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# Treatment of Atrial Fibrillation in Patients Undergoing Mitral Valve Surgery

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## 1. Introduction

Spontaneous sinus rhythm recovery occurs in not more than 10% of patients with preoperative atrial fibrillation and mitral valve disease who undergo mitral valve surgery (Kernis et al, 2004). In a recent review Lee et al (2009) reported that less than 20% of patients with permanent atrial fibrillation undergoing surgery without treatment of atrial fibrillation were in sinus rhythm at 6-8 months from operation. Persistence of atrial fibrillation (AF) is associated with a decreased exercise tolerance, an increased risk of systemic embolization (Reston & Shuhaiber, 2005) and an higher long-term mortality (Khargi et al 2005). Moreover 15% of patients in sinus rhythm before surgery are discharged in atrial fibrillation after treatment of mitral valve disease. At multivariate analysis an enlarged left atrium is associated with an increase risk of development of AF.

The surgical treatment of AF was proposed by James Cox in the 1980s and evolved into the Maze III procedure (Cox et al, 1991). The aim of the intervention was to create numerous atrial surgical incisions that form a maze-like pattern, with the scar tissue providing a conduction block to interrupt propagation of the arrhythmia from sites of electrical instability and favouring the conduction from sinus node to atrio-ventricular node. The procedure involves surgical encircling of pulmonary veins at their entry in left atrium. A lesion between an inferior pulmonary vein and the mitral annulus, and a lesion joining the coronary sinus and the inferior vena cava are usually added to block other trigger zones, in particular in patients with permanent atrial fibrillation. The left atrial appendages is excised or closed to prevent thromboembolism in the event of postoperative AF.

The surgical treatment proposed by Cox has been mainly used in patients with other heart disease with indication to surgery, however it was used also in patients with invalidating "lone atrial fibrillation" not responsive to pharmacological treatment.

Despite an high success rate, from 70% to 90% in relation to population treated, surgical Maze procedure has an elevated technical difficulty, prolongs significantly the times of cardiopulmonary by-pass, increases the risk of post-operative bleeding and has a not negligible risk of mortality. The need for permanent pacing is close to 6%.

Sinus rhythm recovery allows the maintenance of atrial mechanic activity and prevents the development or worsening of tricuspid regurgitation (Je et al, 2008).

Preoperative duration of atrial fibrillation and left atrial volume were independent factors related to sinus rhythm recovery (Benussi et al, 2002; Beukema et al, 2005; Chan et al, 2005).

In the following years, due to the complexity of the “cut and saw” Maze procedure, the research was directed to create the maze pattern with energy ablation rather than incisions (Benussi et al, 2001). These methods have simplified the procedure and increased its application. Energy sources used for intraoperative ablation include cryotherapy, radiofrequency, microwave, laser, and ultrasound.

Radiofrequency probes may be unipolar or bipolar (Williams et al, 2001; Gaynor et al, 2004). The main limitation of monopolar probes is the high probability to not obtain transmural lesions. Bipolar probes have a higher chance to obtain transmural lesions and a reduced risk of damaging adjacent structures such as the esophagus. (Bugge et al, 2005; Benussi et al, 2005). Moreover have been introduced devices for epicardial treatment which allows treatment for example in patients undergoing off-pump coronary revascularization. Irrigated radiofrequency probes have greater efficiency because the cooling effect on the surface of the tissue drives the focus of energy deeper into the tissue and prevents char accumulation on the surface. Radiofrequency treatment of atrial fibrillation usually prolongs the times of the intervention by no more of 20 minutes.

More recently bipolar radiofrequency probes have been introduced to treat “lone atrial fibrillation” through a mini invasive bilateral thoracotomy, thus avoiding the need for sternotomy and related complications (Wolf et al, 2005). Preliminary results are similar to that obtained with the traditional surgical approach.

Microwave energy creates deeper lesions than does radiofrequency energy in a similar length of time and may have more potential for epicardial application. Laser and ultrasound energy are still relatively new energy sources, but both may produce transmural lesions even through epicardial fat (Saltman et al, 2003).

## 2. Literature review

In patients undergoing combined mitral valve and Cox maze surgery, Cox et al (2004) reported 98% cure of AF, Prasad et al (2003) observed a greater than 90% freedom from AF in patients having a Cox maze procedure with concomitant surgery. In contrast, others have used a classic cut-and-sew technique and reported less success. Raanani et al (2001) recorded sinus rhythm in only 75% of patients a mean of 26 months after Cox maze and mitral valve surgery, which is similar to the Mayo Clinic experience of 74% freedom from AF at 2 years (Handa et al, 1999; Shaff et al 2000).

