

The copyright of this thesis rests with the University of Cape Town. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

**SURGICAL MANAGEMENT FOR ATRIAL FIBRILLATION:  
AN ASSESSMENT OF CLINICAL OUTCOME AFTER  
IRRIGATED MONOPOLAR ELECTROCAUTERY ABLATION**

By

**Dr Jacques Scherman  
Student number : SCHJAC015**

Submitted to the University of Cape Town

In fulfilment of the requirements for the degree

Master of Medicine  
In Cardiothoracic Surgery

**Faculty of Health Sciences**

**UNIVERSITY OF CAPE TOWN**

**Date of submission: 21 August 2009**

**Supervisor: Prof. Johan G Brink.  
Chris Barnard Division of Cardiothoracic surgery  
University of Cape Town**

## DECLARATION

I, Jacques Scherman, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: .....

Date: .....

University of Cape Town

## ACKNOWLEDGEMENTS

I would like to express my gratitude to all those who made it possible to complete this thesis. I thank the University of Cape Town (UCT) Research Ethics Committee for permission to undertake the research. . I acknowledge the support of the Chris Barnard Division of Cardiothoracic Surgery at UCT for the use of departmental data to complete this thesis., and for the use of the substantial research resources which facilitated my research

I am indebted to my supervisor Prof Johan G. Brink in the Chris Barnard Division of Cardiothoracic Surgery, whose help, stimulating suggestions and encouragement were instrumental in this research. The novel surgical method which was the subject of this research was his concept and all the surgery performed by him, I also acknowledge his help in the writing of this thesis.

I would like to thank Prof Andrzej. Okreglicki from the Division of Cardiology at UCT for providing assistance in the interpretation of all electrocardiograms during the study.

Especially, I would like to give my special thanks to my wife Tania whose patient love enabled me to complete this work.

## TABLE OF CONTENTS

<b>List of Appendices</b> .....	6
<b>List of Tables</b> .....	6
<b>List of Figures</b> .....	6
<b>Acronyms and Abbreviations</b> .....	7
<b>Definitions</b> .....	8
<b>Executive Summary</b> .....	9
 <b>I – INTRODUCTION: LITERATURE REVIEW</b>	
1. Background.....	10
2. Atrial Fibrillation.....	11
2.1. Pathophysiology.....	11
2.2. Classification.....	12
3. Therapeutic Options.....	12
3.1. Medical Therapy.....	12
3.1.1. Rate and Rhythm control	
3.1.2. Prevention of Thrombo-embolism	
3.2. Catheter-based procedures.....	13
3.3. Evolution of surgery.....	14
3.3.1. The Corridor procedure.....	14
3.3.2. The Cox Maze procedures.....	14
3.3.3. Ablative techniques.....	19
3.3.3.1. Radiofrequency Energy	
3.3.3.2. Microwave Energy	
3.3.3.3. Laser ablation	
3.3.3.4. Cryotherapy	
3.3.3.5. Diathermy	
3.3.4. Predictors of failure or success for Maze surgery.....	29
3.3.4.1. Enlarged Atria	
3.3.4.2. Chronic AF	
3.3.4.3. Ejection Fraction	
3.3.4.4. Concomitant Organic Heart Disease	
3.3.4.5. Fine Atrial Fibrillatory Waves	
3.3.5. Controversies with AF Surgery.....	32
3.3.5.1. Incidence of new onset post operative Atrial Flutter	

3.3.5.2. Atrial Natriuretic Peptide (ANP)	
3.3.5.3. Post Operative Management and Follow Up	
3.3.5.4. Permanent Pacemaker Implantation	
3.3.5.5. Restoration of Atrial transport function	
3.3.5.6. Impact on stroke rates	
3.3.6. The Future.....	36
<b>II – AIMS AND OBJECTIVES</b>	<b>37</b>
<b>III – MATERIALS AND METHODS</b>	<b>38</b>
<b>SECTION A</b>	
1. Patients.....	38
2. Surgical Procedure.....	38
2.1. Description of techniques.....	40
3. Postoperative Management.....	41
<b>SECTION B</b>	
Macroscopical and histological investigation of lesions created on animal hearts using <i>irrigated monopolar electrocautery ablation</i> compared to <i>irrigated radiofrequency ablation</i> .....	42
<b>IV – RESULTS</b>	
<b>SECTION A</b>	
Clinical results of study population at Groote Schuur Hospital	
Preoperative Data.....	44
Operative and Peri-operative Data.....	45
Follow up.....	48
<b>SECTION B</b>	
Macroscopical and Histological findings of lesions created on animal hearts.....	50
<b>V – CONCLUSION</b>	<b>55</b>
<b>VI – DISCUSSION</b>	<b>56</b>
<b>VII – FINAL OBSERVATIONS</b>	<b>59</b>
<b>BIBLIOGRAPHY.....</b>	<b>60</b>

## LIST OF APPENDICES

Table X: Demographics and Pre Operative Data.....	67
Table Y: Operative and Peri-operative Data.....	70

## LIST OF TABLES

1: Literature review on ‘cut and sew’ technique.....	18
2: Literature review on Radiofrequency ablation.....	24
3: Literature review on Microwave ablation.....	27
4: Literature review on Cryoablation.....	27
5: Patient demographics and pre operative data.....	44
6: Operative details.....	45
7: Macroscopical assessment of depth ablation lines at various power settings using irrigated electrocautery ablation.....	50
8: Macroscopical assessment of depth ablation lines at various power settings using irrigated radiofrequency ablation.....	50

## LIST OF FIGURES

1: ECG demonstrating Atrial Fibrillation.....	11
2: Three dimensional depiction of the incisions used for performing the Maze I procedure.....	15
3: Depiction of the incisions made for the Maze III procedure.....	16
4: Schematic illustration of atriotomy scar lesions blocking abnormal electrical pathways.....	16
5: Representations of different left atrial lesion sets being used.....	19
6: Some available radiofrequency ablation systems.....	21
7: Cardioblate™ Surgical Ablation Pen and Generator.....	22
8: Cryoablation hand-held probe and Cryoablation console.....	26
9: Novel irrigated electrocautery ball-tip pen.....	39
10: View inside the left atrium.....	40
11: View inside the right atrium.....	40
12: Example of ablative line on pig heart ventricle using a) irrigated monopolar electrocautery ablation and b) irrigated radiofrequency ablation.....	42
13: Gross specimen preparation in Formalin.....	43
14: ECG rhythm on discharge.....	46
15: ECG rhythm at latest follow up.....	48
16: Gross visual assessment of individual specimens demonstrating ablative lesions created with irrigated monopolar electrocautery ablation at different power settings (Refer to Table 7 for details).....	51
17: Gross visual assessment of individual specimens demonstrating ablative lesions created with irrigated radiofrequency ablation at different power settings (Refer to Table 8 for details).....	52
18: Histological assessment (Irrigated Electrocautery Ablation).....	53
19: Histological assessment (Irrigated Radiofrequency Ablation).....	54

## LIST OF ABBREVIATIONS

ACC:	American College of Cardiology
AF:	Atrial Fibrillation
AHA:	American Heart Association
ANP:	Atrial natriuretic peptide
AV:	Atrio-ventricular
BA:	Bi-atrial
BNP:	Brain natriuretic peptide
CABG:	Coronary artery bypass grafting
CS:	Coronary sinus
ECG:	Electrocardiogram
EF:	Ejection fraction
ESC:	European Society of Cardiology
FO:	Foramen Ovale
FU:	Follow up
HAART:	Highly Active Anti-Retroviral Therapy
HPS:	Haematoxylin phloxine saffron
ICU:	Intensive care unit
INR:	International Normalised Ratio
IPPV:	Intermittent positive pressure ventilation
IVI:	Intra-venous infusion
LA:	Left atrial
LAA:	Left atrial appendage
NYHA:	New York Heart Association
PPM:	Permanent pacemaker
PV:	Pulmonary vein
SICTRA:	Saline-irrigated cooled tip radiofrequency ablation
SR:	Sinus rhythm
SVC:	Superior Vena Cava
TOE:	Trans-Oesophageal Echocardiogram
TV:	Tricuspid valve



## LIST OF DEFINITIONS

Atrial fibrillation:

A supraventricular tachyarrhythmia characterized by uncoordinated electrical activation of the atria (A classification can be found in section 2.2 on page 12).

Maze procedure:

The Maze or Cox-Maze procedure is an open heart cardiac surgical procedure with the aim of eliminating atrial fibrillation. 'Maze' refers to the series of incisions arranged in a maze-like pattern in the atria.

University of Cape Town

## EXECUTIVE SUMMARY

30 to 84% of patients undergoing mitral valve surgery present with associated permanent atrial fibrillation (AF). After mitral surgery up to 20% of these patients will revert to normal sinus rhythm (NSR) but AF will persist in the majority. AF increases the risk of stroke, other associated complications, and patients in AF require more frequent physician visits and hospitalisations.

The “cut and sew” Cox - Maze procedure remains the gold standard for restoring NSR in patients with permanent AF. Due to its complexity, and bleeding complications, alternative methods have been used to create the ablation lines - in particular radiofrequency ablation.

The cost of the commercially available probes has limited the use of surgical radiofrequency ablation at Groote Schuur Hospital. The use of non-irrigated electrocautery ablation has been reported previously. Criticism of this technique includes the tissue charring created and difficulty in achieving transmural atrial lesions. This prompted the development of a novel irrigated monopolar electrocautery ablation to restore NSR in patients with permanent AF.

During the 2½ year period from September 2004 to April 2007, 40 cardiac surgery patients had a modified Maze procedure in addition to concomitant other cardiac surgery. 16 were males and 24 females with a mean age of 47.15 years. All procedures were performed by a single surgeon. 38 had mitral surgery (either isolated or in combination with other procedures); one patient had an isolated ASD repair and one an isolated aortic valve replacement.

Early mortality was 7.5% - none related to the Maze procedure. Mean hospital stay was 10.1 days, with sinus-conversion rate of 70% upon discharge. Follow up was 97.5% complete and ranged from 1 to 30 months (mean 14 months). There were three late valve related mortalities. No late electrical cardioversion was performed and 67% of patients (n=25/36) remained in sinus rhythm at last follow up. This percentage is similar to sinus rhythm maintenance in other series using conventional methods of AF ablation.

# I. INTRODUCTION: LITERATURE REVIEW

## 1. BACKGROUND

Atrial fibrillation (AF) is the most common symptomatic cardiac arrhythmia affecting 0.4% of the general population and about 5% of people older than 60<sup>1,7,9,36</sup>. The risk of stroke is more than five times greater in non-rheumatic patients with AF than in patients in sinus rhythm<sup>7</sup>. Patients in AF require more frequent visits to modify their medications and to monitor anticoagulation. AF accounts for approximately one third of hospitalizations for cardiac rhythm disturbance<sup>40</sup>. Medical therapy is aimed at rate and rhythm control and the prevention of thromboembolism<sup>7,69</sup>. The growing recognition of the deleterious health effects of AF have contributed to the search for methods to fully restore sinus rhythm.

In 1991 Cox proposed the Maze procedure as alternative treatment for lone AF<sup>2</sup>. This procedure aimed at reducing the critical mass of atrial tissue required to sustain fibrillation and to modify the arrhythmogenic substrate by interrupting all possible macro-reentrant circuits responsible for AF. The major indication of the Cox-Maze III procedure was intolerance for anti-arrhythmic medication and medical refractory arrhythmias. Popularity of the bi-atrial 'cut and sew' technique was dampened due to its complexity, the length of the procedure and bleeding complications. Post operative permanent pacemaker implantation rates were as high as 10% and mortality rates between 1-2% for the procedure<sup>3</sup>.

The Maze procedure pre-empted the development of different ablation techniques, whether open or percutaneously. Evidence of the dominance of the left atrium in causing AF emerged in 1996 and this was followed by simplified surgical approaches in the management of AF. Various energy-based treatment modalities (particularly radiofrequency ablation) have been evaluated that are all based on the original Cox Maze pattern.

The use of non-irrigated electrocautery ablation has already been investigated<sup>15</sup>. One concern however lies in the difficulty in achievement of transmural lesions and the intense superficial tissue charring that occurs when using this energy source.

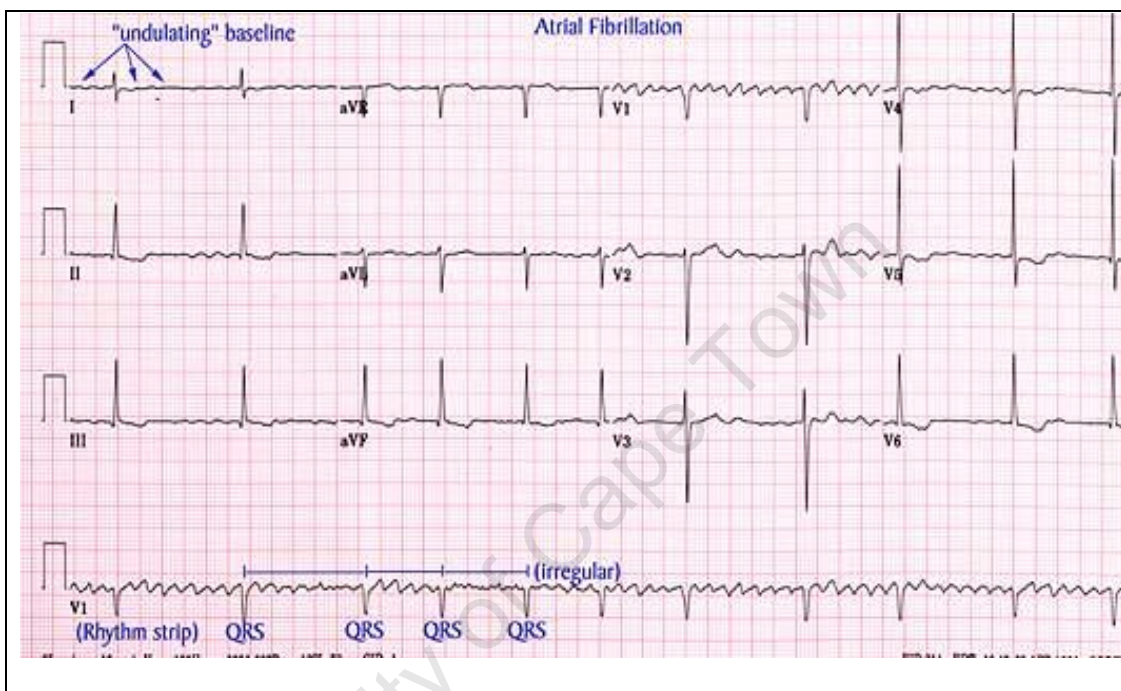
At Groote Schuur Hospital a novel method using irrigated monopolar electrocautery ablation were developed to perform a modified Maze procedure in an attempt to restore sinus rhythm in patients who present with atrial fibrillation and concomitant heart disease. The cost of the commercially available radiofrequency probes has prevented the widespread use of radiofrequency ablation in all our surgical patients. The clinical outcome in our patients who have undergone this procedure has not yet been evaluated. It is also not clear whether certain predictors of success or failure that are published in the literature can be applied to our patient population who mainly suffers from rheumatic heart valve disease.

There is currently no histological evidence available to support the goal of achieving transmural lesions when creating these lesions using irrigated monopolar electrocautery ablation.

## 2. ATRIAL FIBRILLATION

### 2.1. Pathophysiology

AF is defined as a supraventricular tachyarrhythmia characterized by uncoordinated electrical activation of the atria. This leads to deterioration in the transport function of the atria. It is characterized on an electrocardiogram by the absence of P-waves before each QRS-complex.



**Fig 1: ECG demonstrating Atrial Fibrillation.**

Although the exact pathophysiology still remains unclear, it is unlikely that a single pathophysiological mechanism is responsible in all cases of AF. Proposed mechanisms include rapidly firing ectopic foci or single re-entry circuits with fibrillatory conduction, and multi circuit re-entry. The role of these foci is prominent, not only for the initiation but also for the maintenance of AF. These foci are not randomly located in the atria, but are clustered within the pulmonary veins where 80-95% of foci are identified<sup>14</sup>.

Understanding the concept of “triggers” and “drivers” that may initiate and maintain AF is important especially in the current era of less invasive percutaneous or surgically applied ablative lines to treat AF. It has been postulated that the triggers for *paroxysmal* AF are located in the region of the pulmonary vein ostia in 90% of cases and should thus theoretically be cured in up to 90% of cases with pulmonary vein isolation alone. More controversial is the location of the “drivers” for AF. Some authors propose that the foci lie in the pulmonary veins whilst others that the macro-re-entry circuits are located in the atria. If this were the case, pulmonary isolation alone would therefore be inadequate to terminate *chronic (permanent)* AF.

Electrical, contractile and structural remodelling is an important part of the pathophysiology of AF. Previous investigators showed that prolonged AF promotes the maintenance of AF<sup>10,30</sup>.

## 2.2. Classification

According to the American College of Cardiology (ACC), the American Heart Association (AHA) and the European Society of Cardiology (ESC) guidelines, AF can be classified as follows<sup>9</sup>:

- *Paroxysmal AF*: Episodes that start and stop by themselves, generally lasting less than 24 hours but occasionally lasting up to 7 days.
- *Persistent AF*: Episodes lasting more than 7 days.
- *Permanent AF*: Long-standing continuous episodes in which cardioversion has failed.

These definitions apply to episodes of AF of more than 30 seconds duration and which are unrelated to a reversible cause, such as cardiac surgery, myocardial infarction, pulmonary embolism, myocarditis, or hyperthyroidism.

Independent risk factors for the development of AF include increasing age, diabetes, left ventricular hypertrophy, valvular heart disease, increasing left atrial diameter and coronary artery disease.

## 3. THERAPEUTIC OPTIONS

### 3.1. Medical Therapy

#### 3.1.1. Rate and Rhythm Control

Rate and rhythm control and the prevention of thromboembolic events form the mainstay of the medical management for AF<sup>7,69</sup>. Strategies to restore and maintain sinus rhythm also strive to alleviate the need for anticoagulation. Pharmacological rhythm control approaches have failed to show any greater benefit than rate control strategies and it also does not exclude the need for anticoagulation in high-risk patients<sup>9</sup>. Five studies comparing rate versus rhythm control for AF failed to show any significant difference in stroke incidence between rate and rhythm control<sup>12</sup>. It became clear that, in patients with a history of AF and risk factors for stroke, anticoagulant therapy should be continued also for patients in sinus rhythm. Therefore rate control together with anticoagulation is being used in the majority of patients. Pharmacological rate-controlling agents used include Digoxin, Calcium channel blockers and B-blockers.

Cardioversion is aimed at restoring sinus rhythm and can be achieved by electrical or chemical means. Electrical cardioversion is more effective for organized atrial arrhythmias (atrial flutter and atrial tachycardia), and in general also more effective than chemical cardioversion. Due to the increased risk of thromboembolic phenomena during the time of cardioversion, the need for anticoagulation should be

assessed in each individual case. Current recommendations are that anticoagulation could be withheld in patients with AF onset of less than 48 hours (provided that this could be accurately determined and that there is no additional risk factors for stroke). For AF of longer duration or unknown duration, anticoagulation should be instituted. The traditional approach is to maintain a therapeutic INR (2.0-3.0) level for 3 weeks before and 4 weeks after the cardioversion. If trans-oesophageal echo (TOE) is available, this can be used to establish the presence of thrombi in the left atrium. In the absence of any thrombus, the anticoagulation period before the cardioversion can be shortened, but must still be continued for 4 weeks after the cardioversion<sup>69</sup>.

