energy modality in curing AF [20]. Application of cryotherapy at −60°C for 2 min on an arrested heart produces transmural lesions [21]. The success rate of cryotherapy for AF ablation has been reported to be 78% [22]. Limited left atrial cryoablation with isolation of pulmonary veins cures AF in approximately 70% of patients [23]. Unlike radiofrequency ablation, cryoablation generally preserves the integrity of
adjacent anatomic structures, presumably due to its preservation of collagen tissue [16]. Recent molecular-based research suggests that apoptosis may be a mechanism of cell death, particularly in the periphery of the cryogenic lesions [24]. Additionally, in comparison with radiofrequency, cryoablation is not considered thrombogenic and is less expensive [6]. There have been no reports of collateral coronary or esophageal damage [6].

PV isolation for paroxysmal AF has been shown to be effective and safe, but the success rate has been reported to be approximately 70% because of the presence of non-PV foci and persistence of the substrate of AF [4,7]. Left atrial linear lesions at various locations have been demonstrated to modify the substrate and prevent the clinical occurrence of AF. However, the ideal number and positions of linear lesions are unknown [4].

This study presents some information about the feasibility and role of a modified linear cryoablative procedure in comparison with standard bi-atrial cryoablative procedure in the treatment of AF. We achieved an overall success rate of 65.5% after a mean follow-up of 10 ± 2.8 months. The success rate was 67.7% in group A and 60% in group B. This difference was not statistically significant. Meanwhile we observed the same predictors for failure of ablation procedure between the two groups. If we exclude the patients with an LA size of larger than 6 cm in diameter the success rate of our study reaches 75%. However we have only confirmation of transmurality with our device in cadaveric and animal hearts and this may be a reason for our overall reduced sinus conversion rate. Niv Ad and co-workers reported excellent results with an early success rate of 98% and mortality rate of 3.7% by using bi-atrial cryoablation [10]. Bourke reported a success rate of 55% with pulmonary vein catheter ablation and he emphasized that this method is a complex form of ablation with a significant risk of serious complication [5].

Several series have studied predictors of success or failure when performing the Maze procedure. These included large LA size, increased cardiothoracic ratio, AF duration and presence of rheumatic heart disease [2,3,6,9,10,16]. We found the large LA size (6 cm or more) and longer duration of AF rhythm (more than 12 months) as major predictors for failure of this technique. The underlying disease or ablation method did not affect the success rate of the procedure.

Surgical complication in our series was limited to general morbidity of open heart surgery and we did not observe cryoablation-related problems such as PV stenosis, the need for permanent pace-maker insertion, esophageal perforation or thromboembolic events. Since we only used echocardiography, the incidence of pulmonary vein stenosis may be under-estimated.

In conclusion mitral valve surgery with or without other concomitant procedures can safely be combined with a modified cryoablative operation which is simple, time-saving and cost-effective. Addition of this procedure results in restoration of sinus rhythm in significantly more patients as compared to mitral valve surgery alone.

This non-randomized study was small in size and may not be enough to obtain sufficient confidence. Follow-up period was short and we could not yet comment on the long-term efficacy of the procedure and recurrence rate of AF. No microscopic or macroscopic examinations were performed on the cryo-induced lesions, therefore, we cannot speculate on the ablation lesion size or depth. Furthermore, since the antiarrhythmic medications could not be ascertained in the majority of patients we cannot comment on the effects of these agents on our results.

There were no significant differences between the results of PV isolation and bi-atrial ablation in our study; however taking into account the limitations of this study as mentioned above, the cryoablative PV isolation in patients undergoing mitral valve procedures with or without concomitant cardiac procedures may be justified especially when the LA size less than 6 cm.

References


