Recent topics on the surgical treatment of chronic atrial fibrillation: Efficacy and safety of Cryosurgical ablation.

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Background: Although the classical Cox-Maze III is the gold standard surgical therapy with a proved efficacy in atrial fibrillation (AF) therapy, complexity of this procedure dictated a more simple, less invasive & cost-effective method. In an attempt to achievement of this purposes we evaluated the role of cryosurgical ablation.

Patients & Method: Ninety patients (mean age: 50.9+/-12 yr.) with open heart surgeries complicated by chronic AF, underwent cryoablation with a new designed N2O-based cryotherapy device (Danesh Co. Ltd) during the main heart operations. Pulmonary vein isolation with or without left atrial appendage closure (Group A) carried in 65cases & Biatrial Cox-Maze III (Group B) for the others .This additional procedure consuming only about 10 min for P.V isolation group & about 20 min. for Cox-Maze III group. Half of the patient received a beta-blocker after AF ablation.

Results: The overall success rate of cryoablation was 65.5%. Normal sinus rhythm achieved in 26.7% at operating room, 10% at ICU & remaining cases got the sinus rhythm during follow up period. There were no ablation-related serious post-operation complication such as bleeding, thromboembolic events & A-V block. The only predictor for failure of ablative procedure was sever left atrial enlargement (>6 cm).

Conclusion: Although the efficacy rate of cryoablative surgery was not as high as classic Cox-Maze III at present study, it seems that the supplementation of this safe, simple, cost-effective & not time consuming procedure may enhances the cure rate of chronic AF during mitral valve surgeries.

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Introduction:

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia that present in 0.4% of the general population and up to 60-80% of patients undergoing mitral valve operations.[1,2,9] Two main therapeutic strategies includes rate and rhythm control. Rhythm control is better option because it can not only relief the patient's symptom but also reduce the risk of thromboemolic events and improve cardiac performance by reinstituting the synchronized atrial contractions.[2,3] Rhythm control with antiarrhythmic drugs and cardioversions is unsuccessful in almost half of the patients.[3] Cox-maze procedures that was introduced by James L. Cox in 1987 as a cut-and sewn technique has been proven to be highly effective in restoring sinus rhythm in patients with concomitant mitral valve surgeries.[1,2,3] Success rate between 75% and 97% have been reported.[2,3,4,5] The classic 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-clamping times might be prolonged. Therefore other modalities have been introduced to create transmural intra-atrial lesions similar to those used in the original cut and sewn Maze procedure such as cryosurgical AF ablation surgery [1,3,6].

AF is frequently initiated by triggers from the pulmonary veins (PVs). As a result, various pulmonary veins ablation leading to ablative procedures focused on electrically isolate these structures from the atria.[4,7,8] Success rate of these

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procedures without antiarrhythmic drugs is 57-70% but are associated with a 20% to 60% recurrence as the result of non-PV foci or recovery of induced lesion.[4]
The aim of present study was to evaluate the safety, feasibility and effectiveness of a modified cryoablation technique for PV isolation in patients with AF rhythm undergoing mitral valve procedures.

Material & methods

Patient population

Between March 2004 and August 2005, 90 consecutive patients with persistent AF rhythm, which was defined as AF lasting for >4 weeks, and rheumatic mitral valve (MV) disease who scheduled for MV repair or replacement with or without additional cardiac procedures was selected. Of the ninety patients 31 cases were male (34.4%) and 59 were female (65.6%) with median age of 52 years (range between 17 to 74 yr.) The mean AF duration was 16 +/- 11 months (range: 1-84 month (Table 1).

Table1: *Different aspects of patient characteristics between two study groups.*

	Group A	Group B	P value
Mean age (year)	50 +/- 12.4	49+/-12.6	P = NS
Sex (M/F)	24/41	7 / 18	P = NS
AF* rhythm duration (month)	9.4+/-14	14.8+/-20	P < 0.05
Preoperative LVEF** (%)	47+/-5.8	45+/-8	P = NS
Postoperative LVEF (%)	42+/-7.2	39+/-5.5	P = NS
CPB*** time (minute)	120+/-37	141+/-40	P = 0.05
Sever LA**** enlargement	10 (15.4%)	4 (16%)	P = NS
Thromboembolic event	1 (1.5%)	3 (12%)	P <0.05
Preoperative beta blocker use	20 / 65	8 / 25	P = NS

*Atrial fibrillation, **Left ventricular ejection fraction, ***Left atrium.