### 3.1.2. Prevention of Thrombo-embolism

Obvious concerns with anticoagulation include the balance between stroke prevention and risk of bleeding. Warfarin is still considered the drug of choice for anticoagulation. Other drugs include Aspirin and Clopidrogel. Although these drugs are still being evaluated in larger randomized trials, their efficacy is currently not yet proven in the setting of AF. Anti-thrombotic therapy therefore remains problematic in high risk patients who cannot take Warfarin. Guidelines on risk assessment and appropriate drug selection are available in the ACC/AHA/ESC guidelines<sup>7,9</sup>. It is important to understand that success lies in tailoring treatment for each patient.

## 3.2. Catheter-based procedures

Electrophysiologists, stimulated by the Maze operation, performed similar procedures using radiofrequency ablation in both atria by transcutaneous catheter ablation techniques. These ablation lines were initially limited to the right atrium because the risks (thromboembolic events, pericardial effusions and valve damage) were fewer than when dealing with the left atrium. Limited success prompted the need for ablative lesions in the left atrium<sup>5</sup>. Concerns were the risk of transseptal puncture and potential thromboembolic complications. Cury et al studied the relationship between the oesophagus and aorta to the left atrium and pulmonary veins using multidetector computed tomography<sup>13</sup>. From their observations they concluded that the position of the oesophagus can vary in the posterior mediastinum, and therefore care should be taken when applying ablative lines in the region of the left pulmonary vein ostia. The use of modest ablative energies is thus advised when ablating in this region. It is hypothesized that oesophageal injury could occur when the oesophagus is sandwiched between the posterior left atrial wall anteriorly and the posterior structures (thoracic spine or, less frequently, the aorta). These potential complications are more likely when more powerful ablative technologies are used.

The left atrial approach has been demonstrated to be safe in patients affected by *paroxysmal* AF, with restoration of long-term sinus rhythm in 60% of patients<sup>6</sup>. This success rate was obtained by the creation of a long line encircling the pulmonary veins to compartmentalize the left atrium. Different techniques have been described, all focusing on isolation of the pulmonary veins<sup>14</sup>. Concerns about pulmonary vein (PV) stenosis have been real, but the use of circular mapping devices to locate atrio-venous activation points (and thereby preventing unnecessary applications), together with the usage of decreased power limits, have limited the risk<sup>14</sup>.

In general, transvenous catheter based procedures have been preferred in the treatment of patients with symptomatic lone AF. Long term efficacy and morbidity however remain unclear.

In selected patients, catheter radiofrequency ablation of the atrio-ventricular (AV) node with permanent pacemaker insertion can be considered when medical therapy fails to control the rate of AF, or patients remain symptomatic from the AF.

### **3.3. Evolution of Surgery**

Current surgical treatment options to cure AF are largely based on the work done by Garrey and Lewis in the 1910's at Washington University. They made the important observation that a 'critical mass' of atrial tissue was necessary to support AF, by showing that any atrial piece ceases fibrillating when cut small enough<sup>4</sup>.

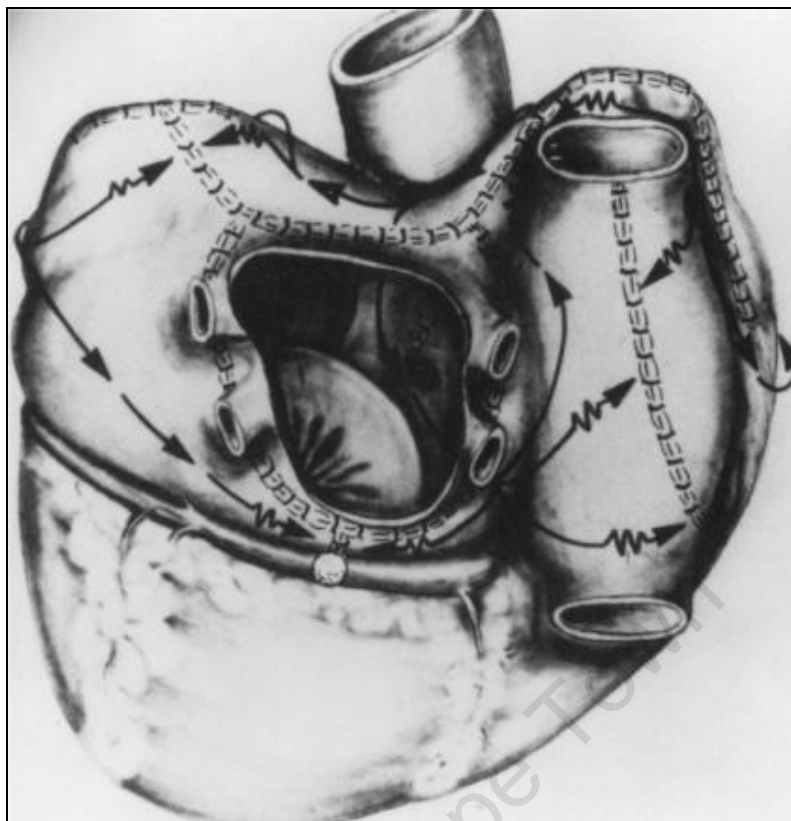
The ACC/AHA Guidelines for Valvular Heart Disease recommends exclusion of the left atrial appendage (LAA) at the time of mitral valve surgery<sup>11</sup>. This is because a high proportion of strokes in AF patients are thromboembolic, and originate from the LAA.

#### **3.3.1. Corridor Procedure**

Guiraudon and colleagues described the Corridor procedure in 1985 as a surgical alternative to His bundle ablation in the treatment of AF<sup>74</sup>. This procedure creates a corridor in the right and left atria that enables electrical activity to propagate from the sino-atrial node to the atrioventricular node. The drawback was the loss of atrial transport function. Because the remaining part of the atria was isolated from this corridor, atrial fibrillation and the associated risk for thrombo-embolism still remained in these parts of the atria<sup>66</sup>. Postoperative incidence of stroke and permanent pacemaker implantation rates, together with the fact that atrial transport function was lost, all contributed to this procedure being abandoned after the introduction of the Cox Maze procedure.

#### **3.3.2. The Cox-Maze procedures**

Dr James Cox first described the initial Maze I procedure in 1991. The aim was to divide the atrium into segments smaller than the critical mass needed for AF. This was achieved by creating a series of atriotomies in the left and right atria. Both atrial appendages were also resected and the coronary sinus cryoablated.

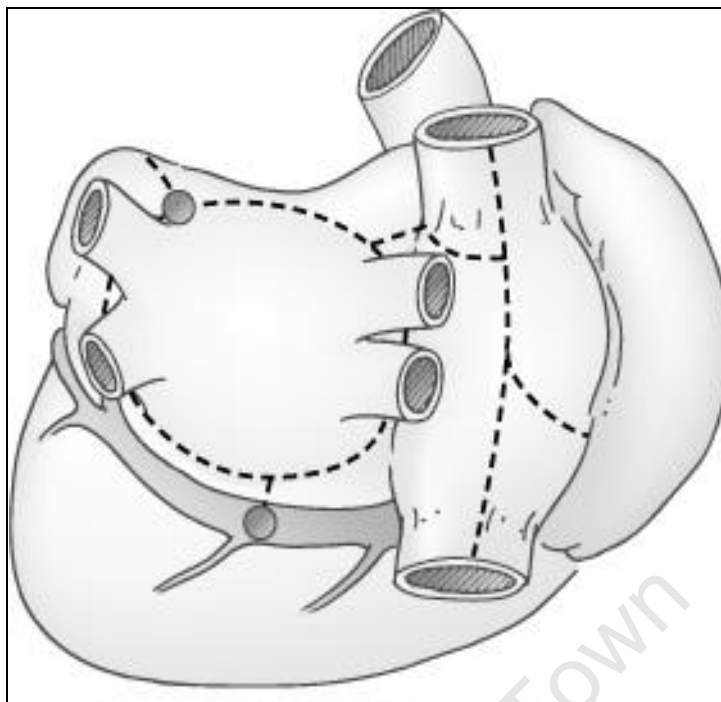


**Figure 2 Three-dimensional depiction of the incisions used for performing the Maze I procedure.** Note the presence of the transmurally cryolesions (*white dot*) of the coronary sinus at the site of the postero-inferior left atriotomy. Both atrial appendages have been excised. The only completely isolated portions of the atrium are the orifices of the pulmonary veins. The impulse originates from the region of the SA node and can escape from that region only by passing inferiorly and anteriorly around the base of the right atrium. The impulse continues to propagate around the anterior right atrium onto the top of the interatrial septum. There, it bifurcates into two wave fronts, one passing through the septum in an anterior-to-posterior direction to activate the posteromedial right and left atria, and the other continuing around the base of the excised left atrial appendage to activate the posterolateral atrial wall. In this manner, all atrial myocardium, except the pulmonary vein orifices, is activated. The activation of this atrial myocardium is fundamental to the preservation of atrial transport function postoperatively.

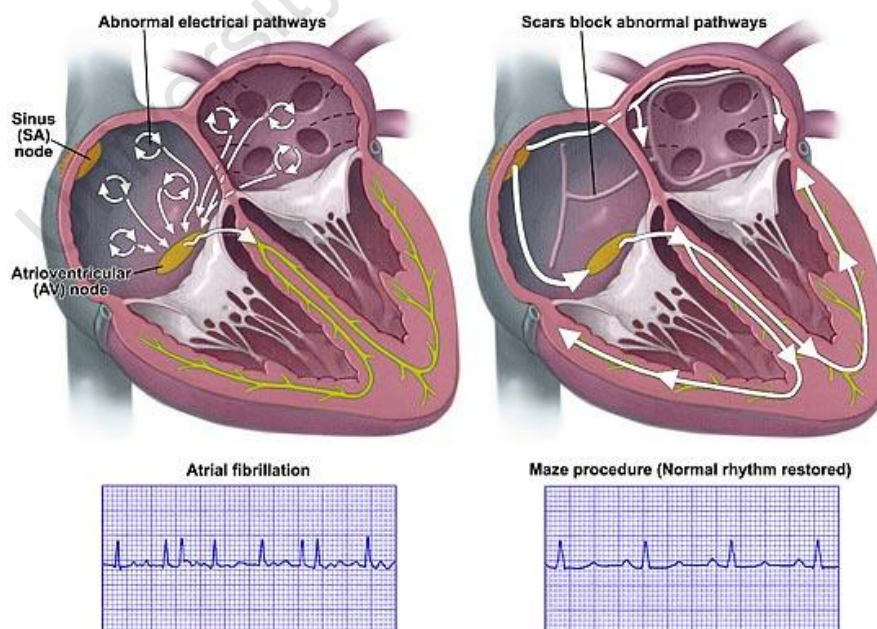
*(From Cox JL, Schuessler RB, D'Agostino HJ Jr, et al: The surgical treatment of atrial fibrillation. Development of a definite surgical procedure. J Thorac Cardiovasc Surg 101:569–583, 1991.)*

Concerns about technical difficulty, increased ischemic times, bleeding complications, high risk of pacemaker implantation rate and impaired chronotropic function led to revision of the atriotomy incisions and thus the Maze II procedure was born. However this was even more technically demanding and a third modification resulted in the Maze III procedure. The Maze III atriotomy lesions are still being considered the “gold standard” for the surgical treatment of atrial fibrillation.





**Figure 3 Depiction of the incisions made for the Maze III procedure.** The modifications include relocation of the posterior septal incision away from the orifice of the superior vena cava (SVC) so that the SVC does not have to be transected, and the transverse atriotomy across the left atrium moves more posterior. (From Cox JL, Schuessler RB, Lappas DG, Boineau JP: An 8 1/2-year clinical experience with surgery for atrial fibrillation. *Ann Surg* 224(3):267–273; discussion 273–275, 1996.)



**Fig 4: Schematic illustration of atriotomy scar lesions blocking abnormal electrical pathways.**

Although originally described for patients with lone AF, its use has expanded to patients with organic heart disease in addition to AF. Today the Maze procedure is performed alone or in conjunction with other cardiac surgical procedures, such as mitral valve repair/replacement or coronary artery bypass grafting<sup>36,42-45,53,57,59,60</sup>. In experienced hands, the Maze procedure requires 45 to 60 minutes of additional cardiopulmonary bypass and aortic cross-clamp times<sup>18</sup>.

The largest series (346 patients) was published by Cox and colleagues, reporting an operative mortality rate of 2% and a cure rate from AF of 99%<sup>19</sup>. Presence of mitral valve disease, left atrial size and the type of AF did not affect the success rates. 15% of the patients required permanent pacemakers after surgery, and this was generally necessary in patients with underlying sinus node dysfunction. The incidence of cerebro-vascular accidents was found to be low.

Jatene and colleagues evaluated the efficacy of the Cox Maze procedure in the treatment of atrial fibrillation with concomitant surgical treatment of rheumatic mitral valve disease and compared this to a group of patients with atrial fibrillation and mitral valve disease who underwent surgical treatment of the mitral valve only<sup>42</sup>. 95% of patients who underwent additional Maze surgery enjoyed freedom from AF at mid-term follow up (39 months), compared to only 24% in the non-Maze group.

Sinus conversion rates in other series using the cut and sew techniques vary between 73%-95%<sup>36,42-45,52,53,55,57,59,60</sup>. Results from the literature are further outlined in Table 1.

**Table 1: Literature review on ‘cut and sew’ technique**

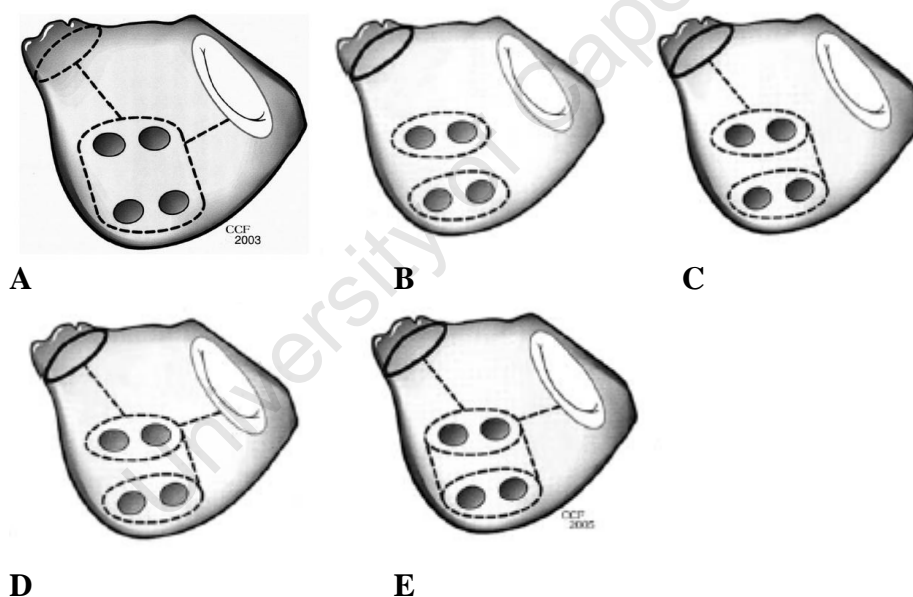
Cut & Sew techniques												
Authors	Year	n=	Age	EF	CCS?	AF duration (months)	BA %	Mort %	PPM	Mean FU (months)	F/U - SR	Proph
Stulak <sup>55</sup>	2006	37	55	45%	No	48	100	0%	8.1%	48	76%	Chemical or electrical CV ad hoc
Hemels <sup>52</sup>	2006	29	48	-	No	<=12	100	0%	6.9%	57	79%	Warfarin prophylaxis for 6/12.
Chiapipini <sup>36</sup>	2004	30	60.9	58%	Yes (> ms)	54	100	6.6%	6%	73	69%	Amio 200/day for 6/12
Romano <sup>57</sup>	2004	36	66	48%	Yes (> ms)	45	100	0%	0%	19	89%	Amio 150/day for at least 1/12
Raanani <sup>45</sup>	2001	47	68	-	ms	>3	100	4.5%	11%	26	75%	Nil
Jatene <sup>42</sup>	2000	20	50.5	69%	rms	30	100	5%	-	39	95%	Nil
Millar <sup>43</sup>	2000	76	59.6	60%	Yes(> rms)	> 6	100	0%	4%	3	90.60%	Nil. Treat post op AF ad hoc.
Izumoto <sup>44</sup>	2000	104	59.7	-	Yes (> ms)	> 3	100	1%	6%	44.6	73%	Nil. Treat post op AF ad hoc.
Kim <sup>59</sup>	1999	75	48	-	rms	67	100	2,7%	2,7%	30	90%	Nil
Kobayashi <sup>60</sup>	1998	220	58.3	-	ms	85	100	1,8%		36	73%	Nil
n=nr of patients, EF=ejection fraction, CCS=concomitant cardiac surgery, ms=mitral surgery, rms=rheumatic mitral surgery, AF=mean preop AF duration, LA=left atrial lesions, BA=biatrial lesions, Mort=in hospital mortality, PPM=postop pacemaker implantation rate, Mean FU=mean follow up, SR=sinus rhythm, Proph=post op prophylaxes, Amio=Amiodarone, CV=cardioversion												

### 3.3.3. Ablative Techniques

To overcome the problems of technical complexity and prolonged aortic cross-clamp times, different energy-based ablative techniques have been investigated in an attempt to create these Maze-like lesions in the atria. The goal is to rapidly create lines of conduction block under direct vision.

In 1994, Kosakai and his associates described a modification of the Cox-Maze III procedure<sup>75</sup>. Cryoprobes were used to create lesions that would replace the atriotomies of the original Cox-Maze III procedure. Medium term results of these modifications however demonstrated lower than expected sinus conversion rates<sup>44</sup>. Complexity and operative times were nevertheless significantly reduced.

On this basis further modifications and different energy sources were evaluated. Evidence suggesting the existence of focal sources initiating AF (especially in the posterior left atrial wall near the pulmonary vein orifices) has led to ablative and isolation techniques of these areas. Less invasive modifications of the Maze procedure include fewer lesion sets, excluding right atrial lesions, and primarily focusing on pulmonary vein isolation.



**Fig 5 (A-E): Representations of different left atrial lesion sets being used.** All ensure that the pulmonary vein orifices are adequately encircled, with or without connecting lines to the posterior mitral valve annulus (top right structure in each diagram), left atrial appendage (top left structure in each diagram) and between the left and right pulmonary veins.

Gillinov and co-workers studied the effectiveness of different lesion sets in the surgical treatment of *permanent* atrial fibrillation in patients undergoing concomitant mitral valve surgery. They compared different limited left atrial only procedures with the classical Cox-Maze procedure and concluded that the minimal lesion set to treat patient with *permanent* AF should include wide isolation of the pulmonary veins, with at least one connection between the right and left pulmonary veins, and a connection to the mitral annulus<sup>71</sup>. In another paper focusing on *paroxysmal* AF, they

concluded that pulmonary vein isolation alone may be adequate treatment especially if the *paroxysmal* AF is of short duration<sup>72</sup>. The patients in this group also underwent mitral valve surgery.

The different energy sources used in the creation of these ablative lines include radiofrequency-, cryo-, microwave- and laser-ablation<sup>8,20</sup>. These energy-based sources create lines of conduction block through thermal injury. On average this adds 15 minutes extra to the operative time depending on the lesion sets created. The two basic principles of surgery for atrial fibrillation must be adhered to when using these techniques. These include the achievement of transmuralty of the lesions as well as continuity of the ablation lines in creating a Maze or acceptable modified Maze pattern<sup>26</sup>. As discussed previously, care must be taken to avoid damage to the surrounding structures, particularly the oesophagus. Some authors advocate the removal of an indwelling trans-oesophageal echo probe before ablation to protect the oesophagus from possible damage<sup>21,24</sup>. Although injury to the circumflex artery has not been reported, some authors make use of cold retrograde cardioplegia to protect this structure during the creation of ablative lines in the left atrium<sup>30</sup>.