The use of RF energy for the creation of the atrial lesions of the Cox maze procedure was associated with significantly less freedom from AF both at hospital discharge and at follow-up (Stulak et al 2007).

The differences of the long-term success rate could be influenced other than by the differences among intraoperative variables, mainly by preoperative variables, such as concomitant valvular surgery and rheumatic valvular heart disease.

The surgical results of the maze procedure for AF associated with rheumatic mitral valve disease have been known to be less effective than for lone or non-rheumatic AF (Raanani et al, 2001). Few clinical studies in the literature compared the results of concomitant AF maze in open heart surgery with those of a concurrent control arm (that is leaving the AF untreated). A control is important to eliminate confounding variables that may influence results of the maze procedure and the determination of clinical outcomes. Absence of a control arm also does not allow discernment of the absolute effect of the maze surgery because we cannot know how many of the patients would convert to sinus rhythm spontaneously.

Wogk and Mak (2006) examined the results of seven matched-controlled and four randomized trials of Maze procedure associated with concomitant mitral valve surgery. In

the matched-controlled studies freedom from AF was 77% to 95% in the maze group versus 4% to 53% in the control group at 2 to 8 years of follow-up. In matched-controlled studies 12-lead electrocardiography was used for rhythm evaluation. The four randomized studies reported a 78% to 88% freedom from AF in the maze group versus 20% to 40% in the control group at 1- to 1.5-year follow-up

About 20–30% of the patients who underwent maze procedures have shown recurrence of AF during the follow-up periods, and there are few reports showing mid- to long-term results and reporting predictors of the maze failure.

Je et al, (2008) showed that preoperative size of the LA larger than 60 mm, cardiothoracic ratio over 60%, fine AF wave in preoperative ECG, no early sinus restoration and SSA were found as independent predictors of maze failure in mid-term follow-up period at multivariate analysis. Patients with left atrial dimension 50 mm or greater had almost twice probability of experience late recurrence of AF.

Besides the acute end point (for example, PV isolation, demonstration of bidirectional block of linear lesions, non-inducibility of AF, etc), the more important result of any ablation strategy is the clinical efficacy in restoring SR without the need for further antiarrhythmic medication. However, comparison of clinical success has been hampered by the absence of a clear AF classification, adequate reporting of underlying cardiac conditions (such as coronary artery disease, heart failure, etc), and the use of symptomatic only follow-up. "Rhythm at last follow-up" may underestimate the recurrence of atrial arrhythmias in the follow-up period, and thus overestimate the success of the procedure. In a consent statement (Calkins et al, 2007) a minimum of sequential Holter recordings is advised, with more stringent recommendations for prospective trials (for example, 7 days of Holter recording or even implantable loop recording).

Finally a "prophylactic" maze procedure has been proposed for patients with preoperative sinus rhythm and a dilated left atrium undergoing surgery for mitral valve disease. The altered atrial tissue in these patients represents an arrhythmogenic substrate, with a high risk (approximately 40%) for the development of postoperative AF even after correction of the mitral valve disease. Clearly, the risks and benefits should be weighed before an additional procedure is performed, which carries intraoperative and long-term (Saad et al, 2003) adjunctive risks other the need of PPM implantation (new permanent pacemakers are required in 10% to 15% of patients) (Gillinov et al, 2004). The indication in almost all was bradycardia due to sinus node dysfunction. Technical modifications to the original Cox-maze operation may however reduce injury to the sinoatrial node.

## 2.1 Personal experience

In our Department the fist Cox maze radiofrequency (RF) ablation was performed in 2002 in one patient undergoing mitral valve repair. Since then at least 350 procedures, initially with monopolar thereafter with bipolar probes, have been performed, usually in association with mitral valve surgery but also with more complex interventions. In present paper we report the results of monopolar radiofrequency ablation in patients with atrial fibrillation undergoing mitral valve surgery.

At present, long terms results of AF radiofrequency ablation associated with mitral valve surgery are poorly defined in literature not allowing the definition of classes of recommendation and levels of evidence concerning the utility and efficacy of the procedure (Padalinam et al., 2005).

