Atrial fibrillation and the Cryo Maze procedure

Version 2

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### Abbreviations

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<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACC</td>
<td>Aortic cross clamping</td>
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<tr>
<td>AAD</td>
<td>Antiarrhythmic drugs</td>
</tr>
<tr>
<td>AF</td>
<td>Atrial Fibrillation</td>
</tr>
<tr>
<td>BPM</td>
<td>Bit per minute</td>
</tr>
<tr>
<td>CABG X3</td>
<td>Coronary artery bypass with 3 grafts</td>
</tr>
<tr>
<td>CK-MB</td>
<td>Creatinine kinase-myocardial band</td>
</tr>
<tr>
<td>DCC</td>
<td>Direct current cardioversion</td>
</tr>
<tr>
<td>ECC</td>
<td>Extracorporeal circulation</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiography</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>MVR</td>
<td>Mitral valve repair</td>
</tr>
<tr>
<td>NOAC</td>
<td>New oral anticoagulants</td>
</tr>
<tr>
<td>PM</td>
<td>Pacemaker</td>
</tr>
<tr>
<td>PV</td>
<td>Pulmonary vein</td>
</tr>
<tr>
<td>PVI</td>
<td>Pulmonary vein isolation</td>
</tr>
<tr>
<td>RF</td>
<td>Radiofrequency</td>
</tr>
<tr>
<td>SEK</td>
<td>Swedish krona</td>
</tr>
<tr>
<td>SR</td>
<td>Sinus rhythm</td>
</tr>
<tr>
<td>TNI</td>
<td>Troponine I</td>
</tr>
<tr>
<td>VKA</td>
<td>Vitamin K antagonist</td>
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</table>
Abstract

Introduction
Atrial fibrillation is the most common supraventricular arrhythmia seen in the general population. The Cryo Maze procedure is a potential alternative in concomitant and lone therapeutic cardiac surgery.

Objective
The Cryo Maze procedure is a further development of the original Cox Maze III procedure with reduced complexity and complications. This study will investigate the current results from this technique to evaluate further usage. This study will also include a wide review of the mechanisms and theories beyond atrial fibrillation and its options of treatment.

Method
Eight patients were retrospectively followed up after concomitant Cryo Maze procedure with mitral valve repair (MVR) or coronary artery bypass graft surgery (CABG). Conversion rates, complications, extracorporeal circulation time, aortic cross clamping time, cardiac enzymes were all monitored and followed up.

Results
87.5% made a Cryo Maze procedure with concomitant MVR surgery. At mean follow up (9.5 months) 75% were free of AF. Complications included postoperative bleeding occurred in 3/8 patients, 2/8 obtained postoperative pacemaker implants, 1/8 got a pneumothorax and 1/8 was afflicted with a mediastinit. Cardiac enzymes were highly elevated in all patients. At follow up all patients were doing well.

Conclusion
The Cryo Maze procedure is a further development with less complexity than the original Cox Maze III procedure. In this study 75% of the included patients were free from AF at the follow up. Postoperative complications were common but transient, and apart from postoperative bradycardia not related to the Cryo Maze itself.
Introduction

Atrial fibrillation is the most common supraventricular tachyarrhythmia seen in the general population [1]. AF is characterized by tachycardia and a disordered irregular ventricular rhythm.

The disease is associated with many complications including thromboembolic events, heart failure, and death [2]. Although some people are asymptomatic, most patients suffering from AF experiencing fatigue, palpitations or other symptoms [3].

Management of AF can be achieved in multiple ways. Unfortunately, in most cases the AF recur over time. The Cryo Maze procedure is a therefor a new and interesting method to be evaluated for prevention of recurring AF.

Definition

In line with the ESC guidelines 2010, AF is determined when ECG shows totally irregular RR intervals, with no distinct P wave and with an atrial cycle length less than 200ms, normally within a 30 second monitoring interval [4].

Classifications

According to the ESC guidelines there are four different classifications of atrial fibrillation: paroxysmal, persistent, long-standing persistent and permanent AF.