The modified Maze III procedure using Danesh Co. cryoablation machine with 3 different shape probes was simultaneously performed with mitral valve replacement (MVR) or mitral valve repair by a single surgeon. According the surgeon's preference the cryoablative Maze procedure was performed as PV isolation with or without left atrial appendage (LAA) in 65 patients (group A) or as Cox-Maze III (biatrial cryoablation) in the other 25 patients (group B). Table 2 shows different types of performed surgical procedures. The patients followed up from 1to 12 months and subsequent data were collected by physical examination, ECC, transthoracic echocardiography (TTE), transesophageal echocardiography and electrophysiologic studies as needed.

Statistical analysis:

Continuous variations were expressed as mean+/- standard deviation. Differences of frequencies were compared using chi-square test and fisher exact test. A p value less than 0.5 was considered statistically significant. The statistical analysis was performed using the SPSS version 11 software package.

Surgical technique:

The heart was exposed through a standard median sternotomy under general anesthesia. Cardiopulmonary bypass was instituted with the use of ascending aorta and bicaval cannulations during moderate hypothermia (32oC). The mitral valve either repaired or replaced with a suitable size prosthetic valve. Additional procedure including coronary artery bypass graft other valves surgery was carried out when needed. The cryoablative Coz-Maze III procedure was performed during re-warming of the patients while the heart has been arrested. In group A patients cryoablation was done with three linear lesion to create isolation of PVs. A linear full thickness lesion extended from lateral side of right superior PV to lateral side of left superior PV, and the second lesion with a same extension for inferior pulmonary veins using a wide-angled probe that was cooled up to -120 oC were created for 2 minutes. A third linear lesion connect these two parallel lesions in mid-portion of left and right sided PVs at posterior aspect of left atrium using a T-shaped probe with the same degree of cooling and timing (Fig 1).

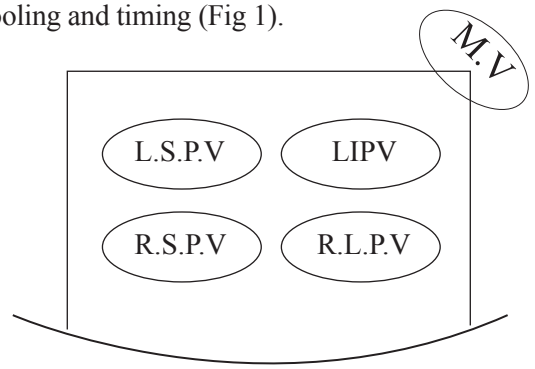

Fig.1 :Schematic view of Pulomonary Vein Isolation (looking from left atriotomy)
Dasehd lines: Cryoablation lines, MV:Mitral valve,
LSPV: left superior pulmonary vein
LIPV: left inferior pulmonary vein, RSPV: right suerior pulmonary vein
RIPV: right inferior pulmonary vein

Then LAA ligated with a non-absorbable suture when there was a clot in or a wide-based appendage after de-clamping the aorta. Figure 2 shows the different type of probes.

In group B patients both atrial cryoablation was performed as modified Cox-maze III. Left –sided cryoablation was performed in arrested heart after doing the MV procedure. In addition to the left atriotomy incision in the interatrial groove, isolation of the right PVs was completed by a unilateral ablation line. Then the left PVs were encircled, and a transversal 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 right-sided cryoablation was carried out during re-warming phase after de-clamping of aorta. The 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 forth ablation line was drawn on the right atrial side of interatrial 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 forth line to the inferior vena cava cannulation site. Intra-operative transesophageal echocardiography was done for almost all patients. Two right ventricular and two right atrial epicardial pace maker wires inserted in all patients for dual-chamber pacing when needed.

Postoperative Management:

All survivors were followed-up closely during the first admission and 1, 3, 6 and 12 months after the operation. Antiarrhythmic drug using propranolol (20-80 mg/day) or metoproterenol (25-100 mg/day) was constituted for at least 6 months All patients received anticoagulant include heparin for first few days and Warfarin to maintaining the INR value of 2.5-4 based on type of surgery and cardiac rhythm. At each follow-up date a medical and clinical history and an electrocardiogram (ECC) .Holter monitoring was performed for patients with normal sinus rhythm and postoperative palpitation. Electrical or medical cardioversion did not perform for patients that Maze III procedure was unsuccessful. Transthoracic echocardiographic assessment was carried out for all survivors at 4th-7th postoperative days and the first follow-up date. Postoperative TEE was used for patients with suspicious prosthetic valve malfunction and who underwent valve repair.