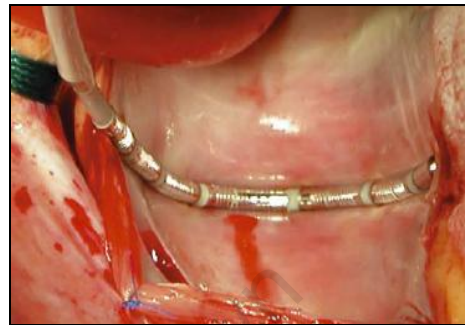
Regardless of the technique used or energy source being applied, it is imperative that surgical strategies should strive to achieve the five goals to treat atrial fibrillation as described by Ferguson and Cox<sup>76</sup>. These include: (1) elimination of atrial fibrillation, (2) restoration of sinus rhythm, (3) re-establish atrioventricular synchrony, (4) restoration of atrial transport function and (5) reduction of the risk of thrombo-embolism.

### 3.3.3.1. Radiofrequency Energy

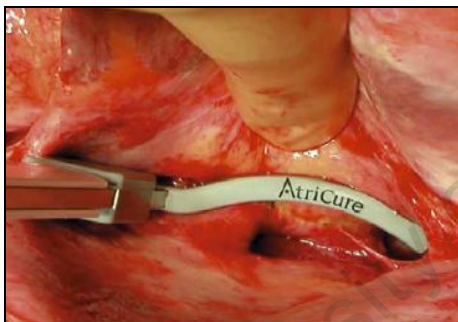
Radiofrequency energy uses alternating electrical currents between 50 KHz and 1 MHz to heat tissue thereby creating ablative lines. A wide variety of catheter probes have been developed for the surgical application of monopolar or bipolar radiofrequency energy. Some of these include the monopolar Cobra®/Thermaline® device and the bipolar Atricure® and Cardioblate® BP2 devices.



Monopolar Cobra® device



Monopolar Thermaline® device



Bipolar AtriCure® device



Bipolar Cardioblate® BP2 Surgical Ablation Device

**Fig 6: Commonly available radiofrequency ablation systems.**

With monopolar probes the energy current is transferred from an active electrode to an indifferent electrode and then back to the generator. The tissue in contact is heated and charring occurs. Disadvantages of monopolar devices include uncertainty about the transmuralty of the lesions created and the possibility of damage to the neighbouring structures, including the oesophagus and aorta. The use of bipolar devices ensures transmuralty of the lesions. In their series, Geidel et al demonstrated a 75% sinus conversion rate at 16.6 months follow up of patients undergoing radiofrequency ablation with different monopolar and bipolar devices for longstanding AF<sup>24</sup>. Concomitant valve and/or revascularization surgery were done at the same setting.

Under direct vision, these probes may be placed on either the epicardial or endocardial surface of the heart. Epicardial beating heart ablation has been developed in the quest to create less invasive techniques and to shorten aortic cross clamp times<sup>28,31</sup>. When comparing epi- and endo-cardial lesion sets however, concerns have been raised with regards to the transmuralty of the lesions when creating ablative lines from the epicardial surface only. Wong has described a method which combines endocardial and epicardial ablation using a monopolar radiofrequency device to improve transmuralty. A 93.3% sinus conversion rate was achieved in this small series<sup>26</sup>.

In contrast to transvenous catheter ablations, there is no circulating blood directly cooling the electrode when using radiofrequency catheter probes. Various authors have made use of different handmade or pre-manufactured irrigated devices<sup>21,23,25-27,29,37,40</sup>. These saline-irrigated cooled tip catheters or bipolar devices allow for delivery of higher amounts of energy. The saline irrigation cools the surface tissue and lowers the impedance at the tissue-electrode interface, thus preventing charring of the tissue and allowing the energy to drive deeper into the atrial tissue and increase the lesion depth<sup>26,29</sup>. Chen and colleagues and Sie and colleagues have demonstrated that these irrigated systems produce adequate transmural lesions with good continuity<sup>23,25</sup>.



**Fig 7: Cardioblade™ Surgical Ablation Pen and Generator**

The decision between biatrial versus isolated left atrial only ablative procedures still remains an issue of debate. There are no large prospective studies available to prove superiority of the one approach over the other. The answer would lie in the identification of the foci that initiate and maintain AF and since the pathogenesis of AF is not completely understood, it is important that patients with different types of AF might require different lesion sets. Guden and colleagues have witnessed better sinus conversion rates and a lower incidence of post operative atrial flutter in patients who underwent biatrial saline-irrigated radiofrequency procedures compared to left atrial only approaches, but this was however not statistically significant in a multivariate analysis due to the population size<sup>29</sup>.

Most published papers on surgery for atrial fibrillation were done on patients undergoing concomitant surgery (mainly mitral surgery). In their series, Khargi et al investigated saline-irrigated cooled tip radiofrequency ablation (SICTRA) of permanent AF in CABG patients<sup>27</sup>. A 75% sinus conversion rate at a mean follow up of 25 months was achieved, with acceptable mortality and morbidity rates.

Comparing published data on radiofrequency ablation is difficult due to major differences in the patient subsets. Important differences between these groups include the type and duration of pre-operative AF, associated cardiac surgery performed (valvular surgery, revascularization surgery or none), type of lesions created, use of irrigated or non-irrigated systems, follow up duration and permanent pacemaker implantation rates.

Table 2 illustrates a literature review on available data with some of these differences and other relevant details.



Table 2: Literature review on Radiofrequency ablation

RADIOFREQUENCY ABLATION																	
Authors	Year	n=	Age (yrs)	EF (%)	CCS?	AF (months)	Irr?	Mono/Bipolar?	Epi/Endo	LA (%)	BA (%)	Mort	PPM	Mean FU (months)	Flutter %	F/U - SR	Post op prophylaxes
Forlani <sup>40</sup>	2006	53	66	58	ms	43	y	mono	Endo	100	0	-	-	21	-	68%	Amio or Sotalol. ECV if this fails. ECV repeated at 1 and 3 months
Halkos <sup>21</sup>	2005	54	64	56	Yes (> ms)	46.3	y	mono	Endo	78	22	12.9%	12.7%	8.7	-	69%	Sotalol or Amio ad hoc.
Fayad <sup>22</sup>	2005	70	64	-	ms	>24	n	mono	Endo	100	0	2.8%	2.8%	22	-	91%	Sotalol or Amio ad hoc. ECV if this fails.
Chen <sup>23</sup>	2005	99	51	61	ms	>36	y	mono	Endo	0	100	0%	-	46.1	0%	83.8%	Nil
Geidel <sup>24</sup>	2005	106	70	56	Yes (> ms)	69.7	n	mono+bi	Endo	100	0	1.9%	1.9%	16.6	0%	75%	Amio or Sotalol in all cases * 3/12. ECV if early AF recurrence.
Golovchiner <sup>37</sup>	2005	50	59	-	ms	50	y	mono	Endo	100	0	6.0%	2%	15	12.7%	79%	Sotalol in all. Attempted ECV at 6 & 12 weeks if this fails.
Khargi <sup>64</sup>	2005	128	67	59	Yes	64	y	mono	Endo	-	-	-	-	12	-	75%	Sotalol and later Metoprolol. ECV if indicated.
Sie <sup>35</sup>	2004	200	68	-	Yes (> ms)	>12	y	mono	Endo	0	100	3.5%	3.5%	40	-	73%	Sotalol or Amio ad hoc. ECV if this fails.
Wong <sup>26</sup>	2004	15	35	-	ms	-	y	mono	Endo & Epi	0	100	0%	0%	6	-	93%	-
Khargi <sup>27</sup>	2004	36	68	54	CABG	67	y	mono	Endo & Epi	58	42	2.8%	2.8%	25.3	8.3%	75%	Metoprolol post op. ECV after 6/12 only.
Chiappini <sup>36</sup>	2004	40	62	57	Yes (> ms)	62	n	mono	Endo	0	100	7.5%	7%	16.5	-	89%	Amio for 6/12
Wisser <sup>39</sup>	2004	19	64.1	56	Yes (> ms)	53.5	y	mono	Endo	0	100	0.0%	21%	12.1	-	42%	Amio ad hoc. ECV if this fails (Max 2 times)
Geidel <sup>58</sup>	2003	29	73.1	59	Yes (ms)	54	n	mono	Endo	100	0	0.0%	0%	6	-	88%	Amio for 3/12
Benussi <sup>28</sup>	2002	132	58.5	59	Yes (> ms)	41.8	n	mono	Endo or Epi	100	0	0.8%	0%	16.9	-	81%	Amio (or Sotalol) for 6/12. ECV if medical Rx fails
Guden <sup>29</sup>	2002	62	52	51	Yes (> ms)	>6	y	mono	Endo	37	63	3.2%	1.6%	3.5	-	81-95%	Amio for 3/12. ECV after 3/12 only
Sie <sup>33</sup>	2001	72	63	-	Yes (> ms)	73	y	mono	Endo	0	100	2.7%	5.5%	20	-	71%	Sotalol or Amio ad hoc. ECV if this fails.
Williams <sup>30</sup>	2001	48	65	-	Yes (> ms)	57	n	mono	Endo	83	17	12.5%	0%	4.5	4.2%	81%	Nil
Melo <sup>31</sup>	2000	65	60	-	Yes (> ms)	59	n	mono	Endo or Epi	100	0	0%	-	6	-	42%	Nil
Benussi <sup>35</sup>	2000	40	58.1	-	Yes (> ms)	43.1	n	mono	Epi	100	0	2.5%	0%	11.6	5%	77%	Amio or Sotalol for 6/12.
Melo <sup>38</sup>	1999	43	59	-	ms	72	n	mono	Endo	100	0	0%	0%	12	-	48%	-

n=nr of patients, EF=ejection fraction, CCS=concomitant cardiac surgery, ms=mitral surgery, rms=rheumatic mitral surgery, CABG=coronary artery bypass grafting, AF=mean preop AF duration  
Irr?=saline irrigated device?, Epi/Endo=epicardial or endocardial lesion sets, LA=left atrial lesions, BA=biatrial lesions, Mort=in hospital mortality, PPM=postop pacemaker implantation rate, Mean FU=mean follow up  
Flutter=post op atrial flutter, SR=sinus rhythm, Proph=post op prophylaxes, Amio=Amiodarone, ECV=electrical cardioversion

### **3.3.3.2. Microwave Energy**

Microwaves cause oscillation of water molecules in tissue, converting electromagnetic energy into heat<sup>39</sup>. This release of the heat creates lesions at a predictive depth. The ablation probe itself need not have permanent contact with the tissue which is often advantageous because it is sometimes difficult to achieve a completely dry field during surgery. Other potential advantages include shorter application times, longer linear lesions with fewer applications and less scarring of the endocardium with reduced risk of thromboembolism<sup>67</sup>. Wisser and colleagues compared freedom from AF in a prospective trial between microwave and radiofrequency ablation for chronic AF with concomitant mitral surgery and observed comparable success rates<sup>39</sup>.

Pruitt and colleagues investigated the application of epicardial microwave ablation on a beating heart using thoroscopic or robot assisted surgery for patients presenting with lone AF (mean duration 73.5 months) and reported a 80% sinus conversion rate at a mean follow up of 7.6 months<sup>54</sup>. There was no mortality in this series and only left sided lesion sets were applied. No patients required post operative permanent pacemaker implantation.

Table 3 contains a short analysis of published data on microwave ablation procedures.

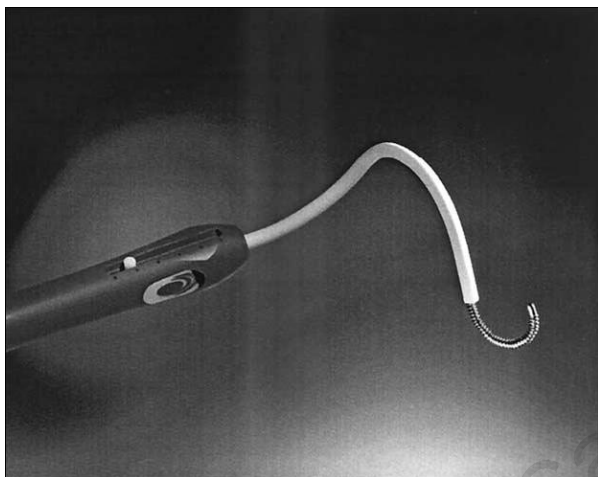
### **3.3.3.3. Laser Ablation**

Clinical experience is very limited but potential advantages include short application times, minimal lateral expansion of the lesion and low tissue temperatures. Perforation remains the major concern.

### 3.3.3.4. Cryotherapy

Cryotherapy causes disruption of cell membranes which creates lesions that will heal by fibrosis<sup>67</sup>. It can be applied both endocardially and epicardially. Previous studies have already documented that cryosurgery has no short or long-term adverse effects on the vascular structures. Cryoablation has also gained popularity due to shorter ablation times.

Devices available include the Surgifrost CryoCath.



*Fig 8. Cryoablation hand-held probe and Cryoablation console (SurgiFrost CryoCath, Endocare Inc, Irvine, CA).*

Gammie and colleagues achieved a 95% sinus conversion rate, maintained at 12 months follow up, in patients undergoing a “CryoMaze” procedure<sup>50</sup>. The traditional bilateral atriotomy maze pattern was replaced with ablative lines using a cryoprobe. The average time to perform the complete Cox-Maze III lesion set was 15-20 minutes. Most patients in this series had concomitant cardiac surgery.

Manasse and associates applied left atrial endocardial ablative lines using cryotherapy in patients (n=95) with longstanding AF (mean duration=65 months) undergoing concomitant cardiac surgery and achieved an 81.4% sinus conversion rate at a mean follow up of 36 months<sup>49</sup>. In this series the rhythm at discharge was identified as a predictor of follow up sinus rhythm.

Table 4 contains a summary of a literature review on cryoablation.

**Table 3: Literature review on Microwave Ablation**

MICROWAVE ABLATION																
Authors	Year	n=	Age (yrs)	EF (%)	CCS?	AF (months)	Device	Epi/Endo	LA (%)	BA (%)	Mort	PPM	Mean FU (months)	F/U - Freedom from AF	F/U - SR	Post op prophylaxes
Pruitt <sup>54</sup>	2006	50	59.1	-	No	73.5	Flex 10 Afx inc.	Epi	100	0	0%	0%	7.6		80%	Amio and Warfarin in all.
Knaut <sup>63</sup>	2005	111	68.5	56.1%	Yes	80	Flex 2 Afx inc	Endo	100	0	1%	-	24		54%	Sotalol in most. Few had metoprolol or amio
Molloy <sup>51</sup>	2005	29	73.2	55%	Yes	-	Afx inc.	Epi	100	0	4%	7%	10.5		86%	Amio in all patients for 2 months (Dose tapered)
Wisser <sup>39</sup>	2004	23	65.8	55.7%	Yes (>ms)	61.9	Afx inc.	Endo	0	100	4%	20%	24.2	81%	53%	Amio ad hoc. ECV if this fails (Max 2 times)
Schuetz <sup>47</sup>	2003	24	64.5	62.8%	Yes	45	Afx inc.	Endo	100	0	4%	-	12	80%		Amio or Sotalol only if in SR post op.
Maessen <sup>76</sup>	2002	24	67.4	-	Yes	53	Afx inc.	Epi	100	0	4%	-	3		87%	Sotalol in all. ECV or Amio if this fails.

n=nr of patients, EF=ejection fraction, CCS=concomitant cardiac surgery, ms=mitral surgery, AF=mean preop AF duration  
Epi/Endo=epicardial or endocardial lesion sets, LA=left atrial lesions, BA=biatrial lesions, Mort=in hospital mortality, PPM=postop pacemaker implantation rate, Mean FU=mean follow up  
SR=sinus rhythm, Proph=post op prophylaxes, Amio=Amiodarone, ECV=electrical cardioversion

**Table 4: Literature review on Cryoablation**

CRYOABLATION																
Authors	Year	n=	Age (yrs)	EF (%)	CCS?	AF (months)	Epi/Endo	LA (%)	BA (%)	Mort	PPM	Mean FU (months)	Flutter	F/U - SR	Post op prophylaxes	
Gammie <sup>30</sup>	2005	38	66	-	Yes	48	Maze III	0	100	2.6%	2.6%	12	-	95%	B Blockers to all patients	
Kondo <sup>32</sup>	2003	31	59.8	-	Yes (> ms)	77.3	Endo	100	0	6.4%	16.1%	37.7	-	72%	Nil	
Doll <sup>48</sup>	2003	28	60	59%	Yes	82	Endo	100	0	0%	14%	6	-	74%	Amio or B Blocker if AF. Electrical CV if this fails.	
Manasse <sup>49</sup>	2003	95	61	-	Yes (> ms)	65	Endo	100	0	3.2%	6.3%	36	-	81.4%	Amio 200/day in all for 3-6 months. Electrical CV if AF/flutter before discharge	
Yamauchi <sup>68</sup>	2002	40	60	-	Yes (> ms)	96	Endo	-	-	-	7.5%	-	0%	77.5%	-	
Kawaguchi <sup>65</sup>	1996	51	58.4	-	Yes (>rms)	90	Endo	0	100	0%	5.8%	32	-	84%	No prophylaxis. Chemical or electrical CV if indicated.	

n=nr of patients, EF=ejection fraction, CCS=concomitant cardiac surgery, ms=mitral surgery, rms=rheumatic mitral surgery, AF=mean preop AF duration  
Epi/Endo=epicardial or endocardial lesion sets, LA=left atrial lesions, BA=biatrial lesions, Mort=in hospital mortality, PPM=postop pacemaker implantation rate, Mean FU=mean follow up  
Flutter=post op atrial flutter, SR=sinus rhythm, Proph=post op prophylaxes, Amio=Amiodarone, ECV=electrical cardioversion

### 3.3.3.5. Diathermy (Electrocautery)

Lam et al have evaluated the use of ordinary diathermy as energy source to create ablative lines for the treatment of atrial fibrillation<sup>16</sup>. Lesions were created on fresh bovine hearts and compared to those created with irrigated monopolar radiofrequency ablation. Although the initial clinical results have been encouraging, this technique (using ordinary diathermy) raises some concerns. Firstly, they have not found diathermy capable of creating adequate transmural lesions histologically. The second concern is the superficial tissue destruction that occurs. This could possibly predispose to thrombo-embolism.

Simha et al have reported on a clinical series using diathermy with acceptable results but again the concern of superficial tissue destruction with charring was of concern as this can either lead to atrial perforation on the one hand or prevent adequate duration of diathermy application before tissue charring, to allow transmural of the lesion created.<sup>15</sup>

These 2 reports prompted our unit to develop a novel *irrigated* electrocautery ablation system as an energy source when performing Maze surgery.

### 3.3.4. PREDICTORS OF FAILURE OR SUCCESS FOR MAZE SURGERY

#### 3.3.4.1. Enlarged Atria

Enlarged left atria, with diameters greater than 60mm, are known to be a determining factor in the development and maintenance of AF. Its presence is usually indicative of longstanding mitral valve disease with secondary changes in the atrial myocardium, such as wall thinning, which may lead to poor contractility and outcome after cardioversion or the Maze procedure. Several authors have confirmed this finding<sup>21,23,24,31,53,60</sup>.