Paroxysmal AF normally terminates within 48 hours, but can remain in up to 7 days. Persistent AF stays for longer than 7 days or requires medical therapy to cease. Long-standing persistent AF stays for longer than 1 year and permanent AF is a condition where the arrhythmia is under control and accepted [4].

Epidemiology and risk factors

The overall prevalence of atrial fibrillation is estimated to 0.95% [5]. The prevalence rate is highly age-dependent and increases with age. The prevalence in patients younger than 50 years are assessed to 0.1% and in individuals older then 80 years the prevalence is more than 9% [5]. There is also a difference between sexes where men are affected 1.5 times more often than women [6]. Lifetime risk to develop AF is about 24% for men and 22% for women aged 55 years [1, 7].
In addition to advancing age and male gender, increased size of left atrium, high systolic blood pressure and presence of valve disease are associated with a higher risk for developing atrial fibrillation [8]. Left ventricular hypertrophy seems to be one of the greatest risk factors with almost a fourfold increased risk in women and threefold increased risk in men [6].

**Etiology and pathogenesis**

Although AF is one of the most common diseases in the frame of cardiovascular medicine the underlying mechanisms are still not fully understood.

Today two different mechanisms are the leading theories behind the pathogenesis of AF: the “multiple-wavelet” hypothesis suggested by Moe et al. in 1962, and focal ectopic beats, proposed by Haissaguerre et al. in 1998. [9]

Ectopic beats are shown to originate primary from PVs (venous foci) but beats from the atrial muscle can also appear (atrial foci, 5.8%). Single or multiple ectopic sites inside ether one or multiple PVs can be responsible for these initiations. [9]

The multiple wavelet theory proposed by Moe et al. in 1962 explains the perpetuating of AF using multiple wavelets conducting through the atrial musculature. These wavelets move in an abrupt and irregular manner and collide to generate daughter wavelets, which perpetuate the fibrillation. The multiple wavelets results in large macro reentry circuits that re-depolarizes atrial tissue that is not longer in the refractory period [10].

**Symptoms**

Most patients suffering from AF experiences symptoms, although some represent a category called silent or asymptomatic AF were symptoms are absent [3]. The prevalence of silent AF will however depend on the method used for detection, which makes the prevalence numbers quite variable and difficult to determine [11].

There is a difference in the severity of the symptoms depending on the classification of AF. The most common symptom in paroxysmal AF is palpitations (79%) while
dyspnea is the most common presentation in AF ongoing more than a month (46.8%). Other symptoms among patients with AF are chest pain, syncope and fatigue [3].

**Complications and comorbidity**

Long-term complications constitute a great health risk in patients with AF and are a common outcome of these individuals. Patients with AF possess a higher risk for cardiovascular events, stroke, heart failure and mortality caused by other events, which is increasing by age. In patients between 80-89 years, diagnosed with AF the attributable risk of stroke reaches 23.5%, which represent a total health care cost around 18 billion SEK in Sweden each year [12, 13].

All cause mortality is doubled in patients with AF [2]. All cause mortality caused by AF also seems to be more common in female sex [2, 14]. Preventing these complications and thereby reducing the morbidity and mortality, is the most important reason for treating AF.

**Management**

Management focuses on symptom relief and prevention of complication, but also avoidance of progress into a more enduring AF. This is achieved through rate control, rhythm control (conversion to SR by either pharmacological therapy or electrical cardioversion) or by using oral anticoagulant therapy to prevent thromboembolisms. Proper management with anticoagulant therapy will prevent avoidable complications, decreasing the mortality, morbidity and total health care cost while the other therapy options reduces the symptoms [13].

Notable is that close to 70% (95% CI 63% to 73%) of AF episodes are self terminating within 72 hours and thereby do not require any treatment, except paroxysmal AF that requires anticoagulation treatment if the CHA2DS2-VASc score is higher than two [15]. Unfortunately, management of AF is rarely a permanent solution and the fibrillation tends to relapse.
Pharmacological management

**Antithrombotic therapy**

Indication of antithrombotic therapy is evaluated according to CHA2DS2-VASc score system, where congestive heart failure, hypertension, diabetes mellitus, vascular disease and age between 65-74 years yield one score point. Age over 75 year or prior stroke/TIA yields two score points. Two score points or more indicates antithrombotic therapy using warfarin [16].