In present investigation we evaluated: overall mortality; cause and time of death ; incidence of stroke; maintenance of sinus rhythm; persistence of sinus rhythm during follow-up; eventual relapse of AF or the onset of other types of arrhythmias; the necessity of permanent

pacings after the procedure; further hospitalization due to cardiac complications; . We even evaluated the relationship between several clinical and echocardiographic parameters and long term clinical outcome.

### 2.1.1 Material and methods

#### Patient population.

From 1/1/2002 to 31/12/2007, 173 patients with AF and mitral valve disease underwent monopolar radiofrequency ablation procedure, associated with mitral valve surgery in the heart surgery Department of the Azienda Ospedaliera Universitaria di Careggi (AOUC).

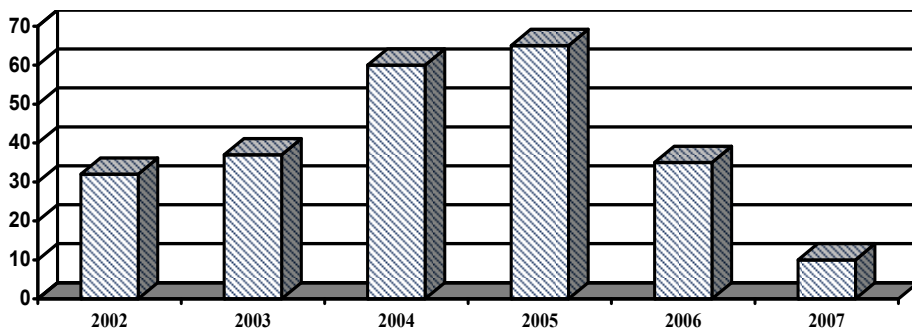


Fig. 1. Monopolar radiofrequency ablation at Florence Heart Surgery Department

In the study were included 101 men and 72 women, with a mean age of  $67 \pm 9$  years.

81.7% were in permanent AF (mean duration  $38 \pm 43$  months) while 18.3% suffered from paroxysmal AF.

A careful clinical evaluation was performed before surgery in order to establish time of onset of AF and NYHA functional class. Electrocardiographic examination was performed to confirm the presence of the arrhythmia.

All patients underwent transthoracic echocardiography using a 2.5 and 3.5 MHz probe (Sequoia C256 Acuson Siemens Mount View, California). Parameters measured were: left atrium M-mode AP diameter (mm) and 2D area ( $\text{cm}^2$ ) and right atrium 2D area ( $\text{cm}^2$ ) from four chamber projection, left ventricular ejection fraction (LVEF)- average value of three measurements. End-diastolic and end-systolic images were synchronized on ECG tracings.

Pulmonary systolic pressure (PAP) was calculated adding RV/RA pressure gradient to estimated right atrial pressure.

For statistical analysis were recorded:

- the surgical procedure (valve replacement with mechanical or biologic valve vs. mitral valve repair; associated surgical procedures).
- associated tricuspid valve repair
- need for electrical cardioversion before discharge.
- need for permanent pacing
- ECG rhythm at the time of discharge. After surgery patients were evaluated after the first and sixth months and later once a year. At every visit we performed a clinical, electrocardiographic and echocardiographic examination. In addition to previously reported parameters in patients in sinus rhythm right and left E and A waves amplitude and E/A ratio were measured to evaluate atrial mechanical activity.

The study was terminated on December 31 2010. Overall duration of follow-up has been  $1743 \pm 845$  days.

### Maze Procedure

The Medtronic Cardioblade surgical ablation system consists of a power generator and a pen. The pen is a handheld, unipolar RF ablation device. The electrode tip is irrigated with saline that cools the tissue and provides a low-impedance path, which allows creation of deeper lesions with less damage to the surrounding tissue. The patient is grounded by an indifferent electrode applied to the skin. After median sternotomy, cardiopulmonary bypass (CPB) was established with bicaval and aortic cannulation under moderate hypothermia (32°C); myocardial protection was assured by antegrade crystalloid cardioplegia. The aorta was cross-clamped and the heart was arrested with cold cardioplegic solution. Access to the inside of the left atrium was gained through a standard atriotomy in the interatrial groove, as for a mitral valve (MV) procedure. After the LAA was excised and sutured, an ablation line from the LAA to the left superior pulmonary vein was created. In addition to the incision in the interatrial groove, isolation of the right pulmonary veins was completed by a circular ablation line. The left pulmonary veins were encircled. Two linear ablations were performed endocardially. The first connected the two encirclings on the posterosuperior atrial wall. This lesion was kept cranial, opposite the transverse sinus, to prevent any possible damage to the esophagus. The last ablation connected the left appendage to the posterior aspect of the mitral annulus. To protect the circumflex artery from heat trauma, the lesion line reached the mitral posterior annulus far from the antero-lateral commissure (figure 2). The transesophageal echocardiographic probe was removed during the ablation to prevent any