Results:

Patient demographics:

The cardiac surgical procedure was completed in all patients without early hospital death. Patients in group A (n=65) and patients in group B (n=25) did not differ in regard to mean age, sex, preoperative LVEF and left atrial size. Table 1 shows the different clinical aspects of patients between two groups. The 6-12 months follow-up was completed in all cases. 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 minutes for group A patients and 22 +/- 5.3 minutes in group B , and the additional ischemic time needed to perform the left sided ablation procedure (Group A) was 10 +/- 3.5 minutes and was 13+/- 5.1 minutes for patients underwent bi-atrial cryoablation (group B) ($P<0.05$).

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 dead patient was a 65 year-old woman that mitral and aortic vale replacement plus tricuspid valve repair was carried out for her. The cause of death was multiple organ failure secondary to low cardiac output.
The late mortality rate was 2.3%. One 63 years old woman in group A died three month after both mitral and tricuspid valve replacement due to congestive heart failure. The second case was a 68 year old man in group B patients died 7 month after mitral valve replacement as a result of right-sided heart failure.
There were no instances of atrial or esophageal perforation and infective endocarditis after operation. No permanent pace-maker implantation was necessary in our cases. Postoperative echocardiographic assessment showed widely patient pulmonary veins and normal pulmonary veins orifices in all patients. The re-exploration rate was 3.3% (3/90) for surgical bleeding control. Pericardial tamponade resulted in hemodynamic compromise and required pericardial drainage in two patients (2.2%). History of thromboembolic cerebrovascular accident was recorded in three cases, but no thromboembolic events was seen post-ablation period. However neurocognitive disorders were observed in three patients (table 3).

Table3: *Incidence of Postoperative complications.*

Post-op complication	NO. (%)
Perforation of esophagus	None
PV* stricture or stenosis	None
Need for transient Pace-maker	3 (3.4)
Need for PPM**	None
Mediastinal bleeding:	
Coagulopathy	2 (2.2)
Re-exploration	3 (3.4)
Thromboembolic events	None
CVA	None
Neurocognitive disorders	3 (3.3)
ARF	4 (4.5)
Respiratory insufficiency	1 (1.1)
Infections:	
Sternal wound infection	1 (1.1)
Deep sternal infection	None
Respiratory infection	1 (1.1)
Endocarditis	None
Pericardial effusion:	
Need for surgical drainage	2 (2.2)
Medical management	3 (3.4)
Post-op MI*	None

*Pulmonary vein, **Permanent Pace-maker, ***Myocardial infarction

Success rate of cryoablation:

The overall success rate of cryoablation was 65.5%. Success rate was 67.7% in group A and 60% in group B (P = 0.68). Normal sinus rhythm achieved in 26.7% at operating room, 10% at ICU & remaining cases got the sinus rhythm during follow up period. At the first postoperative day, 19 patients (29.2%) from group A
& five patients (20%) from group B were in sinus rhythm (P<0.05). During hospitalization period 25 patients (38.5%) in group A & 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 & 60% (15/25) in group B were in sinus rhythm.

Four patients (5.1%) in group A & one case in group that previously got into sinus rhythm converted back to atrial fibrillation(P=0.88). Table 4 shows the postoperative cardiac rhythms in two study group.

Table4: *Postoperative cardiac rhythm observed in 2 study groups.*

	Operation Room No.	ICU* No.	Before Discharge No.	1 Month No.	6 Month No.	12 Month No.	AF** (Not conversion to NSR***) No.	Total
Group A	***19***	***6***	***0***	***10***	***8***	***2***	***20***	***65***
Group B	***5***	***3***	***2***	***4***	***0***	***1***	***10***	***25***
Total	***24***	***9***	***2***	***14***	***8***	***3***	***30***	***90***

*Intensive care unit, **Atrial fibrillation, ***Normal sinus rhythm.

Predictors for failure of ablation:

According to the echocardiographic assessment of left atrial size (LAA), patients were divided in 3 subgroups. LAA size was less than 4 cm for group I, 4-6 cm for group II and more than 6 cm for group III. Overall success rate of cryoablation was significantly low in group III (P<0.05). 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 5).

Table5: *Postoperative cardiac rhythm according to the left atrium size between 3 groups*

	GROUP I NO. (%)	***GROUP II NO. (%)***	***GROUP III NO. (%)***
Conversion to NSR**at OR***	12 (48%)	10 (19.6%)	2(14.3%)
Conversion to NSR At ICU***	1 (4%)	8 (15.7%)	None
Conversion to NSR during hospitalization	2 (8%)	None	None
Conversion to NSR 1 month later	1 (4%)	14 (27.5%)	None
Conversion to NSR 6 month later	2 (8%)	6 (11.8%)	None
Conversion to NSR 1 year later	None	1 (2%)	None
NSR never create	7 (28%)	12 (23.5%)	12 (85.7%)
Total	***2 5 (100%)***	***51 (100%)***	***14 (100%)***

*Left atrium, **Normal sinus rhythm, *** Intensive care unitFig.2 : Danesh Co. Cryoablation machine and different types of probes.