Warfarin is a potent vitamin K antagonist (VKA), shown to reduce the risk of stroke with approximately 60%, presenting an absolute risk reduction of 2.7% per year [17]. The major disadvantage with warfarin, as with all antithrombotic therapy, is the risk of excessive bleeding. However the advantages overcome the disadvantages with antithrombotic treatment in atrial fibrillation and should be considered after evaluation with CHA2DS2-VASc score system.

More recently an alternative to VKA for non-valvular AF has been developed called NOACs (new oral anticoagulants). These drugs have several advantages to VKAs including fewer drug interactions, less hemorrhage complications and no need for coagulation monitoring. These are important aspects that might improve the compliance of drug intake. NOACs are categorized into two classes: oral direct thrombin inhibitors and oral factor Xa inhibitors. Both classes are as effective as, or more effective than VKA in preventing thromboembolisms, but less likely to cause major hemorrhage [18]. As with VKA treatment, NOACs are evaluated according to CHA2DS2-VASc score system.

**Cardioversion therapy with antiarrhythmic drugs**

Generally pharmacological cardioversion is most effective immediately after onset of AF. Available drugs for pharmacological cardioversion are flecainide, amiodarone, ibutilide, propafenone and vernakalant. Choice of substance to use depends on the patient’s history of heart disease. If there is any structural heart disease amiodarone is the first choice. If not, flecainide or propafenone may be the first choice [4].

Pharmacological cardioversion is less effective than direct electrical cardioversion (success rates are highly dependent on substance) but does not require general
anesthesia and is comfortable and simple for the patient and the physician. Another disadvantage with pharmacological cardioversion is the risk of proarrythmic events. The most effective antiarrhythmic drugs seem to be flecainide and propafenone with a success rate between 42% to 93% [19]. It is important to remember that most AF is self converted within 72 hours, which makes it difficult to state the efficacy of different antiarrhythmic substances.

Rate control
AF with high ventricular frequency is associated with more severe symptoms and complications than lower frequency. A target rate lower than 100 bpm should be aimed for, which usually reduces the symptoms, even if optimal rate is still not specified. This may be achieved by administration of β-blockers, non-dihydropyridine calcium channel antagonists or digitalis [4].

Non pharmacological management

Direct current cardioversion
Transthoracic cardioversion is an important method for converting AF to SR. There are currently two different waveforms in use for conversion: the conventional monophasic and the more recent biphasic shock waves. Biphasic shocks seem to be more efficient than monophasic shocks, converting 90% of AF to SR (monophasic shocks convert 53%) in using 200J and maximum three shocks. Biphasic shocks also seems to lower the incidence of dermal injury compared to monophasic shocks (17% in biphasic and 41% in monophasic) [20].

Catheter ablation
As earlier mentioned, most ectopic beats in AF originate from the PVs (pulmonary veins). In catheter ablation the main target is to disable these ectopic foci using a technique called pulmonary vein isolation (PVI). PVI is most often tested in patients’ resistance to AAD therapy.

PVI catheter ablation is using different sources of energy: radiofrequency (RF) and cryoenergy. RF is the main standard choice, and seems to be the most effective and safe method. According to a worldwide survey made by Cappato et al. in 2010 major complications were found in 4.5% of the patients. Tamponade was the greatest major complication according to this study. Pulmonary vein stenosis is another common
complication that required intervention in 0.29% of the patients according to Cappato et al. Despite the risk of complications, the success rates are as high as 67.6%, which makes this method trusted and reliable [21].