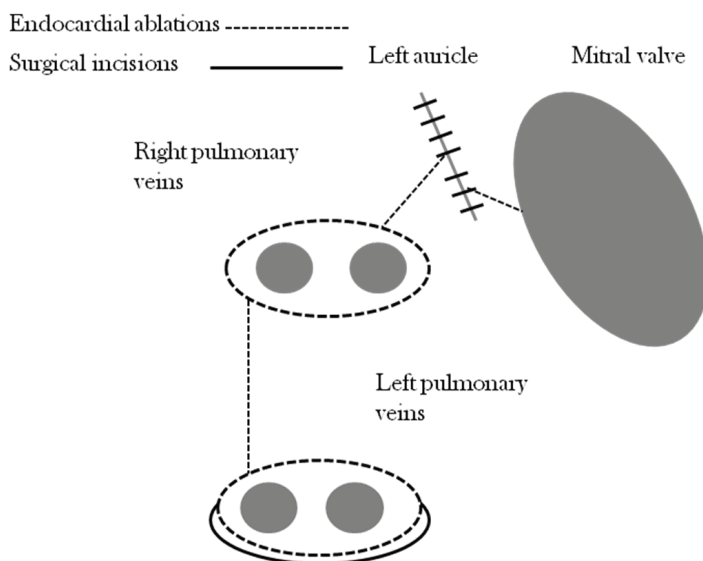


Fig. 2. Modified RF Maze procedure – schematic representation of ablation lines

damage by the transmission of the heat waves to the esophagus. The mitral valve procedure was completed and the left atriotomy was sutured in the standard fashion.

### Postoperative Management

Antiarrhythmic prophylaxis was carried out on a routine basis. Amiodarone, intravenous bolus of 300 mg, followed by a continuous infusion of 1,200 mg/24 h f was administered in

the first 48 hours; thereafter were prescribed 200 mg every 8 hours until discharge, followed by a maintenance regimen of 200 mg/day for 1 month. Recurrences of the arrhythmia after surgery were treated by optimizing the medical treatment. Patients who had AF despite optimal medical therapy had at least one attempt of external cardioversion by biphasic DC-shock. Successful treatment of the arrhythmia was defined as the absence of refractory AF in patients with chronic AF before operation and absence of any episode of sustained arrhythmia in patients with paroxysmal AF preoperatively. Six months after surgery, oral anticoagulants were discontinued in patients with stable SR and with documented atrial contraction after mitral valve repair or replacement with a biological prosthesis.

### 2.1.2 Statistical analysis

Data are presented as means  $\pm$  SDs for continuous variables and as percentages for categorical variables. Continuous variables were compared through the use of Student's 2 tailed unpaired-sample test. Categorical variables were compared using the chi-square test or Fisher's exact test if appropriate. Kaplan-Meier curves were used for the survival analysis. Differences between groups were compared using Log-Rank test.

A probability value  $< 0.05$  was considered significant. Statistical analysis were performed with SPSS 18.0 software (SPSS, Inc., Chicago, IL, USA).

### 2.1.3 Results

Four patients died in the immediate postoperative period (2,3%). One patient died for cerebral hemorrhage, one for myocardial infarction, the other 2 for septic shock.

Therefore 169 patients, 99 men and 70 women, were included in the study. Clinical and echocardiographic characteristics are reported in table 1.