Geidel et al achieved an 88% sinus conversion rate in their series performing non-irrigated radiofrequency ablation in patients with longstanding AF (mean duration=54 months) undergoing concomitant valvular surgery<sup>58</sup>. They also observed that all the patients with a left atrial diameter < 56mm were in sinus rhythm at a mean follow up of 6 months.

On the other hand there is also significant evidence demonstrating that enlarged left atria could not be identified as predictors of post operative AF recurrence after Maze surgery<sup>22,27,49</sup>.

In their series Choo and associates concluded that AF surgery is effective at achieving sinus rhythm and restoring left atrial contractile function after concomitant mitral valve surgery, regardless of the left atrial size<sup>56</sup>. They evaluated 188 patients undergoing the Cox-Maze III procedure or the modified Cryo-Maze procedure.

Romano and co-workers described a biatrial reduction plasty technique in addition to the Cox-Maze procedure for restoration of sinus rhythm in patients with markedly enlarged atria (mean LA diameter of 66mm). This patient group (n=36) also underwent concomitant surgery. At a mean follow up of 19 months they demonstrated an 89% sinus conversion rate. There was no mortality in this series and no need for permanent pacemaker implantation post-operatively<sup>57</sup>.

#### 3.3.4.2. Chronic AF

Prolonged duration of atrial fibrillation – for longer than 6 months, particularly when associated with mitral valve disease – has also been associated with poor sinus conversion rates following the Maze procedure<sup>23,32,53,60</sup>. Conversely, some authors did not find prolonged AF to be statistically significant in predicting post operative AF recurrence<sup>22,27,49,57</sup>.

The central point of controversy however lies in the nature of the preoperative AF. If authors refer to chronicity as the duration of AF even if it is not continuous, this should, by definition, be described as bouts of intermittent *paroxysmal* AF. In these cases better sinus conversion rates could be expected when applying simplified left atrial procedures only, especially those focusing only on isolation of the pulmonary veins<sup>6</sup>. It has been demonstrated that each individual episode of *paroxysmal* AF is dependant on a trigger for induction and that in most cases these triggers are located

in the pulmonary veins<sup>14</sup>. In contrast to this, chronic continuous AF does not need triggers for induction, but rather drivers to sustain it, which is thought to be the macro-reentrant circuits within the atria in most of the cases. In these cases more extensive lesion sets would be more appropriate<sup>62</sup>.

### **3.3.4.3. Ejection Fraction**

Some authors regard impaired preoperative ejection fraction as a relative contra-indication to Maze surgery. This follows from evidence in some series that lower ejection fractions were associated with increased AF recurrence post operatively<sup>22</sup>. Conclusive evidence is however lacking.

Stulak and co-workers demonstrated a significant improvement in systolic function and functional status associated with the restoration of sinus rhythm after the Cox Maze procedure<sup>55</sup>. They evaluated 37 patients with a mean preoperative ejection fraction of 45% undergoing the cut and sew technique for lone AF. There was no mortality in this series and the postoperative pacemaker implantation rate was 8.1%. At a mean follow up of 48 months a 76% sinus conversion rate was maintained. This series suggested that patients with impaired ejection fraction might actually be the ones to gain more from the restoration of sinus rhythm, and therefore does not support the concept that moderately impaired left ventricular ejection fraction should be regarded as a contra-indication to Maze surgery.

Khargi and associates also failed to identify preoperative left ventricular ejection fraction as a predictor of sinus conversion rate<sup>27</sup>. They evaluated saline-irrigated cooled-tip radiofrequency ablation (SICTRA) for patients with chronic AF undergoing concomitant coronary artery bypass grafting (CABG).

Chen et al identified preoperative AF duration of more than 66 months and left atrial diameter of more than 5.68cm as predictors of poor sinus conversion rates in patients undergoing irrigated radiofrequency ablation for persistent atrial fibrillation with concomitant mitral valve surgery<sup>23</sup>. Impaired left ventricular ejection fraction and rheumatic mitral disease were not identified as independent predictors in this series.

### **3.3.4.4. Concomitant Organic Heart Disease**

The concern for potential failure of sinus conversion after Maze surgery with concomitant organic heart disease, especially mitral valve disease, has been documented<sup>22,17</sup>. However, recent reports have demonstrated good results when the Maze procedure is combined with a valvular procedure<sup>21,22,30,42,57,60</sup>.

Kim and associates achieved a 90% sinus conversion rate in patients undergoing the Cox-Maze III procedure with concomitant rheumatic mitral valve surgery. The mean follow up was 30 months and the incidence of post operative pacemaker implantation was 2.7%<sup>59</sup>. This was confirmed by Jatene et al who performed Cox-Maze surgery for chronic AF with concomitant rheumatic valvular surgery when they demonstrated a 95% sinus conversion rate at mean follow up of 39 months<sup>42</sup>.

Similar observations have been made using the alternative energy sources. Khargi et al studied 128 patients undergoing monopolar SICTRA with or without concomitant mitral surgery and found no difference between sinus conversion or survival rates between the groups. The overall sinus conversion rate was 75% at 12 month follow up.

#### **3.3.4.5. Fine Atrial Fibrillatory waves**

It has been suggested that the presence of fine atrial fibrillatory waves measured as less than 1.0mm on a standard 12-lead electrocardiogram has been associated with poor conversion rate.

The series by Romano et al mentioned in paragraph 3.3.4.1 also demonstrated good sinus conversion rates despite the presence of these fine fibrillatory waves<sup>57</sup>.



### 3.3.5. CONTROVERSIES IN AF SURGERY

#### 3.3.5.1. Incidence of new onset post operative Atrial Flutter

Scepticism on the overall benefit of the modified Maze procedures using different ablative technologies have emerged due to the incidence of new post operative atrial flutter in some series. The concern lies in the management of these arrhythmias and some authors are of the opinion that it remains easier to manage AF compared to atrial flutter. Incidence of new onset post operative atrial flutter varies in published series and range from 0%<sup>23,24,43,57,68</sup> to 12.7%<sup>27,30,35,37</sup>. Proposed mechanisms include inadequate continuity of ablative lines as well as failure to achieve transmural ablation<sup>25</sup>. Determining the optimum power of the energy source being used, together with the time of application and temperature at the probe site, remains challenging. The fact remains that atrial tissues are of different thickness in different disease states (e.g. rheumatic vs. degenerative) and also in different parts of each atrium. A simple real time method of confirming transmural ablation of the lesion sets at the time of energy application while using monopolar energy sources is unfortunately not yet available. Nevertheless atrial flutter can easily be managed by post operative catheter ablation techniques<sup>30,31,35</sup>.

In their animal study, Thomas et al investigated the duration of radiofrequency ablation necessary to produce transmural linear lesions<sup>34</sup>. They concluded that most of the lesion (~75%) was formed during the first 30 seconds of ablation. The precise duration required depends on the thickness of the atrial myocardium. Thicker areas such as the roof of the left atrium and the crista terminalis therefore require longer ablation times (>30 seconds). Increasing the target temperature did not prove to be significant in achieving deeper lesion sets. Radiofrequency lesions were also wider than they were deep, so deep penetrating lesions could only be achieved by producing fairly broad lesions.

A second plausible explanation of new onset post operative atrial flutter lies in the current simplified left atrial only ablation techniques which are being used by many centres<sup>35,37</sup>. The nature of this postoperative atrial flutter is however unclear. Some authors report typical right atrial isthmus-dependant flutter and others, atypical flutter. Golovchiner and associates have investigated the incidence and mechanisms of atrial tachyarrhythmias other than AF that occur after mitral valve surgery combined with radiofrequency ablation of the left atrium<sup>37</sup>. They observed a 12.7% (6 patients) incidence of post operative atrial flutter. Electrophysiological studies performed in 5 of these patients demonstrated findings consistent with left atrial flutter in 4 of the patients. One patient with typical isthmus-dependant right atrial flutter underwent successful catheter ablation. This would support the theory of incomplete ablative lines or failure to achieve adequate transmural ablation. In contrast with this, some authors have shown a 0% incidence of post operative atrial flutter using left atrial ablation techniques only<sup>24</sup>.

Another unanswered question is whether structural heart disease may serve as a foundation for flutter circuit formation. Mohr and co-workers found that none of their patients operated solely for AF experienced atrial flutter. By contrast, atrial flutter developed in 5.6% of the patients with concomitant mitral surgery<sup>73</sup>.

### **3.3.5.2. Atrial Natriuretic Peptide (ANP)**

Most patients treated for atrial fibrillation with Maze surgery and who undergo concomitant heart surgery present with heart failure. In these patients the cardiac natriuretic system has been activated to counteract the associated body fluid retention. It has been postulated that ANP secretion from the right atrial appendage of the heart is compromised after excision of this appendage during the classical cut and sew Maze procedures. This could account for post operative fluid retention due to blunted renal sodium and water excretion that is often encountered in these patients<sup>67</sup>. Nakamura and co-workers investigated this phenomenon and found significantly decreased plasma levels of ANP and brain natriuretic peptide (BNP) during the immediate post operative recovery stage in patients who underwent Maze surgery with concomitant cardiac surgery compared to a matched group who did not undergo Maze surgery<sup>61</sup>. Patients in the Maze group had a significantly increased incidence of postoperative pleural and pericardial effusions.

In contrast to this, other authors have not found fluid retention to be a problem during the postoperative period after excision of the atrial appendages<sup>57</sup>.

With the newer modified Maze techniques especially those limited to the left atrium the above problem should theoretically be eliminated. This also holds true for techniques that obliterate the atrial appendages using purse string sutures, rather than excision of the appendages.

### **3.3.5.3. Post Operative Management and Follow Up**

Consensus has not been reached regarding the ideal post operative management of patients who have undergone ablative procedures for atrial fibrillation. Introduction of prophylactic post operative anti-arrhythmic medication (predominantly Amiodarone and Sotalol) remains debatable. Proponents of these drugs argue that the lesion sets created will get deeper with time as is often seen with increased sinus conversion rates at later follow ups<sup>22,27</sup>. Some authors however feel that the introduction of these drugs during the post operative period will obscure the true results of the anti-arrhythmic surgery<sup>31,32</sup>.

Management of patients who revert to atrial fibrillation post-operatively or during the follow up period also differs between institutions. Whether and when chemical or electrical cardioversion is indicated remains unclear. In their series, Manasse and colleagues have demonstrated that the strongest predictor of long term sinus rhythm following modified Maze surgery, were early sinus rhythm restoration, therefore advocating that every effort should be made to discharge patients in sinus rhythm<sup>49</sup>. This makes a strong point for chemical and/or electrical cardioversion in all patients not maintaining sinus rhythm following surgery for atrial fibrillation.

### **3.3.5.4. Permanent Pacemaker Implantation**

Whether due to organic causes such as sick sinus syndrome or as a complication of Maze surgery or concomitant cardiac surgery, postoperative permanent pacemaker

implantation remains an unfortunate reality. Much has improved since the initial series of Maze surgery where pacemaker implantation rates have been quoted as high as 15%<sup>19</sup>. Favourable results have been achieved with the use of radiofrequency ablation with pacemaker implantation rates ranging between 0% and 7%<sup>22,24-30,35-38,58</sup>. Occasionally higher rates have been observed in smaller series. Pacemaker implantation rates following cryoablation have in general been observed to be marginally higher.

Whether different lesion sets (e.g. left atrial only versus bi-atrial) are associated with increased conduction disorders remains to be answered. At present there are no associated factors that could predict patients at higher risk.

### **3.3.5.5. Restoration of Atrial Transport Function**

As previously mentioned, one of the goals of AF surgery is the reestablishment of atrial transport function<sup>76</sup>. This has been achieved and documented by several authors<sup>22,27,28,33,35,38,59,64,65</sup>. The degree of restoration of contractility and transport function however seems to differ with the aetiology of the AF.

Fayad et al showed a 91% sinus conversion rate in patients undergoing left atrial radiofrequency ablation for AF together with mitral valve surgery<sup>22</sup>. They further demonstrated a significant reduction in left and right atrial size in these patients with a recovery in atrial contraction. Preoperative LA size and AF duration did not influence the postoperative AF recurrence rate. Previous mitral surgery, lower left ventricular ejection fraction and rheumatic mitral disease were however independent predictors of higher recurrence rates.

### **3.3.5.6. Impact on stroke rates**

Persistent atrial fibrillation is an important risk factor for ischaemic stroke. Prevention of thromboembolic complications is a major goal in the treatment of atrial fibrillation. As previously mentioned, the ACC/AHA Guidelines for Valvular Heart Disease recommends exclusion of the left atrial appendage (LAA) at the time of mitral valve surgery<sup>11</sup>.

Reston and Shubaiber performed a meta-analysis to determine whether a simultaneous Maze procedure reduces the risk of stroke in patients with chronic or paroxysmal AF who receive mitral valve surgery<sup>70</sup>. The findings of this review suggest that Maze surgery is associated with a reduction in stroke rates, although well-designed randomized controlled trials are still lacking.

The need and use of anticoagulation following Maze surgery is also controversial. Patients with other indications for anticoagulation (e.g. mechanical prosthesis) will need to continue anticoagulation lifelong. The more difficult decision lies within the group of patients demonstrating stable sinus rhythm in the post operative period, with no other indication for anticoagulation. Some authors advocate continuing anticoagulation prophylaxis in all these patients for a period of at least 3-6 months<sup>25,52-54</sup>. Those patients demonstrating stable sinus rhythm after this period with

no other risk factors for stroke would then discontinue the use of warfarin. There are unfortunately no randomized prospective trials supporting this practice. Tailoring therapy to the individual needs of each patient is probably the safest practice at present.

### 3.3.6. THE FUTURE

As technology continues to advance, new minimally invasive treatment modalities are being developed for the treatment of patients with AF. Avoidance of a sternotomy has largely increased patient acceptance of surgical treatment for isolated AF and is the major reason for increased patient referral for anti-arrhythmic surgical treatment. Pruitt and co-workers published a series of 50 patients who underwent thoroscopic or robotic assisted off-pump epicardial microwave ablation who suffered from drug refractory symptomatic lone AF<sup>54</sup>. At a mean follow up of 7.6 months 80% of the patients were in a stable sinus rhythm.

New innovative therapeutic strategies continue to evolve in a quest to cure AF. One of the major limitations of the current available energy-based treatment modalities is the cost of commercial probes and energy generators used in creating these Maze like lesions.

This has prompted Simha and colleagues to use ordinary diathermy as a source of thermal energy<sup>15</sup>. This adds no additional cost to the procedure. They have published their initial results where they used ordinary surgical diathermy to create bi-atrial lesions in a Maze pattern during concomitant mitral valve surgery. They achieved a 96% sinus conversion rate which remained stable over a mean follow-up period of 3.5 years. Criticisms include the charring of tissues that occurs with this technique. A histological study has also shown severe local necrosis without transmural penetration of the lesion when using *non-irrigated* diathermy compared to irrigated radiofrequency ablation<sup>16</sup>.

The latter problem of charring of tissue without evidence of transmural penetration has prompted our unit to use a novel *irrigated diathermy* probe to create atrial lesions in an acceptable Maze pattern to cure atrial fibrillation in patients undergoing concomitant cardiac surgery.

## II. AIMS AND OBJECTIVES

The primary aim was to evaluate the efficacy of irrigated monopolar electrocautery ablation in achieving sustained sinus rhythm when applied in conjunction with other open heart procedures.

The objectives were to:

1. To determine whether lesions created by irrigated monopolar electrocautery ablation are transmural in nature by macroscopical and histological examination of lesions created on animal hearts by irrigated electrocautery compared to radiofrequency ablation (*which is the most commonly used energy source in other centres but due to cost-constraints have limited its use in the South African public sector*).
2. To establish a protocol for follow up of patients who underwent irrigated electrocautery ablation for atrial fibrillation.

### III. MATERIALS AND METHODS

The study is divided into two sections

Section A consists of a retrospective, descriptive, non-comparative study of all patients who underwent irrigated monopolar electrocautery ablation for permanent atrial fibrillation during concomitant cardiac surgery by a single surgeon, in the Chris Barnard Division of Cardiothoracic Surgery at the University of Cape Town from September 2004 to April 2007.

Section B consists of a macroscopical and histological comparison of lesions created on animal hearts using *irrigated monopolar electrocautery ablation* compared to *irrigated radiofrequency ablation*. The issues of surface charring and achievement of transmuralty were specifically investigated.

#### SECTION A

##### 1. PATIENTS

Forty patients who underwent a modified Maze procedure during concomitant cardiac surgery during a two and a half year period from September 2004 to April 2007 at the Groote Schuur Hospital were reviewed. Details were obtained from a review of patients' clinical records and the Cardiothoracic Surgery database. The following pre-operative parameters were analyzed:

- Patient age
- Gender
- Functional status at presentation (New York Heart Association (NYHA))
- Underlying cardiac pathology requiring surgical intervention
- Ejection fraction on echocardiography
- Left atrial diameter on echocardiography

##### 2. SURGICAL PROCEDURE

All the modified Maze procedures were performed by a single surgeon. All operations were performed by means of a median sternotomy using cardiopulmonary bypass with standard aortic and either bicaval or dual stage right atrial cannulation. The heart was arrested by initially infusing a cold crystalloid cardioplegic solution, followed by blood cardioplegia, through the aortic root and moderate hypothermia (28°C to 32°C). Mitral valve surgery was performed through an incision below Waterston's groove. Left atrial ablation lesions were placed before mitral valve repair or replacement was done. In all cases the left atrial appendage was excluded using a purse string suture to obliterate the orifice. Right atrial ablation was performed when tricuspid valve annuloplasty or other procedures requiring right atrial access (atrial septal defect repair) were indicated, or if there was any evidence

of atrial flutter pre-operatively. This was done via an incision into the right atrium parallel to the atrioventricular groove. Aortic valve surgery was performed through a transverse aortotomy above the ostium of the right coronary artery.

We used a novel saline-irrigated monopolar electrocautery system, consisting of a standard diathermy power generator (60 – 80 Watt) and a standard hand-held electrocautery pen with a ball-tip attached. Irrigation with saline was achieved by connecting a standard intravenous transfusion set to the tip of the pen (Fig 10). Flow rate through this system was set at 200-300 mls/hour. With this system continuous endocardial lesions were created under direct vision in an accepted Maze pattern as outlined in figures 11 and 12. The completeness of a lesion was determined by observing tissue colour change to white and a palpable hardening of the underlying tissue. Saline irrigation was used to prevent tissue charring and to achieve transmural lesions by allowing longer tissue contact times.

Temporary atrial and ventricular pacing wires were routinely placed in all patients.

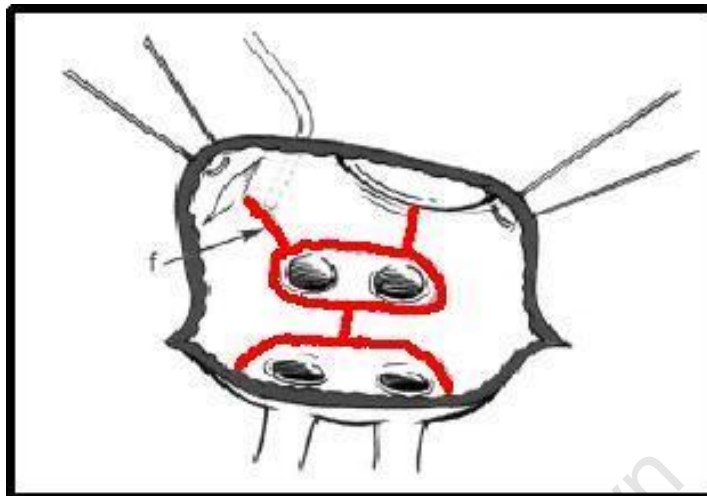
All patients were started on prophylactic anti-arrhythmic therapy after the termination of cardiopulmonary bypass. A loading dose of Amiodarone was given (300mg IVI over 1 hour).