His-ablation is another catheter based ablation technique. As with PVI, RF is the most commonly used energy source in His-ablation, which is performed in patients with severe symptoms with great impact on quality of life where other therapies do not respond. His-ablation will not convert the AF to SR, but it will control the ventricular frequency rate. Because AV-node and the bundle of His are disabled, a subsequent pacemaker insertion is essential, which will follow the patient permanently. This will help slow down the pace, decreasing the ventricular rate and releasing the symptoms with a subsequent increased quality of life [22]. The disadvantage is lifelong pacemaker dependency.

Surgical management

Surgical treatments of AF are based on Moes et al. multiple wavelet hypothesis in terms of AF [10]. The general principle, invented by Dr James Cox in 1987 is called the Cox Maze procedure, is an open-heart surgery where incisions are created, causing scars in the atrium tissue that isolates the conduction from propagating and thereby preventing AF from perpetuating. The technique includes PVI lesions. The technique used today is called the Cox Maze III procedure and is the gold standard method for treating AF during open-heart surgery [9, 23, 24].

The original Cox Maze III procedure is a complex technique that despite its efficacy is not well accepted by surgeons around the world, because of its complexity. This led to further development of this method; now using different energy sources (RF, microwaves and cryoablation) instead of the original ‘cut and sew’, using scalpel and stitches [25]. These ablation technologies are more accepted and do not differ in the conversion rate from the previous classical ‘cut and sew’ method (reaching 96.6% SR conversion rate, depending on material) why this is a promising field in the surgical therapy of AF [26, 27].

The Cryo Maze procedure is based on the Cox Maze III technique, using cryoprobes to make the lesions by freezing and destroying the atrium tissue. The Cryo Maze
procedure is a new technique that has been in use for relatively short time and thereby the documentations are quite limited. The advantage with this process is the simplicity, and the reduced risk of thrombus formation and pulmonary vein stenosis, which makes the Cryo Maze procedure a potential gold standard method in treating drug-refractory AF in open-heart surgery [26, 28].

Today, the Cryo Maze procedure is mostly used as a procedure concomitant to other open-heart surgeries. Because of the lack of multiple studies about the procedure and its results, this study will look at the technique and its results in a minor patient material.

**Method**

In this retrospective descriptive study we included all patients (n = 8) who completed the Cryo Maze procedure with the indication AF in open cardiac surgery during September 2012 to April 2014 at the department of Cardiovascular and Thoracic Surgery, Örebro University Hospital. These patients were followed up 1.5-16 months postoperatively. All patients agreed to take part of this study.

The patients included in this study were found by using the surgery code associated with the Cryo Maze procedure (FPD00 and FPD96) in the Swedish database called “IMX”. We specified the search for the chosen time period (September 2012 to April 2014) and included all patients found.

The procedure was done according to the original Cox Maze III method modified using cryoablation. The heart is exposed through a median sternotomy and cardiopulmonary bypass with extracorporeal circulation is initiated. Cardiac arrest is achieved with a cross clamping of the aorta and infusion of intracoronary cardioplegia solution. After opening of the left atrium, the atriotomy is expanded with a lesion surrounding the PVs, causing PVI, a mitral line from the atriotomy to the mitral valve and a coronary sinus lesion. The lesions are performed with a cryocatheter that releases argon gas, which during its expansion extracts heat from the surrounding tissue, which causes freezing of the tissue. The atriotomy in the left atrium is closed. Through an atriotomy of the right atrium an intercaval lesion, a T-lesion from the
atriotomy to the tricuspid valve are performed and a counter lesion from the tricuspid valve to the right appendix. After closure of the right atriotomy, the aortic cross clamp is released, extracorporeal circulation is ended and the sternotomy closed [24].

Perioperative and postoperative data was collected from the patients’ medical charts, laboratory and clinical variables including time of extracorporeal circulation (ECC-time) and the aortic cross clamping time (ACC), accessed from the perfusionists’ chart notes. The postoperative clinical data we reviewed were complications of any kind related to the surgery including death, occurrence of postoperative permanent PM treatment, current heart rhythm, anticoagulation treatment and apparent symptoms during the follow up period. CK-MB concentration was measured in plasma one day after surgery and TNI was measured in plasma three days after surgery in all patients, both variables expressed in µg/L. Also noted was type of surgery in addition to the Cryo Maze procedure.