Sex (M/F)	99/70
Age (years )	67 $\pm$ 9
AF duration before surgery (months )	38 $\pm$ 43
Left ventricular EF (%)	52 $\pm$ 10
Left atrium diameter (mm)	53.6 $\pm$ 7
Left atrium area (cm <sup>2</sup> )	32.5 $\pm$ 10
Right atrium area (cm <sup>2</sup> )	22.3 $\pm$ 6.7
Systolic pulmonary pressure (mmHg)	45 $\pm$ 15
NHYA class	3 $\pm$ 0.55

Table 1. Clinical and echocardiographic characteristics

	N°	%
Mitral valve prolapse	48	28.6
Rheumatic mitral valve disease	57	33.9
Mitro-aortic rheumatic valve disease	25	15
Ischemic mitral regurgitation	20	11.9
Mitral regurgitation associated with DCM	6	3.5
Other	12	7.1

Table 2. Etiology of mitral valve disease. DCM= dilated cardiomyopathy

Rheumatic mitral valve disease, alone or associated with aortic valve disease, was the most frequent indication to surgery (73/169), followed by mitral valve prolapse (table 2). Mitral valve repair was performed in 46%. In combined mitro-aortic valve disease, aortic valve replacement was combined with mitral valve replacement in more than 60% of patients and with mitral valve repair in the remaining cases. Twenty (12%) patients underwent associated CABG (figure 2).

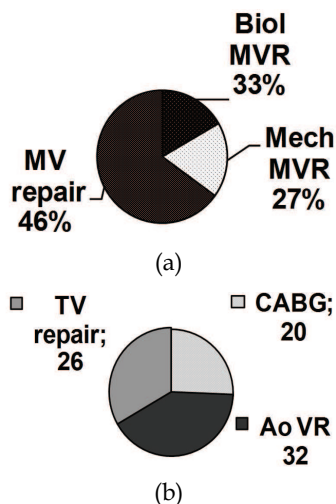


Fig. 3. a) Main surgical procedure (%) b) associated surgery (n°).

26/169 (15%) patients underwent tricuspid valve repair for severe tricuspid regurgitation most (>85%) according to Kay technique. At the time of surgery almost 80% of patients had severe functional impairment (III-IV NYHA class).

NYHA class before surgery		%
I	0	0
II	27	16
III	116	69
IV	24	15

Table 3. Functional NYHA class before surgery

#### Rhythm analysis.

119/169 subjects (70%) were in sinus rhythm at hospital discharge, while sinus rhythm was present in 100 at the end of follow up period. Atrial fibrillation was never resolved in 39. During the period of follow up 42% of patients has been in stable sinus rhythm, while 34% had at least one symptomatic AF recurrence. 7,8% developed arrhythmias different from AF.

Stable sinus rhythm N (%)	AF recurrence N (%)	Permanent AFN (%)
72 (42%)	58 (34%)	39 (24%)

Table 4. Number and percentage of patients with stable sinus rhythm (SR), with AF recurrence and persistent atrial fibrillation (AF)

	Stable sinus rhythm	AF recurrences	Permanent AF	P
Age (years)	68.1 +/- 9.6	67.7 +/- 9.8	71.5 +/- 8	0.0494
Left atrium diameter (mm)	51.6 +/- 6.6	54.2 +/- 8.3	55.5 +/- 8.2	<0.0001
Left atrium area (cm <sup>2</sup> )	30.4 +/- 7.2	32.8 +/- 8.5	36.9 +/- 14.5	<0.0001
Right atrium area (cm <sup>2</sup> )	20.6 +/- 4.5	22.2 +/- 6.3	23.7 +/- 6.2	<0.0159
Systolic PAP (mmHg)	41.2 +/- 12.8	44.7 +/- 15.3	45.3 +/- 15.8	<0.0001
Electrical CV before discharge (%)	9.5	20.5	28.6	0.0092
Hospitalizations (%)	17.4	48.4	30.8	<0.0001

Table 5. Comparison of baseline clinical and echocardiographic parameters in patients with stable sinus rhythm (SR), with AF recurrence and permanent atrial fibrillation (AF)

On average AF recurrence occurred 750 days after surgery.