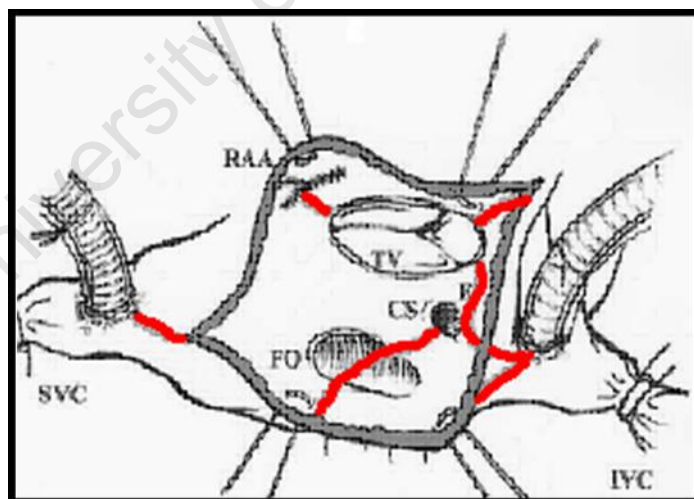
**Fig 9: Novel irrigated electrocautery ball-tip pen**



## 2.1. Description of technique



**Fig 10: View inside the left atrium.** Incision through Waterston's groove and stay sutures placed to expose the left atrium. All ablation lines are placed endocardially. Individual circumferential ablation lesions are placed to encircle the left and right pulmonary veins, with an interconnecting lesion between both sets of pulmonary veins; a linear ablation lesion is placed from the left pulmonary vein lesion to the left atrial appendage, with a circumferential ablation lesion placed around the orifice of the left atrial appendage; and the final ablation lesion is placed from the left inferior pulmonary vein to the posterior mitral valve annulus. The left atrial appendage is excluded by over sewing its orifice from within the atrium using a purse string suture.



Reference <sup>25</sup>

**Fig 11: View inside right atrium.** Bicaval cannulation. All ablation lines are placed endocardially. The isthmus ablation (F) runs from the inferior caval vein (IVC), across the interatrial septum, up to the caudal aspect of the coronary sinus (CS) ostium and over to the posterior tricuspid valve (TV) annulus. (FO = foramen ovale; RAA = obliterated right atrial appendage; SVC = superior vena cava.)

### 3. POSTOPERATIVE MANAGEMENT

After the initial bolus dose in the operating room all patients then received a dose of 900mg Amiodarone over the next 23 hours, accounting for a total dose of 1.2g Amiodarone during the first postoperative day. Thereafter the dose was 400mg bi-daily and after 1 week decreased to 200mg bi-daily orally, and continued for three months unless contraindicated. Prophylactic anti-arrhythmic therapy after three months, was left to the discretion of the treating cardiologist.

Anticoagulation therapy was prescribed according to the guidelines for mechanical valve prostheses. If a mechanical prosthesis was implanted, lifelong warfarin was prescribed. A therapeutic international normalized ratio (INR) was considered to be between 2.0 and 3.5. All patients received low molecular weight heparin prophylaxis until they were fully mobilized and/or achieved therapeutic INR ranges. Patients without mechanical prostheses and without any other indication for anticoagulation therapy did not receive routine postoperative warfarin prophylaxis.

For patients with postoperative AF or atrial flutter, electrical cardioversion was attempted before discharge.

During the stay in the intensive care unit and cardiac surgery ward, a daily 12-lead electrocardiogram was performed in addition to clinical examination until discharge. All patients were seen in an outpatient clinic at 1 week and 6 weeks after the operation and every 3 to 6 months thereafter.

Electrical cardioversion of patients who had reverted to AF after discharge from hospital was at the discretion of the cardiologist, but was disappointingly infrequently done.

The following post-operative details were analyzed by interrogation of patients' clinical records and the cardio-thoracic surgical database.

- Length of intensive care unit (ICU) and hospital stay
- Need for post-operative cardioversion
- Morbidity, including
  - re-operation for post-operative bleeding
  - prolonged ventilation (IPPV > 48 hrs)
  - wound infection
  - other (pneumonia, end-organ failure other than respiratory, sepsis)
- Mortality
  - a. early (defined as in hospital- or <30day mortality)
  - b. late
- Need for post-operative pacemaker implantation
- Discharge rhythm
- Discharge medication
- Adverse events during follow up period
- Rhythm at latest follow up
- Medication during latest follow up

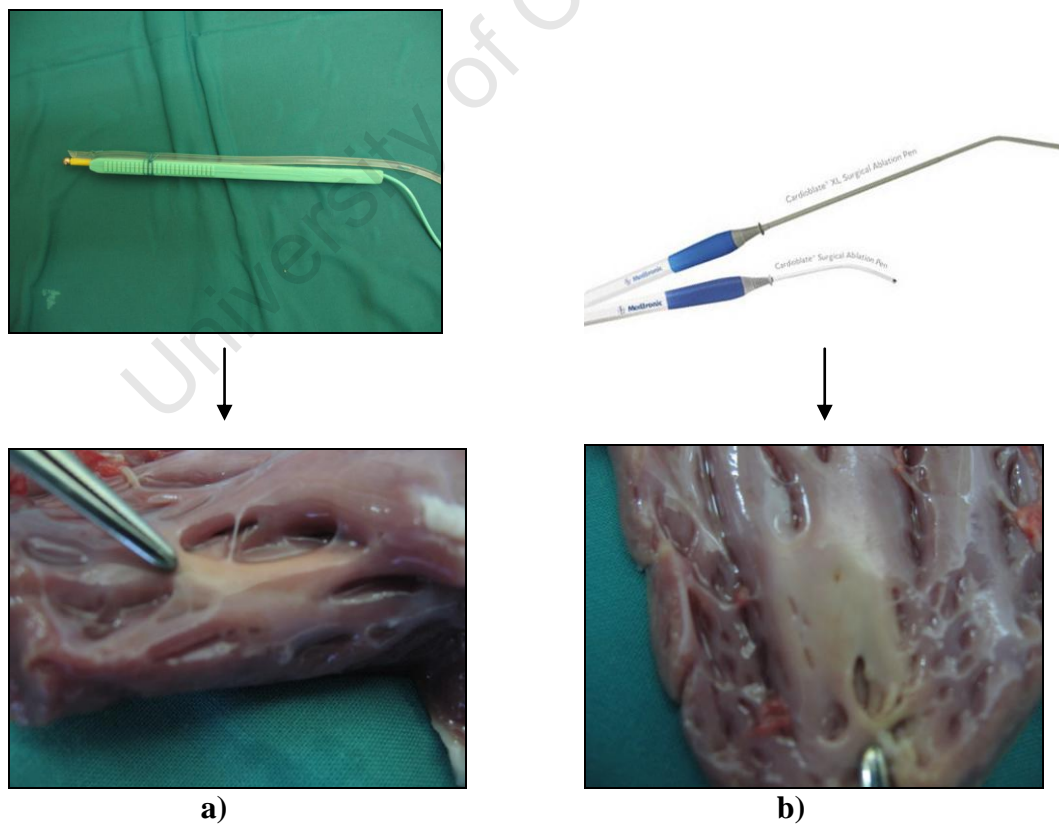
## SECTION B

This section consists of a macroscopical and histological investigation of ablative lesions created on animal hearts using irrigated monopolar electrocautery ablation (Group A) compared to irrigated radiofrequency ablation (Group B). The Medtronic Cardioblate™ radiofrequency ablation pen and generator was used to create the irrigated radiofrequency ablation lines (figure 7).

Fresh pig hearts were obtained from an abattoir and preserved in 4°C saline solution. The atria and ventricles were dissected separately. The average thickness of the atria specimens used was 4.65mm and the average thickness of the ventricle specimens used was 8.87 mm.

In group A (irrigated electrocautery ablation) lesion sets were created on atrial and ventricular tissue using different power settings (50W, 60W and 70W) (Fig 12a). In group B (irrigated radiofrequency ablation) lesions were created in a similar fashion (with power settings 20W, 25W, 30W) using the Medtronic Cardioblate™ radiofrequency ablation pen (Fig 12b).

The difference in power settings used between the two groups was based on the clinical experience of the surgeon gained using the two energy sources to create similar tissue colour changes and palpable hardening of the underlying tissue with comparable contact times.



**Fig 12: Example of ablative line on pig heart ventricle using a) irrigated monopolar electrocautery ablation and b) irrigated radiofrequency ablation.**

Subsequently, each atrial and ventricular segment was grossly appraised, photographed and assigned an identification code prior to submission for histological preparation.

The specimens were fixed in 10% neutral buffered formalin for four days (Fig13). Multiple full thickness sections were taken, sampling the lesions that were apparent on the endocardial surface. The tissues were paraffin embedded and 4  $\mu$ m sections prepared and stained with haematoxylin phloxine saffron (HPS).



**Fig 13: Gross specimen preparation in Formalin**

The slides were examined microscopically by an independent, blinded, observer and evaluated for the presence and maximum depth of the lesions. The depth of the lesions created was measured from the endocardial surface. The specimens were evaluated for the presence of any tissue disruption of the endocardial surface or underlying myocardium.

## IV. RESULTS

### SECTION A

#### Preoperative Data

During the 2½ year period from September 2004 to April 2007, 40 patients who underwent open heart surgery also had a modified Maze procedure done for permanent AF using irrigated monopolar electrocautery ablation. The pre-operative demographics are shown in Table 5. All the Maze procedures were performed by a single surgeon. There were 16 males and 24 females. The mean age of the patients was 47.15 years (range 17 – 80). The mean presenting functional class of the patients was NYHA Class 2.7. More than 90% (n=38/40) of the patients presented primarily for mitral valve surgery. The mean pre-operative left ventricular ejection fraction (EF) as measured by echocardiography was 55.65% (range 24 - 80%) and mean left atrial diameter was 5.56 cm (range 3.42 – 7.1cm). More than 50% (n=23/40) of the patients were on a  $\beta$ -Blocker (mainly Atenolol) before surgery, 72.5% (n=29/40) on digoxin and 62.5% (n = 25/40) were taking Warfarin pre-operatively. Detailed demographics and preoperative data of all the patients are contained in Table X in the appendix.

**Table 5: Patient Demographics and Preoperative data**

		no	%
<b>Gender</b>	Male	16	40
	Female	24	60
<b>Symptomatology</b> NYHA Functional Class	I	3	7.5
	II	10	25
	III	23	57.5
	IV	4	10
<b>Ejection Fraction</b>	Good (>50%)	30	75
	Moderate (30-49%)	8	20
	Poor (<29%)	2	5
<b>LA Size</b>	< 60mm	26	66.6
	≥ 60mm	13	33.3

## Operative and Peri-operative Data

The primary indication for surgery was the underlying cardiac lesion(s) in all of the patients (40/40). Mitral valve surgery was performed in 38 of the patients either as an isolated procedure or in combination with aortic valve replacement, coronary artery bypass grafting or atrial septal defect closure. Isolated aortic valve replacement was performed in one patient (1/40) as was isolated atrial septal defect closure in another (Table 6). Eighteen patients had mechanical prosthesis implanted.

**Table 6: Operative details (n=40 patients)**

Procedures	No.	%
MVR ± TA		
mechanical	13	32.5
tissue	2	5
MVR + AVR	4	10
MVR + AVR + CABG	1	2.5
MVRepair ± TA	11	27.5
MVRepair + AVR	1	2.5
MVRepair + CABG	5	12.5
MVRepair + ASD closure	1	2.5
AVR	1	2.5
ASD closure	1	2.5
	40	100%
<b>Maze procedure</b>		
Left atrial only	36	90
Bi-atrial	4	10
MVR – mitral valve replacement, TA – tricuspid annuloplasty, AVR – aortic valve replacement, CABG – coronary artery bypass grafting, MVRepair – mitral valve repair, ASD – atrial septal defect		

Mean cardiopulmonary bypass and aortic cross clamp-times were 138 minutes (62-243 minutes) and 98 (43-169 minutes) minutes, respectively. Ninety percent of the patients (36/40) had a left atrial only modified Maze procedure performed and ten percent (4/40) had a bi-atrial modified Maze procedure performed. Median intensive care unit stay was 45 hours (range 2 – 427 hours) and mean length of hospital stay was 10 days (1 – 28 days).

### Early Morbidity and Mortality (In hospital or < 30 days post operatively):

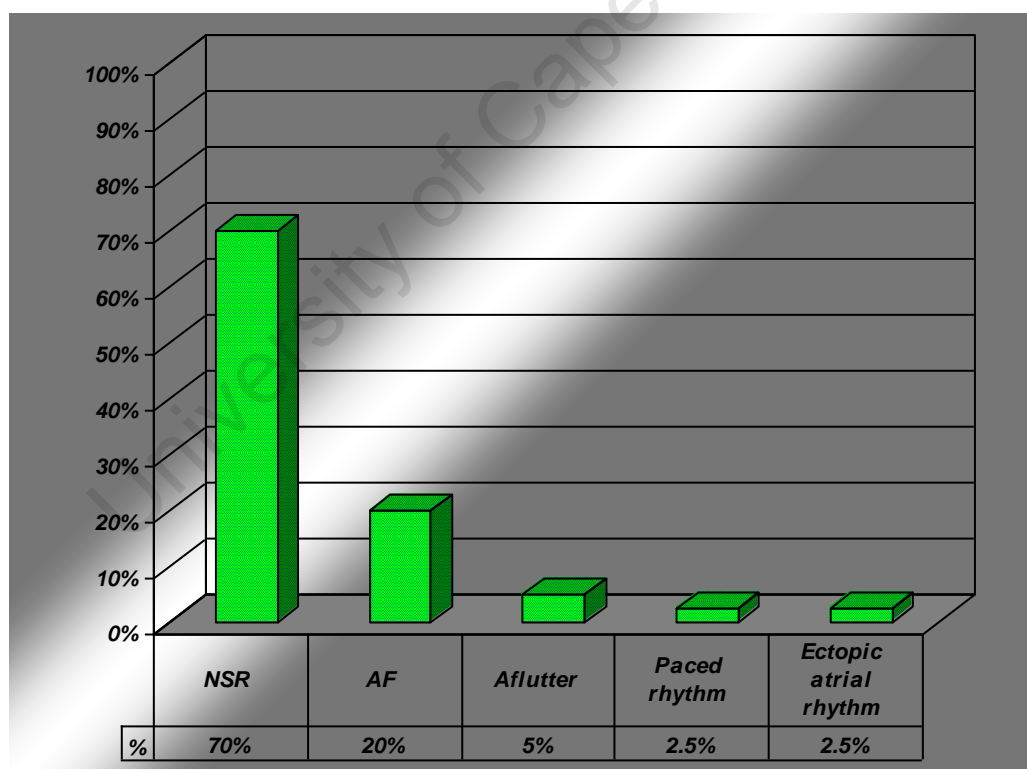
Two patients developed pericardial effusions within the first ten postoperative days, requiring open drainage. One of these was a haemorrhagic effusion secondary to Warfarin toxicity. Three patients required prolonged ventilatory support due to hospital acquired lower respiratory tract infections.

In hospital mortality was 7.5% (n=3). Two patients demised due to systemic septicaemia. (One developed mediastinitis from a septic sternal wound; and the other was found to have diffuse intramyocardial abscesses as well as abscesses in the abdominal viscera at a post mortem examination). The third mortality occurred 3 hours post operatively related to a pulmonary hypertensive crisis with low cardiac output state.

Seven patients underwent attempted in hospital electrical cardioversion, of whom five reverted to sinus rhythm before discharge.

#### Discharge Data:

At the time of hospital discharge (to home / another hospital / in-hospital death) 70% (n=28/40) of the patients were in a normal sinus rhythm. Eight patients (n=8/40) remained in AF, two patients (n=2/40) reverted to an atrial flutter, one patient had atrial bigeminy (n=1/40) and one patient was paced ventricularly (n=1/40) coming back from theatre and demised three hours post operatively from a pulmonary hypertensive crisis. These results are illustrated in Fig 14.



**Fig 14: ECG rhythm on discharge**

Discharge medication included Amiodarone (200mg bd), unless contra-indicated. Twenty five patients (64.1%) were discharged on Amiodarone. Warfarin was prescribed for all patients who had mechanical prosthesis implanted as well as those who had risk factors for thrombo-embolism (e.g. ongoing AF). For patients in sinus

rhythm (at discharge) who had repair procedures done or bioprostheses implanted, without other risk factors for thrombo-embolism, anticoagulation or antiplatelet therapy was prescribed at the surgeon's discretion (in accordance with the 2006 guidelines of the AHA and the ACC). Thirty-three (84.6%) of patients were discharged on Warfarin. Anti-failure therapy included diuretics and ACE-inhibitors.

Detailed operative data of all the patients are contained in Table Y in the appendix

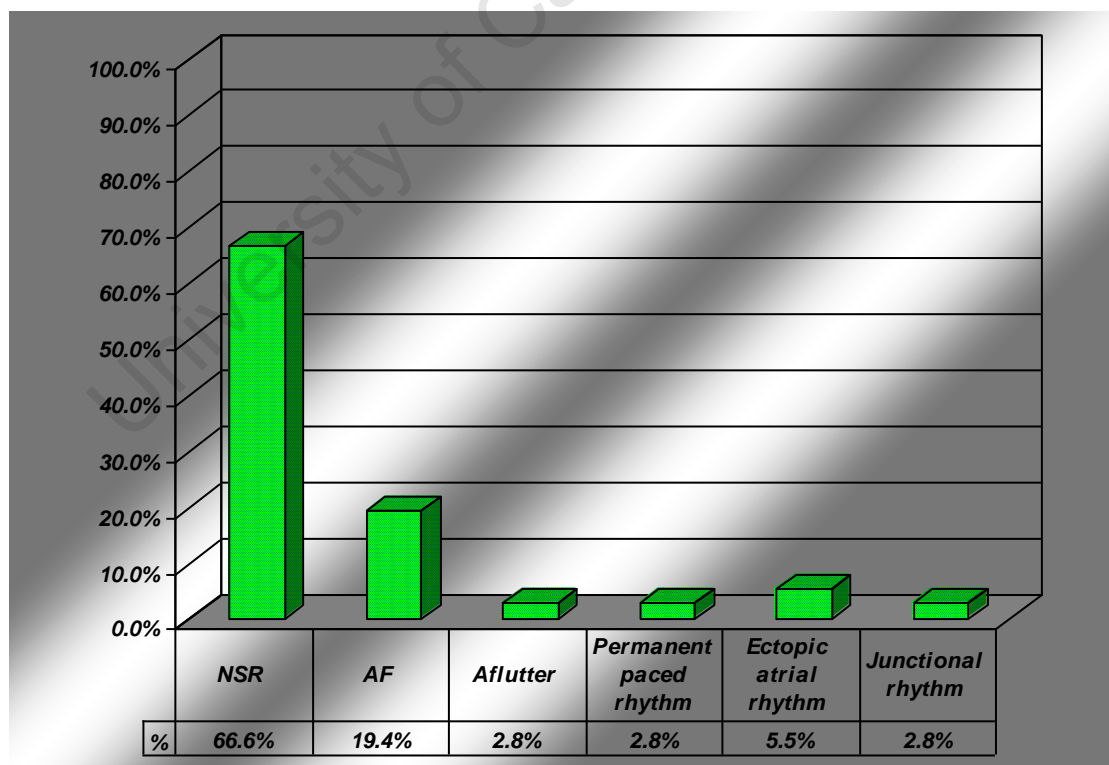
University of Cape Town



## Follow up

All the patients were reviewed at the Cardiac Surgical Outpatient Clinic the week following discharge and thereafter at the Cardiology services or peripheral secondary hospital for distant referrals. Follow up was 97.5% (n=39/40) complete. The one patient who was lost to follow up was in sinus rhythm at the time of hospital discharge. Mean follow up duration was 14 months (range 1 – 30 months). During follow up, medication was adjusted as necessary by the treating cardiologists. For the purpose of this study the patient's rhythm and medication at the latest follow up was recorded. All the latest follow up electrocardiograms were assessed by an independent cardiologist.