Longer duration of AF rhythm was the next important predictive factor for failure of ablation procedure. Non of patients have had AF rhythm for more than 60 months got into sinus rhythm therefore success rate of cryoablative procedure in this patient group was zero in our study, however success rate of operation in whom AF rhythm lasting less than 12 months were 70% or more (P>0.05).

Discussion:

The aim of any AF surgical procedure is to diminish uncomfortable symptoms of the arrhythmia by restoring sinus rhythm, to regain atrial kick to improve hemodynamics, and to reduce the risk of thromboembolic events [2,6,13]. Spontaneous conversion rate to sinus rhythm after mitral valve surgery alone is 8 to 27%.The classic Cox-Maze III procedure has become the most successful surgical treatment for medically refractory AF but is associated with certain imitations such as poor atrial functional recovery and loss of effective atrial contraction [6,11,12]. The success rate of this operation is more than

95% and freedom from AF rhythm has been demonstrated in >95%of patients at 5 year follow-up[3,9].

However, the classic 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 procedure. Even in experienced hands, this operation required about 1 hour on cardiopulmonary bypass [9]. Several modifications were developed to overcome these shortcomings, and some of them such as procedures using cryothermy and radiofrequency showed good results for atrial functional recovery [9]. Reports about the rates of sinus rhythm ranking, is in between 60% up to 90% in patients with mitral valve disease, using either the classical Maze procedure or the modified versions [2,8]. Meanwhile, the introduction of new devices using alternative energy sources added some benefit included simplification and reduction of operative time without compromising the surgical outcome significantly [6,8,9]. Unlike radiofrequency ablation, cryoablation generally preserve the integrity of adjacent anatomic structures, due to its preservation of collagen tissue [9,14]. Recent molecular-based research suggests that apoptosis may be a mechanism of cell death, particularly in the periphery of the cryogenic lesion [15]. Additionally, in comparison with radiofrequency, cryoablation is not considered thrombogenic and is very less expensive [6,14]. There have been no reports of collateral coronary or esophageal damage [6,12].

PV isolation for paroxysmal AF has been shown to be effective and safe, but the success rate has been reported 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 cryoablation in comparison with standard bi-atril cryoablative procedure in the ablation of AF. It showed an overall success rate of 65.5% after a mean follow-up 10+/-2.8 months. Surprisingly this rate was 67.7% in group A and 60% in group B. This difference was not statistically significant and we did not found important difference between characteristics of two patient groups. Meanwhile we observed the same predictors for failure of ablation procedure between two groups. Although results in our series is comparable with some reports of either cryothermy or radiofrequency ablation, but Niv Ad and co –workers reported excellent result with early success rate of 98% and mortality rate of 3.7% by using bi-atrial cryoablation [1,3,6,7,13]. Bourke reported the success rate of 55% with pulmonary vein catheter ablation and he emphasize 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 a Maze procedure. These included increased LA size, increased cardiothoracic ratio, AF duration and presence of rheumatic heart disease [2,3,6,9,11,13]. We found the large LA size (6cm or more) and longer duration of AF rhythm (more than 12 month) as major predictors for failure of cryosurgery for AF ablation. We did not find correlation between age, sex, underlying disease or ablation method and success rate of procedure.

Surgical complications in our series limited to general morbidities in each type of open heart surgeries and we did no observe cryoablation related specific problems such as PV stenosis, need for permanent pace-maker, esophageal perforation or thromboembolic events.

In conclusion as seen in our study, mitral valve surgery with or without other concomitant procedures can safely be combined with a modified simple, time consuming and cost effective Maze III operation. An additional Maze procedure using cryoablation significantly more often restores sinus rhythm in patients with chronic AF compared to patients undergoing mitral valve surgery alone. There were no preferences between PV isolation and Bi-atrial ablation in our study, therefore we recommend the cryoablative PV isolation in patients undergoing mitral valve procedures with or without concomitant cardiac procedures especially when they had LA size less than 6 cm.

Study Limitations:

This non-randomized study was small size and may be not enough to obtain sufficient confidence. Follow–up period was short and we cannot demonstrate about the long-term efficacy of procedure and recurrence rate of AF. No microscopic or macroscopic examinations were performed on the cryo-induced lesions, therefore, we cannot speculate on the effects of the ablation lesion size or depth.

Fig.2 : Danesh Co. Cryoablation machine and different types of probes.

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