### Survival without recurrences

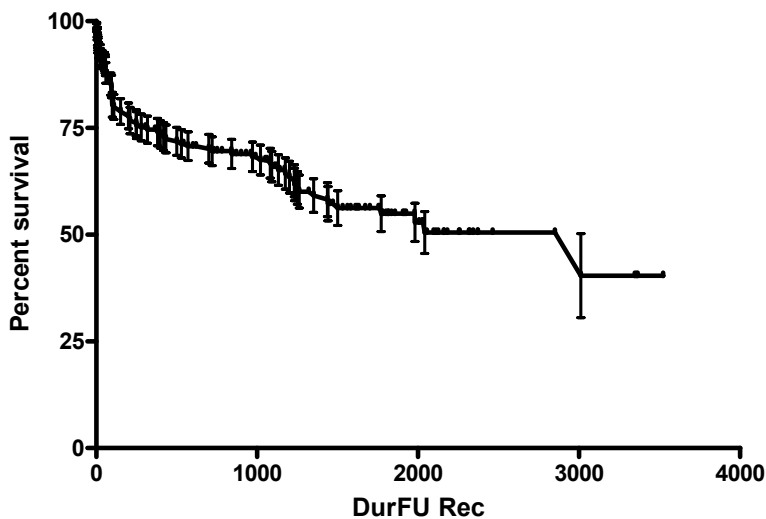


Fig. 4. Survival free from AF recurrences in patients with SR at hospital discharge

In table 5 are reported the clinical and echocardiographic characteristics of the three groups of patients (stable sinus rhythm; AF recurrences; permanent AF) at enrolment.

Patients who were in chronic AF were on average older (3 years) than those who never had AF recurrences or who remained in permanent sinus rhythm ( $p=0,0494$ ; figure 5).

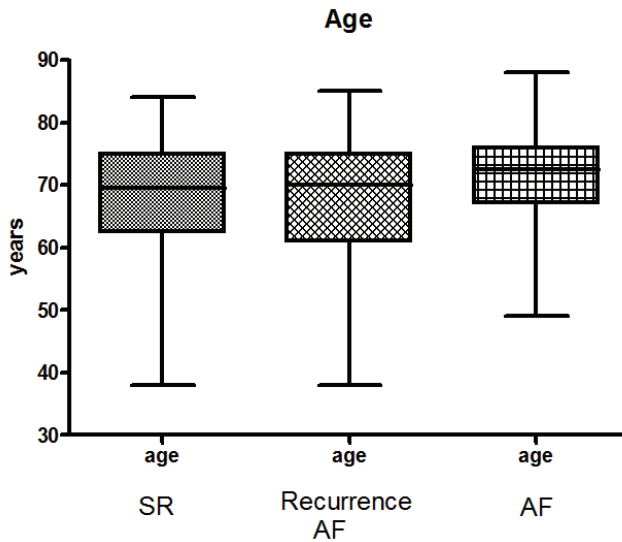


Fig. 5. Baseline mean age in patients in stable sinus rhythm (SR), with AF recurrence and permanent atrial fibrillation (AF)

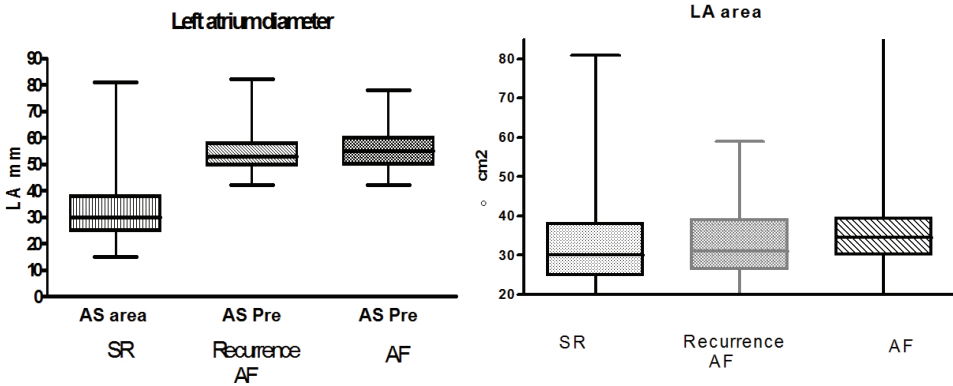


Fig. 6. Baseline left atrium diameter (left) and area (right) in patients in stable sinus rhythm (SR), with AF recurrence and permanent atrial fibrillation (AF)

Left atrium diameter ( $p=0,0001$ ; figure 6,a), left atrium area ( $p<0,0001$ ; figure 6,b) and right atrium area ( $p<0,0159$ ) resulted significantly lower in patients with permanent sinus rhythm in comparison with the other two groups.

Estimated systolic pulmonary artery pressure was higher in patient with AF recurrences or in chronic AF than in those with permanent sinus rhythm ( $p<0,0001$ ; figure 7).