With three early mortalities and one patient who was lost to follow up, 36 patients were evaluated after discharge from hospital. At latest follow up, freedom from AF was 77.7% (n=28/36). Of these patients 66.6% (n=24/36) were in normal sinus rhythm on electrocardiogram. In addition, two patients (n=2/36) were in a regular ectopic atrial rhythm. One patient (n=1/36) required insertion of a permanent pacemaker for sick sinus syndrome. Seven patients (n=7/36) patients remained in AF. One patient had a regular junctional rhythm (n=1/36), and one patient had atrial flutter (n=1/36). The last patient was unfortunately not electrically cardioverted during the follow up. Rhythm at latest follow up is illustrated in Fig 15.



**Fig 15: ECG rhythm at latest follow up (mean = 14 months)**

Late Morbidity and Mortality:

There were three (8.3%) late deaths. One patient was admitted with a thrombosed mechanical prosthesis and demised before surgical intervention. This patient was in sinus rhythm on ECG with a therapeutic INR on admission. The second patient was admitted with a massive left middle cerebral artery- and bilateral anterior cerebral artery infarcts. This patient was admitted in a moribund state and demised soon after admission – a cardiac rhythm was not determined prior to death, but the last known recorded rhythm was sinus rhythm

The third mortality occurred at home and the cause of death is unknown.

One permanent pacemaker was inserted for a patient with sick sinus syndrome on day 48 post operatively. One patient required a redo operation to replace a mitral valve – 5 months following a mitral valve repair procedure. At latest follow up this patient was in sinus rhythm. One patient presented with a pericardial effusion (requiring open drainage) 21 months following the initial surgery. Medication on admission included Atenolol, Enalapril, Warfarin and Highly Active Antiretroviral Therapy (HAART). This patient was discharged and has remained in sinus rhythm during the follow period.

Medication at latest follow up:

At latest follow up 31/36 (86.1%) patients were taking Warfarin. Nine patients (25%) were on Digoxin and eighteen patients (50%) were on a  $\beta$ -blocker (predominantly Atenolol). One patient was still on Amiodarone within the first three month following surgery, but another 6 patients were taking Amiodarone during their follow up visits beyond 6 months postoperatively at the discretion of the treating cardiologist.

## SECTION B

In group A, irrigated monopolar electrocautery ablation was used to create the ablative lesions on the atrial and ventricular tissue. Gross visual assessment of the specimens revealed an average thickness of the atria of 4.83mm and an average thickness of the ventricles of 6.96mm. The average depth of the ablative lesions on the atrial tissue was 3.86mm and 4.13mm on the ventricular tissue. There was no proportional increase in tissue damage observed as the power settings increased. These details are illustrated in Table 7.

**Table 7: Macroscopical assessment of depth of ablation lines at various power settings using irrigated electrocautery ablation**

Specimen no	Pig heart chamber	Specimen thickness	Power setting	Depth of ablation
E50A	Atria	4.2mm	50W	4.1mm
E60A	Atria	5.1mm	60W	4.2mm
E70A	Atria	5.2mm	70W	3.3mm
E50V	Ventricle	7.0mm	50W	4.3mm
E60V	Ventricle	7.8mm	60W	4.2mm
E70V	Ventricle	6.1mm	70W	3.9mm

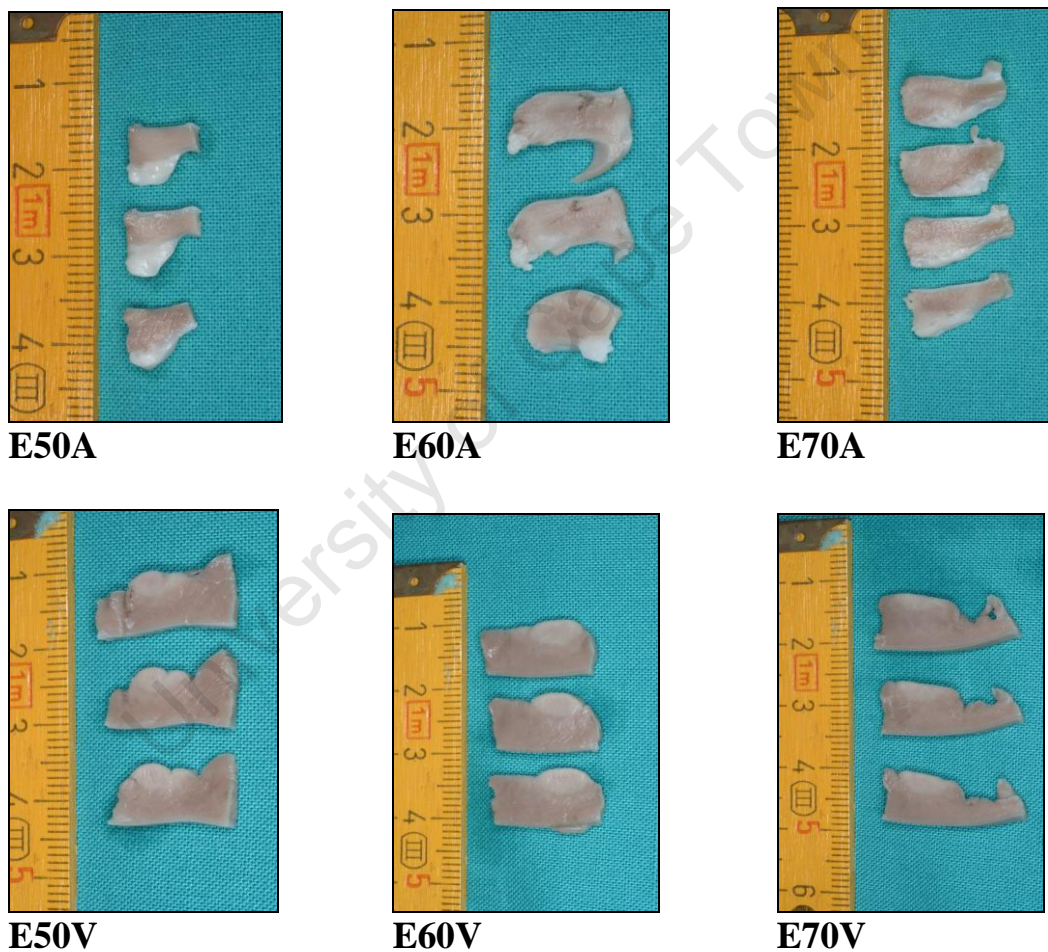
In group B, irrigated radiofrequency ablation was used to create ablative lesions on the atrial and ventricular tissue. Gross visual assessment of the specimens revealed an average thickness of the atria of 4.47mm and an average thickness of the ventricles of 10.77mm. The average depth of the ablative lesions on the atrial tissue was 3.13mm and 3.73mm on the ventricular tissue. There was no proportional increase in tissue damage observed as the power settings increased. These details are illustrated in Table 8.

**Table 8: Macroscopical assessment of depth of ablation lines at various power settings using irrigated radiofrequency ablation**

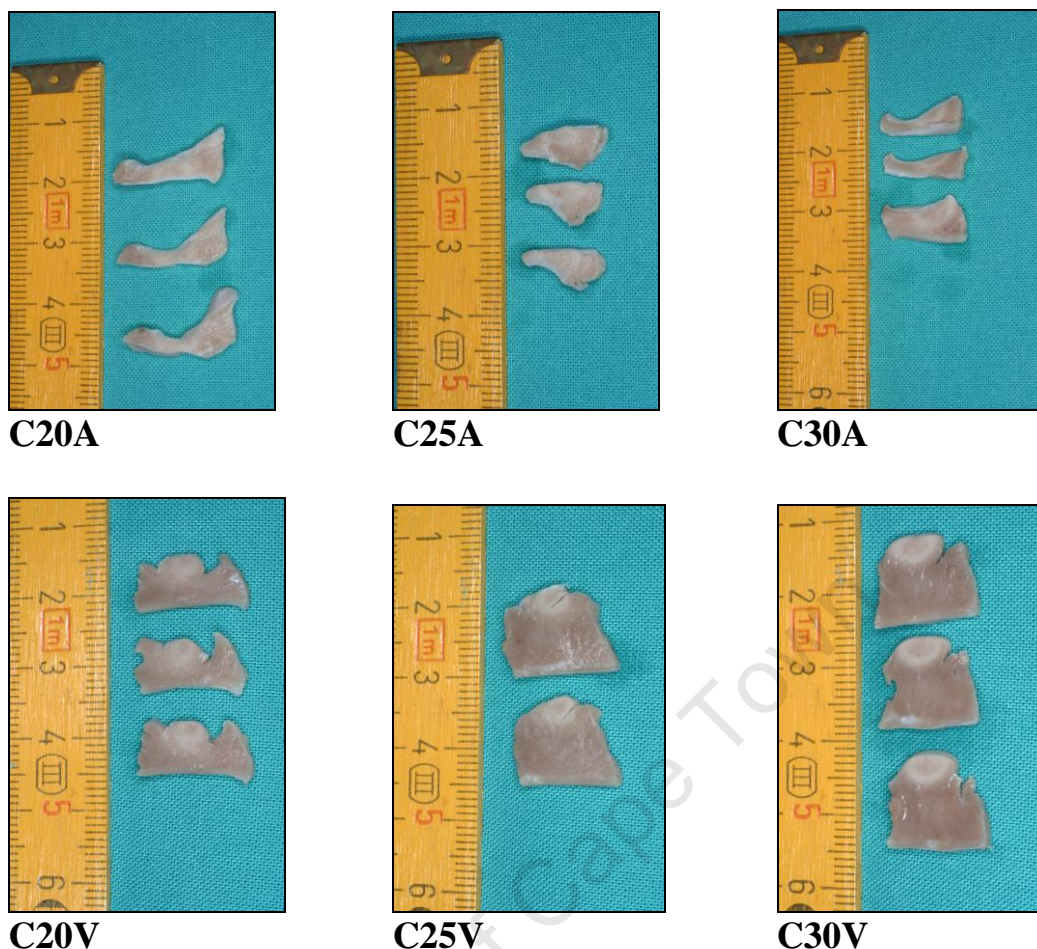
Specimen no	Pig heart chamber	Specimen thickness	Power setting	Depth of ablation
C20A	Atria	3.1mm	20W	3.1mm
C25A	Atria	5.8mm	25W	3.2mm
C30A	Atria	4.5mm	30W	3.1mm
C20V	Ventricle	6.9mm	20W	3.3mm
C25V	Ventricle	12.3mm	25W	3.8mm
C30V	Ventricle	13.1mm	30W	4.1mm

Macroscopical evaluation of the two groups: irrigated electrocautery (figure 16) versus irrigated radiofrequency ablation (figure 17) did not reveal any superficial or deep tissue charring of the endocardial surface or underlying myocardium as has been previously reported in the two reports using *non-irrigated diathermy* to create ablative lines<sup>15,16</sup>.

The average ablation line depth in group A (irrigated electrocautery ablation) was 4mm and comparable to the average ablation line depth in group B (irrigated radiofrequency ablation), which was 3.43mm.

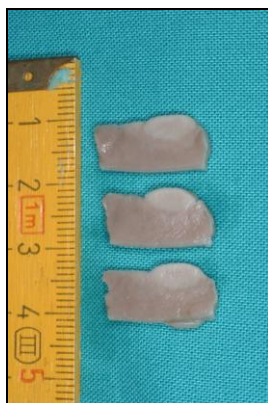


**Fig 16: Gross visual assessment of individual specimens demonstrating ablative lesions created with irrigated monopolar electrocautery ablation at different power settings (Refer to Table 7 for details). Note the whitish discoloration of the endocardial surface where the ablative lines have been created.**

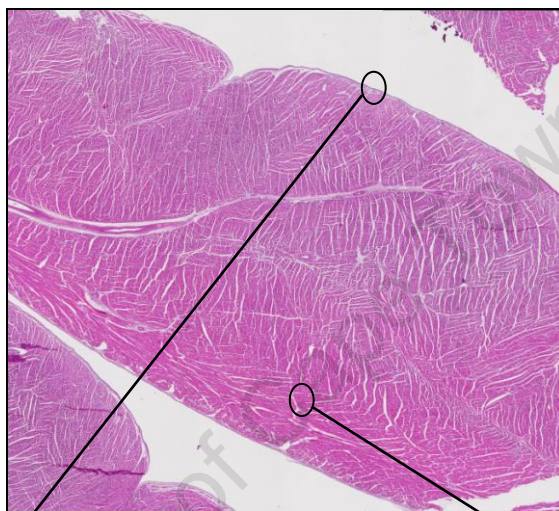


**Fig 17: Gross visual assessment of individual specimens demonstrating ablative lesions created with irrigated radiofrequency ablation at different power settings (Refer to Table 8 for details). Note the whitish discoloration of the endocardial surface where the ablative lines have been created.**

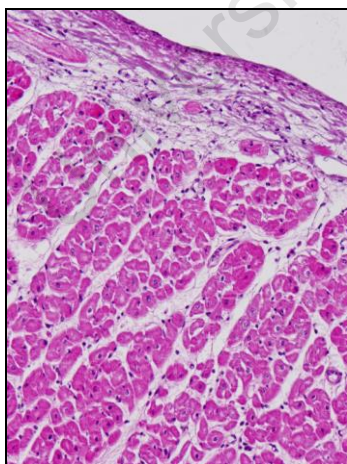
Histological assessment confirmed macroscopical findings of intact endocardial surfaces where the ablative lines had been created. There was no tissue destruction or coagulation necrosis observed as has been previously reported with the use of *non-irrigated electrocautery ablation*<sup>16</sup>. In fact, *irrigated electrocautery ablation* produced necrotic, oedematous myocardium with intact endocardial surfaces; comparable with the histological findings when irrigated radiofrequency ablation was used. These findings are illustrated in Figures 18 and 19.



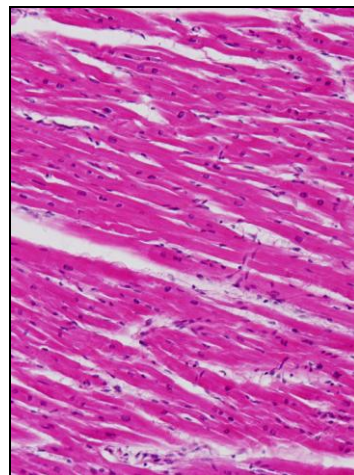
E60V



HMS specimen of ventricle (60 W)



Intact endocardium with necrotic oedematous underlying myocardium

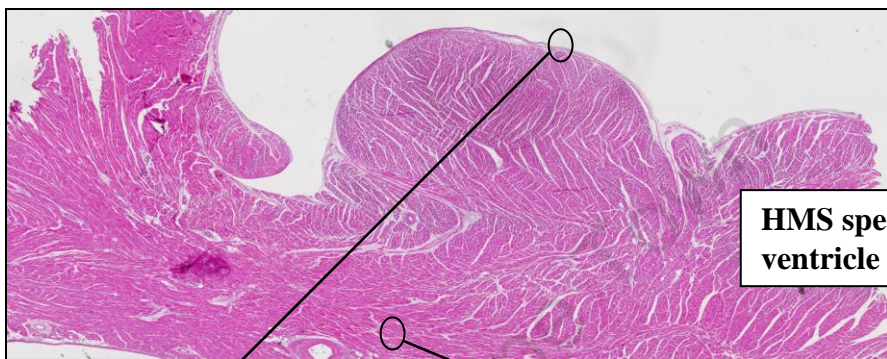


Normal intact underlying myocardium

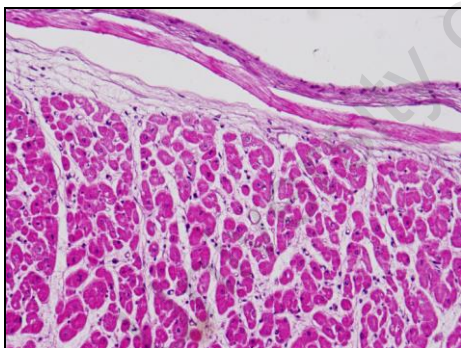
Fig 18: Histological assessment (Irrigated Electrocautery Ablation)



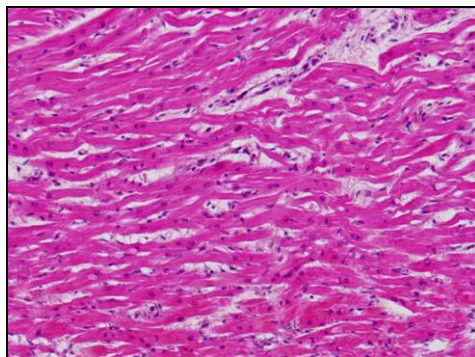
**C20V**



**HMS specimen of ventricle (20 W)**



**Intact endocardium with necrotic oedematous underlying myocardium**



**Normal intact underlying myocardium**

**Fig 19: Histological assessment (Irrigated Radiofrequency Ablation)**

## V. CONCLUSION

This study evaluated the efficacy of a novel solution to the problem of atrial fibrillation surgery in a resource constrained health service in a developing country. The use of irrigated monopolar electrocautery ablation was shown to be a cost-effective alternative to conventional energy sources. Mid-term follow up results are comparable with other methods of AF ablation with regard to sinus rhythm conversion rates.

Macroscopical and histological examination of lesion sets created on animal hearts using irrigated electrocautery compared to radiofrequency ablation demonstrated similar depth of ablative lines without unwanted tissue charring or coagulation necrosis. The use of irrigated electrocautery ablation produces necrotic, oedematous myocardium with intact endothelial surfaces.

At conclusion of this study the author has made the following suggestions relating to indications and the follow up of patients undergoing irrigated monopolar electrocautery ablation for permanent atrial fibrillation.

1. *Indications for Modified Maze procedure*

Anti-arrhythmic surgery should be offered to all patients demonstrating permanent AF, in whom a valve repair is done, or a bioprosthetic valve implanted, to prevent the need for long-term anticoagulation treatment for AF. It is a matter of ongoing debate whether patients requiring long-term anticoagulation for mechanical heart valves should be offered concomitant AF ablative procedures. The author is of the opinion that this should be offered under circumstances where there is no additional cost to performing the ablation – neither in monetary terms nor at the expense of significantly prolonged cardiac ischaemic times. These 2 goals can be achieved with the use of irrigated electrocautery ablation.

2. *Antiarrhythmic agents (Amiodarone)*

All patients should receive anti-arrhythmic agents (unless contra-indicated) during the first three months post operatively, after which period the Amiodarone should be discontinued.

3. *Anticoagulation (Warfarin)*

All patients should receive anticoagulation (Warfarin) for the first three months postoperatively. In patients who had valve repair procedures or bioprostheses implanted, and who demonstrate a stable normal sinus rhythm during the three month follow up period, without any other risk factors for thrombo-embolism, anticoagulation could be discontinued. Patients with mechanical prostheses, patients still in AF and those with other risk factors for thrombo-embolism, should remain on Warfarin.