The patients’ heart rhythms were observed 1.5-16 months postoperatively by either a single ECG, Holter-ECG (24 hours monitoring) or by using R-test monitoring (observing more than 24 hours). There were no exclusion criteria in this study.

**Ethical aspects**
All patients’ included were asked and given approval for being part of this study. Patient data have been obtained and de-identified to ensure patient safety without losing information. Because this is a descriptive study, no patients were associated with any potential risks during the follow up. Ethical aspects of this study have been reviewed and potential issues have been adjusted to avoid ethical disputes.

The Cryo Maze procedure is a new surgical technique and thereby all potential complications and disadvantages may not be fully described, which may affect the patient safety during the procedure. We must therefore inform the patients properly about advantages and disadvantages with new surgical techniques and the potential consequences.

In prior to all surgeries, including the Cryo Maze procedure, an individual evaluation will be preformed to assess if the operation is convenient or not for the patient. This
might be an ethical issue if a patient considers the procedure as convenient, but not
the physician.

**Results**

The mean age at surgery were 71 years (64-80 yr) and the majority of the patients (n = 7/8) were of male sex. Four patients had paroxysmal AF and four patients had a
persistent AF at surgery date. Unfortunately there was no information in the medical
charts for how long the patients had their AF before surgery. All except one (n = 7/8) had a combined Cryo Maze and MVR procedure, reviewed in table 1.

**Table 1. - Procedures**

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryo Maze + MVR</td>
<td>6</td>
</tr>
<tr>
<td>Cryo Maze + MVR + CABG</td>
<td>1</td>
</tr>
<tr>
<td>Cryo Maze + CABG</td>
<td>1</td>
</tr>
</tbody>
</table>

*This table shows the procedures that were done concomitant to the Cryo Maze surgery. MVR (Mitral valve repair), CABG (Coronary artery bypass graft).*

The mean follow up time in this study was 9.5 months (1.5-16 mo.) at which six
patients (75%) got freedom from AF. Four patients were in SR, two patients in AF
and two permanent PM users with DDDR PM-rhythm at this time. The patients with
AF at follow up both had paroxysmal AF at surgery date.

All patients were on anticoagulation with warfarin after surgery, continued during the
full follow up period. However one patient changed this to rivaroxaban because of
gastro intestinal side effects. There were no incidents of stroke or thromboembolism
during the follow up time. There was no mortality during surgery or follow up.

In all patients the surgery was completed without any instant complications.
Postoperative complications are shown in table 2.
Table 2. – Surgery related complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative bleeding</td>
<td>3/8</td>
</tr>
<tr>
<td>Postoperative pacemaker insertion</td>
<td>2/8</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1/8</td>
</tr>
<tr>
<td>Mediastinitis</td>
<td>1/8</td>
</tr>
</tbody>
</table>

This table shown the postoperative complications related to the surgery.

The mean concentration of TNI and CK-MB in plasma three days and one day after surgery was 9.65 µg/L (7.5-15 µg/L) and 113.75 µg/L (51-224 µg/L) respectively, and thereby distinctly elevated from normal preference variables, which confirms the ablation made to the heart tissue. The total ECC time varied between 97 and 167 minutes (average time = 136 min) with no distinct association to operation procedure. The average ACC time was 97 minutes and varied between 73 and 139 minutes, shown in table 3.

Table 3. – Operative data

<table>
<thead>
<tr>
<th>Variables</th>
<th>Results</th>
<th>Reference values [29, 30]</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNI µg/L</td>
<td>9.65 (7.8-15)</td>
<td>&lt; 0.03</td>
</tr>
<tr>
<td>CK-MB µg/L</td>
<td>113.75 (51-224)</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>ECC time (min)</td>
<td>136 (97-167)</td>
<td></td>
</tr>
<tr>
<td>ACC time (min)</td>
<td>97 (73-139)</td>
<td></td>
</tr>
<tr>
<td>Postop-PM</td>
<td>2/8</td>
<td></td>
</tr>
</tbody>
</table>

TNI (Troponine I), CK-MB (Creatinine kinase-myocardial band), ECC-time (Extracorporeal circulation time), ACC time (Aorta cross clamping time), Postop-PM (number of patients that obtained permanent pacemaker after surgery). TNI measured three days after surgery and CK-MB one day after surgery.