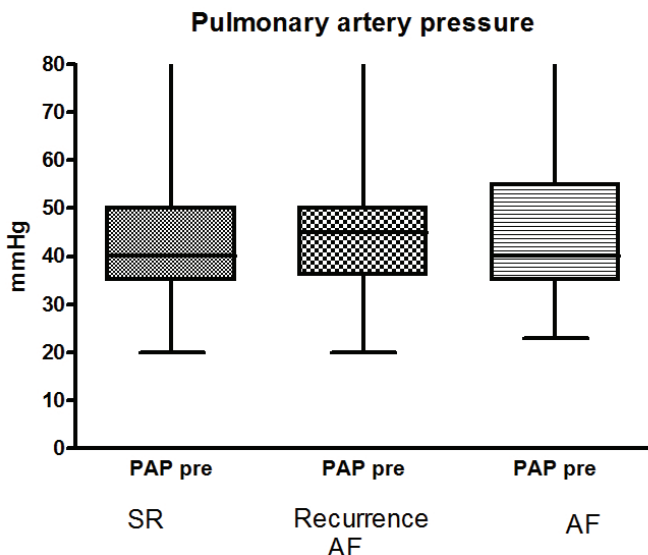


Fig. 7. Baseline systolic pulmonary artery pressure in patients in stable sinus rhythm (SR), with AF recurrence and permanent atrial fibrillation (AF)

The number of patients who needed electrical cardioversion before hospital discharge was significantly lower in the group with stable sinus rhythm than in the other groups ( $p=0.005$ ). Twenty-three patients underwent definitive cardiac electrical stimulation. In 6 patients permanent pacing was needed during hospitalization. In 17 a pace maker was implanted during follow-up period. 3,5% had at least one cerebrovascular accident during the postoperative period.

Baseline mean NYHA class was 2.96 in SR and 3.3 in AF patients. At follow-up a significant improvement was found in SR patients (average NYHA class 1.31 vs 2.33,  $p<0.003$ ).

	NYHA class before surgery	NYHA class at follow-up
I	0	47
II	27	68
III	116	31
IV	24	5

Table 6. NYHA functional class before surgery and at follow-up

33,9% underwent hospitalization due to cardiac cause during the follow up period. Hospitalization percentage was almost twofold in patients with chronic AF compared to patients in sinus rhythm ( $p<0.0001$ ).

### **Mortality**

At the end of the average five years follow-up period survival was 86.4%.

Twenty three patients died: in 62% death was due cardiac causes, in the other 38% the cause of death was not cardiac or unknown. Death occurred on average occurred days after surgery.

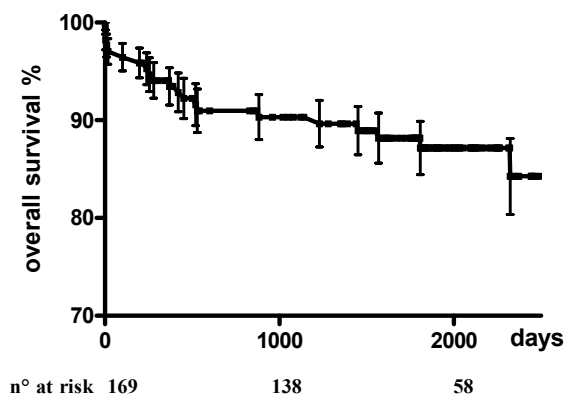


Fig. 8. Actuarial survival curve in patients undergoing RF ablation of AF associated with mitral valve surgery.

Deceased patients were about 5 years older than survivors (mean age of 67 years vs 72 years in the group of deceased patients,  $p=0.005$ ).

Mortality was higher in men than in women (23% vs 9%).

Time free from AF recurrences, right and left atrial are were related to higher mortality.

	Survived	dead	P
AF duration before surgery (months)	37 +/-48	46 +/-46	0.31
Time free from AF recurrence (day after surgery)	937 +/-738	422 +/-485	0.015
LVEF (%)	52+/- 9	52 +/- 10	0.83
Left atrium diameter (mm)	53,4 +/-9	56 +/- 11	0.17
Left atrium area (cm <sup>2</sup> )	31,1 +/- 7	38 +/- 10	0.0116
Right atrium area (cm <sup>2</sup> )	21,6 +/- 6	24,5 +/- 9	0.0128
Systolic pulmonary pressure (mmHg)	44 +/- 14	48 +/- 17	0.26

Table 7. Comparison of clinical and echocardiographic parameters between patients survived and went to death

Overall long-term mortality was higher in patients with rheumatic than in those suffering from mitral valve prolapse (table 8).