4. Electrical Cardioversion

Electrical cardioversion should be attempted on all patients who remain in AF or atrial flutter during the postoperative in-hospital period. Thereafter electrical cardioversion should again be attempted at the three and six month follow up visits for those patients who still remain in AF or atrial flutter. Although not demonstrated in the present series, other series have shown a further 10% conversion rate into stable sinus rhythm using late cardioversion.

University of Cape Town

## VI. DISCUSSION

In the last decade anti-arrhythmic surgery has received much attention with current debates on the indications, patient selection, and refinement of techniques. The universal goal is to restore normal sinus rhythm with an easy reproducible procedure. The high cost of current commercial ablation devices (radiofrequency-, cryotherapy-, microwave-, and laser ablation) in the public sector in South Africa has led to the development of a novel method using irrigated monopolar electrocautery ablation as an energy source to create ablative lines following an acceptable ‘Maze’ pattern<sup>15,16,25</sup>.

Regardless of the technique used or energy source applied, it is imperative that surgical strategies should strive to achieve the five goals to treat atrial fibrillation as described by Ferguson and Cox<sup>76</sup>. These include: (1) elimination of atrial fibrillation, (2) restoration of sinus rhythm, (3) re-establishment of atrioventricular synchrony, (4) restoration of atrial transport function and (5) reduction of the risk of thrombo-embolism.

Patient selection has remained a contentious issue. One question remaining unanswered is whether patients receiving mechanical prostheses would benefit from anti-arrhythmic surgery as they would still need to be anticoagulated. Proponents have argued that restoration of atrial transport function has been sufficiently proven, and therefore would benefit each patient. The degree of restoration and contractility however differs with the aetiology of the AF and this needs further investigation. As concrete evidence is lacking our unit currently offer modified ‘Maze’ surgery only to patients who could potentially discontinue warfarin therapy. Due to the predominantly rheumatic aetiology of valvular heart disease in South Africa, the ratio of repair- versus replacement procedures is unfortunately in favour of valve replacement. The subgroup of patients that could potentially benefit from this surgery is thus much smaller when compared to first world countries.

With regard to techniques used, we have shown that irrigated monopolar electrocautery ablation is effective in creating transmural lesions without any superficial tissue charring in keeping with that achieved by irrigated monopolar radiofrequency ablation.

Due to cost constraints in the public sector, anti arrhythmic surgery using commercially available energy sources has been limited, therefore depriving a subset of the patient population from the potential benefits. The majority (n=36/40) of our patients received left atrial only procedures. This practice is in keeping with published data supporting minimal lesion sets<sup>22,24,28,37,40,58</sup>. We currently perform a concomitant right sided modified ‘Maze’ procedure for patients with preoperative documented atrial flutter, and for patients in whom procedures requiring right atrial access is required (e.g. tricuspid annuloplasty or atrial septal defect closure). Our results have been comparable with the literature with regard to sinus rhythm conversion rates of 70% at discharge and 67% at latest follow up (mean 14 months).

The use of anti-arrhythmic agents during the post operative period remains problematic. Proponents of these drugs argue that the lesion sets created will get

deeper with time as is often seen with increased sinus conversion rates at later follow ups<sup>22,27</sup>. Some authors however feels that introduction of these drugs during the post operative period will obscure the true results of the anti-arrhythmic surgery<sup>31,32</sup>. We have consistently followed a regime for Amiodarone as previously discussed. The termination of Amiodarone at the three month follow up has however been inconsistent as this was left to the discretion of the individual cardiologist. Six patients received Amiodarone at a period beyond six months post operatively. Four of these patients demonstrated normal sinus rhythm beyond the three month follow up. Another problem is the pharmacological interaction between warfarin and amiodarone. In our series one patient required open drainage of a pericardial effusion secondary to Warfarin toxicity. Due to this potential lethal complication an alternative option is the use of  $\beta$ -Blockers (e.g. Sotalol) during the post-operative period.

Some authors have demonstrated that the strongest predictor of long term sinus rhythm following modified Maze surgery, was early sinus rhythm restoration, therefore advocating that every effort should be made to discharge patients in sinus rhythm<sup>49</sup>. This makes a strong point for chemical and/or electrical cardioversion in all patients not maintaining sinus rhythm following surgery for atrial fibrillation. We have therefore adopted a policy of electrical cardioversion for all patients demonstrating AF or atrial flutter during the in hospital post operative period. In our series seven patients received electrical cardioversion during the in hospital period, of whom five reverted to sinus rhythm. At latest follow up four of these patients remained in sinus rhythm as documented on 12 lead ECG. Attempt at electrical cardioversion during the follow up period has however not been consistent and needs to be addressed. Only one patient received successful electrical cardioversion for atrial flutter at 3-months follow up. This patient has also remained in sinus rhythm at latest follow up.

Early mortality included three patients. None of these deaths were related to the concomitant modified 'Maze' procedure. Two patients demised due to systemic septicaemia. One of these patients was admitted in a moribund state and emergency surgery (mechanical mitral and aortic valve replacements and coronary artery bypass grafting) was performed. The patient demised on day 14 post operatively. At post mortem examination this patient was shown to have diffuse intra-myocardial abscesses, and abscesses involving the abdominal viscera. The second mortality occurred in an 80 yr old patient who developed mediastinitis from a septic sternal wound. This patient demised during the third post operative week. Both of these patients were in sinus rhythm at the time of death. The third mortality occurred 3 hours post operatively related to a pulmonary hypertensive crisis with low cardiac output state. This patient was paced (ventricular pacing) from theatre.

Late mortality included three patients. The first patient was admitted with a thrombosed mechanical prosthesis 15 months post operatively and demised before surgical intervention. This patient was in sinus rhythm with a therapeutic INR on admission. The second patient was admitted with a massive left middle cerebral artery- and bilateral anterior cerebral artery infarcts, 9 months post operatively. This patient was admitted in a moribund state and demised soon after admission. The patient was in sinus rhythm at discharge and on Warfarin prophylaxis. The initial surgical procedure in this patient was a mechanical mitral valve replacement and

tricuspid annuloplasty. The third late mortality occurred at home and the cause of death is unknown.

Limitations of the study

This study is observational and data collected retrospectively. Patient follow up was primarily done by the treating cardiologist, resulting in inconsistent use of anti-arrhythmic agents during the follow up period. This also led to inconsistency in the use of electrical cardioversion during the follow up period as discussed.

## VII. FINAL OBSERVATIONS

Between 30 and 84% of patients undergoing elective mitral valve surgery will present with associated chronic AF before the operation<sup>25,35,36,45,49,53</sup>. Up to 20% of these patients will revert to sinus rhythm after correction of the underlying cardiac disease<sup>33,40-42</sup>. In the majority AF will persist after correction of the primary disease<sup>33,41,42,45</sup>.

Pharmacological therapy is mainly aimed at rate or rhythm control and the prevention of thrombo-embolism, and has even been observed to induce intolerable or even life threatening side effects<sup>69</sup>. In response to these limitations, surgical procedures, which directly target the atrial substrate in order to eliminate atrial fibrillation and restore normal atrial function, have been developed.

The Cox-Maze procedure has remained the gold standard to restore sinus rhythm in patients with chronic/permanent AF and concomitant structural heart disease. This is however an extensive surgical procedure and in an attempt to simplify the original Maze procedure several groups have made use of alternative energy sources intraoperatively (most commonly radiofrequency ablation) to create linear ablative lines on the endocardium or epicardium to eliminate AF. Different energy sources and ablation patterns continue to appear demonstrating that the problem has not yet been definitively solved.

Based on previous research<sup>15,16</sup>, our unit has proposed a novel method of performing a modified Maze procedure using *irrigated monopolar electrocautery ablation*. Clinical results have been comparable with other series<sup>21-31,33,36-40,58, 64</sup>. We have demonstrated the achievement of ablative lesions that are macroscopically and histologically comparable to lesions created when using irrigated radiofrequency ablation, without associated unwanted charring of the endocardium which has been a concern in previous studies<sup>15,16</sup>. This method also results in considerable cost-savings and can therefore be offered to patients who present for open heart surgery with associated atrial fibrillation at Groote Schuur Hospital.

What is still unclear is whether patients with mechanical valve replacement should be offered AF ablation but the author favours this because of the low cost and possibility of restoration of atrial transport function.

Due to differences in the pathogenesis of AF and symptoms with which patients present, the future of these procedures will be in defining appropriate patient selection. It is also likely that combinations of different pharmacological and non-pharmacological therapies may be required for the treatment of atrial fibrillation in selected patients.

**BIBLIOGRAPHY**

1. Stefano Benussi. Treatment of atrial fibrillation; Review: *Europ J Cardiothor Surg* 2004;26: S39-S41
2. Cox JL, Schuessler RB, D'Agostino Jr HJ, Stone CM, Chang BC, Cain ME, Corr PB, Boineau JP. The surgical treatment of atrial fibrillation. Development of a definite surgical procedure. *J Thorac Cardiovasc Surg* 1991; 101:569-583
3. 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.
4. Garrey WE. The nature of fibrillatory contraction of the heart: its relation to tissue mass and form. *Am J Physiol* 1914;33:397.
5. Haissaguerre M, Jais P, Shah DC et al. Right and left atrial radiofrequency catheter therapy of paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 1996; 7:1132-44.
6. Carlo Pappone, Salvatore Rosanio. Evolution of non-pharmacological curative therapy for atrial fibrillation. Where do we stand today? *Int J Cardiology* 2003; 88:135-142.
7. Hersi A, Wyse DG. Management of Atrial Fibrillation: *Curr Probl Cardiol*, 2005; 30:175-234
8. Krishna Khargi, Barbara A. Hutten, Bernd Lemke, Thomas Deneke. Surgical treatment of atrial fibrillation; a systematic review: *Europ J Cardiothor Surg* 2005; 27: 258-265
9. Fuster V, Ryden LE, Cannom DS et al. ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines. (Writing Committee to revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation): Developed in Collaboration with the European Heart Rhythm Association and the Heart Rhythm Society: *Circulation*, Aug 2006; 114: e257-e354

10. Wijffels MC, Kirchhof CJ, Dorland R, Allesie MA. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. *Circulation* 1995;92:1954-68.
11. ACC/AHA guidelines for the management of valvular heart disease. A report of the American College of Cardiology/American Heart Association. Task Force on Practice Guidelines. *J Am Coll Cardiol* 1998;32:1486-588.
12. Wellens HJJ. Cardiac Arrhythmias: The Quest for a Cure. A Historical perspective. *J Am Coll Cardiol* 2004;44:1155– 63
13. Cury RC, Abbara S et al. Relationship of the esophagus and aorta to the left atrium and pulmonary veins: Implications for catheter ablation of atrial fibrillation. *Heart Rhythm* 2005; 2: 1317-1323.
14. Jais P, Weerasooriya R et al. Ablation therapy for atrial fibrillation (AF): Past, present and future. *Cardiovascular Research* 2002;54: 337-346.
15. Simha P, Bhat PSA, Prabhudeva N. The Electrocautery Maze – How I Do It. *The Heart Surgery Forum* 2001; 4: 340-345.
16. Lam B, Boodhwani M, Veinot JP et al. Surgical Treatment of Atrial Fibrillation with Diathermy: An In Vitro Study. *Eur J Cardiothorac Surg* 2005; 27: 456-461.
17. Izumoto H, Kawazoe K, Kitahara H et al. Operative results after the Cox-Maze procedure combined with a mitral valve operation. *Ann Thorac Surg* 1998; 66: 800-804.
18. Gillinov AM, Wolf K. Surgical Ablation of Atrial Fibrillation. *Progress in Cardiovasc disease* 2005;48: 169-177.
19. Cox JL, Ad N, Palazzo T, et al. Current status of the Maze procedure for the treatment of atrial fibrillation. *Semin Thorac Cardiovasc Surg* 2000;12: 15-19.
20. Jahangiri M, Weir G, Mandal K, Savelieva I, Camm J. Current strategies in the management of atrial fibrillation. *Ann Thorac Surg* 2006;82: 357-364.
21. Halkos ME, Craver JM, Thourani VH et al. Intraoperative Radiofrequency ablation for the treatment of Atrial Fibrillation during concomitant cardiac surgery. *Ann Thorac Surg* 2005;80: 210-216.
22. Fayad G, Le Tourneau T, Modine T et al. Endocardial Radiofrequency ablation during mitral valve surgery: Effect on cardiac rhythm, atrial size, and function. *Ann Thorac Surg* 2005; 79: 1505-1511.
23. Chen M, Chang J, Chang H et al. Clinical determinants of sinus conversion by radiofrequency Maze procedure for persistent atrial fibrillation in patients

- undergoing concomitant mitral valvular surgery. *Am J Cardiol* 2005; 96: 1553-1557.
24. Geidel S, Ostermeyer J, Lass M et al. Three years experience with monopolar and bipolar radiofrequency ablation surgery in patients with permanent atrial fibrillation. *Eur J Cardiothor Surg* 2005; 27: 243-249.
  25. Sie HT, Beukema WP, Elvan A et al. Long-term results of irrigated radiofrequency modified Maze procedure in 200 patients with concomitant cardiac surgery: Six year experience. *Ann Thorac Surg* 2004; 77: 512-517.
  26. Wong JWW. Ensuring transmuralty using irrigated radiofrequency modified Maze in surgery for atrial fibrillation – A simple and effective way. *Heart Lung and Circulation* 2004; 13: 302-308.
  27. Khargi K, Lemke B, Haardt H et al. Concomitant anti-arrhythmic surgery, using irrigated cooled-tip radiofrequency ablation to treat permanent atrial fibrillation in CABG patients: expansion of the indication? *Eur J Cardiothorac Surg* 2004; 25: 1018-1024.
  28. Benussi S, Nascimbene S, Agricola E. Surgical ablation of atrial fibrillation using the epicardial radiofrequency approach: Mid-Term results and risk analysis. *Ann Thorac Surg* 2002; 74: 1050-1057.
  29. Guden M, Akpınar B, Sanisoglu I et al. Intraoperative Saline Irrigated Radiofrequency Modified Maze Procedure For Atrial Fibrillation. *Ann Thorac Surg* 2002; 74: S1301-1306.
  30. Williams MR, Stewart JR, Bolling SF et al. Surgical Treatment of Atrial Fibrillation Using Radiofrequency Energy. *Ann Thorac Surg* 2001; 71: 1939-1944.
  31. Melo J, Adragao P, Neves J et al. Endocardial and epicardial radiofrequency ablation in the treatment of atrial fibrillation with a new intra-operative device. *Eur J Cardiothorac Surg* 2000; 18: 182-186.
  32. Kondo N, Takahashi K, Minakawa M et al. Left Atrial Maze Procedure: A Useful Addition to Other Corrective Operations. *Ann Thorac Surg* 2003; 75: 1490-1494.
  33. Sie HT, Beukema WP, Misier ARR et al. The radiofrequency modified Maze procedure. A less invasive surgical approach to atrial fibrillation during open-heart surgery. *Eur J Cardiothorac Surg* 2001; 19: 443-447.
  34. Thomas SP, Nicholson IA, Nunn GR, Ross DL. Radiofrequency lesions produced by handheld temperature controlled probes for use in atrial fibrillation surgery. *Eur J Cardiothorac Surg* 2001; 20: 1188-1193.



35. Benussi S, Pappone C, Nascimbene S et al. A simple way to treat atrial fibrillation during mitral valve surgery: the epicardial radiofrequency approach. *Eur J Cardiothorac Surg* 2000; 17: 524-529.
36. Chiappini B, Martin-Suarez S, LoForte A et al. Cox-Maze III Operation Versus Radiofrequency Ablation for the Surgical Treatment of Atrial Fibrillation: A Comparative Study. *Ann Thorac Surg* 2004; 77: 87-92.
37. Golovchiner G, Mazur A, Kogan A et al. Atrial Flutter after Surgical Radiofrequency Ablation of the Left Atrium for Atrial Fibrillation. *Ann Thorac Surg* 2005; 79: 108-112.
38. Melo J, Adragao P, Neves J et al. Surgery for Atrial Fibrillation using Radiofrequency Catheter Ablation: Assessment of results at one year. *Eur J Cardiothorac Surg* 1999; 15: 851-855.
39. Wisser W, Khazen C, Deviatko E et al. Microwave and Radiofrequency Ablation yield similar success rates for treatment of Chronic Atrial Fibrillation. *Eur J Cardiothorac Surg* 2004; 25: 1011-1017.
40. Forlani S, De Paulis R, Wolf LG et al. Conversion to Sinus Rhythm by Ablation Improves Quality of Life in Patients Submitted to Mitral Valve Surgery. *Ann Thorac Surg* 2006; 81:863-867.
41. Jessurun ER, van Hemel NM, Kelder JC et al. Mitral valve surgery and atrial fibrillation: Is atrial fibrillation surgery also needed? *Eur J Cardiothorac Surg* 2000; 17: 530-537.
42. Jatene MB, Marcial MB, Tarasoutchi F et al. Influence of the Maze procedure on the treatment of rheumatic atrial fibrillation – evaluation of rhythm control and clinical outcome in a comparative study. *Eur J Cardiothorac Surg* 2000; 17: 117-124.
43. Millar RC, Arcidi JM, Alison PJM et al. The Maze III Procedure for Atrial Fibrillation. Should the Indications be Expanded. *Ann Thorac Surg* 2000; 70: 1580-1586.
44. Izumoto H, Kawazoe K, Eishi K and Kamata J. Medium Term Results after the Modified Cox-Maze Procedure Combined with other Cardiac Surgery. *Eur J Cardiothorac Surg* 2000; 17: 25-29.
45. Raanani E, Albage A, David TE et al. The efficacy of the Cox-Maze procedure combined with mitral valve surgery: a matched control study. *Eur J Cardiothorac Surg* 2001; 19: 438-442.
46. Maessen JG, Nijs JFMA, Smeets JLRM et al. Beating-Heart Surgical Treatment of Atrial Fibrillation with Microwave Ablation. *Ann Thorac Surg* 2002; 74: 1307-1311.

47. Scheutz A, Schulze CJ, Sarvanakis KK et al. Surgical treatment of permanent atrial fibrillation using microwave energy ablation: a prospective randomized clinical trial. *Eur J Cardiothorac Surg* 2003; 24: 475-480.
48. Doll N, Kiaii BB, Fabricius AM et al. Intraoperative Left Atrial Ablation (for Atrial Fibrillation) Using a New Argon Cryocatheter: Early Clinical Experience. *Ann Thorac Surg* 2003; 76: 1711-1715.
49. Manasse E, Gaita F, Ghiselli S et al. Cryoablation of the left posterior atrial wall: 95 patients and 3 years of mean follow-up. *Eur J Cardiothorac Surg* 2003; 24: 731-740.
50. Gammie JS, Laschinger JC, Brown JM et al. A Multi-Institutional Experience With the Cryo-Maze Procedure. *Ann Thorac Surg* 2005; 80: 876-880.
51. Molloy TA. Midterm Clinical Experience With Microwave Surgical Ablation for Atrial Fibrillation. *Ann Thorac Surg* 2005; 79: 2115-2118.
52. Hemels MEW, Gu YL, Tuinenberg AE et al. Favourable Long Term Outcome for Maze Surgery in Patients with Lone Atrial Fibrillation. *Ann Thorac Surg* 2006; 81: 1773-1779.
53. Itoh A, Kobayashi J, Bando K et al. The impact of mitral valve surgery combined with Maze procedure. *Eur J Cardiothorac Surg* 2006; 29: 1030-1035.
54. Pruitt JC, Lazarra RR, Dworkin GH et al. Total Endoscopic Ablation of Lone Atrial Fibrillation: Initial Clinical Experience. *Ann Thorac Surg* 2006; 81: 1325-1331.
55. Stulak JM, Dearani JA, Daly RC et al. Left Ventricular Dysfunction in Atrial Fibrillation: Restoration of sinus rhythm by the Cox-Maze Procedure Significantly Improves Systolic Function and Functional Status. *Ann Thorac Surg* 2006; 82: 494-501.
56. Choo SJ, Park NH, Lee SK et al. Excellent results for atrial fibrillation surgery in the presence of giant left atrium and mitral valve disease. *Eur J Cardiothorac Surg* 2004; 26: 336-341.
57. Romano MA, Bach DS, Pagani FD et al. Atrial Reduction Plasty Cox-Maze Procedure: Extended Indications For Atrial Fibrillation Surgery. *Ann Thorac Surg* 2004; 77: 1282-1287.
58. Geidel S, Lass M, Boczor S et al. Surgical Treatment of Permanent Atrial Fibrillation During Heart Valve Surgery. *Interactive Cardiovascular and Thoracic Surgery* 2003; 2: 160-165.
59. Kim K, Cho KR, Sohn D et al. The Cox-Maze III Procedure for Atrial Fibrillation Associated With Rheumatic Mitral Valve Disease. *Ann Thorac Surg* 1999; 68: 799-804.