All patients included in this study were feeling well at follow up, experiencing a relief in symptoms after surgery.
Discussion

The classical Cox Maze III procedure has been the gold standard method for treating AF in concomitant cardiac surgery for many years. Despite great results, the procedure has been of limited use because of its complexity and long operation times. This might be one of the reasons why lone Cox Maze III surgeries are fairly uncommon and is performed only in special cases. New techniques have been developed including the use of cryoablation, which is a promising field in the treatment of AF in concomitant and lone cardiac surgery because of its reduced complexity. The Cryo Maze procedure using the original Cox Maze III lesion set with cryoablation is less complex and equally effective [25, 31, 32].

Original studies about the Cryo Maze procedure have shown 98% freedom of symptoms of AF. More recent studies have shown a lower freedom of AF (76-84.9%) depending on time and patient material, based on ECG monitoring, which makes the studies more reliable [26, 31, 33]. In this study, however, 75% of the patients’ included were free from AF at follow up, which is in accordance with previous studies, given the small number of patients. Freedom of AF includes patients that obtained a DDDR PM due to postoperative sinus bradycardia, because they are considered to have sinus rhythm.

As expected the cardiac enzymes levels (TNI and CK-MB) were elevated (TNI 9.65 µg/L and CK-MB 113.75 µg/L, mean concentrations), but correspond relatively well to the enzyme concentrations shown in similar studies. This most likely reflects the ablation myocardial injury, but does not seem to correlate to any further ischemia or irreversible damage to the heart [32, 34].

The ACC and ECC time are reduced in this study compared with the original Cox Maze III procedure. This might be an indicator of less complexity with the Cryo Maze technique and thereby a reduced time requirement. This might also be an important factor for further usage of this method because long aortic cross clamping times been associated with higher mortality, prolonged hospital stay and multiple complications [33, 35].
Including all Cryo Maze patients during a specific time period is a great strength of this study, minimizing the probability of errors during the patient selection. Another benefit in this study includes the fact that the Cryo Maze procedure truly gave results on freedom of AF, which no other concomitant surgery (MVR or CABG) are capable of doing. Also all patients were observed with ECG-monitoring during the follow up, which increases the power of true freedom of AF, compared with a follow up based on symptoms only.

This is a small study only including eight patients, which makes it difficult to make any conclusions about the procedure overall. This is also the reason why no statistical analysis has been made in this study. What we did achieve was a follow up result with current variables and data according to these eight patients, which can give indications to the current results of this procedure.

In this review, no Cryo Maze procedures were done lone, but concomitant with MVR or CABG operations. This might reflect the results and makes it difficult to make any conclusions about the lone Cryo Maze procedure. However the Cryo Maze procedure is less complex than the original Cox Maze III procedure and discussion about upcoming lone Cryo Maze procedure might be of interest.

Also we did not have any control group in this study, which is a major limitation of the results. Instead we compared the results with other studies using the same technique to evaluate the results from this review.

Since this is a study dependable on documented data in medical charts there is a possibility that important information has been left out by the physicians. The medical charts were written with different quality, depending on what physician responsible for the patient. This might affect the quality of this review.

Another potential weakness is occurrence of publication bias. There are currently not many studies documenting the Cryo Maze procedure and outcome. Most of the published studies are made from large materials from bigger hospitals. Smaller studies with lower success rates may be less likely to be published and are thereby more difficult to be accessed.
**Conclusion**
The Cryo Maze procedure is a further development with less complexity than the original Cox Maze III procedure. In this study 75% of the included patients were free from AF at the follow up. Postoperative complications were common but transient, and apart from postoperative bradycardia not related to the Cryo Maze itself.
References