Etiology	Mortality n (%)
Mitral valve prolapse	4 (8.8%)
Rheumatic mitral valve disease	13 (22%)
Mitro-aortic rheumatic valve disease	2 (8%)
Ischemic mitral regurgitation	3 (15%)
Mitral regurgitation associated with DCM	1 (16%)
Other	0 (0%)

Table 8. Relationship between mortality and etiology of mitral valve disease

Relationship between mortality and type of procedure performed is illustrated in table 9:

Intervention	Mortality n (%)
Mitral valve replacement (mechanical)	5 (20%)
Mitral valve replacement (biological)	5 (17%)
Mitral valve repair	7 (12%)
Mitral valve replacement/repair plus aortic valve replacement	1 (4%)
Mitral valve repair plus CABG	3 (16%)
Mitral valve replacement plus CABG	2 (40%)
Other	0 (0%)

Table 9. Relationship between mortality and type of intervention performed

Tricuspid valve repair was significantly associated with an higher mortality: it was performed in 40% of deceased patients in comparison to 12% of survivors ( $p = 0.005$ ). Preoperative NYHA class was not statistically related to survival. The percentage of patients in advanced NYHA class (III-IV) was similar in the two groups (82% of survivors vs 91 % of patients went to death).

NYHA class	Survived (%)	Dead (%)
I	0	0
II	25	2
III	102	15
IV	19	6

Table 10. Relationship between mortality and NYHA class before surgery

Failure to restore sinus rhythm with RF ablation was related to a worse prognosis. Mortality at five years was 30% in patients discharged form hospital in AF in comparison to 10% of those discharged in sinus rhythm.

Moreover survival was higher in patients with stable sinus rhythm during follow up respect to patients with recurrences and finally patients with permanent AF (table 10).

Figure 9 shows the survival curves in patients with persistent sinus rhythm, patients with AF recurrences and patients with permanent AF (Log Rank test- $p=0.0022$ ).

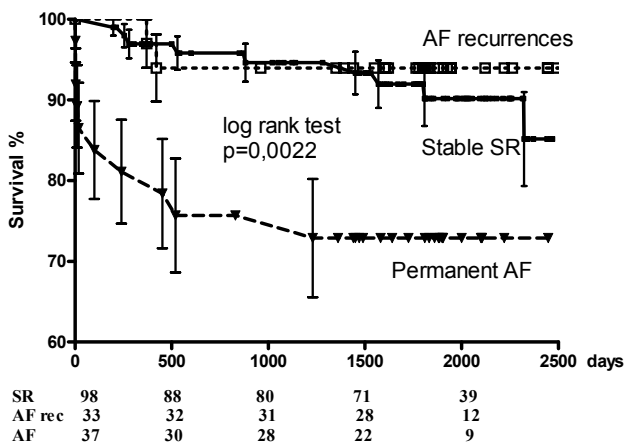


Fig. 9. Kaplan-Meier survival curves in patients in stable sinus rhythm (SR), with AF recurrence and permanent atrial fibrillation (AF)

### 3. Conclusion

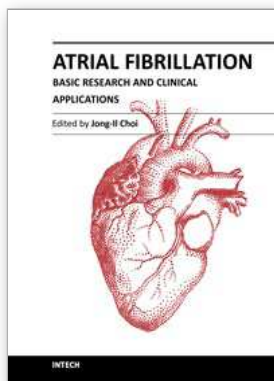
The ideal goal of AF surgery is a safe, simple, effective, and tailored approach to eradicate the most likely mechanism of AF. New technologies in AF surgery have evolved in creating the lines of block faster, easier, safer, and transmurally.

The merits of various alternative energy sources used to create the lines of block of the maze are subject of debate. But more important AF surgery should be able to demonstrate that maintenance of SR is associated with improved clinical outcomes. Results from our investigation support the hypothesis that in patients remained in sinus rhythm after RF ablation not only the quality of life is improved, as demonstrated by the lower NYHA functional class in patients with stable SR in comparison to patients with permanent AF, but also significantly affects mortality. Properly conducted, larger, randomized studies with adequate follow-up however are needed to determine the true impact of concomitant maze surgery on clinical outcomes.

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## **Atrial Fibrillation - Basic Research and Clinical Applications**

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