60. Kobayashi J, Kosakai Y, Nakano K et al. Improved success rate of the Maze procedure in mitral valve disease by new criteria for patients' selection. *Eur J Cardiothorac Surg* 1998; 13: 247-252.
61. Nakamura M, Niinuma H, Chiba M et al. Effect of the Maze Procedure for Atrial Fibrillation on Atrial and Brain Natriuretic Peptide. *Am J Cardiol* 1996; 79: 966-970.
62. Cox JL. The central controversy surrounding the interventional surgical treatment of atrial fibrillation. *J Thorac Cardiovasc Surg* 2005; 129: 1-4.
63. Knaut M, Tugtekin SM, Spitzer S et al. Mortality after Cardiac Surgery with or without Microwave Ablation in Patients with Permanent Atrial Fibrillation. *J Heart Valve Dis* 2005; 14: 531-537.
64. Khargi K, Lemke B, Deneke T. Concomitant anti-arrhythmic procedures to treat permanent atrial fibrillation in CABG and AVR patients are as effective as in mitral valve patients. *Eur J Cardiothorac Surg* 2005; 1-6.
65. Kawaguchi AT, Kosakai Y, Sasako Y et al. Risks and Benefits of Combined Maze Procedure for Atrial Fibrillation Associated With Organic Heart Disease. *J Am Coll Cardiol* 1996; 28: 985-990.
66. Keane D, Zou L, Ruskin J. Nonpharmacological Therapies for Atrial Fibrillation. *Am J Cardiol* 1998; 81(5A): 41C-45C.
67. Sie HT, Beukema WP, Elvan A et al. New strategies in the surgical treatment of atrial fibrillation. *Cardiovascular Research* 2003; 58: 501-509.
68. Yamauchi S, Ogasawara H, Saji Y et al. Efficacy of Intraoperative Mapping to Optimize the Surgical Ablation of Atrial Fibrillation in Cardiac Surgery. *Ann Thorac Surg* 2002; 74: 450-457.
69. Prystowsky EN. Management of Atrial Fibrillation: Therapeutic Options and Clinical Decisions. *Am J Cardiol* 2000; 85: 3D-11D.
70. Reston JT, Shuhaiber JH. Meta-analysis of clinical outcome of Maze-related surgical procedures for medically refractory atrial fibrillation. *Eur J Cardiothorac Surg* 2005; 28: 724-730.
71. Gillinov AM, Bhavani S, Blackstone EH et al. Surgery for Permanent Atrial Fibrillation: Impact of Patient Factors and Lesion Set. *Ann Thorac Surg* 2006; 82: 502-514.
72. Gillinov AM, Bakaeen F, McCarthy M et al. Surgery for Paroxysmal Atrial Fibrillation in the Setting of Mitral Valve Disease: A Role for Pulmonary Vein Isolation? *Ann Thorac Surg* 2006; 81: 19-28.

73. Mohr FW, Fabricius AM, Falk V et al. Curative Treatment of Atrial Fibrillation with intraoperative radiofrequency ablation: short-term and midterm results. *J Thorac Cardiovasc Surg* 2002; 123: 919-927.
74. Guiraudon GM, Campbell CS, Jones DL et al. Combined sinoatrial node and atrioventricular node isolation. A surgical alternative to His bundle ablation in patient with atrial fibrillation. *Circulation* 1985; 72(suppl III): iii-20.
75. Kosakai Y, Kawaguchi AT, Isobe F et al. Cox-Maze Procedure for Chronic Atrial Fibrillation Associated with Mitral Valve Disease. *J Thorac Cardiovasc Surg* 1994; 108: 1049-1055.
76. Ferguson TB, Cox JL. Surgery for Atrial Fibrillation. In: Zipes DP, Jalife J, editors. *Cardiac electrophysiology: from cell to bedside*. 2<sup>nd</sup> edition. 1995: 1563-1576

**APPENDIX**  
**Raw Data: Clinical Audit**

**Table X: Demographics and Pre Operative Data**

<b>Demographics and Pre-operative Data</b>							
<b>n</b>	<b>Age</b>	<b>Gender</b>	<b>Pathology</b>	<b>EF %</b>	<b>LA Size</b>	<b>Presenting Sx</b>	<b>Meds on admission</b>
					<b>cm</b>	<b>NYHA/CCS</b>	
1	27	F	Severe MR, mild TR	35	7	IV/0	a,d,l, phenytoin
2	67	F	Mod MR, MS, Mod TR	64	4.8	III/0	d,w,l
3	27	F	MS, severe MR	59	6.6	II/0	a,e,d,w,l
4	70	M	mod MS, severe MR, mild AS, mild AR	50		III/0	d,w,l, spiro
5	37	F	mod MS, ,severe MR	75	5.1	III/0	a,d,w,l, spiro
6	69	M	severe MR	54	5.12	III/II	a,e,d,l, statin, aspirin
7	55	F	mod MS, severe MR	62	5.3	III/0	a,e,d,w,l
8	60	F	MS, mod MR, mod AR	76	4.1	III/I	a,e,d,w
9	36	F	secundum ASD	67	3.7	I/0	nil
10	35	F	MS, severe MR	57	5.5	IV/0	m,e,d
11	34	M	mild AR, MS, severe MR	55	5.9	II/0	e,w,l,a
12	34	M	mod MR	26	4.29	III/III	m,e,d,statin
13	20	M	MS, severe MR	70	5.26	III/0	d,l,w
14	72	F	AS, mod MR, severe TR	24	4.7	IV/0	a,d,statin, aldactone
<p>n = number of patients, EF = ejection fraction, LA size = left atrial size, Presenting Sx = Presenting symptoms, cm = centimetre            NYHA = New York Heart Association, CCS = , F= female, M = male            MR = mitral regurgitation, MS = mitral stenosis, AR = aortic regurgitation, AS = aortic stenosis, ASD = atrial septal defect            TR = tricuspid regurgitation, MMVD = mixed mitral valve disease.            a = atenolol, m = metoprolol, e = enalapril, d = digoxin, w = warfarin, l = lasix, hctz = hydrochlorothiazide</p>							

**Table X continue ...**

**Table X: Demographics and Pre Operative Data (continue)**

<b>Demographics and Pre-operative Data</b>							
<b>n</b>	<b>Age</b>	<b>Gender</b>	<b>Pathology</b>	<b>EF %</b>	<b>LA Size</b>	<b>Presenting Sx</b>	<b>Meds on admission</b>
					<b>cm</b>	<b>NYHA/CCS</b>	
15	50	F	severe MR	56	7.1	IV/0	a,e,d,w,l
16	53	F	MS, severe MR	31	5.9	III/0	a,d,w,l
17	58	M	severe MR	77	6.2	II/0	e,d,l
18	67	F	AS	63	4.4	III/0	a,w,l
19	17	F	AS, mod AR, severe MR	60	5.3	III/0	D,l
20	40	M	MS, mild MR	60	5.6	I/II	a,d,w,l
21	58	M	AS, mild AR, mod MR	35	5.75	II/0	e,d,w,l, hctz
22	70	F	severe MR	74	4.28	III/II	e,l, statin, aspirin
23	38	M	severe MR	37	7	II/0	E,w
24	80	M	severe MR	60	3.42	III/0	l, statin
25	42	F	MS, severe MR, severe TR	53	5.9	III/0	a,d,w,l, aspirin
26	52	F	AS, mod AR, MS, mod MR	34	5.12	II/0	a,e,d,w,l
27	51	F	mod MR, mild TR, secundum ASD	80	4.13	II/0	d,w,l
28	29	F	severe MMVD, mild AR	53	5.58	III/0	e,d,w,l
n = number of patients, EF = ejection fraction, LA size = left atrial size, Presenting Sx = Presenting symptoms, cm = centimetre							
NYHA = New York Heart Association, CCS = , F= female, M = male							
MR = mitral regurgitation, MS = mitral stenosis, AR = aortic regurgitation, AS = aortic stenosis, ASD = atrial septal defect							
TR = tricuspid regurgitation, MMVD = mixed mitral valve disease.							
a = atenolol, m = metoprolol, e = enalapril, d = digoxin, w = warfarin, l = lasix, hctz = hydrochlorothiazide							

**Table X continue ...**

**Table X: Demographics and Pre Operative Data (continue)**

<b>Demographics and Pre-operative Data</b>							
<b>n</b>	<b>Age</b>	<b>Gender</b>	<b>Pathology</b>	<b>EF %</b>	<b>LA Size</b>	<b>Presenting Sx</b>	<b>Meds on admission</b>
					<b>cm</b>	<b>NYHA/CCS</b>	
29	32	F	Mod MS, mild MR	68	6.68	III/0	d,w,l, hctz
30	67	F	mod MR	58	6.27	II/0	e,d,w
31	60	M	severe MR	46	6.97	III/0	d,w,l, carvedilol
32	28	F	Severe MR	47	6.8	III/0	e,d,w,l
33	42	F	Mod MD, mod MR	60	6.41	III/0	d,w,l, verapamil
34	35	F	Mild MS, mod MR	56	5.4	III/0	l,spiro, carvedilol
35	36	M	Severe MR, mod TR	61	6.1	II/0	E, amio,l
36	18	M	Severe MR	37	6	III/0	a,d,w,l
37	78	M	Mod MR, mild TR	60	5.5	II/0	D,l,spiro
38	45	M	Mod MS, mild MR	69	6.3	I/0	a,w,l
39	71	M	Severe MR, SV CAD	63	4.6	III/III	a,e,w,statin,aspirin,l
40	26	F	Severe MR	54	6.8	III/0	l, pen VK
n = number of patients, EF = ejection fraction, LA size = left atrial size, Presenting Sx = Presenting symptoms, cm = centimetre							
NYHA = New York Heart Association, CCS = , F= female, M = male							
MR = mitral regurgitation, MS = mitral stenosis, AR = aortic regurgitation, AS = aortic stenosis, ASD = atrial septal defect							
TR = tricuspid regurgitation, MMVD = mixed mitral valve disease.							
a = atenolol, m = metoprolol, e = enalapril, d = digoxin, w = warfarin, l = lasix, hctz = hydrochlorothiazide							

**Table Y: Operative and Peri-operative Data**

<b>Operative and Peri-operative Data</b>									
<b>n</b>	<b>Procedure</b>	<b>Valve types and sizes</b>	<b>Maze procedure</b>	<b>CPB Time minutes</b>	<b>Xclamp minutes</b>	<b>ICU stay hours</b>	<b>Hosp stay days</b>	<b>Discharge rhythm</b>	<b>Discharge Meds</b>
1	MVR, TA	31mm MIRA mech	LA	125	84	37.9	9	SR	w, phenytoin, amio
2	MVR, TA	27mm CE bio	LA	97	58	68.8	15	Aflutter	w, l, amio
3	MVR	29mm MIRA mech	LA	136	108	38.3	8	SR	a, w, l, amio
4	MVR, AVR	31mm, 25mm On-X mech	LA	151	139	70.5	7	AF	d, w, l
5	MVR	27mm St Jude mech	LA	109		39.3	7	SR	w, l, amio
6	TV CABG, MV Rep	CG Future Band	LA	243	101	60	15	SR	a, w, statin, aspirin
7	MV Rep	30mm CG Future Band	LA			64.6	8	Atrial bigeminy	a, w, l, amio
8	MVR, AVR, CABG	25mm, 21mm MIRA mech	LA	214	135	279.5	14	SR	Amio, w, heparin, vanco
9	ASD Repair	-	Bi-atrial	62	43	39	7	SR	Nil
10	MVR	29mm MIRA mech	LA	85	62	40.1	8	SR	w, amio
11	MVR, TA	27mm MIRA mech	LA	125	92	37.8	9	SR	w, amio
12	CABG, MV Rep	-	LA	141		45.2	15	SR	m, e, w, l, statin, amio
13	MVR	25mm MIRA mech	LA	127	98	110.8	12	SR	a, w
14	AVR, MV Rep, TA	21mm CE bio, 28mm Physio ring	LA	204	142	255.5	28	AF	l, aspirin, amio
n = number of patients, CPB = cardiopulmonary bypass, Xclamp = aortic cross clamp, ICU = intensive care unit									
MVR = mitral valve replacement, TA = tricuspid annuloplasty, MV Rep = mitral valve repair, TV CABG = triple vessel coronary artery bypass grafting									
CABG = coronary artery bypass grafting, AVR = aortic valve replacement, ASD = atrial septal defect, OPCAB = Off pump coronary artery bypass grafting									
LA = left atrial, SR = sinus rhythm, Aflutter = atrial flutter, AF = atrial fibrillation									
a = atenolol, m = metoprolol, e = enalapril, d = digoxin, w = warfarin, l = lasix, hctz = hydrochlorothiazide, amio = Amiodarone, vanco = vancomycin									

**Table Y continue ...**



**Table Y: Operative and Peri-operative Data (continue)**

<b>Operative and Peri-operative Data</b>									
<b>n</b>	<b>Procedure</b>	<b>Valve types and sizes</b>	<b>Maze procedure</b>	<b>CPB Time minutes</b>	<b>Xclamp minutes</b>	<b>ICU stay hours</b>	<b>Hosp stay days</b>	<b>Discharge rhythm</b>	<b>Discharge Meds</b>
15	MVR	31mm St Jude's	LA	106	76	39.9	9	AF	A,e,d,l
16	MVR,TA	25mm MIRA mech	LA	145	75	67.8	10	SR	a,e,w,l
17	MVRep, OPCAB	30mm Future Band Ring	LA			66	6	SR	e,aspirin, l
18	AVR	23mm Perimount bio	LA	93	76	68.5	8	AF	a,d,w,l
19	MVR,AVR	31mm, 19mm St Jude's	LA			45.1	8	SR	w,l, amio
20	MVR	27mm MIRA mech	LA			41.9	7	SR	w,l, amio
21	MVR,AVR	31mm, 25mm MIRA mech	LA	219	151	34.5	7	Aflutter	e,w,l,amio
22	MV Rep, CABG	30mm CG Future Band	LA	192	78	44.5	8	SR	e,l, statin, aspirin, amio
23	MV Rep	32mm Physio ring	LA	121	84	67.5	11	SR	m,e,w, amio
24	MV Rep, TA	28mm CG Future Band	LA			427.8	18	SR	a,l, aspirin
25	MVR, TA	27mm St Jude's	LA	140	109	39.5	6	SR	w, amio
26	MVR,AVR	27mm, 21mm St Jude's	LA	194	155	40	10	AF	a,e,w,l, amio
27	MVRep, TA, ASD	Future Band	Bi-atrial	132	118	89.2	8	SR	w,l, amio
28	MVR,TA	25mm St Jude's	LA	109	82	45.3	9	SR	e,w,l,amio
n = number of patients, CPB = cardiopulmonary bypass, Xclamp = aortic cross clamp, ICU = intensive care unit									
MVR = mitral valve replacement, TA = tricuspid annuloplasty, MVRep = mitral valve repair, TV CABG = triple vessel coronary artery bypass grafting									
CABG = coronary artery bypass grafting, AVR = aortic valve replacement, ASD = atrial septal defect, OPCAB = Off pump coronary artery bypass grafting									
LA = left atrial, SR = sinus rhythm, Aflutter = atrial flutter, AF = atrial fibrillation									
a = atenolol, m = metoprolol, e = enalapril, d = digoxin, w = warfarin, l = lasix, hctz = hydrochlorothiazide, amio = Amiodarone, vanco = vancomycin									

**Table Y continue ...**

**Table Y: Operative and Peri-operative Data (continue)**

<b>Operative and Peri-operative Data</b>									
<b>n</b>	<b>Procedure</b>	<b>Valve types and sizes</b>	<b>Maze procedure</b>	<b>CPB Time minutes</b>	<b>Xclamp minutes</b>	<b>ICU stay hours</b>	<b>Hosp stay days</b>	<b>Discharge rhythm</b>	<b>Discharge Meds</b>
29	MVRep,TA	-	LA	144	52	66.5	19	SR	e,w,l, spiro, amio
30	MvRep	32mm Future Band ring	LA	108	77	40.8	17	SR	d,w,l
31	MVRep	32mm Future Band ring	LA	126	84	45.5	8	SR	l, aspirin, amio
32	MVRep	32mm Future Band ring	LA	114	96	47.5	8	AF	e,w,l
33	MVR	25mm MIRA mech	LA	116	90	63.2	14	AF	e,d,w,l,amio
34	MVR	25mm Mosaic bioprosthesis	Bi-atrial	198	169	2	0	Paced	mortality
35	redo- MVRep	34mm CG Medtronic Futureband	Bi-atrial	134	111	45.8	8	SR	e,w
36	MVRep	30mm CG Future Band	LA	73	44	19	8	SR	e,w,amio
37	MVRep	30mm CG Future Band	LA	156	130	46.8	11	AF	amio , w, a, l,colchicine
38	MVR	27mm St Jude's	LA	136	110	40.2	7	SR	w,l,amio
39	MV Rep, CABG	32mm CG Future Band,	LA			44.8	8	SR	a, statin, l, w
40	MV Rep	30mm CG Future Band	LA	163	143	43.5	10	SR	A, w, l
n = number of patients, CPB = cardiopulmonary bypass, Xclamp = aortic cross clamp, ICU = intensive care unit									
MVR = mitral valve replacement, TA = tricuspid annuloplasty, MVRep = mitral valve repair, TV CABG = triple vessel coronary artery bypass grafting									
CABG = coronary artery bypass grafting, AVR = aortic valve replacement, ASD = atrial septal defect, OPCAB = Off pump coronary artery bypass grafting									
LA = left atrial, SR = sinus rhythm, Aflutter = atrial flutter, AF = atrial fibrillation									
a = atenolol, m = metoprolol, e = enalapril, d = digoxin, w = warfarin, l = lasix, hctz = hydrochlorothiazide, amio = Amiodarone, vanco = vancomycin									

---

University of Cape Town

---

66

55  
52  
36  
57  
45  
42  
43  
44  
59  
60

8  
.20

University of Cape Town

---

40  
21  
22  
23  
24  
37  
64  
25  
26  
27  
36  
39  
58  
28  
29  
33  
30  
31  
35  
38

University of Cape Town

---

54  
63  
51  
39  
47  
46  
50  
32  
48  
49  
68  
65  
16

University of Cape Town

---

University of Cape Town

---

16  
16

University of Cape Town